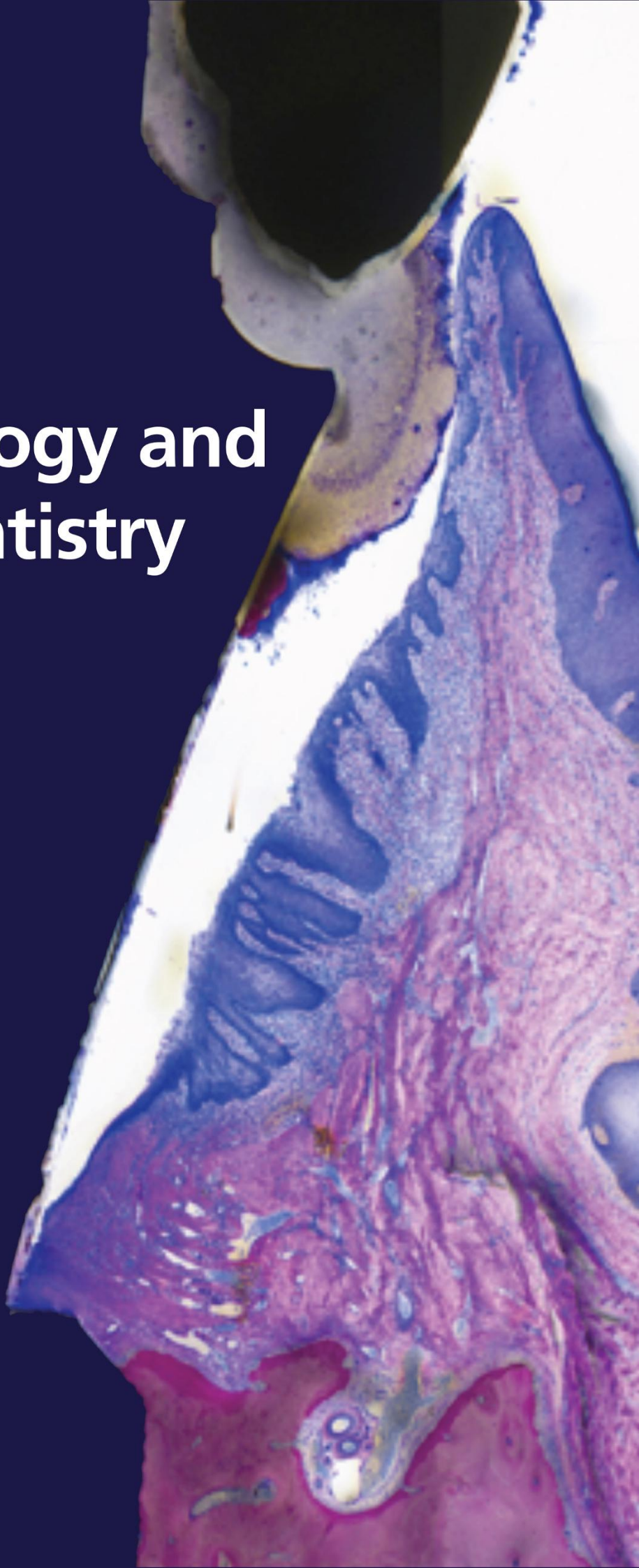
TWO-VOLUME SET

Clinical Periodontology and Implant Dentistry

SIXTH EDITION

Edited by
Niklaus P. Lang
Jan Lindhe



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Edited by

Niklaus P. Lang
and
Jan Lindhe

Associate Editors
Tord Berglundh
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Volume 1
BASIC CONCEPTS

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Jan Lindhe
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Preface

In an age when the internet is providing numerous options of treatment based on not always properly validated concepts presented by clinicians of sometimes unclear background, the practitioner is left with a confusing image of the profession. The questions of what is right and what is a professional error are becoming increasingly difficult to determine. It is evident that such online education – while occasionally having its undisputed benefits – bears the danger of distributing treatment philosophies that are most likely not scientifically scrutinized and, hence, may even be detrimental to the patient.

Given these facts, one may wonder what the role of a textbook becomes, when everything is so easily accessible through electronic media. Obviously, a textbook still represents a unique source of professional information containing a treatment philosophy that must be based on scientific evidence rather than on trial and error or personal preference. *Clinical Periodontology and Implant Dentistry* has always emphasized the evidence-based treatment approach.

The textbook originated from Scandinavia and documented various treatment procedures with clinical research data. In later years, the authorship became more international, which led to the success of the text throughout the world. In the fourth edition some aspects of implant dentistry were incorporated, and by the time that fifth edition was prepared implant dentistry had become an important part of clinical periodontology. Owing to the increased content, the first of the now two volumes presented the basic aspects, applying biological principles to both periodontal and peri-implant tissues, whereas the second volume was devoted to treatment aspects. It had become evident that periodontology also affects the biology of implants.

Consequently, these two fields of dentistry have become merged and married to each other. The new sixth edition of this textbook incorporates the important topic of the strictly prosthetic aspects of treating mutilated dentition. An essential part of comprehensive therapy is treatment planning according to biological principles, to which special attention has been given. The installation of oral implants and their healing are covered in detail, and novel concepts of tissue integration are also addressed. Last, but not least, clinical experience from latter years has revealed that biological complications occur with oral implants. The sixth edition gives special attention to coping with such adverse events and also to issues related to the maintenance of periodontal and peri-implant health. All in all, the sixth edition represents a thoroughly revised syllabus of contemporary periodontology and implant dentistry.

If a textbook is to maintain its role as a reference source and guide for clinical activities it has to be updated at regular intervals. The sixth edition follows the fifth edition by 7 years, and 90% of the content has been revised in the last 2 years. Several chapters have been reconceived or completely rewritten by a new generation of internationally recognized researchers and master clinicians. As we thank our contributors to this new masterpiece for their enormous effort in keeping the text updated, we hope that the sixth edition of *Clinical Periodontology and Implant Dentistry* will maintain its status as the master text of periodontology and implant dentistry for the entire profession worldwide.

We express our gratitude to the numerous coworkers at Wiley, our publisher, who contributed to the realization of the project, and special thanks go to Nik Prowse (freelance project manager), Lucy Gardner (freelance copy-editor) and Susan Boobis (freelance indexer).

However, most of our thanks go to you, as reader, student, colleague, specialist clinician or researcher in clinical periodontology and implant dentistry. We hope that you enjoy this new edition, with its new clothes and new outline.

Niklaus P. Lang

Jan Lindhe

February 2015

Part 1: Anatomy

Chapter 1

Anatomy of Periodontal Tissues

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Introduction

This chapter provides a brief description of the characteristics of the normal periodontium. It is assumed that the reader has prior knowledge of oral embryology and histology.

The periodontium (peri = around, odontos = tooth) comprises the following tissues: (1) *gingiva* (G), (2) *periodontal ligament* (PL), (3) *root cementum* (RC), and (4) *alveolar bone proper* (ABP) (Fig. 1-1). ABP lines the alveolus of the tooth and is continuous with the alveolar bone; on a radiograph it may appear as *lamina dura*. The *alveolar process* that extends from the basal bone of the maxilla and mandible consists of the alveolar bone and the *alveolar bone proper*.

The main function of the periodontium is to attach the tooth to the bone tissue of the jaws and to maintain the integrity of the surface of the masticatory mucosa of the oral cavity. The periodontium, also called "the attachment apparatus" or "the supporting tissues of the teeth", constitutes a developmental, biologic, and functional unit which undergoes certain changes with age and is, in addition, subjected to morphologic changes related to functional alterations and alterations in the oral environment.

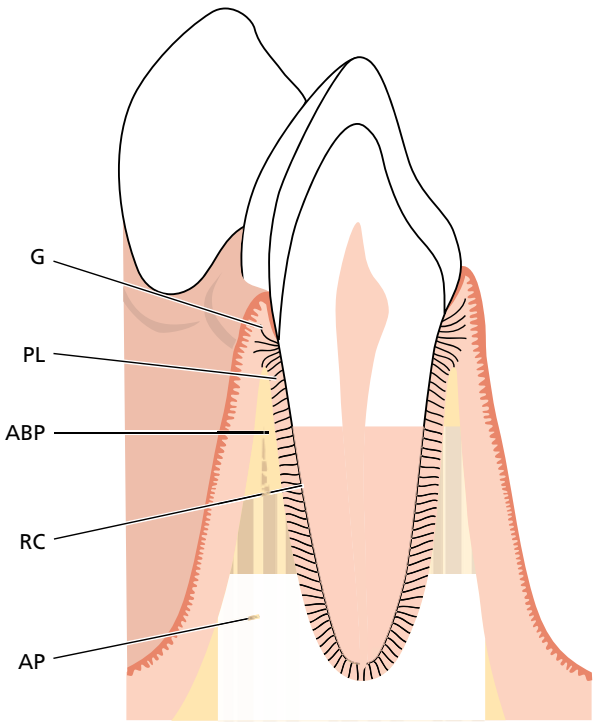


Fig. 1-1

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

The development of the periodontal tissues occurs during the development and formation of teeth. This process starts early in the embryonic phase when cells from the neural crest (from the neural tube of the embryo) migrate into the first branchial arch. In this position, the neural crest cells form a band of *ectomesenchyme* beneath the epithelium of the stomatodeum (the primitive oral cavity). After the uncommitted neural crest cells have reached their location in the jaw space, the epithelium of the stomatodeum releases factors which initiate epithelial–ectomesenchymal interactions. Once these interactions have occurred, the ectomesenchyme takes the dominant role in the further development. Following the formation of the *dental lamina*, a series of processes are initiated (bud stage, cap stage, bell stage with root development) which result in the formation of a tooth and its surrounding periodontal tissues, including the alveolar bone proper. During the cap stage, condensation of ectomesenchymal cells appears in relation to the dental epithelium (the dental organ [DO]), forming the *dental papilla* (DP) that gives rise to the dentin and the pulp, and the *dental follicle* (DF) that gives rise to the periodontal supporting tissues (Fig. 1-2). The decisive role played by the ectomesenchyme in this process is further established by the fact that the tissue of the dental papilla apparently also determines the shape and form of the tooth.

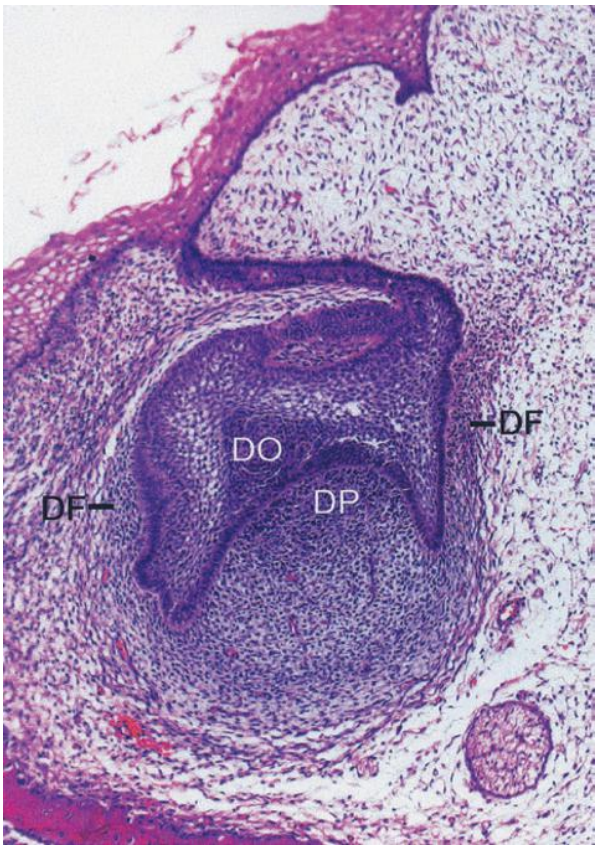


Fig. 1-2

If a tooth germ in the bell stage of development is dissected and transplanted to an ectopic site (e.g. the connective tissue or the anterior chamber of the eye), the tooth formation process continues. The crown and the root are formed, and the supporting structures (i.e. cementum, periodontal ligament, and a thin lamina of alveolar bone proper) also develop. Such experiments document that all information necessary for the formation of a tooth and its attachment apparatus resides within the tissues of the dental organ and the surrounding ectomesenchyme. The dental organ is the formative organ of enamel, the dental papilla is the formative organ of the dentin–pulp complex, and the dental follicle is the formative organ of the attachment apparatus (cementum, periodontal ligament, and alveolar bone proper).

The development of the root and the periodontal supporting tissues follows that of the crown. Epithelial cells of the external and internal dental epithelium (the dental organ) proliferate in an apical direction, forming a double layer of cells called *Hertwig's epithelial root sheath* (RS). The odontoblasts (OBs) forming the dentin of the root differentiate from ectomesenchymal cells in the dental papilla under the inductive influence of the inner epithelial cells (Fig. 1-3). The dentin (D) continues to form in an apical direction, producing the framework of the root. During formation of the root, the periodontal supporting tissues, including the acellular cementum, develop. Some of the events in cementogenesis are still unclear, but the following concept is gradually emerging.

At the start of dentin formation, the inner cells of Hertwig's epithelial root sheath synthesize and secrete enamel-related proteins, probably belonging to the amelogenin family. At the end of this period, the epithelial root sheath becomes fenestrated and ectomesenchymal cells from the dental follicle penetrate through these fenestrations and contact the root surface. The ectomesenchymal cells in contact with the enamel-related proteins differentiate into cementoblasts and start to form cementoid. This cementoid represents the organic matrix of the cementum and consists of a ground substance and collagen fibers, which intermingle with collagen fibers in the not yet fully mineralized outer layer of the dentin. It is assumed that the cementum becomes firmly attached to the dentin through these fiber interactions. The formation of the cellular cementum, which often covers the apical third of the dental roots, differs from that of acellular cementum in that some of the cementoblasts become embedded in the cementum.

The remaining parts of the periodontium are formed by ectomesenchymal cells from the dental follicle lateral to the cementum. Some of them differentiate into periodontal fibroblasts and form the fibers of the periodontal ligament, while

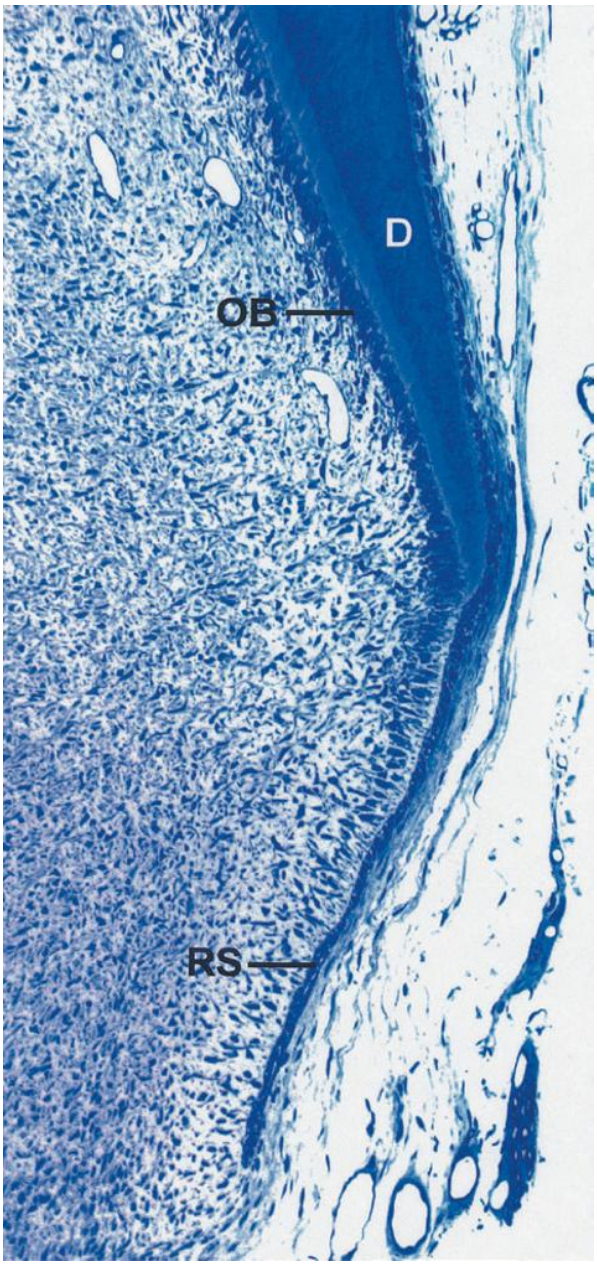


Fig. 1-3

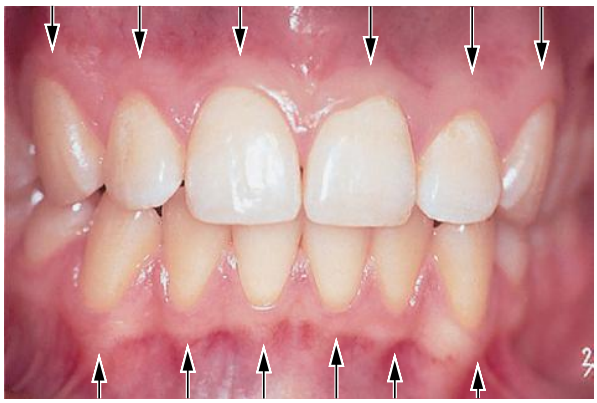


Fig. 1-4

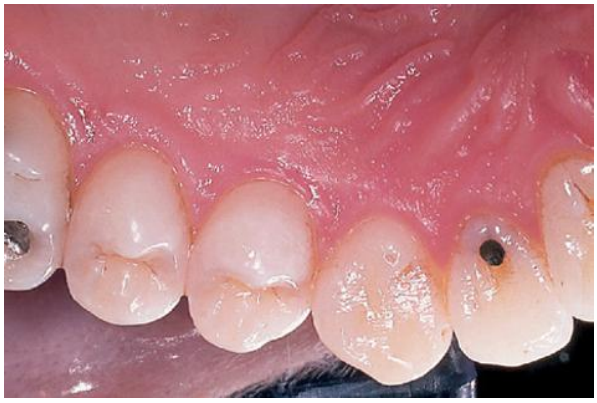


Fig. 1-5

others become osteoblasts and form the alveolar bone proper in which the periodontal fibers are anchored. In other words, the primary alveolar wall is also an ectomesenchymal product. It is likely, but still not conclusively documented, that ectomesenchymal cells remain in the mature periodontium and take part in the turnover of this tissue.

Gingiva

Macroscopic anatomy

The oral mucosa (mucous membrane) is continuous with the skin of the lips and the mucosa of the soft palate and pharynx. The oral mucosa consists of (1) the *masticatory mucosa*, which includes the gingiva and the covering of the hard palate; (2) the *specialized mucosa*, which covers the dorsum of the tongue; and (3) the remaining part, called the *lining mucosa*.

Figure 1-4 The gingiva is that part of the masticatory mucosa which covers the alveolar process and surrounds the cervical portion of the teeth. It consists of an epithelial layer and an underlying connective tissue layer called the *lamina propria*. The gingiva obtains its final shape and texture in conjunction with eruption of the teeth.

In the coronal direction, the coral pink gingiva terminates in the *free gingival margin*, which has a scalloped outline. In the apical direction, the gingiva is continuous with the loose, darker red *alveolar mucosa* (lining mucosa) from which the gingiva is separated by a usually easily recognizable border called either the mucogingival junction (arrows) or the mucogingival line.

Figure 1-5 There is no mucogingival line present in the palate since the hard palate and the maxillary alveolar process are covered by the same type of masticatory mucosa.

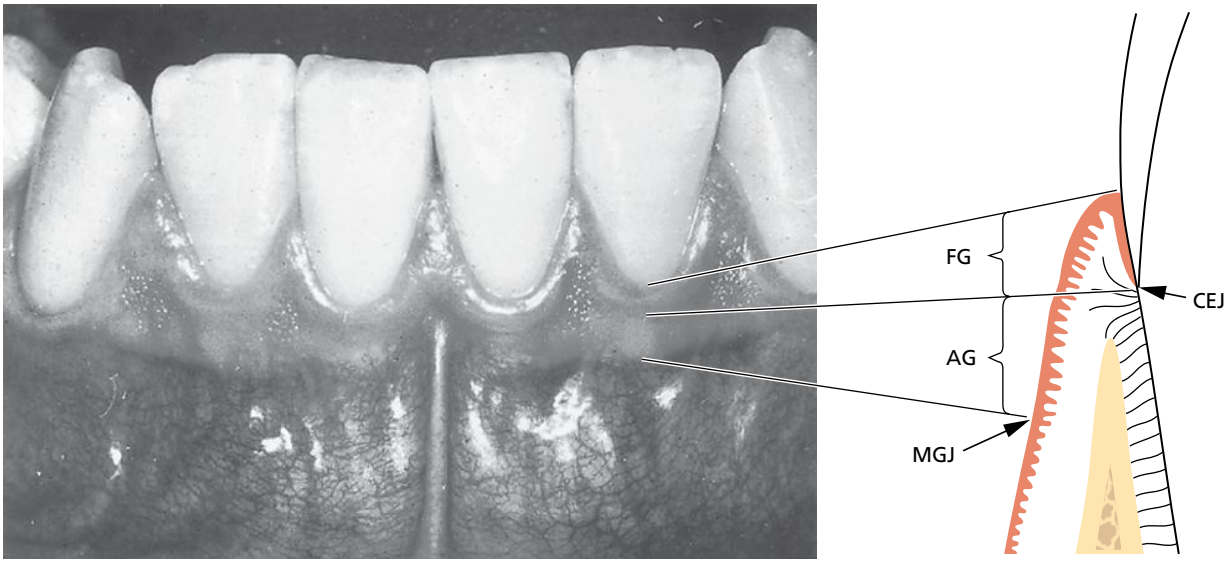


Fig. 1-6

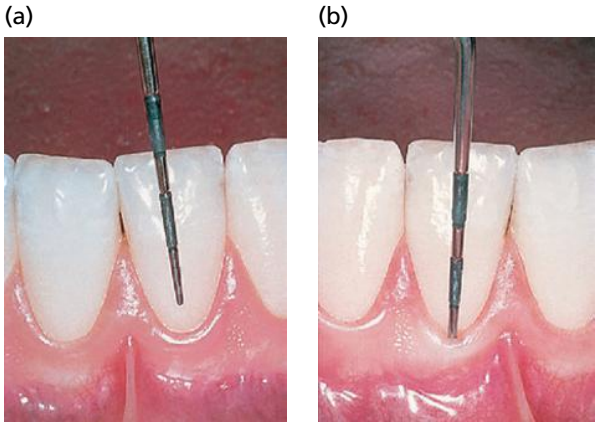


Fig. 1-7

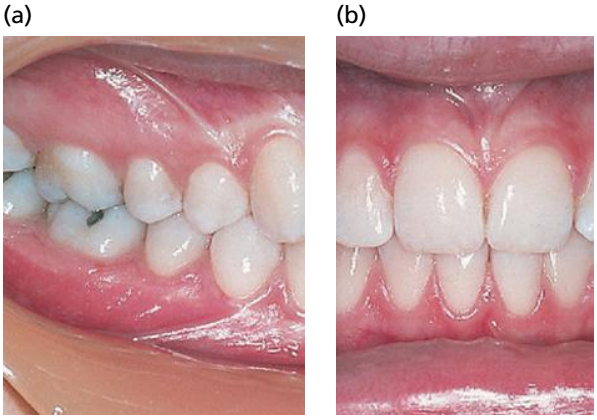


Fig. 1-8

Figure 1-6 Three parts of the gingiva can be identified:

1. Free gingiva (FG)
2. Interdental gingiva
3. Attached gingiva (AG).

The free gingiva is coral pink, has a dull surface and a firm consistency. It comprises the gingival tissue at the vestibular and lingual/palatal aspects of the teeth. On the vestibular and lingual sides of the teeth, the free gingiva extends from the gingival margin in an apical direction to the *free gingival groove*, which is positioned at a level corresponding to the level of the *cementoenamel junction* (CEJ). The attached gingiva is demarcated by the mucogingival junction (MGJ) in the apical direction.

Figure 1-7 The free gingival margin is often rounded in such a way that a small invagination or sulcus is formed between the tooth and the gingiva (Fig. 1-7a).

When a periodontal probe is inserted into this invagination and, further apically, towards the CEJ, the gingival tissue is separated from the tooth and a "*gingival pocket*" or "*gingival crevice*" is artificially opened. Thus, in normal or clinically healthy gingiva there is in fact no "gingival pocket" or "gingival crevice" present, but the gingiva is in close contact with the enamel surface. In Fig. 1-7b, a periodontal probe has been inserted into the tooth–gingiva interface and a "gingival crevice" artificially opened approximately to the level of the CEJ.

After complete tooth eruption, the free gingival margin is located on the enamel surface approximately 1.5–2 mm coronal to the CEJ.

Figure 1-8 The shape of the *interdental gingiva (the interdental papilla)* is determined by the contact relationships between the teeth, the width of the approximal tooth surfaces, and the course of the CEJ. In anterior regions of the dentition, the interdental papilla is of pyramidal form (Fig. 1-8b), while in the molar regions, the papillae are flatter in the buccolingual direction (Fig. 1-8a). Due to the presence of interdental papillae, the free gingival margin follows a more or less accentuated, scalloped course through the dentition.

Figure 1-9 In the premolar/molar regions of the dentition, the teeth have approximal contact surfaces (Fig. 1-9a) rather than contact points. Since the shape of

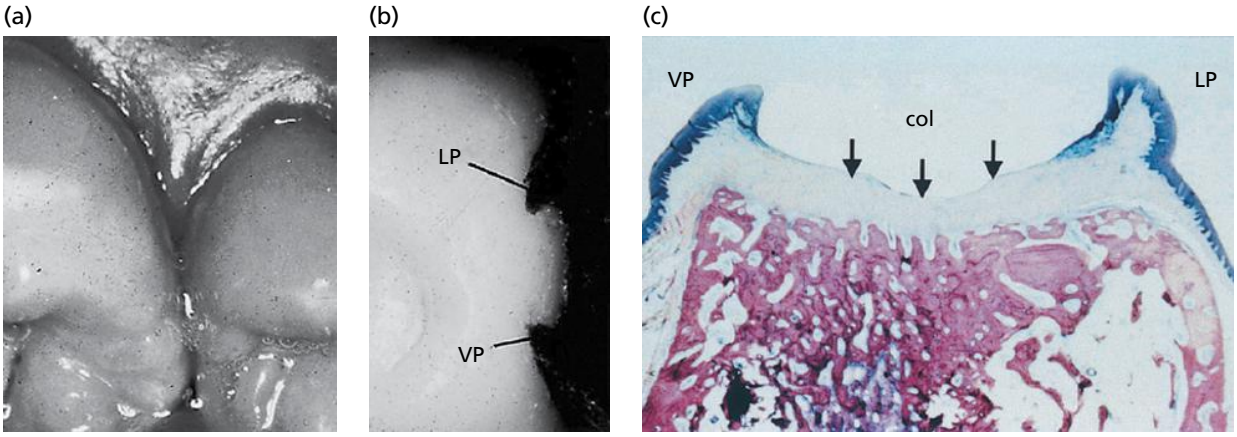


Fig. 1-9

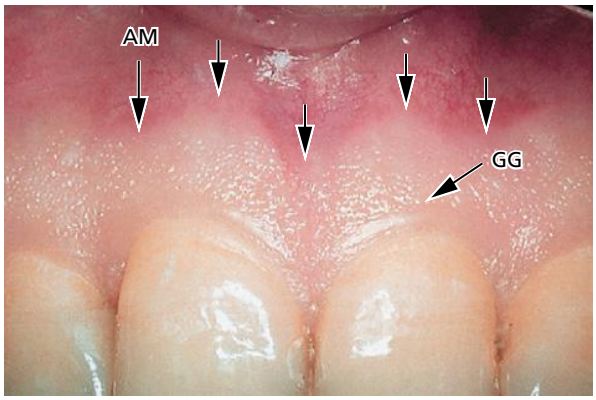


Fig. 1-10

the interdental papilla conforms with the outline of the interdental contact surfaces, a concavity – *a col* – is established in the premolar and molar regions, as demonstrated in Fig. 1-9b, where the distal tooth has been removed. Thus, the interdental papillae in these areas often have one vestibular (VP) and one lingual/palatal portion (LP) separated by the col region. The col region, as demonstrated in the histologic section (Fig. 1-9c), is covered by a thin non-keratinized epithelium (arrows). This epithelium has many features in common with the junctional epithelium (see Fig. 1-34).

Figure 1-10 The attached gingiva is demarcated in the coronal direction by the free gingival groove (GG) or, when such a groove is not present, by a horizontal plane placed at the level of the CEJ. In clinical examinations, it was observed that a free gingival groove is only present in about 30–40% of adults.

The free gingival groove is often most pronounced on the vestibular aspect of the teeth, occurring most frequently in the incisor and premolar regions of the mandible, and least frequently in the mandibular molar and maxillary premolar regions.

The attached gingiva extends in the apical direction to the mucogingival junction (arrows), where it becomes continuous with the alveolar (lining) mucosa (AM). It is of firm texture, coral pink in color, and often shows small depressions on the surface. The depressions, called "stippling", give the appearance of orange peel. The

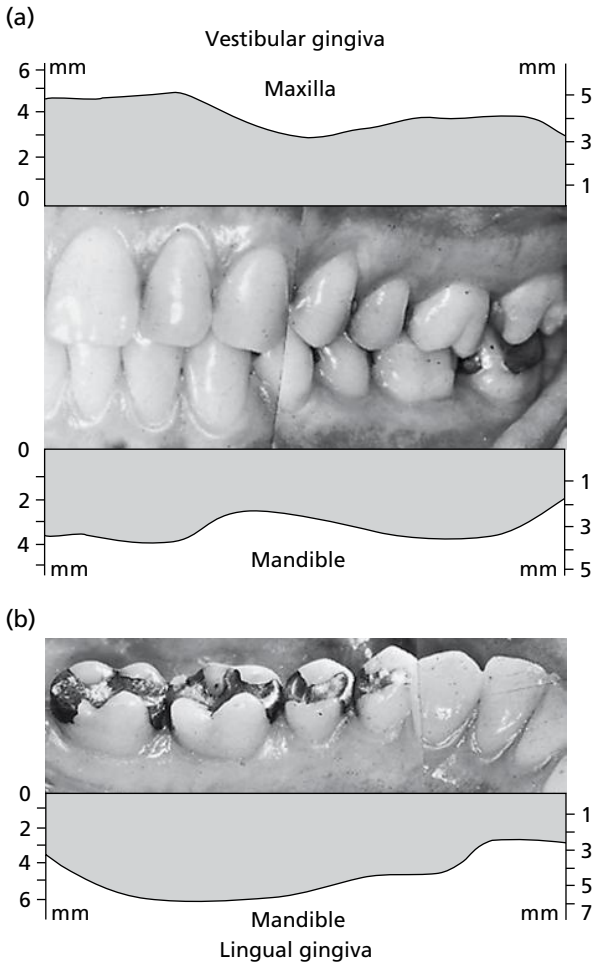


Fig. 1-11

gingiva is firmly attached to the underlying alveolar bone and cementum by connective tissue fibers, and is, therefore, comparatively immobile in relation to the underlying tissue. The darker red alveolar mucosa (AM) located apical to the mucogingival junction, on the other hand, is loosely bound to the underlying bone. Therefore, in contrast to the attached gingiva, the alveolar mucosa is mobile in relation to the underlying tissue.

Figure 1-11 shows how the width of the gingiva varies in different parts of the dentition. In the maxilla

(Fig. 1-11a), the vestibular gingiva is generally widest in the area of the incisors and narrowest adjacent to the premolars. In the mandible (Fig. 1-11b), the gingiva on the lingual aspect is particularly narrow in the area of the incisors and wide in the molar region. The range of variation is 1–9 mm.

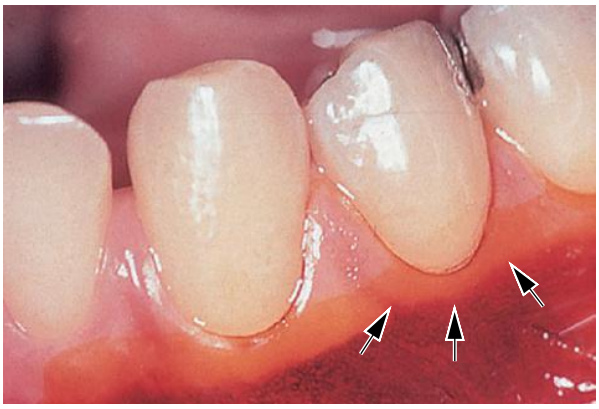


Fig. 1-12

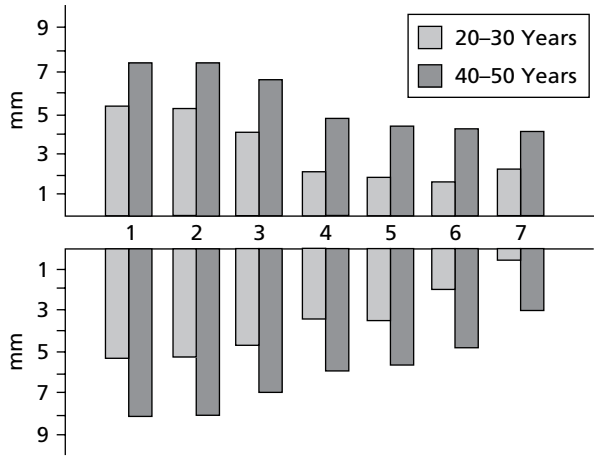


Fig. 1-13

Figure 1-12 illustrates an area in the mandibular premolar region where the gingiva is extremely narrow. The arrows indicate the location of the mucogingival junction. The mucosa has been stained with an iodine solution in order to distinguish more accurately between the gingiva and the alveolar mucosa.

Figure 1-13 depicts the result of a study in which the width of the attached gingiva was assessed and related to the age of the patients examined. It was found that the gingiva in 40–50-year olds was significantly wider than that in 20–30-year olds. This observation indicates that the width of the gingiva tends to increase with age. Since the mucogingival junction remains stable throughout life in relation to the lower border of the mandible, the increasing width of the gingiva may suggest that the teeth, as a result of occlusal wear, erupt slowly throughout life.

Microscopic anatomy

Oral epithelium

Figure 1-14a A schematic drawing of a histologic section (see Fig. 1-14b) describing the composition of the gingiva and the contact area between the gingiva and the enamel (E).

Figure 1-14b The free gingiva comprises all epithelial and connective tissue structures (CT) located coronal to a horizontal line placed at the level of the cementoenamel junction (CEJ). The epithelium covering the free gingiva may be differentiated as follows:

- *Oral epithelium* (OE), which faces the oral cavity
- *Oral sulcular epithelium* (OSE), which faces the tooth without being in contact with the tooth surface

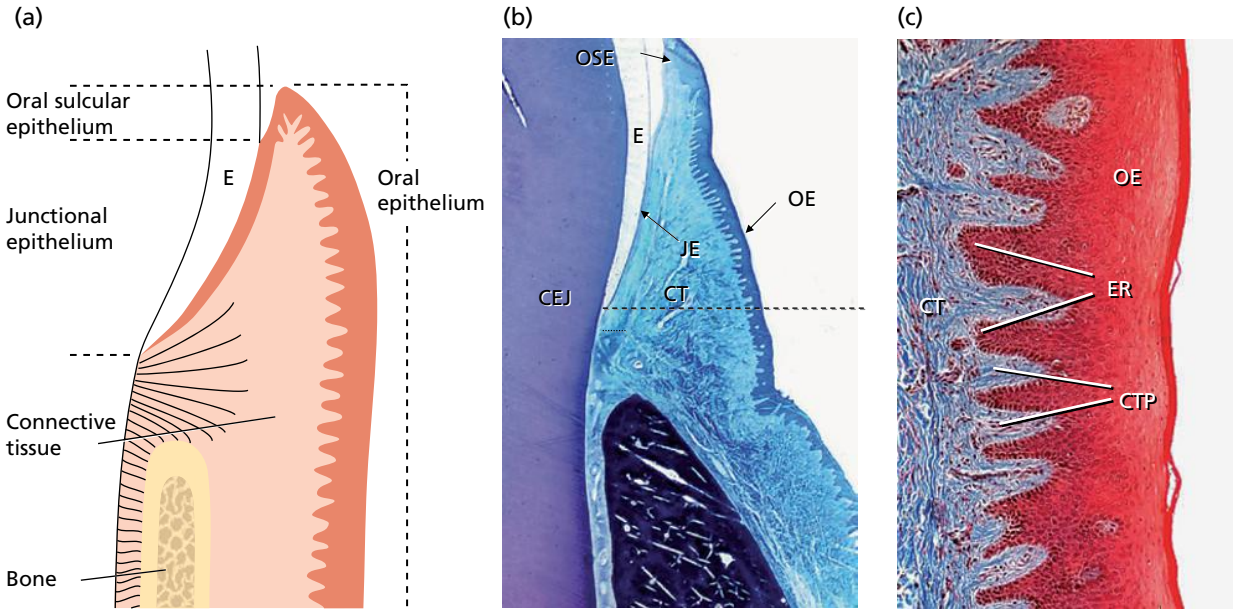


Fig. 1-14

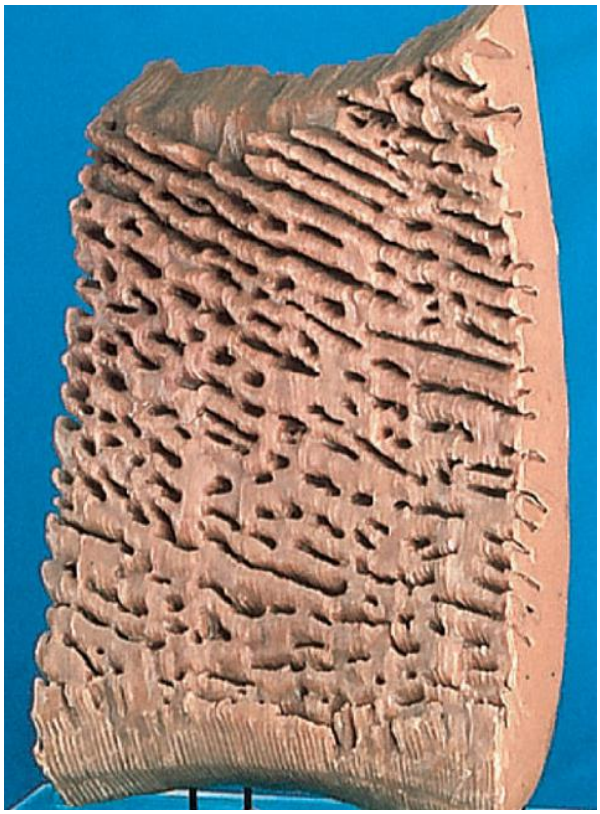


Fig. 1-15

- *Junctional epithelium* (JE), which provides the contact between the gingiva and the tooth.

Figure 1-14c The boundary between the oral epithelium (OE) and underlying connective tissue (CT) has a wavy course. The connective tissue portions which project into the epithelium are called *connective tissue papillae* (CTP) and are separated from each other by *epithelial ridges* – so-called *rete pegs* (ER). In normal, non-inflamed gingiva, rete pegs and connective tissue papillae are lacking at the boundary between the junctional epithelium and its underlying connective tissue (Fig. 1-14b). Thus, a characteristic morphologic feature of the oral epithelium and the oral sulcular epithelium is the presence of rete pegs: these structures are lacking in the junctional epithelium.

Figure 1-15 presents a model, constructed on the basis of magnified serial histologic sections, showing the subsurface of the oral epithelium of the gingiva after the connective tissue has been removed. The subsurface of the oral epithelium (i.e. the surface of the epithelium facing the connective tissue) exhibits several depressions corresponding to the connective tissue papillae (see Fig. 1-16) which project into the epithelium. It can be seen that the epithelial projections, which in histologic sections separate the connective tissue papillae, constitute a continuous system of epithelial ridges.

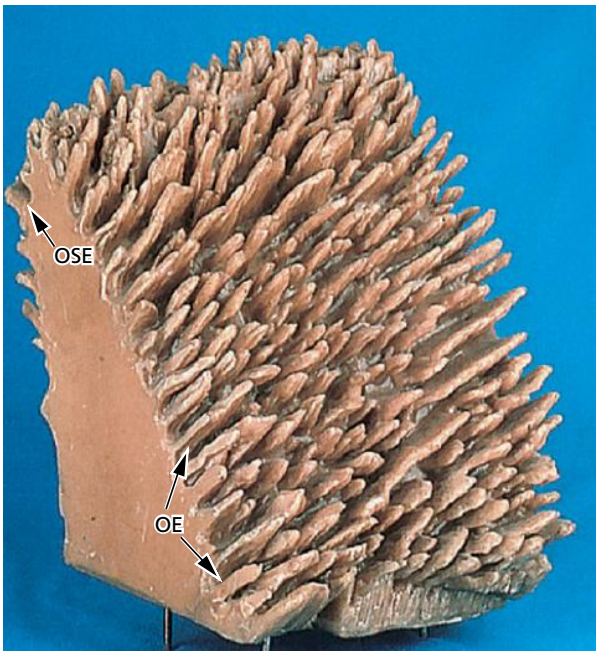


Fig. 1-16

Figure 1-16 presents a model of the connective tissue, corresponding to the model of the epithelium shown in Fig. 1-15. The epithelium has been removed, thereby making the vestibular aspect of the gingival connective tissue visible. Note the connective tissue papillae which project into the space that was occupied by the oral epithelium (OE) in Fig. 1-15 and by the oral sulcular epithelium (OSE) at the back of the model.

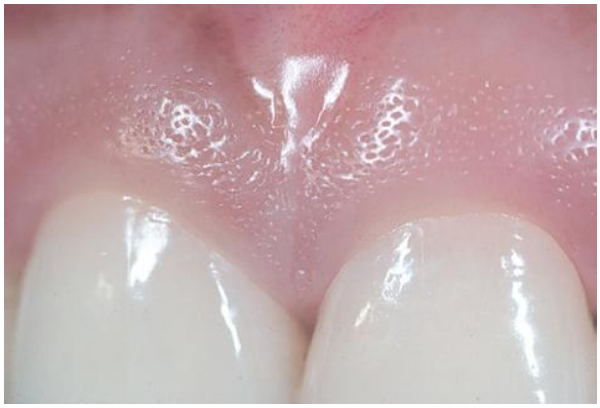
Figure 1-17a In most adults the attached gingiva shows a stippling on the surface. The photograph shows a case where this stippling is conspicuous (see also Fig. 1-10).

Figure 1-17b presents a magnified model of the outer surface of the oral epithelium of the attached gingiva. The surface exhibits the minute depressions (1–3) which give the gingiva its characteristic stippled appearance.

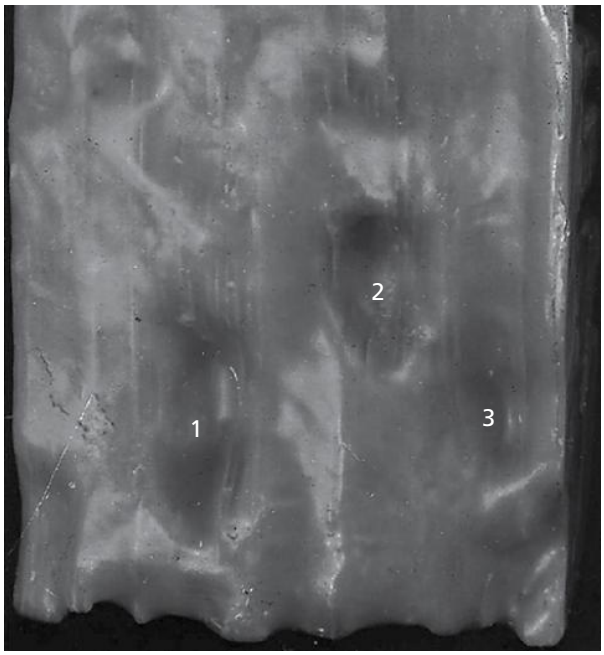
Figure 1-17c shows a photograph of the subsurface (i.e. the surface of the epithelium facing the connective tissue) of the model shown in Fig. 1-17b. The subsurface of the epithelium is characterized by the presence of epithelial ridges which merge at various locations (1–3). The depressions seen on the outer surface of the epithelium (1–3 in Fig. 1-17b) correspond to these fusion sites (1–3) between the epithelial ridges. Thus, the depressions on the surface of the gingiva occur in the areas of fusion between various epithelial ridges.

Figure 1-18 (a) A portion of the oral epithelium covering the free gingiva is illustrated in this photomicrograph. The oral epithelium is a *keratinized*, *stratified*,

(a)



(b)



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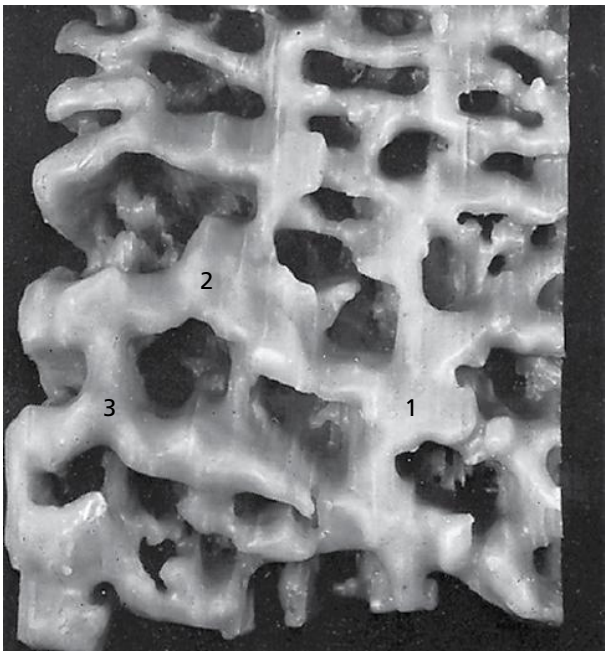
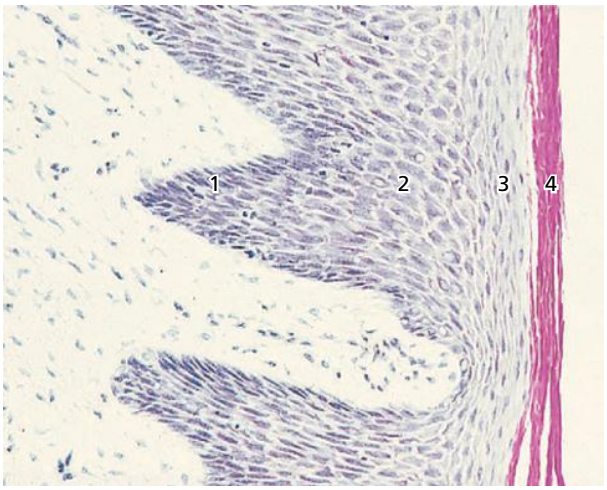


Fig. 1-17

(a)



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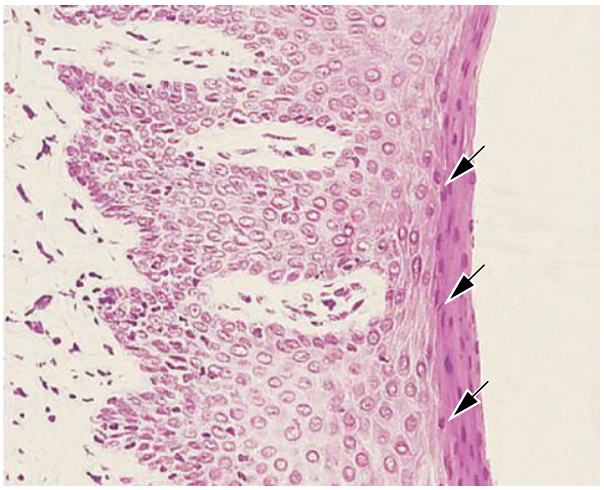

Fig. 1-18

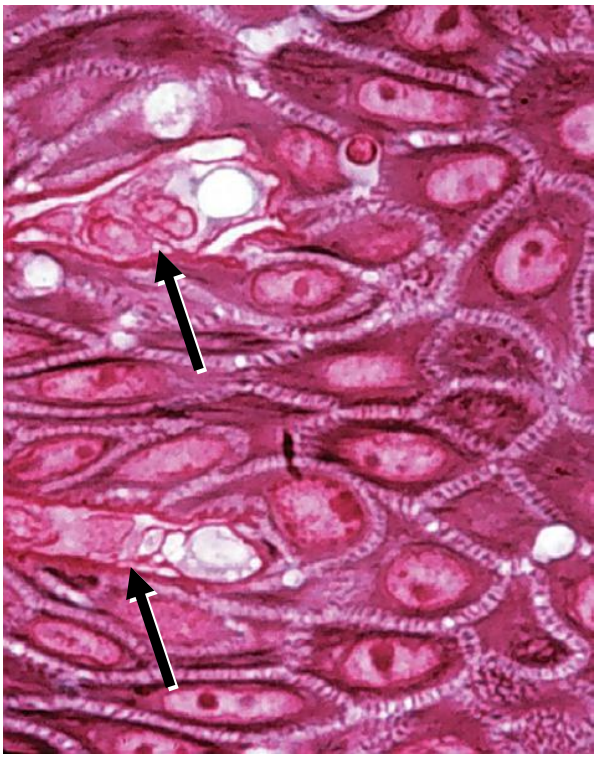

Fig. 1-19

squamous epithelium which, on the basis of the degree to which the keratin-producing cells are differentiated, can be divided into the following cell layers:

1. *Basal layer* (stratum basale or stratum germinativum)
2. *Prickle cell layer* (stratum spinosum)
3. *Granular cell layer* (stratum granulosum)
4. *Keratinized cell layer* (stratum corneum).

It should be observed that in this section, cell nuclei are lacking in the outer cell layers. Such an epithelium is denoted *orthokeratinized*. Often, however, the cells of the stratum corneum of the epithelium of human gingiva contain remnants of the nuclei as seen in Fig. 1-18b (arrows). In such a case, the epithelium is denoted *parakeratinized*.

Figure 1-19 In addition to the keratin-producing cells, which comprise about 90% of the total cell population, the oral epithelium contains the following types of cell:

- *Melanocytes*
- *Langerhans cells*
- *Merkel's cells*
- *Inflammatory cells.*

These cell types are often stellate and have cytoplasmic extensions of various size and appearance. They are also called "clear cells" since in histologic sections, the zone around their nuclei appears lighter than that in the surrounding keratin-producing cells.

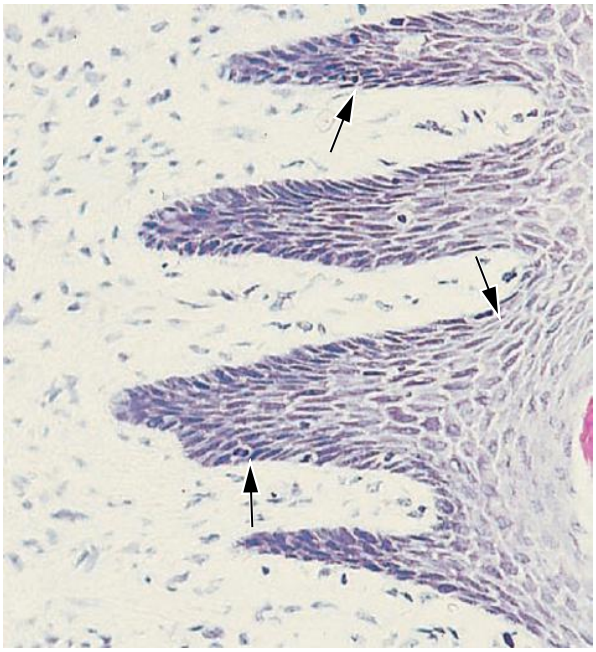

Fig. 1-20

The photomicrograph shows "clear cells" (arrows) located in or near the stratum basale of the oral epithelium. With the exception of the Merkel's cells, these "clear cells", which do not produce keratin, lack desmosomal attachment to adjacent cells. The melanocytes are pigment-synthesizing cells and are responsible for the melanin pigmentation occasionally seen on the gingiva. However, both lightly and darkly pigmented individuals have melanocytes in the epithelium.

The Langerhans cells are believed to play a role in the defense mechanism of the oral mucosa. It has been suggested that the Langerhans cells react with antigens which are in the process of penetrating the epithelium. An early immunologic response is thereby initiated, inhibiting or preventing further antigen penetration of the tissue. The Merkel's cells have been suggested to have a sensory function.

Figure 1-20 The cells in the basal layer are either cylindric or cuboid, and are in contact with the *basement membrane* that separates the epithelium and the connective tissue. The basal cells possess the ability to divide, that is undergo mitotic cell division. The cells marked with arrows in the photomicrograph are in the process of dividing. It is in the basal layer that the epithelium is renewed. Therefore, this layer is also termed *stratum germinativum*, and can be considered the *progenitor cell compartment* of the epithelium.

Figure 1-21 When two daughter cells (D) have been formed by cell division, an adjacent "older" basal cell (OB) is pushed into the spinous cell layer and starts, as a *keratinocyte*, to traverse the epithelium. It takes approximately 1 month for a keratinocyte to reach the outer epithelial surface, where it is shed from the stratum corneum. Within a given time, the

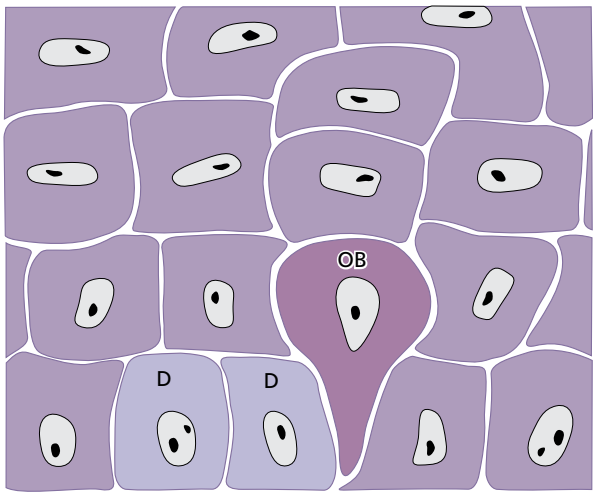

Fig. 1-21

Fig. 1-22

number of cells which divide in the basal layer equals the number of cells which are shed from the surface. Thus, under normal conditions there is equilibrium between cell renewal and cell loss so that the epithelium maintains a constant thickness. As the basal cell migrates through the epithelium, it becomes flattened with its long axis parallel to the epithelial surface.

Figure 1-22 The basal cells are found immediately adjacent to the connective tissue and are separated from this tissue by the basement membrane, probably produced by the basal cells. Under the light microscope this membrane appears as a structureless zone approximately 1–2 µm wide (arrows) and reacts positively to a periodic acid-Schiff (PAS) stain. This positive reaction demonstrates that the basement membrane contains carbohydrate (glycoproteins). The epithelial cells are surrounded by an extracellular substance which also contains protein–polysaccharide complexes. At the ultrastructural level, the basement membrane has a complex composition.

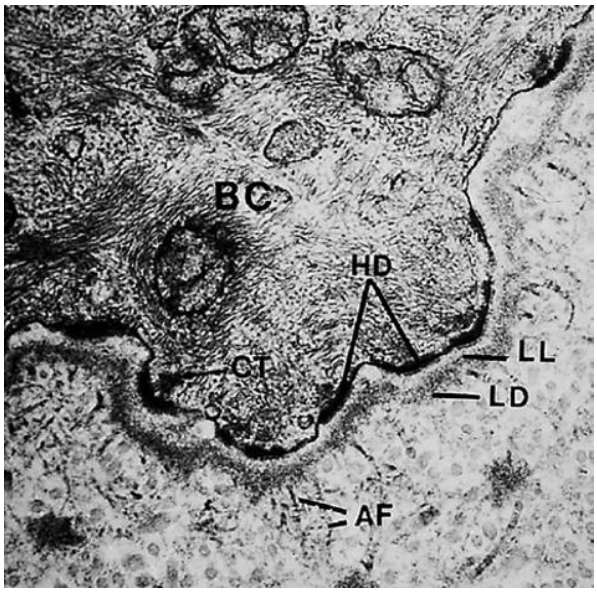

Fig. 1-23

Figure 1-23 is an electron micrograph (magnification × 70 000) of an area including part of a basal cell, the basement membrane, and part of the adjacent connective tissue. The basal cell (BC) occupies the upper portion of the micrograph. Immediately beneath the basal cell, an approximately 400-Å wide electron-lucent zone can be seen, which is called the *lamina lucida* (LL). Beneath the lamina lucida, an electron-dense zone of approximately the same thickness can be observed. This zone is called *lamina densa* (LD). From the lamina densa so-called *anchoring fibers* (AF) project in a fan-shaped fashion into the connective tissue. The anchoring fibers are approximately 1 µm in length and terminate freely in the connective tissue. The basement membrane, which under the light microscope appears as an entity, thus, in the electron micrograph, appears to comprise one lamina lucida and one lamina densa with adjacent connective tissue fibers (anchoring fibers). The cell membrane of the epithelial cells facing the lamina lucida harbors a number of electron-dense, thicker zones appearing at various intervals along the cell membrane. These structures are called *hemidesmosomes* (HD). The cytoplasmic *tonofilaments* (CT) in the cell converge towards the hemidesmosomes. The hemidesmosomes are involved in the attachment of the epithelium to the underlying basement membrane.

Figure 1-24 illustrates an area of stratum spinosum in the gingival oral epithelium. Stratum spinosum consists of 10–20 layers of relatively large, polyhedral cells, equipped with short cytoplasmic processes resembling spines. The cytoplasmic processes (arrows) occur at regular intervals and give the cells a prickly appearance. Together with intercellular protein–carbohydrate complexes, cohesion between the cells is provided by numerous "desmosomes" (pairs of hemidesmosomes) which are located between the cytoplasmic processes of adjacent cells.

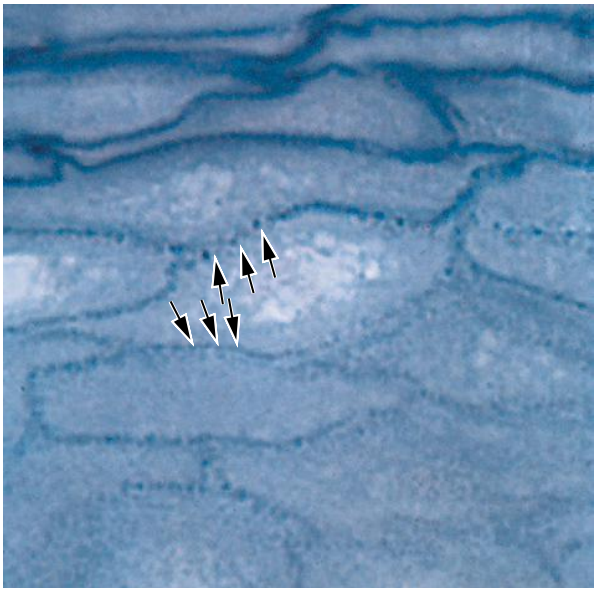

Fig. 1-24

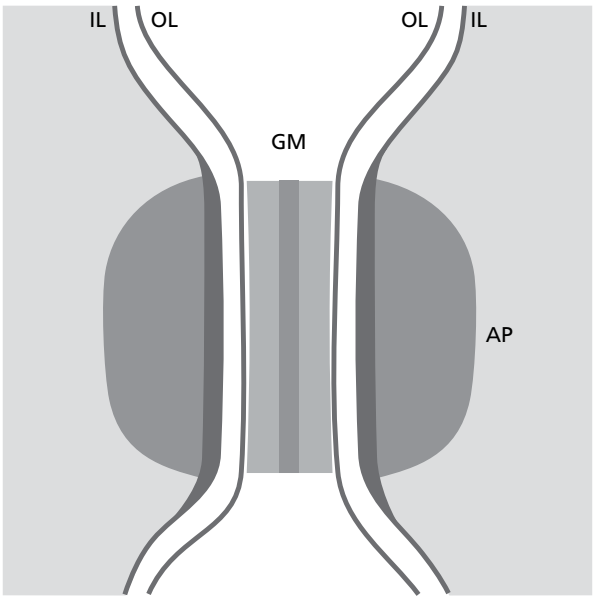

Fig. 1-26

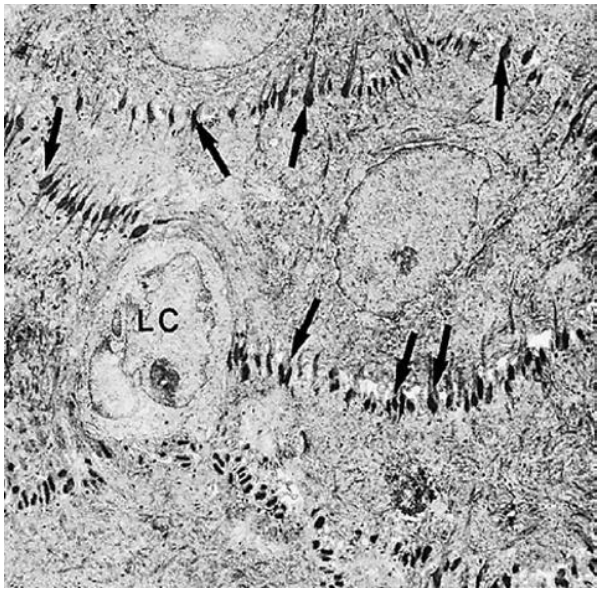

Fig. 1-25

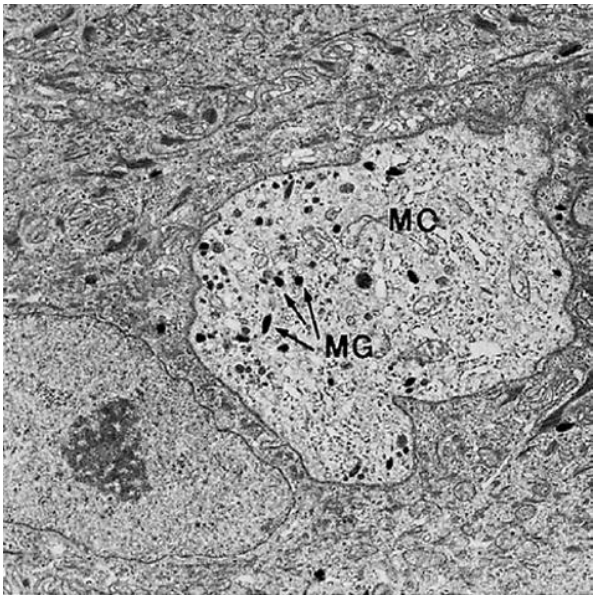

Fig. 1-27

Figure 1-25 shows an area of stratum spinosum in an electron micrograph. The dark-stained structures between the individual epithelial cells represent the *desmosomes* (arrows). A desmosome may be considered to be two hemidesmosomes facing one another. The presence of a large number of desmosomes indicates that the cohesion between the epithelial cells is solid. The light cell (LC) in the center of the micrograph harbors no hemidesmosomes and is, therefore, not a keratinocyte but rather a "clear cell" (see also Fig. 1-19).

Figure 1-26 is a schematic drawing showing the composition of a desmosome. A desmosome can be considered to consist of two adjoining hemidesmosomes separated by a zone containing electron-dense granulated material (GM). Thus, a desmosome comprises the following structural components: (1) the *outer leaflets* (OL) of the cell membranes of two adjoining cells, (2) the thick *inner leaflets* (IL) of the cell membranes, and (3) the *attachment plaques* (AP), which represent granular and fibrillar material in the cytoplasm.

Figure 1-27 As mentioned previously, the oral epithelium also contains melanocytes, which are responsible for the production of the pigment melanin. Melanocytes are present in individuals with marked pigmentation of the oral mucosa as well as in individuals in whom no clinical signs of pigmentation can be seen. In this electron micrograph, a melanocyte (MC) is present in the lower portion of the stratum spinosum. In contrast to the keratinocytes, this cell contains melanin granules (MG) and has no tonofilaments or hemidesmosomes. Note the large number of tonofilaments in the cytoplasm of the adjacent keratinocytes.

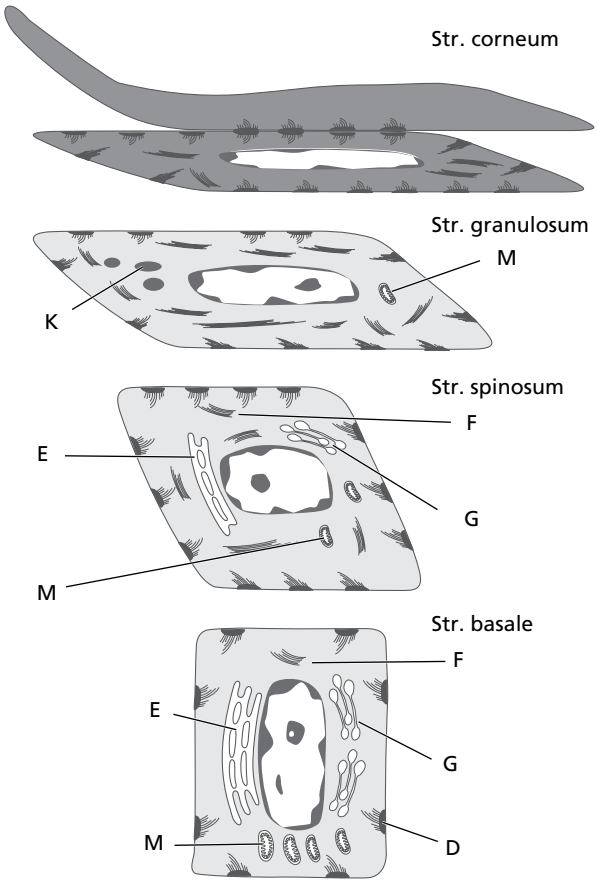

Fig. 1-28

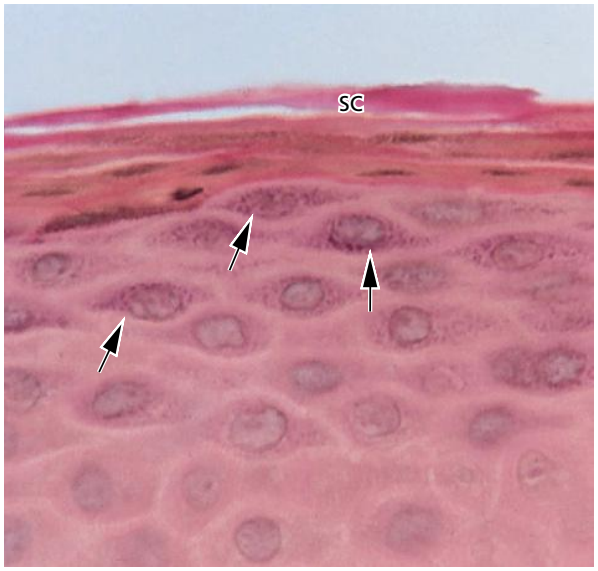

Fig. 1-29

Figure 1-28 When traversing the epithelium from the basal layer to the epithelial surface, the keratinocytes undergo continuous differentiation and specialization. The many changes which occur during this process are indicated in this diagram of a keratinized stratified squamous epithelium. From the basal layer (stratum basale) to the granular layer (stratum granulosum) both the number of tonofilaments (F) in the cytoplasm and the number of desmosomes (D) increase. In contrast, the number of organelles, such as mitochondria (M), lamellae of rough endoplasmic reticulum (E), and Golgi complexes (G) decrease in the keratinocytes on their way from the basal layer towards the surface. In the stratum granulosum, electron-dense *keratohyalin bodies* (K) and clusters of glycogen-containing granules start to appear. Such granules are believed to be related to the synthesis of keratin.

Figure 1-29 is a photomicrograph of the stratum granulosum and stratum corneum. Keratohyalin granules (arrows) are seen in the stratum granulosum. There is an abrupt transition of the cells from the stratum granulosum to the stratum corneum. This is indicative of a very sudden keratinization of the cytoplasm of the keratinocyte and its conversion into a horny squame. The cytoplasm of the cells in the stratum corneum (SC) is filled with keratin and the entire apparatus for protein synthesis and energy production, that is the nucleus, the mitochondria, the endoplasmic reticulum, and the Golgi complex, is lost. In a parakeratinized epithelium, however, the cells of the stratum corneum contain remnants of nuclei. Keratinization is considered a process of differentiation rather than degeneration. It is a process of protein synthesis which requires energy and is dependent on functional cells, that is cells containing a nucleus and a normal set of organelles.

Summary: The keratinocyte undergoes continuous differentiation on its way from the basal layer to the surface of the epithelium. Thus, once the keratinocyte has left the basement membrane it can no longer divide, but maintains a capacity for production of protein (tonofilaments and keratohyalin granules). In the granular layer, the keratinocyte is deprived of its energy- and protein-producing apparatus (probably by enzymatic breakdown) and is abruptly converted into a keratin-filled cell which, via the stratum corneum, is shed from the epithelial surface.

Figure 1-30 illustrates a portion of the epithelium of the alveolar (lining) mucosa. In contrast to the epithelium of the gingiva, the lining mucosa has no stratum corneum. Note that cells containing nuclei can be identified in all layers, from the basal layer to the surface of the epithelium.

Dentogingival epithelium

The tissue components of the dentogingival region achieve their final structural characteristics in conjunction with the eruption of the teeth. This is illustrated in Fig. 1-31a–d.

Figure 1-31a When the enamel of the tooth is fully developed, the enamel-producing cells (ameloblasts) become reduced in height, produce a basal lamina, and form, together with cells from the outer enamel epithelium, the so-called reduced dental epithelium

(RE). The basal lamina (epithelial attachment lamina [EAL]) lies in direct contact with the enamel. The contact between this lamina and the epithelial cells is maintained by hemidesmosomes. The reduced enamel epithelium surrounds the crown of the tooth from the moment the enamel is properly mineralized until the tooth starts to erupt.

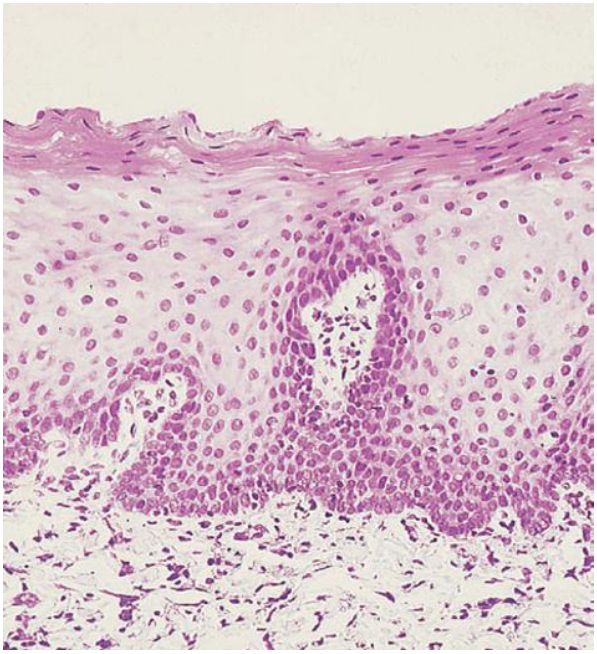

Fig. 1-30

Figure 1-31b As the erupting tooth approaches the oral epithelium, the cells of the outer layer of the reduced dental epithelium (RE), as well as the cells of the basal layer of the oral epithelium (OE), show increased mitotic activity (arrows) and start to migrate into the underlying connective tissue. The migrating epithelium produces an epithelial mass between the oral epithelium and the reduced dental epithelium so that the tooth can erupt without bleeding. The former ameloblasts do not divide.

Figure 1-31c When the tooth has penetrated into the oral cavity, large portions immediately apical to the incisal area of the enamel are covered by a junctional epithelium (JE) containing only a few layers of cells. The cervical region of the enamel, however, is still covered by ameloblasts (AB) and outer cells of the reduced dental epithelium.

Figure 1-31d During the later phases of tooth eruption, all cells of the reduced enamel epithelium are replaced by a junctional epithelium (JE). This epithelium is continuous with the oral epithelium and

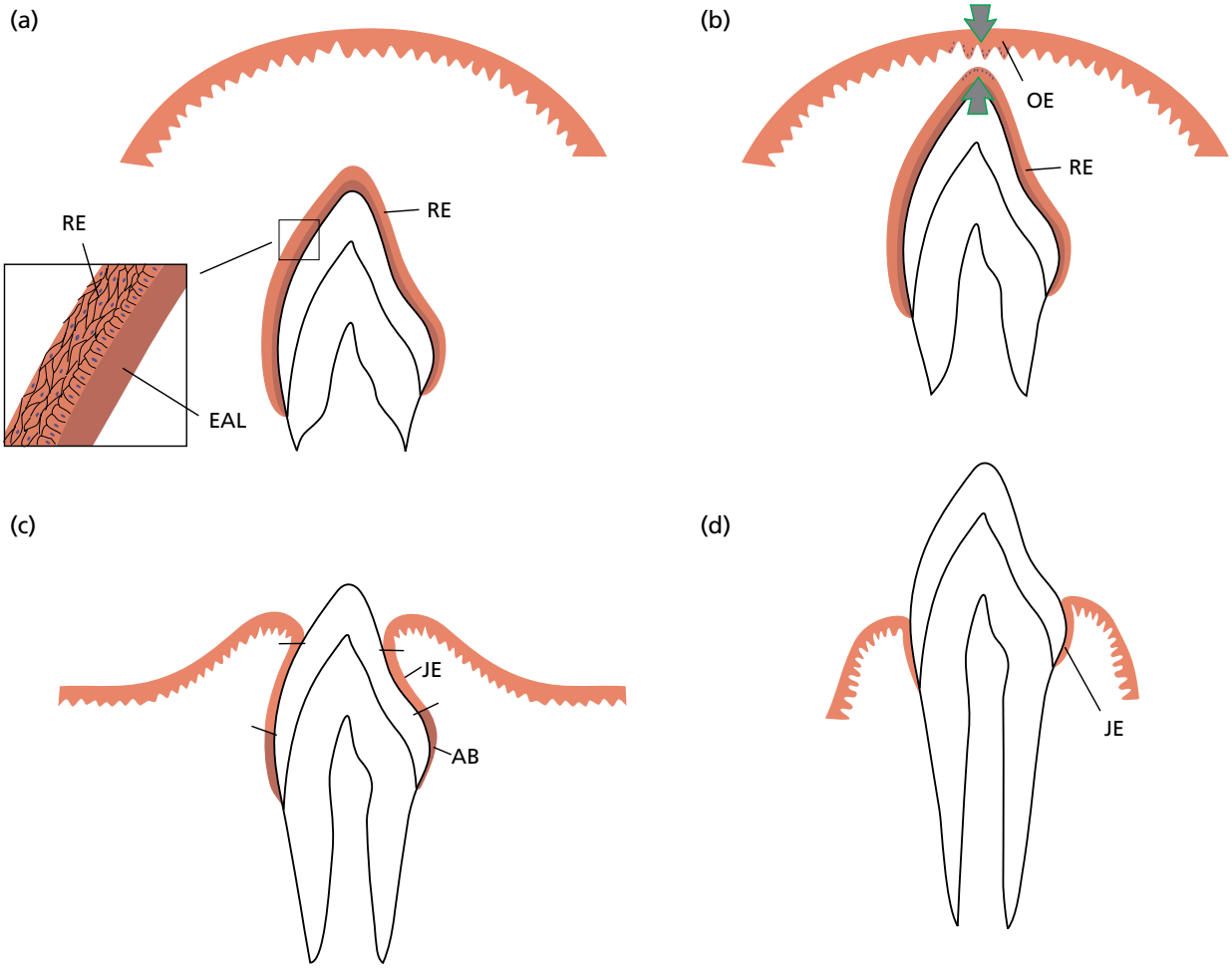

Fig. 1-31

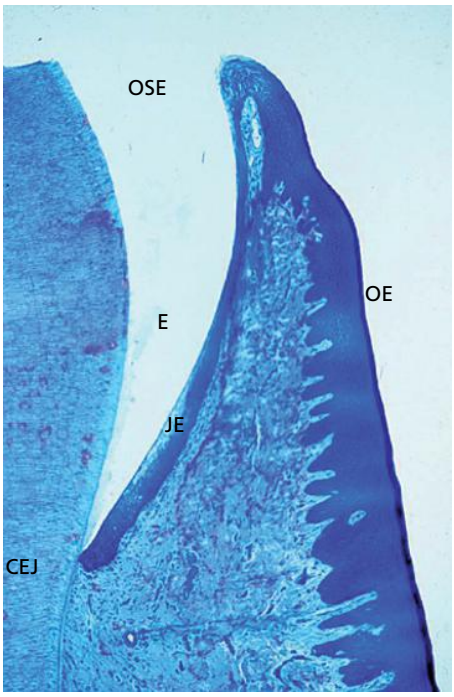

Fig. 1-32

provides the attachment between the tooth and the gingiva. If the free gingiva is excised after the tooth has fully erupted, a new junctional epithelium, indistinguishable from that found following tooth eruption, will develop during healing. The fact that this new junctional epithelium has developed from the oral epithelium indicates that the cells of the oral epithelium possess the ability to differentiate into cells of the junctional epithelium.

Figure 1-32 is a histologic section through the border area between the tooth and the gingiva, that is the *dentogingival region*. The enamel (E) is to the left. To the right are the *junctional epithelium* (JE), the *oral sulcular epithelium* (OSE), and the *oral epithelium* (OE). The oral sulcular epithelium covers the shallow groove, the gingival sulcus, located between the enamel and the top of the free gingiva. The junctional epithelium differs morphologically from the oral sulcular epithelium and oral epithelium, while the latter two are structurally very similar. Although individual variation may occur, the junctional epithelium is usually widest in its coronal portion (about 15–20 cells), but becomes thinner (3–4 cells) towards the cementoenamel junction (CEJ). The borderline between the junctional epithelium and the underlying connective tissue does not have epithelial rete pegs, except when inflamed.

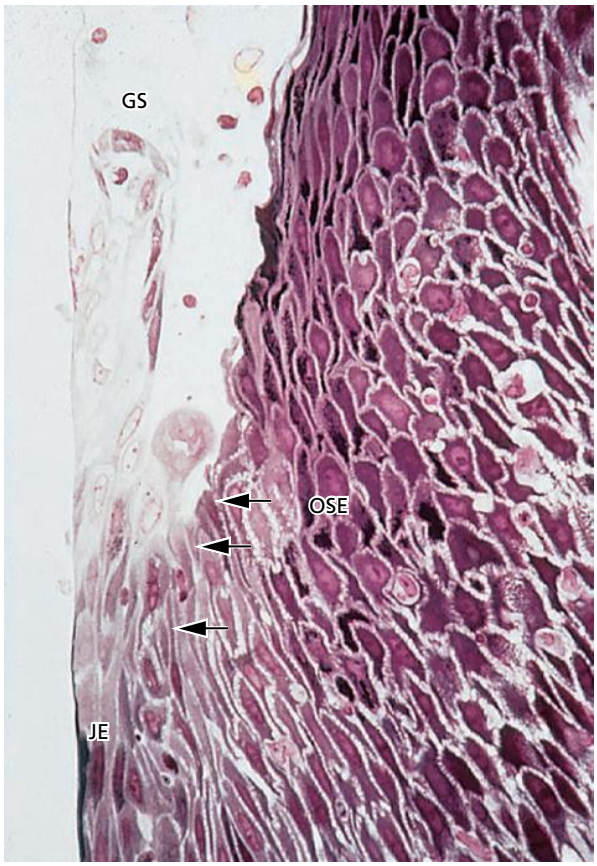

Fig. 1-33

Figure 1-33 The junctional epithelium has a free surface at the bottom of the *gingival sulcus* (GS). Like the oral sulcular epithelium and the oral epithelium, the junctional epithelium is continuously renewed through cell division in the basal layer. The cells migrate to the base of the gingival sulcus from where they are shed. The border between the junctional epithelium (JE) and the oral sulcular epithelium (OSE) is indicated by arrows. The cells of the oral sulcular epithelium are cuboidal and the surface of this epithelium is non-keratinized.

Figure 1-34 illustrates different characteristics of the junctional epithelium. As can be seen in Fig. 1-34a, the cells of the junctional epithelium (JE) are arranged into one basal layer (BL) and several suprabasal layers (SBL). Fig. 1-34b demonstrates that the basal cells as well as the suprabasal cells are flattened with their long axis parallel to the tooth surface. (CT, connective tissue; E, enamel space.)

There are distinct differences between the oral sulcular epithelium, the oral epithelium, and the junctional epithelium:

- The size of the cells in the junctional epithelium is, relative to the tissue volume, larger than in the oral epithelium.
- The intercellular space in the junctional epithelium is, relative to the tissue volume, comparatively wider than in the oral epithelium.
- The number of desmosomes is smaller in the junctional epithelium than in the oral epithelium.

Note the comparatively wide intercellular spaces between the oblong cells of the junctional epithelium, and the presence of two neutrophilic granulocytes (PMN) which are traversing the epithelium.

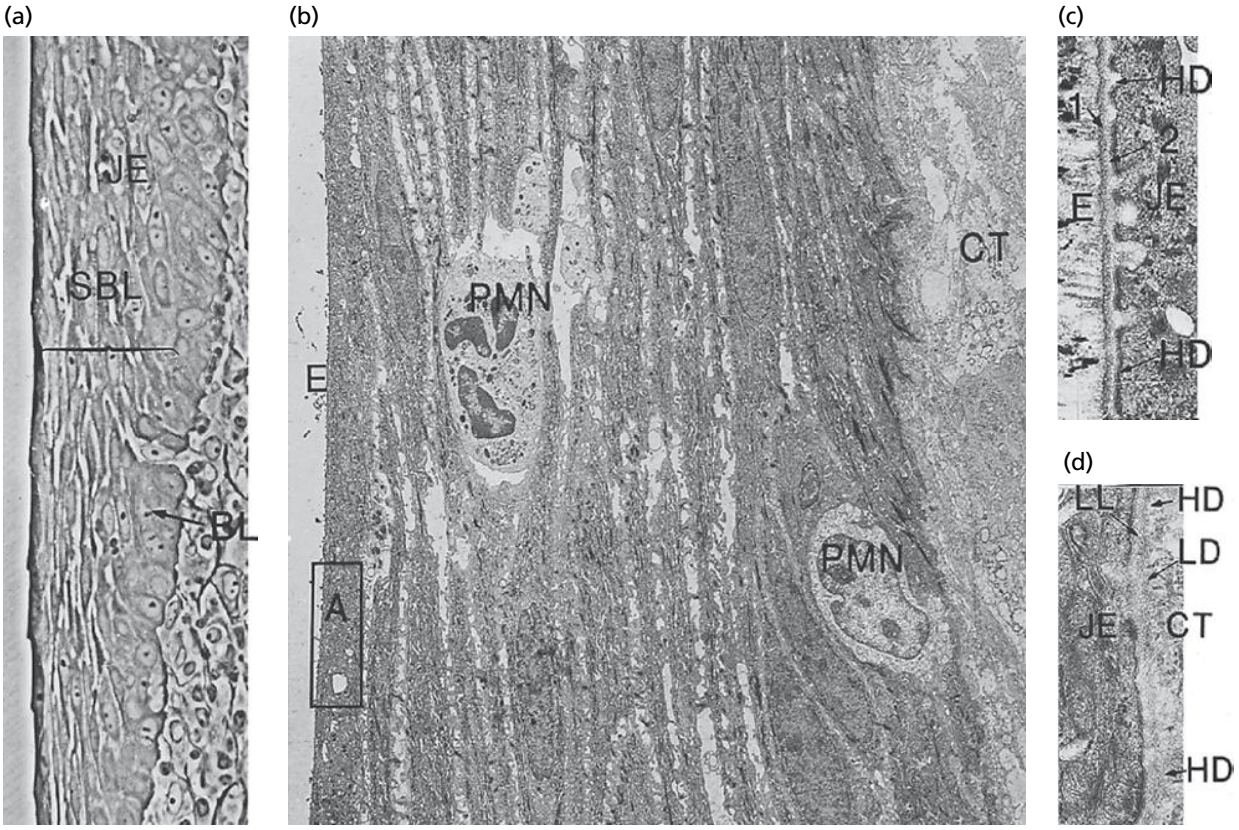

Fig. 1-34

The framed area (A) is shown in a higher magnification in Fig. 1-34c, from which it can be seen that the basal cells of the junctional epithelium are not in direct contact with the enamel (E). Between the enamel and the epithelium (JE), one electron-dense zone (1) and one electron-lucent zone (2) can be seen. The electron-lucent zone is in contact with the cells of the junctional epithelium (JE). These two zones have a structure very similar to that of the lamina densa (LD) and lamina lucida (LL) in the basement membrane area (i.e. the epithelium [JE]–connective tissue [CT] interface) described in Fig. 1-23. Furthermore, as seen in Fig. 1-34d, the cell membrane of the junctional epithelial cells harbors hemidesmosomes (HD) towards the enamel and towards the connective tissue. Thus, the interface between the enamel and the junctional epithelium is similar to the interface between the epithelium and the connective tissue.

Figure 1-35 is a schematic drawing of the most apically positioned cell in the junctional epithelium. The enamel (E) is depicted to the left. It can be seen that the electron-dense zone (1) between the junctional epithelium and the enamel can be considered a continuation of the lamina densa (LD) in the basement membrane of the connective tissue side. Similarly, the electron-lucent zone (2) can be considered a continuation of the lamina lucida (LL). It should be noted, however, that at variance with the epithelium–connective tissue interface, there are no anchoring fibers (AF) attached to the lamina densa-like structure

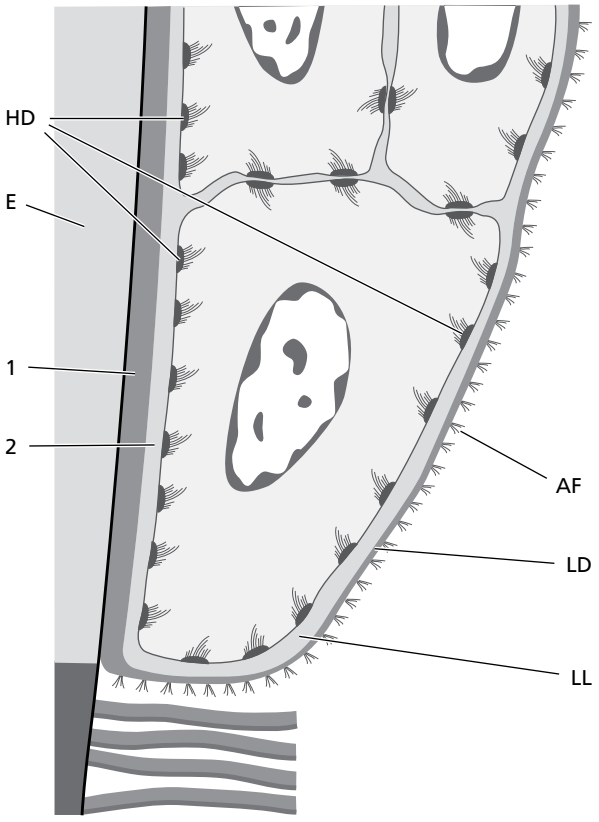

Fig. 1-35

(1) adjacent to the enamel. On the other hand, like the basal cells adjacent to the basement membrane (at the connective tissue interface), the cells of the junctional epithelium facing the lamina lucida-like structure

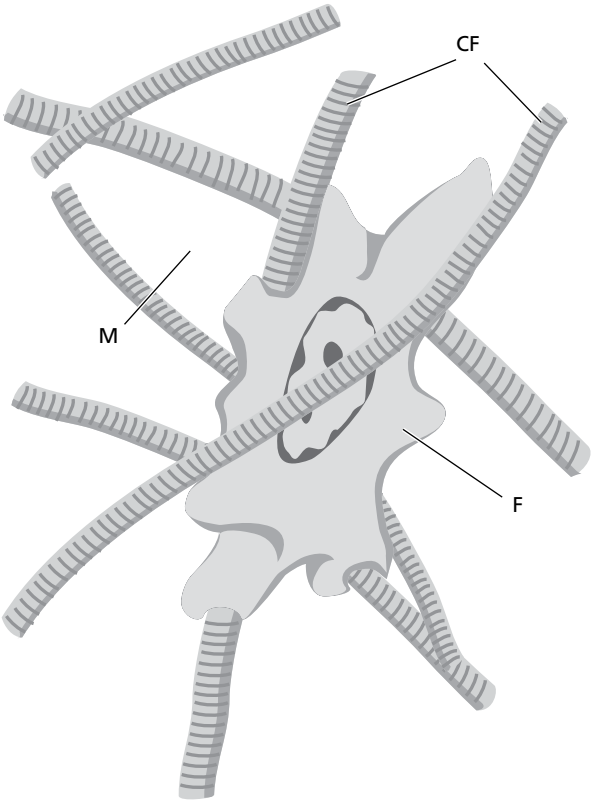

Fig. 1-36

(2) harbor hemidesmosomes (HD). Thus, the interface between the junctional epithelium and the enamel is structurally very similar to the epithelium–connective tissue interface, which means that the junctional epithelium is not only in contact with the enamel but is actually physically attached to the tooth via hemidesmosomes.

Lamina propria

The predominant tissue component of the gingiva is the connective tissue (lamina propria). The major components of the connective tissue are *collagen fibers* (around 60% of connective tissue volume), *fibroblasts* (around 5%), *vessels and nerves* (around 35%), which are embedded in an amorphous ground substance (matrix).

Figure 1-36 The drawing illustrates a fibroblast (F) residing in a network of connective tissue fibers (CF). The intervening space is filled with matrix (M), which constitutes the "environment" for the cell.

Cells

The different types of cell present in the connective tissue are: (1) *fibroblasts*, (2) *mast cells*, (3) *macrophages*, and (4) *inflammatory cells*.

Figure 1-37 The *fibroblast* is the predominant connective tissue cell (65% of the total cell population). The fibroblast is engaged in the production of various types of fibers found in the connective tissue, but is also instrumental in the synthesis of the connective

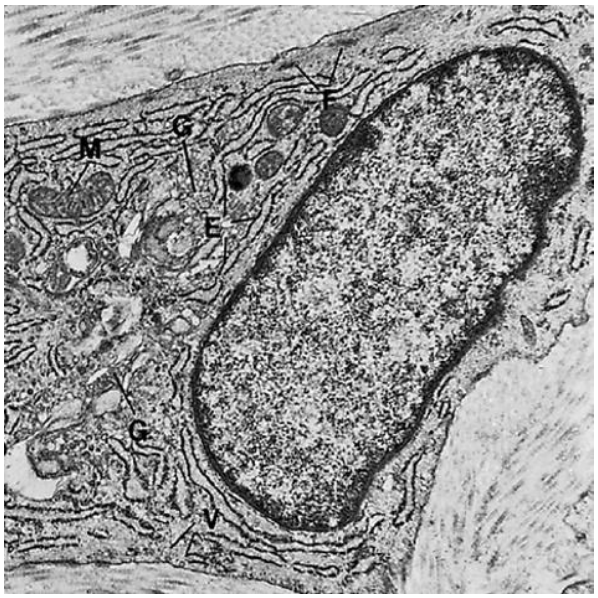

Fig. 1-37

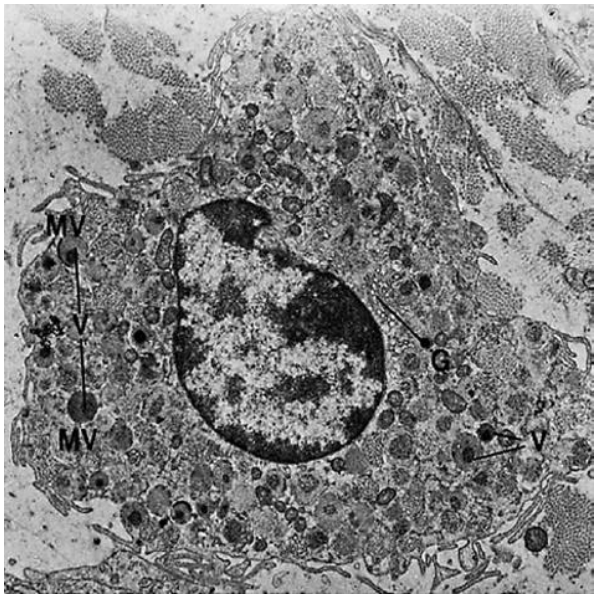

Fig. 1-38

tissue matrix. The fibroblast is a spindle-shaped or stellate cell with an oval-shaped nucleus containing one or more nucleoli. A part of a fibroblast is shown in electron microscopic magnification. The cytoplasm contains a well-developed granular endoplasmic reticulum (E) with ribosomes. The Golgi complex (G) is usually of considerable size and the mitochondria (M) are large and numerous. Furthermore, the cytoplasm contains many fine tonofilaments (F). Adjacent to the cell membrane, all along the periphery of the cell, a large number of vesicles (V) can be seen.

Figure 1-38 The *mast cell* is responsible for the production of certain components of the matrix. This cell also produces vasoactive substances, which can affect the function of the microvascular system and control the flow of blood through the tissue. A mast cell is

presented in electron microscopic magnification. The cytoplasm is characterized by the presence of a large number of vesicles (V) of varying size. These vesicles contain biologically active substances such as proteolytic enzymes, histamine, and heparin. The Golgi complex (G) is well developed, while granular endoplasmic reticulum structures are scarce. A large number of small cytoplasmic projections, that is microvilli (MV), can be seen along the periphery of the cell.

Figure 1-39 The *macrophage* has a number of different phagocytic and synthetic functions in the tissue. A macrophage is shown in electron microscopic magnification. The nucleus is characterized by numerous invaginations of varying size. A zone of electron-dense chromatin condensations can be seen along the periphery of the nucleus. The Golgi complex (G) is well developed and numerous vesicles (V) of varying size are present in the cytoplasm. Granular endoplasmic reticulum (E) is scarce, but a certain number of free ribosomes (R) are evenly distributed in the cytoplasm. Remnants of phagocytosed material are often found in lysosomal vesicles: phagosomes (PH). In the periphery of the cell, a large number of microvilli of varying size can be seen. Macrophages are particularly numerous in inflamed tissue. They are derived from circulating blood monocytes which migrate into the tissue.

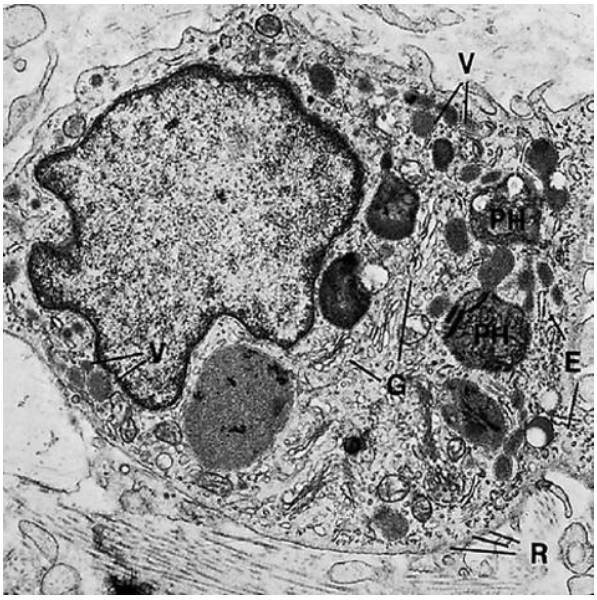

Fig. 1-39

Figure 1-40 Besides fibroblasts, mast cells, and macrophages, the connective tissue also harbors *inflammatory cells* of various types, for example neutrophilic granulocytes, lymphocytes, and plasma cells.

The *neutrophilic granulocytes*, also called *polymorphonuclear leukocytes*, have a characteristic appearance (Fig. 1-40a). The nucleus is lobulated and numerous lysosomes (L), containing lysosomal enzymes, are found in the cytoplasm.

The *lymphocytes* (Fig. 1-40b) are characterized by an oval to spherical nucleus containing localized areas of electron-dense chromatin. The narrow border of cytoplasm surrounding the nucleus contains numerous free ribosomes, a few mitochondria (M), and, in localized areas, endoplasmic reticulum with fixed ribosomes. Lysosomes are also present in the cytoplasm.

The *plasma cells* (Fig. 1-40c) contain an eccentrically located spherical nucleus with radially deployed electron-dense chromatin. Endoplasmic reticulum (E) with numerous ribosomes is found randomly distributed in the cytoplasm. In addition, the cytoplasm contains numerous mitochondria (M) and a well-developed Golgi complex.

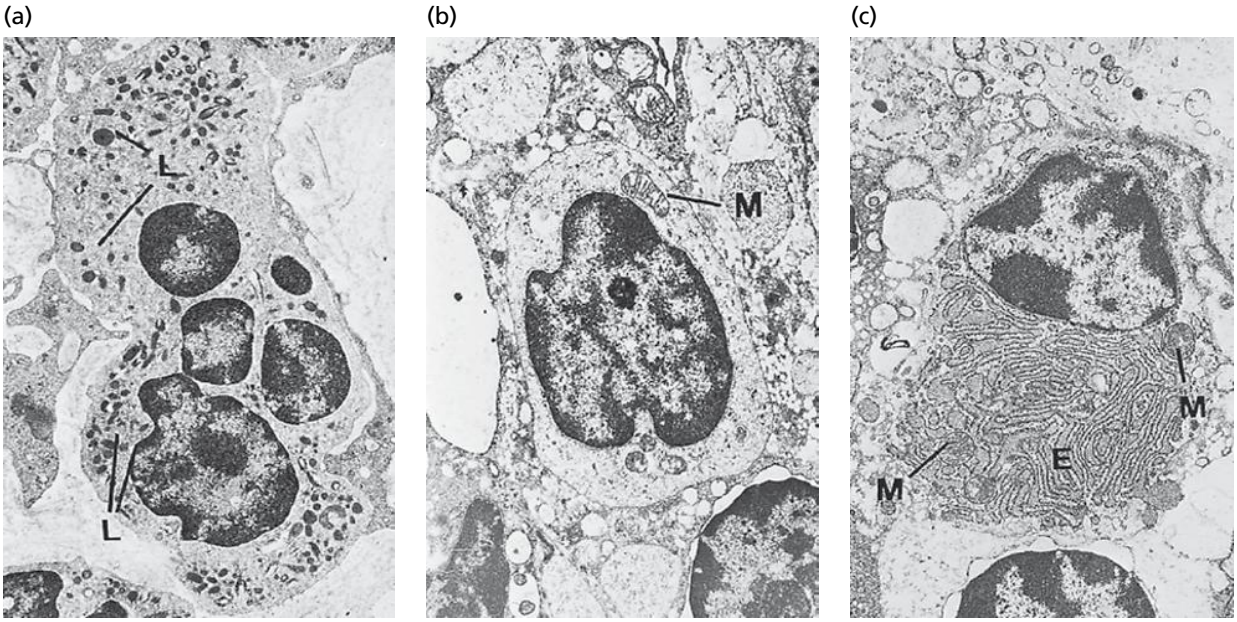

Fig. 1-40

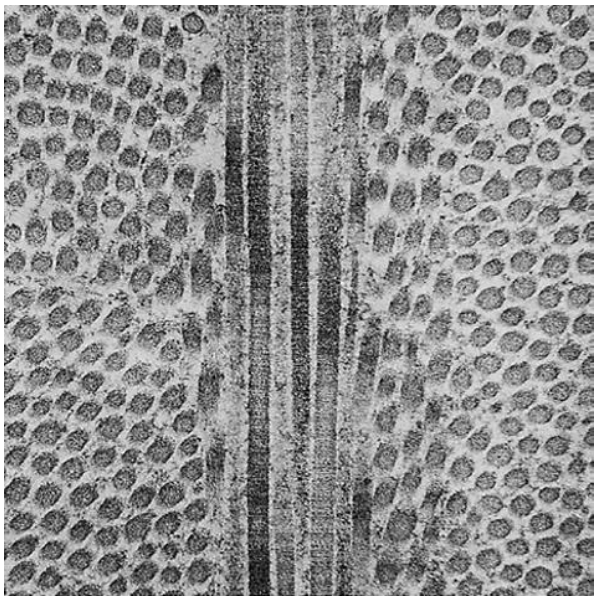

Fig. 1-41

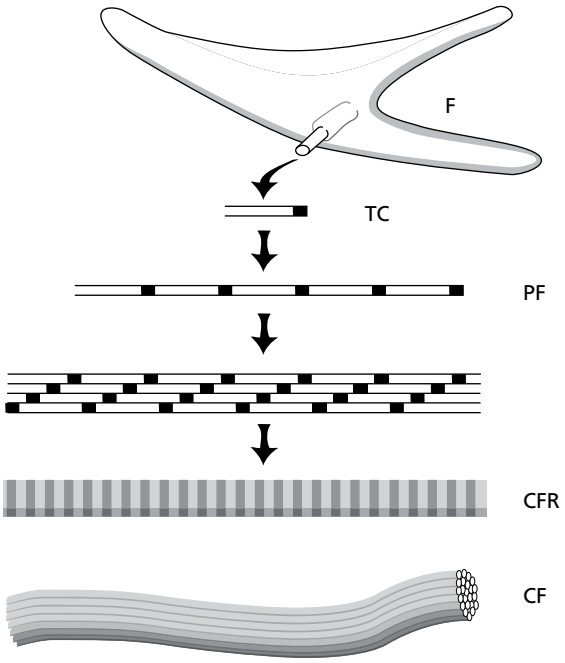

Fig. 1-42

Fibers

The connective tissue fibers are produced by the fibroblasts and can be divided into: (1) *collagen fibers*, (2) *reticulin fibers*, (3) *oxytalan fibers*, and (4) *elastic fibers*.

Figure 1-41 The *collagen fibers* predominate in the gingival connective tissue and constitute the most essential components of the periodontium. The electron micrograph shows cross-sections and longitudinal sections of collagen fibers. The collagen fibers have a characteristic cross-banding with a periodicity of 700 Å between the individual dark bands.

Figure 1-42 illustrates some important features of the synthesis and the composition of collagen fibers produced by fibroblasts (F). The smallest unit, the collagen molecule, is often referred to as *tropocollagen*. A tropocollagen molecule (TC), which is seen in the upper portion of the drawing, is approximately 3000 Å long and has a diameter of 15 Å. It consists of three polypeptide chains intertwined to form a helix. Each chain contains about 1000 amino acids. One-third of these are glycine and about 20% proline and hydroxyproline, the latter being found almost exclusively in collagen. Tropocollagen synthesis takes place inside the fibroblast from which the tropocollagen molecule is secreted into the extracellular space. Thus, the polymerization of tropocollagen molecules to collagen fibers takes place in the extracellular compartment. First, tropocollagen molecules are aggregated longitudinally to form *protofibrils* (PF), which are subsequently laterally aggregated parallel to *collagen fibrils* (CFR), with the tropocollagen molecules overlapping by about 25% of their length. Due to the fact that special refraction conditions develop after staining at the sites where the tropocollagen molecules adjoin, a cross-banding with a periodicity of approximately 700 Å is seen under light microscopy. The *collagen fibers* (CF) are bundles of collagen fibrils, aligned in such a way that the fibers also exhibit a cross-banding with a periodicity of 700 Å. In the tissue, the fibers are usually arranged in bundles. As the collagen fibers mature, covalent cross-links are formed between the tropocollagen molecules, resulting in an age-related reduction in collagen solubility.

Cementoblasts and *osteoblasts* are cells which also possess the ability to produce collagen.

Figure 1-43 *Reticulin fibers*, as seen in this photomicrograph, exhibit argyrophilic staining properties and are numerous in the tissue adjacent to the basement membrane (arrows). However, reticulin fibers also occur in large numbers in the loose connective tissue surrounding the blood vessels. Thus, reticulin fibers are present at the epithelium–connective tissue and the endothelium–connective tissue interfaces.

Figure 1-44 *Oxytalan fibers* are scarce in the gingiva but numerous in the periodontal ligament. They are composed of long thin fibrils with a diameter of approximately 150 Å. These connective tissue fibers can be demonstrated under light microscopy only after previous oxidation with peracetic acid. The photomicrograph illustrates oxytalan fibers (arrows) in the periodontal ligament, where they have a course mainly parallel to the long axis of the tooth. The function of these fibers is as yet unknown. The cementum is seen to the left and the alveolar bone to the right.

Figure 1-45 *Elastic fibers* in the connective tissue of the gingiva and periodontal ligament are only present in association with blood vessels. However, as seen in this photomicrograph, the lamina propria and submucosa of the alveolar (lining) mucosa contain

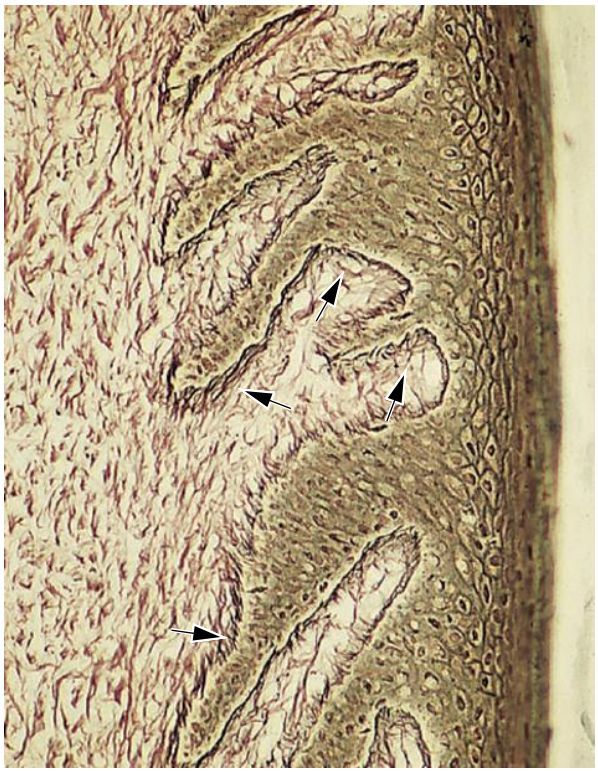

Fig. 1-43

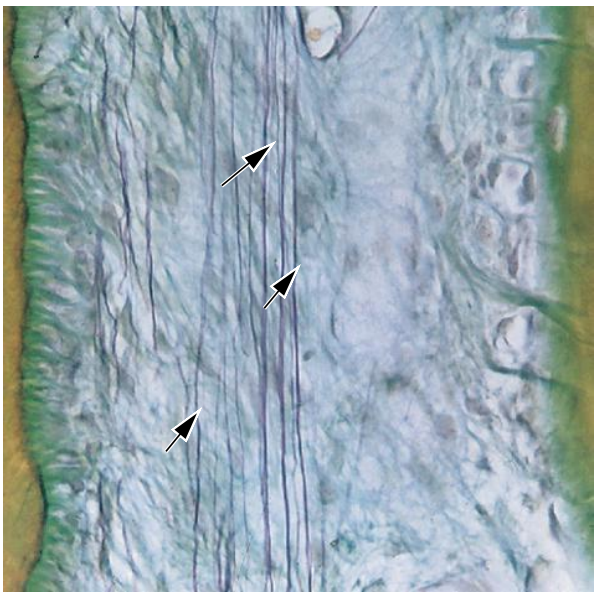

Fig. 1-44

numerous elastic fibers (arrows). The gingiva (G) seen coronal to the mucogingival junction (MGJ) contains no elastic fibers except in association with the blood vessels.

Figure 1-46 Although many of the collagen fibers in the gingiva and the periodontal ligament are irregularly or randomly distributed, most tend to be arranged in groups of bundles with a distinct orientation. According to their insertion and course in the tissue, the oriented bundles in the gingiva can be divided into the following groups:

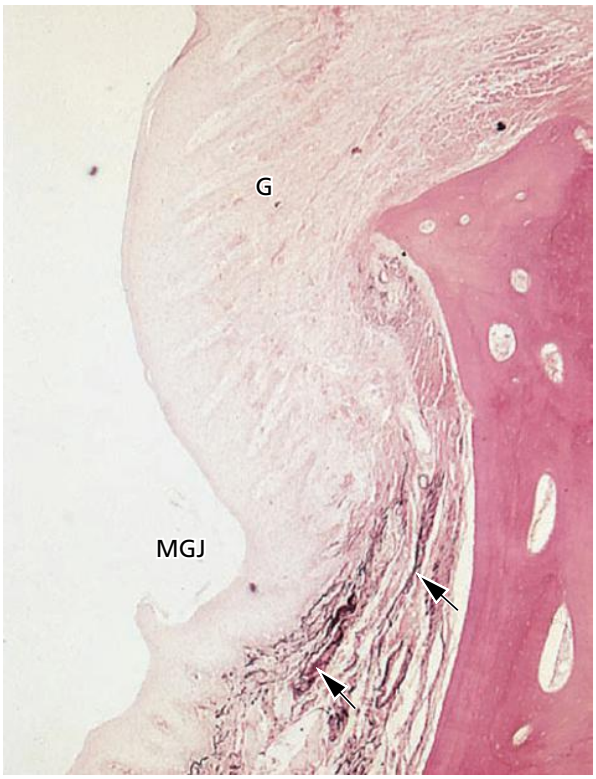

Fig. 1-45

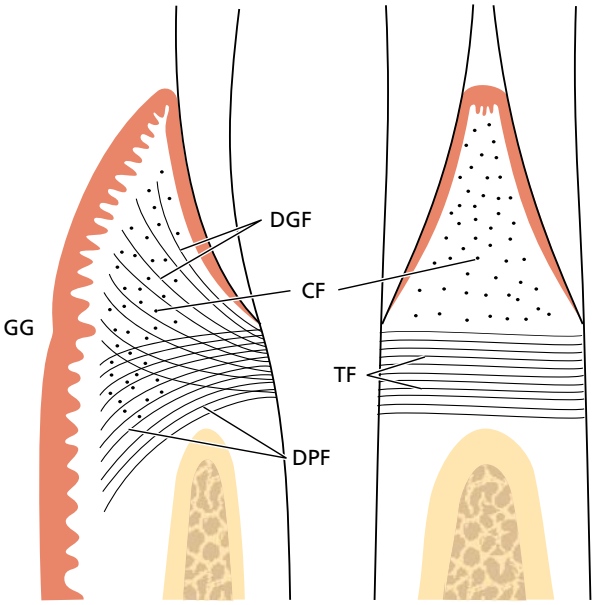

Fig. 1-46

1. *Circular fibers* (CF) are fiber bundles which run their course in the free gingiva and encircle the tooth in a cuff- or ring-like fashion.
2. *Dentogingival fibers* (DGF) are embedded in the cementum of the supra-alveolar portion of the root and project out from the cementum in a fan-like configuration into the free gingival tissue of the facial, lingual, and interproximal surfaces.
3. *Dentoperiosteal fibers* (DPF) are embedded in the same portion of the cementum as the dentogingival fibers, but run their course apically over the

vestibular and lingual bone crest and terminate in the tissue of the attached gingiva. In the border area between the free and attached gingiva, the epithelium often lacks support from underlying oriented collagen fiber bundles. In this area, the free gingival groove (GG) is often present.

4. *Trans-septal fibers* (TF), seen on the drawing to the right, extend between the supra-alveolar cementum of approximating teeth. The trans-septal fibers run straight across the interdental septum and are embedded in the cementum of adjacent teeth.

Figure 1-47 illustrates in a histologic section the orientation of the trans-septal fiber bundles (asterisks) in the supra-alveolar portion of the interdental area. It should be observed that, besides connecting the cementum (C) of adjacent teeth, the trans-septal fibers also connect the supra-alveolar cementum (C) with the crest of the alveolar bone (AB). The four groups of collagen fiber bundles shown in Fig. 1-46 reinforce the gingiva and provide the resilience and tone which is necessary for maintaining its architectural form and the integrity of the dentogingival attachment.

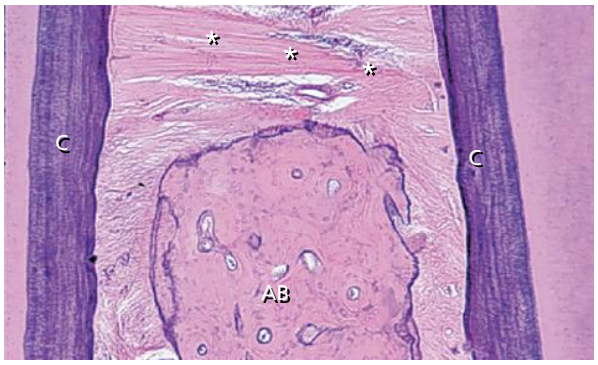

Fig. 1-47

Matrix

The *matrix* of the connective tissue is produced mainly by the fibroblasts, although some constituents are produced by mast cells and others are derived from the blood. The matrix is the medium in which the connective tissue cells are embedded and it is essential for the maintenance of the normal function of the connective tissue. Thus, the transportation of water, electrolytes, nutrients, metabolites, etc., to and from the individual connective tissue cells occurs within the matrix. The main constituents of the connective tissue matrix are protein–carbohydrate macromolecules. These complexes are normally divided into *proteoglycans* and *glycoproteins*. The proteoglycans contain *glycosaminoglycans* as the carbohydrate units (hyaluronan sulfate, heparan sulfate, etc.), which are attached to one or more protein chains via covalent bonds. The carbohydrate component is always predominant in the proteoglycans. The glycosaminoglycan, called hyaluronan or "hyaluronic acid", is probably not bound to protein. The glycoproteins (fibronectin, osteonectin, etc.) also contain polysaccharides, but these macromolecules are different from glycosaminoglycans. The protein component predominates in glycoproteins. In the macromolecules, mono- or oligo-saccharides are connected to one or more protein chains via covalent bonds.

Figure 1-48 Normal function of the connective tissue depends on the presence of proteoglycans and glycosaminoglycans. The carbohydrate moieties of the proteoglycans, the glycosaminoglycans (), are large, flexible, chains of negatively charged molecules, each of which occupies a rather large space (Fig. 1-48a). In such a space, smaller molecules, for example water and electrolytes, can be incorporated, while larger molecules are prevented from entering (Fig. 1-48b).

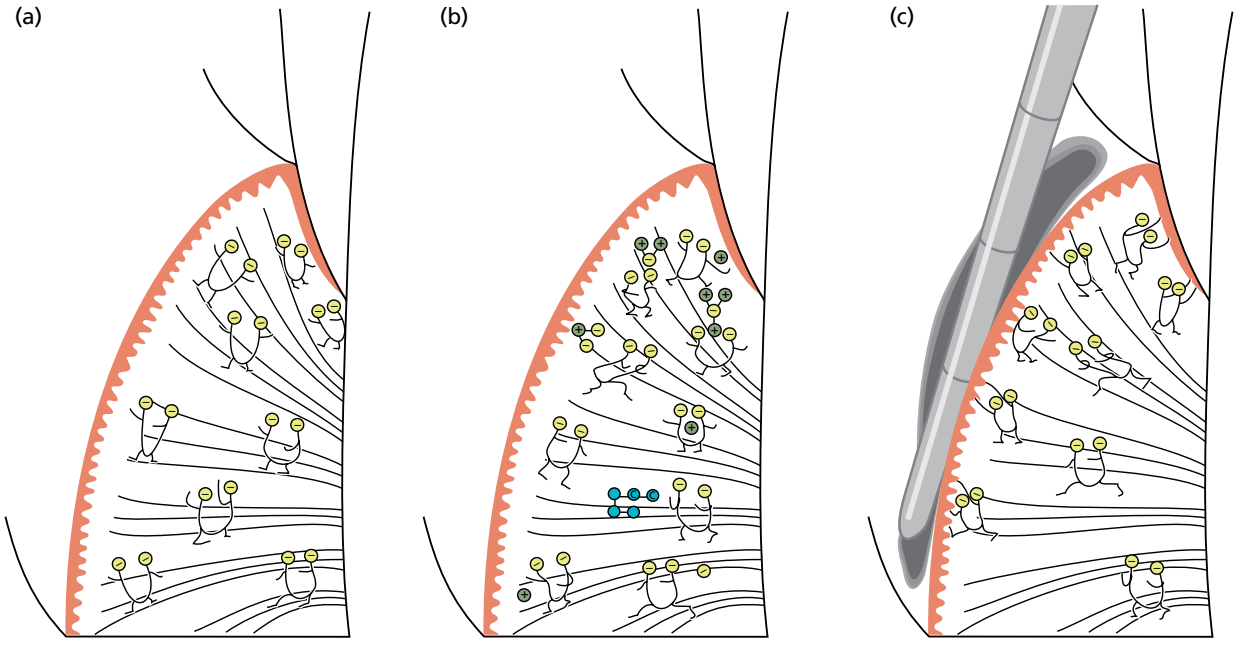

Fig. 1-48

The proteoglycans thereby regulate diffusion and fluid flow through the matrix and are important determinants for the fluid content of the tissue and the maintenance of the osmotic pressure. In other words, the proteoglycans act as a molecule filter and, in addition, play an important role in the regulation of cell migration (movement) in the tissue. Due to their structure and hydration, the macromolecules resist deformation, thereby serving as regulators of the consistency of the connective tissue (Fig. 1-48c). If the gingiva is suppressed, the macromolecules become deformed. When the pressure is eliminated, the macromolecules regain their original form. Thus, the macromolecules are important for the resilience of the gingiva.

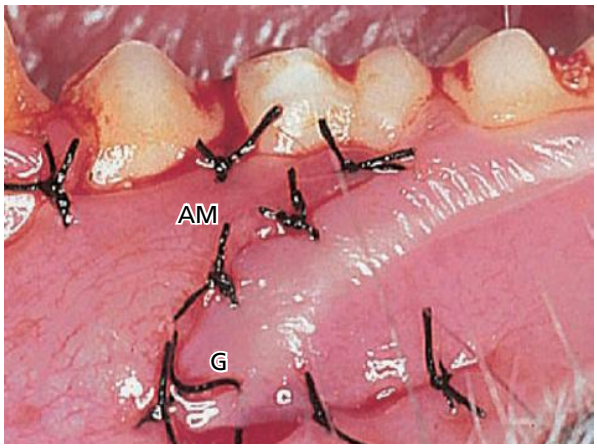

Fig. 1-49

Epithelial–mesenchymal interaction

During the embryonic development of various organs, a mutual inductive influence occurs between the epithelium and the connective tissue. The development of the teeth is a characteristic example of this phenomenon. The connective tissue is, on the one hand, a determining factor for normal development of the tooth bud while, on the other, the enamel epithelia exert a definite influence on the development of the mesenchymal components of the teeth.

It has been suggested that tissue differentiation in the adult organism can be influenced by environmental factors. The skin and mucous membranes, for instance, often display increased keratinization and hyperplasia of the epithelium in areas which are exposed to mechanical stimulation. Thus, the tissues seem to adapt to environmental stimuli. The presence of keratinized epithelium on the masticatory mucosa has been considered to represent an adaptation to mechanical irritation released by mastication. However, research has demonstrated that the characteristic features of the epithelium in such areas are genetically determined. Some pertinent observations are reported in the following images.

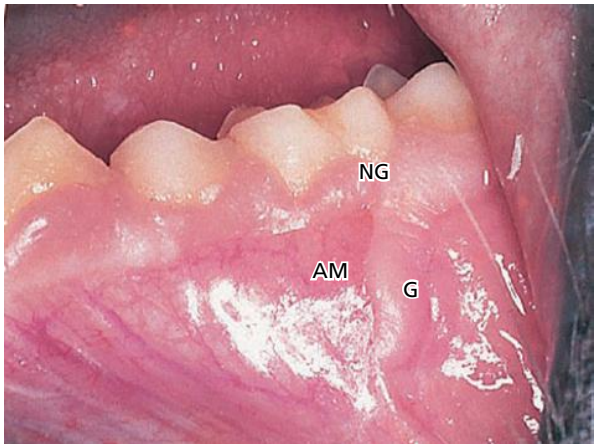

Fig. 1-50

Figure 1-49 shows an area in a monkey where the gingiva (G) and the alveolar mucosa (AM) have been transposed by a surgical procedure. The alveolar mucosa is placed in close contact with the teeth, while the gingiva is positioned in the area of the alveolar mucosa.

Figure 1-50 shows the same area as seen in Fig. 1-49, 4 months later. Despite the fact that the transplanted gingiva (G) is mobile in relation to the underlying bone, like the alveolar mucosa (AM), it has retained its characteristic morphologic features of a masticatory mucosa. A narrow zone of new keratinized gingiva (NG) has formed between the alveolar mucosa and the teeth.

Figure 1-51 shows a histologic section through the transplanted gingiva seen in Fig. 1-50. Since elastic fibers are lacking in the gingival connective tissue

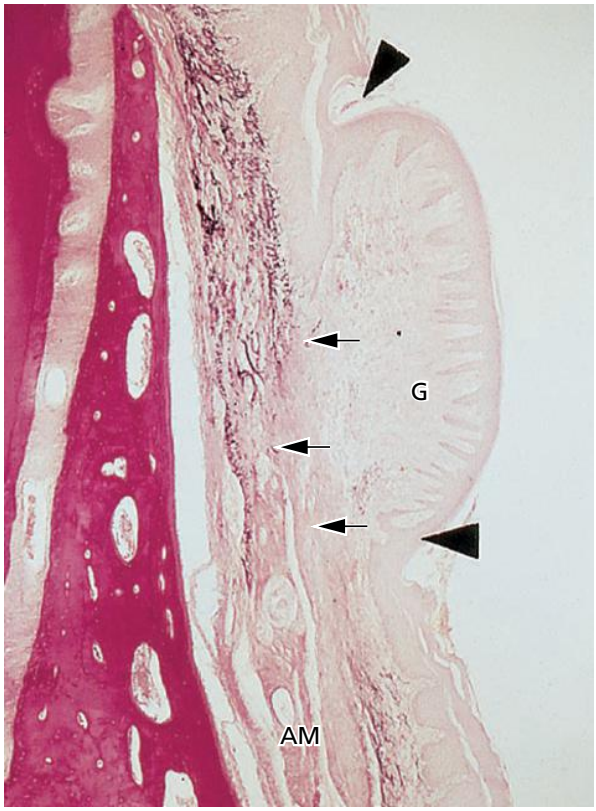

Fig. 1-51

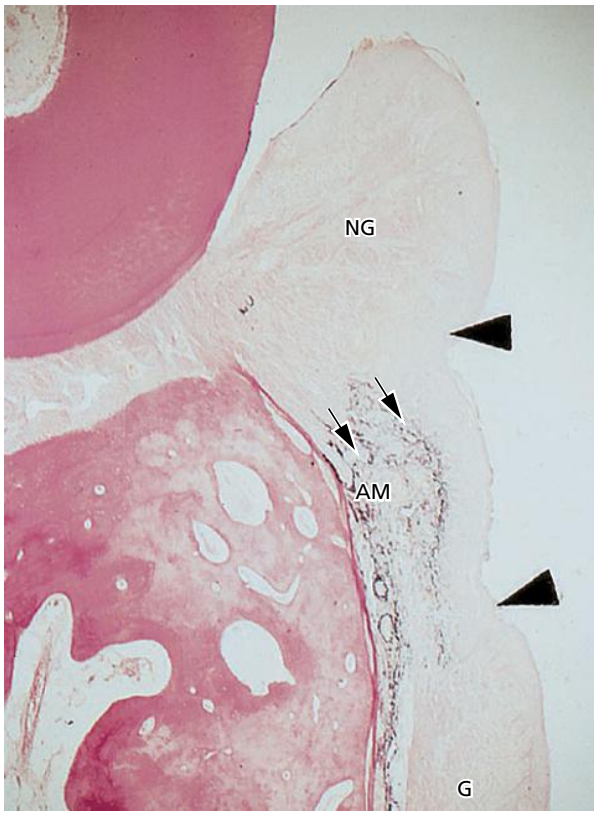

Fig. 1-52

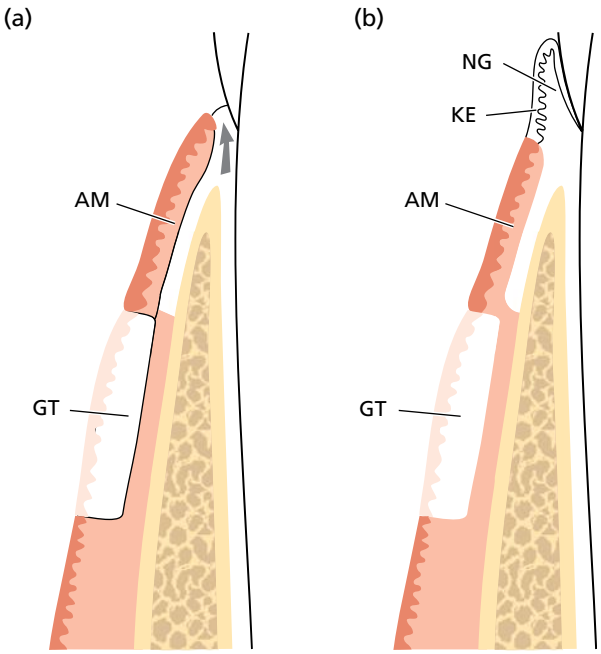

Fig. 1-53

(G), but are numerous (small arrows) in the connective tissue of the alveolar mucosa (AM), the transplanted gingival tissue can readily be identified. The epithelium covering the transplanted gingival tissue exhibits a distinct keratin layer (between arrowheads) on the surface, and the configuration of the epithelium–connective tissue interface (i.e. rete pegs and connective tissue papillae) is similar to that of normal non-transplanted gingiva. Thus, the heterotopically located gingival tissue has maintained its original specificity. This observation demonstrates that the characteristics of the gingiva are genetically determined rather than being the result of functional adaptation to environmental stimuli.

Figure 1-52 shows a histologic section through the coronal portion of the area of transplantation shown in Fig. 1-50. The transplanted gingival tissue (G) shown in Fig. 1-51 can be seen in the lower portion of the photomicrograph. The alveolar mucosa transplant (AM) is seen between the arrowheads in the middle of the micrograph. After surgery, the alveolar mucosa transplant was positioned in close contact with the teeth, as seen in Fig. 1-49. After healing, a narrow zone of keratinized gingiva (NG) developed coronal to the alveolar mucosa transplant (see Fig. 1-50). This new zone of gingiva (NG), which can be seen in the upper portion of the histologic section, is covered by keratinized epithelium and the connective tissue contains no purple-stained elastic fibers. In addition, it is important to note that the junction between keratinized and non-keratinized epithelium (arrowheads) corresponds exactly to the junction between "elastic" and "non-elastic" connective tissue (small arrows). The connective tissue of the new gingiva has regenerated from the connective tissue of the supra-alveolar and periodontal ligament compartments and has separated the alveolar mucosal transplant (AM) from the tooth (see Fig. 1-53). It is likely that the epithelium which covers the new gingiva has migrated from the adjacent epithelium of the alveolar mucosa. This indicates that it is the connective tissue that determines the quality of the epithelium.

Figure 1-53 shows a schematic drawing of the development of the new, narrow zone of keratinized gingiva (NG) seen in Figs. 1-50 and 1-52.

Figure 1-53a Granulation tissue (GT) has proliferated coronally along the root surface (arrow) and has separated the alveolar mucosa transplant (AM) from its original contact with the tooth surface.

Figure 1-53b Epithelial cells have migrated from the alveolar mucosal transplant (AM) to the newly formed gingival connective tissue (NG). Thus, the newly formed gingiva has become covered with a keratinized epithelium (KE) which originated from the non-keratinized epithelium of the alveolar mucosa (AM). This implies that the newly formed gingival connective tissue possesses the ability to induce changes in the differentiation of the epithelium originating from the alveolar mucosa. This epithelium, which is normally non-keratinized, apparently differentiates to keratinized epithelium because of stimuli arising from the newly formed gingival connective tissue. (GT, gingival transplant.)

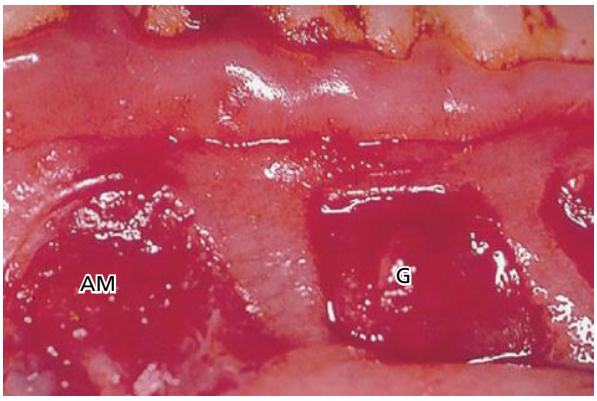

Fig. 1-54

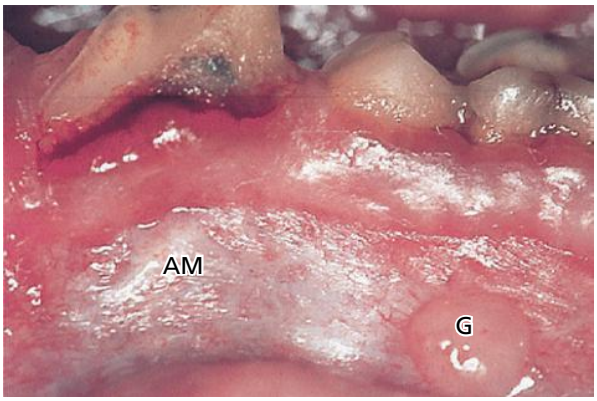

Fig. 1-55

Figure 1-54 shows a portion of gingival connective tissue (G) and alveolar mucosal connective tissue (AM) which, after transplantation, has healed into wound areas in the alveolar mucosa. Epithelialization of these transplants can only occur through migration of epithelial cells from the surrounding alveolar mucosa.

Figure 1-55 shows the transplanted gingival connective tissue (G) after re-epithelialization. This tissue portion has attained an appearance similar to that of the normal gingiva, indicating that this connective tissue is now covered by keratinized epithelium. The transplanted connective tissue from the alveolar mucosa (AM) is covered by non-keratinized epithelium, and has the same appearance as the surrounding alveolar mucosa.

Figure 1-56 shows two histologic sections through the area of the transplanted gingival connective tissue. The section shown in Fig. 1-56a is stained for elastic fibers (arrows). The tissue in the middle without elastic fibers is the transplanted gingival connective tissue (G). Figure 1-56b shows an adjacent section stained with hematoxylin and eosin. By comparing Figs. 1-56a and 1-56b, it can be seen that:

- Transplanted gingival connective tissue is covered by keratinized epithelium (between arrowheads).
- Epithelium–connective tissue interface has the same wavy course (i.e. rete pegs and connective tissue papillae) as seen in normal gingiva.

The photomicrographs shown in Figs. 1-56c and 1-56d illustrate, at a higher magnification, the border area between the alveolar mucosa (AM) and the transplanted gingival connective tissue (G). Note the distinct relationship between keratinized epithelium (arrow) and "inelastic" connective tissue (arrowheads), and between non-keratinized epithelium and "elastic" connective tissue. The establishment of such a close relationship during healing implies that the transplanted gingival connective tissue possesses the ability to alter the differentiation of epithelial cells, as previously suggested (Fig. 1-53). While starting as non-keratinizing cells, the cells of the epithelium of the alveolar mucosa have evidently become keratinizing cells. This means that the specificity of the gingival epithelium is determined by genetic factors inherent in the connective tissue.

Periodontal ligament

The periodontal ligament is the soft, richly vascular and cellular connective tissue which surrounds the roots of the teeth and joins the root cementum with the socket wall. In the coronal direction, the periodontal ligament is continuous with the lamina propria of the gingiva and is demarcated from the gingiva by the collagen fiber bundles which connect the alveolar bone crest to the root (the alveolar crest fibers).

Figure 1-57 is a radiograph of a mandibular premolar–molar region. On radiographs two types of alveolar bone can be distinguished:

1. The part of the alveolar process which covers the alveolus, denoted "lamina dura" (LD).
2. The portion of the alveolar process which, on the radiograph, has the appearance of a meshwork, denoted "trabecular bone".

The periodontal ligament is situated in the space between the roots of the teeth and the lamina dura (LD) or the alveolar bone proper. The alveolar bone surrounds the tooth from the apex to a level approximately 1 mm apical to the cementoenamel junction (CEJ). The coronal border of the bone is called the *bone crest* (BC).

The periodontal ligament space has the shape of an hourglass and is narrowest at the mid-root level. The width of the periodontal ligament is approximately 0.25 mm (range 0.2–0.4 mm). The presence of a periodontal ligament permits forces, elicited during masticatory function and other tooth contacts, to be distributed to and resorbed by the alveolar process via the alveolar bone proper. The periodontal ligament is also essential for the mobility of the teeth.

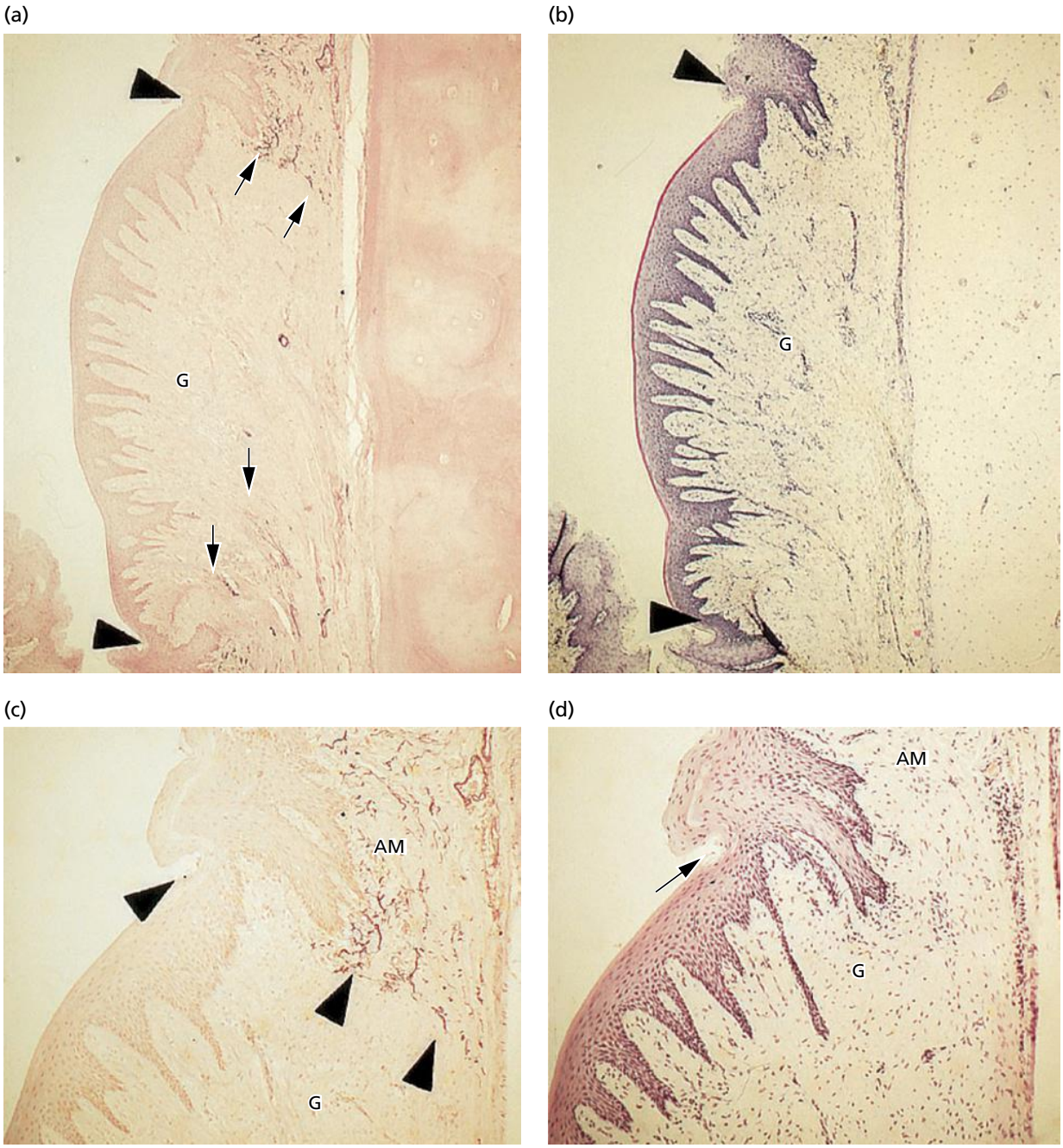

Fig. 1-56

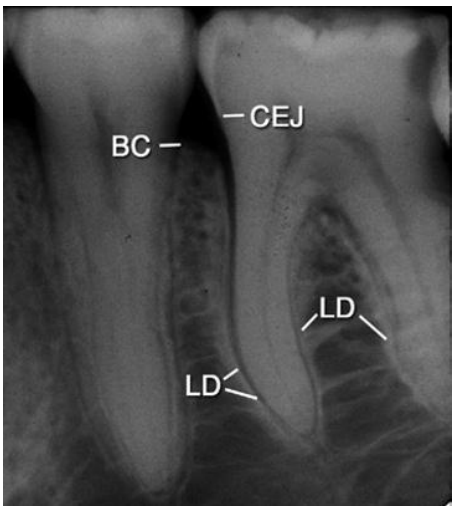

Fig. 1-57

Tooth mobility is to a large extent determined by the width, height, and quality of the periodontal ligament (see Chapters 16 and 52).

Figure 1-58 illustrates in a schematic drawing how the periodontal ligament is situated between the alveolar bone proper (ABP) and the root cementum (RC). The tooth is joined to the bone by bundles of collagen fibers which can be divided into the following main groups according to their arrangement:

1. *Alveolar crest fibers* (ACF)
2. *Horizontal fibers* (HF)
3. *Oblique fibers* (OF)
4. *Apical fibers* (APF).

Figure 1-59 The periodontal ligament and the root cementum develop from the loose connective tissue (the follicle) which surrounds the tooth bud. The schematic drawing depicts the various stages in the organization of the periodontal ligament which forms concomitantly with the development of the root and the eruption of the tooth.

Figure 1-59a The tooth bud is formed in a crypt of the bone. The collagen fibers produced by the fibroblasts in the loose connective tissue around the tooth bud are embedded, during the process of their maturation, into the newly formed cementum immediately apical to the cementoenamel junction (CEJ). These fiber bundles oriented towards the coronal portion of the bone crypt will later form the dentogingival fiber group, the dentoperiosteal fiber group, and the trans-septal fiber group, which belong to the oriented fibers of the gingiva (see Fig. 1-46).

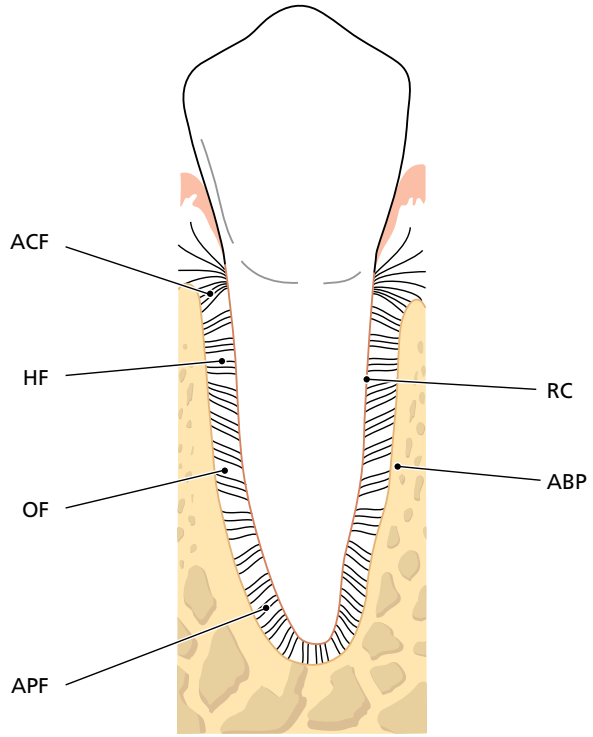

Fig. 1-58

Figure 1-59b The true periodontal ligament fibers, the *principal fibers*, develop in conjunction with the eruption of the tooth. First, fibers can be identified entering the most marginal portion of the alveolar bone.

Figure 1-59c Later, more apically positioned bundles of oriented collagen fibers are seen.

Figure 1-59d The orientation of the collagen fiber bundles alters continuously during the phase of tooth eruption. First, when the tooth has reached contact in occlusion and is functioning properly, the fibers of the periodontal ligament associate into groups of well-oriented dentoalveolar collagen fibers (see Fig. 1-58). These collagen structures undergo constant remodeling (i.e. resorption of old fibers and formation of new ones). (DGF, dentogingival fibers; DPF, dentoperiosteal fibers; HF, horizontal fibers; OF, oblique fibers; APF, apical fibers.)

Figure 1-60 This schematic drawing illustrates the development of the principal fibers of the periodontal ligament. The alveolar bone proper (ABP) is seen to the left, the periodontal ligament (PL) in the center, and the root cementum (RC) to the right.

Figure 1-60a First, small, fine, brush-like fibrils are detected arising from the root cementum and projecting into the periodontal ligament space. At this stage the surface of the bone is covered by osteoblasts. From the surface of the bone only a small number of radiating, thin collagen fibrils can be seen.

Figure 1-60b Later on, the number and thickness of fibers entering the bone increase. These fibers radiate towards the loose connective tissue in the mid-portion of the periodontal ligament space, which contains more or less randomly oriented collagen fibrils. The fibers originating from the cementum are

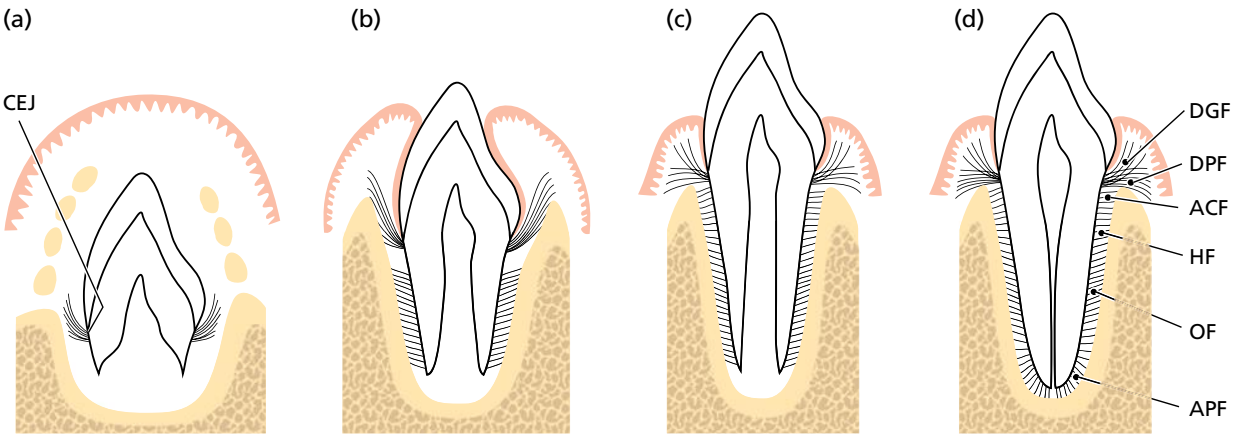

Fig. 1-59

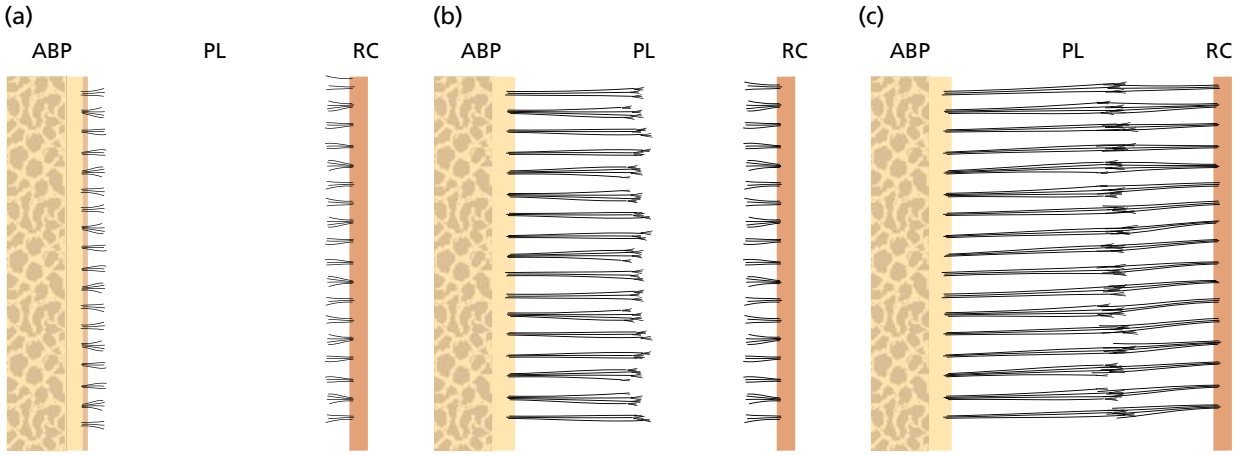

Fig. 1-60

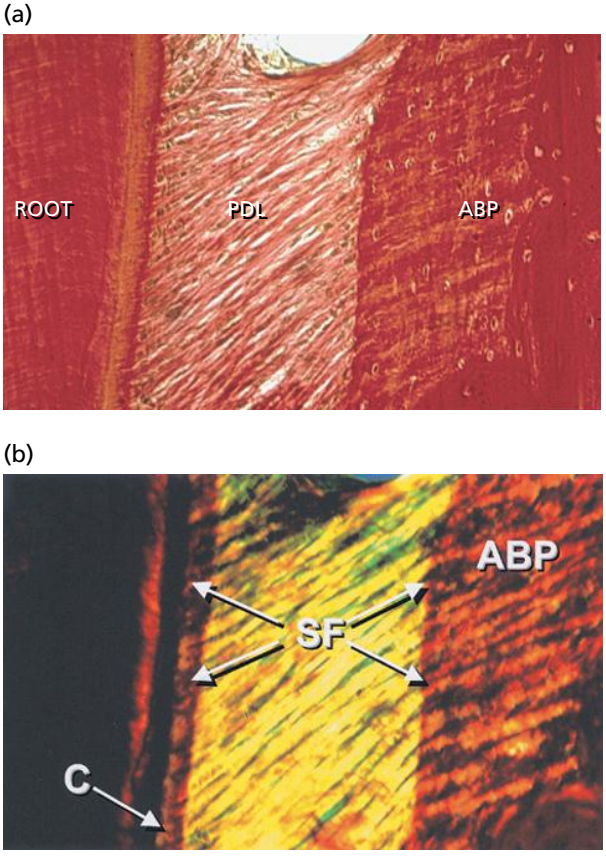

Fig. 1-61

still short, while those entering the bone gradually lengthen. The terminal portions of these fibers carry finger-like projections.

Figure 1-60c The fibers originating from the cementum subsequently increase in length and thickness and fuse in the periodontal ligament space with the fibers originating from the alveolar bone. When the tooth, following eruption, reaches contact in occlusion and starts to function, the principal fibers become organized into bundles and run continuously from the bone to the cementum.

Figure 1-61a shows how the principal fibers of the periodontal ligament (PDL) run continuously from the root cementum to the alveolar bone proper (ABP). The principal fibers embedded in the cementum (Sharpey's fibers) have a smaller diameter, but are more numerous than those embedded in the alveolar bone proper.

Figure 1-61b shows a polarized version of Fig. 1-61a. In this image the Sharpey's fibers (SF) can be seen penetrating not only the cementum (C) but also the entire width of the alveolar bone proper (ABP). The periodontal ligament also contains a few elastic fibers associated with the blood vessels. Oxytalan fibers (see Fig. 1-44) are also present in the periodontal ligament. They have a mainly apico-occlusal orientation and are located in the ligament closer to the tooth than to the alveolar bone. Very often they insert into the cementum. Their function has not been determined.

The cells of the periodontal ligament are: *fibroblasts*, *osteoblasts*, *cementoblasts*, *osteoclasts*, as well as *epithelial cells* and *nerve fibers*. The fibroblasts are aligned along the principal fibers, while cementoblasts line the surface of the cementum and the osteoblasts line the bone surface.

Figure 1-62a shows the presence of clusters of epithelial cells (ER) in the periodontal ligament (PDL). These cells, called the *epithelial cell rests of Mallassez*, represent remnants of the Hertwig's epithelial root sheath. The epithelial cell rests are situated in the periodontal ligament at a distance of 15–75 µm from the cementum (C) on the root surface. A group of such epithelial cell rests is seen in a higher magnification in Fig. 1-62b.

Figure 1-63 Under the electron microscopic it can be seen that the epithelial cell rests are surrounded by a basement membrane (BM) and that the cell membranes of the epithelial cells exhibit the presence of desmosomes (D) as well as hemidesmosomes (HD).

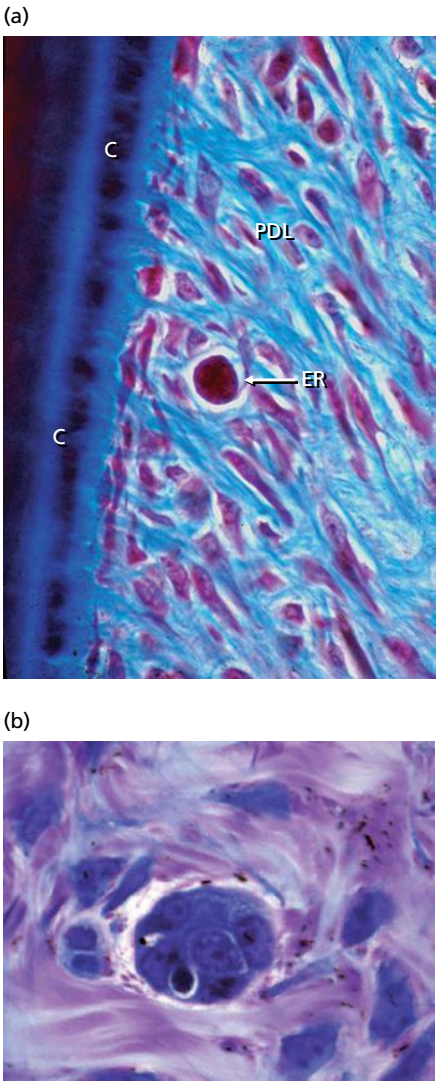

Fig. 1-62

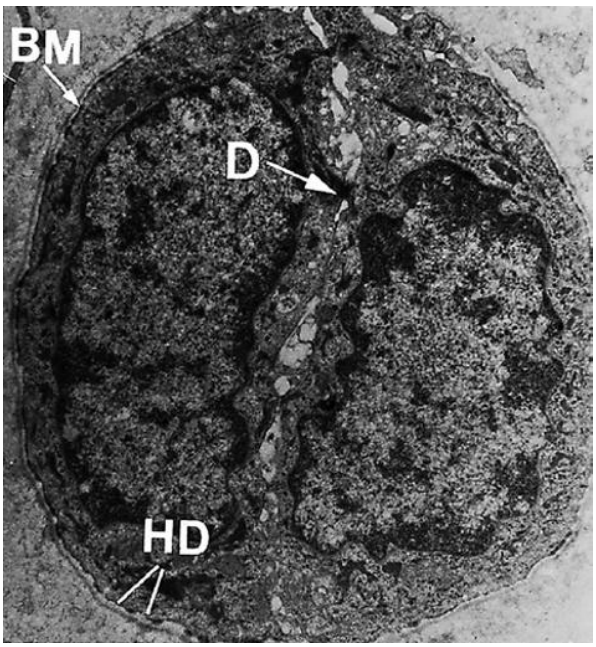

Fig. 1-63

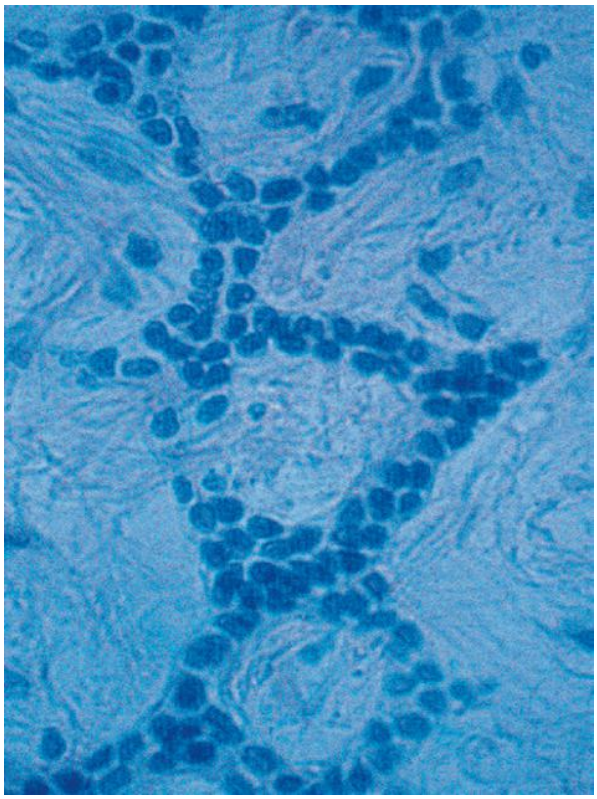

Fig. 1-64

The epithelial cells contain only a few mitochondria and have a poorly developed endoplasmic reticulum. This means that they are vital, but resting, cells with minute metabolism.

Figure 1-64 is a photomicrograph of a periodontal ligament removed from an extracted tooth. This specimen, prepared tangential to the root surface, shows that the epithelial cell rests of Mallassez, which in ordinary histologic sections appear as isolated groups of epithelial cells, in fact form a continuous network of epithelial cells surrounding the root. Their function is unknown at present.

Root cementum

The cementum is a specialized mineralized tissue covering the root surfaces and, occasionally, small portions of the crown of the teeth. It may also extend into the root canal. Unlike bone, the cementum contains no blood or lymph vessels, has no innervation, does not undergo physiologic resorption or remodeling, but is characterized by continuing deposition throughout life. Like other mineralized tissues, it contains collagen fibrils embedded in an organic matrix. Its mineral content, which is mainly hydroxyapatite, is about 65% by weight, a little more than that of bone (60%). Cementum serves different functions. It attaches the principal periodontal ligament fibers to the root and contributes to the process of repair after damage to the root surface. It

may also serve to adjust the tooth position to new requirements.

Different forms of cementum have been described:

1. *Acellular afibrillar cementum* (AAC) is found mainly at the cervical portion of the enamel.
2. *Acellular extrinsic fiber cementum* (AEFC) is found in the coronal and middle portions of the root and contains mainly bundles of Sharpey's fibers. This type of cementum is an important part of the attachment apparatus and connects the tooth with the bundle bone (alveolar bone proper).
3. *Cellular mixed stratified cementum* (CMSC) occurs in the apical third of the roots and in the furcations. It contains both extrinsic and intrinsic fibers as well as cementocytes.
4. *Cellular intrinsic fiber cementum* (CIFC) is found mainly in resorption lacunae and it contains intrinsic fibers and cementocytes.

Figure 1-65a shows a ground section viewed under polarized light. The principal collagen fibers of the periodontal ligament (PDL) span between the root covered with cementum (C) and the alveolar process covered with bundle bone (BB). The portions of the principal fibers of the periodontal ligament that are embedded in the root cementum and in the bundle bone are called *Sharpey's fibers*. (D, dentin.) (Courtesy of D.D. Bosshardt.)

Figure 1-65b The oxytalan fibers in the periodontal ligament (PDL) run in an apicocoronal direction; some (arrows) insert into acellular extrinsic fiber cementum (AEFC). Many oxytalan fibers are seen around the blood vessels (BV) in the periodontal ligament. Oxytalan fibers may have a function in mechanotransduction between the tooth root and the periodontal ligament. (BB, bundle bone; D, dentin.) (Courtesy of D.D. Bosshardt.)

Figure 1-66a shows the presence of acellular afibrillar cementum (AAC) in the region of the dentinocemental junction. The acellular afibrillar cementum covers minor areas of the cervical enamel. It neither contains cells nor collagen fibrils. It may form isolated patches on the enamel or be contiguous with the acellular extrinsic fiber cementun (AEFC). The acellular afibrillar cementum may form when the reduced enamel epithelium recedes or focally disintegrates so that the exposed enamel surface comes into contact with the surrounding soft connective tissue. (D, dentin; ES, enamel space.) (Courtesy of D.D. Bosshardt.)

Figure 1-66b shows the morphology of the acellular afibrillar cementum (AAC) under the transmission electron microscope. The acellular afibrillar cementum extends from the acellular extrinsic fiber cementum (AEFC) in the coronal direction. The layered appearance of the acellular afibrillar

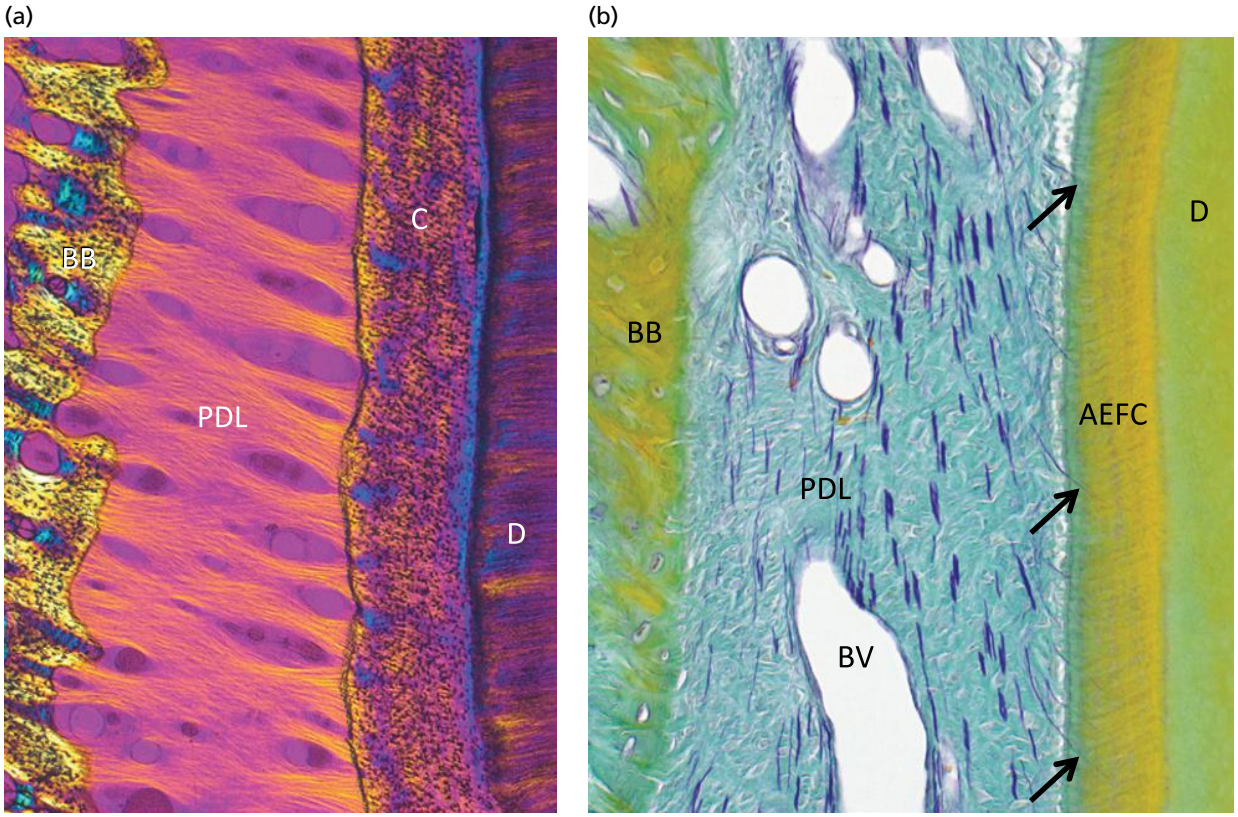

Fig. 1-65

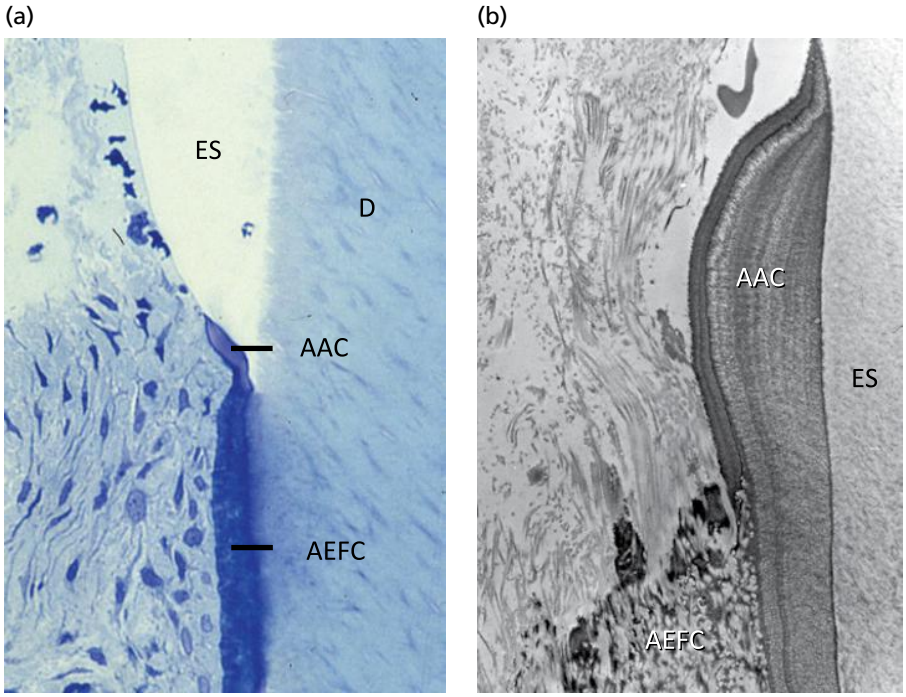

Fig. 1-66

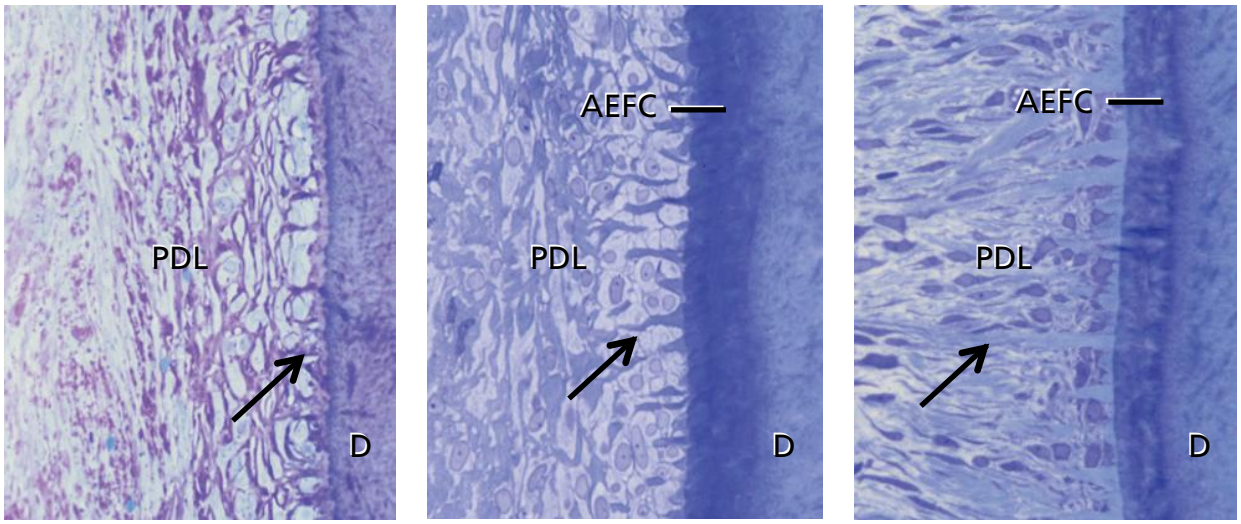

Fig. 1-67

cementum is indicative of periods of deposition and rest. The function of the acellular afibrillar cementum is unclear. The moderately electron-dense material in the enamel space (ES) adjacent to the acellular afibrillar cementum represents residual enamel matrix.

Figure 1-67 illustrates the three stages of development of the acellular extrinsic fiber cementum (AEFC). The acellular extrinsic fiber cementum is formed concomitantly with the formation of the root dentin. At the beginning of root development, the epithelial sheath of Hertwig, which lines the newly formed predentin, is fragmented. Cementoblasts then begin to synthesize collagen fibers that are implanted at a right angle to the surface. During the continuous formation of acellular extrinsic fiber cementum, portions of these short collagen fibers adjacent to the root become embedded in the mineralized tissue.

Figure 1-67a shows the short collagen fibers (arrow) protruding from the dentin (D) surface into the periodontal ligament (PDL), which constitute the future Sharpey's fibers. However, a cementum layer is not yet visible.

Figure 1-67b shows the short collagen fibers (arrow) protruding from the root surface, but their bases are now embedded as Sharpey's fibers in the mineralized cementum.

Figure 1-67c shows that most collagen fibers are now elongated and continue into the periodontal ligament space.

These micrographs demonstrate that the Sharpey's fibers in the cementum are a direct continuation of the principal fibers in the periodontal ligament and the supra-alveolar connective tissue. The AEFC increases throughout life with a very slow growth rate of 1.5–4.0 µm/year.

Figure 1-68a represents a scanning electron micrograph of a non-decalcified fracture surface of acellular extrinsic fiber cement (AEFC). Note that the extrinsic fibers attach to the dentin (D), traverse the mineralized cementum layer as Sharpey's fibers, and are continuous with the collagen fibers (CF) of the periodontal ligament (PDL). (Courtesy of D.D. Bosshardt.)

Figure 1-68b shows a transmission electron micrograph of acellular extrinsic fiber cementum (AEFC). Sharpey's fibers (i.e. the extrinsic collagen fibers of acellular extrinsic fiber cementum) pass from the dentin (D) surface through the mineralized cementum layer and continue outside the cementum as principal collagen fibers (CF) into the periodontal ligament. Cementoblasts (CB) occupy the spaces between the protruding collagen fibers.

Figure 1-69a shows a transmission electron micrograph of acellular extrinsic fiber cementum (AEFC) at the mineralization front. The Sharpey's fibers leave the cementum at the mineralization front and continue as principal periodontal ligament fibers. Cementoblasts (CB) occupy the space between the densely packed collagen fibrils. The characteristic cross-banding of the collagen fibrils is masked in the cementum because of the presence of non-collagenous proteins. Mineralization occurs by the deposition of hydroxyapatite crystals, first within the collagen fibers, later upon the fiber surface, and finally in the interfibrillar matrix.

Figure 1-69b shows high-resolution immunolabeling of acellular extrinsic fiber cementum (AEFC) at the mineralization front. The tissue section was processed for immunogold labeling with an antibody against bone sialoprotein. This non-collagenous protein has a function in the regulation of mineralization of collagen-based hard tissues. Gold particles label the interfibrillar matrix of the mineralized cementum, whereas the unmasked collagen fibrils that leave the cementum and extend into the periodontal ligament space are not labeled.

Figure 1-70a shows an unstained, undecalcified ground section viewed under polarized light. The micrograph demonstrates the structure of cellular mixed stratified cementum (CMSC) that consists of alternating layers of acellular extrinsic fiber

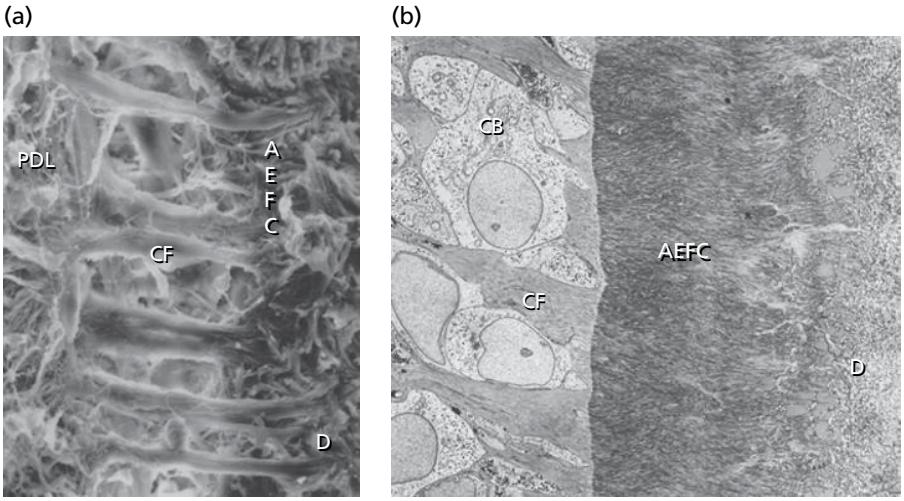

Fig. 1-68

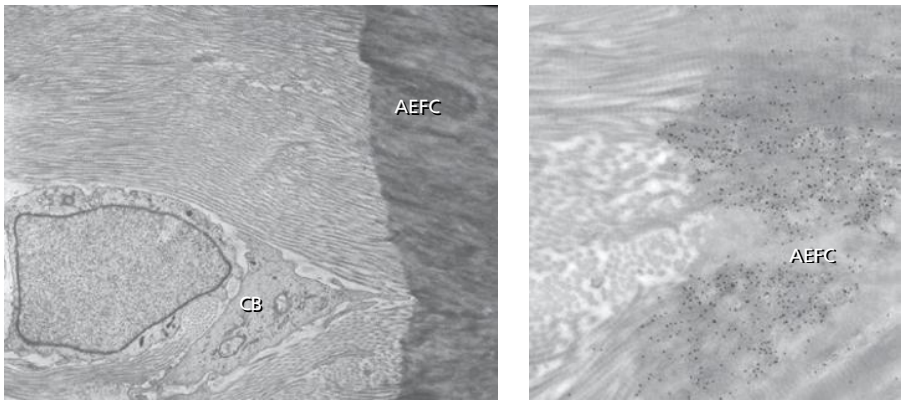

Fig. 1-69

cementum and cellular intrinsic fiber cementum. In contrast to acellular extrinsic fiber cementum, cellular intrinsic fiber cementum contains cells and intrinsic fibers. While the extrinsic Sharpey's fibers traverse the cementum layer and leave it at the mineralization front, the intrinsic fibers reside completely within the cementum. The cells that are incorporated into the cementum are called *cementocytes*. The cellular mixed stratified cementum is laid down throughout the functional period of the tooth. The stratification of cellular mixed stratified cementum is usually irregular. Cellular mixed stratified cementum is found at the mid-root and apical root surfaces and in the furcations. The cementum becomes considerably wider in the apical portion of the root than in the cervical portion. In the apical root portion, the cementum is often 150–250 µm wide or even more. The cementum often contains incremental lines, indicating alternating periods of formation and rest.

Figure 1-70b shows an unstained, undecalcified ground section viewed under polarized light. Cementocytes (black cells) reside in lacunae in the cellular intrinsic fiber cementum (CIFC), which is found in the cellular mixed stratified cementum. Cementocytes communicate with each other through a network of cytoplasmic processes (arrow) running through canaliculi in the cementum. Most cell processes point to the cementum surface (to the left). The cementocytes also communicate with the cementoblasts on the surface through cytoplasmic processes. The presence of cementocytes allows transportation of nutrients and waste products through the cementum, and contributes to the maintenance of the vitality of this mineralized tissue.

Figure 1-71a shows a transmission electron micrograph from the surface of cellular intrinsic fiber cementum (CIFC). The cementoid is lined by typical

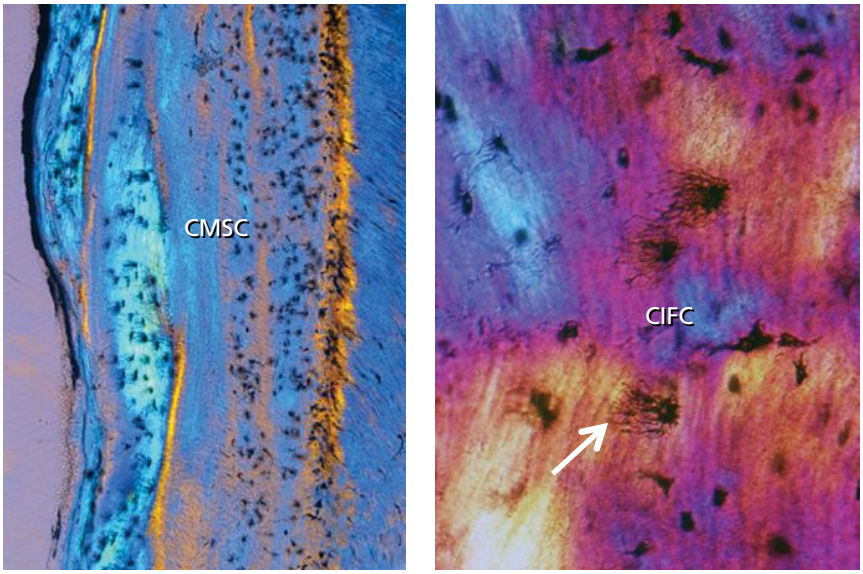

Fig. 1-70

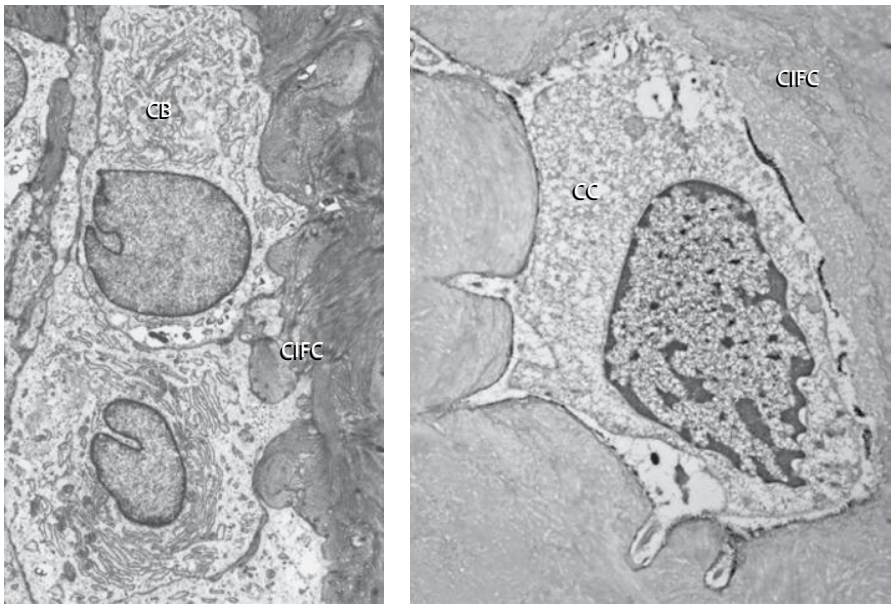

Fig. 1-71

cementoblasts (CB). They are large, cuboidal cells with a round, euchromatin-rich nucleus. The abundance of rough endoplasmic reticulum indicates that these cells are highly active and produce proteins that are secreted into the extracellular space. They elaborate a cementoid seam consisting of a collagenous matrix that later mineralizes. Generally, the acellular extrinsic fiber cementum is more mineralized than cellular mixed stratified cementum and cellular intrinsic fiber cementum. Sometimes only the periphery of the Sharpey's fibers of the cellular mixed stratified cementum is mineralized, leaving an unmineralized core within the fiber.

Figure 1-71b is a transmission electron micrograph that illustrates a cementocyte (CC) in cellular intrinsic fiber cementum (CIFC). Cementocytes are cementoblasts that become entrapped in the cementum matrix. They are present in lacunae from which several canaliculi traverse the cementum matrix and communicate with neighboring cementocytes. Cementocyte lacunae in deeper portions of the cementum often appear empty, which may be because the critical distance for exchange of metabolites is surpassed.

Bone of the alveolar process

Macroscopic anatomy

The alveolar process is defined as the parts of the maxilla and the mandible that form and support the sockets of the teeth. The alveolar process extends from the basal bone of the jaws and develops in conjunction with the development and eruption of the teeth (see Fig. 1-59). The alveolar process consists of bone that is formed both by cells from the dental follicle (to produce the alveolar bone proper) and cells which are independent of this follicle (to produce the alveolar bone). Together with the root cementum and the periodontal membrane, the alveolar bone proper constitutes the attachment apparatus of the teeth, the main function of which is to distribute forces generated by, for example, mastication and other tooth contacts.

Figure 1-72 shows a cross-section through the alveolar process (pars alveolaris) of the maxilla at the mid-root level of the teeth. Note that the bone which covers the root surfaces is considerably thicker at the palatal than at the buccal aspect of the jaw. Anatomically, the walls of the sockets (alveolar bone proper; arrows), as well as the outer walls of the alveolar process are made up of *cortical bone. The* area enclosed by the cortical bone walls is occupied by *cancellous (spongy) bone*. Thus, the cancellous bone occupies most of the interdental septa but only a relatively small portion of the buccal and palatal bone walls. The cancellous bone contains *bone trabeculae,* the architecture and size of which are partly genetically determined and partly the result of the forces to which the teeth are exposed during function. Note how the bone on the buccal and palatal aspects of the alveolar process varies in thickness from one region to another.

Figure 1-73 shows cross-sections through the mandibular alveolar process at levels corresponding to the coronal (Fig. 1-73a) and apical (Fig. 1-73b) thirds of the roots. The bone lining the wall of the sockets

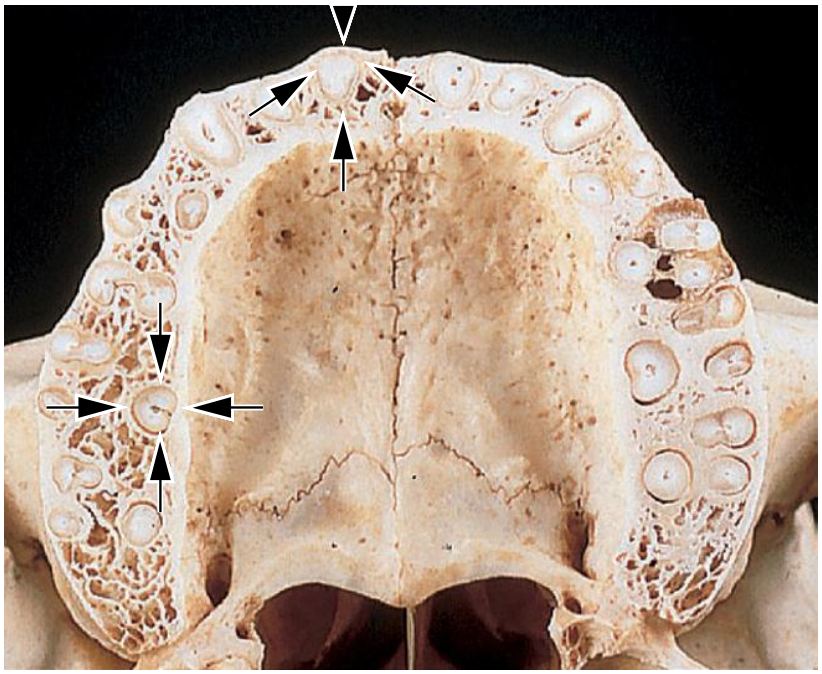

Fig. 1-72

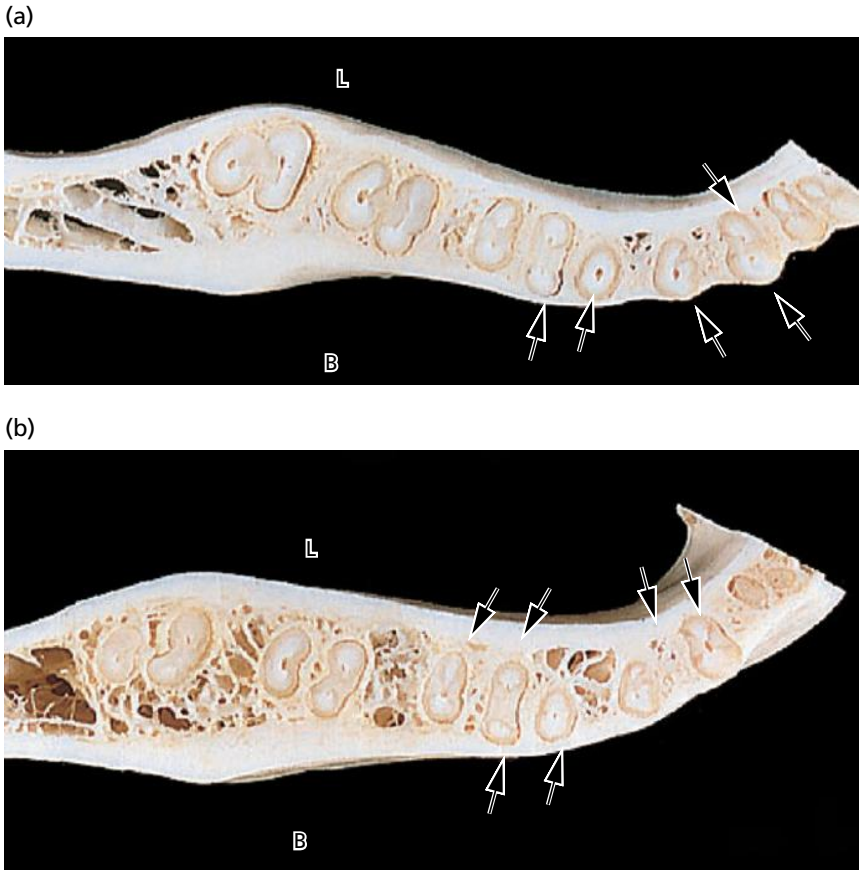

Fig. 1-73

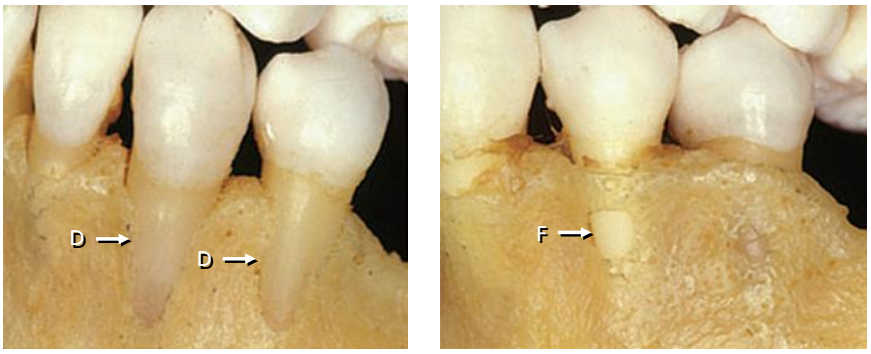

Fig. 1-74

(alveolar bone proper) is often continuous with the compact or cortical bone at the lingual (L) and buccal (B) aspects of the alveolar process (arrows). Note how the bone on the buccal and lingual aspects of the alveolar process varies in thickness from one region to another. In the incisor and premolar regions, the bone plate at the buccal aspects of the teeth is considerably thinner than at the lingual aspect. In the molar region, the bone is thicker at the buccal aspect than at the lingual aspect.

Figure 1-74 At the buccal aspect of the jaws, the bone coverage of the roots is occasionally very thin or entirely missing. An area without bone coverage in the marginal portion of the root is called *dehiscence* (D). If some bone is present in the most coronal portion of the buccal bone but the defect is located more apically, it is denoted *fenestration* (F). These defects often occur where a tooth during eruption is displaced out of the arch and are more frequent over anterior than posterior teeth. The root in such defects is covered only by a connective tissue attachment and overlying mucosa.

Figure 1-75 shows vertical sections through various regions of the mandibular dentition. The bone wall at the buccal (B) and lingual (L) aspects of the teeth varies considerably in thickness, for example from the premolar to the molar region. Note, for instance, how

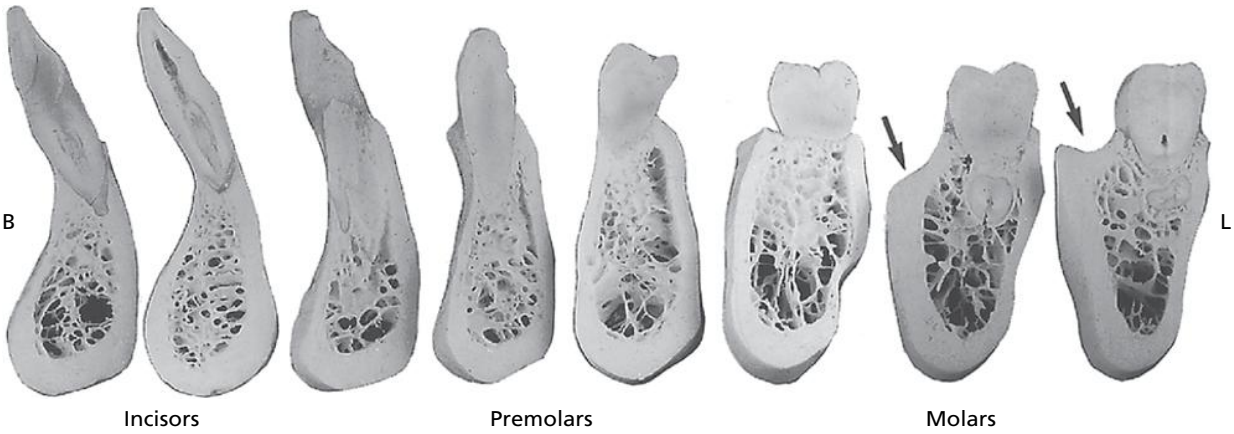

Fig. 1-75

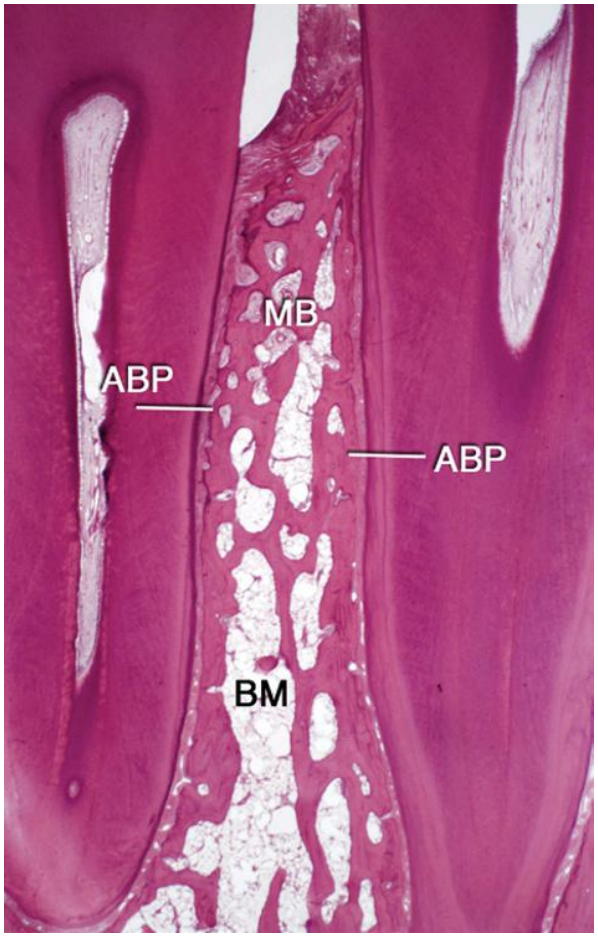

Fig. 1-76

the presence of the oblique line (*linea obliqua*) results in a shelf-like bone process (arrows) at the buccal aspect of the second and third molars.

Microscopic anatomy

Figure 1-76 illustrates a section through the interproximal septum between two premolars. Dense alveolar bone proper (ABP) is facing the periodontal ligament of the two teeth, while cancellous bone occupies the area between the alveolar bone proper. The cancellous bone is comprised of mineralized bone (MB) and bone marrow (BM).

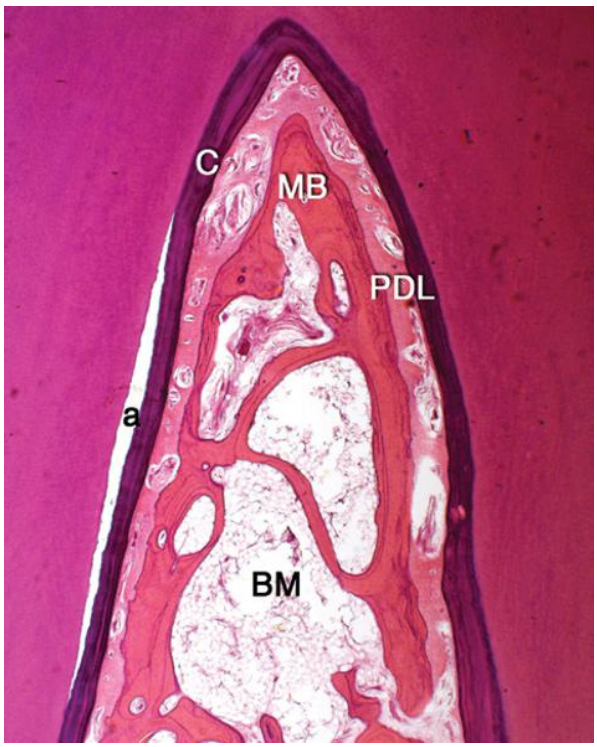

Fig. 1-77

Figure 1-77 The bone tissue within the furcation area of a mandibular molar (C, root cementum; PDL, periodontal ligament; MB, mineralized bone, BM, bone marrow; a, artifact). The mineralized bone in the furcation, as well as in the septum (Fig. 1-76), is made up of lamellar bone (including circumferential lamellae, concentric lamellae osteons, and interstitial lamellae), while the bone marrow contains adipocytes, vascular structures, and undifferentiated mesenchymal cells. Hydroxyapatite is the main mineral of the bone.

Figure 1-78 The mineralized bone facing the periodontal ligament, the alveolar bone proper (ABP) or the bundle bone, is about 250–500 µm wide. The alveolar bone proper is made up of lamellar bone including circumferential lamellae. The location of the alveolar bone proper in this image of a furcation area is indicated by the arrows. The alveolar bone (AB) is a tissue of mesenchymal origin and it is not

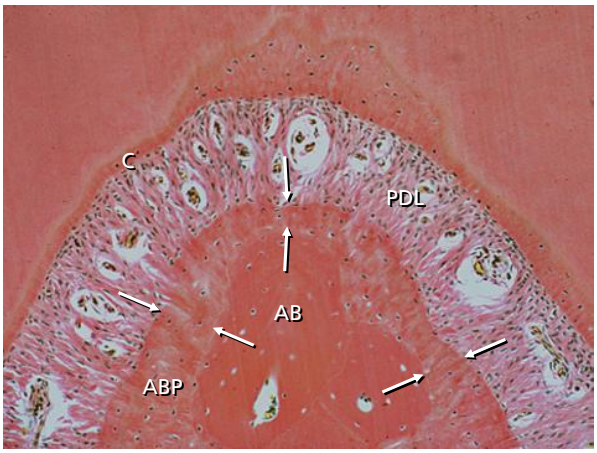

Fig. 1-78

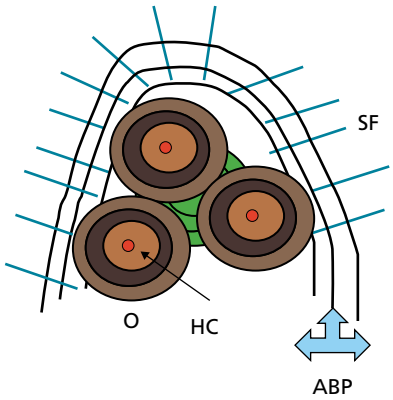

Fig. 1-79

considered as part of the genuine attachment apparatus. As stated above, alveolar bone proper, together with the periodontal ligament (PDL) and the cementum (C), is responsible for the attachment between the tooth and the skeleton. Both alveolar bone and alveolar bone proper may, as a result of altered functional demands, undergo adaptive changes.

Figure 1-79 The schematic drawing illustrates the composition of the hard tissue of the furcation area. The lamellar bone includes three brown osteons (O) with a blood vessel (red) in the centrally located Haversian canal (HC). An interstitial lamella (green) is located between the osteons (O) and represents an old and partly remodeled osteon. The alveolar bone proper (ABP) lines the lamellae and is represented by the dark lines. Sharpey's fibers (SF) insert into the alveolar bone proper.

Figure 1-80 describes a portion of lamellar bone. The hard tissue at this site contains *osteons* (white circles) each of which harbors a blood vessel in the Haversian canal (HC). The space between the different osteons is filled with so-called interstitial lamellae. The osteons are not only structural but also metabolic units. Thus, the nutrition of the bone cells (osteoblasts, osteocytes, osteoclasts) is secured by the blood vessels in the Haversian canals and the vessels in the so-called Volkmann canals.

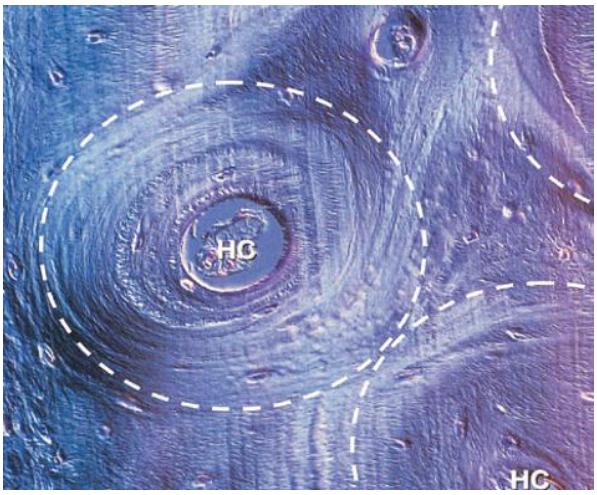

Fig. 1-80

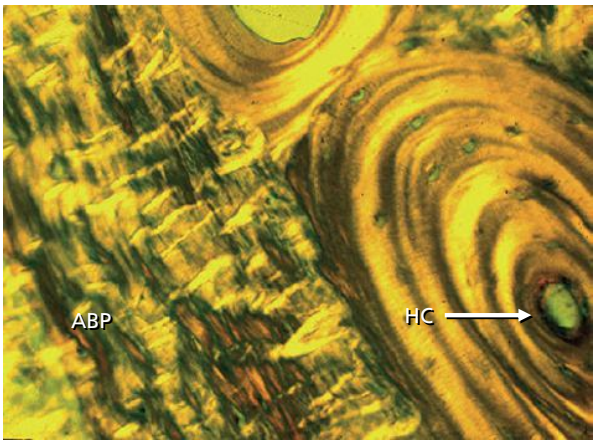

Fig. 1-81

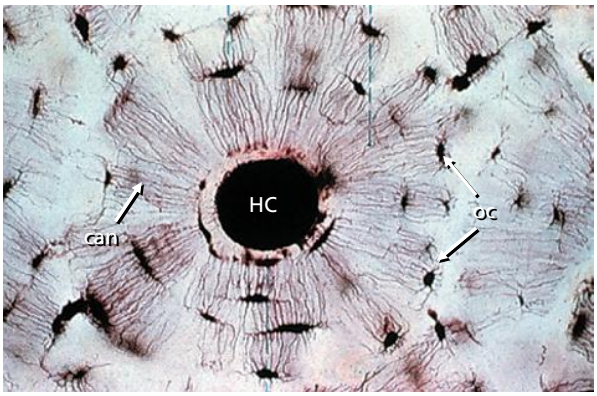

Fig. 1-82

Figure 1-81 The histologic section shows the borderline between the alveolar bone proper (ABP) and the alveolar bone that includes an osteon. The Haversian canal (HC) is in the center of the osteon. The alveolar bone proper (ABP) contains Sharpey's fibers (striations), which in lateral direction (left) extend into the periodontal ligament.

Figure 1-82 The osteon contains a large number of osteocytes (OC) that reside in lacunae within the lamellar bone. The osteocytes connect via canaliculi

(can) that contain cytoplasmic protrusions of the osteocytes. (HC, Haversian canal.)

Figure 1-83 The schematic drawing illustrates how osteocytes (OC) present in the mineralized bone also communicate with osteoblasts on the bone surface through canaliculi.

Figure 1-84 All active bone-forming sites harbor osteoblasts. The outer surface of the bone is lined by a layer of such osteoblasts which, in turn, are organized into a periosteum (P) that also contains densely packed collagen fibers. On the "inner surface" of the bone, that is in the bone marrow space, there is an endosteum (E), which has features similar to those of the periosteum.

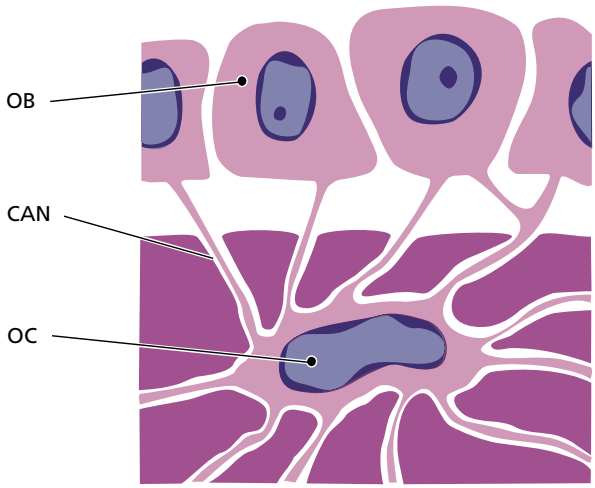

Fig. 1-83

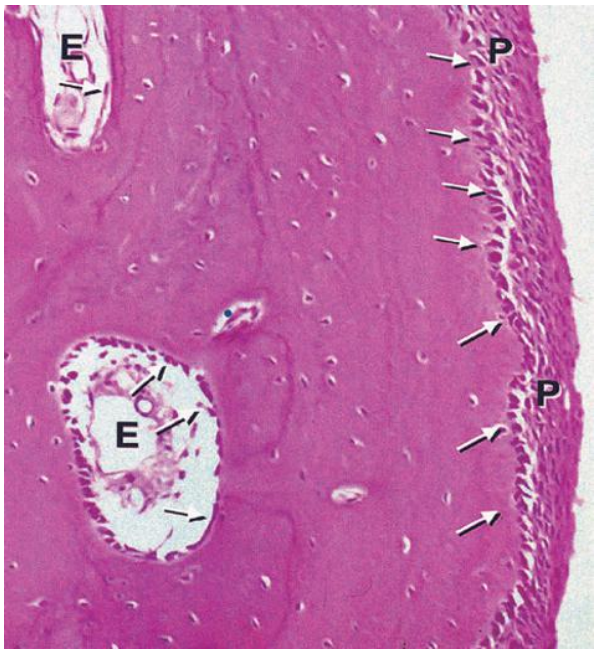

Fig. 1-84

Figure 1-85 shows an osteocyte residing in a lacuna in the bone. It can be seen that cytoplasmic processes radiate in different directions.

Figure 1-86 A schematic drawing showing how the long and delicate cytoplasmic processes of osteocytes (OC) communicate within the canaliculi (CAN) in the bone. The resulting canalicular–lacunar system is essential for cell metabolism by allowing diffusion of nutrients and waste products. The surface between the osteocytes, with their cytoplasmic processes on one side and the mineralized matrix on the other, is very large. It has been calculated that the interface

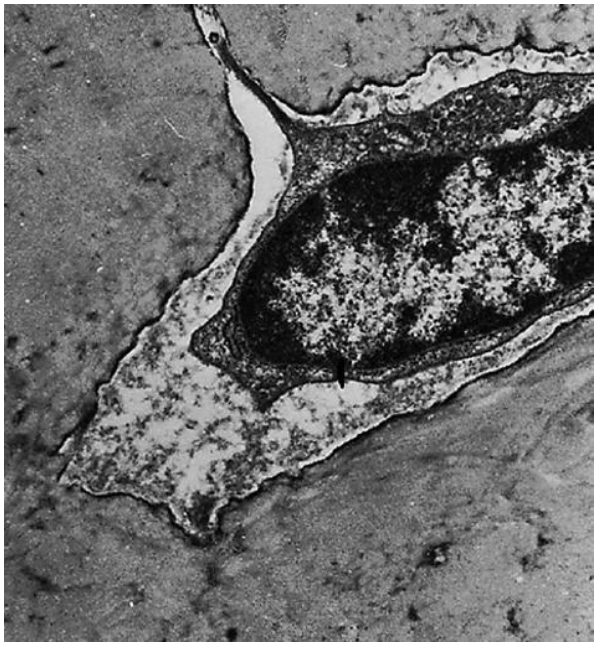

Fig. 1-85

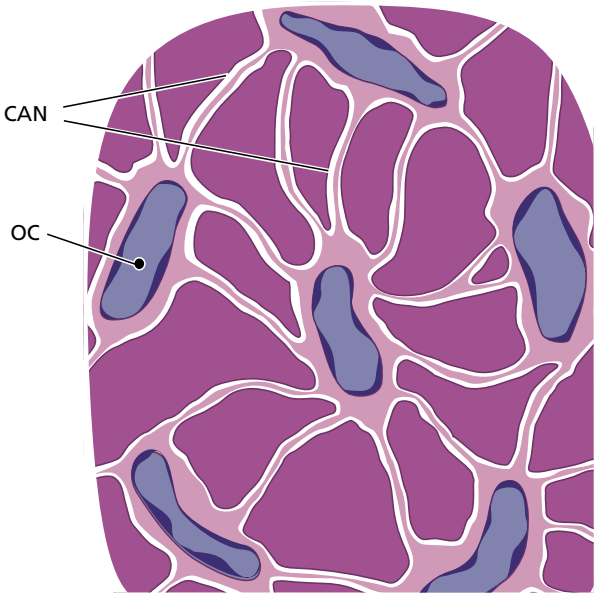

Fig. 1-86

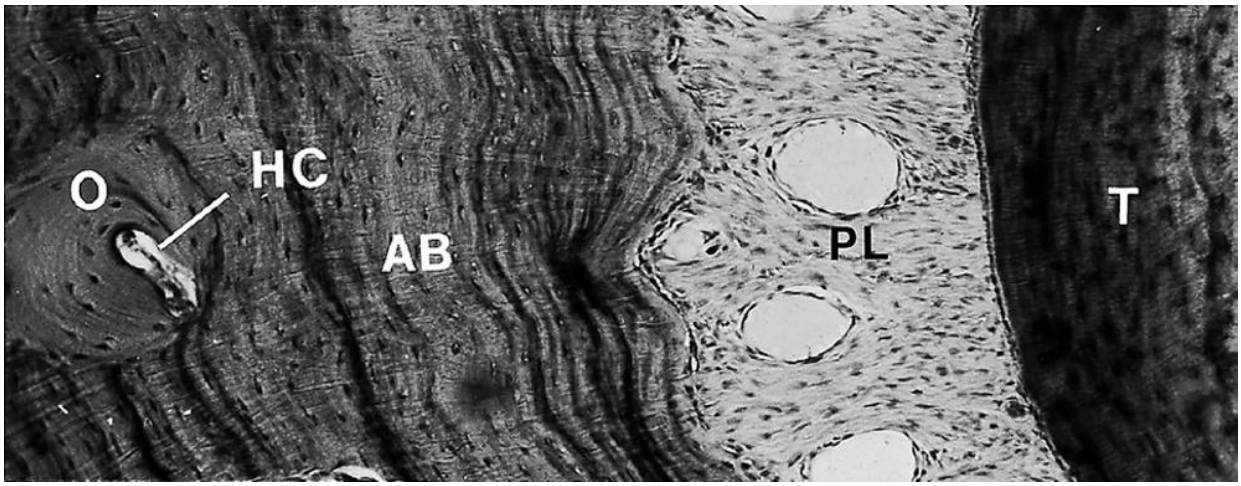

Fig. 1-87

between cells and matrix in a cube of bone, 10 × 10 × 10 cm, amounts to approximately 250 m^2. This enormous surface of exchange serves as a regulator for, for example, serum calcium and serum phosphate levels via hormonal control mechanisms.

Figure 1-87 The alveolar bone is constantly renewed in response to functional demands. The teeth erupt and migrate in a mesial direction throughout life to compensate for attrition. Such movement of the teeth implies remodeling of the alveolar bone. During the process of remodeling, the bone trabeculae are continuously resorbed and reformed, and the cortical bone mass is dissolved and replaced by new bone. During breakdown of the cortical bone, resorption canals are formed by proliferating blood vessels. Such canals, which contain a blood vessel in the center, are subsequently refilled with new bone by the formation of lamellae arranged in concentric layers around the blood vessel. A new Haversian system (O) is seen in the photomicrograph of a horizontal section through the alveolar bone (AB), periodontal ligament (PL), and tooth (T). (HC, Haversian canal.)

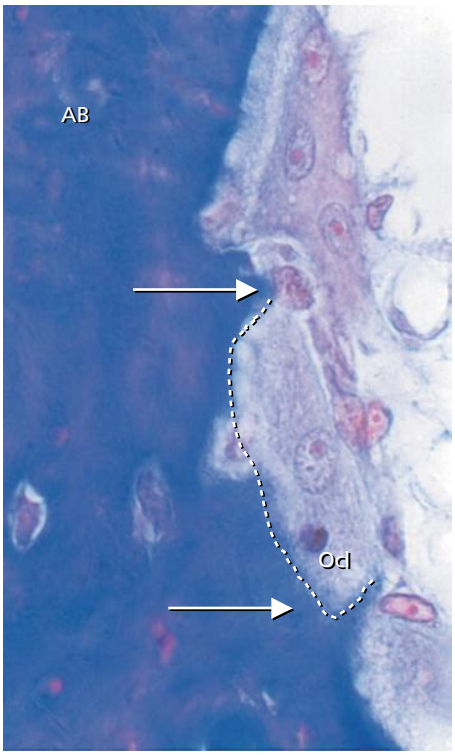

Fig. 1-88

Figure 1-88 The resorption of bone is always associated with *osteoclasts* (Ocl). These cells are large, multinucleated cells specialized in the breakdown of matrix and minerals. The osteoclasts are hematopoetic cells (derived from monocytes in the bone marrow). Hard tissue resorption occurs by the release of acid products (lactic acid, etc.), which form an acidic environment in which the mineral salts become dissolved. Remaining organic substances are eliminated by enzymes and osteoclastic phagocytosis. Actively resorbing osteoclasts adhere to the bone surface through receptors and produce lacunar pits called *Howship's lacunae* (dotted line). The osteoclasts are mobile and capable of migrating over the bone surface. The photomicrograph demonstrates osteoclastic activity (between arrows) at the surface of alveolar bone (AB).

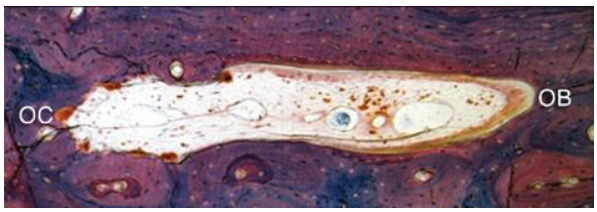

Fig. 1-89

Figure 1-89 Bone multicellular units are always present in bone tissue undergoing active remodeling. The bone multicellular unit has one resorption front (left) characterized by the presence of osteoclasts (OC) and one formation front (right) characterized by the presence of osteoblasts (OB).

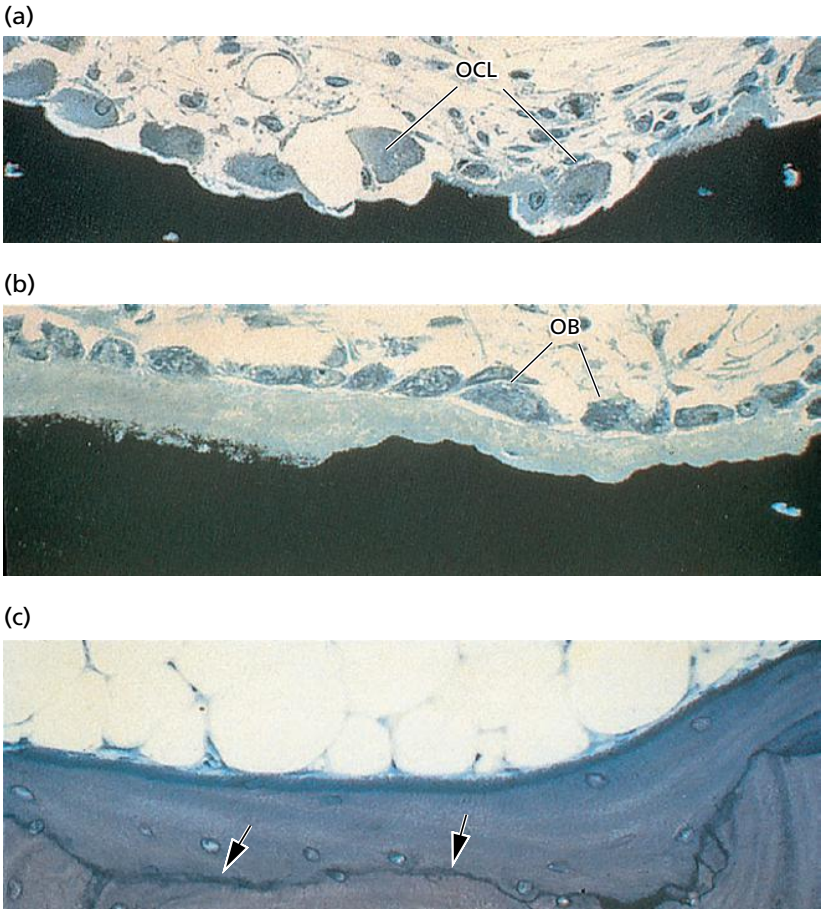

Fig. 1-90

Figure 1-90 Both the cortical and cancellous alveolar bone are constantly undergoing remodeling (i.e. resorption followed by formation) in response to tooth drifting and changes in functional forces acting on the teeth. Remodeling of the trabecular bone starts with resorption of the bone surface by osteoclasts (OCL) (Fig. 1-90a). After a short period, osteoblasts (OB) start depositing new bone (Fig. 1-90b) and finally a new bone multicellular unit is formed, clearly delineated by a reversal line (Fig. 1-90c, arrows).

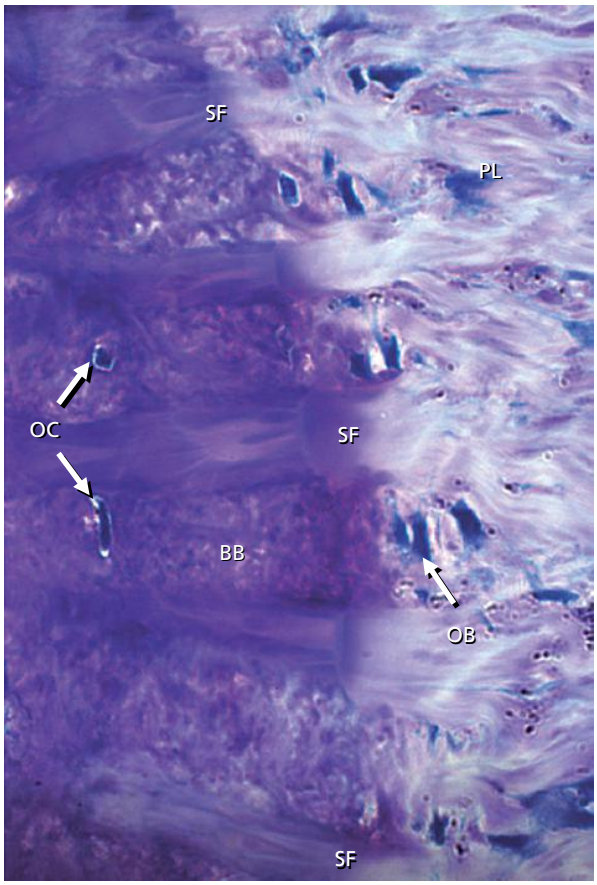

Fig. 1-91

Figure 1-91 Collagen fibers of the periodontal ligament (PL) insert in the mineralized bone which lines the wall of the tooth socket. This bone, called alveolar bone proper or bundle bone (BB), has a high turnover rate. The portions of the collagen fibers which are inserted inside the bundle bone are called Sharpey's fibers (SF). These fibers are mineralized at their periphery, but often have a non-mineralized central core. The collagen fiber bundles inserting in the bundle bone generally have a larger diameter and are less numerous than the corresponding fiber bundles in the cementum on the opposite side of the periodontal ligament. Individual bundles of fibers can be followed all the way from the alveolar bone to the cementum. However, despite being in the same bundle of fibers, the collagen adjacent to the bone is always less mature than that adjacent to the cementum. The collagen on the tooth side has a low turnover rate. Thus, while the

collagen adjacent to the bone is renewed relatively rapidly, the collagen adjacent to the root surface is renewed slowly or not at all. Note the occurrence of osteoblasts (OB) and osteocytes (OC).

Blood supply of the periodontium

Figure 1-92 The schematic drawing depicts the blood supply to the teeth and the periodontal tissues. The *dental artery* (a.d.), which is a branch of the *superior* or *inferior* alveolar artery (a.a.i.), dismisses the *intraseptal artery* (a.i.) before it enters the tooth socket. The terminal branches of the *intraseptal artery* (*rami perforantes*, rr.p.) penetrate the alveolar bone proper in canals at all levels of the socket (see Fig. 1-76). They anastomose in the periodontal ligament space, together with blood vessels originating from the apical portion of the periodontal ligament and with other terminal branches from the intraseptal artery (a.i.). Before the dental artery (a.d.) enters the root canal it puts out branches which supply the apical portion of the periodontal ligament.

Figure 1-93 The gingiva receives its blood supply mainly through *supraperiosteal* blood vessels which are terminal branches of the *sublingual artery* (a.s.), the *mental artery* (a.m.), the *buccal artery* (a.b.), the *facial artery* (a.f.), the *greater palatine artery* (a.p.), the *infra orbital artery* (a.i.), and the *posterior superior dental artery* (a.ap.).

Figure 1-94 depicts the course of the greater palatine artery (a.p.) in a monkey specimen which was perfused with plastic at sacrifice. Subsequently, the soft tissue was dissolved. The greater palatine artery, which is a terminal branch of the *ascending palatine artery* (from the *maxillary*, "internal maxillary", artery), runs through the *greater palatine canal* (arrow) to the palate. As this artery runs in a frontal direction, it puts out branches which supply the gingiva and the masticatory mucosa of the palate.

Figure 1-95 The various arteries are often considered to supply certain well-defined regions of the dentition. In reality, however, there are numerous anastomoses present between the different arteries. Thus, the *entire system of blood vessels*, rather than individual groups of vessels, should be regarded as the unit

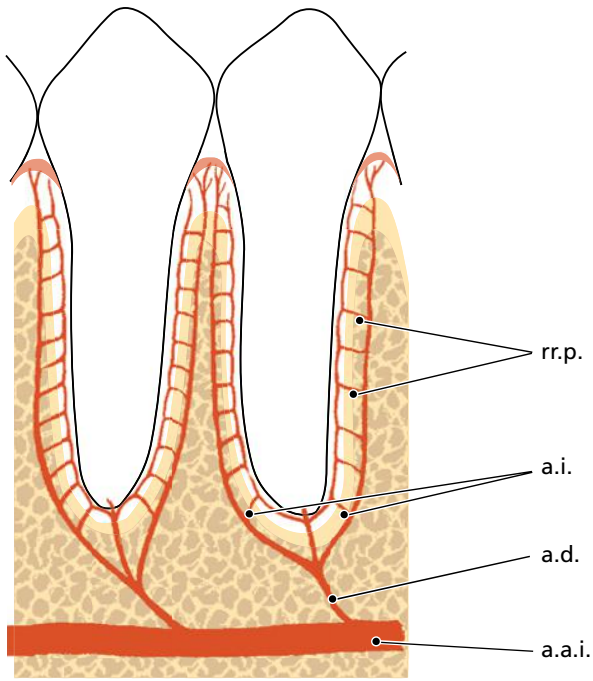

Fig. 1-92

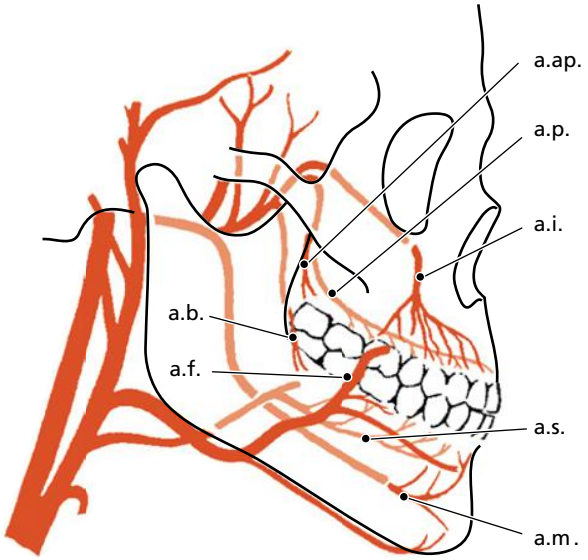

Fig. 1-93

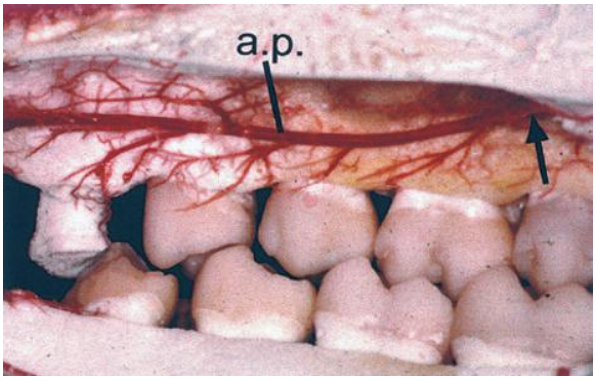

Fig. 1-94

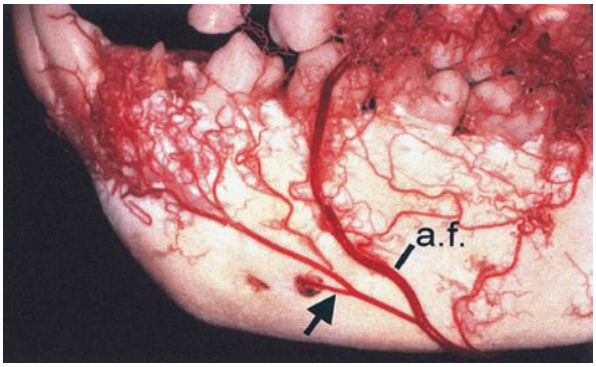

Fig. 1-95

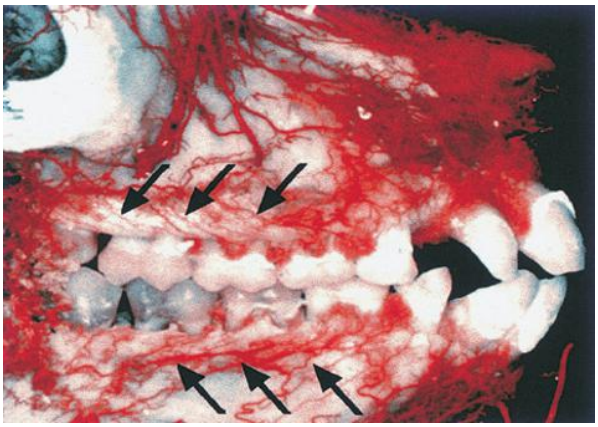

Fig. 1-96

Fig. 1-97

supplying the soft and hard tissue of the maxilla and the mandible, for example in this image there is an anastomosis (arrow) between the *facial artery* (a.f.) and the blood vessels of the mandible.

Figure 1-96 shows a vestibular segment of the maxilla and mandible from a monkey which was perfused with plastic at sacrifice. Note that the blood supply of the vestibular gingiva is mainly through *supraperiosteal* blood vessels (arrows).

Figure 1-97 Blood vessels (arrows) originating from vessels in the periodontal ligament pass the alveolar bone crest and contribute to the blood supply of the free gingiva.

Figure 1-98 shows a specimen from a monkey perfused with ink at the time of sacrifice. Subsequently, the specimen was treated to make the tissue transparent (cleared specimen). To the right, the supraperiosteal blood vessels (sv) can be seen. During their course towards the free gingiva, they put forth numerous branches to the *subepithelial plexus* (sp), located immediately beneath the oral epithelium of the free and attached gingiva. This subepithelial

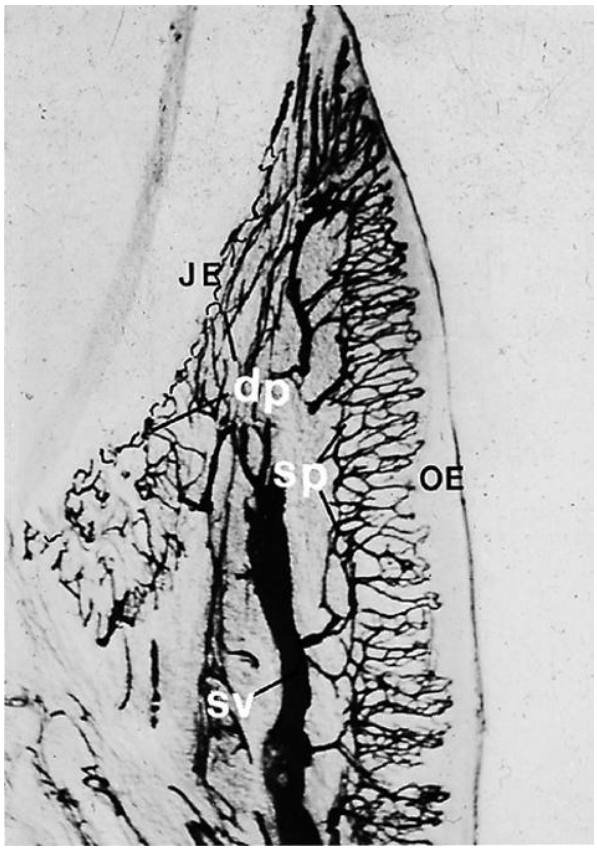

Fig. 1-98

plexus in turn yields thin *capillary loops* to each of the connective tissue papillae projecting into the oral epithelium (OE). The number of such capillary loops is constant over a very long time and is not altered by application of epinephrine or histamine to the gingival margin. This implies that the blood vessels of the lateral portions of the gingiva, even under normal circumstances, are fully utilized and that the blood flow to the free gingiva is regulated entirely by velocity alterations. In the free gingiva, the supraperiosteal blood vessels (sv) anastomose with blood vessels from the periodontal ligament and the bone. Beneath the junctional epithelium (JE), seen to the left, is a plexus of blood vessels termed the *dentogingival plexus* (dp). The blood vessels in this plexus have a thickness of approximately 40 µm, which means that they are mainly venules. In healthy gingiva, no capillary loops occur in the dento-gingival plexus.

Figure 1-99 This specimen illustrates how the subepithelial plexus (s.p.), beneath the oral epithelium of the free and attached gingiva, yields thin capillary loops to each connective tissue papilla. These capillary loops have a diameter of approximately 7 µm, which means they are the size of true capillaries.

Figure 1-100 shows the dentogingival plexus in a section parallel to the subsurface of the junctional epithelium. As can be seen, the dentogingival plexus consists of a fine-meshed network of blood vessels. In the upper portion of the image, capillary loops

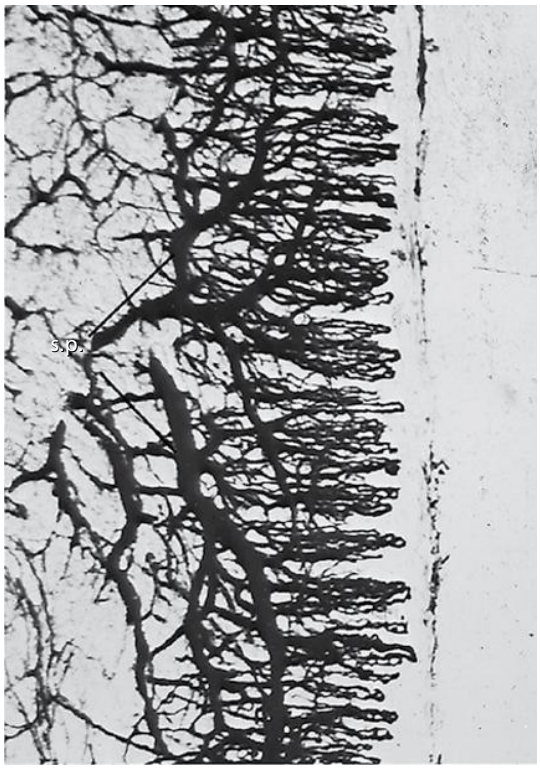

Fig. 1-99

Fig. 1-100

belonging to the subepithelial plexus can be seen beneath the oral sulcular epithelium.

Figure 1-101 is a schematic drawing of the blood supply to the free gingiva. As stated earlier, the main blood supply of the free gingiva derives from the *supraperiosteal* blood vessels (SV) which, in the gingiva, anastomose

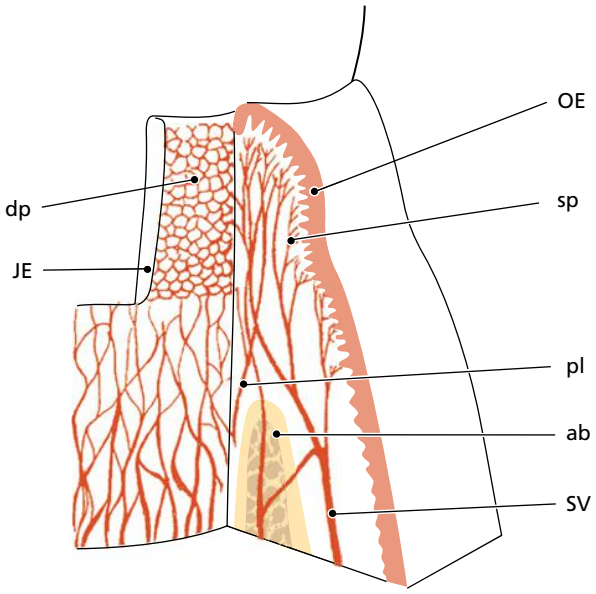

Fig. 1-101

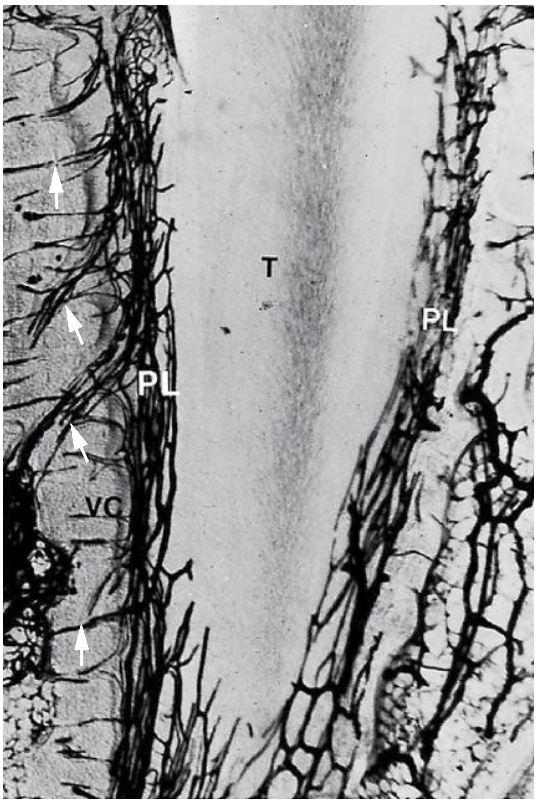

Fig. 1-102

with blood vessels from the *alveolar bone* (ab) and *periodontal ligament* (pl). To the right, the oral epithelium (OE) is depicted with its underlying subepithelial plexus of vessels (sp). To the left beneath the junctional epithelium (JE), the dentogingival plexus (dp) can be seen, which, under normal conditions, comprises a fine-meshed network without capillary loops.

Figure 1-102 shows a section prepared through a tooth (T) with its periodontium. Blood vessels (perforating rami; arrows) arising from the intraseptal

Fig. 1-103

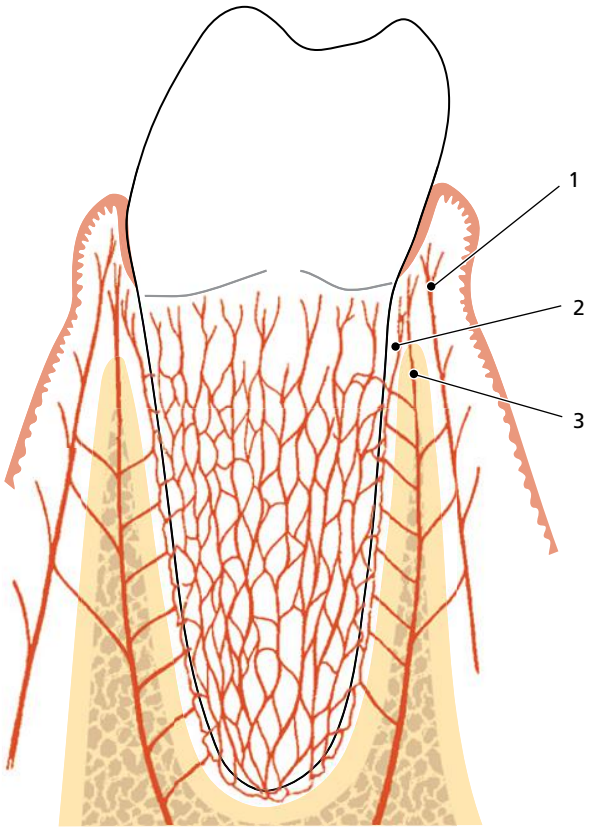

Fig. 1-104

artery in the alveolar bone run through canals (Volkmann's canals) in the socket wall (VC) into the periodontal ligament (PL), where they anastomose.

Figure 1-103 shows blood vessels in the periodontal ligament in a section parallel to the root surface. After entering the periodontal ligament, the blood vessels (perforating rami; arrows) anastomose and form a polyhedral network which surrounds the root like a stocking. The majority of the blood vessels in the periodontal ligament are found close to the alveolar bone. In the coronal portion of the periodontal ligament, blood vessels run in a coronal direction, passing the alveolar bone crest, into the free gingiva (see Fig. 1-97).

Figure 1-104 is a schematic drawing of the blood supply of the periodontium. The blood vessels in the periodontal ligament form a polyhedral network surrounding the root. Note that the free gingiva receives its blood supply from (1) supraperiosteal blood vessels, (2) the blood vessels of the periodontal ligament, and (3) the blood vessels of the alveolar bone.

Figure 1-105 illustrates schematically the so-called *extravascular* circulation through which nutrients and other substances are carried to the individual cells and metabolic waste products are removed from the

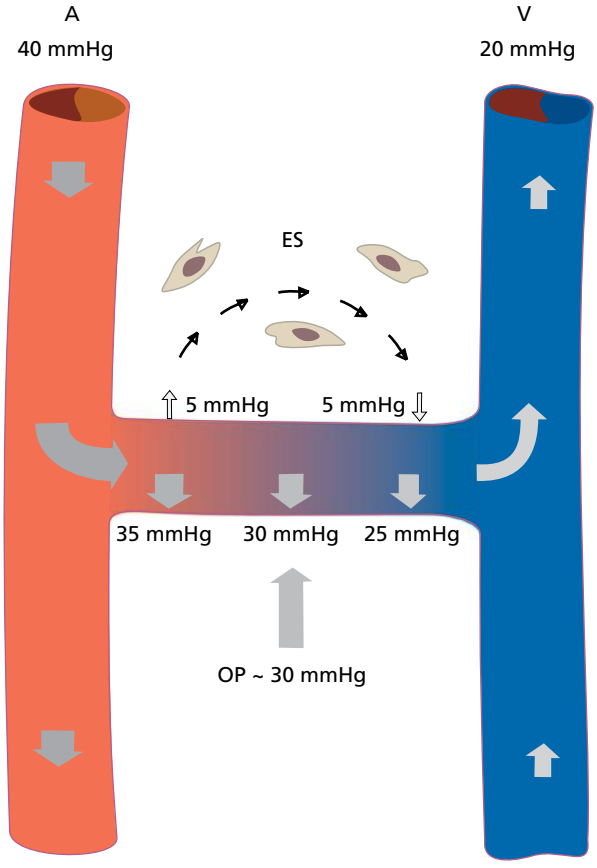

Fig. 1-105

tissue. In the arterial (A) end of the capillary, on the left, a hydraulic pressure of approximately 35 mmHg is maintained as a result of the pumping function of the heart. Since the hydraulic pressure is higher than the osmotic pressure (OP) in the tissue (approximately 30 mmHg), transportation of substances will occur from the blood vessels to the extravascular space (ES). In the venous (V) end of the capillary system, on the right, the hydraulic pressure has decreased to approximately 25 mmHg (i.e. 5 mmHg lower than the osmotic pressure in the tissue). This allows transportation of substances from the extravascular space to the blood vessels. Thus, the difference between the hydraulic pressure and the osmotic pressure results in transportation of substances from the blood vessels to the extravascular space in the arterial part of the capillary, while in the venous part, transportation of substances occurs from the extravascular space to the blood vessels. An extravascular circulation is hereby established (small arrows).

Lymphatic system of the periodontium

Figure 1-106 The smallest lymph vessels, the *lymph capillaries*, form an extensive network in the connective tissue. The wall of the lymph capillary consists of a single layer of endothelial cells. For this reason such capillaries are difficult to identify in an ordinary histologic section. The lymph is absorbed from the tissue fluid through the thin walls into the lymph capillaries. From the capillaries, the lymph passes into larger lymph vessels which are often in the vicinity of corresponding blood vessels. Before the lymph enters the blood stream, it passes through one or more *lymph nodes* in which the lymph is filtered and supplied with lymphocytes. The lymph vessels are like veins in that they have valves. The lymph from the periodontal tissues drains to the lymph nodes of the head and neck. The labial and lingual gingiva of the mandibular incisor region is drained to the *submental lymph nodes* (sme). The palatal gingiva of the maxilla is drained to the *deep cervical lymph nodes* (cp). The buccal gingiva of the maxilla and the buccal and lingual gingiva in the mandibular premolar–molar region are drained to *submandibular lymph nodes* (sma). Except for the third molars and mandibular incisors, all teeth with their adjacent periodontal tissues are drained to the submandibular lymph nodes. The third molars are drained to the *jugulodigastric lymph node* (jd) and the mandibular incisors to the *submental lymph nodes*.

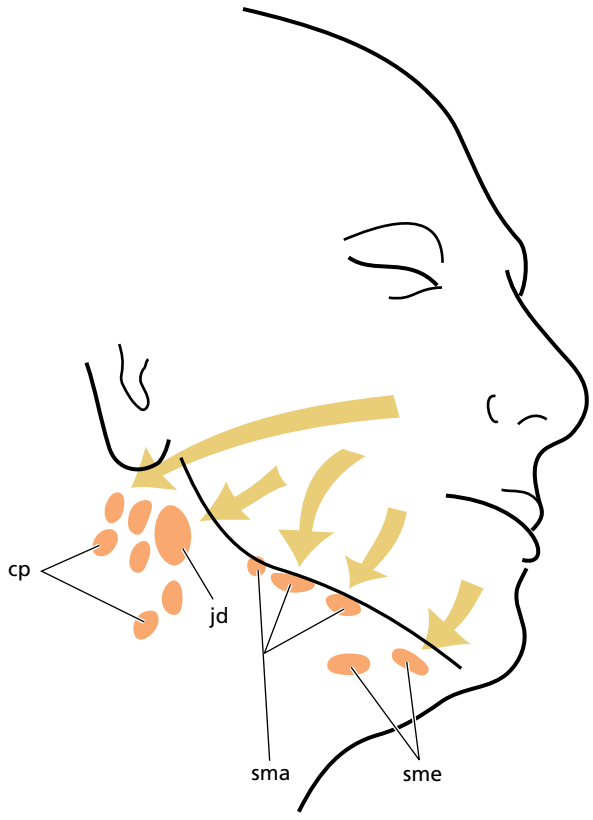

Fig. 1-106

Nerves of the periodontium

Like other tissues in the body, the periodontium contains receptors which record pain, touch, and pressure (*nociceptors* and *mechanoreceptors*). In addition to the different types of sensory receptors, nerve components are found innervating the blood vessels of the periodontium. Nerves recording pain, touch, and pressure have their trophic center in the *semilunar ganglion* and are brought to the periodontium via the *trigeminal nerve* and its end branches. Owing to the presence of receptors in the periodontal ligament, small forces applied on the teeth may be identified. For example, the presence of a very thin (10–30 µm) metal foil strip placed between the teeth during occlusion can readily be identified. It is also well known that a movement which brings the teeth of the mandible in contact with the occlusal surfaces of the maxillary teeth is arrested reflexively and altered into an opening movement if a hard object is detected in the chew. Thus, the receptors in the periodontal ligament, together with the proprioceptors in muscles and tendons, play an essential role in the regulation of chewing movements and chewing forces.

Figure 1-107 shows the various regions of the gingiva which are innervated by end branches of the trigeminal nerve. The gingiva on the labial aspect of maxillary incisors, canines, and premolars is innervated by *superior labial branches* from the *infraorbital nerve* (n. infraorbitalis) (Fig. 1-107a). The buccal gingiva in the maxillary molar region is innervated by branches from the *posterior superior dental nerve* (rr. alv. sup. post) (Fig. 1-107a). The palatal gingiva is innervated by the *greater palatal nerve* (n. palatinus major) (Fig. 1-107b), except for the area of the incisors, which is innervated by the *long sphenopalatine nerve* (n. pterygopalatini). The lingual gingiva in the

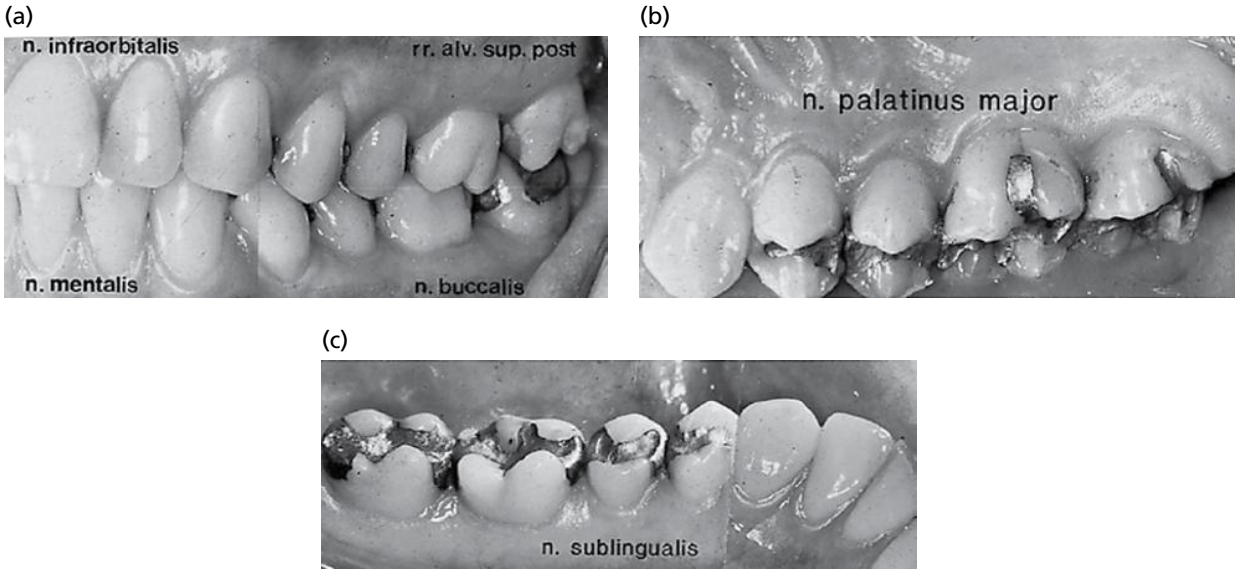

Fig. 1-107

Fig. 1-108

mandible is innervated by the *sublingual nerve* (n. sublingualis) (Fig. 1-107c), which is an end branch of the *lingual nerve*. The gingiva at the labial aspect of mandibular incisors and canines is innervated by the *mental nerve* (n. mentalis), and the gingiva at the buccal aspect of the molars by the *buccal nerve* (n. buccalis) (Fig. 1-107a). The innervation areas of these two nerves frequently overlap in the premolar region. The teeth in the mandible, including their periodontal ligament, are innervated by the *inferior alveolar nerve* (n. alveolaris inf.), while the teeth in the maxilla are innervated by the *superior alveolar plexus* (n. alveolares sup).

Figure 1-108 The small nerves of the periodontium follow almost the same course as the blood vessels. The nerves to the gingiva run in the tissue superficial to the periosteum and put out several branches to the oral epithelium on their way towards the free gingiva. The nerves enter the periodontal ligament through the perforations (Volkmann's canals) in the socket wall (see Fig. 1-102). In the periodontal ligament, the nerves join larger bundles which take a course parallel to the long axis of the tooth. The photomicrograph shows small nerves (arrows) which have emerged from larger bundles of ascending nerves in order to supply certain parts of the periodontal ligament tissue. Various types of neural terminations, such as free nerve endings and Ruffini's corpuscles, have been identified in the periodontal ligament.

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Chapter 2

Bone as a Living Organ

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Introduction

Bone is a complex organ composed of multiple specialized tissues (osseous, periosteum/endosteum, and bone marrow) that act synergistically and serve multiple functions (Fig. 2-1). Its composition allows the bone tissue to: (1) resist load, (2) protect highly sensitive organs from external forces, and (3) participate as a reservoir of cells and minerals that contribute to systemic homeostasis of the body. Therefore, the concept of "bone as a living organ" integrates the structurally dynamic nature of bone with its capacity to orchestrate multiple mechanical and metabolic functions with important local and systemic implications. Multiple factors exert an effect in this system (e.g. biochemical, hormonal, cellular, biomechanical) and will collectively determine its quality (Ammann & Rizzoli 2003; Marotti & Palumbo 2007; Bonewald & Johnson 2008; Ma *et al.* 2008). The purpose of this chapter is to provide the foundation knowledge of bone development, structure, function, healing, and homeostasis.

Development

During embryogenesis, the skeleton forms by either a direct or indirect ossification process. In the case of the mandible, maxilla, skull, and clavicle, mesenchymal progenitor cells condensate and undergo direct differentiation into osteoblasts, a process known as *intramembranous osteogenesis.*

In contrast, in the mandibular condyle, the long bones and vertebrae form initially through a cartilage template, which serves as an anlage that is gradually replaced by bone. The cartilage-dependent bone formation and growth process is known as *endochondral osteogenesis* (Ranly 2000) (Fig. 2-2).

Intramembranous bone formation

During intramembranous osteogenesis, an ossification center develops through mesenchymal condensation. As the collagen-rich extracellular matrix develops and matures, osteoprogenitor cells undergo further osteoblastic differentiation. On the outer surfaces of the ossification center, a fibrous periosteum forms over a layer of osteoblasts. As new osteoblasts form from the underside of the periosteum, appositional growth occurs. A subpopulation of osteoblasts becomes embedded in the mineralizing matrix and gives rise to the osteocyte lacunocanalicular network. Within the craniofacial complex, most bones develop and grow through this mechanism.

Endochondral bone growth

During endochondral osteogenesis, bones develop through the formation of a cartilaginous template (hyaline cartilage model) that mineralizes and is later

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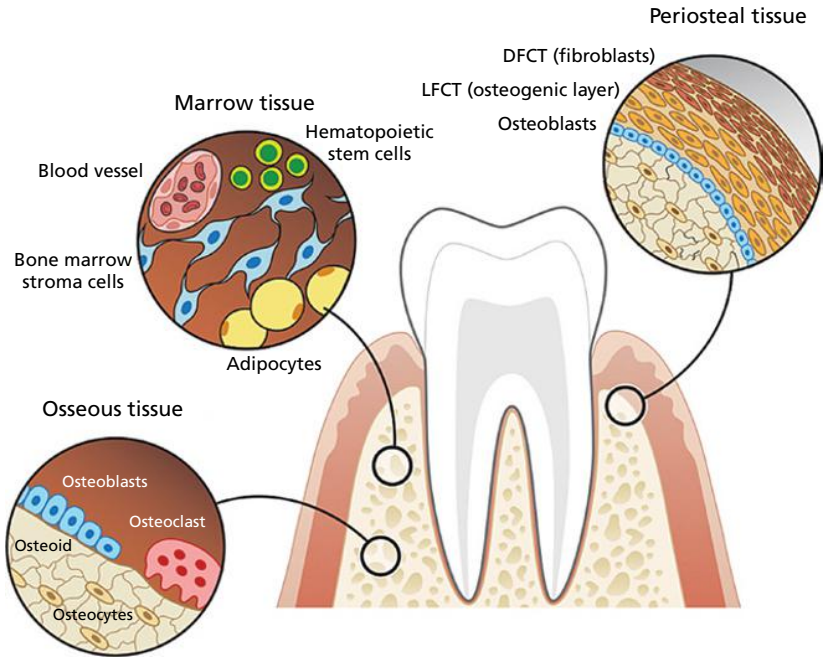


Fig. 2-1 Bone as an organ. The bone organ encompasses a number of complex tissues that synergize during health to execute a number of functions. It serves as a source of stem cells and a reservoir of minerals and other nutrients; it protects a number of delicate organs; and it acts as a mechanosensoring unit that adapts to the environment and individual demands. This figure highlights three main tissues, the cells that are involved in these roles, and the maintenance of the structure and function of bone as an organ. (DFCT, dense fibrous connective tissue; LFCT, loose fibrous connective tissue.)

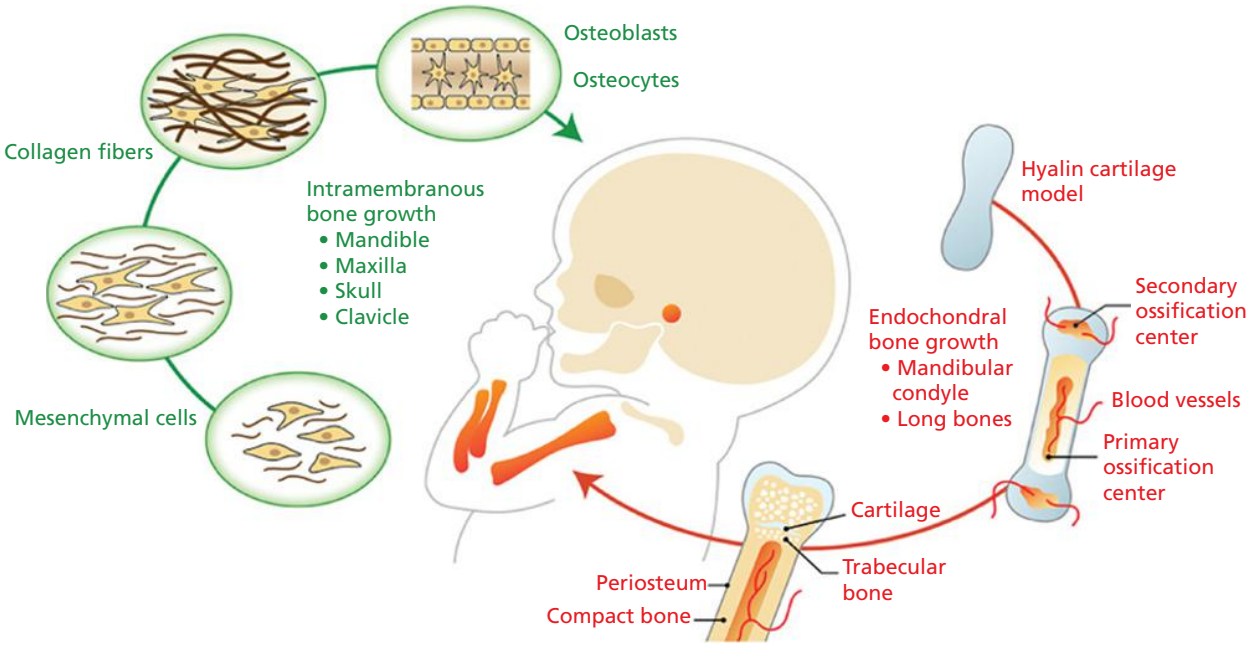


Fig. 2-2 Bone development. There are two types of processes involved in bone development: Intramembranous ossification (green arrow) and endochondral ossification (orange arrow). They primarily differ in the presence of a cartilaginous template during endochondral bone growth. During intramembranous osteogenesis, an ossification center develops through mesenchymal condensation. As the collagen-rich extracellular matrix develops and matures, osteoprogenitor cells undergo further osteoblastic differentiation. A subpopulation of osteoblasts becomes embedded in the mineralizing matrix and gives rise to the osteocyte lacunocanalicular network. Within the craniofacial complex, most bones develop and grow through this mechanism. On the other hand, long bones within the skeleton and the mandibular condyle initially develop through the formation of a cartilaginous template that mineralizes and is later resorbed by osteoclasts and replaced by bone. The endochondral bone growth process leads to the formation of primary and secondary ossification centers that are separated by a cartilaginous structure known as the growth plate. As bone develops and matures through these two processes, structurally distinct areas of compact bone and trabecular bone are formed and maintained through similar bone remodeling mechanisms.

resorbed by osteoclasts and replaced by bone that is laid down afterwards. This process begins during the third month of gestation. The endochondral bone growth process leads to the formation of primary and secondary ossification centers that are separated by a cartilaginous structure known as the growth plate. Following the formation of the primary ossification center, bone formation extends towards both ends of the bone from the center of the shaft. The cartilage cells on the leading edges of ossification die. Osteoblasts cover the cartilagenous trabeculae with woven, spongy bone. Behind the advancing front of ossification, osteoclasts absorb the spongy bone and enlarge the primary marrow cavity. The periosteal collar thickens and extends toward the epiphyses to compensate for the continued hollowing of the primary cavity.

The processes of osteogenesis and resorption occur in all directions. The spaces between the trabeculae become filled with marrow tissue. As the new bone matrix remodels, osteoclasts assist in the formation of primary medullary cavities which rapidly fill with bone marrow hematopoietic tissue. The fibrous, non-mineralized lining of the medullary cavity is the endosteum. Osteoblasts form in the endosteum and begin the formation of endosteal bone. The appositional growth of endosteal bone is closely regulated to prevent closure of the primary marrow cavities and destruction of bone marrow.

Structure

Osseous tissue

Osseous tissue is a specialized connective tissue composed of organic and inorganic elements that mineralizes and is populated by highly specialized cells that regulate its stability (Fig. 2-3a).

Matrix

The organic matrix of bone makes up approximately 30–35% of the total bone weight and is formed of 90% collagen type I and 10% non-collagenous proteins, proteoglycans, glycoproteins, carbohydrates,

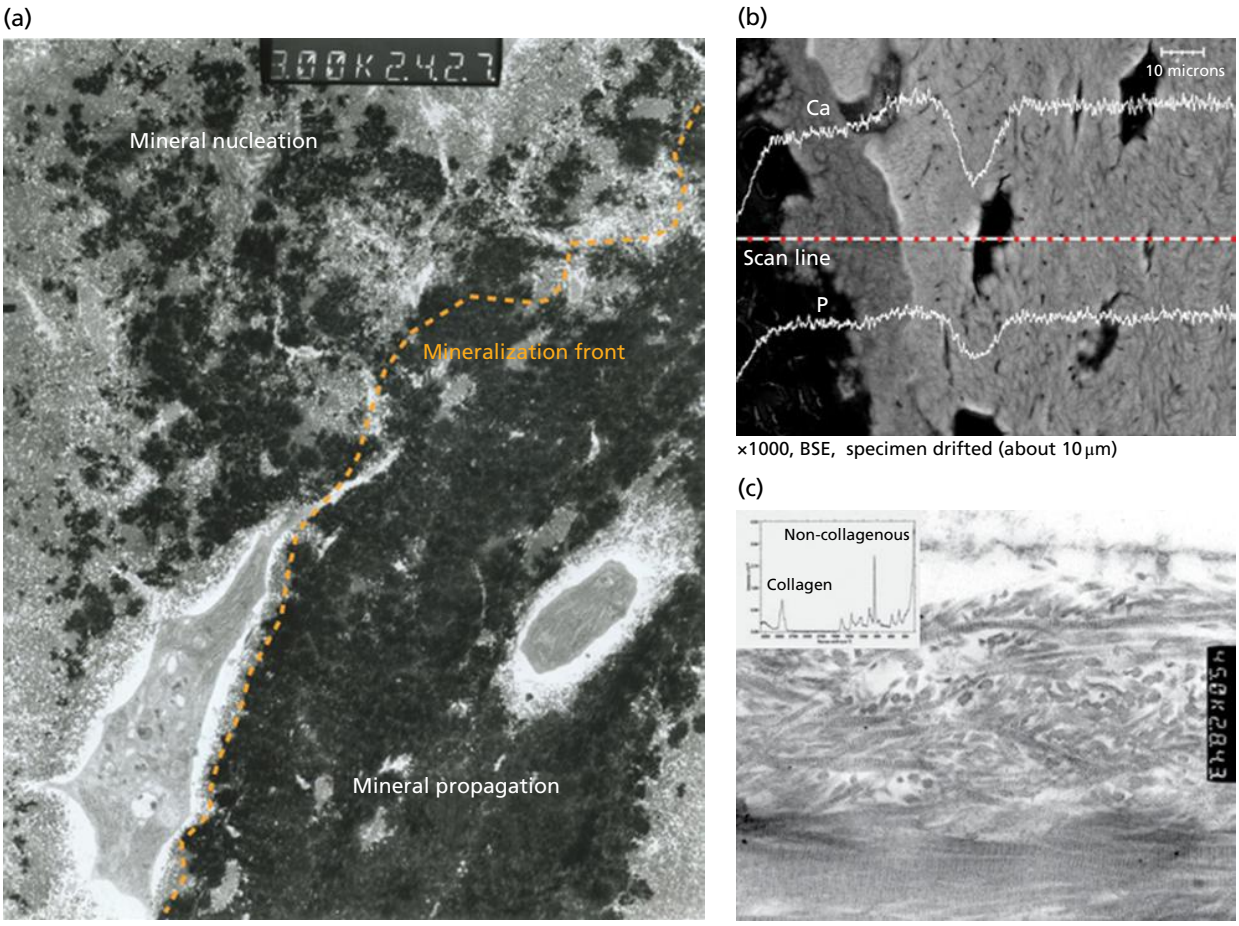


Fig. 2-3 Osseous matrix. The extracellular matrix in bone is particularly abundant as compared to its cellular counterpart. (a) Osseous matrix has the unique ability to mineralize: a process that requires the support of organic components and the assistance of highly specialized cells. (b) Calcium and phosphorus are present in the form of hydroxyapatite crystals. These crystals tend to follow the organic scaffold in the bone matrix. The orange dashed line represents a linear scan that emphasizes the high content of calcium and phosphorus in the mature bone, as shown by the energy dispersive X-ray spectroscopy analysis. (c) Collagen fibers as well as non-collangenous proteins are abundant in the matrix and are often found to be arranged in a preferential direction, as shown by the Raman spectroscopy.

and lipids. The organic matrix is synthesized by osteoblasts, and while it is still unmineralized, is known as osteoid. Within the collagen fibers, mineral nucleation occurs as calcium and phosphate ions are laid down and ultimately form hydroxyapatite crystals. Non-collagenous proteins along the surface of the collagen fibers assist in the propagation of the mineral and the complete mineralization of the matrix.

Inorganic components

Hydrated calcium and phosphate in the form of hydroxyapatite crystals [$3Ca_3(PO_4)_2(OH)_2$] are the principal inorganic constituent of the osseous matrix. Mineralization is clearly depicted in backscatter scanning electron imagines as a bright signal (Fig. 2-3b). Different degrees of mineralization are noticeable within the mature bone. Specific elements within the mineral can be further identified by energy-dispersive X-ray spectroscopy (EDS). In Fig. 2-3b, characteristic peaks of calcium and phosphorus are significantly pronounced in bone, as expected from their high content within the hydroxyapatite crystals.

Organic components

Bone is initially laid down as a purely organic matrix rich in collagen as well as in other non-collagenous molecules (Fig. 2-3c). Chemical analysis of bone by Raman spectroscopy clearly highlights this organic counterpart in the matrix. The transition from a purely organic matrix to a mineralized matrix is clearly depicted in the transmission electron micrograph in Fig. 2-3a as an osteocyte becomes embedded within the mineralized mature matrix. As the matrix matures, mineral nucleation and propagation is mediated by the organic components in the extracellular matrix. Figure 2-3a shows the aggregation of mineral crystals, forming circular structures. As the mineral propagates along the collagen fibrils, a clear mineralization front forms and clearly demarcates the transition between the osteoid area and the mature bone.

Mineralization

The initiation of the mineral nucleation within osteoid typically occurs within a few days of the laying down of calcium and phosphate ions, but maturation is completed through the propagation of the hydroxyapatite crystals over several months and as new matrix is synthesized (Fig. 2-3a). In addition to providing the bone with its strength and rigidity to resist load and protect highly sensitive organs, the mineralization of the osteoid allows the storage of minerals that contribute to systemic homeostasis.

Cells

Within bone, different cellular components can be identified. The distinct cell populations include osteogenic precursor cells, osteoblasts, osteoclasts, osteocytes, and hematopoietic elements of bone marrow. This chapter will focus on the three main functional cells that are ultimately responsible for the proper skeletal homeostasis.

Osteoblasts (Fig. 2-4)

Osteoblasts are the primary cells responsible for the formation of bone; they synthesize the organic extracellular matrix (ECM) components and control the mineralization of the matrix (Fig. 2-4a, b). Osteoblasts are located on bone surfaces exhibiting active matrix deposition and may eventually differentiate into two different types of cells: bone lining cells and osteocytes. Bone lining cells are elongated cells that cover a surface of bone tissue and exhibit no synthetic activity. The osteoblasts are fully differentiated cells and lack the capacity for migration and proliferation. Thus, for bone formation at a given site, undifferentiated mesenchymal progenitor cells, driven by the expression of a gene known as Indian hedgehog (*Ihh*) and later by *RUNX2*, and osteoprogenitor cells migrate to the site and proliferate to become osteoblasts (Fig. 2-4c). The determined osteoprogenitor cells are present in the bone marrow, in the endosteum, and in the periosteum that covers the bone surface. Such cells possess an intrinsic capacity to proliferate and differentiate into osteoblasts. The differentiation and development of osteoblasts from osteoprogenitor cells are dependent on the release of osteoinductive or osteopromotive growth factors (GFs), such as bone morphogenetic proteins (BMPs), and other growth factors, such as insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF).

Osteocytes (Fig. 2-5)

Osteocytes are stellate-shaped cells that are embedded within the mineralized bone matrix in spaces known as lacunae (Fig. 2-5a, b). They maintain a network of cytoplasmic processes known as dendrites (Fig. 2-5c). These osteocyte cytoplasmic projections extend through cylindrical encased compartments commonly referred to as canaliculi (Bonewald 2007). They extend to different areas and contact blood vessels and other osteocytes (Fig. 2-5d, e). The osteocyte network is therefore an extracellular and intracellular communication channel that is sensitive at the membrane level to shear stress caused by the flow of fluid within the canaliculi space as the result of mechanical stimuli and bone deformation. Osteocytes translate mechanical signals into biochemical mediators that will assist with the orchestration of anabolic and catabolic events within bone. This arrangement allows osteocytes to (1) participate in the regulation of blood calcium homeostasis and (2) sense mechanical loading and transmit this information to other cells within the bone to further orchestrate osteoblast and osteoclast function (Burger *et al*. 1995; Marotti 2000). Different bone diseases and disorders affect the arrangement of the osteocyte lacunocanalicular system, causing significant alteration to this important cellular network (Fig. 2-6).

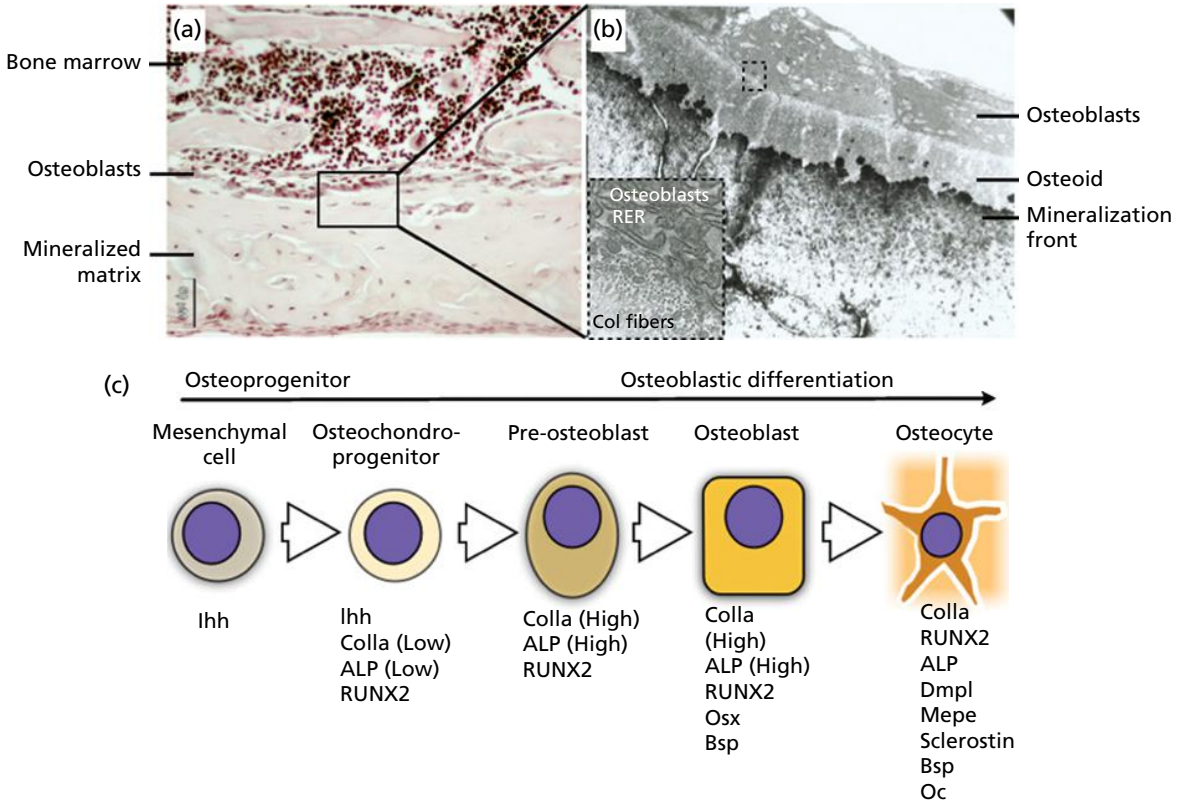


Fig. 2-4 Osteoblast. Osteoblasts are derived from bone marrow osteoprogenitor cells and are responsible for the synthesis of the immature bone matrix known as osteoid. (a) Group of osteoblasts that line the mature bone that contains cells embedded within the mineralized matrix. (b) Further detail of the osteoblasts lining the mature bone is clearly visualized with transmission electron microscopy (TEM). The abundant rough endoplasmic reticulum (RER) and Golgi apparatus within these cells reflect their high metabolic activity. (c) The key molecules involved in the differentiation of an osteoprogenitor cell through to a mature terminally differentiated osteocyte.

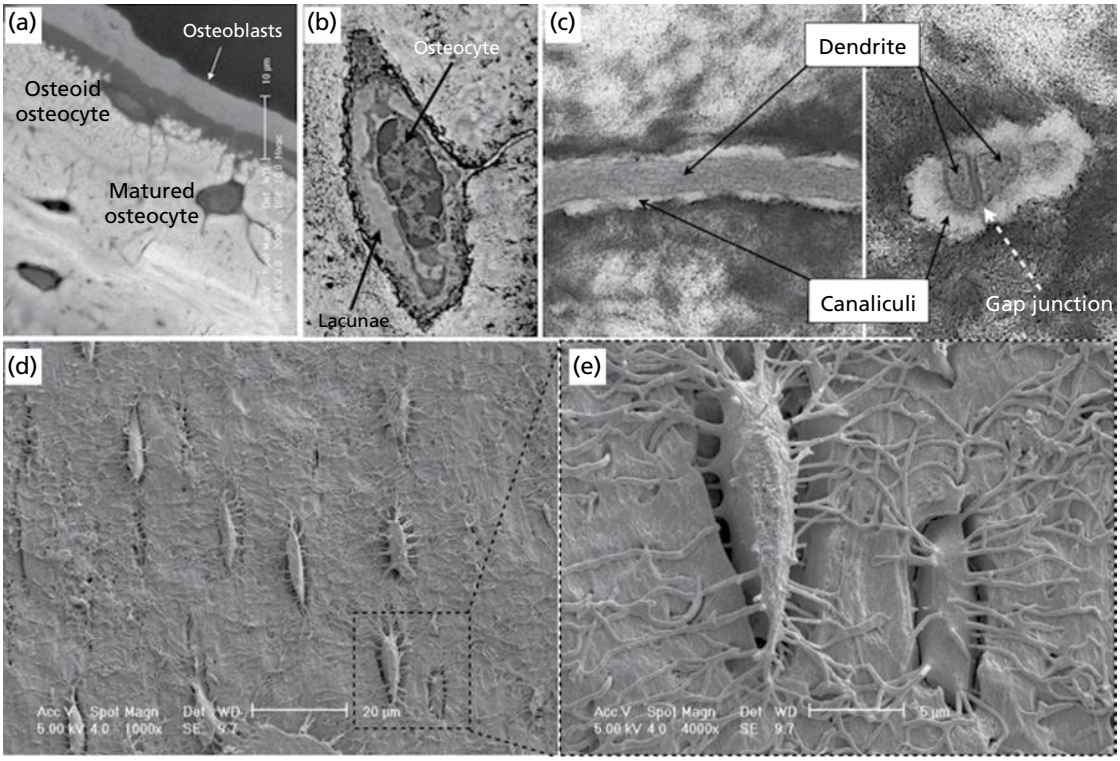


Fig. 2-5 Osteocytes. The osteocyte can be defined as the orchestrator of the remodeling process within bone. (a) As bone matrix is synthesized, a number of osteoblasts become embedded within the osteoid, which later mineralizes and resides in the mature matrix as osteocytes, as shown in this backscatter scanning electron micrograph (SEM) treated with osmium to allow the visualization of the cell. (b) Osteocytes reside within a well-defined space in bone known as the osteocyte lacuna. (c) Transmission electron micrograph of a dendrite within a canaliculi, showing the space through which fluid flows; the shear stress from this stimulates the surface of the osteocyte cell membrane. This unique biologic architectural characteristic of the osteocyte and the lacunocanalicular network represent the foundation that allows the conversion of mechanical stimuli into the biochemical signals necessary for bone homeostasis. (d and e) SEM of a casted lacunocanalicular network allows the visualization of the degree of connectivity between osteocytes and the regularly arranged canalicular structures.

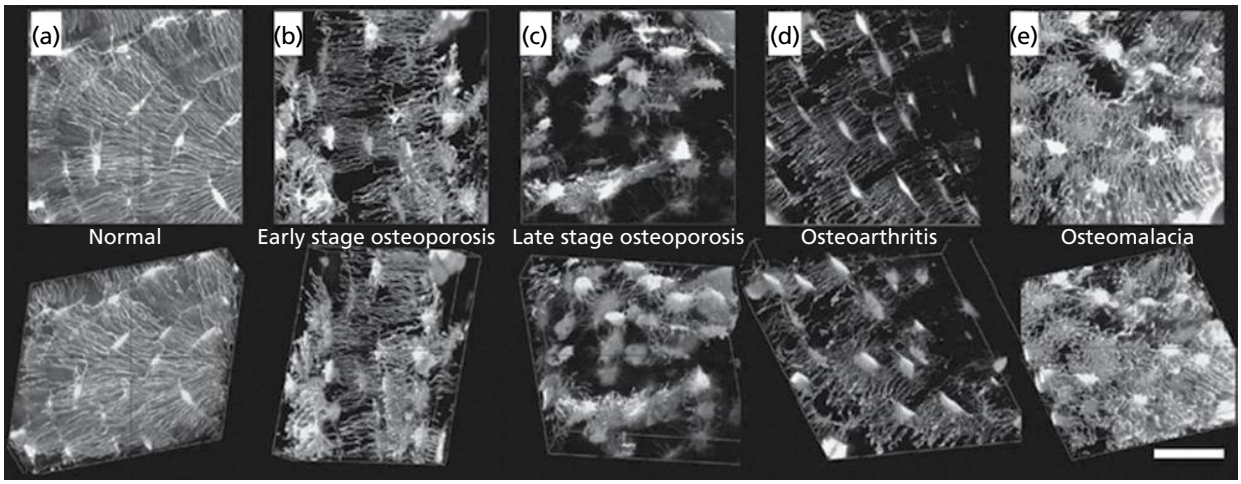


Fig. 2-6 Osteocytes: Lacunocanalicular system in disease. (a) In healthy bone, a high density osteocyte system is established throughout the mature matrix and is characterized by high cellular interconnectivity. With disease, the system is significantly disrupted, leading to important functional alterations. (b, c) In osteoporosis, osteocytic density changes and an apparent decrease in cellular interconnectivity is observed. (d) In osteoarthritis, the canalicular system is altered, but with no major lacunar changes. (e) In osteomalacia, the entire osteocyte lacunocanalicular system appears disrupted due to the altered mineralization pattern. (Source: Knothe Tate *et al*. 2004. Reproduced with permission from Elsevier.)

Osteoclasts

The bone formation activity is consistently coupled to bone resorption that is initiated and maintained by osteoclasts. These cells have the capacity to develop and adhere to bone matrix and then to secrete acid and lytic enzymes that degrade and break down the mineral and organic components of bone and calcified cartilage (Fig. 2-7a–c). The matrix degradation process results in the formation of a specialized extracellular compartment known as *Howship's lacuna* (Rodan 1992; Vaananen & Laitala-Leinonen 2008). Osteoclasts are specialized multinucleated cells that originate from the monocyte/macrophage hematopoietic lineage. The differentiation process is driven initially by the expression of the transcription factor PU-1. Macrophage colony-stimulating factor (M-CSF) engages osteoclasts in the differentiation pathway and promotes their proliferation and expression of RANKL. At this stage, RANKL-expressing stromal cells interact with preosteoclasts and further commit them to differentiation along the osteoclast lineage (Figs. 2-7d, 2-8).

Periosteal tissue

The periosteum is a fibrous sheath that lines the outer surface a long bone's shaft (diaphysis), but not the articulating surfaces. Endosteum lines the inner surface of all bones. The periosteum consists of dense irregular connective tissue. The periosteum is divided into a dense, fibrous, vascular layer (the "fibrous layer") and an inner, more loosely arranged, connective tissue inner layer (the "osteogenic layer") (see Fig. 2-1). The fibrous layer is mainly formed of fibroblasts, while the inner layer contains osteoprogenitor cells.

Osteoblasts derived from the "osteogenic layer" are responsible for increasing the width of long bones and the overall size of the other bone types. In the context of a fracture, progenitor cells from the periosteum differentiate into osteoblasts and chondroblasts, which are essential in the process of stabilizing the wound.

In contrast to the osseous tissue, the periosteum has nociceptive nerve endings, making it very sensitive to manipulation. It also allows the passage of lymphatics and blood vessels into and out of bone, providing nourishment. The periosteum anchors tendons and ligaments to bone by strong collagenous fibers in the "osteogenic layer", called Sharpey's fibers, which extend to the outer circumferential and interstitial lamellae. It also provides an attachment for muscles and tendons.

Bone marrow

The bone marrow consists of hematopoietic tissue islands, stromal cells, and adipose cells surrounded by vascular sinuses interspersed within a meshwork of trabecular bone (see Fig. 2-1). The bone marrow is the major hematopoietic organ, a primary lymphoid tissue (responsible for the production of erythrocytes, granulocytes, monocytes, lymphocytes, and platelets) and an important source of stem cells.

Types

There are two types of bone marrow: red marrow, which consists mainly of hematopoetic tissue, and yellow marrow, which is mainly made up of adipocytes. Erythrocytes, leukocytes, and platelets arise in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries. At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type; only around half of adult bone marrow is red. In cases of severe blood loss, the body can convert yellow marrow back to red marrow to increase blood cell production.

Cells

The stroma of the bone marrow is not directly involved in the primary function of hematopoiesis. However, it serves an indirect role by indirectly providing the

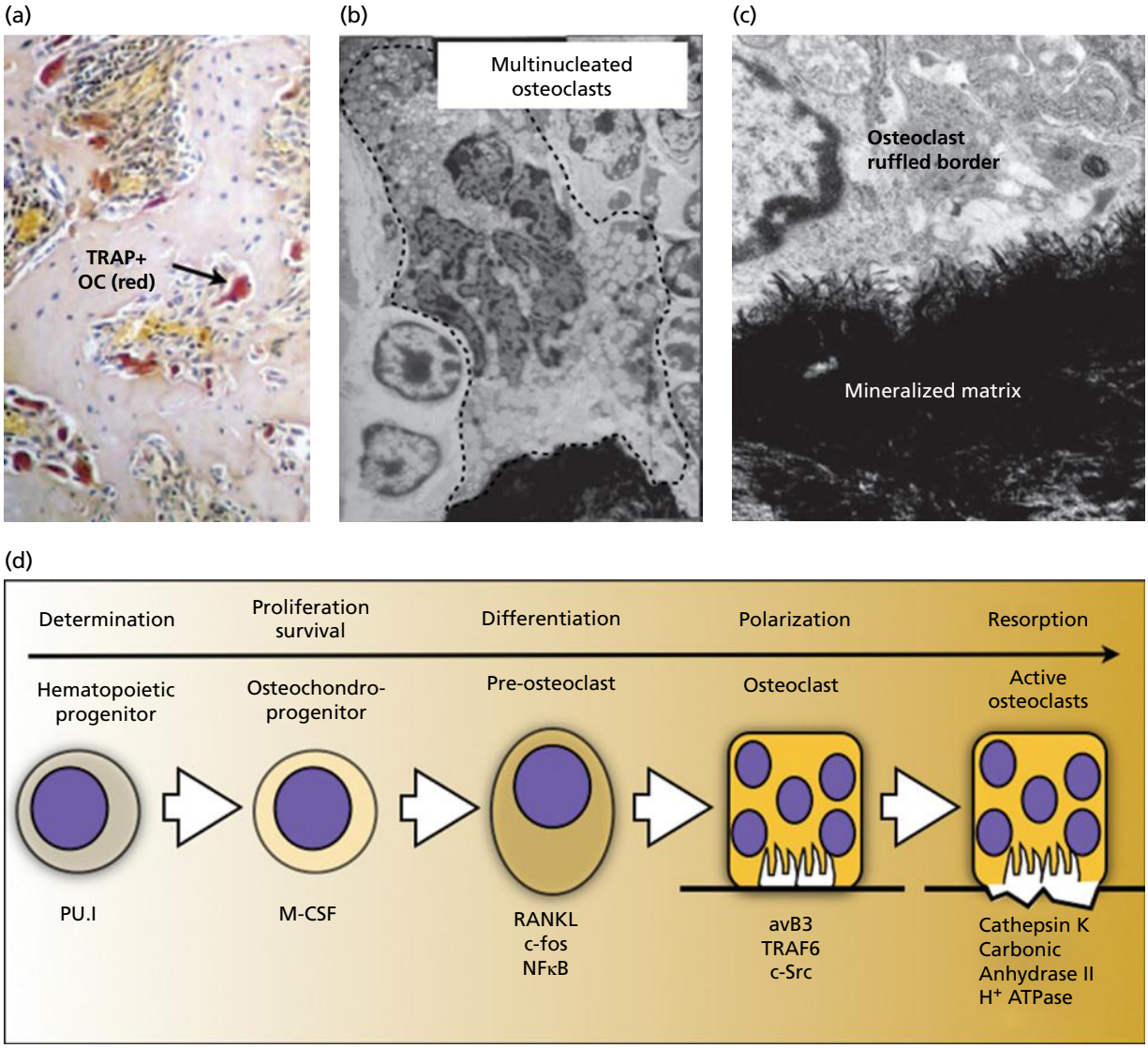


Fig. 2-7 Osteoclasts. (a) Histologically, osteoclasts can be depicted morphologically as multinucleated cells attached to bone matrix using special staining such as with the tartrate resistant acid phosphatase (TRAP) stain (arrow). (OC, osteoclast). (b) Transmission electron micrograph of a multinucleated osteoclast attached to the mineralized bone matrix is delineated by the dotted line. (c) Ruffled border at the resorbing end of the cells. (d) Osteoclasts are derived from cells of the macrophage/monocyte lineage and represent the bone resorbing units within the skeleton. The key molecules involved in the early events of differentiation of a hematopoietic progenitor through to a mature functional osteoclast are shown.

ideal hematopoietic microenvironment. For instance, it generates colony stimulating factors, which have a significant effect on hematopoiesis. Cells that constitute the bone marrow stroma are:

- Fibroblasts
- Macrophages
- Adipocytes
- Osteoblasts
- Osteoclasts
- Endothelial cells.

Stem cells

The bone marrow stroma contains mesenchymal stem cells (MSCs), also called *marrow stromal cells*. These are multipotent stem cells that can differentiate into a variety of cell types. MSCs have been shown to differentiate, *in vitro* or *in vivo*, into osteoblasts, chondrocytes, myocytes, adipocytes, and beta-pancreatic

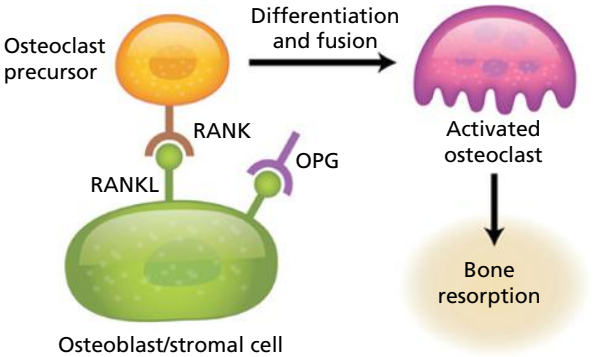


Fig. 2-8 Bone formation/resorption coupling. Bone formation and resorption processes are intimately linked. The osteoblastic/stromal cells provide an osteoclastogenic microenvironment by presenting RANKL to the osteoclast precursor, triggering their further differentiation and fusion, and leading to the formation of multinucleated and active osteoclasts. This process is modulated by inhibitors of these interactions such as osteoprotegerin (OPG). In addition, bone formation by osteoblasts depends on the preceding resorption by osteoclasts.

islet cells. MSCs can also transdifferentiate into neuronal cells. In addition, the bone marrow contains hematopoietic stem cells, which give rise to the three classes of blood cells that are found in the circulation: leukocytes, erythrocytes, and platelets.

Function

The main functions of bone are to provide locomotion, organ protection, and mineral homeostasis. Mechanical tension, local environment factors, and systemic hormones influence the balance between bone resorption and deposition. The distinct mechanical properties of bone contribute to its strength and ability to allow movement. In addition, an intricate series of interactions between cells, matrix, and signaling molecules maintains calcium and phosphorus homeostasis within the body, which also contributes to mechanical strength.

Mechanical properties

Bone is a highly dynamic tissue that has the capacity to adapt based on physiologic needs. Hence, bone adjusts its mechanical properties according to metabolic and mechanical requirements (Burr *et al*. 1985; Lerner 2006). As mentioned earlier, calcium and phosphorus comprise the main mineral components of bone in the form of calcium hydroxyapatite crystals. Hydroxyapatite regulates both the elasticity, stiffness, and tensile strength of bone. The skeletal adaptation mechanism is primarily executed by the processes of bone resorption and bone formation, referred to collectively as bone remodeling (Fig. 2-9). Bone is resorbed by osteoclasts, after which new bone is deposited by osteoblasts (Raisz 2005). From the perspective of bone remodeling, it has been proposed that osteoclasts recognize and are attracted to skeletal sites of compromised mechanical integrity, and initiate the bone remodeling process for the purpose of inducing the generation of new bone that is mechanically competent (Parfitt 1995, 2002).

In general, bone tissue responds to patterns of loading by increasing matrix synthesis, and altering composition, organization, and mechanical properties (Hadjidakis & Androulakis 2006). Evidence indicates that the same holds true for bone under repair. When bone experiences mechanical loading, osteoclast mechanoreceptors are directly stimulated, which begins the bone turnover process to regenerate and repair bone in the area. In addition, pressure increases M-CSF expression, increasing osteoclast differentiation in the bone marrow (Schepetkin 1997). Osteoclasts are also indirectly stimulated through osteoblasts and chondrocytes secreting prostaglandins in response to mechanical pressure. The extracellular matrix can also promote bone turnover through signaling. Mechanical deformation of the matrix induces electric potentials that stimulate osteoclastic resorption.

Bone strength is determined by a combination of bone quality, quantity, and turnover rate. It is well established that a loss of bone density, or quantity, decreases bone strength and results in increased fracture incidence. However, several pathologic conditions characterized by increased bone density, such as Paget's disease, are also associated with decreased bone strength and increased fracture incidence, so quality of bone is also an important factor in determining bone strength.

Metabolic properties

Calcium homeostasis is of major importance for many physiologic processes that maintain health (Bonewald 2002; Harkness & Bonny 2005). Osteoblasts deposit calcium by mechanisms including phosphate and calcium transport with alkalinization to absorb acid produced by mineral deposition; cartilage calcium mineralization occurs by passive diffusion

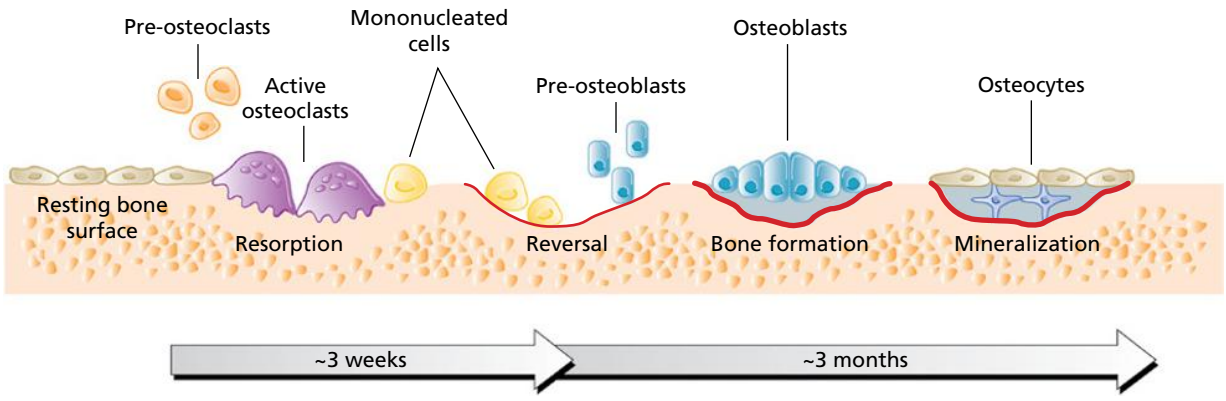


Fig. 2-9 Bone remodeling. The bone remodeling cycle involves a complex series of sequential steps that are highly regulated. The "activation" phase of remodeling is dependent on the effects of local and systemic factors on mesenchymal cells of the osteoblast lineage. These cells interact with hematopoietic precursors to form osteoclasts in the "resorption" phase. Subsequently, there is a "reversal" phase during which mononuclear cells are present on the bone surface. They may complete the resorption process and produce the signals that initiate bone formation. Finally, successive waves of mesenchymal cells differentiate into functional osteoblasts, which lay down matrix in the "formation" phase. (Source: McCauley & Nohutcu 2002. Reproduced from the American Academy of Periodontology.)

and phosphate production. Calcium mobilization by osteoclasts is mediated by acid secretion. Both bone-forming and bone-resorbing cells use calcium signals as regulators of differentiation and activity (Sims & Gooi 2008). This has been studied in more detail in osteoclasts: both osteoclast differentiation and motility are regulated by calcium.

Calcium is obtained from the diet even though bone is the major store of calcium and a key regulatory organ for calcium homeostasis. Bone, in major part, responds to calcium-dependent signals from the parathyroid glands and via vitamin D metabolites, although it responds directly to extracellular calcium if parathyroid regulation is lost. Serum calcium homeostasis is achieved through a complex regulatory process whereby a balance between bone resorption, absorption, and secretion in the intestine, and reabsorption and excretion by the kidneys is tightly regulated by osteotropic hormones (Schepetkin 1997). The balance of serum ionized calcium blood concentrations results from a complex interaction between parathyroid hormone (PTH), vitamin D, and calcitonin. Other osteotropic endocrine hormones that influence bone metabolism include thyroid hormones, sex hormones, and retinoic acids. In addition, fibroblast growth factor aids in phosphate homeostasis. Figure 2-10 reflects how input from the diet and from the bones and excretion via the gastrointestinal tract and urine maintain homeostasis.

Vitamin D is involved in the absorption of calcium, while PTH stimulates calcium release from the bone, reduces its excretion from the kidney, and assists in the conversion of vitamin D into its biologically active form (1,25-dihydroxycholecalciferol) (Holick 2007). Decreased intake of calcium and vitamin D and estrogen deficiency may also contribute to calcium deficiency (Lips *et al.* 2006). Hormonal factors such as retinoids, thyroid and steroid hormones are capable of passing through biologic membranes and interacting with intracellular receptors to have a major impact on the rate of bone resorption. Lack of estrogen increases bone resorption as well as decreases the formation of new bone (Harkness & Bonny 2005). Osteocyte apoptosis has also been documented in estrogen deficiency. In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition.

Circulating PTH regulates serum calcium and is released in conditions of hypocalcemia. PTH binds to osteoblast receptors, increasing the expression of RANKL and the binding of RANKL to RANK on osteoclasts (McCauley & Nohutcu 2002). This signaling stimulates bone remodeling by activating osteoclasts with the final goal of promoting calcium

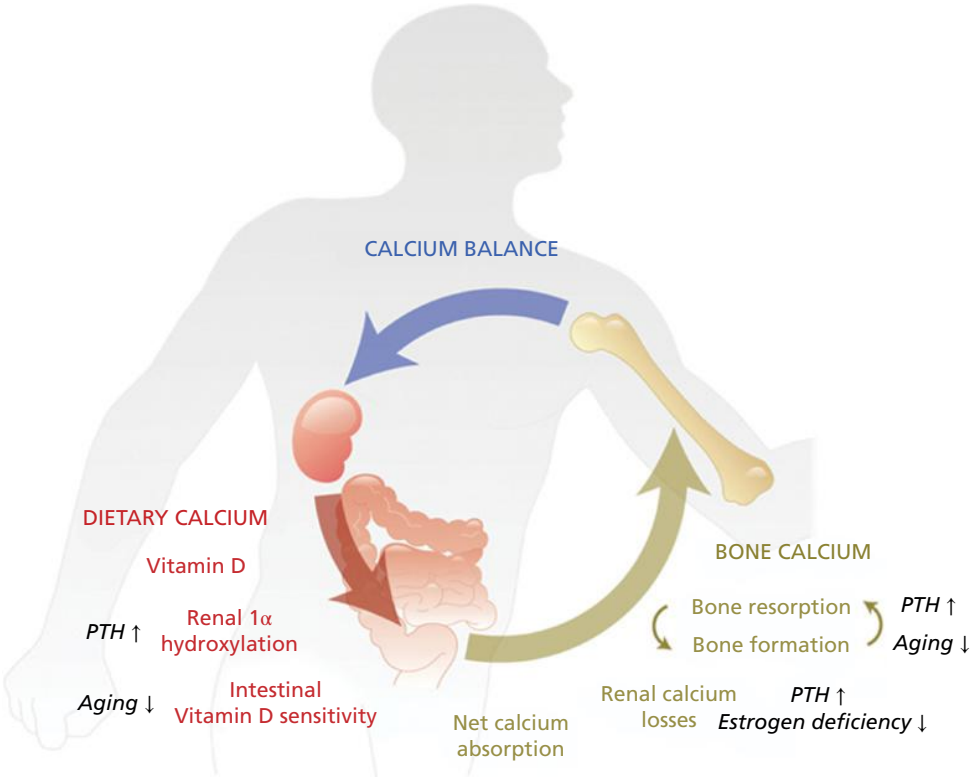


Fig. 2-10 Calcium and bone metabolism. Calcium homeostasis is of major importance for many physiologic processes that maintain health. The balance of serum ionized calcium blood concentrations results from a complex interaction between parathyroid hormone (PTH), vitamin D, and calcitonin. The figure reflects how input from the diet and from the bones, and excretion via the gastrointestinal tract and urine, maintain homeostasis. Vitamin D is involved in the absorption of calcium, while PTH stimulates calcium release from the bone, reduces its excretion from the kidney, and assists in the conversion of vitamin D into its biologically active form (1,25-dihydroxycholecalciferol). Decreased intake of calcium and vitamin D, and estrogen deficiency may also contribute to calcium deficiency.

release from bone. A secondary function of PTH is to increase calcium reabsorption from the kidney. When administered therapeutically at low, intermittent doses, PTH can act as an anabolic agent to promote bone formation, although the mechanism of this action is not well understood.

T cells produce calcitonin, a 32-amino acid peptide whose main physiologic role is the suppression of bone resorption. Calcitonin receptors are present in high numbers on osteoclasts and their precursors (Schepetkin 1997). Thus, calcitonin is able to act directly on osteoclast cells at all stages of their development to reduce bone resorption through preventing fusion of mononuclear preosteoclasts, inhibiting differentiation, and preventing resorption by mature osteoclasts (McCauley & Nohutcu 2002). The concentration and phosphorylation of calcitonin receptors decreases in the presence of calcitonin. As a result, the effect of calcitonin on osteoclasts is transient and thus is not used for clinical therapeutic applications.

Skeletal homeostasis

Healing

Healing of an injured tissue usually leads to the formation of a tissue that differs in morphology or function from the original tissue. This type of healing is termed *repair*. Tissue *regeneration*, on the other hand, is a term used to describe a healing that leads to complete restoration of morphology and function. The healing of bone tissue includes both regeneration and repair phenomena, depending on the nature of the injury.

Repair

Trauma to bone tissue, whether repeated stress or a single, traumatic episode, most commonly results in fracture. When bone is damaged, a complex and multistage healing process is immediately initiated in order to facilitate repair. Tissue and cell proliferation are mediated at different stages by carious growth factors, inflammatory cytokines, and signaling molecules. Although it is a continuous process, bone repair can be roughly divided into three phases: inflammation, reparative, and remodeling (Hadjidakis & Androulakis 2006).

The inflammation phase begins immediately after tissue injury and lasts for approximately 2 weeks (Fazzalari 2011). The initial step in the repair process is the formation of a blood clot. Cytokine release from injured cells then recruits inflammatory cells into the area, where macrophages begin phagocytosis of damaged tissue and cells. Osteoclasts begin the process of resorbing damaged bone in the area to recycle mineral components. In addition, cells from myeloid and mesenchymal cell lineages are recruited to the area where they begin to differentiate into osteoblasts and chondroblasts. At this point, the RANKL-to-osteoprotegerin (OPG) ratio is reduced.

The reparative phase is characterized by the formation of a soft callous where new bone matrix and cartilage scaffolding begins to form. Osteoblasts and chondroblasts produce a protein scaffold to create this callus, which is slowly mineralized to form a hard callus. The hard callus is composed of immature woven bone. The initiation of cartilage and periosteal woven bone formation is primarily mediated through early up-regulation of interleukin 6 (IL-6), OPG, vascular endothelial growth factor (VEGF), and BMPs (Fazzalari 2011). The process of soft to hard callus formation occurs approximately 6–12 weeks from the time of bone fracture.

In the final stage of repair, known as the remodeling phase, the bone matrix and cartilage are remodeled into mature bone. Woven bone is eventually converted into mature lamellar bone through normal bone turnover mediated by osteoblast–osteoclast coupling. Adequate vitamin D and calcium are critical for proper bone repair and their levels may, in part, dictate the rate of repair. The time for the remodeling stage varies depending upon individual bone metabolism, but usually require months from the time of injury.

Regeneration

Ideal bone healing promotes tissue formation in such a way that the original structure and function is preserved. This is in contrast to tissue repair, which merely replaces lost tissue with immature tissue and does not completely restore function.

Over time, bone sustains damage from mechanical strain, overloading, and other forms of tissue injury that results in microfractures and other defects in the bony architecture. In order to prevent greater injury, the bone undergoes a natural remodeling process to regenerate or renew itself. The turnover rates of individual bones is unique, although the average turnover rate is 10% (McCauley & Nohutcu 2002).

Regeneration of bone tissue involves the coupling of bone formation and resorption in a basic multicellular unit (BMU) (Sims & Gooi 2008) (Fig. 2-11). In this process, bone resorption by osteoclasts occurs first over a period of 3–4 weeks, along with cellular signaling to promote osteoblast recruitment to the area. Osteoblasts then form bone for a period of 3–4 months, with a quiescent period between bone resorption and formation, called the reversal phase. Trabecular bone undergoes a significantly higher degree of bone turnover than cortical bone (McCauley & Nohutcu 2002). In a rodent alveolar bone healing model, this process occurs more rapidly, allowing appreciation of the cellular and molecular events that occur during the maturation of the newly regenerated bone (Figs. 2-12, 2-13) (Lin *et al*. 2011).

Bone regeneration is a normal process, but in some cases there is a need to regenerate bone at an increased rate or to overcome the effects of pathologic bone disorders. Therapeutic strategies to promote bone

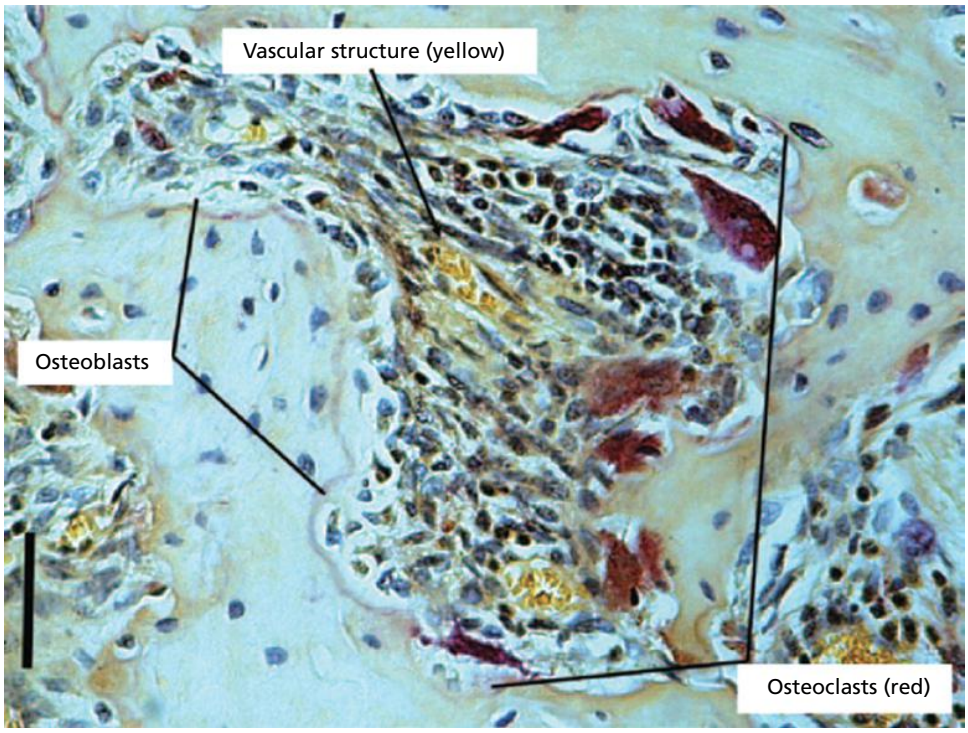


Fig. 2-11 Bone multicellular units (BMUs). Bone remodeling occurs in local groups of osteoblasts and osteoclasts called BMUs; each unit is organized into an osteoclast reabsorbing front, followed by a trail of osteoblasts reforming the bone to fill the defect left by osteoclasts. The red staining (tartrate acid phosphatase) highlights the resorption front. Note the increased number of multinucleated osteoclasts in this area.

regeneration include bone grafting from various sources, epithelial–occlusive barrier membranes, antiresorptive agents, anabolic agents, and growth factors to promote osteoblast differentiation and proliferation.

When alterations in bone turnover occur, skeletal homeostasis is disrupted, resulting in conditions of increased or decreased bone mineral density (BMD), or bone necrosis, and often accompanied by a decrease in bone strength. A wide variety of conditions can alter bone homeostasis and these include cancer, menopause, medications, genetic conditions, nutritional deficiencies, or infection. Some of these etiologies, such as vitamin D deficiency, are easily treatable, whereas others, such as genetic mutations, are typically treated through managing symptoms. Alterations in bone homeostasis cause a wide array of symptoms, including increased fracture incidence, bone pain, and other skeletal deformities that result in a high degree of morbidity and in some cases mortality. A brief review of the more common conditions is given below.

Disorders

Osteoporosis

Osteoporosis is a common condition characterized by both alterations in the macro- and micro-architecture of the bone (Fig. 2-14). There are multiple etiologies of this systemic disease, including post-menopausal, age-associated, glucocorticoid-induced, secondary to cancer, androgen ablation, and aromatase inhibitors (Kanis 2002). All forms result in reduced bone strength and increased fracture risk, accompanied by a high degree of morbidity and mortality.

Post-menopausal osteoporosis is the most common form of the disease and results from a decline in gonadal hormone secretion following menopause. Rapid loss of trabecular BMD and, to a lesser extent, cortical loss are common in this condition (Kanis 2002).

Diagnosis is made by comparing the BMD of a patient to that of a healthy 20–29-year-old adult of the same gender. Systemic BMD at least 2.5 standard deviations below the average, referred to as a T-score, is used by the World Health Organization (WHO) to define osteoporosis (WHO 1994). Osteopenia, a less severe form of the disease, is diagnosed when T-scores are between –1.0 and –2.5 (Fig. 2-15).

Osteopetrosis

Osteopetrosis is a group of related diseases in which there is a pronounced increase in BMD due to abnormal bone turnover, and in some ways this is the opposite of osteoporosis. These conditions are inherited and the mode of transmission varies from autosomal dominant to autosomal recessive. Increases in BMD in this patient population are due to a variety of defects in osteoclastic bone resorption. These include higher or lower osteoclast numbers, impaired differentiation, deficiencies in carbonic anhydrase, the ability to form a ruffled border, and alterations in signaling pathways (Stark & Savarirayan 2009). In most cases, it is the ability of the osteoclast to create an acidic environment in the lacunae to resorb bone

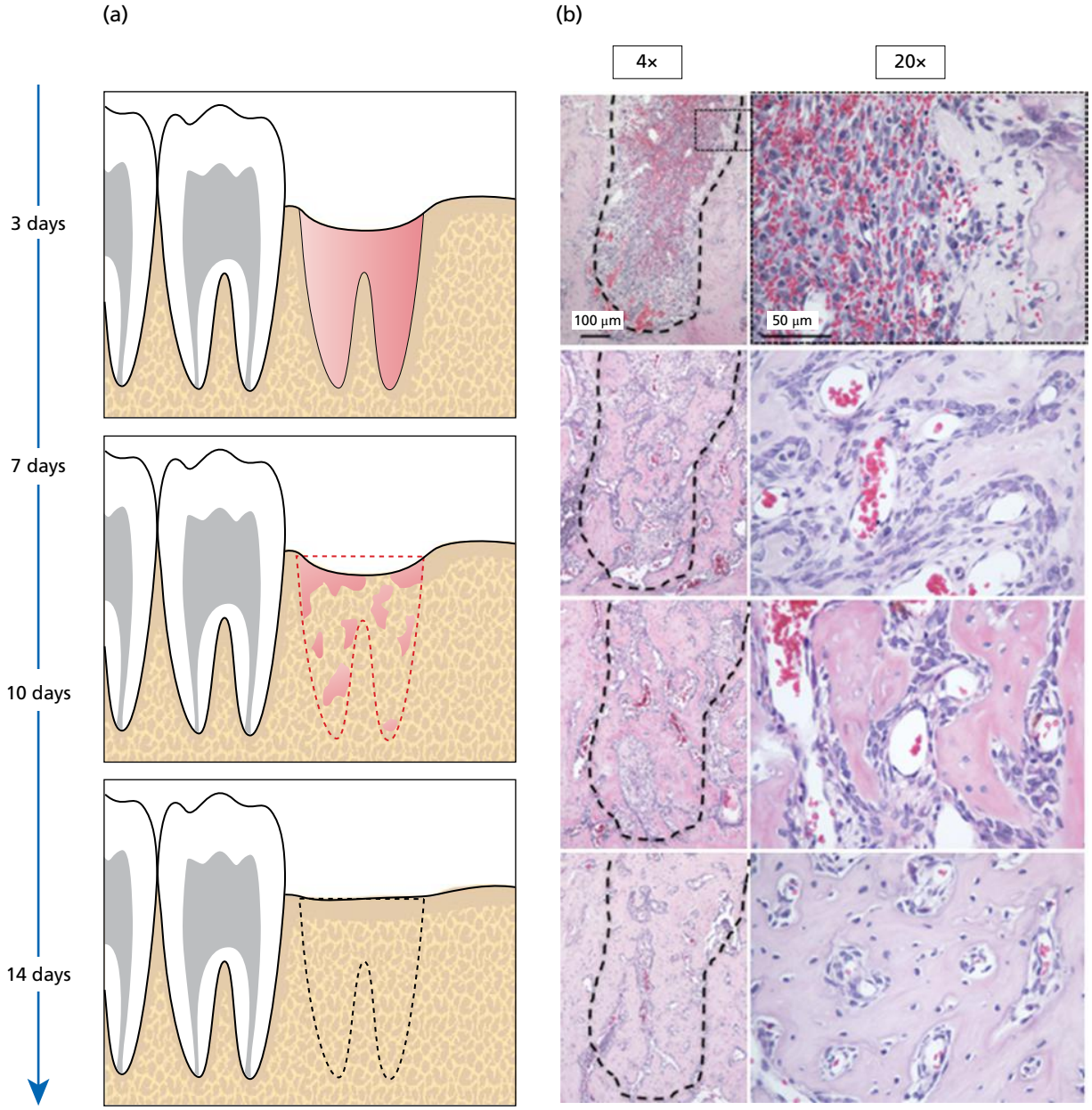


Fig. 2-12 Alveolar socket healing sites over time. (a) Rodent extraction model. Sequence of events that characterizes healing during the initial 14 days. (b) Hematoxylin and eosin (H&E) staining for tooth extraction site healing. The histologic images to the right of the healing area (black dashed lines) clearly capture the regeneration of the bone within the alveolar process. Note the clearly visible blood clot at day 3 (3d). At day 7 (7d), the cell density in the defect area is higher. At day 10 (10d), the defect site appears to be filled by a condensed mesenchymal tissue. Finally, by day 14 (14d), an integration of the newly formed bone to the original socket walls is noted.

that is in some way compromised, ultimately resulting in a net increase in bone formation (Fig. 2-16).

Osteomalacia

Vitamin D is essential for the metabolism of calcium and phosphorus in the body, which are the key minerals required for bone formation (Holick 2007). Vitamin D deficiency, or the inability to absorb the vitamin, is a common condition, especially in Northern climates since vitamin D is obtained primarily through sunlight exposure and diet. Other conditions may also predispose to vitamin D deficiency, such as oncogenic or benign tumors and liver disease.

When inadequate vitamin D is available, mineralization of the bones is impaired, resulting in a condition referred to as osteomalacia. When the disease occurs in children, it is referred to as rickets. The key features of osteomalacia are bones that contain a normal collagen matrix and osteoid structure, but lack proper mineralization, resulting in the softening of bones (Russell 2010). Osteomalacia differs from osteoporosis in that osteomalacia alters bone as it is developing, whereas osteoporosis weakens bones that have already formed (Fig. 2-17).

Severity ranges widely from an asymptomatic presentation to death in early childhood. Despite the increase in bone density, the newly formed bone is of

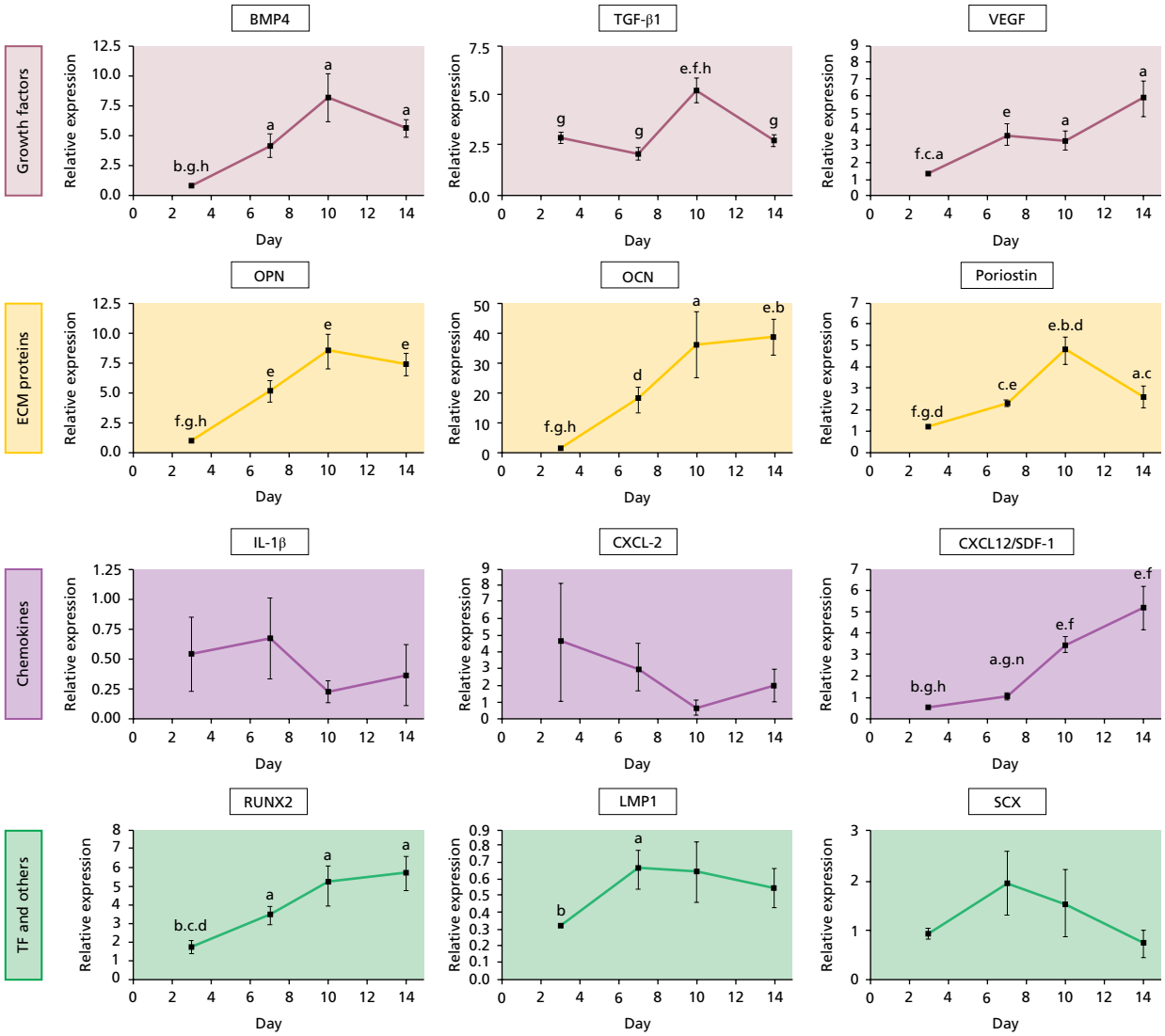


Fig. 2-13 Gene expression pattern of tooth extraction healing sites. Laser capture microdissection (LCM) analysis of genes associated with wound healing categorized them into three different groups: those for growth factors/chemokines, extracellular matrix proteins (ECM), and transcription factors (TF). The evaluation of gene expression over time captured the molecular dynamics that drive the bone healing process. Three expression patterns were evident. (1) Genes whose expression was slowly increased during the healing process: those for growth factors (*BMP4*, *BMP7*, *Wnt10b*, and *VEGF*), transcription factors (*RUNX2*), and extracellular matrix proteins related to mineralized tissue (*OPN* and *OCN*) were in this group; very interestingly, CXCL12 (SDF-1) gradually increased during extraction socket healing. Transforming growth factor beta 1 (TGF-β1) increased at the mid-stage of healing (day 10) and then decreased, and periostin (POSTN), a target gene of TGF-β1, had the same expression pattern. (2) Genes that were highly expressed at early time points and were down-regulated at later stages. Genes for chemokines IL-1β, CXCL2, and CXCL5 belonged to this category, although no statistical difference was seen due to the limited number of animals analyzed. Expression of *Wnt5a* and *Wnt4* also seemed to decrease during healing. (3) Genes that were constitutively expressed. LIM domain mineralization protein (*LMP-1*) and tendon-specific transcription factor *SCX* were in this group.

poor quality and symptoms include increased fracture incidence, neuropathy, and short stature. Treatment of osteomalacia involves reversing the vitamin D deficiency status, usually through dietary supplementation combined with removing the cause of the deficiency. Early management of this condition may involve a bone marrow transplant.

Osteonecrosis

When ischemia occurs in bone for an extended period of time, often due to an interruption in blood supply, cell death occurs. Cells from a hematopoetic lineage are most prone to the negative effects of ischemia and cannot survive for >12 hours without an adequate blood supply (Steinberg 1991). Cells directly responsible for bone mineralization and turnover – osteoblasts, osteoclasts, and osteocytes – are less prone to anoxia, although cell death occurs in these cells after 48 hours of anoxia. If the blood supply resumes quickly, healing may occur and the bone may recover. However, after this critical time period passes, the bone in question will necrose, requiring partial or total resection, followed by reconstruction.

Osteonecrosis has multiple etiologies including radiation, bisphosphonate use, steroid use, hypertension, and in some cases arthritis or lupus. Bisphosphonate-related osteonecrosis of the jaw (ONJ) is of growing concern in the dental field. ONJ is defined as an area of exposed bone that does not heal within 8 weeks after identification by

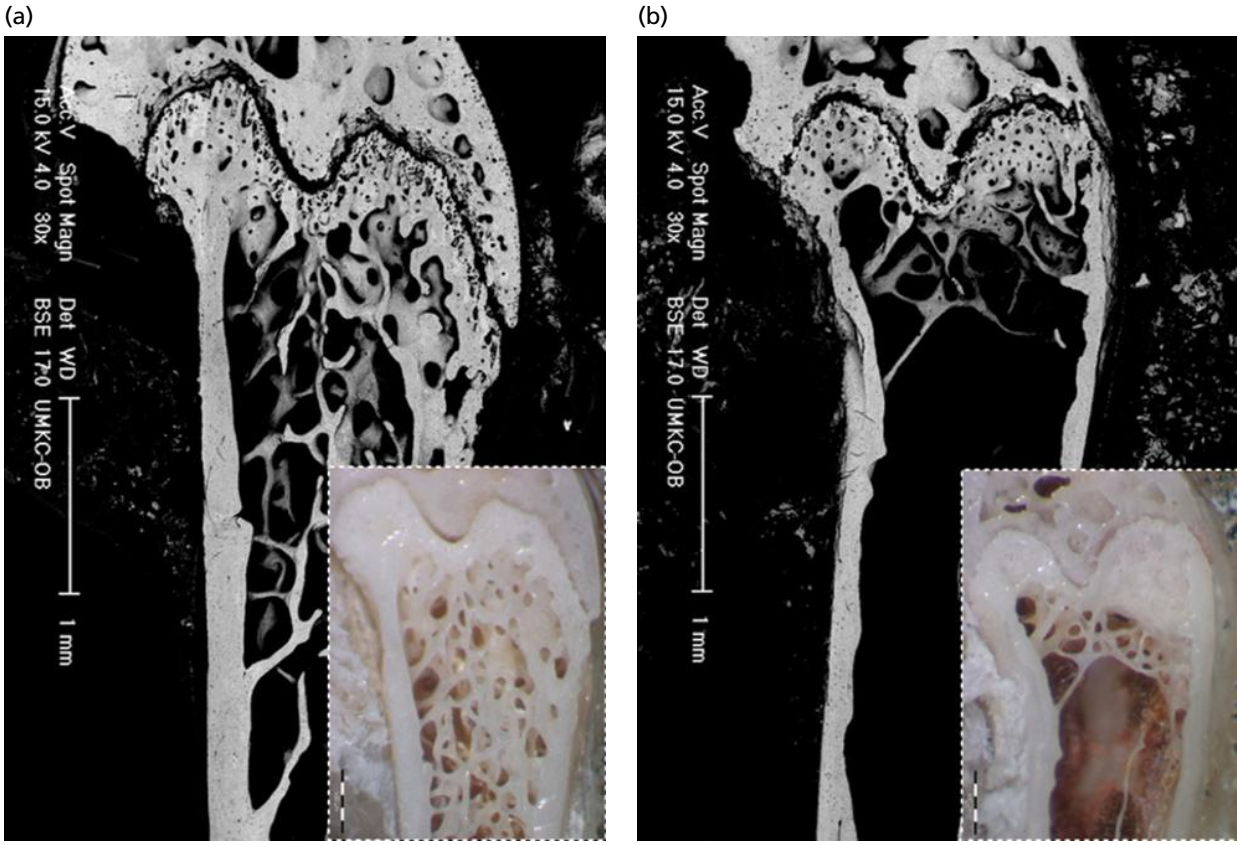
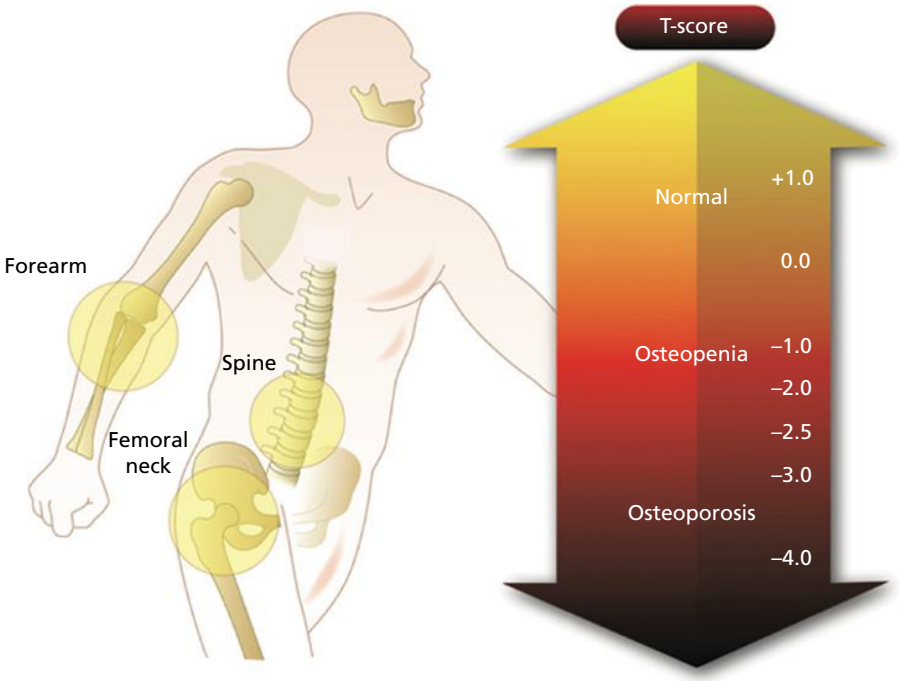


Fig. 2-14 Osteoporosis. In contrast to the image in (a), that in (b) illustrates microscopic bone morphologic changes associated with osteoporosis, such as decreased cortical thickness, in addition to a marked decrease in trabecular number and connectivity. As this process continues over time, there is further deterioration of the internal architecture with a significant impact on the ability of the bone to sustain compressive forces without failure.



$$\text{T-Score} = \frac{\text{Measured BMD} - \text{young adult mean BMD}}{\text{Young adult standard deviation}}$$

Fig. 2-15 Bone mineral density (BMD). Dual-energy X-ray absorptiometry (DEXA) is considered the preferred technique for measurement of BMD. The sites most often used for DEXA measurement of BMD are the spine, femoral neck, and forearm. The World Health Organization defines osteoporosis based on "T-scores". T-scores refer to the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex as the patient.

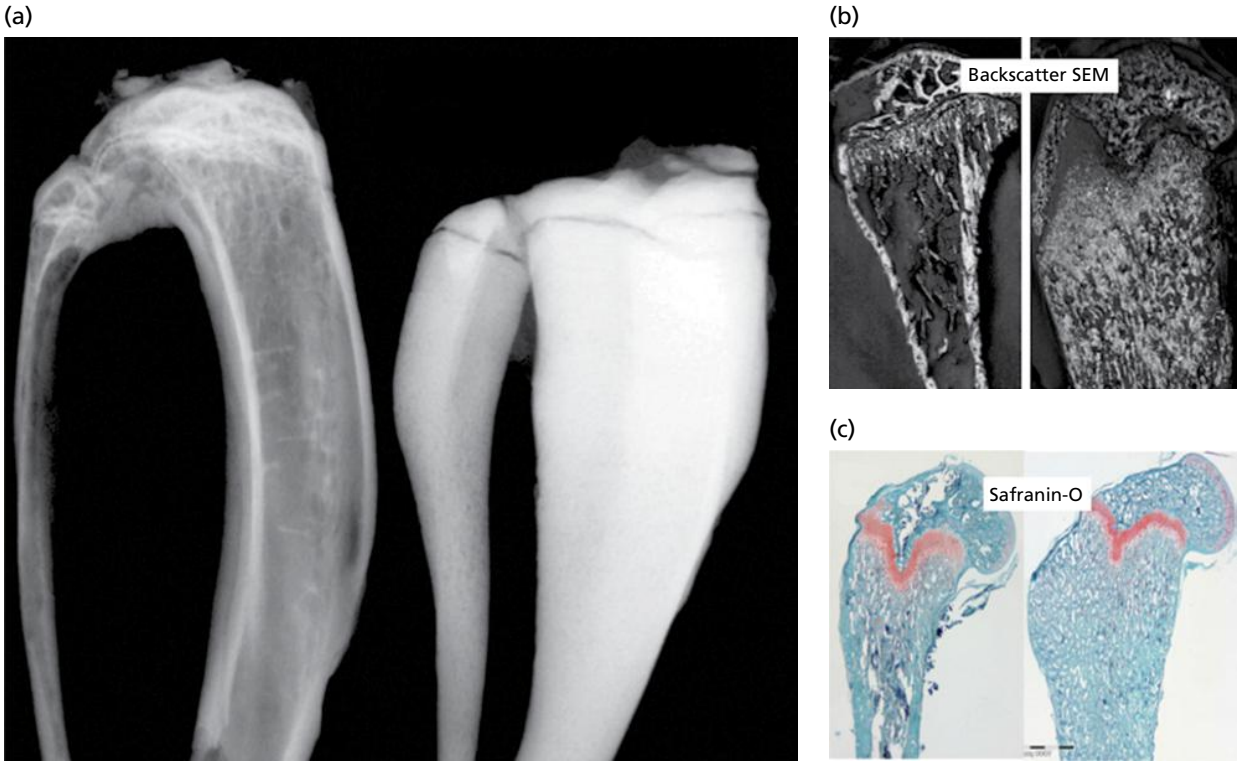


Fig. 2-16 Osteopetrosis. Increased density and deposits of mineralized bone matrix are a common finding in those with osteopetrosis. (a) Obliteration of the bone marrow cavity; (b) backscatter SEM; (c) staining with safranin-O.

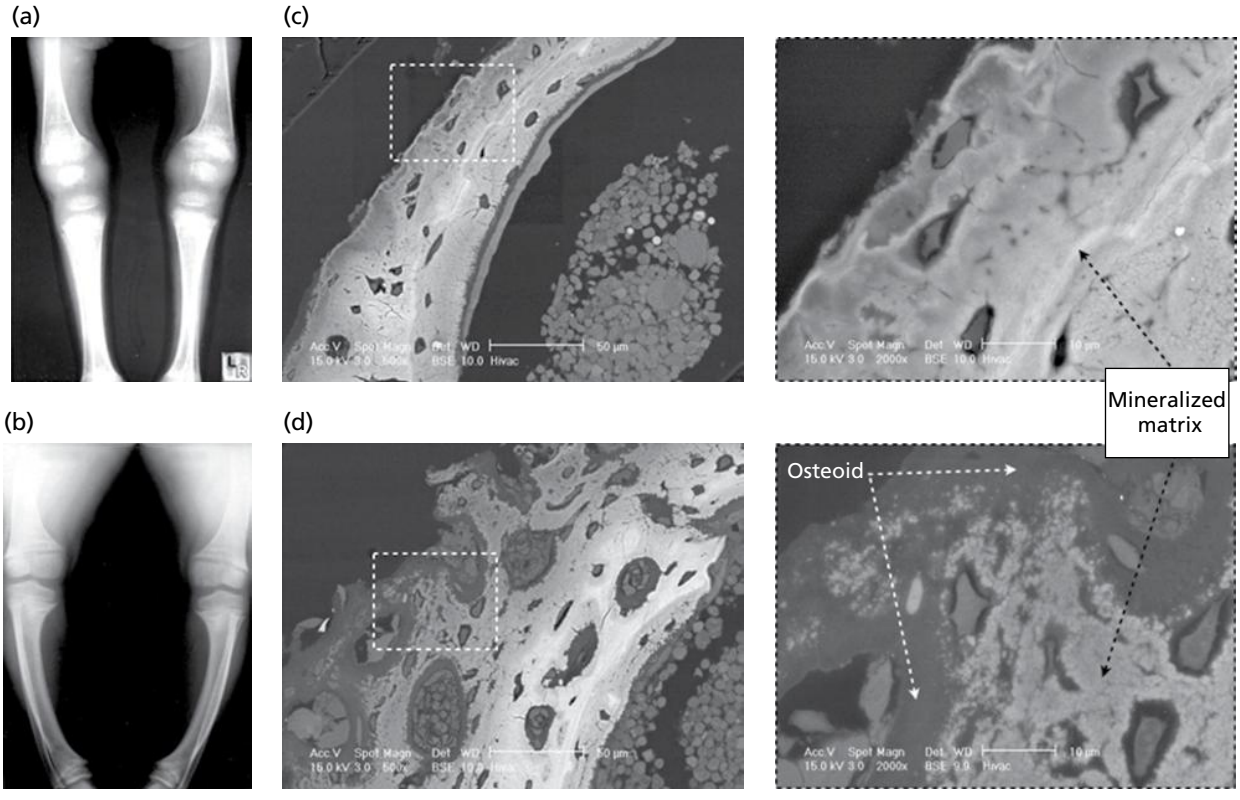


Fig. 2-17 Osteomalacia. (a, c) Normal matrix mineralization and maturation. (b, d) In osteomalacia, large hypomineralized zones accompanied by an increase in osteoid/immature matrix deposits are present.

a healthcare provider (Khosla *et al*. 2008). Patients diagnosed with bisphosphonate-related ONJ cannot have had prior radiation to the craniofacial regions. Oral bisphosphonate use is associated with lower risk and an incidence of 0.01–0.04%, compared to patients taking intravenous bisphosphonates who have a higher incidence of ONJ at 0.8–12% (Vescovi & Nammour 2011). This is likely

due to the higher dosing regimen and disease being treated. Oral bisphosphonates are typically used to treat osteoporosis, whereas intravenous bisphosphonates are given for the treatment of Paget's disease, multiple myeloma, and other conditions.

Osteomyelitis

Osteomyelitis is an infection of the bone and can be classified according to the source of infection, prognosis, bone anatomy, host factors, and clinical presentation (Calhoun & Manring 2005). Open fractures, surgery, and conditions such as diabetes mellitus and peripheral vascular disease increase the risk of developing osteomyelitis. Osteomyelitis from a hematogenous source is much more common in the pediatric population.

A definitive diagnosis of osteomyelitis is made by isolation of the bacteria in conjunction with diagnostic imaging, but can be challenging. Treatment involves antibiotic therapy in conjunction with drainage, debridement, and other appropriate surgical management, including bone stabilization and skin grafting (Conterno & da Silva Filho 2009).

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a group of genetic disorders of impaired collagen formation leading to decreased bone quality. Fractures, bone fragility, and osteopenia are common features of the disease. OI is relatively rare, with an incidence of 1 in 10 000 births. Autosomal dominant and recessive forms exist, although the autosomal dominant form is more common (Michou & Brown 2011).

The clinical presentation of OI has features in common with other diseases of bone metabolism, including fractures, bone deformities, and joint laxity. In addition, distinct features of OI include hearing loss, vascular fragility, blue sclerae, and dentinogenesis imperfecta. Type I collagen defects, including interruptions in interactions between collagen and non-collagenous proteins, weakened matrix, defective cell–cell and cell–matrix relationships, and defective tissue mineralization contribute to the etiology of the autosomal dominant form (Forlino *et al*. 2011). In the recessive form, deficiency of any of the three components of the collagen prolyl 3-hydroxylation complex results in a reduced ability of type I procollagen to undergo post-translational modification or folding. The severity of the disease, as well as the presence of defining features, varies widely.

Multiple therapeutic options are employed to treat the symptoms of OI, including surgery, collaboration with hearing, dental, and pulmonary specialists, and medication such as bisphosphonates and recombinant human growth hormone.

Other disorders

Several other conditions can affect bone homeostasis, including primary and secondary hyperparathyroidism, Paget's disease, and fibrous dysplasia.

Hyperparathyroidism is an overproduction of PTH, which promotes resorption of calcium and phosphorus from bone to increase serum calcium to normal levels (Unnanuntana *et al*. 2011). Primary hyperparathyroidism is most commonly caused by a parathyroid gland adenoma, whereas secondary hyperparathyroidism occurs when PTH production is overstimulated in response to low serum calcium. Hyperparathyroidism often presents with no symptoms and is discovered at routine screenings. The clinical presentation is very similar to that of rickets. Treatment includes identifying and eliminating the initiating cause.

Paget's disease is a condition where bone metabolism is significantly higher than normal, with boneformation exceeding that of resorption (Noor & Shoback 2000). This results in excessive bone formation and may affect one or multiple bones. The pelvic bone is most commonly affected. The affected bones, despite having increased bone formation, are weak and deformed. This is due to irregular collagen fiber formation within the bones. Bisphosphonate therapy is effective at decreasing bone turnover in this patient population, although this carries with it an increased risk of developing ONJ. Approximately 0.01–0.04% of patients taking bisphosphonates for the treatment of Paget's disease develop ONJ (Vescovi & Nammour 2011).

Fibrous dysplasia may affect multiple bones, but in 60% of cases, only one bone is affected (Michou & Brown 2011). It most commonly presents in childhood. Fibrous dysplasia lesions form in the medullary cavity extending to the cortical bone and are comprised of hyaline cartilage, immature woven bone, and osteoblast progenitor cells. Symptoms of this condition include fractures and bone pain. Notably, this condition has other craniofacial symptoms, including craniofacial bone deformities, exophthalmos, and dental abnormalities.

Conclusion

It can be appreciated that the dynamic nature of bone and its associated structures serves as an important organ system that supports form and function of the skeleton. This chapter serves to demonstrate the complexity of the developmental process of dental and craniofacial bone formation and homeostasis during health and disease.

Acknowledgments

The authors appreciate the assistance of Mr Chris Jung with the figures. This work was supported in part by NIH DE 13397 to WVG, 1K23DE019872 to HFR, and the Osteology Foundation.

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Chapter 3

The Edentulous Ridge

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Clinical considerations

The alveolar process extends from the basal bone of the maxilla or the mandible and forms a boundary between the outer portion of the maxilla and the inner portion of the mandible (Pietrokovski *et al*. 2007). The alveolar process forms in harmony with the development and eruption of the teeth, and gradually regresses when the teeth are lost. In other words, the formation as well as the preservation of the alveolar process is dependent on the continued presence of teeth. Furthermore, the morphologic characteristics of the alveolar process are related to the size and shape of the teeth, events occurring during tooth eruption, as well as the inclination of the erupted teeth. Thus, subjects with long and narrow teeth, compared with subjects who have short and wide teeth, appear to have a more delicate alveolar process and, in particular in the front tooth regions, a thin, sometimes fenestrated, buccal bone plate (Fig. 3-1).

The tooth and its surrounding attachment tissues – the root cementum, the periodontal ligament, and the bundle bone – establish a functional unit (Fig. 3-2). Hence, forces elicited, for example during mastication, are transmitted from the crown of the tooth via the root and the attachment tissues to the load-carrying hard tissue structures in the alveolar process, where they are dispersed.

The loss of teeth and the loss or change of function within and around the socket will result in a series of adaptive alterations of the now edentulous portion of the ridge. Thus, it is well documented that following *multiple tooth* extractions and the subsequent restoration with removable dentures, the size of the ridge will become markedly reduced, not only in the horizontal but also in the vertical dimension (Figs. 3-3, 3-4). An important long-term study of dimensional ridge alterations in 42 complete denture wearers was presented by Bergman & Carlsson (1985). Cephalometric radiographic examinations were performed in a cephalostat and profiles of the edentulous mandible and maxilla were depicted 2 days after tooth extraction, and subsequently after 5 years and 21 years (Fig. 3-5). The authors concluded that during the observation interval most of the hard tissue component of the ridge was lost. However, there was wide variation in the degree of bone resorption and amount of remaining bone among the patients (Tallgren 1957, 1966; Atwood 1962, 1963; Johnson 1963, 1969; Carlsson *et al*. 1967).

Also, following the removal of *single* teeth, the ridge at the site will be markedly diminished (Fig. 3-6). The magnitude of this change was studied and reported by Pietrokovski and Massler (1967). The authors had access to 149 dental cast models (72 maxillary and 77 mandibular) in which one tooth was missing on one side of the jaw. The outer contours of the buccal and lingual (palatal) portions of the ridge at a tooth site and at the contralateral edentulous site were determined by the use of a profile stylus and an imaging technique. Their findings are reported in Table 3-1.

It was concluded that the amount of tissue resorption (hard and soft tissues combined) following the loss

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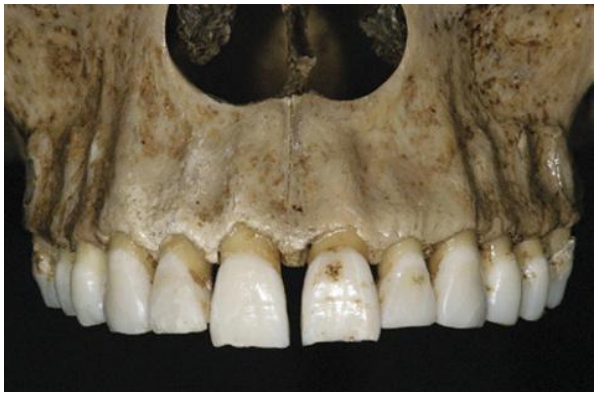
(a)



(b)

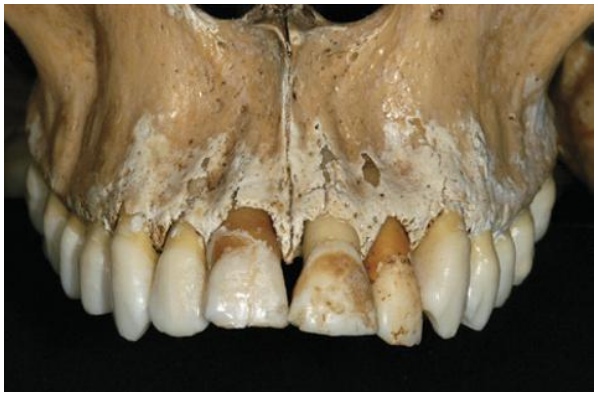


Fig. 3-1 Buccal aspect of adult skull preparations illustrating a dentate maxilla of one subject with a relatively thick (a) and another subject with a relatively thin (b) biotype.

of a single tooth was substantial and that the reduction of the ridge was twice as large at the buccal aspect as along the lingual and palatal aspect in all teeth groups examined. The absolute amounts of tissue loss varied from one group of teeth to the next. As a result of this tissue modeling, the center of the edentulous site shifted toward the lingual or palatal aspect of the ridge. The observations made by Pietrokovski and Massler (1967) were supported by findings presented by Schropp *et al*. (2003). They studied bone and soft tissue volume changes that took place during a 12-month period following the extraction of single premolars and molars. Clinical as well as cast model measurements were made immediately after tooth extraction and subsequently after 3, 6, and 12 months of healing. It was observed that the bucco-lingual/-palatal dimension during the first 3 months was reduced by about 30%, and after 12 months the edentulous site had lost at least 50% of its original width. Furthermore, the height of the buccal bone plate was reduced and after 12 months of healing the buccal prominence was located 1.2 mm apical of its lingual/palatal counterpart.

The information provided by Pietrokovski and Massler (1967) and Schropp *et al*. (2003) suggests that if an alveolar process includes a tooth that has a horizontal width of, for example, 12 mm, the edentulous site will be only 6 mm wide 12 months after healing following tooth extraction. During this 12-month interval, 4 mm of tissue will be lost from the buccal and 2 mm from the lingual aspect of the site.

(a) (b)

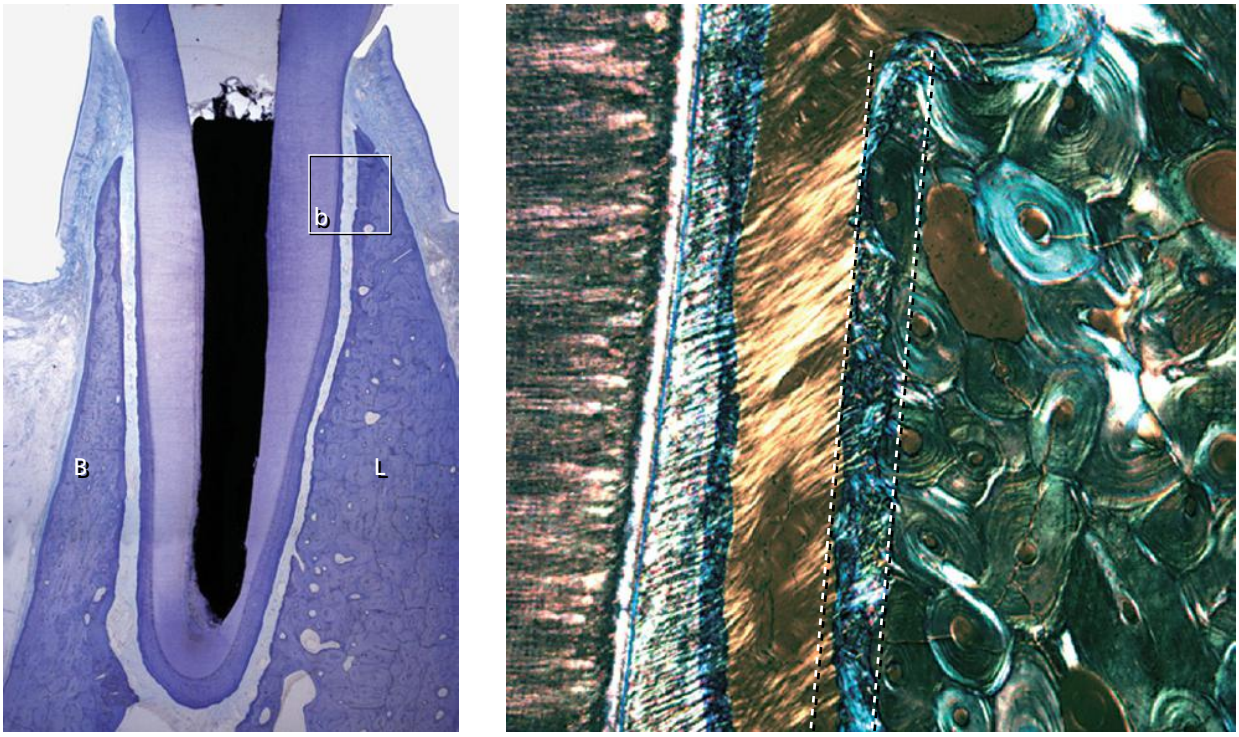


Fig. 3-2 Buccolingual histologic section of the alveolar process. (a) Tooth is surrounded by its attachment tissues (cementum, periodontal ligament, alveolar bone proper). (B, buccal aspect; L, lateral aspect.) (b) Higher magnification of the attachment tissues. Note that the dentin is connected to the alveolar bone via the root cementum, and the periodontal ligament. The alveolar bone is characterized by its content of circumferential lamellae. The portion of the bone that is facing the periodontal ligament (between the dotted lines) is called the alveolar bone proper or the bundle bone.

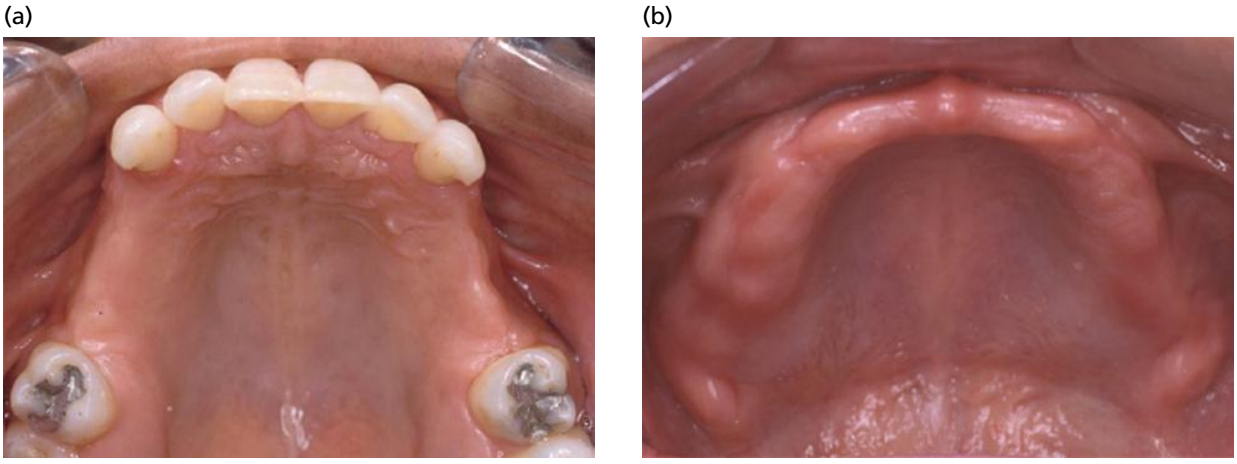


Fig. 3-3 (a) Clinical view of a partially edentulous maxilla. Note that the crest of the edentulous portions of the ridge is narrow in the buccopalatal direction. (b) Clinical view of a fully edentulous and markedly resorbed maxilla. Note that *papilla incisiva* is located in the center of the ridge. This indicates that the entire buccal and also a substantial portion of the palatal ridge are missing.

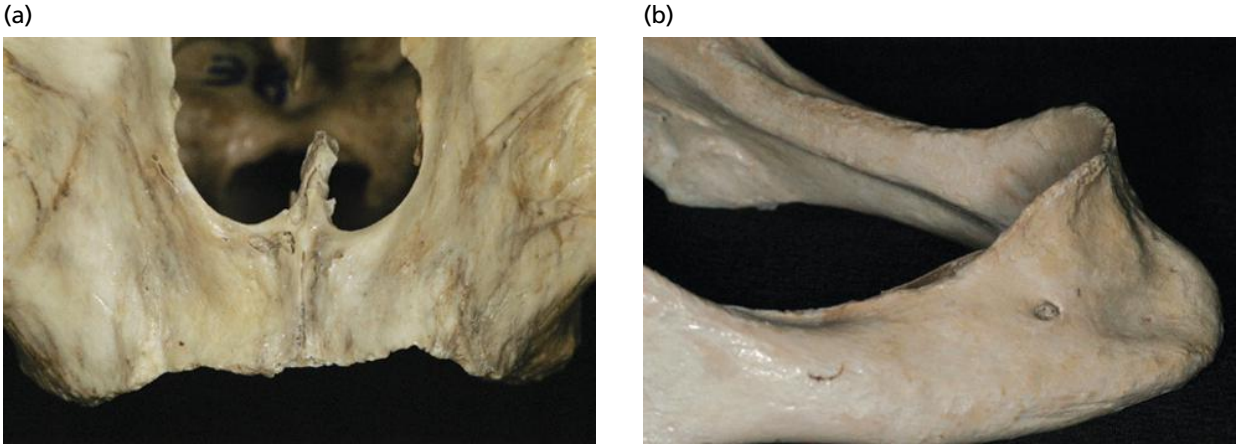


Fig. 3-4 Buccal aspect of a skull preparation illustrating a fully edentulous maxilla (a) and mandible (b). The small segments of the alveolar ridge that still remain are extremely thin in the bucco-palatal/-lingual direction.

In a clinical study (Sanz *et al*. 2010; Tomasi *et al*. 2010) it was observed that the degree of early (4 months) resorption of the buccal bone plate following tooth extraction was dependent on its original dimension. Thus, bone plates that were <1 mm wide lost substantially more dimension (width and height) than plates that were >1 mm wide.

In this context it is important to acknowledge that the buccal bone plate in the frontal tooth region in humans is frequently (>80% of sites) <1 mm wide (Januário *et al*. 2011; Braut *et al*. 2011; Nowzari *et al*. 2012). Hence, it can be anticipated that tooth loss in this part of the dentition may result in marked dimension alterations (horizontal as well as vertical) of the ridge and that this in turn may cause esthetic concerns.

Conclusion: The extraction of single as well as multiple teeth induces a series of adaptive changes in the soft and hard tissues that result in an overall regression of the edentulous site(s). Resorption appears to be more pronounced at the buccal than at the lingual/palatal aspects of the ridge.

It should be realized that the alveolar process might also undergo change as the result of tooth-related disease processes, such as aggressive, chronic,

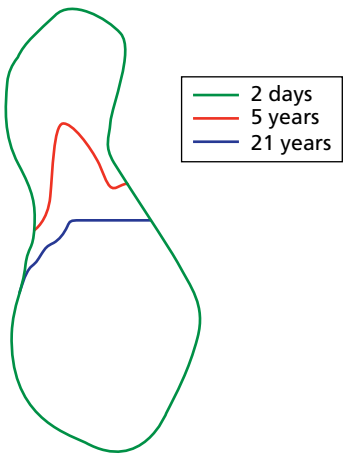


Fig. 3-5 Profile of the mandibular bone following tooth extraction at 2 days, 5 years, and 21 years after tooth removal. (Source: Bergman & Carlsson 1985. Reproduced with permission from Elsevier.)

and necrotizing forms of marginal periodontitis, as well as periapical periodontitis. Furthermore, traumatic injuries (including from improper tooth removal techniques) may cause marked damage to the alveolar process of the maxilla and mandible.

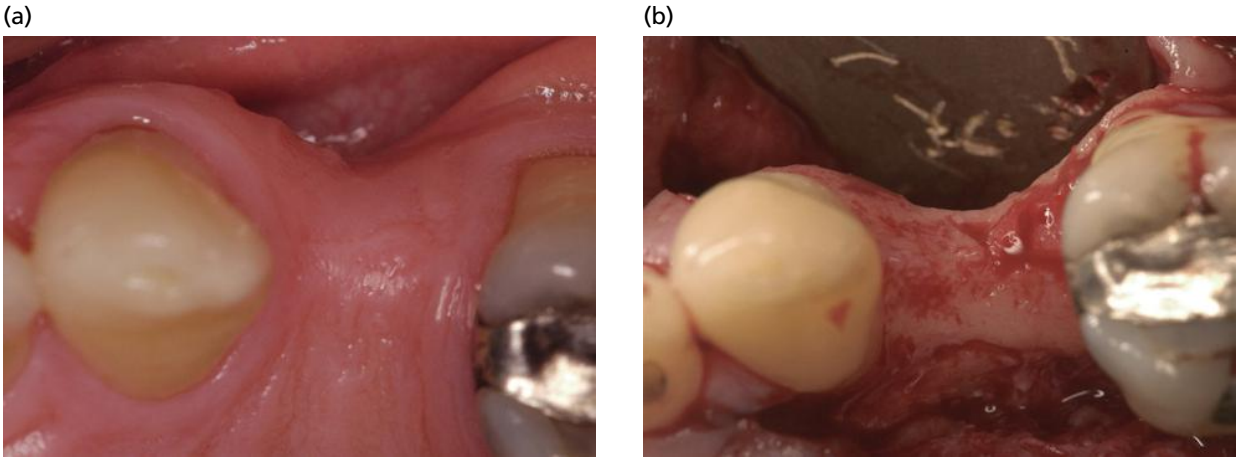


Fig. 3-6 Clinical view of an edentulous ridge in the maxillary premolar region. The premolar was extracted several years before the clinical documentation was made. (a) Note the presence of a buccal invagination of the ridge. (b) Following flap elevation, the crest region of the severely resorbed buccal portion of the alveolar process is disclosed.

Table. 3-1 Average amount of resorption of tooth extraction in different tooth areas.[a]

Tooth	Average amount of resorption (mm)		Difference
	Buccal surface	Lingual/ palatal surface	
Mandibular teeth			
Central incisor	2.08	0.91	1.17
Lateral incisor	3.54	1.41	2.13
Canine	3.25	1.59	1.66
First premolar	3.45	1.40	2.05
Second premolar	3.28	0.75	2.53
First molar	4.69	2.79	1.90
Second molar	4.30	3.00	1.30
Maxillary teeth			
Central incisor	3.03	1.46	1.57
Lateral incisor	3.47	0.86	2.61
Canine	3.33	1.91	1.42
First premolar	3.33	2.04	1.29
Second premolar	2.58	1.62	0.96
First molar	5.25	3.12	2.13

[a] "The amount of resorption was greater along the buccal surface than along the lingual or palatal surface in every specimen examined, although the absolute amounts and differences varied very widely. This caused a shift in the center of the edentulous ridge toward the lingual or palatal side of the ridge with a concomitant *decrease* in arch length in the mandible as well as the maxillae" (Pietrokovski & Massler 1967).

Remaining bone in the edentulous ridge

In the publication by Schropp *et al*. (2003), bone tissue formation in single extraction sockets was studied by means of subtraction radiography. Thus, radiographs of the study sites were obtained using a standardized technique immediately after tooth extraction and then after 3, 6, and 12 months of healing (Fig. 3-7). It was observed that in the first few months, some bone loss (height) took place in the alveolar crest region. Most of the bone gain in the socket occurred in the first 3 months. There was additional gain of bone in the socket between 3 and 6 months. In the interval between 6 and 12 months, the newly formed bone obviously remodeled and the amount of mineralized tissue was reduced. In other words, in the later phases of socket healing, small amounts of mineralized tissue may have remained in the center of the edentulous site.

The bony part of the edentulous ridge in humans was examined in biopsies sampled from the posterior portions of the jaw by Lindhe *et al*. (2012). The peripheral borders of the ridge were consistently lined with dense cortical bone. More central parts harbored cancellous bone and included trabeculae made up mainly of lamellar bone (Fig. 3-8a). The trabeculae that were embedded in bone marrow varied in shape, and frequently had a haphazard orientation. The bone marrow was dominated by adipocytes, vascular structures, and scattered inflammatory cells. The hard tissue component of the ridge was comprised of a mixture of mineralized bone (about 60%), bone marrow (about 20%), and fibrous tissue (about 15%) (Fig. 3-8b).

Classification of remaining bone

Based on the volume of remaining mineralized bone, the edentulous sites may, according to Lekholm and Zarb (1985), be classified into five different groups (Fig. 3-9). In groups A and B, substantial amounts of the ridge still remain, whereas in groups C, D, and E, only minute amounts of hard tissue remain. Lekholm and Zarb (1985) also classified the "quality" of the bone in the edentulous site. Class 1 and class 2 characterized a location in which the walls – the cortical plates – of the site are thick and the volume of bone

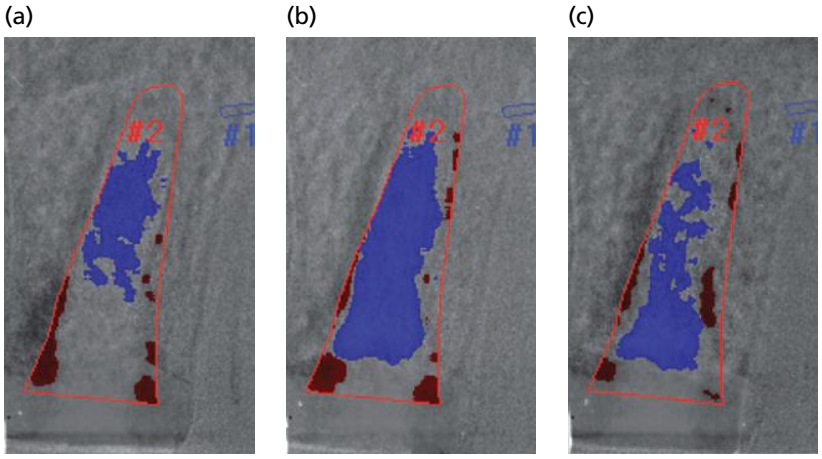


Fig. 3-7 Radiographic (subtraction radiography) images of an extraction site obtained after (a) 3 months, (b) 6 months, and (c) 12 months of healing. The blue color represents areas of new bone formation. During the first 6 months, the deposition of new bone was intense. Between 6 and 12 months, some of the newly formed bone was remodeled. (Courtesy of L. Schropp.)

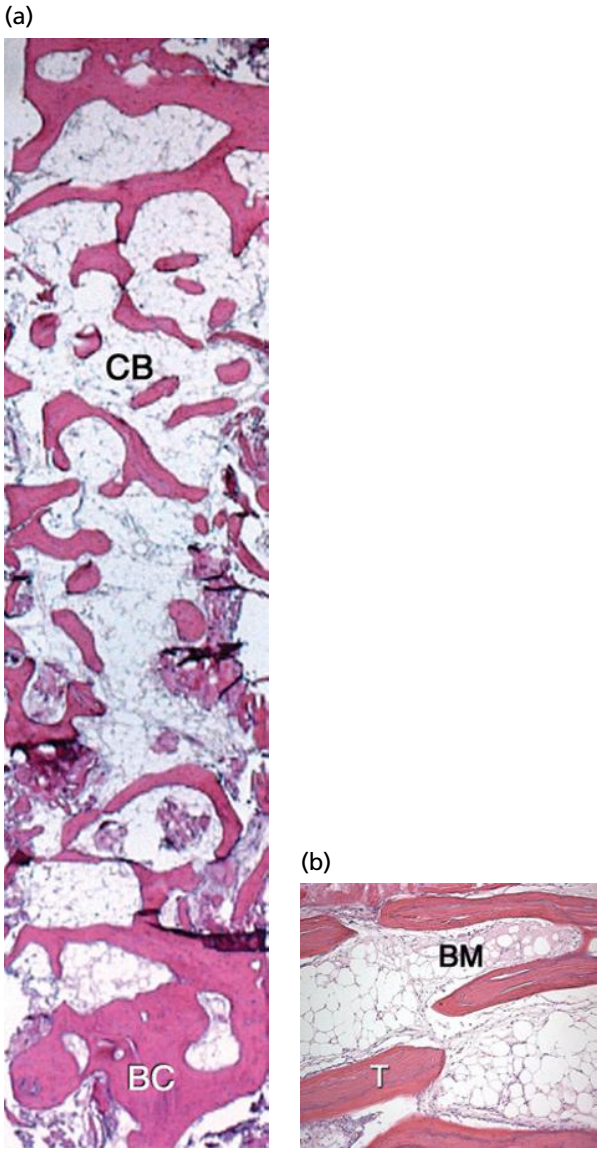


Fig. 3-8 Histologic sections of an edentulous site obtained from the maxillary premolar region in man. (a) The marginal portion of the ridge (BC) is protected by a cortical cap made up of lamellar bone, while more central regions house the cancellous bone (CB). (b) The cancellous bone is characterized by the trabeculae of mineralized bone (T) within the bone marrow (BM) compartment.

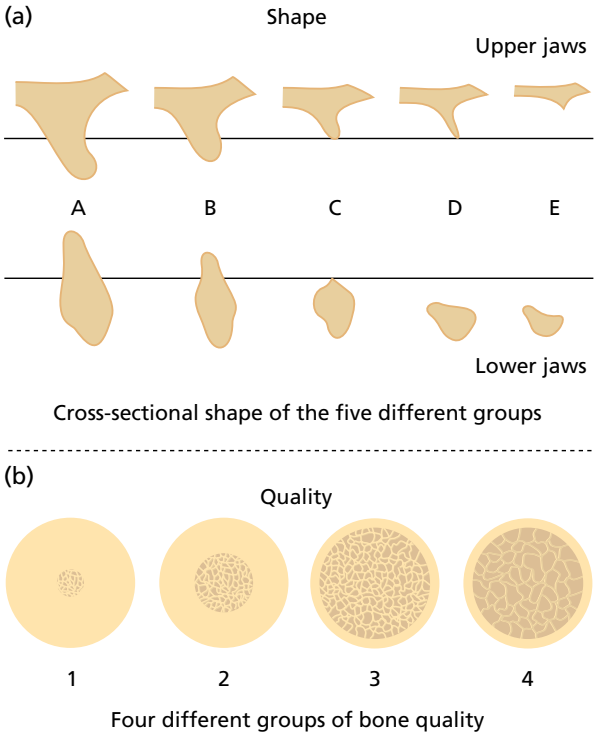


Fig. 3-9 Schematic drawings showing (a) a classification of residual jaw shape and (b) jaw bone quality. (Source: Lekholm & Zarb 1985. Reproduced from Quintessence.)

marrow is small. Relatively thin walls of cortical bone, however, will border sites that belong to class 3 and class 4, while the amount of cancellous bone (spongiosa), including trabeculae of lamellar bone and marrow, is large.

Topography of the alveolar process

The alveolar process that houses the roots of the teeth extends from the basal bone (Fig. 3-10a) of the maxilla and the mandible. The shape and dimensions (height and width) of the basal bone vary considerably from subject to subject (Figs. 3-10a, b) and from site to site in the same individual. There

is no distinct boundary between the alveolar process and the basal bone of the jaws.

At sites of the jaws where the teeth erupt in "normal" orientation in the developing alveolar process, hard tissue will be present on the facial (buccal) as well as on the lingual (palatal) aspect of the roots (Fig. 3-10c). However, at sites where the teeth erupt with a facial orientation, the facial (buccal) bone of the alveolar process will become thin and at times even disappear (dehiscence, fenestration) (Fig. 3-10d).

The outer walls of the alveolar process – facial (buccal), marginal, and lingual (palatal) aspects – are continuous with the outer walls of the basal bone. The walls are comprised of dense cortical bone, while more central portions harbor trabecular bone (radiographic term; spongy bone, anatomic term; cancellous bone, histologic term) that contains bone trabeculae within the bone marrow.

The cortical walls (plates) of the alveolar process are continuous with the bone that lines the sockets, that is the alveolar bone proper or the bundle bone (see Fig. 3-2b). The cortical plates (the outer walls) of the alveolar process meet the alveolar bone proper at the crest of the interdental septum. In subjects (sites) with healthy periodontium, the crest of the septum is located 1–2 mm apical of the cementoenamel junction.

In some portions of the dentition (such as in the symphysis region of the mandible), the trabecular bone component of the alveolar process may be absent.

From an alveolar process to an edentulous ridge

The alterations that occur in the alveolar process following the extraction of a single tooth can, for didactic reasons, be divided in two interrelated series of events, namely *intra-alveolar processes* and *extra-alveolar processes.*

Intra-alveolar processes

The healing of extraction sockets in human volunteers was studied by, for example, Amler (1969) and Evian *et al.* (1982). Although the biopsy technique

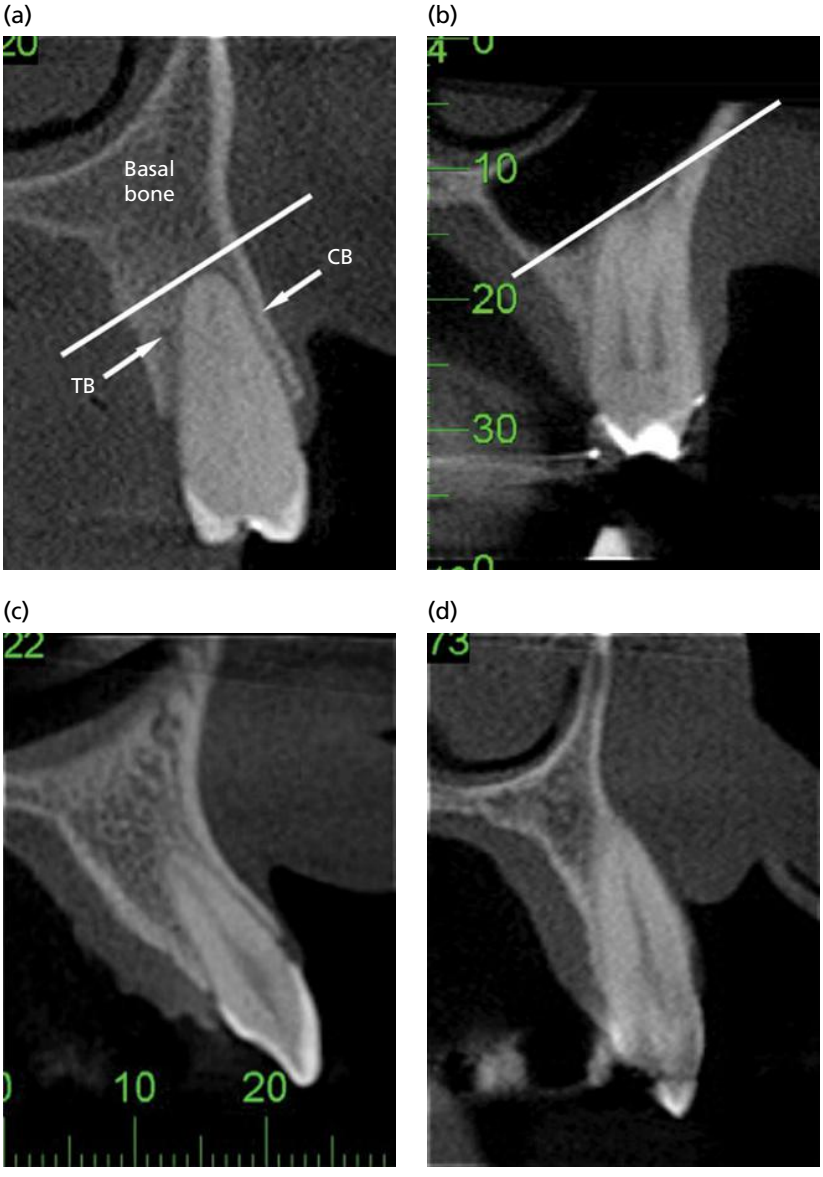


Fig. 3-10 (a) Cone-beam tomogram of the premolar region of the maxilla. The alveolar process is continuous with the voluminous basal bone of the maxilla. (CB, cortical bone plate; TB, trabecular bone.) (b) Cone-beam tomogram of the premolar region of the maxilla. Note that at this site the dimension of the basal bone is very small. (c) Tomogram of an anterior maxillary tooth with a "normal" direction of eruption. The incisor resides within the bony compartment of the alveolar process. (d) Tomogram of a canine tooth that erupted in a facial orientation. The facial (buccal) bone of the alveolar process is thin or even absent.

used by Amler only allowed the study of healing in the marginal portions of the empty socket, his findings are often referred to.

Amler stated that following tooth extraction, the first 24 hours are characterized by the formation of a *blood clot* in the socket. Within 2–3 days the blood clot is gradually replaced with *granulation tissue.* After 4–5 days, the *epithelium* from the margins of the soft tissue starts to proliferate to cover the granulation tissue in the socket. One week after extraction, the socket contains granulation tissue and *young connective tissue*, and *osteoid* formation is ongoing in the apical portion of the socket. After 3 weeks, the socket contains connective tissue and there are signs of mineralization of the osteoid. The *epithelium* covers the wound. After 6 weeks of healing, bone formation in the socket is pronounced and trabeculae of newly formed bone can be seen.

Amler's study was of short duration, so it could only evaluate events that took place in the marginal portion of the healing socket. His experimental data did not include the important later phase of socket healing that involves the processes of modeling and remodeling of the newly formed tissue in various parts of the alveolus. Thus, the tissue composition of the fully healed extraction site was not documented in the study.

In a later and longer-term study, Trombelli *et al*. (2008) examined socket healing in biopsies sampled during a 6-month period from human volunteers. They confirmed most of Amler's findings and reported that in the early healing phase (tissue modeling), the socket was filled with granulation tissue that was subsequently replaced with a provisional connective tissue and woven bone. In biopsies sampled in later phases of healing, it was observed that the process by which woven bone was replaced by lamellar bone and marrow, that is remodeling, was slow and exhibited great individual variation. In only a limited number of specimens representing 6 months of healing had woven bone been replaced with bone marrow and trabeculae of lamellar bone. It can be assumed therefore that tissue modeling following tooth extraction in humans is a rather rapid process, while the subsequent remodeling is slow and may take years to be completed.

The results from experiments using the dog model (Cardaropoli *et al*. 2003, Araújo & Lindhe 2005) will be used in this chapter to describe details of the various phases of socket healing, including processes of both modeling and remodeling. It should be remembered that healing of the post-extraction sites in these animal studies, including phases of modeling and remodeling, was a rapid process compared to socket healing in humans. Thus, the extraction socket was in most instances completely healed (filled with cancellous bone) after 2–3 months.

The model

Buccal and lingual full-thickness flaps are elevated and the distal roots of mandibular premolars extracted (Fig. 3-11a). The mucosal flaps are subsequently replaced to provide soft tissue coverage of the fresh extraction wound (Fig. 3-11b). Healing of the experimental sites is monitored in biopsy specimens obtained at time intervals varying from 1 day to 6 months (Fig. 3-11c).

Overall pattern of socket healing

Figure 3-12 shows a mesiodistal section of a fresh extraction socket bordered by adjacent roots. The socket walls are continuous with the alveolar bone proper of the neighboring teeth. The tissue inside the interdental (inter-radicular) septa is made up of cancellous bone and includes trabeculae of lamellar bone within bone marrow.

The empty socket is first filled with blood and a *coagulum* (clot) forms (Fig. 3-13a). Inflammatory cells (polymorphonuclear leukocytes and monocytes/macrophages) migrate into the coagulum and start to phagocytose elements of necrotic tissue. The process of wound cleansing is initiated (Fig. 3-13b). Sprouts of newly formed vessels and mesenchymal cells (from the severed periodontal ligament) enter the coagulum and *granulation tissue* is formed. The granulation tissue is gradually replaced with *provisional connective tissue* (Fig. 3-13c) and subsequently immature bone (*woven bone*) is laid down (Fig. 3-13d). The hard tissue walls of the socket – the alveolar bone proper or the bundle bone – are gradually resorbed and the socket becomes filled with immature woven bone (Fig. 3-13e). The initial phase of the healing process (tissue modeling) is now complete. In subsequent phases, the woven bone in the socket will be gradually remodeled into lamellar bone and marrow (Fig. 3-13f–h).

Important events in socket healing

Blood clotting

Immediately after tooth extraction, blood from the severed vessels will fill the socket. Proteins derived from vessels and damaged cells initiate a series of events that lead to the formation of a fibrin network (Fig. 3-14). *Platelets* form aggregates and interact with the fibrin network to produce a *coagulum* (a blood clot) that effectively plugs the severed blood vessels and stops the bleeding. The blood clot acts as a physical matrix that directs cellular movements and it contains substances that are of importance for the forthcoming healing process. Thus, the clot contains substances (i.e. *growth factors*) that (1) influence mesenchymal cells and (2) enhance the activity of inflammatory cells. Such substances will thus induce and amplify the migration of various types of cells into the socket wound, as well as their proliferation, differentiation, and synthetic activity within the coagulum.

Although the blood clot is crucial in the initial phase of wound healing, its removal is mandatory to allow the formation of new tissue. Thus, within a few days after the tooth extraction, the blood clot will

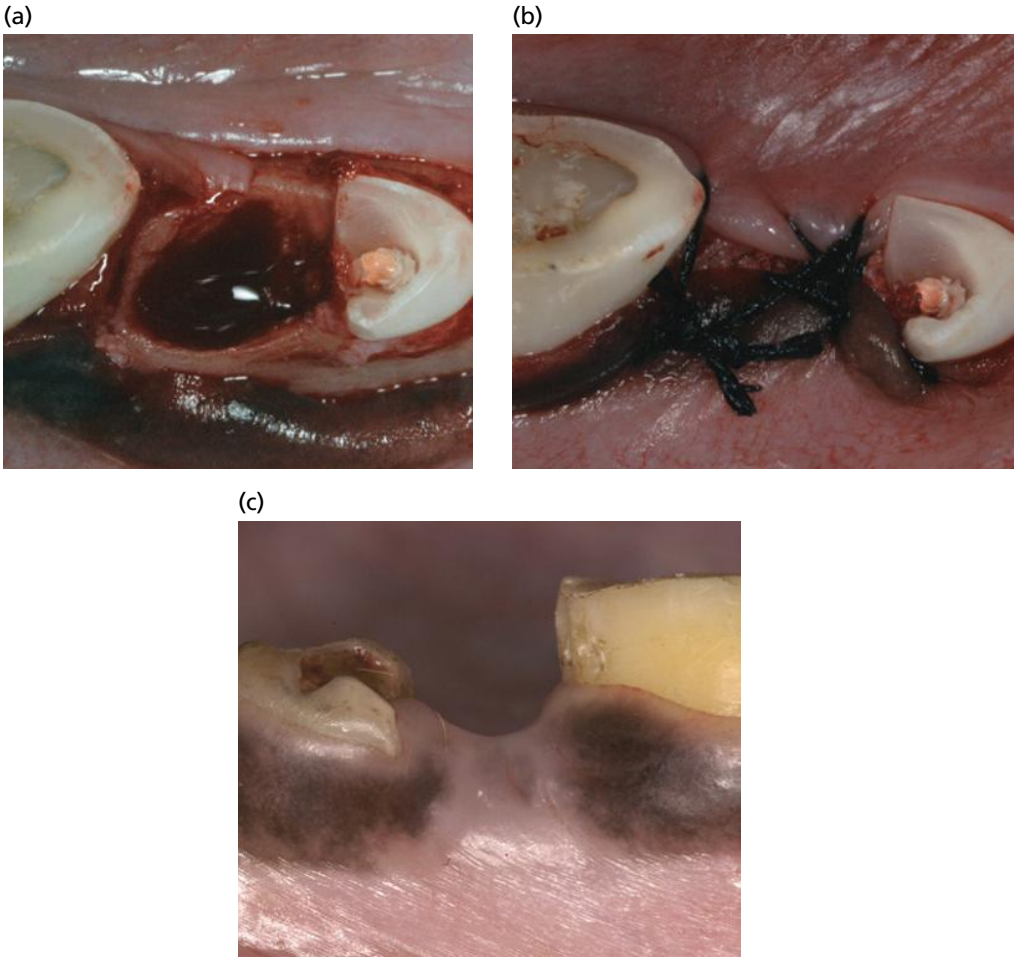


Fig. 3-11 (a) Photograph illustrating a mandibular premolar site (from a dog model) from which the distal root of the fourth premolar had been removed. (b) Mucosal, full-thickness flaps were replaced and sutured to close the entrance of the socket. (c) Site after 6 months of healing. Note the saddle-shaped outline (loss of tissue) of the alveolar crest region.

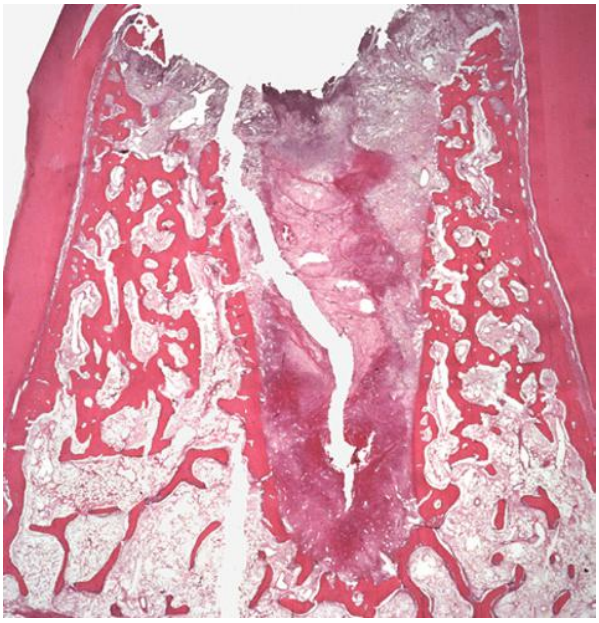


Fig. 3-12 Histologic section showing the mesiodistal aspect of a fresh extraction socket bordered by two neighboring roots. Note that the alveolar bone from the tooth sites is continuous with the walls of the empty socket. The interdental septum contains cancellous bone including trabeculae of lamellar bone and marrow.

start to break down, that is the process of "fibrinolysis" is initiated (Fig. 3-15).

Wound cleansing

Neutrophils and macrophages migrate into the wound, engulf bacteria and damaged tissue, and clean the site before the formation of new tissue can start. The neutrophils enter the wound early, while macrophages appear somewhat later. The macrophages are not only involved in the cleaning of the wound but they also release growth factors and cytokines that further promote the migration, proliferation, and differentiation of mesenchymal cells. Once the debris has been removed and the wound has been "sterilized", the neutrophils undergo a programmed cell death (*apoptosis*) and are removed from the site through the action of macrophages. The macrophages subsequently withdraw from the wound.

Tissue formation

Sprouts of vascular structures (from the severed periodontal ligament) as well as mesenchymal, fibroblast-like cells (from the periodontal ligament and from adjacent bone marrow regions) enter the socket. The mesenchymal cells start to proliferate and deposit

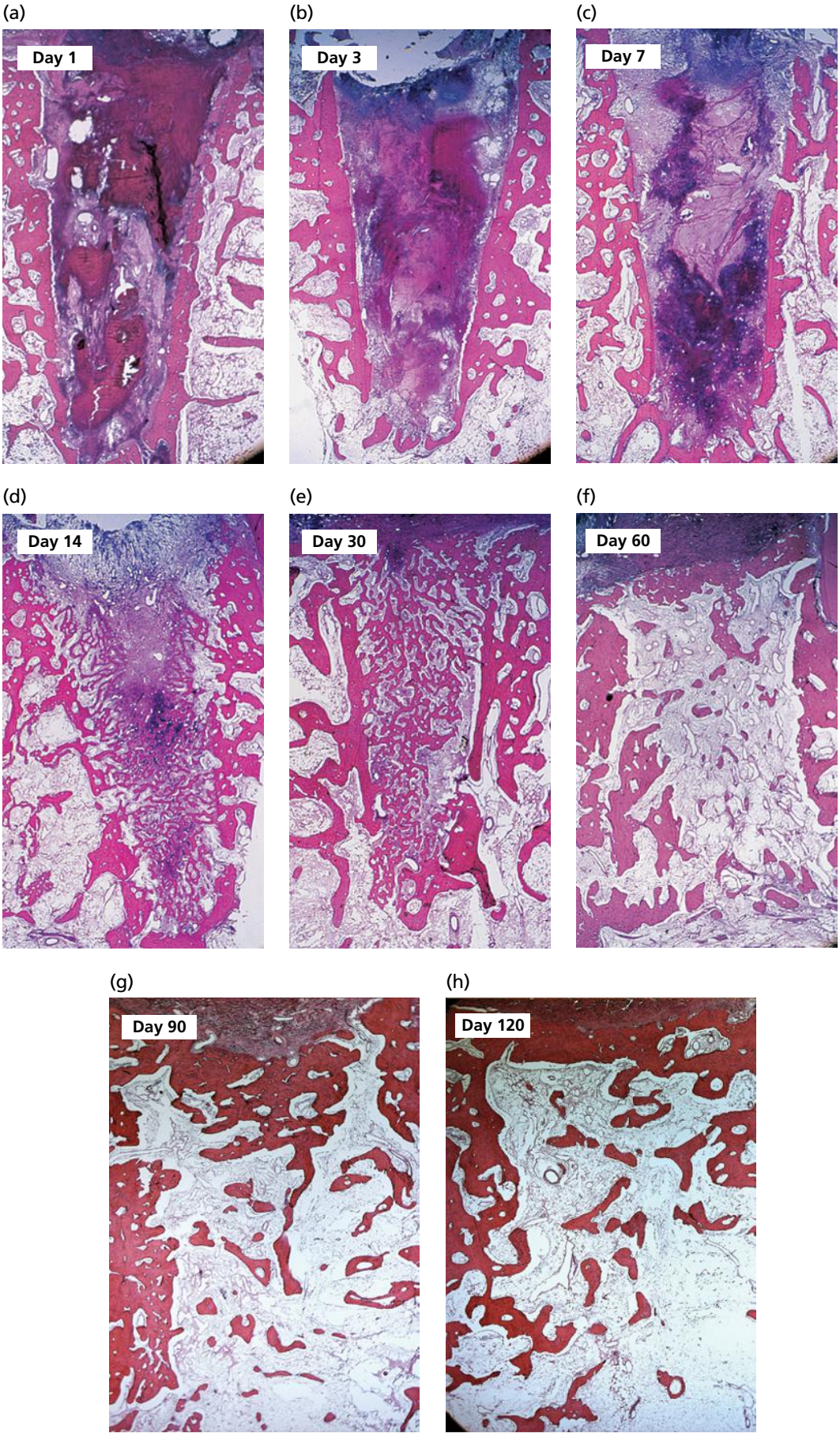


Fig. 3-13 (a–h) Overall pattern of bone formation in an extraction socket. For details see text.

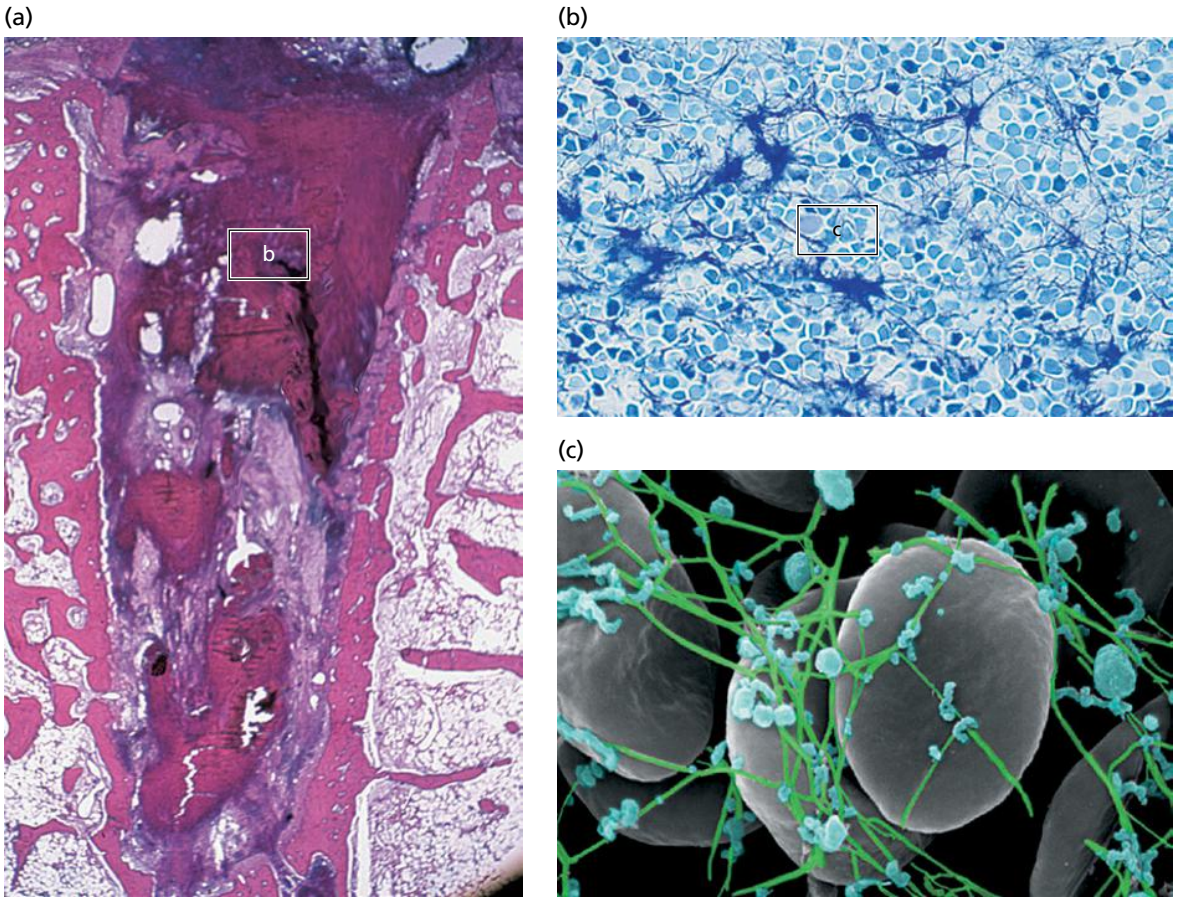


Fig. 3-14 Histologic section (mesiodistal aspect) representing 1 day of healing (a). The socket is occupied with a blood clot that contains large numbers of erythrocytes (b) entrapped in a fibrin network, as well as platelets [blue in (c)].

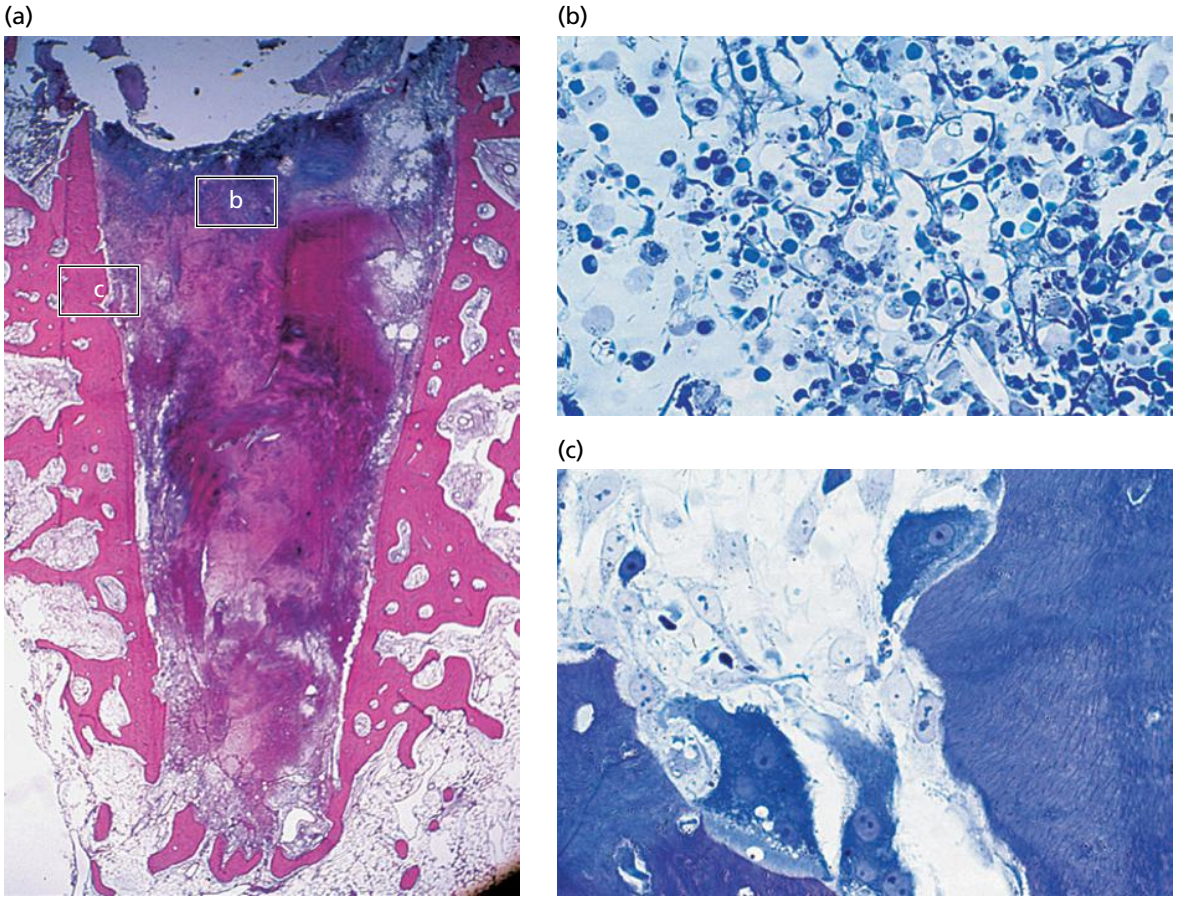


Fig. 3-15 (a) Histologic section (mesiodistal aspect) representing 3 days of healing. (b) Note the presence of neutrophils and macrophages that are engaged in wound cleansing and the breakdown of the blood clot. (c) Osteoclastic activity occurs on the surface of the old bone in the socket walls.

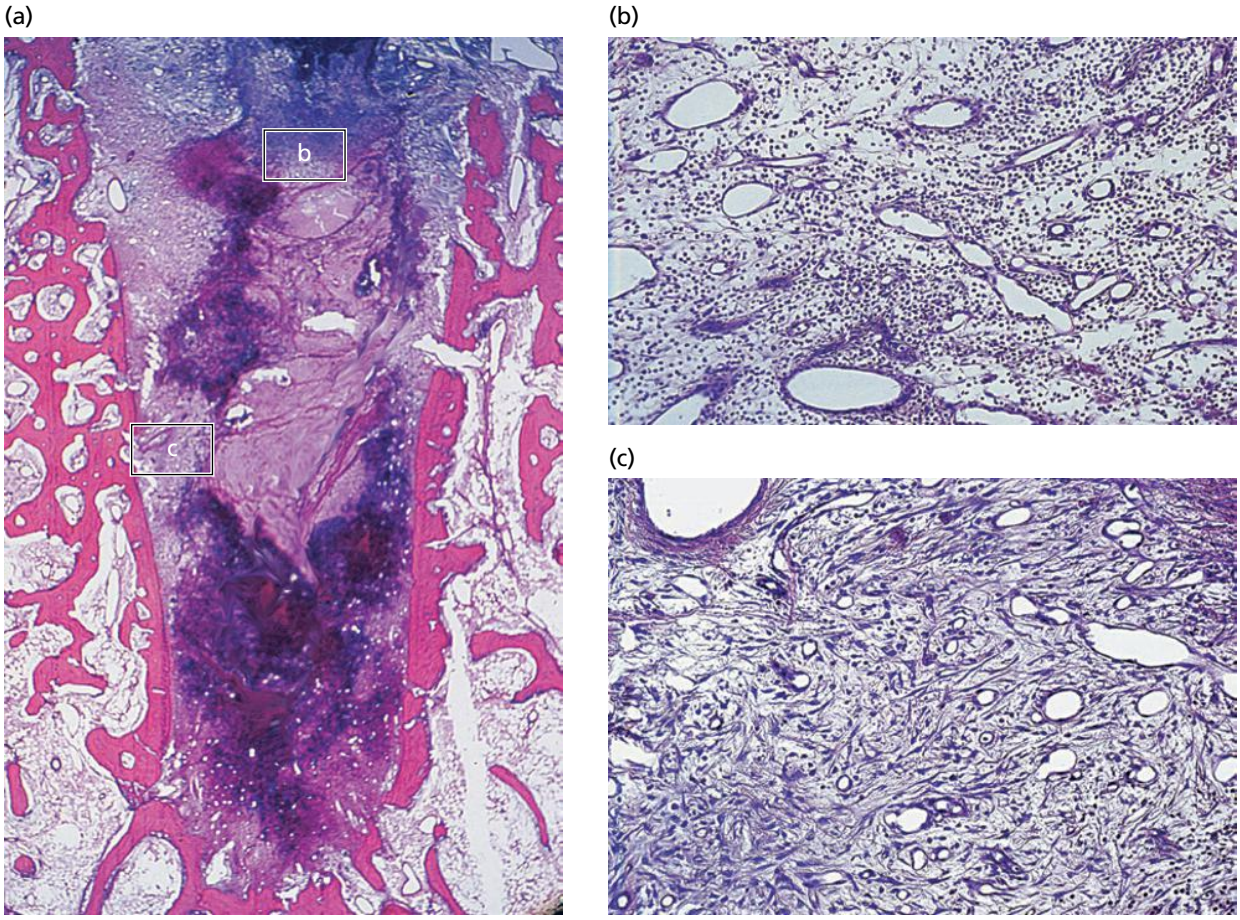


Fig. 3-16 (a) Histologic section (mesiodistal aspect) representing 7 days of healing. (b) Note the presence of a richly vascularized early granulation tissue with large numbers of inflammatory cells in the upper portion of the socket. (c) In more apical areas, a tissue including large numbers of fibroblast-like cells is present (late granulation tissue).

matrix components in an extracellular location (Fig. 3-16); *granulation tissue* will gradually replace the blood clot. This granulation tissue eventually contains macrophages and a large number of fibroblast-like cells, as well as numerous newly formed blood vessels. The fibroblast-like cells continue to (1) release growth factors, (2) proliferate, and (3) deposit a new extracellular matrix that guides the ingrowth of additional cells and allows the further differentiation of the tissue. The newly formed vessels provide the oxygen and nutrients that are needed for the increasing number of cells that occur in the new tissue. The intense synthesis of matrix components exhibited by the mesenchymal cells is called *fibroplasia*, while the formation of new vessels is called *angiogenesis*. A *provisional connective tissue* is established through the combination of fibroplasia and angiogenesis (Fig. 3-17).

The transition of the provisional connective tissue into bone tissue occurs along the vascular structures. Thus, osteoprogenitor cells (e.g. pericytes) migrate and gather in the vicinity of the vessels. They differentiate into osteoblasts that produce a matrix of collagen fibers, which takes on a woven pattern. The *osteoid* is formed. The process of mineralization is initiated within the osteoid. The osteoblasts continue to lay down osteoid and occasionally such cells are trapped in the matrix and become osteocytes. This newly formed bone is called *woven bone* (Figs. 3-17, 3-18).

The woven bone is the first type of The transition of the provisional connective tissue into bone tissue occurs along the vascular structures. Thus, osteoprogenitor cells (e.g. pericytes) migrate and gather in the vicinity of the vessels. They differentiate into osteoblasts that produce a matrix of collagen fibers, which takes on a woven pattern. The *osteoid* is formed. The process of mineralization is initiated within the osteoid. The osteoblasts continue to lay down osteoid and occasionally such cells are trapped in the matrix and become osteocytes. This newly formed bone is called *woven bone* (Figs. 3-17, 3-18).bone to be formed and is characterized by (1) its rapid deposition as finger-like projections along the route of vessels, (2) the poorly organized collagen matrix, (3) the large number of osteoblasts that are trapped in its mineralized matrix, and (4) its low load-bearing capacity. Trabeculae of woven bone are shaped around and encircle the vessel. The trabeculae become thicker through the deposition of additional woven bone. Cells (osteocytes) become entrapped in the bone tissue and the first set of osteons, the *primary osteons*, are organized. The woven bone is occasionally reinforced by the deposition of so-called *parallel-fibered bone* (collagen fibers organized not in a woven but in a concentric pattern).

It is important to realize that during this early phase of healing most of the bone tissue in the walls of the socket (the bundle bone) is removed.

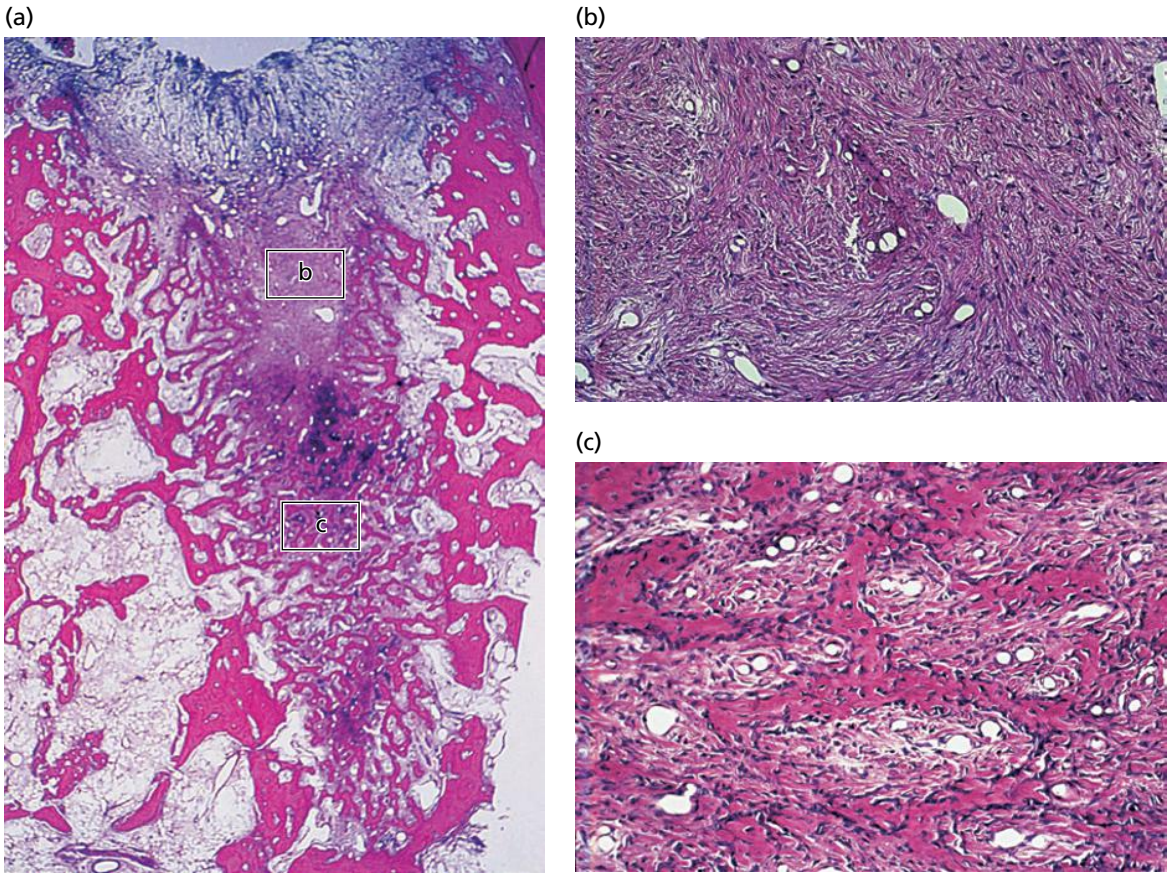


Fig. 3-17 (a) Histologic section (mesiodistal aspect) representing 14 days of healing. (b) In the marginal portion of the wound, a provisional connective tissue rich in fibroblast-like cells is present. (c) The formation of woven bone has at this time interval already begun in the apical and lateral regions of the socket.

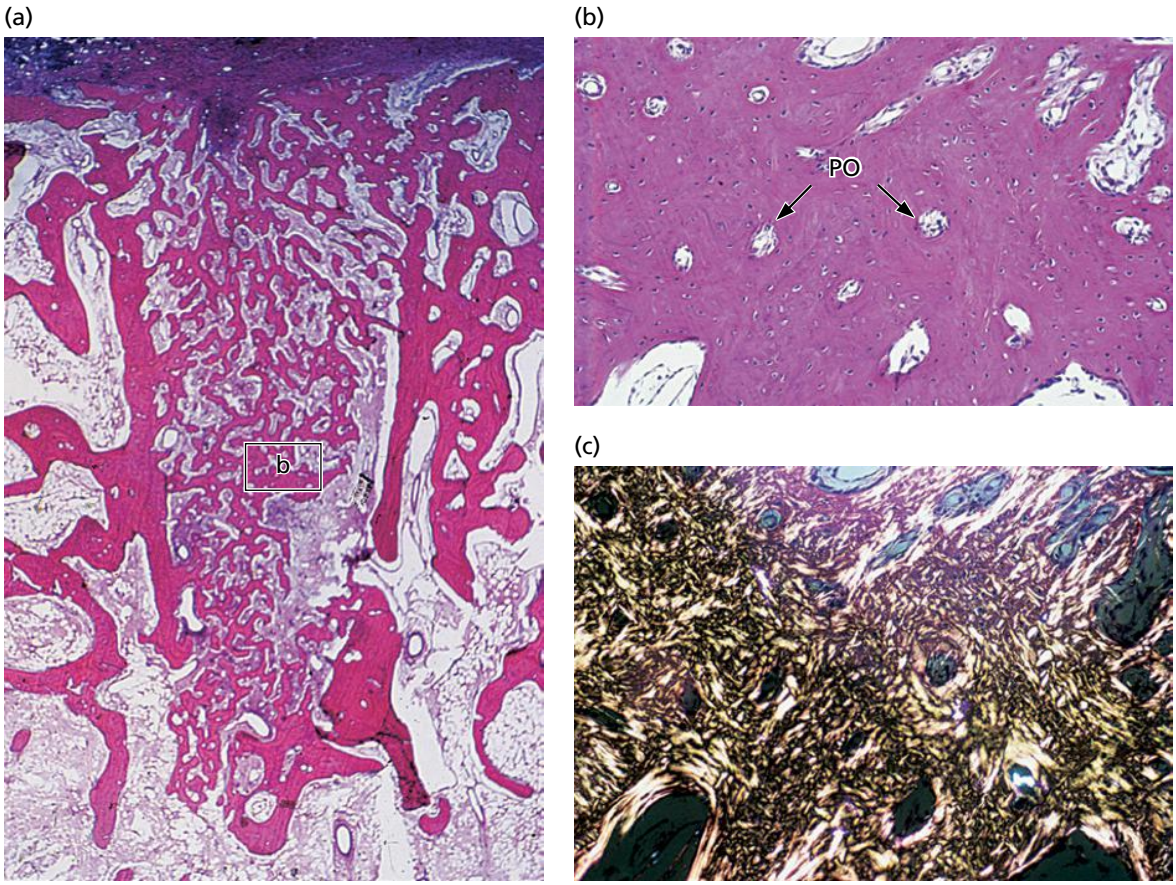


Fig. 3-18 (a) Histologic section (mesiodistal aspect) representing 30 days of healing. The socket is filled with woven bone. (b) Woven bone contains a large number of cells and primary osteons (PO). (c) The woven pattern of the collagen fibers of this type of bone is illustrated (polarized light).

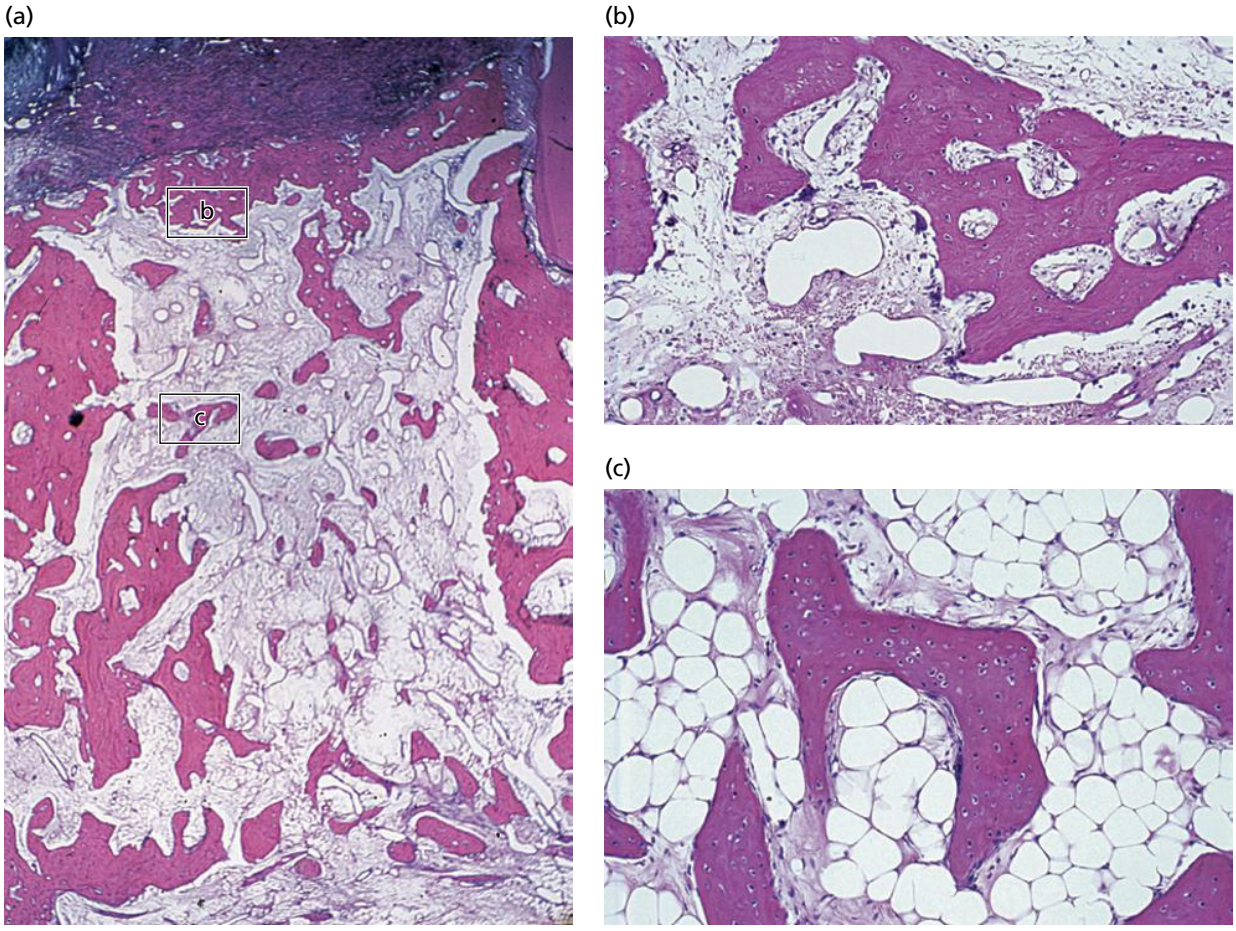


Fig. 3-19 (a) Histologic section (mesiodistal aspect) representing 60 days of healing. (b) A large portion of the woven bone has been replaced with bone marrow. (c) Note the presence of a large number of adipocytes residing in a tissue that still contains woven bone.

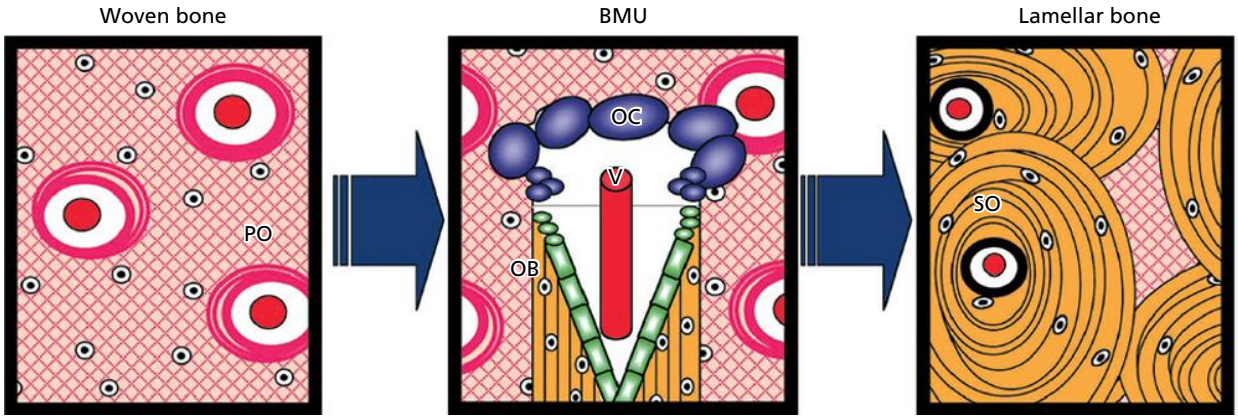


Fig. 3-20 Schematic drawing showing how woven bone is replaced by lamellar bone. Woven bone with primary osteons (PO) is substituted by lamellar bone in a process that involves the presence of bone multicellular units (BMU). The BMU contains osteoclasts (OC), as well as vascular structures (V) and osteoblasts (OB). Thus, the osteoblasts in the BMU produce bone tissue in a concentric fashion around the vessel, and lamellar bone with secondary osteons (SO) is formed.

Tissue modeling and remodeling

The initial bone formation in this dog model is a fast process. Within a few weeks, the entire extraction socket is filled with woven bone or, as this tissue is also called, *primary bone spongiosa*. The woven bone offers (1) a stable scaffold, (2) a solid surface, (3) a source of osteoprogenitor cells, and (4) an ample blood supply for cell function and matrix mineralization.

The woven bone with its primary osteons is gradually replaced with lamellar bone and bone marrow (Fig. 3-19). In this process, the primary osteons are replaced with *secondary osteons*. The woven bone is first resorbed to a certain level. The level of the resorption front will establish a so-called *reversal line*, which is also the level from which new bone with secondary osteons will form (Fig. 3-20). Although this remodeling may start early during socket healing, it will take several months until all woven bone in the extraction socket has been replaced with lamellar bone and marrow.

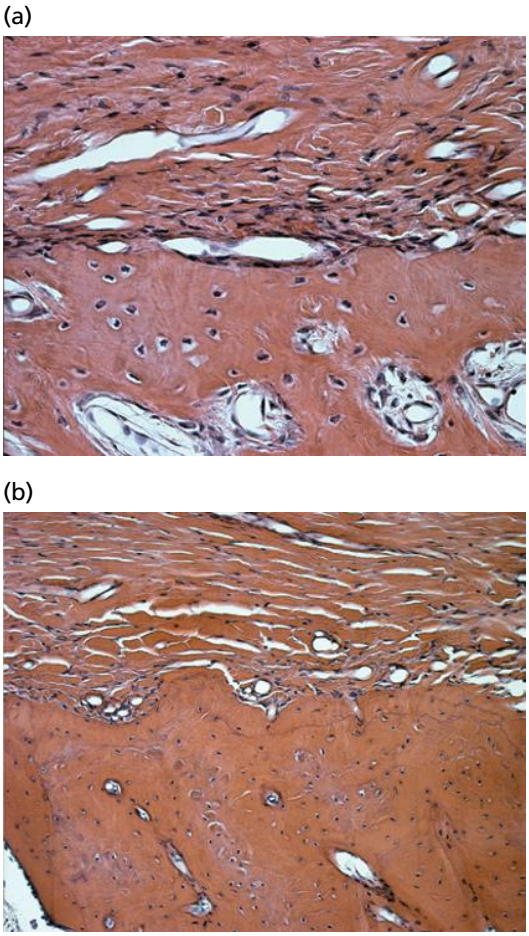


Fig. 3-21 Histologic sections (mesiodistal aspect) describing the hard tissue that has formed at the entrance of a healing extraction socket and the process of corticalization. (a) Woven bone with primary osteons occupies the socket entrance after 60 days of healing. (b) After 180 days, the woven bone has mainly been replaced with lamellar bone.

An important part of socket healing involves the formation of a *hard tissue cap* that will close the marginal entrance to the socket. This cap is initially comprised of woven bone (Fig. 3-21a), but is subsequently remodeled and replaced with lamellar bone that becomes continuous with the cortical plate at the periphery of the edentulous site (Fig. 3-21b). This process is called corticalization.

The wound is now healed, but the tissues in the site will continue to adapt to functional demands. Since there is no stress from forces elicited during mastication and other occlusal contacts, there is no demand on the mineralized bone in the areas previously occupied by the tooth. Thus, in this model the socket apical of the hard tissue cap will remodel mainly into marrow.

Extra-alveolar processes

In an experiment using the dog model (Araújo & Lindhe, 2005), alterations in the profile of the edentulous ridge that occurred following tooth extraction were carefully examined. In this study the third and fourth mandibular premolars were hemi-sected. Buccal and lingual full-thickness flaps were raised; the distal roots were carefully removed. The flaps were replaced and sutured to cover the fresh extraction socket. Biopsy specimens, including an individual extraction socket and adjacent roots, were obtained after 1, 2, 4, and 8 weeks of healing. The blocks were sectioned in the *buccolingual* plane.

- *1 week after tooth extraction* (Fig. 3-22). At this interval the socket is occupied by a coagulum. Furthermore, a large number of osteoclasts can be seen on the outside as well as on the inside of the buccal and

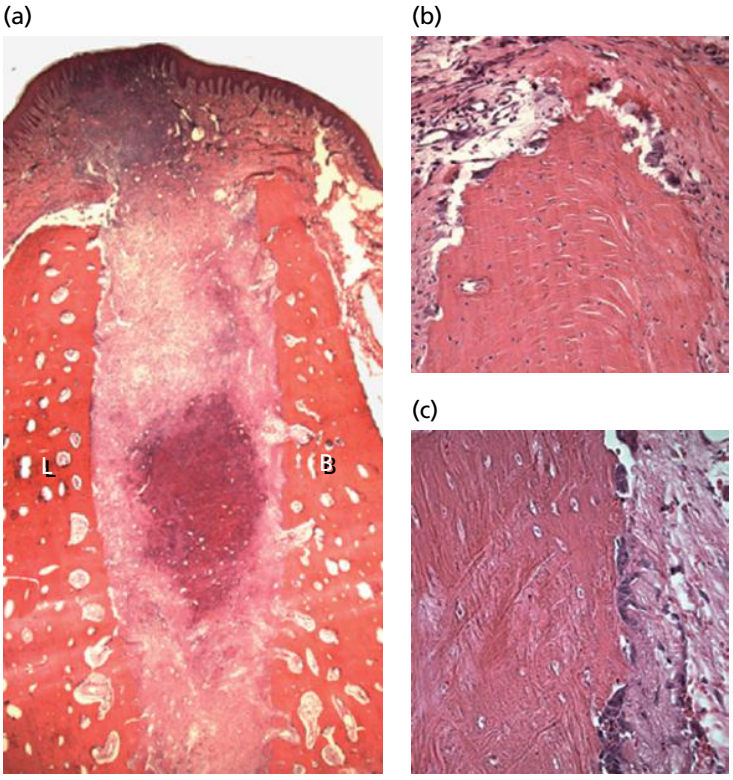


Fig. 3-22 (a) Histologic section (buccolingual aspect) of the socket after 1 week of healing. Note the presence of a large number of osteoclasts on the crestal portion (b) and inner portion (c) of the buccal wall. (B, buccal bone; L, lingual bone.)

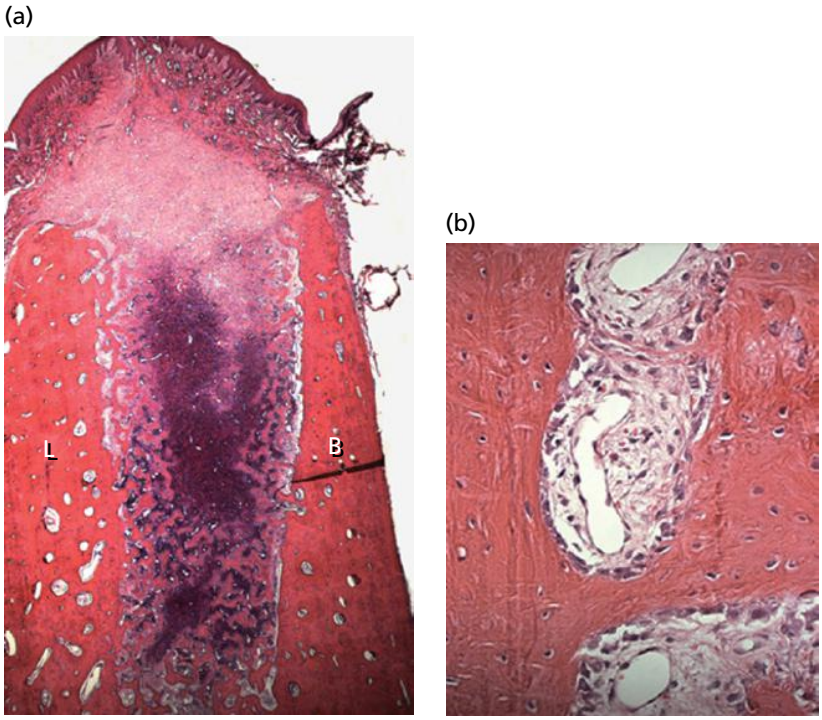


Fig. 3-23 (a) Histologic section (buccolingual aspect) of the socket after 2 weeks of healing. (b) Note that the bundle bone in the lingual aspect of the socket is being replaced with woven bone. (B, buccal bone; L, lingual bone.)

lingual bone walls. The presence of osteoclasts on the inner surface of the socket walls indicates that the bundle bone is being resorbed.

- *2 weeks after tooth extraction* (Fig. 3-23). Newly formed immature bone (woven bone) resides in the apical and lateral parts of the socket, while more central and marginal portions are occupied by a provisional connective tissue. In the marginal and outer portions of the socket walls, numerous osteoclasts can be seen. In several parts of the socket walls the bundle bone has been replaced with woven bone.
- *4 weeks after tooth extraction* (Fig. 3-24). The entire socket is occupied with woven bone at this stage of healing. Large numbers of osteoclasts are present in the outer and marginal portions of the hard tissue walls. Osteoclasts also line the trabeculae of woven bone present in the central and lateral aspects of the socket. In other words, the newly formed woven bone is being replaced with a more mature type of bone.
- *8 weeks after tooth extraction* (Fig. 3-25). A layer of cortical bone covers the entrance to the extraction site. Corticalization has occurred. The woven bone that was present in the socket at the 4-week interval is replaced with bone marrow and some trabeculae of lamellar bone in the 8-week specimens. On the outside and on the top of the buccal and lingual bone wall there are signs of ongoing hard tissue resorption. The crest of the buccal bone wall is located apical of its lingual counterpart.

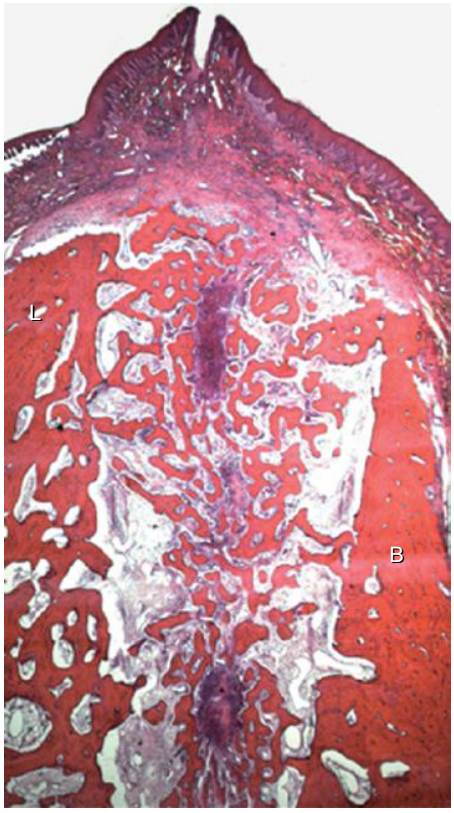


Fig. 3-24 Histologic section (buccolingual aspect) of the socket after 4 weeks of healing. The extraction socket is filled with woven bone. On the top of the buccal wall, the old bone in the crest region is being resorbed and replaced with either connective tissue or woven bone. (B, buccal bone; L, lingual bone.)

The relative change in the location of the crest of the buccal and lingual bone walls that took place during the 8 weeks of healing is illustrated in Fig. 3-26. While the level of the margin of the lingual wall remained reasonably unchanged, the margin of the buccal wall shifted several millimeters in an apical direction. The reason why more bone loss occurred in the buccal than in the lingual wall during socket healing in this animal model is not completely understood.

Prior to tooth extraction, the marginal 1–2 mm of the crest of the thin buccal bone wall was occupied by bundle bone. Only a minor fraction of the crest of the wider lingual wall contained bundle bone. Bundle bone, as stated above, is a tooth-dependent tissue and will gradually disappear after tooth extraction. Thus, since there is relatively more bundle bone in the crest region of the buccal than of the lingual wall, hard tissue loss may become most pronounced in the buccal wall.

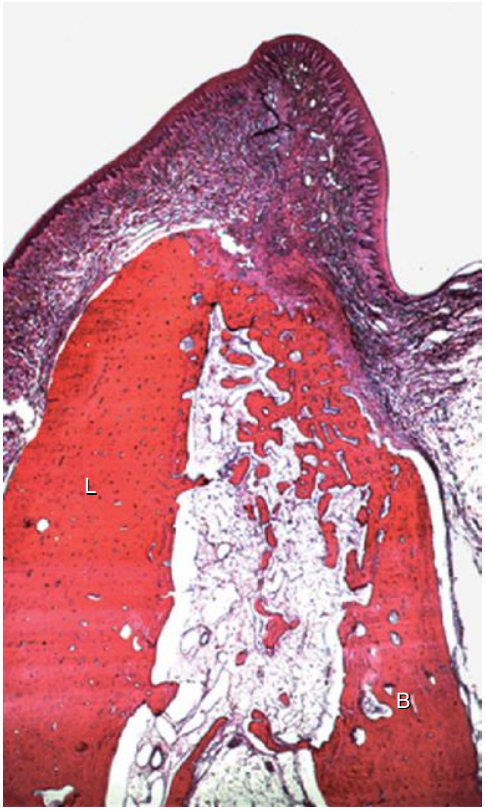


Fig. 3-25 Histologic section (buccolingual aspect) of the socket after 8 weeks of healing. The entrance of the socket is sealed with a cap of newly formed mineralized bone. Note that the crest of the buccal wall is located apical of the crest of the lingual wall. (B, buccal bone; L, lingual bone.)

Topography of the edentulous ridge: Summary

As described previously in this chapter, the processes of modeling and remodeling that occur following tooth extraction (loss) result in resorption of the various components of the previous alveolar process. The amount of tissue loss that occurs in these processes varies considerably from subject to subject and from site to site in the same individual (Figs. 3-27, 3-28).

As a rule, the resorption of the buccal bone wall is more pronounced than the resorption of the lingual/palatal wall and hence the center of the ridge will move in a lingual/palatal direction. In the extreme case, the entire alveolar process may be lost following tooth removal and then only the basal bone of the mandible and the maxilla may remain to constitute the ridge.

The outer (cortical) walls of the remaining portion of the alveolar ridge (basal bone and residues of the alveolar process) are comprised of lamellar bone. The cortical plates of the ridge often enclose the cancellous bone that harbors trabeculae of lamellar bone and marrow (Fig. 3-29). The bone marrow contains numerous vascular structures as well as adipocytes and pluripotent mesenchymal cells.

Depending on factors such as the type of jaw (maxilla or mandible), location (anterior, posterior) in the jaw, depth of the buccal and lingual vestibule, and amount of hard tissue resorption, the edentulous ridge may be lined with either masticatory, keratinized mucosa, or lining, non-keratinized mucosa.

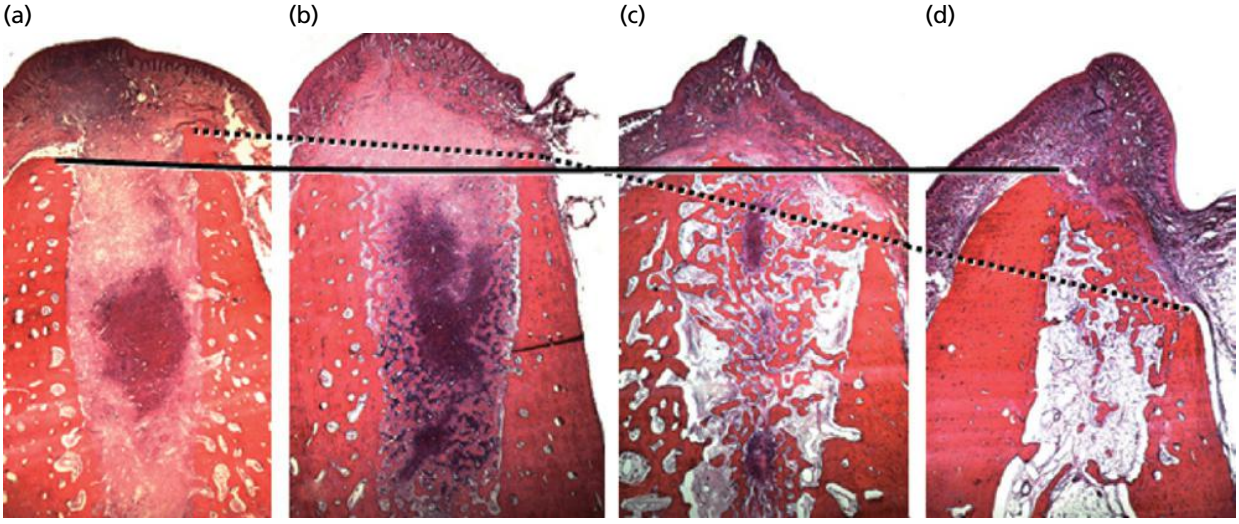


Fig. 3-26 Histologic sections (buccolingual aspects) showing the profile of the edentulous region in the dog after (a) 1, (b) 2, (c) 4, and (d) 8 weeks of healing following tooth extraction. While the marginal level of the lingual wall was maintained during the process of healing (solid line), the crest of the buccal wall was displaced >2 mm in the apical direction (dotted line).

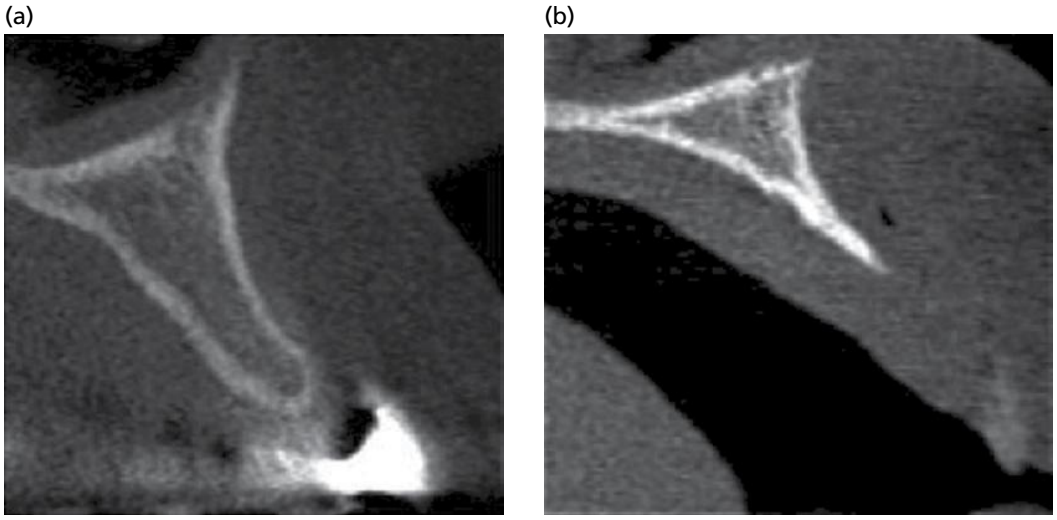


Fig. 3-27 Cone-beam computed tomograms that illustrate edentulous incisor sites of the maxilla with (a) large amounts of remaining hard tissue (cortical bone as well as trabecular bone) and (b) minute remnants of ridge tissue (only cortical bone).

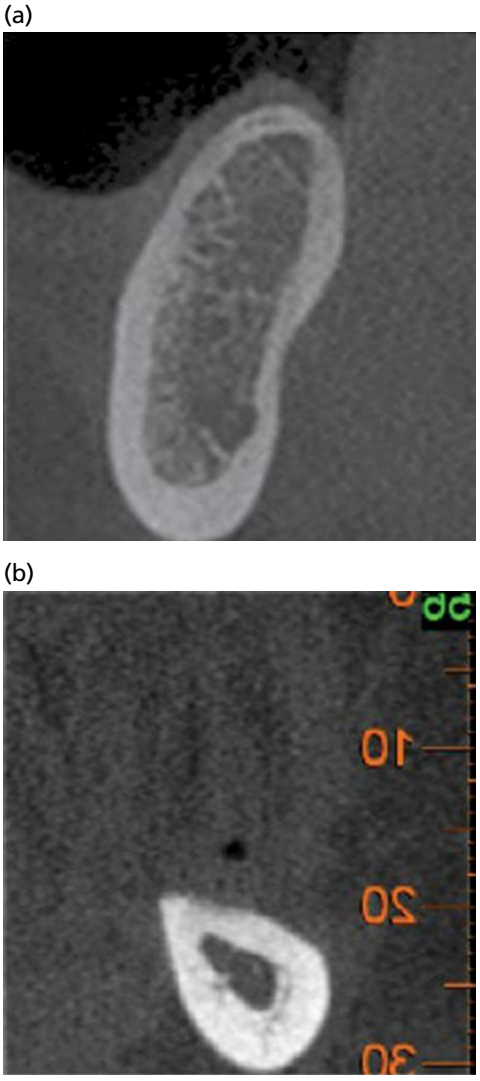


Fig. 3-28 Cone-beam computed tomograms illustrating edentulous regions of the first molar region of the mandible. (a) Remaining bone of the ridge is voluminous, is lined by dense cortical bone, and harbors large amounts of trabecular bone. (b) In this edentulous site, the entire alveolar process is lost and only the tissue of the corpus mandibulae remains.

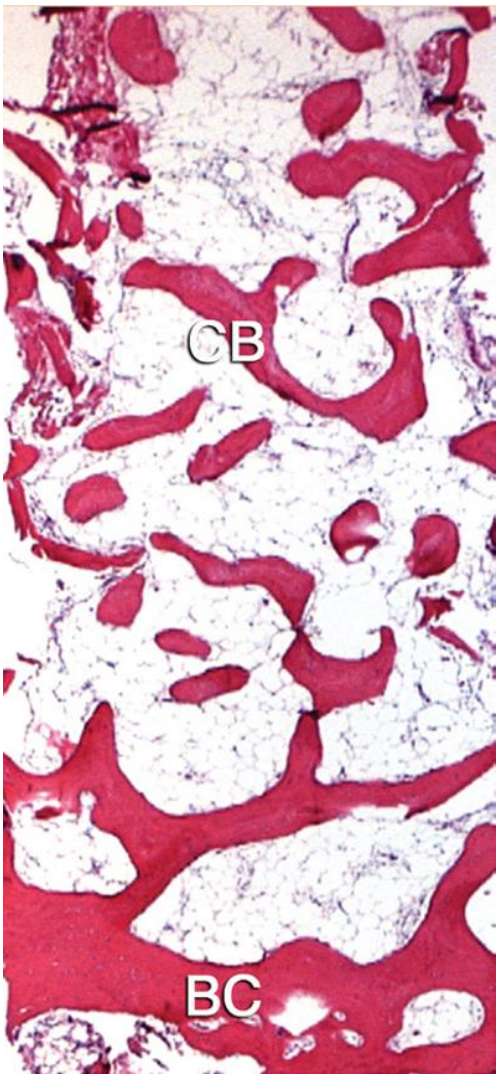


Fig. 3-29 Histologic section representing an edentulous maxilla. The biopsy was obtained >6 months post extraction. The marginal portion of the tissue (the bone crest [BC]) is comprised of dense lamellar bone, while more central portions harbor the cancellous bone (CB).

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Chapter 4

The Mucosa at Teeth and Implants

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Gingiva

Biologic width

A term frequently used to describe the dimensions of the soft tissues that face the teeth is the *biologic width of the soft tissue attachment*. The development of the *biologic width concept* was based on studies and analyses by, among others, Gottlieb (1921), Orban and Köhler (1924), and Sicher (1959), who documented that the soft tissue attached to the teeth was comprised of two parts, one of fibrous tissue and one of epithelium. In a publication by Gargiulo *et al*. (1961) called "Dimensions and relations of the dentogingival junction in humans", sections from autopsy block specimens that exhibited different degrees of "passive tooth eruption" (i.e. periodontal tissue breakdown) were examined. Histometric assessments were made to describe the length of the sulcus (not part of the attachment), the epithelial attachment (today called the junctional epithelium), and the connective tissue attachment (Fig. 4-1). It was observed that the length of the connective tissue attachment varied within narrow limits (1.06–1.08 mm), while the length of the attached epithelium was about 1.4 mm at sites with normal periodontium, 0.8 mm at sites with moderate and 0.7 mm at sites with advanced periodontal tissue breakdown. In other words, (1) the biologic width of the attachment varied between about 2.5 mm in the normal case and 1.8 mm in the advanced disease case, and (2) the most variable part of the attachment was the length of the epithelial attachment (junctional epithelium).

Dimensions of the buccal tissue

The morphologic characteristics of the gingiva are related to the dimension of the alveolar process, the form (anatomy) of the teeth, events that occur during tooth eruption, and the eventual inclination and position of the fully erupted teeth (Wheeler 1961; O'Connor & Biggs 1964; Weisgold 1977). Oschenbein and Ross (1969) and Becker *et al*. (1997) proposed (1) that the anatomy of the gingiva is related to the contour of the osseous crest and (2) that two basic types of gingival architecture may exist, namely the "*pronounced scalloped*" and the "*flat*" biotype.

Subjects who belong to the "*pronounced scalloped*" biotype have long and slender teeth with tapered crown form, delicate cervical convexity, and minute interdental contact areas that are located close to the incisal edge (Fig. 4-2). The maxillary front teeth of such individuals are surrounded by a thin free gingiva, the buccal margin of which is located at or apical of the cementoenamel junction. The zone of gingiva is narrow, and the outline of the gingival margin is highly scalloped (Olsson *et al*. 1993). On the

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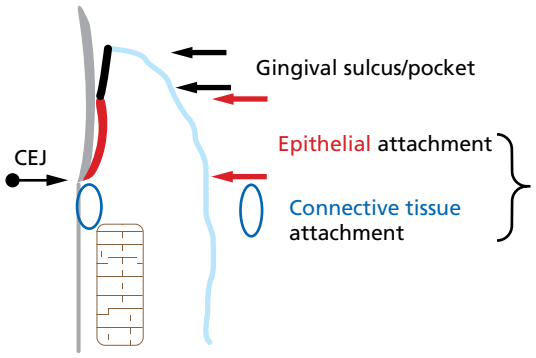


Fig. 4-1 Schematic drawing describing the "biologic width" of the soft tissue attachment at the buccal surface of a tooth with healthy periodontium. The combined length of the junctional epithelium (epithelial attachment) and the connective tissue attachment is considered to represent the "biologic width" of the soft tissue attachment. Note the gingival sulcus is *not* part of the attachment.

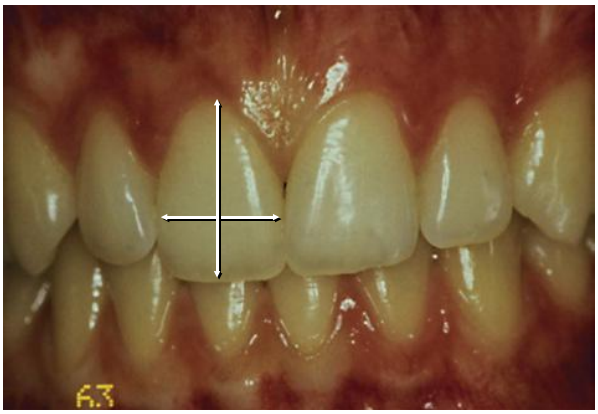


Fig. 4-2 Clinical photograph of a subject who belongs to the "pronounced scalloped" gingival biotype. The crowns of the teeth are comparatively long and slender. The papillae are comparatively long, the gingival margin is thin, and the zone of attached gingiva is short.

other hand, subjects who belong to the "*flat*" gingival biotype have incisors with squared crown form with pronounced cervical convexity (Fig. 4-3). The gingiva of such individuals is wider and more voluminous, the contact areas between the teeth are large and more apically located, and the interdental papillae are short. It was reported that subjects with a pronounced scalloped gingiva often exhibited more advanced soft tissue recession in the anterior maxilla than subjects with a flat gingiva (Olsson & Lindhe 1991).

Kan *et al*. (2003) measured the dimension of the gingiva – as determined by bone sounding – at the buccomesial and buccodistal aspects of maxillary anterior teeth. Bone sounding determines the distance between the soft tissue margin and the crest of the bone and, hence, provides an estimate that is about 1 mm greater than that obtained in a regular probing pocket depth measurement. The authors reported that the thickness of the gingiva varied between subjects of different gingival biotypes. Thus, the height of the gingiva at the buccal-approximal surfaces in subjects who belonged to the flat biotype was, on average, 4.5 mm, while in subjects belonging

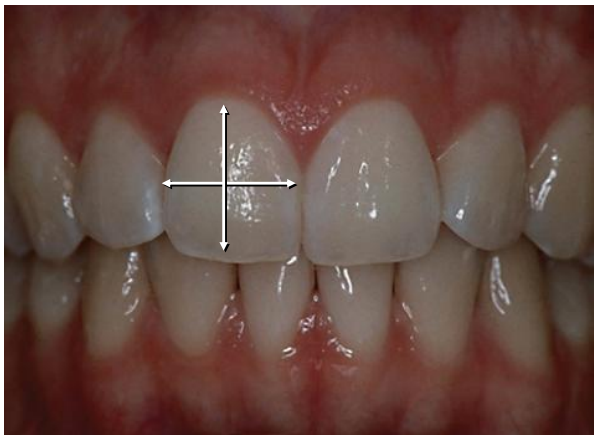


Fig. 4-3 Clinical photograph of a subject who belongs to the "flat" gingival biotype. The crowns of the teeth are comparatively short but wide. The papillae are comparatively short but voluminous and the zone of attached gingiva is wide.

to the pronounced scalloped biotype the corresponding dimension (3.8 mm) was significantly smaller. This indicates that subjects who belong to the flat biotype have more voluminous soft buccal/approximal tissues than subjects who belong to the pronounced scalloped biotype.

Pontoriero and Carnevale (2001) evaluated the reformation of the gingival unit at the buccal aspect of teeth exposed to crown lengthening procedures using a denudation technique. At the 1-year follow-up examination after surgery, the regain of soft tissue – measured from the level of the denuded osseous crest – was greater in patients with a thick (flat) biotype than in those with a thin (pronounced scalloped) biotype (3.1 mm versus 2.5 mm). No assessment was made of the bone level change that had occurred between the baseline and the follow-up examination. It must, however, be anticipated that some bone resorption had taken place during healing and that the biologic width of the new connective tissue attachment had been re-established coronal to the level of the resected osseous crest.

The dimensions of the buccal gingiva may also be affected by the buccolingual position of the tooth within the alveolar process. A change of the tooth position in the buccal direction results in reduced dimensions of the buccal gingiva, while an increase is observed following a lingual tooth movement (Coatoam *et al*. 1981; Andlin-Sobocki & Brodin 1993). In fact, Müller and Könönen (2005) demonstrated in a study of the variability of the thickness of the buccal gingiva of young adults that most of the variation in gingival thickness was due to the tooth position and that the contribution of subject variability (i.e. flat and pronounced scalloped biotypes) was minimal.

Dimensions of the interdental papilla

The interdental papilla in a normal, healthy dentition has one buccal and one lingual/palatal component that are joined in the col region (see Chapter 1;

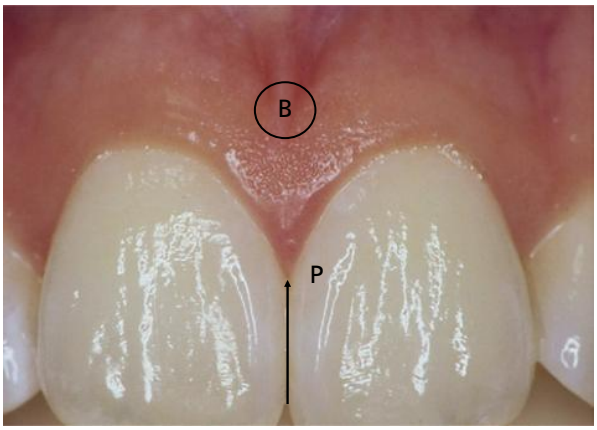


Fig. 4-4 Tarnow *et al.* (1992) measured the distance between the contact point (P) between the crowns of the teeth and the bone crest (B) using sounding (transgingival probing).

Figs. 1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9). Experiments performed in the 1960s (Kohl & Zander 1961; Matherson & Zander 1963) revealed that the shape of the papilla in the col region was not determined by the outline of the bone crest, but by the shape of the contact relationship that existed between adjacent teeth.

Tarnow *et al*. (1992) studied whether the distance between the contact point (area) between teeth and the crest of the corresponding interproximal bone could influence the degree of papilla fill that occurred at the site. Presence or absence of a papilla was determined visually in periodontally healthy subjects. If there was no space visible apical of the contact point, the papilla was considered complete. If a "black space" was visible at the site, the papilla was considered incomplete. The distance between the facial level of the contact point and the bone crest (Fig. 4-4) was measured by sounding. The measurement thus included not only the epithelium and connective tissue of the papilla, but in addition the entire supraalveolar connective tissue in the interproximal area (Fig. 4-5). The authors reported that the papilla was always complete when the distance from the contact point to the crest of the bone was ≤5 mm. When this distance was 6 mm, papilla fill occurred in about 50% of cases and when ≥7 mm, it was incomplete in about 75% of cases. Considering that the supracrestal connective tissue attachment is about 1 mm high, these data indicate that the papilla height may be limited to about 4 mm in most cases. Interestingly, papillae of similar height (3.2–4.3 mm) were found to reform following surgical denudation procedures (van der Velden 1982; Pontoriero & Carnevale 2001), but to a greater height in patients with a thick (flat) than in those with a thin (pronounced scalloped) biotype.

Summary

- *Flat gingival (periodontal) biotype*: the buccal marginal gingiva is comparatively thick, the papillae are often short, the bone of the buccal cortical wall is thick, and the vertical distance between the interdental bone crest and the buccal bone is short (about 2 mm).
- *Pronounced scalloped gingival (periodontal) biotype*: the buccal marginal gingiva is delicate and may often be located apical of the cementoenamel junction (receded), the papillae are high and slender, the buccal bone wall is often thin, and the vertical distance between the interdental bone crest and the buccal bone is long (>4 mm).

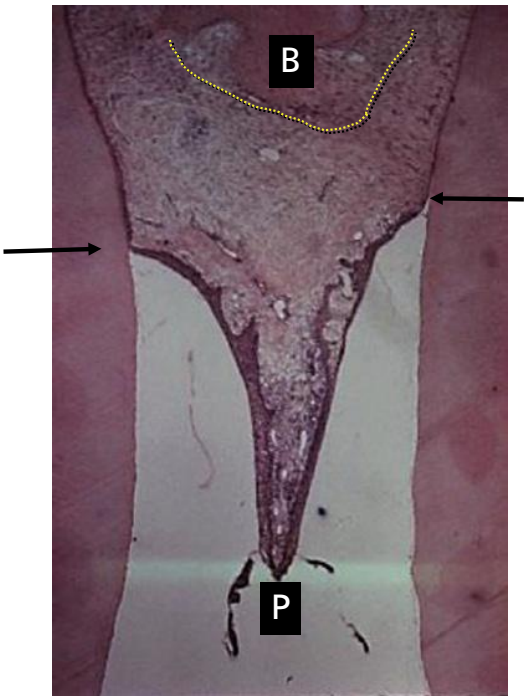


Fig. 4-5 Mesiodistal section of the interproximal area between the two central incisors. Arrows indicate the location of the cementoenamel junction. Dotted line indicates the outline of the marginal bone crest. The distance between the contact point (P) between the crowns of the teeth and the bone crest (B) indicates the height of the papilla.

Peri-implant mucosa

The soft tissue that surrounds dental implants is termed *peri-implant mucosa*. Features of the peri-implant mucosa are established during the process of wound healing that occurs subsequent to the closure of mucoperiosteal flaps following implant installation (one-stage procedure) or following abutment connection (two-stage procedure) surgery. Healing of the mucosa results in the establishment of a soft tissue attachment (transmucosal attachment) to the implant. This attachment serves as a seal that prevents products from the oral cavity reaching the bone tissue, and thus ensures osseointegration and the rigid fixation of the implant.

The peri-implant mucosa and the gingiva have several clinical and histologic characteristics in common. Some important differences, however, also exist between the gingiva and the peri-implant mucosa.

Biologic width

The structure of the mucosa that surrounds implants made of titanium has been examined in humans and several animal models (for review, see Berglundh 1999). In an early study in the dog, Berglundh *et al.* (1991) compared some anatomic features of the gingiva at teeth and the mucosa at implants. Details of the research model used in this study are briefly outlined here, as this model was used in subsequent experiments that will be described in this chapter.

The mandibular premolars on one side of the mandible were extracted, leaving the corresponding teeth in the contralateral jaw quadrant. After 3 months of healing following tooth extraction (Fig. 4-6), the fixture part of the implants (Brånemark System®; Nobel Biocare, Gothenburg, Sweden) were installed (Fig. 4-7) and submerged according to the guidelines in the manual for the system. Another 3 months later, abutment connection was performed (Fig. 4-8) in a second-stage procedure, and the animals were placed in a carefully monitored plaque-control program. Four months subsequent to abutment connection, the dogs were exposed to a clinical examination following which biopsy specimens of several tooth and all implant sites were harvested.

The clinically healthy gingiva and peri-implant mucosa had a pink color and a firm consistency (Fig. 4-9). On radiographs obtained from the tooth sites, it was observed that the alveolar bone crest was located about 1 mm apical of a line connecting the cementoenamel junction of neighboring premolars (Fig. 4-10). The radiographs from the implant sites disclosed that the bone crest was close to the junction between the abutment and the fixture part of the implant (Fig. 4-11).

Histologic examination of the sections revealed that the two soft tissue units, the gingiva and the peri-implant mucosa, had several features in common. The oral epithelium of the gingiva was well

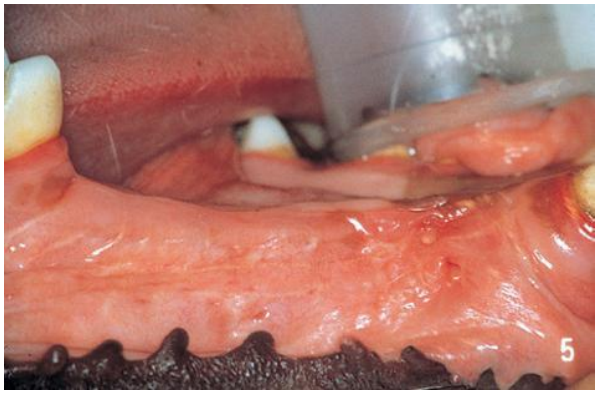


Fig. 4-6 Edentulous mandibular right premolar region 3 months following tooth extraction. (Source: Berglundh *et al.* 1991. Reproduced with permission from John Wiley & Sons.)

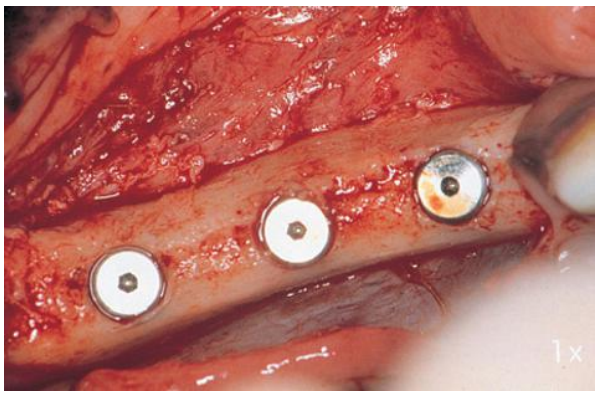


Fig. 4-7 Three titanium implants (i.e. the fixture part and cover screw; Brånemark System®) are installed.

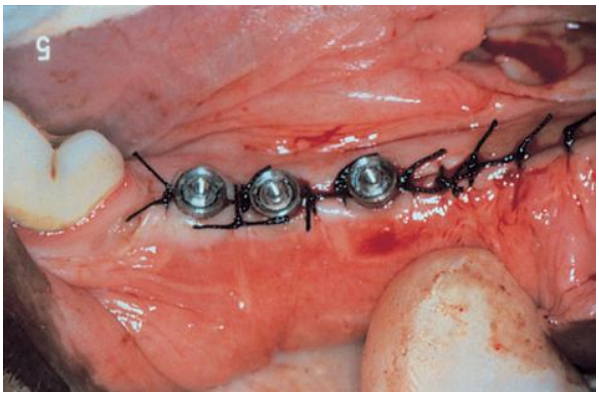
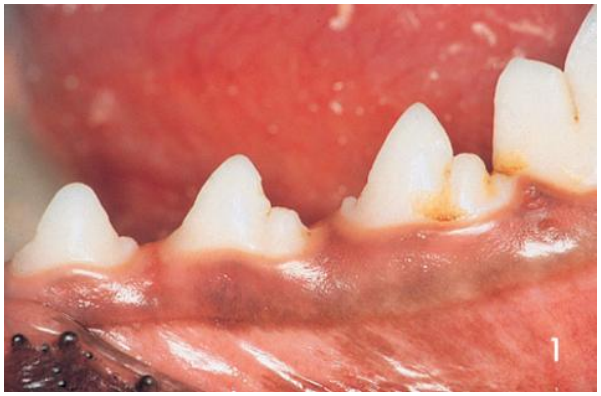


Fig. 4-8 Abutment connection is performed and the mucosa sutured with interrupted sutures.

(a)



(b)

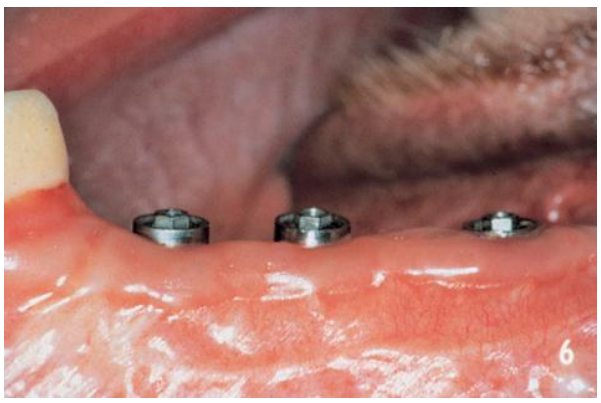


Fig. 4-9 After 4 months of careful plaque control, the gingiva (a) and the peri-implant mucosa (b) are clinically healthy.

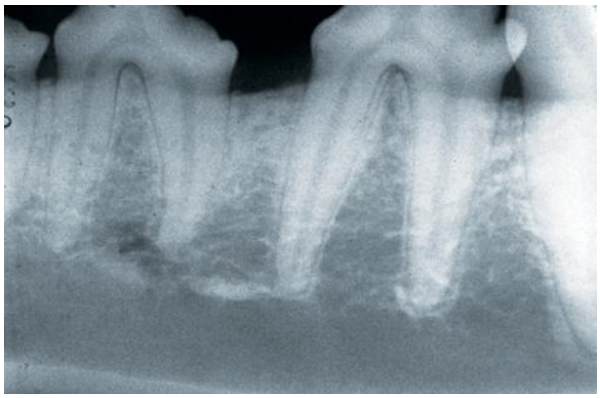


Fig. 4-10 Radiograph obtained of the premolars in the left side of the mandible.

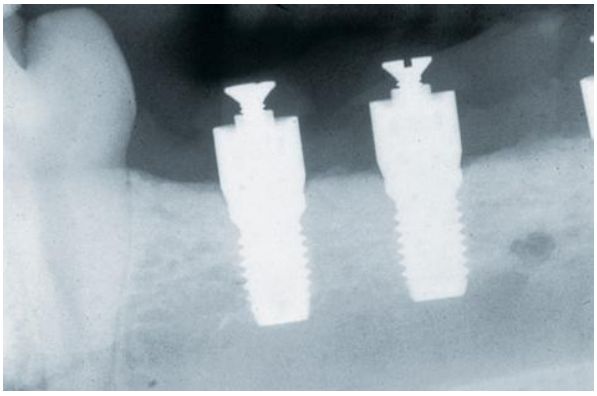


Fig. 4-11 Radiograph obtained of the implants in the right side of the mandible.

keratinized and continuous with the thin junctional epithelium that faced the enamel and that ended at the cementoenamel junction (Fig. 4-12). The supra-alveolar connective tissue was about 1 mm high and the periodontal ligament about 0.2–0.3 mm wide. The principal fibers were observed to extend from the root cementum in a fan-shaped pattern into the soft and hard tissues of the marginal periodontium (Fig. 4-13).

The outer surface of the peri-implant mucosa was also covered by a keratinized oral epithelium, which in the marginal border connected with a thin barrier epithelium (similar to the junctional epithelium at the teeth) that faced the abutment part of the implant (Fig. 4-14). It was observed that the barrier epithelium was only a few cell layers thick (Fig. 4-15) and that the epithelial structure terminated about 2 mm apical of the soft tissue margin (Fig. 4-14) and 1–1.5 mm from the bone crest. The connective tissue in the compartment above the bone appeared to be in direct contact with the surface (TiO_2) of the implant (Figs. 4-14, 4-15, 4-16). The collagen fibers in this connective tissue apparently originated from the periosteum of the bone crest and extended towards the margin of the soft tissue in directions parallel to the surface of the abutment.

The observation that the barrier epithelium of the healthy mucosa consistently ended at a certain

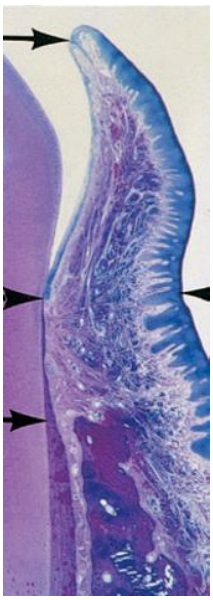


Fig. 4-12 Microphotograph of a cross-section of the buccal and coronal part of the periodontium of a mandibular premolar. Note the position of the soft tissue margin (top arrow), the apical cells of the junctional epithelium (center arrowheads), and the crest of the alveolar bone (bottom arrow). The junctional epithelium is about 2 mm long and the supracrestal connective tissue portion about 1 mm high.

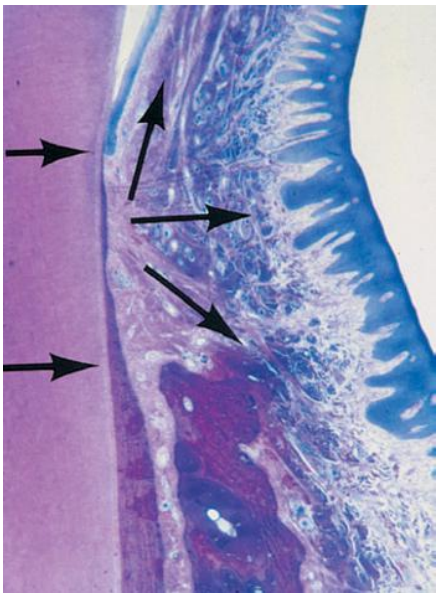


Fig. 4-13 Higher magnification of the supracrestal connective tissue portion seen in Fig. 4-12. Note the direction of the principal fibers (arrows).

distance (1–1.5 mm) from the bone is important. During healing following implant installation surgery, fibroblasts of the connective tissue of the mucosa apparently formed a biologic attachment to the TiO_2 layer of the "apical" portion of the abutment portion of the implant. This attachment zone was evidently not recognized as a wound and was therefore not covered with an epithelial lining.

In further dog experiments (Abrahamsson *et al.* 1996, 2002), it was observed that a similar mucosal attachment formed when different types of implant

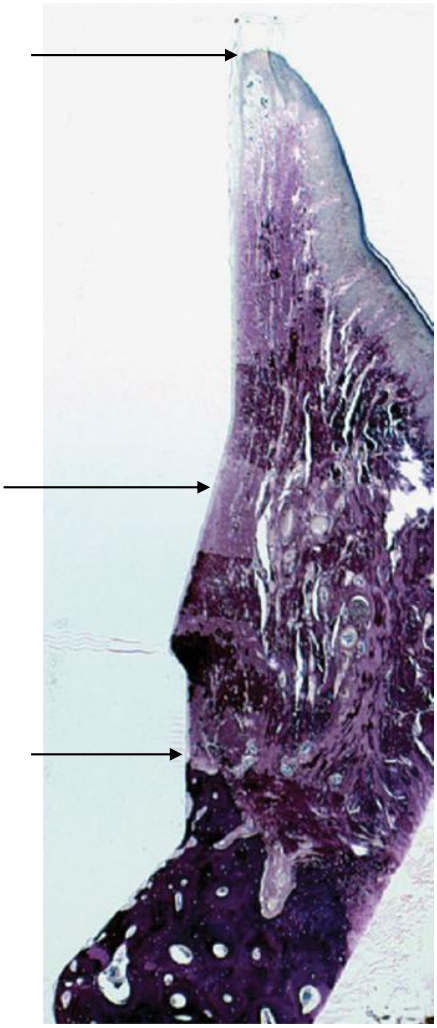


Fig. 4-14 Microphotograph of a buccolingual section of the peri-implant mucosa. Note the position of the soft tissue margin (top arrow), the apical cells of the junctional epithelium (center arrow), and the crest of the marginal bone (bottom arrow). The junctional epithelium is about 2 mm long and the implant–connective tissue interface about 1.5 mm high.

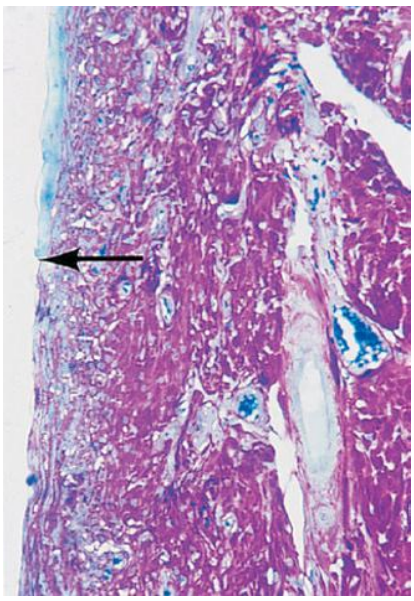


Fig. 4-15 Higher magnification of the apical portion of the barrier epithelium (arrow) in Fig. 4-14.

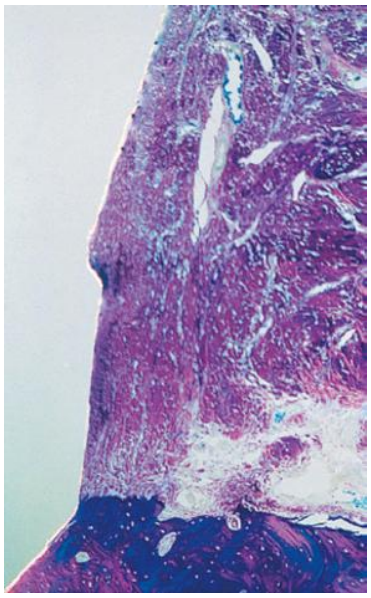


Fig. 4-16 Microphotograph of a section (buccolingual) of the implant–connective tissue interface of the peri-implant mucosa. The collagen fibers invest in the periosteum of the bone and project in directions parallel to the implant surface towards the margin of the soft tissue.

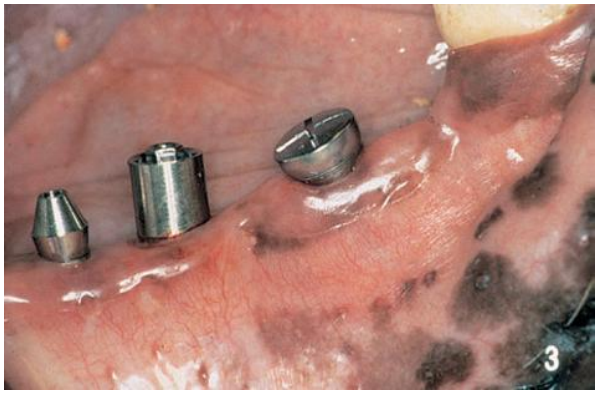


Fig. 4-17 Implants of three systems installed in the mandible of a Beagle dog. AstraTech Implants® Dental System (left), Brånemark System® (center) and ITI® Dental Implant System (right).

systems were used (e.g. AstraTech Implant System, AstraTech Dental, Mölndal, Sweden; Brånemark System®; Straumann® Dental Implant System, Straumann AG, Basel, Switzerland; 3i® Implant System, Implant Innovation Inc., West Palm Beach, FL, USA). In addition, the formation of the attachment appeared to be independent of whether the implants were initially submerged or not (Figs. 4-17, 4-18).

In subsequent studies (Abrahamsson *et al*. 1998; Welander *et al*. 2008), it was demonstrated that the material used in the abutment part of the implant was of decisive importance for the location of the connective tissue portion of the transmucosal attachment. Abutments made of aluminum-based sintered ceramic (Al_2O_3) and zirconium dioxide (ZrO_2) allowed for the establishment of a mucosal attachment similar to that which occurred at titanium abutments. Abutments made of a gold alloy or dental

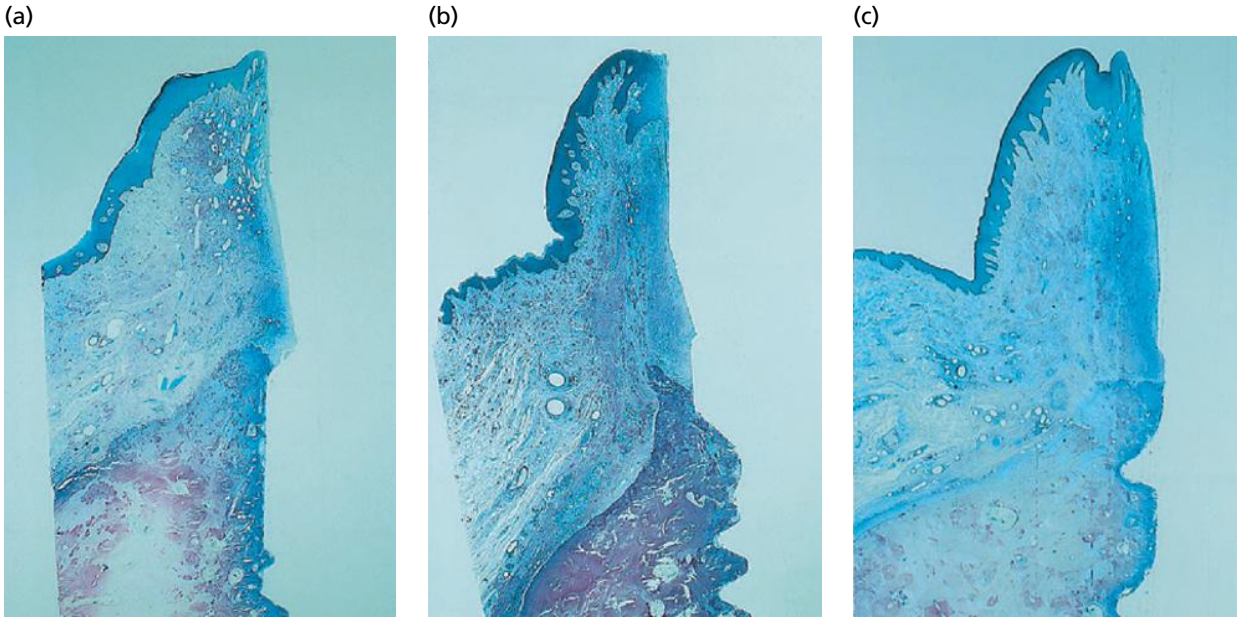


Fig. 4-18 Microphotographs illustrating the mucosa (buccolingual view) facing the three implant systems. (a) AstraTech Implants® Dental System. (b) Brånemark System®. (c) ITI® Dental Implant System.

porcelain, however, provided conditions for inferior mucosal healing. When such materials were used, the connective tissue attachment failed to develop at the abutment level. Instead, the connective tissue attachment occurred in a more apical location. Thus, during healing following the abutment connection surgery, some resorption of the marginal peri-implant bone took place to expose the titanium portion of the fixture (Brånemark System®) to which the connective tissue attachment eventually formed.

The location and dimensions of the transmucosal attachment were examined in a dog experiment by Berglundh and Lindhe (1996). Implants (fixtures) of the Brånemark System® were installed in edentulous premolar sites and submerged. After 3 months of healing, abutment connection was performed. On the left side of the mandible, the volume of the ridge mucosa was maintained, while on the right side the vertical dimension of the mucosa was reduced to 2 mm or less (Fig. 4-19) before the flaps were replaced and sutured. In biopsy specimens obtained after another 6 months, it was observed that the transmucosal attachment at all implants included a barrier epithelium component that was about 2 mm long and a zone of connective tissue that was about 1.3–1.8 mm high.

Further examination disclosed that at sites with a thin mucosa, wound healing had consistently included marginal bone resorption to establish space for a mucosa that eventually could harbor both the epithelial and the connective tissue components of the transmucosal attachment (Figs. 4-20, 4-21).

The dimensions of the epithelial and connective tissue components of the transmucosal attachment at implants are established during wound healing following implant surgery. As is the case for bone healing after implant placement (see Chapter 5),

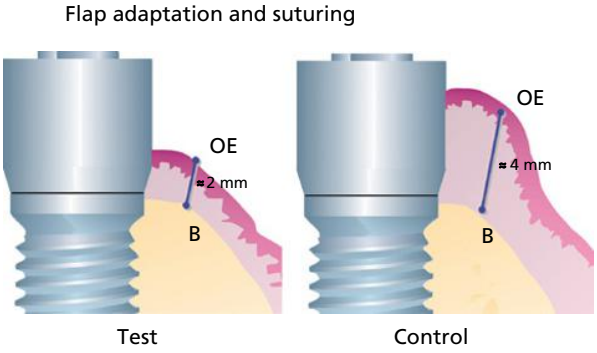


Fig. 4-19 Schematic drawing illustrating that the mucosa at the test site was reduced to about 2 mm. (Source: Berglundh *et al.* 1991. Reproduced with permission from John Wiley & Sons.)

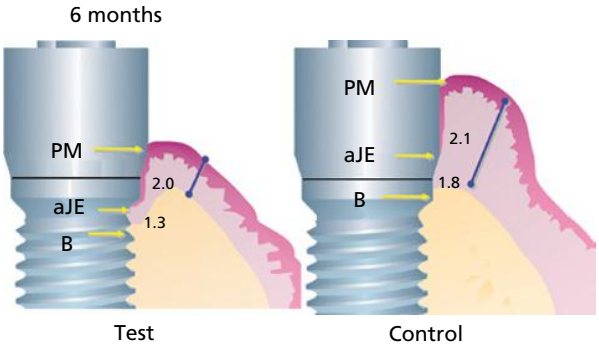


Fig. 4-20 Schematic drawing illustrating that the peri-implant mucosa at both control and test sites contained a 2-mm long barrier epithelium and a zone of connective tissue that was about 1.3–1.8 mm high. Bone resorption occurred in order to accommodate the soft tissue attachment at sites with a thin mucosa. (Source: Berglundh & Lindhe 1996. Reproduced with permission from John Wiley & Sons.)

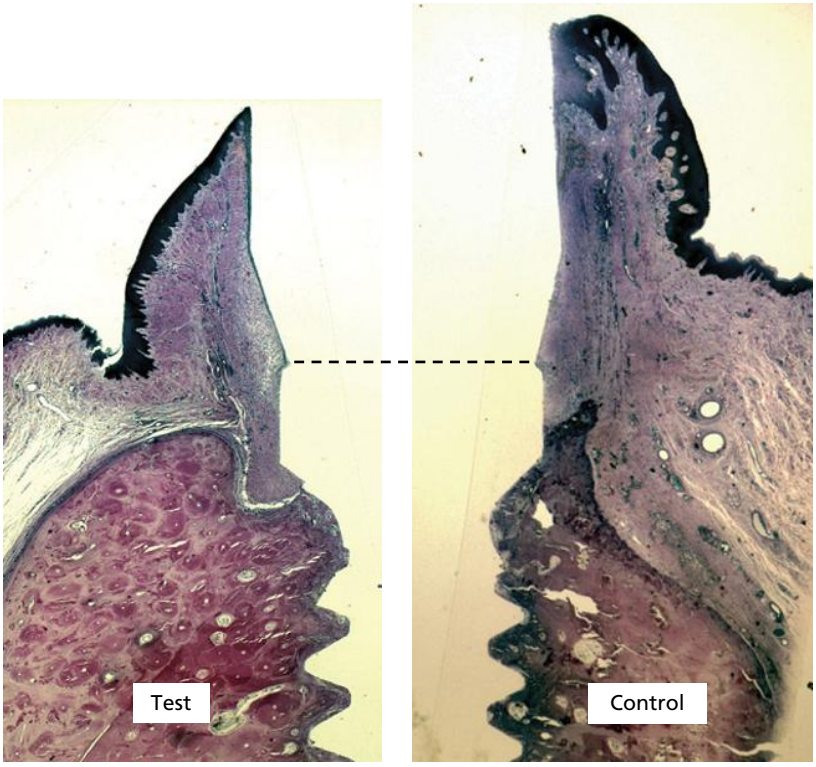


Fig. 4-21 Microphotograph illustrating the peri-implant mucosa of a normal dimension (Control) and reduced dimension (Test). Note the angular bone loss that had occurred at the site with the thin mucosa.

the wound healing in the mucosa around implants is a delicate process that requires several weeks of tissue remodeling.

In an animal experiment, Berglundh *et al*. (2007) described the morphogenesis of the mucosa attachment to implants made of c.p. titanium. A non-submerged implant installation technique was used and the mucosal tissues were secured to the conical marginal portion of the implants (Straumann® Dental Implant System) with interrupted sutures. The sutures were removed after 2 weeks and a plaque-control program was initiated. Biopsies were performed at various intervals to provide healing periods extending from day 0 (2 hours) to 12 weeks. It was reported that large numbers of neutrophils infiltrated and degraded the coagulum that occupied the compartment between the mucosa and the implant during the initial phase of healing. The first signs of epithelial proliferation were observed in specimens representing 1–2 weeks of healing and a mature barrier epithelium was seen after 6–8 weeks. It was also demonstrated that the collagen fibers of the mucosa were organized after 4–6 weeks of healing. Thus, prior to this time interval, the connective tissue is not properly arranged.

Summary: The junctional and barrier epithelia are about 2 mm long and the zones of supra-alveolar connective tissue are between 1 and 1.5 mm high. Both epithelia are attached via hemi-desmosomes to the tooth/implant surface (Gould et al. 1984). The main attachment fibers (the principal fibers) invest in the root cementum of the tooth, but at the implant site the equivalent fibers run in a direction parallel to the implant and fail to attach to the metal body. The soft tissue attachment to implants is properly established several weeks following surgery.

Quality

The quality of the connective tissue in the supra-alveolar compartments at teeth and implants was examined by Berglundh *et al*. (1991). The authors observed that the main difference between the mesenchymal tissue present at a tooth and at an implant site was the occurrence of cementum on the root surface in the former. From this cementum (Fig. 4-22), coarse dentogingival and dentoalveolar collagen fiber bundles projected in lateral, coronal, and apical directions (see Fig. 4-13). At the implant site, the collagen fiber bundles were orientated in an entirely different manner. Thus, the fibers invested in the periosteum at the bone crest and projected in directions parallel to the implant surface (Fig. 4-23). Some of the fibers became aligned as coarse bundles in areas distant from the implant (Buser *et al*. 1992).

The connective tissue in the supracrestal area at implants was found to contain more collagen fibers, but fewer fibroblasts and vascular structures, than the tissue in the corresponding location at teeth. Moon *et al*. (1999), in a dog experiment, reported that the attachment tissue close to the implant (Fig. 4-24) contained only a few blood vessels, but a large number of fibroblasts that were orientated with their long axes parallel to the implant surface (Fig. 4-25). In more lateral compartments, there were fewer fibroblasts, but more collagen fibers and

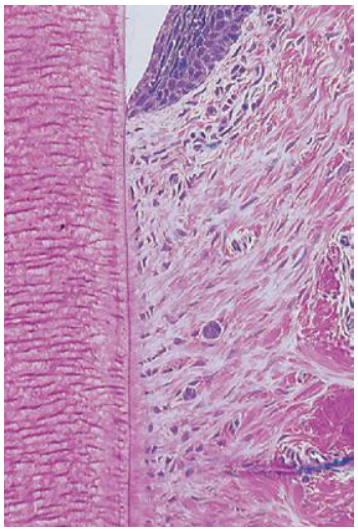


Fig. 4-22 Microphotograph of a tooth with marginal periodontal tissues (buccolingual section). Note on the tooth side the presence of an acellular root cementum with inserting collagen fibers. The fibers are orientated more or less perpendicular to the root surface.

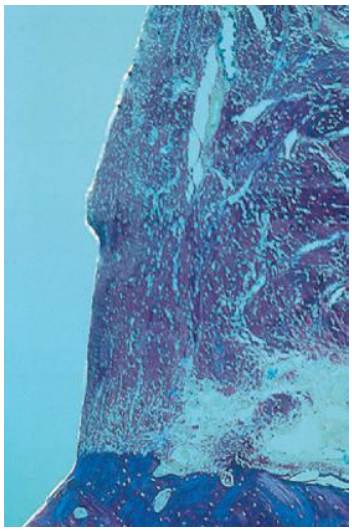


Fig. 4-23 Microphotograph of the peri-implant mucosa and the bone at the tissue–titanium interface. Note that the orientation of the collagen fibers is more or less parallel (not perpendicular) to the titanium surface.

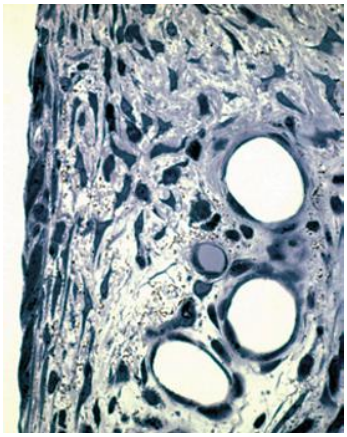


Fig. 4-24 Microphotograph of the implant–connective tissue interface of the peri-implant mucosa. A large number of fibroblasts reside in the tissue next to the implant.

Fig. 4-25 Electron micrograph of the implant–connective tissue interface. Elongated fibroblasts are interposed between thin collagen fibrils (magnification ×24 000).

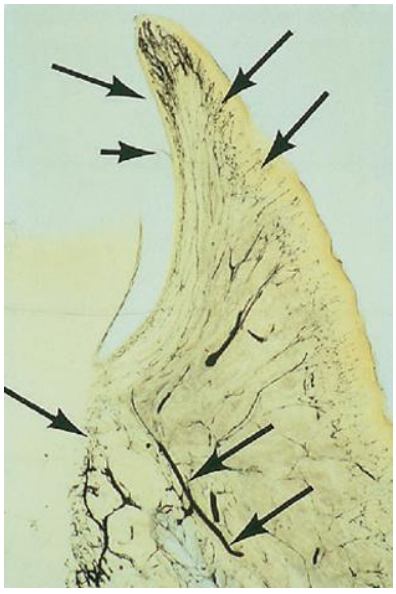


Fig. 4-26 Buccolingual cleared section of a Beagle dog gingiva. The vessels have been filled with carbon (arrows). Note the presence of a supraperiosteal vessel on the outside of the alveolar bone, the presence of a plexus of vessels within the periodontal ligament, as well as vascular structures in the very marginal portion of the gingiva.

more vascular structures. From these and other similar findings, it may be concluded that the connective tissue attachment between the titanium surface and the connective tissue is established and maintained by fibroblasts.

Vascular supply

The vascular supply to the gingiva comes from two different sources (Fig. 4-26). The first source is represented by the large *supraperiosteal blood vessels* that put forth branches to form (1) the capillaries of the connective tissue papillae under the oral epithelium and (2) the vascular plexus lateral to the junctional epithelium. The second source is the *vascular*

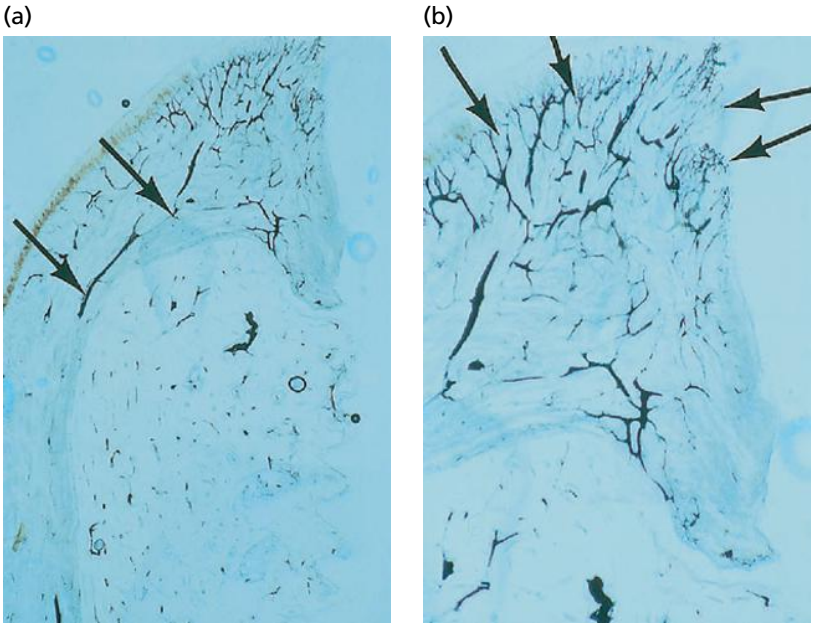


Fig. 4-27 (a) Buccolingual cleared section of a Beagle dog mucosa facing an implant (the implant was positioned to the right). Note the presence of a supraperiosteal vessel on the outside of the alveolar bone (arrows), but also that there is no vasculature that corresponds to the periodontal ligament plexus. (b) Higher magnification (of a) of the peri-implant soft tissue and the bone implant interface. Note the presence of a vascular plexus lateral to the junctional epithelium (arrows), but the absence of vessels in the more apical portions of the soft tissue facing the implant and the bone.

plexus of the periodontal ligament, from which branches run in a coronal direction and terminate in the supra-alveolar portion of the free gingiva. Thus, the blood supply to the zone of supra-alveolar connective tissue attachment in the periodontium is derived from two apparently independent sources (see Chapter 1).

Berglundh *et al.* (1994) observed that the vascular system of the peri-implant mucosa of dogs (Fig. 4-27) originated *solely* from the large *supraperiosteal blood vessel* on the outside of the alveolar ridge. This vessel gave off branches to the supra-alveolar mucosa and formed (1) the capillaries beneath the oral epithelium and (2) the vascular plexus located immediately lateral to the barrier epithelium. The connective tissue part of the transmucosal attachment to titanium implants contained only a few vessels, all of which could be identified as terminal branches of the *supraperiosteal blood vessels.*

Summary: The gingiva at teeth and the mucosa at dental implants shave some characteristics, but differ in the composition of the connective tissue, the alignment of the collagen fiber bundles, and the distribution of vascular structures in the compartment apical of the barrier epithelium.

Probing gingiva and peri-implant mucosa

It was assumed for many years that the tip of the probe in a pocket depth measurement identified the most apical cells of the junctional (pocket) epithelium or the marginal level of the connective tissue attachment. This assumption was based on findings by, for example, Waerhaug (1952), who reported that the "epithelial attachment" (e.g. Gottlieb 1921; Orban & Köhler 1924) offered no resistance to probing. Waerhaug (1952) inserted, "with the greatest caution", thin blades of steel or acrylic into the gingival pocket of various teeth of >100 young subjects without signs of periodontal pathology. In several sites the blades were placed in approximal pockets, "in which position radiograms were taken of them". It was concluded that the insertion of the blades could be performed without resulting in bleeding and that the device consistently reached the cementoenamel junction (Fig. 4-28). Thus, the epithelium or the epithelial attachment offered no resistance to the insertion of the device.

In subsequent studies it was observed, however, that the tip of a periodontal probe in a pocket depth measurement only identified the base of the dentogingival epithelium by chance. In the absence of an inflammatory lesion, the probe frequently failed to reach the apical part of the junctional epithelium (e.g. Armitage *et al.* 1977; Magnusson & Listgarten 1980). If an inflammatory lesion, rich in leukocytes and poor in collagen, was present in the gingival connective tissue, however, the probe penetrated beyond the epithelium to reach the apicolateral border of the infiltrate.

Probing depth measurements at *implant sites* was examined in various animal models. Ericsson and Lindhe (1993) used the model of Berglundh *et al.* (1991) referred to earlier and, hence, had both teeth and implants available for examination. The gingiva at mandibular premolars and the mucosa at correspondingly positioned implants (Brånemark System®) were, after extended periods of plaque control, considered clinically healthy. A probe with a tip diameter of 0.5 mm was inserted into the buccal "pocket" using a standardized force of 0.5 N. The probe was anchored to the tooth or to the implant and biopsies from the various sites were performed. The histologic examination of the biopsy material revealed that probing

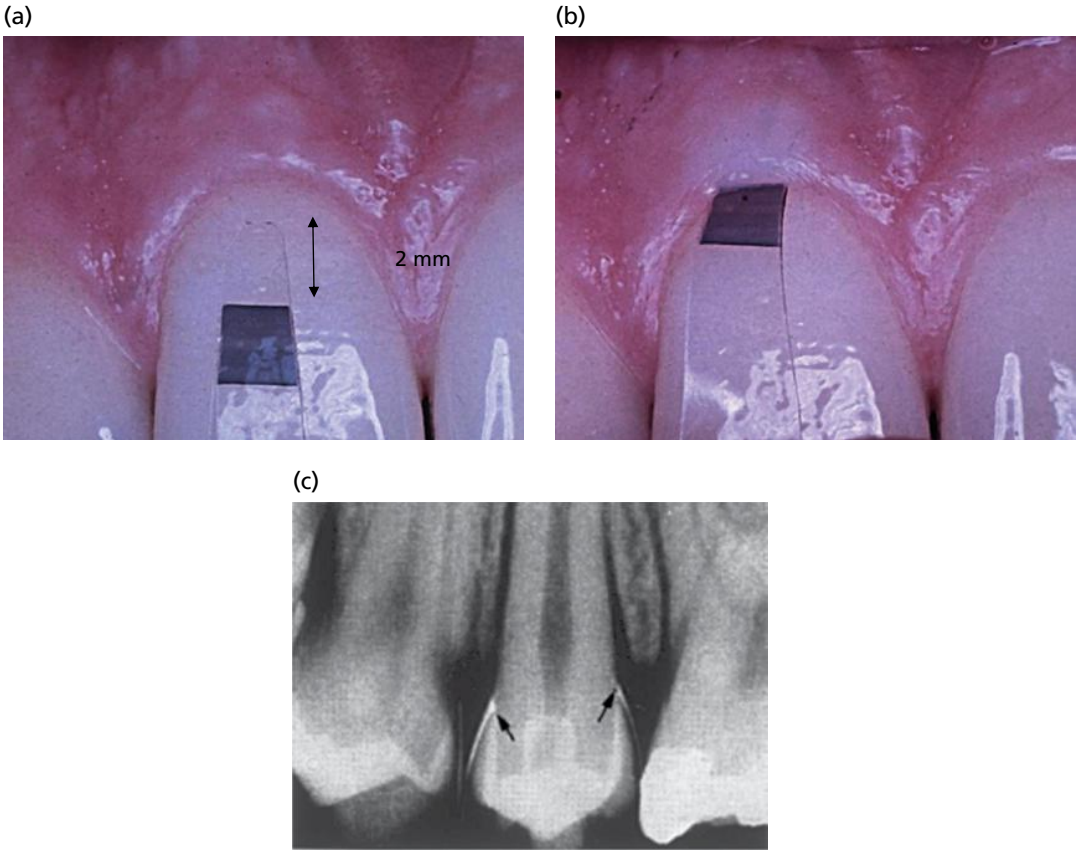


Fig. 4-28 Acrylic strip with a blue zone located 2 mm from the strip margin (a) prior to and (b) after its insertion into a buccal "pocket". With a light force the strip could be inserted 2 mm into the "pocket". (c) Thin blades of steel were inserted into pockets at approximal sites of teeth with healthy periodontal tissue. On radiographs, Waerhaug (1952) could observe that the blades consistently reached the cementoenamel junction.

the dentogingival interface had resulted in a slight compression of the gingival tissue. The tip of the probe was located coronal to the apical cells of the junctional epithelium. At the implant sites, probing caused both compression and a lateral dislocation of the peri-implant mucosa, and the average "histologic" probing depth was markedly deeper than at the tooth site: 2.0 mm versus 0.7 mm. The tip of the probe was consistently positioned deep in the connective tissue–abutment interface and apical of the barrier epithelium. The distance between the probe tip and the bone crest at the tooth sites was about 1.2 mm. The corresponding distance at the implant site was 0.2 mm. The findings presented by Ericsson and Lindhe (1993) regarding the difference in probe penetration in healthy gingiva and peri-implant mucosa are not in agreement with data reported in subsequent animal experiments.

Lang *et al*. (1994) used Beagle dogs and prepared the implant (Straumann® Dental Implant System) sites in such a way that on probing some were healthy, a few exhibited signs of mucositis, and some exhibited peri-implantitis. Probes with different geometry were inserted into the pockets using a standardized probing procedure and a force of only 0.2 N. The probes were anchored and block biopsy specimens were harvested. The probe locations were studied in histologic ground sections. The authors reported that the mean "histologic" probing depth at healthy sites was about 1.8 mm, that is similar to the depth (about 2 mm) recorded by Ericsson and Lindhe (1993). The corresponding depth at sites with mucositis and peri-implantitis was about 1.6 mm and 3.8 mm, respectively. Lang *et al*. (1994) further stated that at healthy and mucositis sites, the probe tip identified "the connective tissue adhesion level" (i.e. the base of the barrier epithelium), while at peri-implantitis sites, the probe exceeded the base of the ulcerated pocket epithelium by a mean distance of 0.5 mm. At such peri-implantitis sites, the probe reached the base of the inflammatory cell infiltrate.

Schou *et al*. (2002) compared probing measurements at implants and teeth in eight cynomolgus monkeys. Ground sections were produced from tooth and implant sites that were (1) clinically healthy, (2) slightly inflamed (mucositis/gingivitis), and (3) severely inflamed (peri-implantitis/periodontitis) and in which probes had been inserted. An electronic probe (Peri-Probe®) with a tip diameter 0.5 mm and a standardized probing force of 0.3–0.4 N was used. It was demonstrated that the probe tip was located at a similar distance from the bone in healthy tooth sites and implant sites. On the other hand, at implants exhibiting mucositis and peri-implantitis, the probe

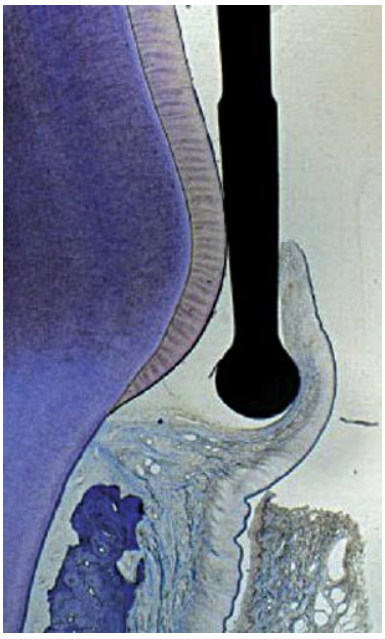


Fig. 4-29 Buccolingual ground section from a tooth site illustrating the probe tip position in relation to the bone crest. (Source: Abrahamsson & Soldini 2006. Reproduced with permission from John Wiley & Sons.).

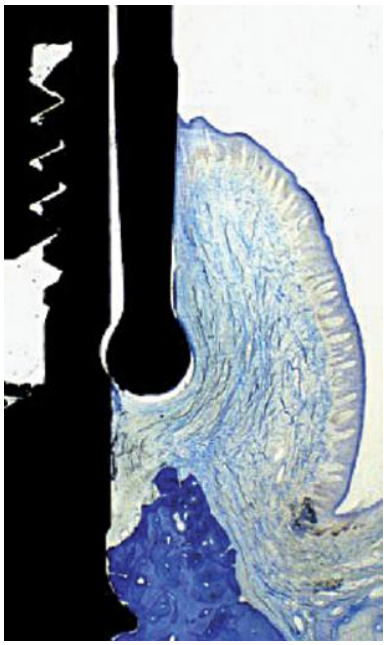


Fig. 4-30 Buccolingual ground section from an implant site illustrating the probe tip position in relation to the bone crest. (Source: Abrahamsson & Soldini 2006. Reproduced with permission from John Wiley & Sons.)

tip was consistently identified at a more apical position than at corresponding tooth sites (gingivitis and periodontitis). The authors concluded that (1) probing depth measurements at implant and teeth yielded different information, and (2) small alterations in probing depth at implants may reflect changes in soft tissue inflammation rather than loss of supporting tissues.

Abrahamsson and Soldini (2006) evaluated the location of the probe tip in healthy periodontal and peri-implant tissues in dogs. It was reported that probing with a force of 0.2 N resulted in a probe penetration that was similar at implants and teeth. Furthermore, the tip of the probe was often at or close to the apical cells of the junctional/barrier epithelium. The distance between the tip of the probe and the bone crest was about 1 mm at both teeth and implants (Figs. 4-29, 4-30). Similar observations were reported from clinical studies in which different implant systems were used (Buser *et al*. 1990; Quirynen *et al*. 1991; Mombelli *et al*. 1997). In these studies, the distance between the probe tip and the bone was assessed in radiographs and was found to vary between 0.75 and 1.4 mm when a probing force of 0.25–0.45 N was used.

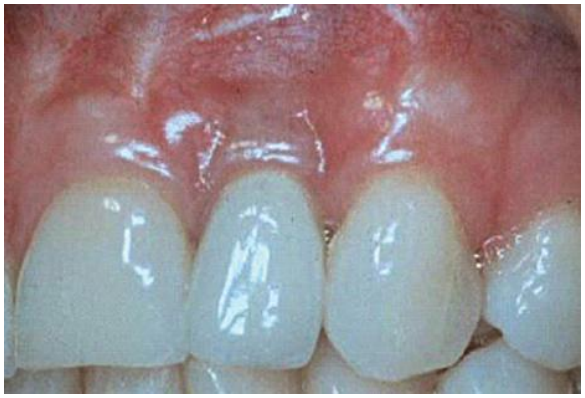
By comparing the findings from the studies reported above, it becomes apparent that probing depth and probing attachment level measurements are also meaningful at implant sites. When a "normal" probing force is applied to healthy tissues, the probe seems to reach similar levels at implant and tooth sites. Probing inflamed tissues at both tooth and implant sites will, however, result in a more advanced probe penetration and the tip of the probe may come closer to the bone crest.

Dimensions of the buccal soft tissue at implants

Chang *et al*. (1999) compared the dimensions of the periodontal and peri-implant soft tissues of 20 subjects who had been treated with an implant-supported single-tooth restoration in the esthetic zone of the maxilla and who had a non-restored natural tooth in the contralateral position (Fig. 4-31). In comparison to the natural tooth, the implant-supported crown was bordered by a thicker buccal mucosa (2.0 mm versus 1.1 mm), as assessed at a level corresponding to the bottom of the probeable pocket, and had a greater probing pocket depth (2.9 mm versus 2.5 mm) (Fig. 4-32). It was further observed that the soft tissue margin at the implant was more apically located (about 1 mm) than the gingival margin at the contralateral tooth.

Kan *et al*. (2003) studied the dimensions of the peri-implant mucosa at 45 single implants that had been placed in the anterior maxilla for an average of 33 months. Bone sounding measurements performed at the buccal aspect of the implants showed that the height of the mucosa was 3–4 mm in the majority of the cases. Less than 3 mm of mucosa height was found at only 9% of the implants. It was suggested that implants in this category (1) were found in subjects who belonged to a *thin periodontal biotype*, (2) had been placed too labially, and/or (3) had the emergence of an over-contoured facial prosthetic. A peri-implant soft tissue dimension of >4 mm was usually associated with a *thick periodontal biotype.*

(a)



(b)

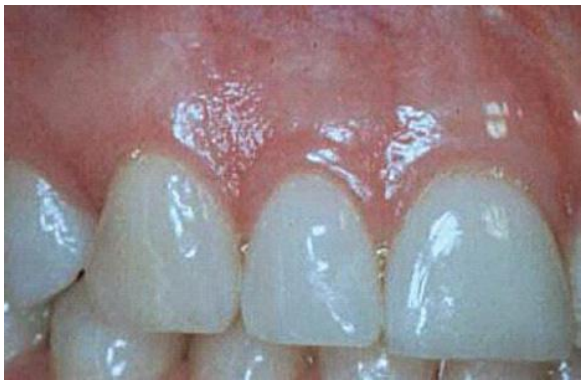


Fig. 4-31 Clinical photographs of (a) an implant-supported single-tooth replacement in position 12 and (b) the natural tooth in the contralateral position. (Source: Chang *et al.* 1999. Reproduced with permission from John Wiley & Sons.)

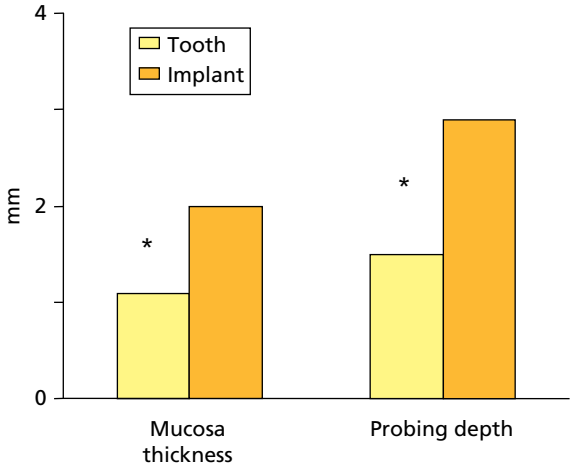


Fig. 4-32 Comparison of mucosa thickness and probing depth at the facial aspect of single-implant restorations and the natural tooth in the contralateral position. (Source: Chang *et al.* 1999. Reproduced with permission from John Wiley & Sons.)

Dimensions of the papilla between teeth and implants

In a study by Schropp *et al.* (2003), it was demonstrated that following single-tooth extraction the height of the papilla at the adjacent teeth was reduced by about 1 mm. Concomitant with this reduction (recession) of the papilla height, the pocket depth was reduced and some loss of clinical attachment occurred.

Following single-tooth extraction and subsequent implant installation, the height of the papilla in the tooth–implant site will be dependent on the attachment level of the tooth. Choquet *et al.* (2001) studied the papilla level adjacent to single-tooth dental implants in 26 patients and a total of 27 implant sites. The distance between the apical extension of the contact point between the crowns and the bone crest, as well as the distance between the soft tissue level and the bone crest, was measured on radiographs. The examinations were made 6–75 months after the insertion of the crown restoration. The authors observed that the papilla height consistently was about 4 mm and, depending on the location of the contact point between adjacent crown papilla, fill was either complete or incomplete (Fig. 4-33). The closer the contact point was to the incisal edge of the crowns (restorations), the less complete was the papilla fill.

Chang *et al.* (1999) studied the dimensions of the papillae at implant-supported single-tooth restorations in the anterior region of the maxilla and at non-restored contralateral natural teeth. They found that the papilla height at the implant-supported crown was significantly shorter and showed less fill of the embrasure space than the papilla at the natural tooth (Fig. 4-34). This was particularly evident for the distal papillae of implant-supported restorations in the central incisor position, both in comparison to the distal papilla at the contralateral tooth and to the papilla at the mesial aspect of the implant crown. This indicates that the anatomy of the adjacent natural teeth (e.g. the diameter of the root, the proximal outline/curvature of the cementoenamel junction/connective tissue attachment level) may have a profound influence on the dimension of the papilla lateral to an implant. Hence, the wider faciolingual root diameter and the higher proximal curvature of the cementoenamel junction of the maxillary central incisor – in comparison to corresponding dimensions of the lateral incisor (Wheeler 1966) – may favor the maintenance of the height of the mesial papilla at the single-implant–supported restoration.

Kan *et al.* (2003) assessed the dimensions of the peri-implant mucosa lateral to 45 single implants placed in the anterior maxilla and the 90 adjacent teeth using bone sounding measurements. The bone sounding measurements were performed at the mesial and distal aspects of the implants and at the mesial and distal aspects of the teeth. The authors reported that the thickness of the mucosa at the mesial/distal surfaces of the implant sites was on average 6 mm, while the corresponding dimension at the adjacent tooth sites was about 4 mm. It was further observed that the dimensions of the peri-implant mucosa of subjects who belonged to the *thick periodontal biotype* were significantly greater than those of subjects with a *thin biotype*.

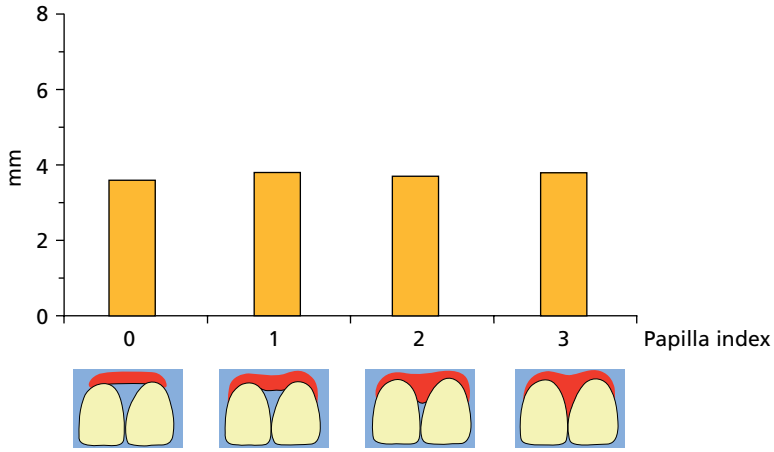


Fig. 4-33 Soft tissue height adjacent to single-tooth dental implants in relation to the degree of papilla fill. (Source: Choquet *et al*. 2001. Reproduced from the American Academy of Periodontology.)

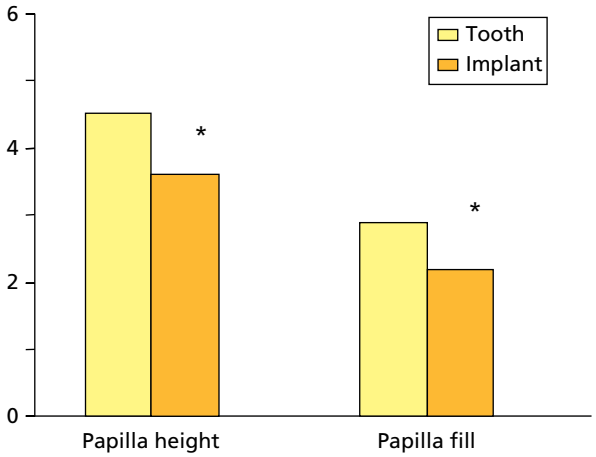
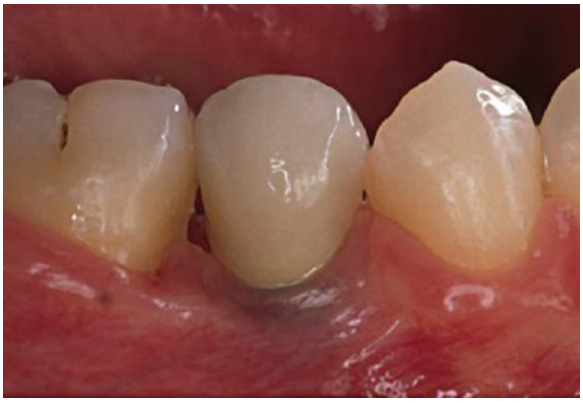


Fig. 4-34 Comparison of papilla height and papilla fill adjacent to single-implant restorations and the natural tooth in the contralateral position. (Source: Chang *et al*. 1999. Reproduced with permission from John Wiley & Sons.)

The level of the connective tissue attachment on the adjacent tooth surface and the position of the contact point between the crowns are obviously key factors that determine whether or not a complete papilla fill will be obtained at the single-tooth implant-supported restoration (Fig. 4-35). Although there are indications that the dimensions of the approximal soft tissue may vary between individuals having thin and thick periodontal biotypes, the height of the papilla at the single-implant restoration seems to have a biologic limit of about 4 mm (compare this with the dimension of the interdental papilla). Hence, to achieve a complete papilla fill of the embrasure space, a correct location of the contact area between the implant crown and the tooth crown is mandatory. In this respect it must also be recognized that the papilla fill at single-tooth implant restorations is unrelated to whether the implant is inserted according to a one- or two-stage protocol and whether a crown restoration is inserted immediately following surgery or delayed until the soft tissues have healed (Jemt 1999; Ryser *et al*. 2005).

(a)



(b)

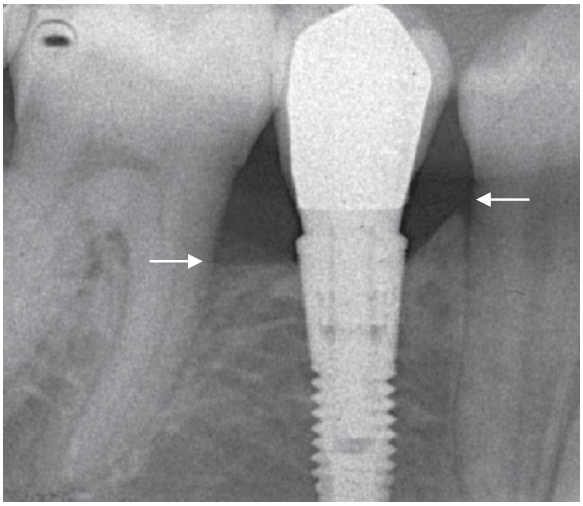


Fig. 4-35 Single implant in a mandibular premolar region. (a) Papilla fill between the implant and the first premolar is optimal, while the papilla fill between the implant and the molar is compromised and a black space is visible. (b) Radiograph from the same site showing the position of the cementoenamel junction (on the premolar) and the marginal bone level (on the molar) (arrows).

Dimensions of the "papilla" between adjacent implants

When two neighboring teeth are extracted, the papilla at the site will be lost (Fig. 4-36). Hence, at replacement of the extracted teeth with implant-supported

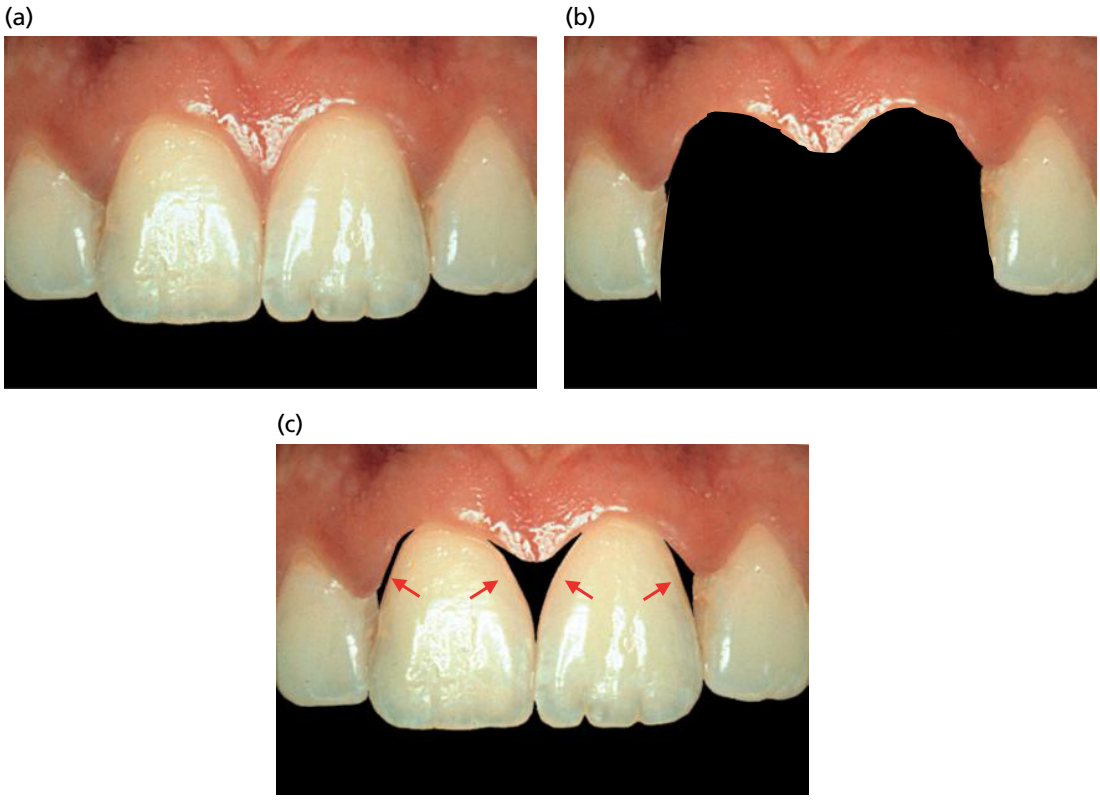


Fig. 4-36 See text for details. Arrows indicate the position of the soft tissue borders prior to the removal of the incisors.

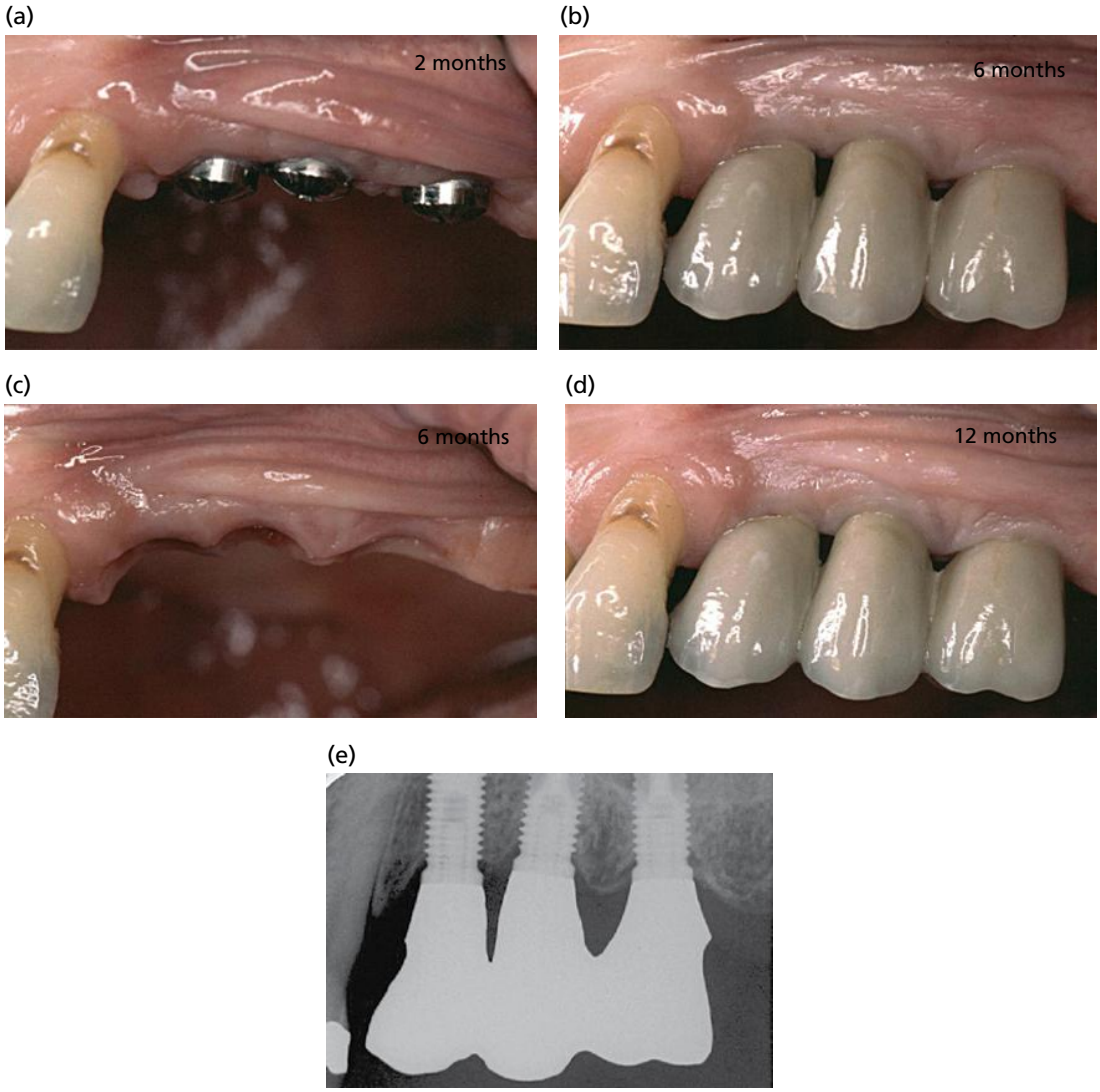


Fig. 4-37 See text for details.

restorations, the topography of the bone crest and the thickness of the supracrestal soft tissue portion are the factors that determine the position of the soft tissue margin in the interimplant area ("implant papilla"). Tarnow *et al*. (2003) assessed the height above the bone crest of the interimplant soft tissue ("implant papilla") by transmucosal probing at 136 anterior and posterior sites in 33 patients who had maintained implant-supported prostheses for at least 2 months. It was found that the mean height of the "papillae" was 3.4 mm, with 90% of the measurements in the range of 2–4 mm.

The dimension of the soft tissues between adjacent implants seems to be independent of the implant design. Lee *et al.* (2006) examined the soft tissue height between implants of two different systems (Brånemark Implant® and AstraTech Implant® systems), as well as the potential influence of the horizontal distance between implants. The height of the interimplant "papilla", that is the height of soft tissue coronal to the bone crest measured on radiographs, was about 3.1 mm for both implant systems. No difference was found regarding the "papilla" height for either of the implant systems at sites with a horizontal distance between the implants of <3 mm and those with a distance of 3 mm or greater. Gastaldo *et al.* (2004) evaluated the presence or absence of "papilla" at 96 interimplant sites in 58 patients. It was reported that the "papilla" filled the entire space between the implants only when the distance from the bone crest to the base of the contact point between the crown restorations, assessed by sounding, was <4 mm. Thus, taken together, these observations indicate that the soft tissue between two implants will have a maximum height of 3–4 mm, and that the location of the contact point between the crown restorations in relation to the bone crest level determines whether a complete soft tissue fill will be obtained in the embrasure space between two implants (Fig. 4-37).

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Chapter 5

Osseointegration

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Introduction

The fully healed site of the edentulous ridge (see Chapter 3) is most often covered by a masticatory mucosa that is about 2–3 mm thick. The masticatory mucosa is covered by a keratinized epithelium and includes a connective tissue rich in collagen fibers and fibroblasts that are firmly attached to the bone via the periosteum. The outer walls of the edentulous ridge, the cortical plates, are comprised of lamellar bone and enclose the cancellous bone that contains trabeculae of lamellar bone that are embedded in bone marrow The bone marrow contains numerous vascular structures as well as adipocytes and pluripotent mesenchymal cells.

Different implant systems have been used to replace missing teeth, including subperiosteal implants, endosseous implants with fibrous encapsulation, and endosseous implants with direct bone contact (*osseointegrated*).

One definition of *osseointegration* [a term originally proposed by Brånemark *et al*. (1969)] was provided by Albrektsson *et al*. (1981) who suggested that this was "a direct functional and structural connection between living bone and the surface of a load carrying implant". Another definition was provided by Zarb and Albrektsson (1991) who proposed that *osseointegration* was "a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading".

Schroeder *et al*. (1976, 1981, 1995) used the term *"functional ankylosis"* to describe the rigid fixation of the implant to the jaw bone, and stated that "new bone is laid down directly upon the implant surface, provided that the rules for atraumatic implant placement are followed and the implant exhibits primary stability".

Thus, in order to acquire proper conditions for osseointegration (or functional ankylosis), the implant must exhibit proper initial fixation (primary stability) following installation in the recipient site. This initial or primary stability is the result of the contact relationship or friction that is established between mineralized bone (often the cortical bone) at the recipient site and the metal device.

Implant installation

Tissue injury

Basic rule: The less traumatic the surgical procedure and the smaller the tissue injury (the damage) in the recipient site during implant installation, the more expeditious is the process through which new bone is formed and laid down on the implant surface.

The various steps used at implant installation, such as (1) *incision* of the mucosa, often but not always followed by (2) the elevation of *mucosal flaps* and the separation of the periosteum from the cortical plates, (3) the preparation of the *canal* in the cortical and

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spongy (cancellous) bone of the recipient site, and (4) the insertion of the titanium device (the implant) into this canal, bring to bear a series of mechanical insults and injury to both the mucosa and the bone tissue. The host responds to this injury with an inflammatory reaction, the main objective of which is to eliminate the damaged portions of the tissues and prepare the site for regeneration or repair. To the above described injury to the hard tissues must be added the effect of the so-called "press fit", that is when the inserted implant is slightly wider than the canal prepared in the host bone. In such situations, (1) the mineralized bone tissue around the implant is compressed and exhibits a series of microfractures, (2) the blood vessels, particularly in the cortical portion, of the canal will collapse, (3) the nutrition to the bone in this portion is compromised, and (4) the affected tissues most often become non-vital.

The injury to the soft and hard tissues of the recipient site, however, also initiates the process of wound healing that ultimately ensures that (1) the implant becomes "ankylotic" with the bone, that is osseointegrated, and (2) a delicate mucosal attachment (see Chapter 4) is established and a soft tissue seal forms that protects the bone tissue from substances in the oral cavity.

Wound healing

The healing of the severed bone following implant installation is a complex process that apparently involves different events in different compartments of the surgical site.

In the *cortical bone compartment*, the non-vital mineralized tissue must first be removed (resorbed) before new bone can form. In the *spongy (cancellous) compartment* of the recipient site, on the other hand, the surgically inflicted damage (preparation of the canal and the installation of the implant) results mainly in soft tissue (marrow) injury that initially involves localized bleeding and clot (coagulum) formation. The coagulum is gradually resorbed and becomes replaced with granulation tissue; in-growth (from the walls of the prepared canal) of blood vessels, leukocytes, and mesenchymal cells. As a result of the continuous migration of mesenchymal cells from the surrounding marrow, the granulation tissue in turn is replaced with provisional connective tissue (provisional matrix) and eventually with osteoid. In the osteoid, deposition of hydroxyapatite crystals will occur in the collagen network around the newly formed vascular structures. Hereby, immature woven bone is formed (for detail see Chapter 3) and sequentially osseointegration occurs.

Cutting and non-cutting implants

In this chapter only screw-shaped implants made of c.p. titanium will be discussed. The design of the metal device and the installation protocol followed may influence the speed of the process that leads to osseointegration.

Fig. 5-1 "Non-cutting" implant (solid screw: Straumann® Implant System). (Courtesy of Institut Straumann AG.)

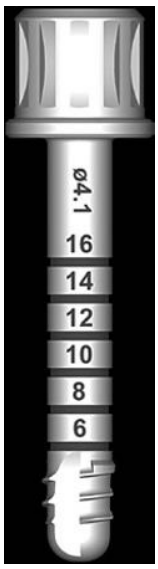

Fig. 5-2 Thread-tap (Straumann® Implant System) that is used to cut a track in the walls of the hard tissue canal. Following this preparation, the cavity in the host tissue and the implant are congruent. (Courtesy of Institut Straumann AG.)

"*Non-cutting*" implants (Fig. 5-1) require meticulous handling of the recipient site, including the preparation of a standardized track (thread) on the inside of the hard tissue canal. This track (thread) is prepared (precutting) using a thread-tap that is fitted with cutting edges (Fig. 5-2).

Figure 5.1 shows a "non-cutting" implant (e.g. solid screw, 4.1 mm: Straumann® Implant System) that is designed as a cylinder with a rounded "apical" base. The diameter of the cylinder is 3.5 mm. Pilot and twist drills of gradually increasing dimension are used to prepare the hard tissue canal of the recipient site to a final diameter of 3.5 mm. On the surface of the cylinder, the implant is designed with a helix-shaped pitch that is 0.3 mm high. The diameter of the entire screw-shaped device therefore becomes 4.1 mm.

In sites with a high bone density, a thread-tap (Fig. 5-2) is used to cut a 4.1-mm wide helix-shaped track in the walls of the hard tissue canal. The implant and the cavity prepared in the hard tissues of the recipient site become congruent. When the implant is

Fig. 5-3 Ground section of a "non-cutting" implant and surrounding tissues obtained from a biopsy performed 24 hours after implant installation.

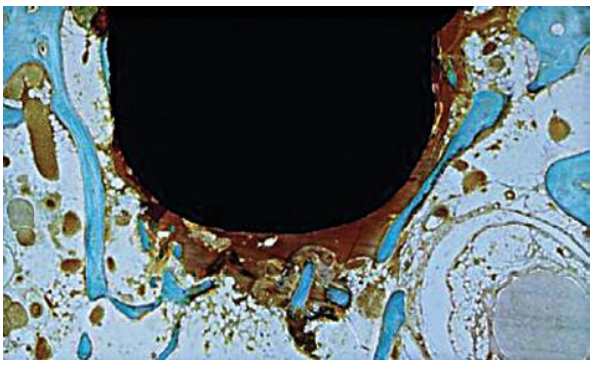

Fig. 5-4 Detail from the apical region of the implant described in Fig. 5-3. Note the presence of a coagulum in the bone marrow.

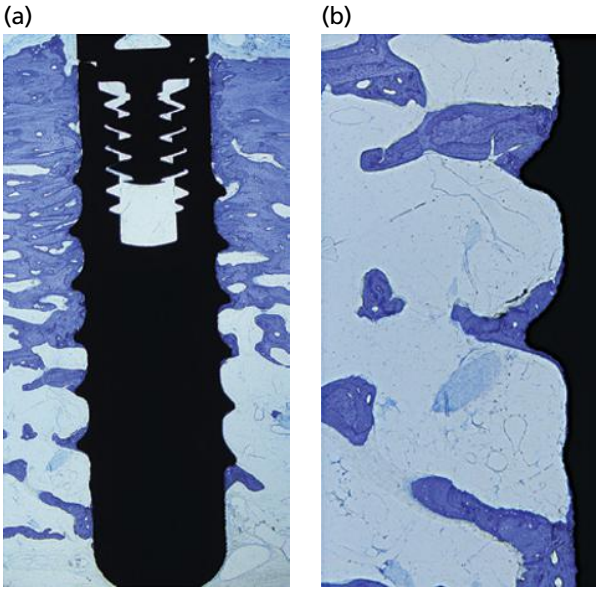

Fig. 5-5 (a) Ground section showing a "non-cutting" implant and surrounding bone after 16 weeks of healing. In the cortical portion of the recipient site, the bone density is high. (b) Detail of (a). In more apical areas, a thin coat of bone is present on the implant surface. Note also the presence of trabeculae of lamellar bone that extend from the implant into the bone marrow.

Fig. 5-6 "Cutting" implant (AstraTech® Implant System). Note the presence of cutting edges in the "apical" portion of the implant. During insertion this implant will cut a 0.3-mm wide chip from the lateral border of the canal prepared in the recipient site. (Courtesy of AstraTech.)

installed, the pitch on the device will capture and follow the helix-shaped track on the walls of the hard tissue canal and thereby guide the implant with a minimum of force into the preprepared position (Fig. 5-3).

Figure 5-3 illustrates a "non-cutting" Straumann® solid screw with surrounding tissues in a biopsy sampled 24 hours after implant installation. Proper initial fixation (stability) of the implant was obtained by the large contact area that was achieved between the metal screw and the buccal and lingual bone walls in the cortical compartment of the recipient site. During site preparation and placement of the implant, bone trabeculae in the spongy compartment of the site were obviously dislocated into the bone marrow. Blood vessels in the marrow compartment were severed, bleeding provoked, and a coagulum formed (Fig. 5-4).

After 16 weeks of healing (Fig. 5-5) the marginal portions of the "non-cutting" implant are surrounded by dense lamellar bone that is in direct contact with the rough surface of the metal device. Also, in the apical portion of the implant, a thin coat of mature bone can be seen to contact the implant surface and to separate the titanium screw from the bone marrow.

Cutting or self-tapping implants (e.g. AstraTech® Implant System, diameter 4.0 mm) (Fig. 5-6) are designed with cutting edges placed in the "apical" portion of the screw-shaped device. The threads of the screw are prepared during manufacturing by cutting

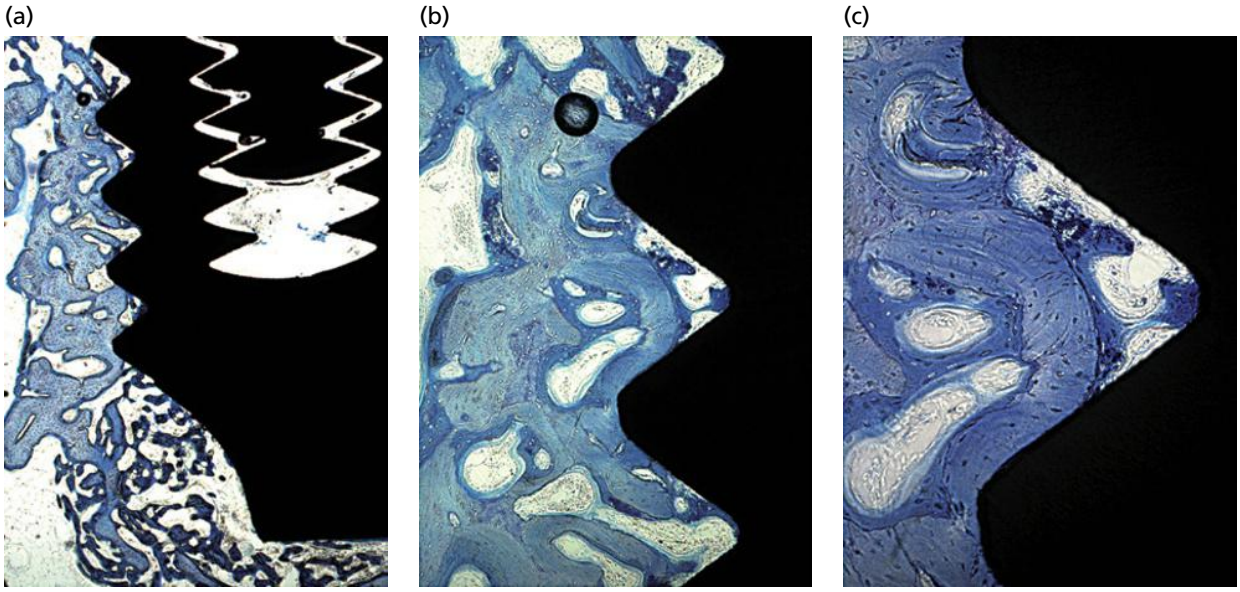

Fig. 5-7 (a) Ground section of an implant (AstraTech® Implant System) site from a biopsy sampled after 2 weeks of healing. In the apical area, large amounts of woven bone have formed. (b) Detail of (a). In the threaded region, newly formed bone can be seen to reach contact with the implant surface. (c) Higher magnification of (b). Newly formed bone extends from the old bone and reaches the titanium surface in the invagination between two consecutive "threads".

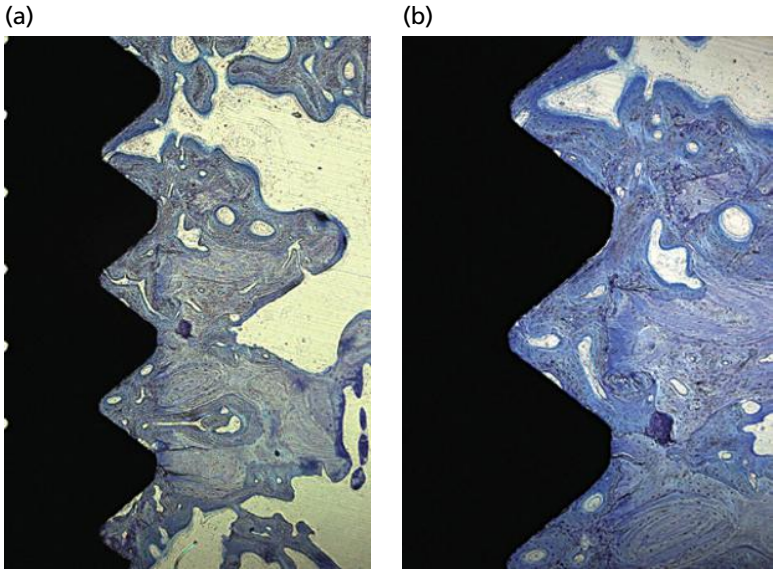

Fig. 5-8 Ground section of an implant site (AstraTech® self-tapping implant) from a biopsy specimen obtained after 6 weeks of healing. (a) In the marginal area, a continuous layer of bone covers most of the TiOblast® surface. (b) Higher magnification. Note the zone of newly formed (darker stained) bone that is in direct contact with the implant surface.

a continuous groove into the body of the titanium cylinder. When a self-tapping 4.0-mm wide implant is to be placed, the recipient site is first prepared with pilot and twist drills to establish a hard tissue canal that may have a final diameter of 3.7 mm. During insertion, the cutting edges in the "apical" portion of the implant create a 0.3-mm wide track in the walls of the canal and thereby establish the final 4.0 mm dimension. When the implant has reached its insertion depth, contact has been established between the outer portions of the threads and the mineralized bone in the cortical compartment (initial or primary fixation is thereby secured) and with the severed bone marrow tissue in the spongy (cancellous) bone compartment.

Figure 5-7 illustrates a recipient site with a self-tapping implant (AstraTech® implant). This implant is designed with a rough surface modification. The biopsy was harvested 2 weeks after installation surgery. The outer portion of the thread is in contact with the "old" bone, while new bone formation is the dominant feature in the invaginations between the threads and in areas lateral to the "apical" portions of the implant. Thus, discrete areas of newly formed bone can be seen also in direct contact with the implant surface. In sections representing 6 weeks of healing (Fig. 5-8), it was observed that a continuous layer of newly formed bone covers most of the rough implant surface. This newly formed bone is also in contact with the old, mature bone that is present in the periphery of the recipient site. After 16 months of healing (Fig. 5-9), the bone tissue in the zone of osseointegration has remodeled and the entire hard tissue bed for the implant is comprised of lamellar bone including both concentric and interstitial lamella.

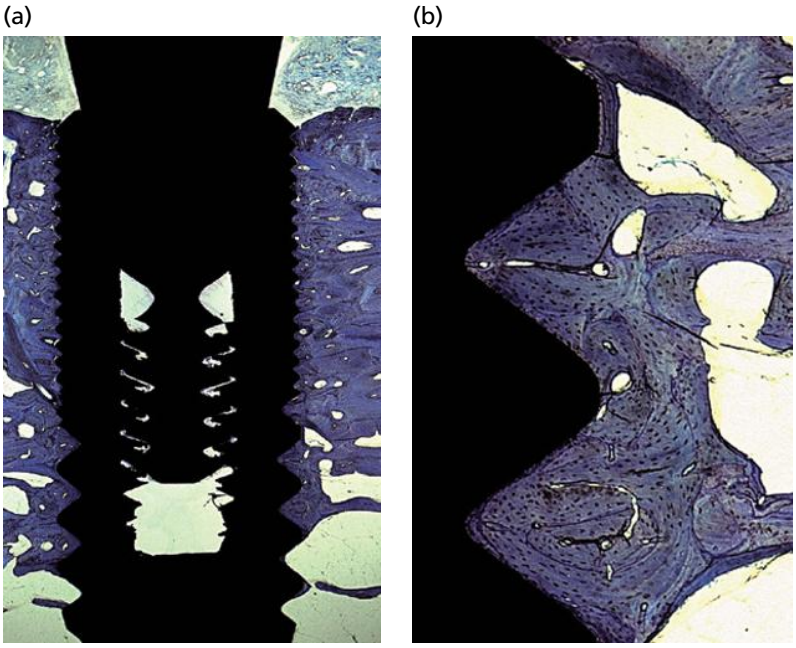

Fig. 5-9 Ground section of an implant site representing 16 months of healing. (a) The implant is surrounded by dense lamellar bone. (b) Higher magnification.

Process of osseointegration

De novo bone formation in the severed alveolar ridge following implant placement was studied in experiments in various experimental animal models (for review see Schroeder *et al*. 1995).

More recently, Berglundh *et al*. (2003) and Abrahamsson *et al*. (2004) described various steps involved in bone formation and osseointegration to implants placed in the mandible of dogs.

The device: Custom-made implants (made of c.p. titanium) in the shape of a solid screw and configured with a rough surface topography were utilized (Fig. 5-10). In the implant device, the distance between two consecutive profiles of the pitch (i.e. the threads in a vertical cross-section) was 1.25 mm. A 0.4-mm deep U-shaped circumferential trough had been prepared within the thread region during manufacturing (Fig. 5-11). The tip of the pitch was left untouched. Following the installation of the non-cutting device (Fig. 5-12), the pitch was engaged in the hard tissue walls prepared by the cutting/tapping device. This provided initial or primary fixation of the device. The void between the pitch and the body of the implant established a geometrically well-defined wound chamber (Fig. 5-13). Biopsies were performed to provide healing periods extending from 2 hours following implant insertion to 12 weeks of healing. The biopsy specimens were prepared for ground sectioning as well as for decalcified sectionings.

The wound chamber: Figure 5.13 illustrates a cross-section (ground section) of an implant with surrounding soft and hard tissues from a biopsy specimen sampled 2 hours after installation of the metal device. The peripheral portions of the pitch were in contact with the invaginations of the track prepared by the tap in the cortical bone. The wound

Fig. 5-10 Device used in the dog experiment. The implant is a modification of a solid screw (Straumann® Implant System). The distance between two consecutive threads is 1.25 mm. The depth of the trough is 0.4 mm. (Courtesy of AstraTech.)

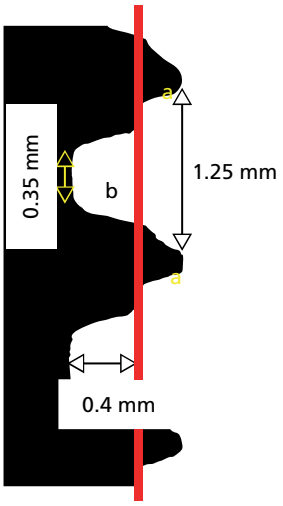

Fig. 5-11 The device. Schematic drawing illustrating the dimensions of the "wound chamber".

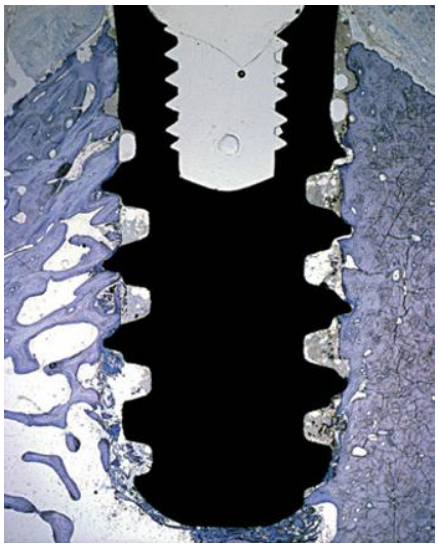

Fig. 5-12 Ground section showing the implant and adjacent tissues immediately after implant installation. The pitch region is engaged in the hard tissue walls. The void between two consecutive pitch profiles includes the wound chamber.

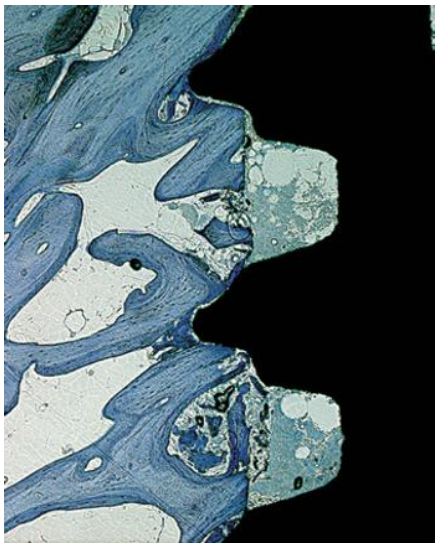

Fig. 5-13 Detail of Fig. 5-12. The wound chamber was filled with blood and a coagulum has formed.

chambers (Fig. 5-14a) were occupied with a blood clot in which erythrocytes, neutrophils, and monocytes/macrophages occurred in a network of fibrin (Fig. 5-14b). The leukocytes were apparently engaged in the wound cleansing process.

Fibroplasia: Figure 5-15a illustrates a device with surrounding tissues after 4 days of healing. The coagulum had in part been replaced with granulation tissue that contained numerous mesenchymal cells, matrix components, and newly formed vascular structures (angiogenesis) (Fig. 5-15b). A *provisional connective tissue (matrix)* had been established.

Bone modeling: After 1 week of healing, the provisional connective tissue in the wound chambers was rich in vascular structures and contained numerous mesenchymal cells (Fig 5-16a). The number of remaining inflammatory cells was relatively small. In several compartments of the chamber, a cell-rich immature bone (woven bone) was seen in the provisional connective tissue that surrounded the blood vessels. Woven bone formation occurred in the center of the chamber as well as in discrete locations that apparently were in direct contact with the surface of the titanium device (Fig. 5-16b). This was considered to represent the very first phase of osseointegration; contact between the implant surface and newly formed woven bone.

After 2 weeks of healing, woven bone formation appeared to be pronounced in all compartments, apical as well as lateral, surrounding the implant (Fig. 5-17a). Large areas of woven bone were found in the bone marrow regions "apical" of the implant. In the wound chamber, portions of the newly formed woven bone apparently extended from the old bone into the provisional connective tissue (Fig. 5-17b) and had in many regions reached the surface of the titanium device. At this interval, most of the implant surface was occupied by newly formed bone and a more comprehensive and mature osseointegration had been established (Fig. 5-17c). In the pitch regions, there were signs of ongoing new bone formation (Fig. 5-17d). Thus, areas

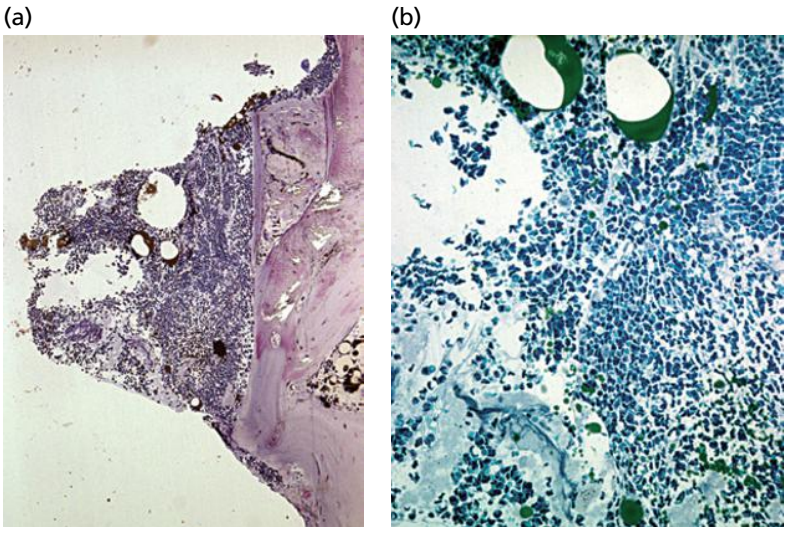

Fig. 5-14 Wound chamber 2 hours after implant installation. Decalcified sections. (a) The wound chamber is filled with blood. (b) Erythrocytes, neutrophils, and macrophages are trapped in a fibrin network.

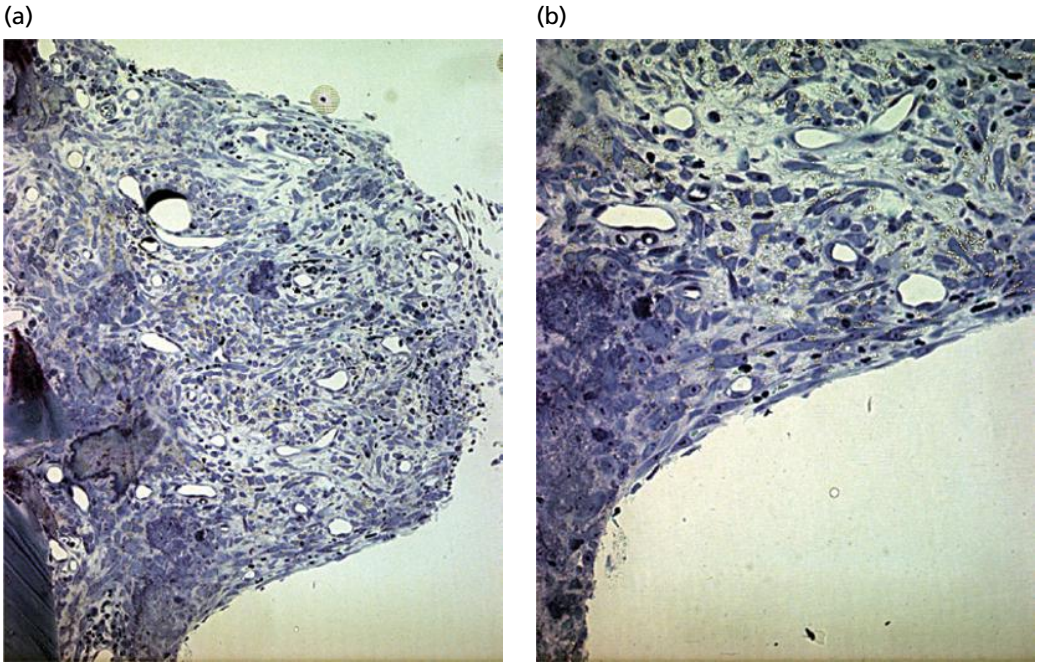

Fig. 5-15 Wound chamber after 4 days of healing (decalcified sections). (a) Most portions of the wound chamber are occupied by granulation tissue (fibroplasia). (b) In some areas of the chamber, provisional connective tissue (matrix) is present. This tissue includes large numbers of mesenchymal cells.

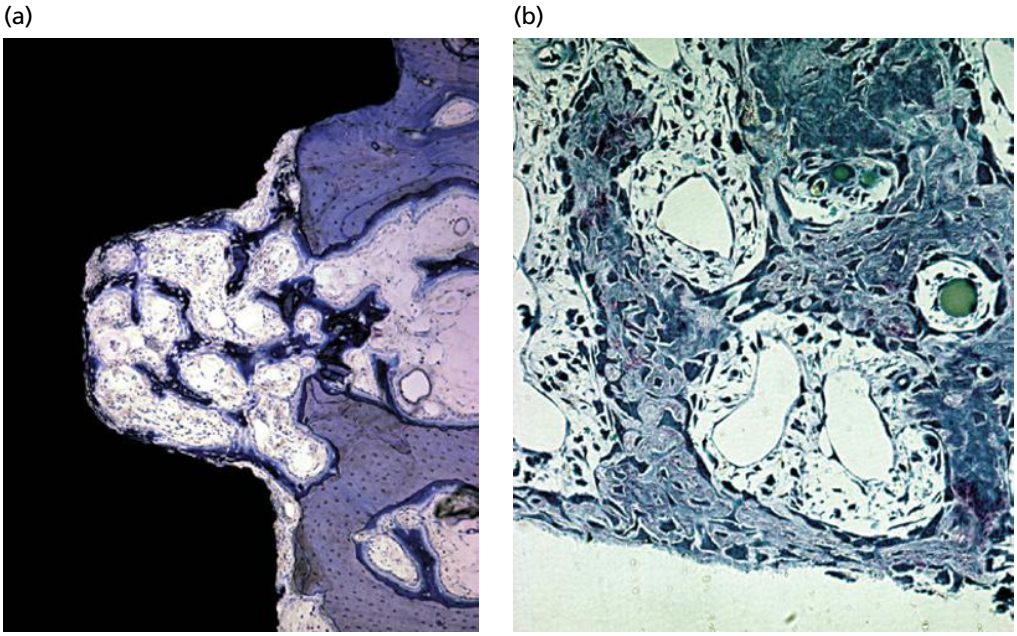

Fig. 5-16 (a) Ground section representing 1 week of healing. Note the presence of newly formed woven bone in the wound chamber. (b) Decalcified section. The woven bone is in direct contact with the implant surface.

of the recipient site located lateral to the device, that were in direct contact with the host bone immediately following installation surgery and provided initial fixation for the implant, had undergone resorption and were also involved in new bone formation after 2 weeks of healing.

At 4 weeks (Fig. 5-18a), the newly formed mineralized bone extended from the cut bone surface into the chamber and a continuous layer of cell-rich, woven bone covered most of the titanium wall of the chamber. The central portion of the chamber was filled with a primary spongiosa (Fig. 5-18b), rich in vascular structures and a multitude of mesenchymal cells.

Remodeling: After 6–12 weeks of healing, most of the wound chambers were filled with mineralized bone (Fig. 5-19). Bone tissue, including primary and secondary osteons, could be seen in the newly formed tissue and in the mineralized bone that made contact with the implant surface. Bone marrow that contained

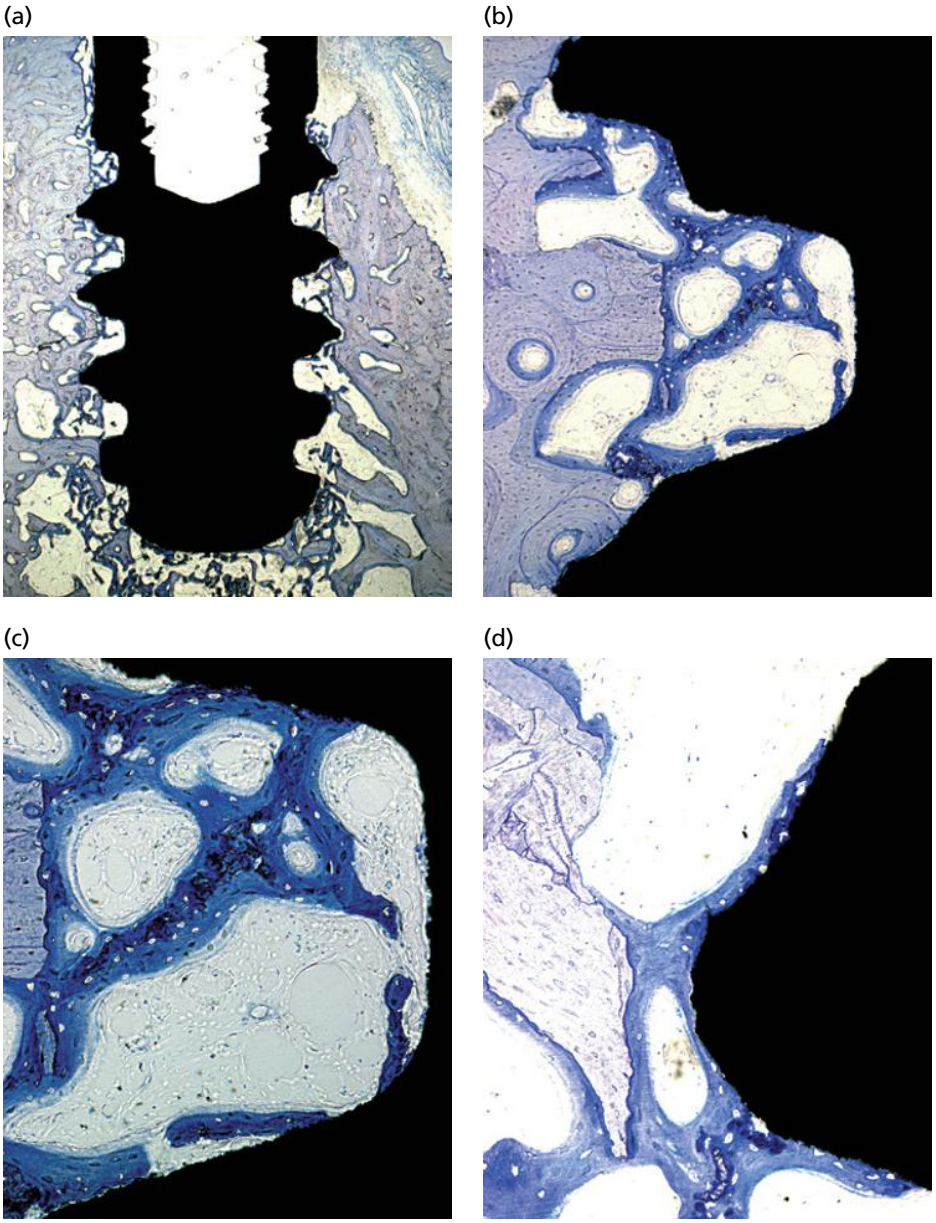

Fig. 5-17 Ground sections showing, in various magnifications, the tissues in the wound chamber after 2 weeks of healing. (a) Darker stained woven bone is observed in the apical area of the metal device. (b–d) Most portions of the implant surface are coated with bone.

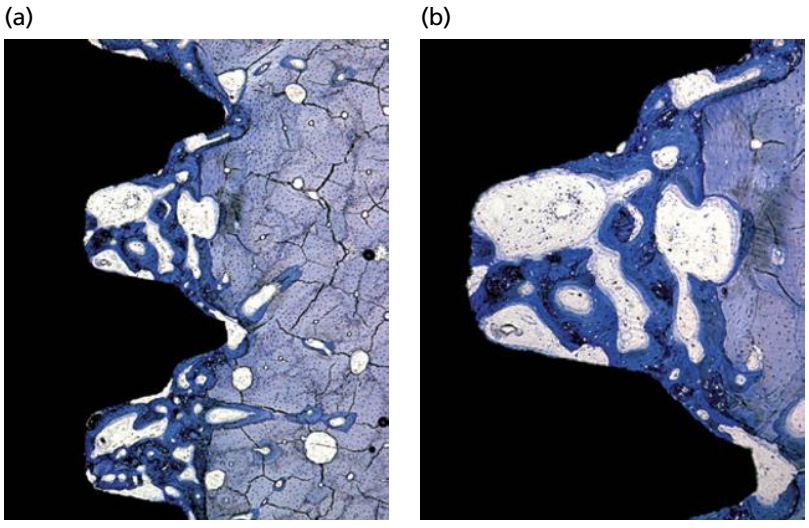

Fig. 5-18 Ground sections representing 4 weeks of healing. (a) Newly formed bone (dark blue) extends from the "old" bone into the wound chamber. (b) Appositional growth. Note the presence of primary osteons.

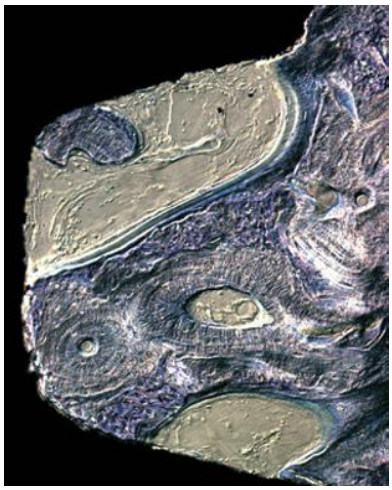

Fig. 5-19 Ground section representing 12 weeks of healing. The woven bone is being replaced with lamellar bone and marrow. Note the formation of secondary osteons.

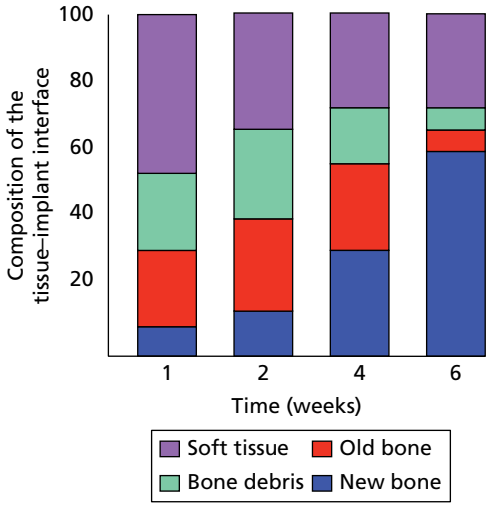

Fig. 5-20 Histogram showing the percentages of new bone, old bone, bone debris, and soft tissue in the "tissue–implant interface" after 1, 2, 4, and 6 weeks of healing. Note that the percentage of old bone, soft tissue, and bone debris that was present in the zone next to the implant surface decreased over time and that the amount of newly formed bone increased. There are reasons to suggest that (1) the contact between old bone and the implant established the initial "mechanical" stablility of the titanium device while (2) the newly formed bone subsequently achieved osseointegration. (Courtesy of D.D. Bosshardt.)

blood vessels, adipocytes, and mesenchymal cells was observed to surround the trabeculae of mineralized bone.

Summary: The wound chambers were first occupied with a coagulum. With the in-growth of vessels and migration of leukocytes and mesenchymal cells, the coagulum was replaced with granulation tissue. The migration of mesenchymal cells continued and the granulation tissue was replaced with a provisional matrix, rich in vessels, mesenchymal cells, and fibers. The process of *fibroplasia* and angiogenesis had started. Formations of newly formed bone could be recognized already during the first week of healing; the newly formed woven bone projected from the lateral wall of the cut bony bed (appositional bone formation; distance osteogenesis) (Davies 1998), but *de novo* formation of new bone could also be seen on the implant surface, that is at a distance from the parent bone (contact osteogenesis) (Davies 1998). During subsequent weeks, the trabeculae of woven bone were replaced with mature bone, that is lamellar bone and marrow (bone remodeling).

Morphogenesis of osseointegration

A series of publications have described the process of osseointegration of titanium implants placed in human volunteers (Bosshardt *et al*. 2011; Donos *et al*. 2011; Ivanovski *et al*. 2011; Lang *et al*. 2011). In these studies, solid screw devices (Institute Straumann AG, Basel, Switzerland) with a moderately rough surface were placed in the retromolar region of the mandible and submerged healing conditions were established. Biopsies including the implant with surrounding tissues were retrieved with the use of a trephine drill after 1, 2, 4, and 6 weeks. The examination of the samples included histologic and morphometric measurements and particular attention was paid to tissue elements that were in direct contact with or close to the implant surface (the tissue–implant interface), for example old bone, osteoid, newly formed bone, and non-mineralized mesenchymal soft tissue. In addition, at all examination intervals bone debris and solid bone particles were present in the wound lateral to the implant. Such constituents were obviously remnants of the drilling procedure used to prepare the hard tissue canal into which the implant was subsequently introduced.

Overall pattern of implant integration

Figure 5-20 describes the changes in the morphometric measurements in the tissue–implant interface region during the course of the study. After 1 week of healing, about 40% of the interface region was made up of soft tissue (granulation tissue, provisional connective tissue) and an additional 45% of bone debris and old bone. After 2 weeks, the amount of newly formed bone was still small, but the amount of soft tissue was markedly reduced. In the interval between 2 and 4 weeks, new bone formation was apparently pronounced in the interface zone. Thus, in this interval, newly formed bone increased from about 10% to about 30%, while the amount of hard tissue debris was markedly reduced. Also, in the period between 4 and 6 weeks, new bone formation was pronounced (from 30% to about 60%) and the diminution of old bone and bone debris markedly decreased. In other words, in humans the process of osseointegration appears to be most active in the interval between 2 and 6 weeks.

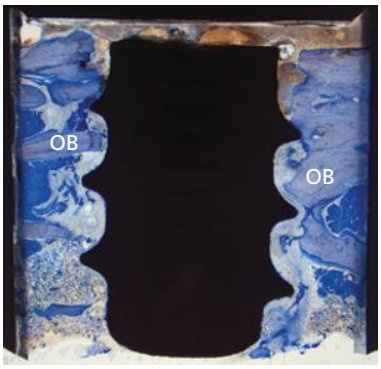

Fig. 5-21 Longitudinal ground section through a biopsy including a solid screw implant device. While compact old bone (OB) is found in contact with the coronal portion of the implant, the apical portion is comprised of less dense tissues and debris.

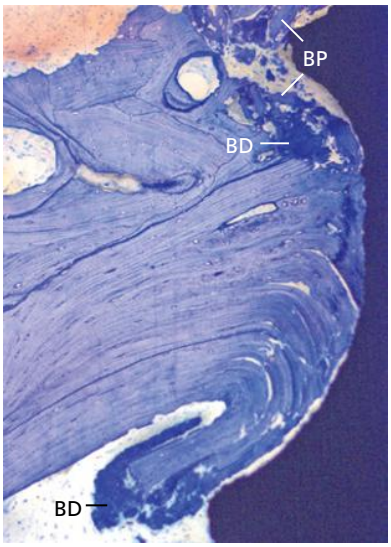

Fig. 5-22 Compact bone in direct contact with the implant surface in the coronal portion after 1 week of healing. Note the presence of bone particles (BP) and bone debris (BD) of varying size close to the implant surface. (Courtesy of D.D. Bosshardt.)

Summary: During the 6 weeks of healing that was monitored in this particular study in humans, it was observed that while the amount of old bone, bone debris, and soft tissue that initially occurred in close proximity to the implant gradually decreased, the amount of newly formed bone increased (Fig. 5-20). This pattern of healing that eventually resulted in osseointegration is in close agreement with the results obtained from the animal experiments reported earlier in this chapter.

Biopsy sample observations

Early wound

An implant with surrounding tissues sampled in the early phase after the surgical installation of the device is shown in Fig. 5-21. Note the presence of old bone, particularly in the cortical (marginal) region of the site. This old compact bone appeared to be in direct contact with the implant and obviously facilitated the initial mechanical stability of the device. Note also that more apical portions of the implant were surrounded by non-mineralized tissue, bone debris, and bone particles.

Healing process

After *1 week of healing*, substantial amounts of old bone occupied the marginal portion of the surgically prepared site. This bone tissue appeared to be in close contact with the implant device (Fig. 5-22). As stated above, this close fit between the remaining old bone and the titanium device was most likely a prerequisite for initial implant stability and of importance in establishing optimal healing conditions in the hard tissue wound. At this early interval, newly formed bone occurred on the surface of old bone tissue (Fig. 5-23), while areas of bone resorption could be identified in adjacent regions of the tissue wound. In other words, phenomena such as hard tissue apposition and resorption characterized the healing process in this early phase.

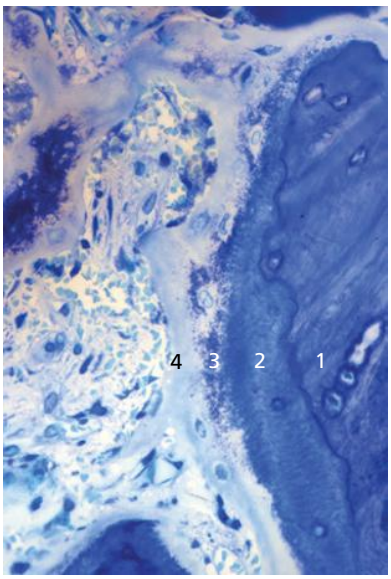

Fig. 5-23 Initial stage of bone apposition onto the surface of old bone occurring at a distance from the implant surface after 1 week of healing. 1, old bone; 2, new mineralized bone matrix; 3, mineralization foci at the mineralization front; 4, osteoid lined by osteoblasts.

Bone debris, bone particles, soft mesenchymal tissue as well as thin layers of osteoid tissue were also frequently found on or close to the implant surface (Figs. 5-24, 5-25).

At the *2-week interval*, remnants of old bone apparently still remained in the marginal portion of the implant site. Areas of hard tissue resorption (Howship´s lacunae; Fig. 5-26) could be found immediately adjacent to as well as at a distance from the implant. In addition, minute areas of newly formed bone occurred on or immediately lateral to the surface of the implant device. This formation of woven bone was the first sign of what may be called

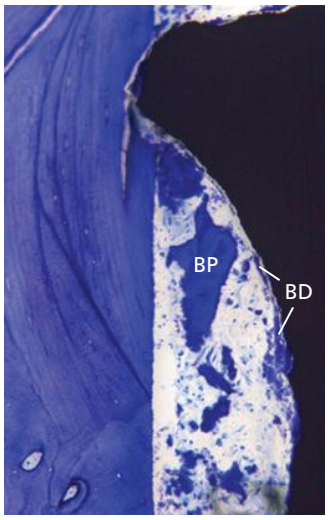

Fig. 5-24 After 1 week of healing, a considerable amount of bone debris (BD) and larger bone particles (BP) are present in the gap between the implant surface and the cut bone bed. (Courtesy of D.D. Bosshardt.)

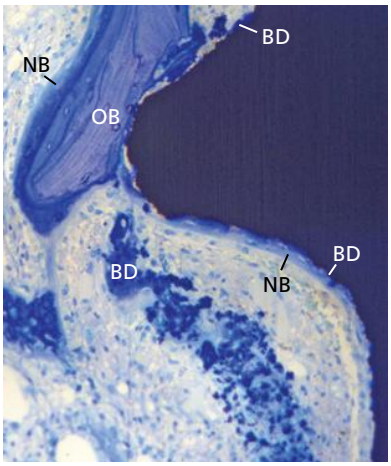

Fig. 5-25 After a healing period of 1 week, old bone (OB) is still in contact with the pitch of the implant thread. Newly formed bone (NB) is present (1) on the ledges of old bone and (2) on the implant surface. Bone debris (BD) is found adhering to the implant surface, but is also embedded in the adjacent mesenchymal soft tissue. The newly formed bone mainly consists of a partly mineralized osteoid lined by osteoblasts.

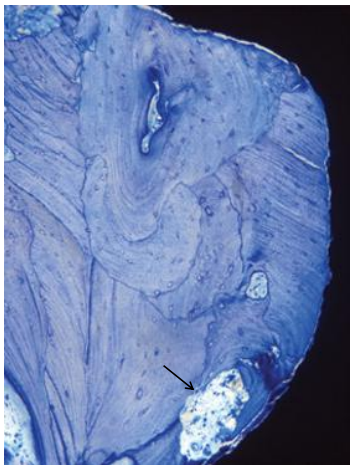

Fig. 5-26 Area of compact old bone in contact with the most coronal portion of the implant after a healing period of 2 weeks. Note the presence of bone resorption at the bottom of the micrograph (arrow).

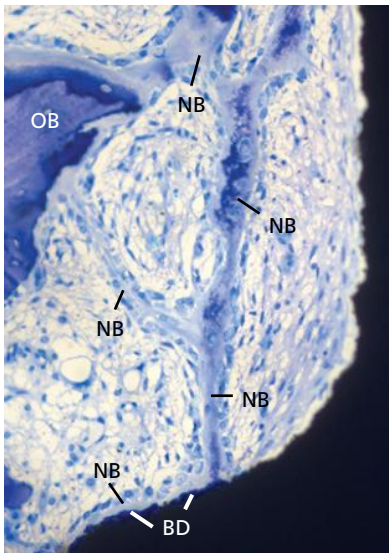

Fig. 5-27 Site characterized by active tissue modeling, in other words woven bone formation. The newly formed trabeculae of woven bone extend from old bone into the provisional connective tissue. (OB, old bone; NB, new bone; BD, bone debris.)

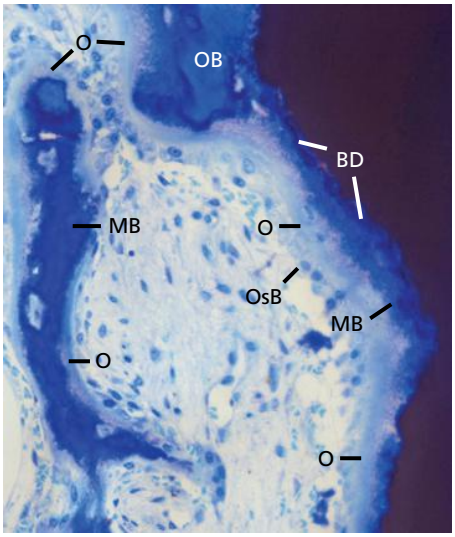

Fig. 5-28 Micrograph showing the implant–tissue interface of an implant site after 2 weeks of healing. The area is filled with a provisional connective tissue matrix and zones of new bone are discernible as well as osteoid tissue on the implant surface. Note the presence of bone debris (BD) on the surface of the implant. Tissue elements, including mineralized matrix of immature bone (MB) as well as osteoid tissue (O) and old bone (OB), are in contact with the implant surface. OsB, bodet between osteoid and connective tissue. (Courtesy of D.D. Bosshardt.)

osseointegration (Figs. 5-27, 5-28). Furthermore, at this interval, tiny ledges of newly formed woven bone apparently connected old bone to the titanium screw device (Fig. 5-28) .

At the *4-week interval*, the healing process features of modeling and remodeling were pronounced. Thus, in some areas close to the implant surface resorptive processes were discernible, while in adjacent areas woven bone had formed (Fig. 5-29).

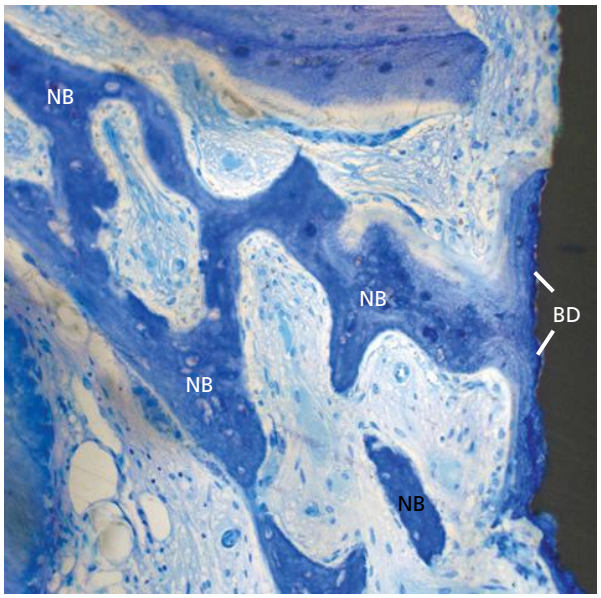

Fig. 5-29 Micrograph showing the implant–tissue interface and the peri-implant tissues of an implant after 4 weeks of healing. The newly formed bone (NB) forms a tiny trabecular network connecting the surface of the old bone with the implant surface. Deposition of new bone on the implant surface was associated with the presence of bone debris (BD). (Courtesy of D.D. Bosshardt.)

At the *6-week interval*, large amounts of newly formed woven bone (Fig. 5-30), but also lamellar bone and marrow, were present in close proximity to the implant device. This kind of newly formed hard tissue was apparently part of a more stable "bone–implant contact", in other words osseointegration.

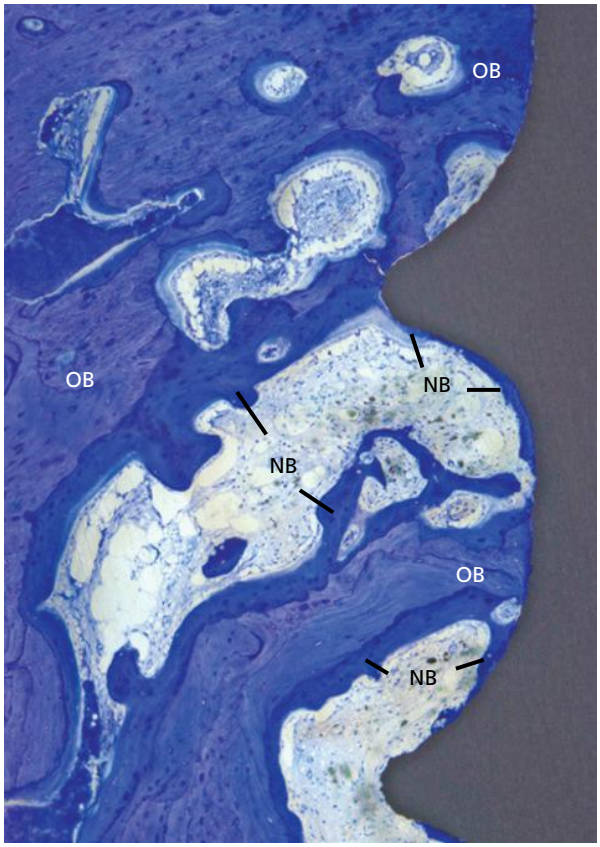

Fig. 5-30 Microphotograph showing the implant–tissue interface after 4–6 weeks of healing. New bone (NB) is found on the surface of old bone (OB) and on the implant surface. (Courtesy of D.D. Bosshardt.)

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Chapter 6

From Periodontal Tactile Function to Peri-implant Osseoperception

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Introduction

Perception is the ability to detect external stimuli through vision, audition, balance, somatic function, taste or smell (Martin 1991). In this chapter, only perception via the somatosensory system is explored. The preponderance of this system is illustrated by its major representation, along with that of the hand, in the sensory homunculus proposed by Penfield (Penfield & Rasmussen 1950). Generally speaking, the somatosensory function is essential for the fine-tuning of limb movements.

Likewise, tactile function of teeth plays a crucial role in refinement of jaw motor control. Periodontal mechanoreceptors and especially those located in the periodontal ligament, are extremely sensitive to external mechanical stimuli (Jacobs & van Steenberghe 1994). The periodontal ligament can thus be considered as a keystone for masticatory and other oral motor behaviors. Any condition that may influence periodontal mechanoreceptors could alter the sensory feedback pathway and thus affect tactile function and fine-tuning of jaw motor control (e.g. periodontal breakdown, bruxism, re-implantation, anesthesia).

The most dramatic change may occur after extraction of teeth, as this eliminates all periodontal ligament receptors. This condition may persist after implant placement, as functional re-innervation has not yet been proven in humans. Surprisingly, patients with implant-supported prostheses often seem to function quite well. The underlying mechanism of this so-called "osseoperception" phenomenon remains a matter of debate, but the response of assumed peri-implant receptors might help to restore the proper peripheral feedback pathway. This hypothesized physiologic integration might thus lead to better acceptance, improved psychological integration, and more natural functioning.

This chapter will unravel periodontal tactile function and guide the reader through the mysteries of peri-implant osseoperception in order to find neuroanatomic, histologic, physiologic, and psychophysical evidence to confirm the hypothesis.

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Neurophysiologic background

Trigeminal neurosensory pathway

The sensory inputs of the oral region are carried by the mandibular and maxillary divisions of the trigeminal nerve via the trigeminal ganglion to the brainstem. This is part of an important sensory feedback pathway that refines jaw movements. The afferent signals are transmitted either to the main sensory nucleus of the trigeminal nerve (responsive to tactile senses, light touch, and pressure) or to the descending spinal tract nuclei (responsive to sensation of oral mucosa, pain, temperature, and deep pressure). From these, signals are transferred across the midline and sent to the thalamus and, via thalamocortical projections, to the respective cortical areas involved in orofacial sensation, where they can result in conscious perception.

Neurovascularization of the jaw bones

The jaws are richly supplied by neurovascular structures, and it is thus of utmost importance to identify vital anatomic structures before carrying out a surgical procedure. During a radiographic preoperative planning procedure, neurovascular structures need to be precisely localized so that they can be avoided in surgical treatment. Studies reveal that edentulous and dentate anterior jaws present significant variation in jaw bone neurovascularization (for review see Jacobs *et al*. 2007). All these canal structures contain a neurovascular bundle whose diameter may be large enough to cause clinically significant trauma if damaged. Surgeons need to avoid the nervous structures to avoid this trauma, and also because these critical structures may be essential in the potential re-innervation of peri-implant bone. Indeed, the remaining neurovascular bundles in the edentulous jaw bone may support nerves that regenerate after tooth extraction and implant placement. This assumption is the basis of the so-called osseoperception phenomenon and will be further outlined below.

Mandibular neuroanatomy

The mandibular nerve runs forward through the mandibular canal. At the mental foramen it gives off the mental nerve. Additional mental foramina exist, with a reported prevalence of 9%. These canals are often smaller and located more posteriorly (Oliveira-Santos *et al*. 2011). Meanwhile, the mandibular nerve continues to run anteriorly as the mandibular incisive nerve (Mraiwa *et al*. 2003a, b) (Fig. 6-1). Conventional intraoral and panoramic radiographs often fail to show the so-called incisive canal (Jacobs *et al*. 2004). Cross-sectional imaging may, however, be used to locate the canal and as such protect it from the risk for neurovascular damage (Jacobs *et al*. 2002a) The mandibular incisive canal undeniably contains a true neurovascular bundle with nervous sensory structures (Fig. 6-2). Its existence in edentulous patients is underlined by reported surgical complications. Indeed, sensory disturbances, caused by direct trauma to the mandibular incisive canal bundle, have been reported after implant placement in the interforaminal region (Jacobs *et al*. 2007) (Fig. 6-3). Sensory disorders may also result from indirect trauma caused by a hematoma in the canal, and as the latter acts as a closed chamber, pressure is exerted on the mandibular incisive canal bundle and this spreads to the main mental branch (Mraiwa *et al*. 2003b).

Other anatomic landmarks to be noted are the superior and inferior genial spinal foramina and their bony canals, situated in the midline of the mandible in 85–99% of mandibles (Liang *et al*. 2005a, b; Jacobs *et al*. 2007) (Fig. 6-4). The superior genial spinal foramen has been found to contain a branch of the lingual artery, vein, and nerve. Furthermore, a branch of the mylohyoid nerve together with branches or anastomoses of sublingual and/or submental arteries and veins have been identified in the inferior genial spinal foramen. This artery can be of a size that, if it is damaged, a hemorrhage intraosseously or in the connective soft tissue can be provoked and may be difficult to control (Liang *et al*. 2005a, b) (Figs. 6-5, 6-6).

Fig. 6-1 These human dry mandibular bone sections illustrate the presence and dimensional importance of the mandibular incisive nerve, even in edentulism. The middle section actually shows the mandibular midline, confirming that there is no true connection between the left and right sections.

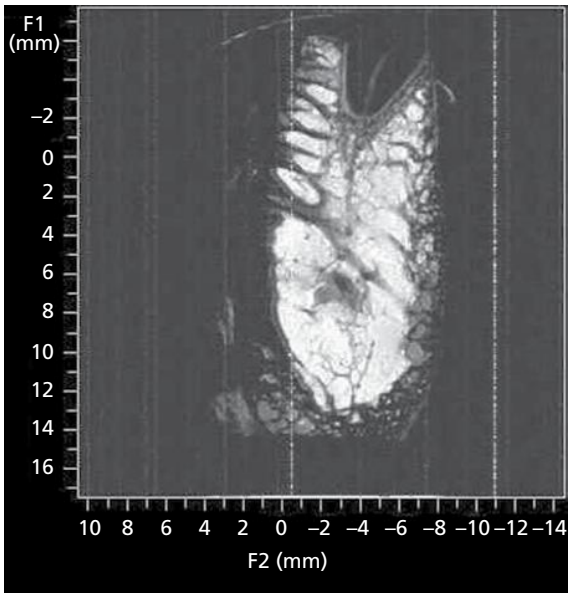


Fig. 6-2 Single cross-sectional slice of a high resolution MRI dataset localized at the incisor region of a dentate anterior human mandible, with the fatty marrow colored white. A black root-form structure corresponds to the root of an incisor tooth. It is surrounded by a small band of intermediate signal intensity, representing the periodontal ligament. Furthermore, the dental neurovascular supply is seen as a line of intermediate signal intensity in the middle of the root. The latter is descending to the level of a larger structure of intermediate signal intensity (incisive nerve) with a black oval area on top (vascular structure). (Source: Jacobs *et al*. 2007. Reproduced with permission from Elsevier.)

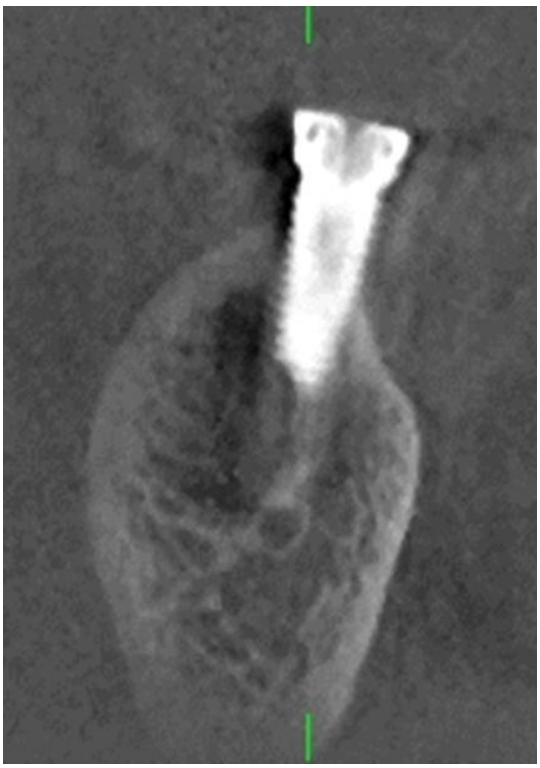


Fig. 6-3 Cross-sectional slice of a cone-beam CT dataset showing an osseointegrated implant placed in an edentulous lateral incisor region, on top of a prominent incisive canal lumen. Chronic pressure on the incisive nerve resulted in neuropathic pain. (Source: Jacobs & Steenberghe 2006. Reproduced with permission from John Wiley & Sons.)

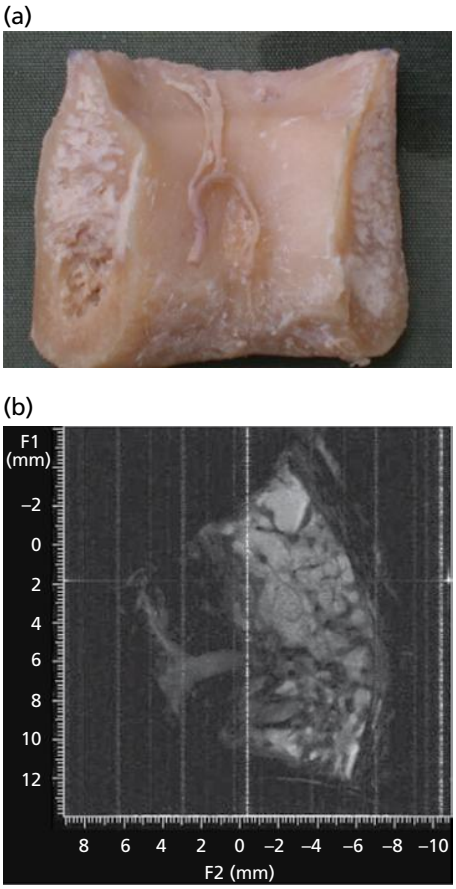


Fig. 6-4 (a) Macroanatomic view of a human anterior mandible showing a clear neurovascular bundle entering the superior genial spinal foramen. (b) Matching horizontal slice acquired through high-resolution MRI confirms the entry of a neurovascular bundle into the superior genial spinal foramen. (Courtesy of I. Lambrichts, University of Hasselt.)

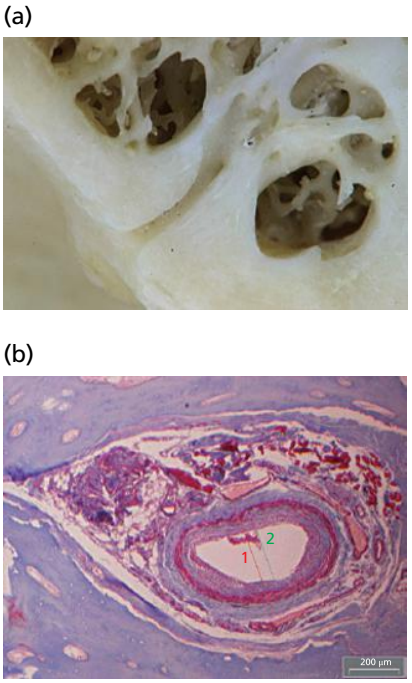


Fig. 6-5 (a) Stereomicroscopic image showing a single genial spinal canal section. (b) Neurovascular content of the canal is confirmed histologically. The artery in this image has a diameter of about 0.5 mm (red and green lines denote the inner and outer wall dimensions, respectively).

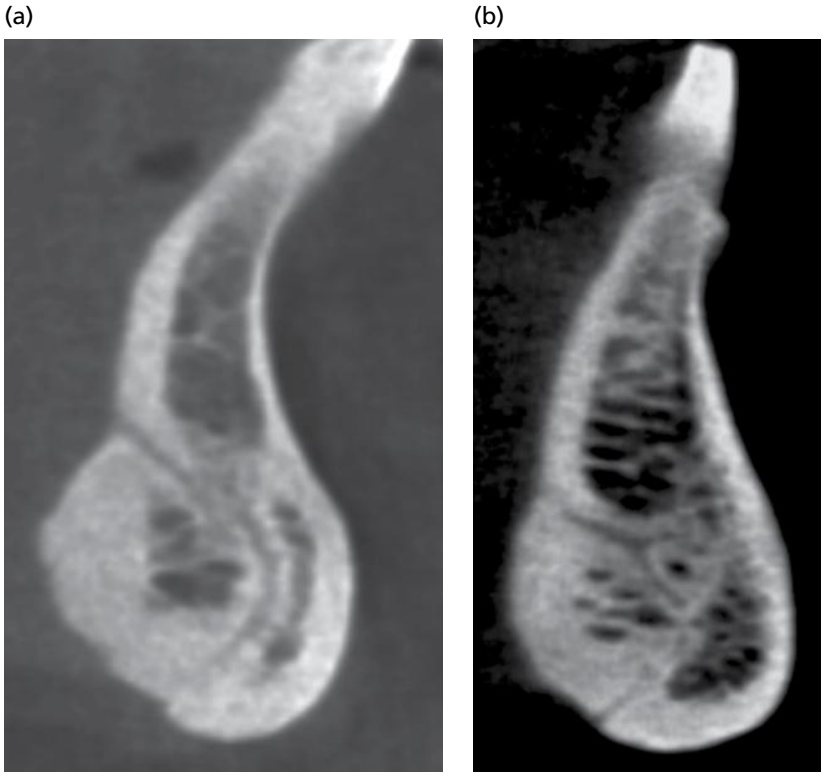


Fig. 6-6 Cone-beam CT cross-sectional images showing the relation and communication between the superior and inferior genial spinal canal (a) and the incisive canal (b).

The observation that immediate loading of implants in the anterior mandible, using the Brånemark Novum® concept rather than a conventional implant-supported overdenture, results in a significant reduction of tactile function could be explained by contact with the aforementioned neurovascular bundles in the anterior mandible (Abarca *et al*. 2006).

Maxillary neuroanatomy

The maxillary nerve is a sensory nerve, with its superior nasal and alveolar branches supplying the palate, nasal and maxillary sinus mucosa, upper teeth and their periodontium. The anterior superior alveolar nerve sometimes runs in a clearly defined canal, palatally of the canine (canalis sinuosus) (Shelley *et al*. 1999). Care should therefore be taken to avoid neurovascular trauma during canine implant installation. Another branch of importance during implant placement is the superior nasal branch, denoted the nasopalatine nerve. It descends to the roof of the mouth through the nasopalatine canal and communicates with the corresponding nerve of the opposite side and with the anterior palatine nerve (Mraiwa *et al*. 2004). Typically, it has been described as forming a Y-shape with the orifices of two lateral canals, and terminating at the nasal floor level in the foramina of Stenson (Fig. 6-7). Occasionally, two additional minor canals carry the nasopalatine nerves (foramina of Scarpa) (Fig. 6-7a). Mraiwa *et al*. (2004) point out a significant variability in both the dimensions and morphologic appearance of the nasopalatine canal. To avoid disturbing neurovascular bundles and causing further complications, implant placement in the maxillary incisor region should consider this important structure (Fig. 6-8).

Histologic background

Periodontal innervation

Periodontal receptors are located within the gingiva, jaw bone, periosteum, and periodontal ligament. Most receptors seem to have mechanoreceptive characteristics, contributing to a sophisticated exteroceptive tactile function. This tactile information is not primarily used for protective purposes, but rather to improve oral motor behavior and fine-tuning of biting and chewing (Trulsson 2006).

It is clear that periodontal ligament plays a predominant role in this dedicated mechanoreceptive function. It has an extremely rich sensory nerve supply, especially in those locations that are more prone to displacement (periapical, buccal, and lingual). It contains three types of nerve endings: free nerve endings, Ruffini-like endings, and lamelated corpuscles (Lambrichts *et al*. 1992). Free nerve endings stem from both unmyelinated and myelinated nerve fibers. Lamellated corpuscles are found in close contact with each other. Most mechanoreceptive endings are however Ruffini-like, and predominantly present in the apical part of the periodontal ligament. Morphologic studies indicate that these endings are in close contact with collagen fibers of the surrounding tissues

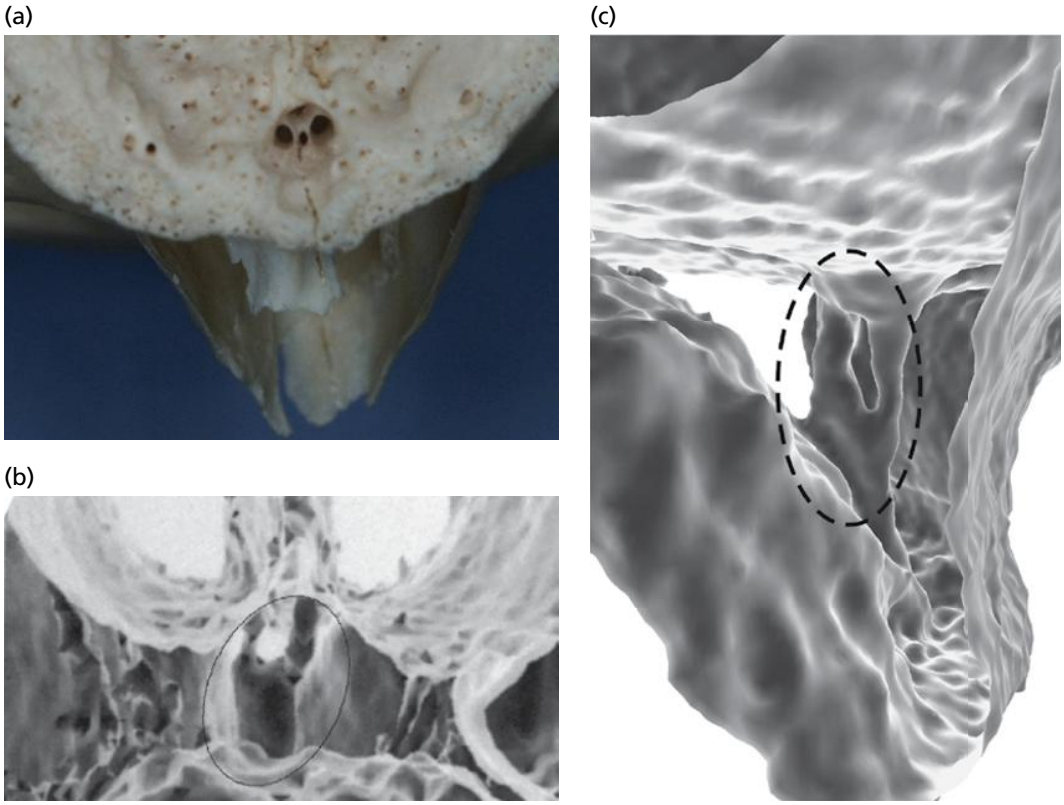


Fig. 6-7 Anatomy of the nasopalatine canal. (a) View from the palate of an edentulous dry skull showing the nasopalatine foramen, formed at the articulation of both maxillae, behind the incisor teeth. In the depth of the canal, the orifices of two lateral canals are seen. As an anatomic variant, two minor canals can be observed on the midline, one anterior and one posterior to the major nasopalatine canals. (b, c) Three-dimensional reconstruction of the palate and the floor of the nose, seen from a posterior angle (b) and from the side view (c). The outline of the common Y morphology of the nasopalatine canal is circled.

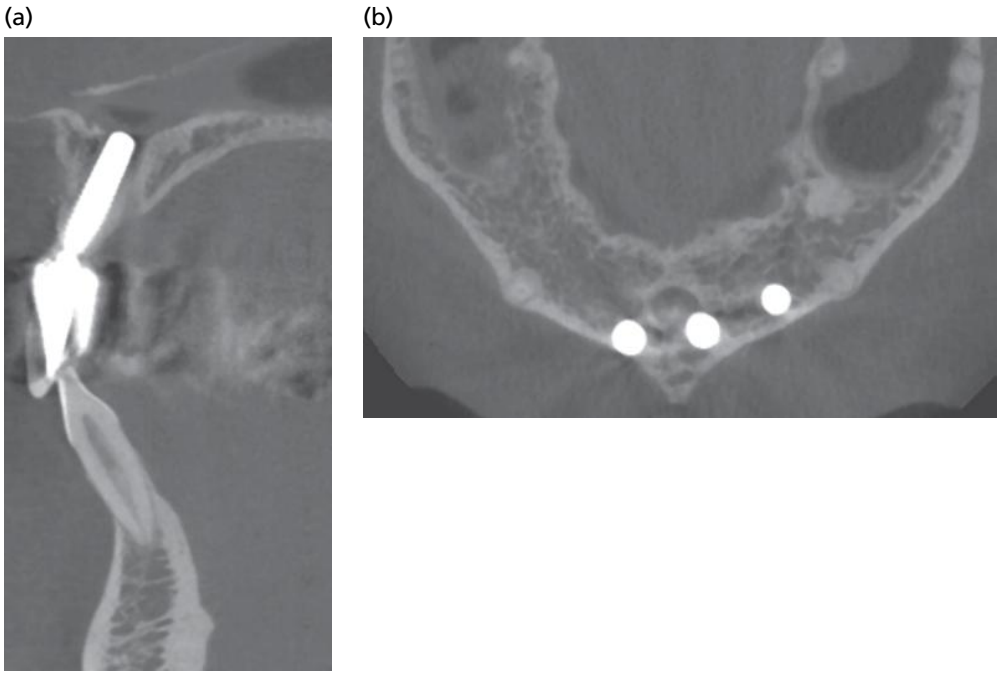


Fig. 6-8 Cone-beam CT sagittal (a) and axial (b) views showing implant 21 in the nasopalatine canal, which prevents osseointegration and creates a pathologic pocket as well as causing sensory disturbances.

(Lambrichts *et al*. 1992) (Fig. 6-9). This particular association may explain their extremely high sensitivity upon loading a tooth. This results in low threshold levels for periodontal tactile function (≤10 µm), and is considered as the basis of an elaborate sensory apparatus that may be linked to a number of clinical phenomena.

The mechanoreceptive function of the periodontal ligament signals the differential information about the mechanical events that occur during biting and

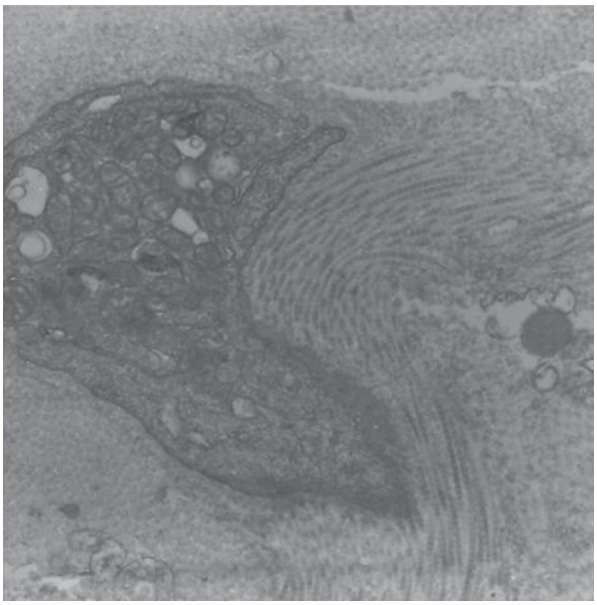


Fig. 6-9 Electron microscope image at the level of the human periodontal ligament, showing collagen fibrils inserted into the basal lamina of an ensheathing cell in a Ruffini-like receptor. (Source: Jacobs & Steenberghe 2006. Reproduced with permission from John Wiley & Sons.)

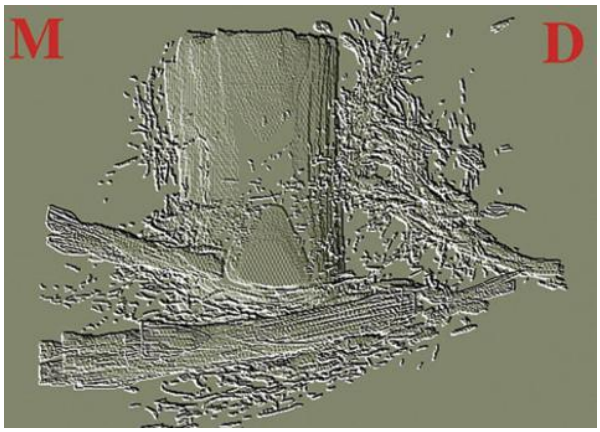


Fig. 6-10 Reconstruction of histologic slices showing the regeneration of nerve tissue 3 months after implantation of a cylindrical oral implant in a dog's jaw bone. (M, mesial; D, distal.) (Source: Wang *et al*. 1998. Reproduced with permission from R. Jacobs, Department of Periodontology, KU Leuven.)

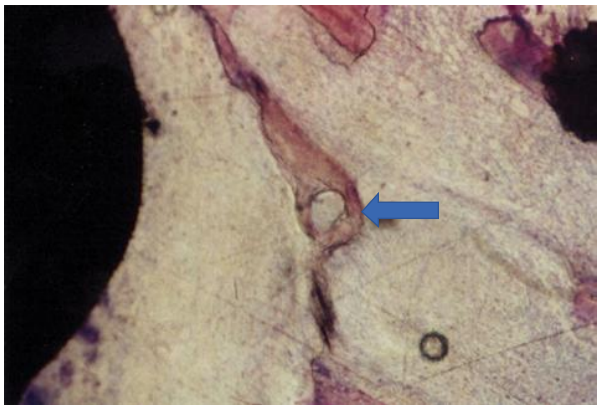


Fig. 6-11 Bone–implant specimen obtained from a cat model and subjected to immunohistochemical detection of neural structures under light microscopy. Elaborate neural structures in the bone trabeculae are seen surrounding the titanium implant. This histologic slice shows the titanium implant–bone tissue, with a bundle of myelinated nerve fibers in the bone trabeculum (arrow). (Source: Lambrichts *et al*. 1992. Reproduced with permission of Ivo Lambrichts, University of Hasselt and R. Jacobs, editor-publisher Osseoperception, Department of Periodontology, KU Leuven).

chewing (Trulsson 2006). The detailed differential signaling allows the brain to analyze and characterize these specific mechanical events, enabling further processing for fine-tuning and resulting in an optimized masticatory sequence (Trulsson 2006). Considering this crucial role, it is clear that some sensory–motor interactions are impaired or even lost when the periodontal ligament is altered or damaged. When teeth are extracted and thus ligament receptors eliminated, tactile functioning may be hampered. Indeed, Haraldson (1983) described a similar muscle activity during the entire masticatory sequence in patients with implant-supported fixed prosthesis. In subjects with natural teeth, the chewing pattern gradually changes as the food bolus properties change. Jacobs and van Steenberghe (1995) identified a silent period in muscle activity (reflex response) when teeth or implants neighboring teeth, but not implants in a fully edentulous jaw bone, were tapped. These findings may illustrate the modulatory role of periodontal ligament input in jaw muscle activity.

Peri-implant innervation

Tooth extraction damages a large number of sensory nerve fibers and corresponds to an amputation, where the target organ and peripheral nervous structures have been destroyed (Mason & Holland 1993). After extraction of teeth, the myelinated fiber content of the inferior alveolar nerve is reduced by 20% (Heasman 1984). This finding indicates that fibers originally innervating the tooth and periodontal ligament are still present in the inferior alveolar nerve. Linden and Scott (1989) succeeded in stimulating nerves of periodontal origin in healed extractions sockets, which implies that some nerve endings remain functional. Nevertheless, most of the surviving mechanoreceptive neurons represented in the mesencephalic nucleus may lose some functionality (Linden & Scott 1989). These experiments have been the basis for a long-lasting debate on the presence and potential function of sensory nerves fibers in the bone and peri-implant environment. Histologic evidence indicates that there may be some re-innervation around osseointegrated implants (Wang *et al*. 1998; Lambrichts 1998) (Figs. 6-10, 6-11). Indeed, it has been shown that the surgical trauma from implantation of endosseous implants may lead to degeneration of surrounding neural fibers. Soon, however, new fibers are observed to sprout and the number of free nerve endings close to the bone–implant interface gradually increases during the first weeks of healing (Wada *et al*. 2001). A more recent study in the

dog succeeded in partially regenerating the periodontal ligament on an implant surface (Jahangiri *et al*. 2005). Whether such regeneration can also induce restoration of the peripheral feedback pathway needs further verification.

On the other hand, existing mechanoreceptors in the periosteum may also play a role in tactile function upon implant stimulation. It is evident that oral implants offer a different type of loading and force transfer from teeth, given the intimate bone–implant contact with elastic bone properties instead of the characteristic viscoelasticity of the periodontal ligament. Thus, forces applied to osseointegrated implants are directly transferred to the bone and bone deformation may lead to receptor activation in the peri-implant bone and, more specifically, in the neighboring periosteum.

Testing tactile function

Exteroceptive function can be examined by neurophysiologic as well as psychophysical methods.

Neurophysiologic assessment

Neurophysiologic investigations of the sensory function of the human trigeminal system are risky and therefore rarely reported (Johansson *et al*. 1988a, b; Trulsson *et al*. 1992). Alternatively, non-invasive approaches may be considered to evaluate oral tactile function. The first approach is the recording of the so-called trigeminal somatosensory evoked potentials (TSEPs) after stimulation of receptors in the oral cavity. Unfortunately, SEPs from the trigeminal branches are, in contrast to those recorded from limbs, weak and difficult to discriminate from the background noise. Advanced signal analysis is required to gain reliable information (van Loven *et al*. 2000, 2001). Another non-invasive method to assess sensory function is to visualize brain activities by functional magnetic resonance imaging (fMRI) (Borsook *et al*. 2006). This is a complex method, which has received hardly any attention in relation to tactile function of teeth and implants (Lundborg *et al*. 2006; Miyamoto *et al*. 2006; Habre-Hallage *et al*. 2010). When combining fMRI with other techniques such as psychophysics and TSEPs, it may offer a new non-invasive approach to evaluate human oral somatosensory function.

Psychophysical assessment

Sensory function can also be evaluated by psychophysical testing, relying on the patient's response. This technique has often been applied to test oral tactile function (Jacobs *et al*. 2002b–d). A major advantage of psychophysical testing is that it employs simple non-invasive techniques that may be performed in a clinical environment. When carried out under strictly standardized conditions, the psychophysical response can be directly linked to the neural receptor activation (Vallbo & Johansson 1984).

Periodontal tactile function: Influence of dental status

Oral tactile function is influenced by tooth position and dental status (Jacobs & van Steenberghe 2006). The tactile function of teeth is primarily determined by the presence of periodontal ligament receptors. Vital or non-vital teeth may show a comparable tactile function. However, when periodontal ligament receptors are reduced or eliminated (e.g. through periodontitis, bruxism, chewing, extraction, anesthesia), tactile function is impaired (Table 6-1). Clinically, this implies that a patient's ability to detect occlusal inaccuracies (e.g. induced by restorative treatment) is decreased in these situations. Indeed, exteroceptors inform the nervous system on the characteristics of the stimulus, which then allows modulation of the motor neuron pool to optimize jaw motor activity and avoid overloading. Elimination of these exteroceptors by tooth extraction may reduce the tactile function to an important extent (for review see Jacobs & van Steenberghe 2006). Even after rehabilitation with a prosthesis, tactile function remains impaired and inappropriate exteroceptive feedback may thus present a risk for overloading the prosthesis (Jacobs & van Steenberghe 2006). In comparison to the tactile function of natural dentitions, the active thickness detection threshold is seven to eight times higher for dentures, but only three to five times higher for implants (see Table 6-1). For the passive detection of forces applied to upper teeth, thresholds for dentures are increased 55 times and for implants 50 times (see Table 6-1). The large discrepancies between active and passive thresholds can be explained by the fact that several receptor groups may respond to active thickness detection, while the passive force

Table 6-1 Factors influencing the tactile function of teeth (for review see Jacobs *et al*. 2002b; Jacobs & van Steenberghe 2006)

Influencing factor	Active threshold: thickness detection	Passive threshold: force detection
Vital tooth	20 µm	2 g
Avital tooth	20 µm	2 g
Anesthesia	↑	↑
Periodontitis	↑	↑ (>5 g)
Chewing	↑	↑
Bruxism	↑	↑
Extraction	↑	↑
Re-implantation	↑	↑
Denture	150 µm	150 g
Implant-supported prosthesis	50 µm	100 g
Aging	↑	↑
Polyneuropathy	↑	↑

↑, increase in threshold level implies decrease in tactile function and hampered feedback.

application selectively activates only periodontal ligament receptors. The latter are eliminated after extraction, which may explain the reduced tactile function in edentulous patients.

After rehabilitation with a bone-anchored prosthesis however, edentulous patients seem to function quite well. These patients perceive mechanical stimuli exerted on osseointegrated implants in the jaw bone. Some even note a special sensory awareness with the bone-anchored prosthesis, coined "osseoperception". This can be defined as perception of external stimuli transmitted via the implant through the bone by activation of receptors located in the peri-implant environment, periosteum, skin, muscles, and/or joints, with periosteal innervation playing a key role (Jacobs 1998). From the existence of the osseoperception phenomenon it can be hypothesized that the feedback pathway to the sensory cortex is partly restored with a representation of the prosthesis in the sensory cortex, which modulates of the motor neuron pool, leading to a more natural functioning and avoidance of overload.

From periodontal tactile function to peri-implant osseoperception

Neurophysiologic evidence for the cortical plasticity with representation of the implant in the sensory cortex can be found in some experiments evoking TSEPs upon implant stimulation. By triggering sweeps in the electroencephalogram by means of an implant stimulation device and by cumulative and advanced analysis of the sweeps, significant waves can be noted (Fig. 6-12). These experiments indicate that endosseous and/or periosteal receptors around the implants convey the sensation (Van Loven *et al*. 2000). These mechanisms could be the basis for implant-mediated sensory–motor control, which may have important clinical implications for a more natural functioning with implant-supported prostheses.

Evidence for cortical plasticity may open the way to complete integration of implants in the human body. Henry *et al*. (2005) extracted lower incisors in mole rats and with fMRI analysis showed a reorganization of the orofacial representation in the *primary sensory cortex* 5–8 months later. This study may indicate that a cortical representation of teeth may lead to significant restructuring after tooth loss. Likewise, an fMRI study by Lundborg *et al*. (2006) demonstrated that upon tactile stimulation of an osseointegrated prosthetic thumb, the primary somatosensory cortex is bilaterally activated in an area corresponding to that of the hand. As only stimulation of the healthy thumb would be expected to activate the contralateral cortex, the presence of bilateral cortical activation upon implant stimulation may be explained by some compensatory mechanism that recruits additional sensory areas after amputation (Lundborg *et al*. 2006). Following the stimulation protocol of Habre-Hallage *et al*. (2010) with 1-Hz punctuate tactile stimuli applied to teeth and implants, this group recently found that upon stimulation of implants and teeth, the somatosensory cortex was activated (Habre-Hallage 2011). The implant activated a larger bilateral cortical network outside the somatosensory areas. This novel study demonstrates that punctuate mechanical stimulation of oral implant activates cortical somatosensory areas and induces brain plasticity (Habre-Hallage 2011) (Fig. 6-13). This activation may represent the underlying mechanism of osseoperception and confirms that some related cortical plasticity may truly exist.

However, the central neural pathways and neural characteristics contributing to implant-mediated sensory–motor control remain unclear. Future research should therefore try to visualize cortical plasticity after tooth extraction and further functional rehabilitation with implants in humans. It should be considered that an extraction and immediate implant rehabilitation protocol might induce a different cortical remodeling from that with a traditional two-stage implant rehabilitation protocol. An interesting phenomenon with respect to sensory–motor integration of osseointegrated implants may be the so-called phantom tooth (after extraction) or phantom limb (after amputation), allowing perception of lost body parts (Jacobs *et al*.

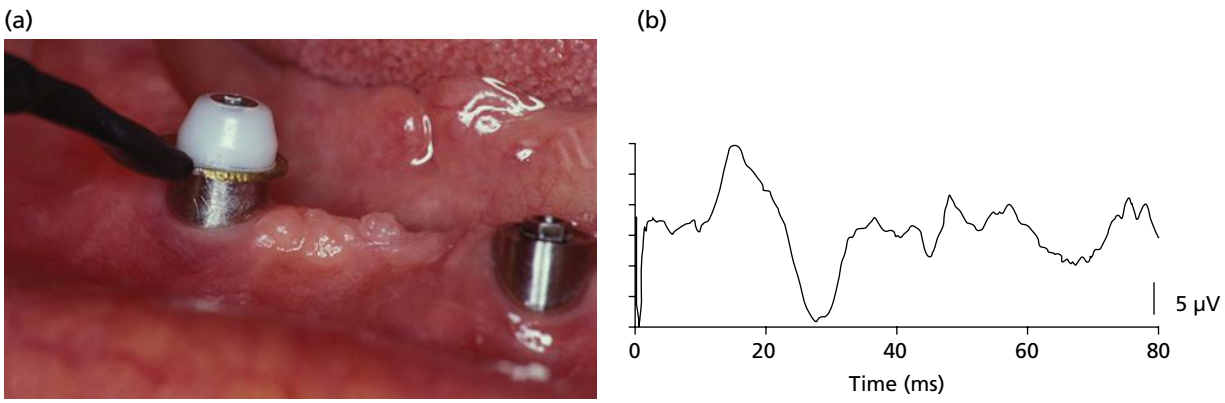


Fig. 6-12 (a) Electrical stimulation of an osseointegrated implant using a ring-shaped stimulation electrode fixed by a cover screw. (b) Trigeminal evoked potential elicited by electrical stimulation of an osseointegrated implant in the mandible. A similar potential could be maintained after topical anesthesia of the peri-implant soft tissues, indicating that the trigeminal potentials originated from other peri-implant structures such as bone and periosteal receptors.

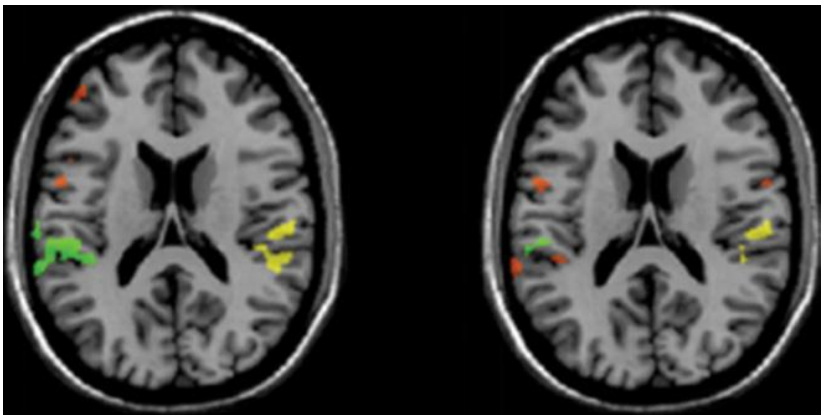


Fig. 6-13 Functional MRI showing cortical activation during tactile stimulation (1 Hz) of implant 21 (a) and tooth 23 (b) in the same subject (random effect analysis of subject sample). The primary somatosensory area is displayed in green, the secondary somatosensory area in yellow, and the other foci of activation in orange. (Source: Habre-Hallage *et al*. 2012, with permission of Pascale Habre, KU Leuven.)

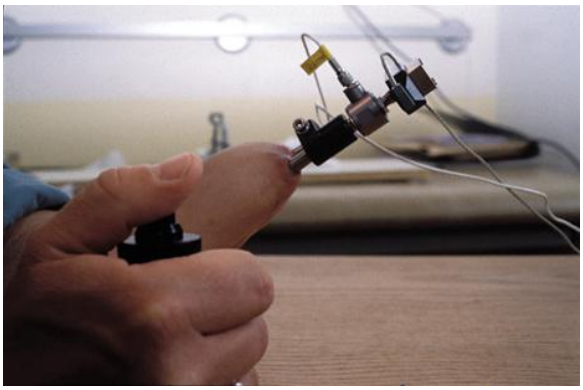
2002c). In fact, it could be assumed that such a phantom feeling of the lost limb may overlap with or enforce the feeling of a bone-anchored prosthetic limb (Jacobs *et al*. 2000). In this way, phantom sensations might contribute to physiologic integration of a bone-anchored prosthesis in the human body.

Once neuroplasticity after amputation and osseointegration is fully unraveled, it may be a consideration during treatment as it could optimize adaptation to oral rehabilitation and implant placement (Feine *et al*. 2006).

From osseoperception to implant-mediated sensory–motor interactions

During the last few decades, millions of patients have been rehabilitated by means of osseointegrated implants. Even though part of the peripheral feedback mechanism is lost after tooth extraction, edentulous patients seem to function quite well, especially when rehabilitated with a prosthesis retained by or anchored to osseointegrated implants (Jacobs 1998). These findings correspond well to those in amputees rehabilitated with a bone-anchored prosthesis rather than a socket prosthesis. During skeletal reconstruction, psychophysical testing reveals an improved tactile and vibrotactile capacity with osseointegrated implants and bone-anchored prosthetic limbs (Fig. 6-14). Furthermore, both edentulous patients and amputees seem to report an improved awareness and special feeling with the implant-supported prosthesis, suggesting the hypothesis that the peripheral feedback pathway is partially restored with a representation of the artificial limb feeling in the sensory cortex (Lundborg *et al*. 2006). If this hypothesis can be confirmed, osseointegrated implants in the jaw or other skeletal bones might contribute to implant-mediated sensory motor control, allowing physiologic integration of the implant into the human body and as a result, a more natural functioning (Jacobs & van Steenberghe 2006).

(a)



(b)

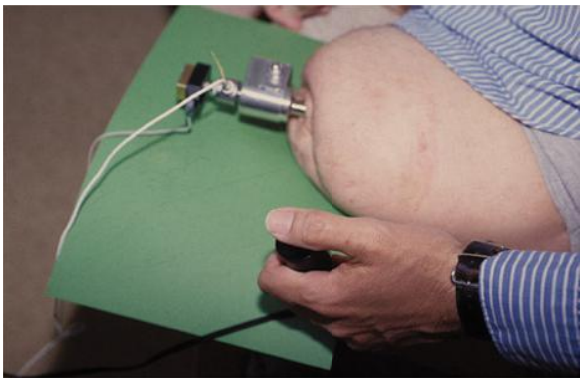


Fig. 6-14 Psychophysical test set-up using patient-controlled remote control for a vibrotactile stimulator fixed to a radial (a) and femoral (b) osseointegrated implant. This particular test set-up yields a superior perception for implants and bone-anchored prosthetic limbs as compared to socket prostheses. (Source: Jacobs *et al*. 2000. Reproduced with permission from Sage.)

Clinical implications of implant-mediated sensory–motor interactions

Psychophysical testing of various bone-anchored prostheses confirms an improved tactile function leading to a better physiologic integration of the limb. If perception upon implant stimulation is working well, peripheral feedback mechanism may be

restored and help fine-tune motor control. This implant-mediated sensory–motor interaction may thus help to achieve a more natural function with the bone-anchored prosthesis. Osseointegrated thumb prostheses even allow patients to perform the activities of daily life without any problem, which can be attributed to bone-anchorage and bilateral cortical representation after prosthesis stimulation. Considering the increased tactile threshold level for oral implant stimulation, a few clinical implications should be considered. During rehabilitation by means of implant-supported prostheses, a dentist should not rely on the patient's perception of occlusion. In this respect, the dentist should also be aware of the gradually increasing tactile function during the healing period after implant placement. This may be of particular importance when dealing with immediate loading protocols. To avoid any overloading related to suboptimal feedback mechanisms, patients should be encouraged to limit chewing forces by eating only soft foods during the healing period. Furthermore, parafunctional habits such as grinding or clenching might have a negative impact during the implant healing phase, but further research is needed to confirm this assumption (Lobbezoo *et al*. 2006). Until further evidence is available, bruxism may be considered as a relative contraindication to immediate loading protocols (Glauser *et al*. 2001).

Conclusion

Sensory feedback plays an essential role in the fine-tuning of jaw and limb motor control. Periodontal mechanoreceptors, and more specifically those located in the periodontal ligament, are extremely sensitive to external mechanical stimuli. These receptors play the key role in tactile function of teeth, yielding detection thresholds of a thickness of about 20 µm between antagonistic teeth and 1–2 g upon tooth loading. It is the sensory characteristics and related peripheral feedback that dedicate the periodontal ligament receptors to the fine-tuning of masticatory and other oral motor behaviors.

It is clear that any condition that may influence periodontal mechanoreceptors may also alter the sensory feedback pathway, and thus influence tactile function and modulation of jaw motor control (e.g. periodontal breakdown, bruxism, re-implantation, anesthesia). After extraction of teeth, the periodontal ligament is lost and so are its mechanoreceptors. After placement of oral implants, detection thresholds are increased to a thickness of at least 50-100 µm and 50–100 g upon tooth loading.

Surprisingly, patients rehabilitated by means of osseointegrated implants seem to function quite well and/or sense even better. In accordance with this, amputated patients rehabilitated with a lower limb prosthesis anchored to the bone by means of an osseointegrated implant have reported that they could sense the type of surface they were walking on, and those with a bone-anchored thumb prosthesis had a conscious perception of fingers.

The underlying mechanism of this so-called "osseoperception" phenomenon remains a matter of debate, but it is assumed that mechanoreceptors in the peri-implant bone and neighboring periosteum may be activated upon implant loading. Histologic, neurophysiologic, and psychophysical evidence of osseoperception has been amassed, making the assumption more likely that a proper peripheral feedback pathway can be restored when using osseointegrated implants. This implant-mediated sensory–motor control may have important clinical implications, because a more natural functioning can be attempted with implant-supported prostheses. This may open doors for physiologic and psychophysical integration of implants in the human body.

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Part 2: Epidemiology

Chapter 7

Epidemiology of Periodontal Diseases

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Introduction

The term epidemiology is of Hellenic origin; it consists of the preposition "epi", which means "among" or "against", and the noun "demos", which means "people". As denoted by its etymology, epidemiology is defined as "the study of the distribution of disease or a physiological condition in human populations and of the factors that influence this distribution" (Lilienfeld 1978). A more inclusive description by Frost (1941) emphasizes that "epidemiology is essentially an inductive science, concerned not merely with describing the distribution of disease, but equally or more with fitting it into a consistent philosophy". Thus, the information obtained from an epidemiologic investigation should extend beyond a mere description of the distribution of the disease in different populations (*descriptive* epidemiology). It should be further expanded to (1) elucidate the etiology of a specific disease by combining epidemiologic data with information from other disciplines such as genetics, biochemistry, microbiology, sociology, etc. (*etiologic* epidemiology); (2) evaluate the consistency of epidemiologic data with hypotheses developed clinically or experimentally (*analytical* epidemiology); and (3) provide the basis for developing and evaluating preventive procedures and public health practices (*experimental* epidemiology).

Based on the above, epidemiologic research in periodontology must (1) fulfil the task of providing data on the *prevalence* of periodontal diseases (the frequency of their occurrence) in different populations, as well as on the *severity* of such conditions, that is the amount of pathologic changes; (2) elucidate aspects related to the *etiology* and the *determinants* of these diseases (*causative* and *risk* factors); and (3) provide documentation concerning the effectiveness of preventive and therapeutic measures on a population basis.

Methodologic issues

Examination methods: Index systems

Examination of the periodontal status of a given individual includes clinical assessments of inflammation in the gingiva, recordings of probing depths and clinical attachment levels, as well as radiographic assessments of the amount of loss of supporting alveolar bone. A variety of index systems for the scoring of these parameters have been developed, some of which were designed exclusively for examination of patients in a dental practice set-up, while others were developed for use in epidemiologic research. The design of the index systems and the definition

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of the various scores inevitably reflect the knowledge of the etiology and pathogenesis of periodontal diseases at the time these systems were introduced, as well as concepts related to the contemporary therapeutic approaches and strategies. This section will not provide a complete list of all available scoring systems, but rather give a brief description of a limited number of indices that are either currently used or are likely to be encountered in the recent literature. For a description of earlier scoring systems and a historical perspective of their development, the reader is referred to Ainamo (1989).

Assessment of inflammation of the periodontal tissues

Presence of inflammation in the gingiva is usually recorded by the use of a probe, and often according to the principles of the Gingival Index System outlined by Löe (1967). According to this system, absence of visual signs of inflammation in the gingival unit is scored as 0, while a slight change in color and texture is scored as 1. Visual inflammation and bleeding tendency from the gingival margin right after a periodontal probe is briefly run along the gingival margin is scored as 2, while overt inflammation with a tendency for spontaneous bleeding is scored as 3. A parallel index scores plaque deposits (Plaque Index System) on a scale from 0 to 3 (Silness & Löe 1964): the absence of plaque is scored as 0, plaque disclosed after running the periodontal probe along the gingival margin as 1, visible plaque as 2, and abundant plaque as 3. Simplified variants of both the Gingival and the Plaque indices (Ainamo & Bay 1975) have been extensively used, assessing presence/absence of inflammation or plaque, respectively, in a binomial fashion (*dichotomous scoring*). In such systems, bleeding from the gingival margin and visible plaque correspond to a score of 1, while absence of bleeding and no visible plaque correspond to a score of 0.

Bleeding after probing to the base of the probeable pocket (Gingival Sulcus Bleeding Index) has been a common way of establishing the occurrence of subgingival inflammation, characterized by the presence of an inflammatory infiltrate adjacent to the ulcerated pocket epithelium (Mühlemann & Son 1971). In this dichotomous registration, cases where bleeding emerges within 15 seconds after probing are scored as 1.

Assessment of loss of periodontal tissue support

One of the early indices providing indirect information on the loss of periodontal tissue support was the Periodontal Index (PI) developed in the 1950s by Russell (1956), and until the 1980s it was the most widely used index in epidemiologic studies of periodontal disease. Its criteria are applied to each tooth and the scoring is as follows: a tooth with healthy periodontium scores 0, a tooth with gingivitis around only part of the tooth circumference scores 1, a tooth with gingivitis encircling the tooth scores 2, pocket formation scores 6, and loss of function due to excessive tooth mobility scores 8. Due to the nature of the criteria used, the PI is a reversible scoring system; in other words, after treatment, a tooth or an individual can have the score lowered or reduced to 0.

In contrast to the PI system, the Periodontal Disease Index (PDI), developed by Ramfjord (1959), is a system designed to assess *destructive* disease; it measures *loss of attachment* instead of *pocket depth* and is, therefore, an irreversible index. The scores, ranging from 0 to 6, denote periodontal health or gingivitis (scores 0–3) and various levels of attachment loss (scores 4–6).

In contemporary epidemiologic studies, loss of periodontal tissue support is assessed by measurements of probing pocket depth (PPD) and probing attachment level (PAL). PPD is defined as the distance from the gingival margin to the apical location of the tip of a periodontal probe that is inserted into the pocket using a moderate probing force. Likewise, PAL or clinical attachment level (CAL) is defined as the distance from the cementoenamel junction (CEJ) to the location of the probe tip. Probing assessments are usually carried out at several locations along the tooth circumference (buccal, lingual, mesial, and distal). The number of probing assessments per tooth has varied in epidemiologic studies from two to six, while the examination may include either all teeth present (*full-mouth*) or a subset of *index* teeth (*partial-mouth* examination).

Carlos *et al*. (1986) proposed an index system which records loss of periodontal tissue support. The index was denoted the Extent and Severity Index (ESI) and consists of two components (*bivariate* index): (1) the *Extent*, describing the proportion of tooth sites of a subject showing signs of destructive periodontitis, and (2) the *Severity*, describing the amount of PAL at the diseased sites, expressed as a mean value. An attachment loss threshold of >1 mm was set as the criterion that qualified a tooth site as affected by the disease. The introduction of a threshold value serves a dual purpose: (1) it readily distinguishes the fraction of the dentition affected by disease at levels exceeding the error inherent in the clinical measurement of attachment loss; and (2) it prevents unaffected tooth sites from contributing to the individual subject's mean attachment loss value. In order to limit the number of measurements to be performed, a partial examination comprising the mid-buccal and mesiobuccal aspects of the upper right and lower left quadrants was recommended. It has to be emphasized that the system was designed to assess the cumulative effect of destructive periodontal disease rather than the presence of the disease itself. The bivariate nature of the index facilitates a

rather detailed description of attachment loss patterns: for example, an ESI of (90, 2.5) suggests a generalized but rather mild form of destructive disease, in which 90% of the tooth sites are affected by an average attachment loss of 2.5 mm. In contrast, an ESI of (20, 7.0) describes a severe, localized form of disease. Validation of various partial extent and severity scoring systems against the full-mouth estimates has been performed (Papapanou *et al*. 1993).

Radiographic assessment of alveolar bone loss

The potential and the limitations of intraoral radiography to describe loss of supporting periodontal tissues were reviewed in classical publications (Lang & Hill 1977; Benn 1990) and recent reports (Vandenberghe *et al*. 2010). Radiographs have been commonly employed in cross-sectional epidemiologic studies to evaluate the result of periodontal disease on the supporting tissues rather than the presence of the disease itself, and are thought to provide valid estimates of the extent and severity of destructive periodontitis (Pitiphat *et al*. 2004). Radiographic assessments have been particularly common as screening methods for detecting subjects suffering from juvenile periodontitis as well as a means for monitoring periodontal disease progression in longitudinal studies. Assessments of bone loss in intraoral radiographs are usually performed by evaluating a multitude of qualitative and quantitative features of the visualized interproximal bone, including (1) the presence of an intact lamina dura, (2) the width of the periodontal ligament space, (3) the morphology of the bone crest ("even" or "angular" appearance), and (4) the distance between the CEJ and the most coronal level at which the periodontal ligament space is considered to exhibit normal width. The threshold for bone loss (the CEJ–bone crest distance considered to indicate that bone loss has occurred) varies between 1 and 3 mm in different studies. Radiographic data are usually presented as (1) mean bone loss scores per subject (or group of subjects) and (2) number or percentage of tooth surfaces per subject (or group of subjects) exhibiting bone loss exceeding certain thresholds. In early studies, bone loss was frequently recorded using "ruler" devices, describing the amount of lost or remaining bone as a percentage of the length of the root or the tooth (Schei *et al*. 1959; Lavstedt *et al*. 1975).

Assessment of periodontal treatment needs

An index system aimed at assessing the need for periodontal treatment in large population groups was developed, on the initiative of the World Health Organization (WHO), by Ainamo *et al*. (1982). The principles of the Community Periodontal Index for Treatment Needs (CPITN) can be summarized as follows:

1. The dentition is divided into six *sextants* (one anterior and two posterior tooth regions in each dental arch). The treatment need in a sextant is recorded when two or more teeth not intended for extraction are present. If only one tooth remains in the sextant, the tooth is included in the adjoining sextant.
2. Probing assessments are performed either around all teeth in a sextant or around certain index teeth (the latter approach has been recommended for epidemiologic surveys). Only the most severe measure in the sextant is chosen to represent the sextant.
3. The periodontal conditions are scored as follows:
   - *Code 0* is given to a sextant with no pockets, calculus or overhangs of fillings and no bleeding on probing
   - *Code 1* is given to a sextant with no pockets, calculus or overhangs of fillings, but in which bleeding occurs after gentle probing in one or several gingival units
   - *Code 2* is assigned to a sextant if there are no teeth with pockets exceeding 3 mm, but in which dental calculus and plaque-retaining factors are identified subgingivally
   - *Code 3* is given to a sextant that harbors teeth with 4–5-mm deep pockets
   - *Code 4* is given to a sextant that harbors teeth with pockets that are 6 mm deep or deeper.
4. The treatment needs (TNs) scores range from 0 to 4 and are based on the most severe periodontal condition code in the entire dentition, recorded as above. Thus, TN 0 indicates no need for periodontal therapy in the presence of gingival health (*Code 0*), TN 1 need for improved oral hygiene (*Code 1*); TN 2 need for scaling, removal of overhangs, and improved oral hygiene (*Codes 2 + 3*); and TN 3 more advanced treatment needs (*Code 4*).

Although not designed for epidemiologic purposes, this index system has been extensively used, and CPITN-based studies have often been the sole source of epidemiologic information on periodontal conditions, particularly those from developing countries. A later modification of the index, termed Community Periodontal Index (WHO 1997), places more emphasis on the assessment of periodontal conditions rather than the assessment of periodontal treatment needs. A substantial amount of data generated by the use of CPITN/CPI have been accumulated in the WHO Global Oral Data Bank (Miyazaki *et al*. 1992; Pilot & Miyazaki 1994; Petersen & Ogawa 2005; Petersen *et al*. 2010) and are accessible electronically through servers maintained at the WHO Collaborating Centers at the Niigata University, Japan and the University of Malmö, Sweden.

Periodontitis "case definition" in epidemiologic studies

A fundamental prerequisite for any meaningful comparative assessment of prevalence is a valid and accurate definition of the disease under investigation.

Unfortunately, no uniform criteria have been established in periodontal research for this purpose. Epidemiologic studies have employed, in an inconsistent manner, a wide array of symptoms, including gingivitis, probing pocket depth, clinical (or probing) attachment level, and radiographically assessed alveolar bone loss. Considerable variation characterizes the threshold values employed for defining periodontal pockets as "deep" or "pathologic", or the clinical attachment level and alveolar bone scores required for assuming that loss of periodontal tissue support has in fact occurred. In addition, the number of "affected" tooth surfaces required for assigning an individual subject as a "case", that is as suffering from periodontal disease, has varied. These inconsistencies in the definitions inevitably affect the data describing the distribution of the disease (Papapanou 1996; Kingman & Albandar 2002; Demmer & Papapanou 2010) and, consequently, the identification of risk factors (Borrell & Papapanou 2005). Any review of the literature charged with the task of comparing disease prevalence or incidence in different populations or at different time periods must first confront the interpretation of the published data and literally "decode" them in order to extract relevant information that is amenable to inter-study comparisons. These problems have been addressed in the literature and three specific aspects have attracted special attention, namely (1) the ability of partial recordings to reflect full-mouth conditions, (2) the use of the CPITN system in studies of periodontal disease, and (3) the definition of a "periodontitis case" in epidemiologic studies.

It is clear that an optimal examination of periodontal conditions should include circumferential probing assessments around all teeth. Nevertheless, the majority of epidemiologic studies have, for practical reasons, employed partial recording methodologies. The rationale for the use of partial examinations has been the assumption that (1) the time required for carrying out a partial recoding is significantly decreased, resulting in lower cost and better patient acceptance, and (2) the amount of information lost is kept to a minimum, assuming that the examined segments adequately reflect the periodontal condition of the entire dentition. However, attempts to accurately quantify the amount of information lost through the different partial recording systems made by several investigators (Diamanti-Kipioti *et al*. 1993, Eaton *et al*. 2001; Susin *et al*. 2005a; Kingman *et al*. 2008) have revealed that the discrepancy between the findings obtained by means of partial- and full-mouth surveys may be substantial. These studies have typically employed full-mouth data for a series of periodontal parameters and compared them with the values obtained by assessments of a subset of teeth or tooth surfaces. Their results suggest that:

1. High correlations between full-mouth and half-mouth clinical attachment loss scores should be expected in adult populations, due to the apparent symmetry of periodontal conditions around the midline.
2. The performance of a partial recording system is directly dependent on the actual prevalence and extent of periodontal disease in the population in question and, consequently, on the age of the subjects examined; the less frequent the disease is in the population and the lower the number of sites that are affected in each individual, the more difficult it becomes for the partial examination to accurately portray the full-mouth periodontal status.
3. A full-mouth examination provides the best means of accurately assessing the prevalence and severity of periodontal disease in a population.

The use of the CPITN system in epidemiologic studies of periodontal disease was critically evaluated in a number of publications (Schürch *et al*. 1990; Butterworth & Sheiham 1991; Baelum *et al*. 1993a, b, 1995; Baelum & Papapanou 1996; Benigeri *et al*. 2000). At the time the system was designed, the conversion from periodontal health to periodontitis was thought to follow a continuum of conditions of increasing severity, ranging from health to gingivitis, calculus deposition, formation of deep pockets, and destructive, progressive disease. Consequently, treatment approaches were primarily focused on probing depths to determine the choice between non-surgical and more complex, surgical periodontal therapy. As mentioned earlier, the CPITN system was originally intended for population screening in order to determine treatment needs and to facilitate preventive and therapeutic strategies; it was not meant to describe the prevalence, extent, and severity of periodontal disease and several studies have questioned the suitability of the CPITN for such purposes. For example, Butterworth and Sheiham (1991) examined the ability of CPITN to reflect changes in periodontal conditions in patients of a general dental practice before and after periodontal therapy. Despite a substantial improvement in periodontal status, that is a reduction in gingivitis, calculus scores, and deep pockets, the CPITN scores were only marginally improved. Furthermore, in a rural Kenyan subject sample, Baelum *et al*. (1993b) refuted the validity of the *hierarchical principle* of the CPITN, that is the assumption that a tooth with calculus is assumed to be also positive for bleeding on probing, or that a tooth with deep pockets is assumed to be positive for both calculus and bleeding. In a companion paper, results from a full-mouth examination were compared with those generated by the use of the ten index teeth recommended by the WHO for surveys of adults (Baelum *et al*. 1993a). The study revealed that the partial CPITN methodology seriously underestimated the more severe periodontal conditions both in terms of prevalence and severity, by failing to detect a substantial proportion of subjects with periodontal pockets. Finally, an examination of the relationship

between CPITN findings and the prevalence and severity of clinical attachment loss demonstrated that the CPITN scores do not consistently correlate with clinical attachment loss measures, but tend to overestimate prevalence and severity among younger subjects and underestimate such parameters in elderly populations (Baelum *et al*. 1995). Collectively, the above data call for caution in the interpretation of epidemiologic studies based on the CPITN/CPI systems.

As mentioned earlier, a concise "case definition" is essential for assessing disease prevalence and incidence and to generate comparable data across populations. The currently used classification of periodontal diseases was introduced by the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions and encompasses eight main categories, namely:

I Gingival diseases
II Chronic periodontitis
III Aggressive periodontitis
IV Periodontitis as a manifestation of systemic diseases
V Necrotizing periodontal diseases
VI Abscesses of the periodontium
VII Periodontitis associated with endodontic lesions
VIII Developmental or acquired deformities and conditions.

According to the above scheme, the principal forms of periodontitis, which this chapter will mainly focus on, fall under categories II and III, that is *chronic* and *aggressive periodontitis*. *Chronic periodontitis* is the more "common" form that occurs primarily in adults, progresses at a relatively slow rate, resulting in an extent and severity of periodontal tissue loss that is largely commensurate with the presence of local etiologic factors. In contrast, *aggressive periodontitis* is less frequent, affects primarily, but not exclusively, young, systemically healthy individuals, progresses rapidly, and results in substantial loss of periodontal tissue support that may be disproportionate to the occurrence of local etiology. Importantly, *aggressive periodontitis* shows *familial aggregation*, that is it appears to affect parents and siblings within the same family, indicating that genetic predispositions and common environmental exposures are important determinants of the disease. However, none of the three primary features of *aggressive periodontitis* (systemically healthy patient; rapid attachment loss and bone loss; familial aggregation) (Lang 1999) can facilitate the differential diagnosis between *chronic* and *aggressive periodontitis* in the setting of an epidemiologic study: the first because it is entirely non-specific; the second because it requires at least two examinations over time to determine how "rapidly" the periodontal destruction has occurred; and the third because it is subject to *reporting bias*, and requires extensive interviewing and verification to ascertain reliably. As a result, very sparse epidemiologic data have been generated to date by strictly adhering to the primary criteria of these principal forms of periodontitis. Instead, several studies have reported periodontitis prevalence data using the periodontitis case definition introduced by a working group from the Centers for Disease Control (CDC) and the American Academy of Periodontology (AAP) that is based on a combination of probing depth and clinical attachment level assessments (Page & Eke 2007). The CDC/AAP case definition does not distinguish chronic and aggressive forms of periodontitis, but defines (1) *severe periodontitis* as the presence of two or more interproximal sites with ≥6 mm of clinical attachment loss, not on the same tooth, *and* the presence of at least one interproximal site with a ≥5-mm probing depth; and (2) *moderate periodontitis* as the presence of two or more interproximal sites with ≥4 mm of clinical attachment loss occurring at two or more different teeth *or* two or more interproximal sites with a ≥5-mm probing depth, not on the same tooth. An alternative, two-level periodontitis case definition for use in epidemiologic studies was developed by a working group of the 5th European Workshop in Periodontology (Tonetti & Claffey 2005), and consisted of a *sensitive* definition (proximal attachment loss of ≥3 mm in two or more non-adjacent teeth) and a *specific* definition (proximal attachment loss of ≥5 mm in ≥30% of the teeth present). The former definition aimed at capturing incipient forms of the disease, while the latter was meant to reflect periodontitis of substantial extent and severity. Lastly, Demmer and Papapanou (2010) recently proposed a method for differentiating chronic and aggressive forms of periodontitis in epidemiologic studies of young individuals (≤35 years old) based on a combination of *age* and *extent/severity* of periodontitis. Specifically, these authors suggested that for those aged ≤25 years, the presence of two or more interproximal, non-adjacent sites with ≥4 mm of attachment loss at a minimum of two different teeth, and accompanied by bleeding on probing, signifies the presence of *aggressive periodontitis*, while a more demanding threshold of attachment loss (≥6 mm) is required to arrive at the same diagnosis in individuals aged between 26 and 35 years. In other words, according to this classification approach, extent and severity of periodontal disease exceeding the above thresholds in a young individual is incompatible with a diagnosis of *chronic periodontitis*, as the *de facto* substantial loss of periodontal tissue support early in life indicates rapid progression of the disease and thus justifies its diagnosis as *aggressive periodontitis*. This age-adjusted approach obviously fails to facilitate the differential diagnosis between severe chronic and aggressive periodontitis in a subject over the age of 35 years. Access to disease progression data derived from sequential examinations and/or confirmation of familial aggregation according to the 1999 consensus report are therefore necessary in

order to distinguish the two forms of periodontitis in older patients, but the feasibility of such an approach in the setting of an epidemiologic study remains highly questionable.

Given the lack of universal consensus on the definitions of periodontitis and the continuously evolving epidemiologic approaches, in the following text we have opted to summarize the available data on the prevalence and progression of periodontal disease according to the age range of the examined cohorts. We thus first present findings from epidemiologic studies in adults, including studies exclusively targeting elderly populations, followed by corresponding findings derived from children, adolescents, and young adults. This strategy was adopted under the assumption that the former studies primarily reflect features of *chronic periodontitis*, while the latter studies largely refer to *aggressive periodontitis*.

Prevalence of periodontal diseases

Periodontitis in adults

It is important to briefly mention some older epidemiologic studies to acquire some historical perspective and appreciate how the concepts of both the descriptive and the analytical epidemiology of periodontitis have evolved over the years. Starting with a study performed during the 1950s in India, Marshall-Day *et al*. (1955) used assessments of alveolar bone height to distinguish gingivitis and destructive periodontal disease in 1187 dentate subjects. The authors reported (1) a decrease in the percentage of subjects with "gingival disease without any bone involvement" with increasing age concomitant with an increase in the percentage of subjects with "chronic, destructive periodontal disease", and (2) a 100% occurrence of destructive periodontitis after the age of 40 years. Findings from other epidemiologic studies from the same period verified a high prevalence of destructive periodontal disease in the adult population in general, and a clear increase in disease prevalence with age. In the 1960s, Scherp (1964) reviewed the available literature on the epidemiology of periodontal disease and concluded that (1) periodontal disease appears to be a major, global public health problem affecting the majority of the adult population after the age of 35–40 years; (2) the disease starts as gingivitis in youth, which, if left untreated, leads to progressive destructive periodontitis; and (3) >90% of the variance of the periodontal disease severity in the population can be explained by age and oral hygiene. These notions, based on established concepts of the pathogenesis of periodontal disease of that time, dominated the periodontal literature until the late 1970s.

Studies performed during the 1980s provided a more thorough description of the site-specific features of periodontal disease and the high variation in periodontal conditions between and within different populations. Contrary to previous custom, the prevalence issue was no longer addressed through assigning individuals simply to a "periodontitis-affected" or a "disease-free" group, based on presence or absence of attachment or alveolar bone loss. Instead, studies began to unravel details concerning the *extent* to which the dentition was affected by destructive disease (i.e. the percentage of tooth sites involved) and the *severity* of the defects (expressed as the magnitude of the tissue support lost due to the disease). The traditional description of pocket depth and attachment loss scores in terms of *subject mean values* was soon complemented by *frequency distributions*, revealing percentages of tooth sites exhibiting probing depth or attachment level of varying severity. Such an additional analysis appeared necessary after it became clear that mean values offer a crude description of periodontal conditions and fail to reflect the variability in the severity of periodontal disease within and between individuals. In an article presenting different methods of evaluating periodontal disease data in epidemiologic research, Okamoto *et al*. (1988) proposed the use of *percentile plots* in the graphic illustration of attachment loss data. As exemplified by Fig. 7-1, such plots make it possible to illustrate simultaneously both the proportion of subjects exhibiting attachment loss of different levels and the severity of the loss within the subjects. Similar plots

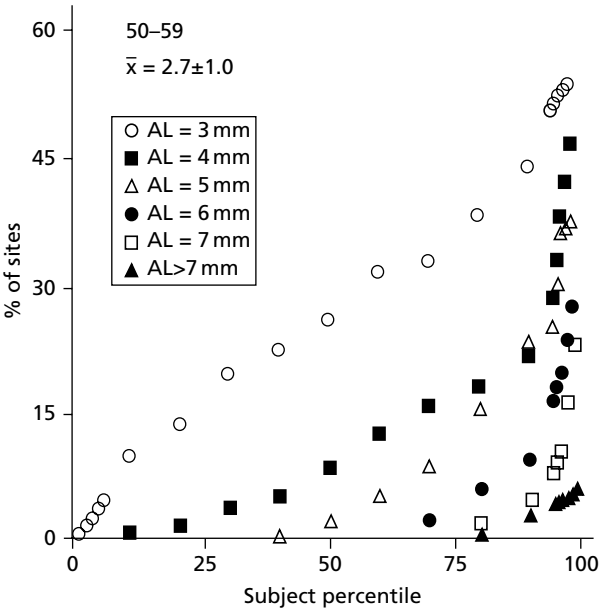

Fig. 7-1 Attachment loss in a group of Japanese subjects aged 50–59 years. The mean value of attachment level and the standard deviation are shown in the top of the figure. The x-axis represents the subject percentile and the y-axis represents the percentage of sites in the subjects showing attachment loss of 3, 4, 5, 6, 7, and >7 mm (represented by 8). Subjects with no or only minor signs of attachment loss are reported to the left and subjects with increasing amounts of periodontal destruction are reported to the right of the graph. For example, the median subject (50th percentile) exhibited 5-mm attachment loss at 2%, 4-mm loss at 8%, and 3-mm loss at 25% of its sites. (Source: Okamoto *et al*. 1988. Reproduced with permission from John Wiley & Sons.)

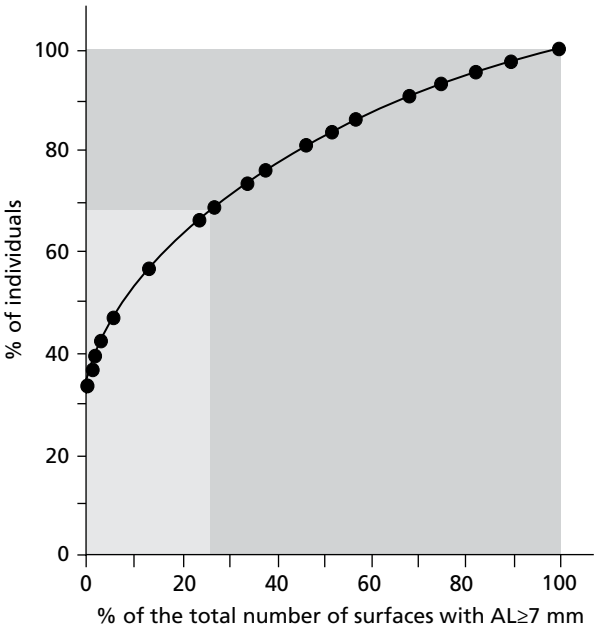

Fig. 7-2 Cumulative distribution of individuals aged ≥50 years according to the cumulated proportion of surfaces with attachment loss (AL) of ≥7 mm. All individuals are arranged according to increasing number of surfaces with AL of ≥7 mm present in each individual. Thus, individuals with few such surfaces are represented on the left side of the diagram and those with many such surfaces on the right side. It is seen that 31% (69–100%) of the individuals account for 75% (25–100%) of the total number of surfaces with AL of ≥7 mm present (shaded area). (Source: Baelum *et al*. 1986. Reproduced with permission from John Wiley & Sons.)

may be produced for other parameters, such as gingivitis, probing depths, and gingival recession, and may provide a comprehensive description of both the prevalence and the severity of periodontal disease in a given sample.

Baelum *et al*. (1986) described cross-sectional findings for dental plaque, calculus, gingivitis, loss of attachment, periodontal pockets, and tooth loss in a sample of adult Tanzanians aged 30–69 years. Despite the fact that the subjects examined exhibited large amounts of plaque and calculus, pockets deeper than 3 mm and attachment loss of >6 mm occurred at <10% of the tooth surfaces. Edentulism was virtually nonexistent, and a very small percentage of subjects had experienced major tooth loss. Of particular interest was the analysis of the distribution of sites within subjects (Fig. 7-2). This analysis revealed that 75% of the tooth sites with attachment loss of >6 mm were found in 31% of the subjects, indicating that a subset of the sample was responsible for the majority of the observed periodontal breakdown. In other words, advanced periodontal disease was not evenly distributed in the population and not readily correlated to supragingival plaque levels; instead, the majority of the subjects examined exhibited negligible periodontal problems, while a limited group was affected by advanced disease.

In a study of similar design performed in Kenya, the same investigators analyzed data from 1131 subjects aged 15–65 years and confirmed their earlier observations (Baelum *et al*. 1988a). Poor oral hygiene in the sample was reflected by high plaque, calculus, and gingivitis scores. However, pockets ≥4 mm deep were found in <20% of the surfaces and the proportion of sites per individual with deep pockets and advanced loss of attachment revealed a pronounced skewed distribution. The authors suggested that "destructive periodontal disease should not be perceived as an inevitable consequence of gingivitis which ultimately leads to considerable tooth loss" and called for a more specific characterization of the features of periodontal breakdown in those individuals who seem particularly susceptible.

At approximately the same time, Löe *et al*. (1986) published data from a longitudinal study that showed distinct patterns for the *progression* of untreated periodontitis. In a population never exposed to any preventive or therapeutic intervention related to oral diseases in Sri Lanka, a cohort of 480 14–31-year-old male tea-plantation laborers was recruited in 1970 and underwent subsequent follow-up examinations. A total of 161 individuals among those originally enrolled were re-examined in 1985, essentially generating data on the natural history of periodontal disease between the ages of 14 and 46 years. Despite poor plaque control and virtually ubiquitous gingival inflammation in the entire sample, three distinct patterns of progression of periodontitis were observed over the follow-up period, based on interproximal longitudinal attachment loss and tooth mortality rates: one group, comprising approximately 8% of the total, exhibited rapid progression of periodontal disease (RP); another group (approximately 11%) exhibited no progression (NP) of periodontal disease beyond gingivitis; and a third group between these two extremes (approximately 81%) exhibited moderate progression (MP). The mean loss of attachment in the RP group was 9 mm and 13 mm at the ages of 35 and 45 years, respectively, as opposed to 1 mm and 1.5 mm in the NP group, and 4 mm and 7 mm in the MP group. As a result, the annual rate of longitudinal attachment loss in the RP group varied between 0.1 and 1.0 mm, in the MP group between 0.05 and 0.5 mm, and in the NP group between 0.05 and 0.09 mm. Thus, this study clearly demonstrated huge variability in progression of periodontitis in a seemingly homogeneous population, and suggested that variables other than age, plaque, and gingival inflammatory status are important determinants of periodontal deterioration over time.

Several more recent epidemiologic studies verify the above principals. In these studies, periodontal disease has been assessed by means of clinical examination of the periodontal tissues (Brown *et al*. 1990; Albandar *et al*. 1999; Susin *et al*. 2004a; Thomson *et al*. 2006); radiographic assessments of alveolar bone loss (Papapanou *et al*. 1988; Jenkins & Kinane 1989; Salonen *et al*. 1991; Diamanti-Kipioti *et al*. 1995); or a combination of clinical and radiographic means (Papapanou *et al*. 1990; Hugoson *et al*. 1992, 1998a, 2005).

Table 7-1 Selected prevalence studies of periodontitis in adults.

Authors/country	Sample/methodology	Findings
Löe *et al*. (1978) Norway/Sri Lanka	Two samples, one comprising 565 Norwegian students and academicians and the other 480 Sri Lankan tea laborers, in ages 16–30+ years; assessments of plaque, gingivitis, calculus, PD, and AL at the mesial and facial aspects of all teeth	Norwegian group: excellent oral hygiene, negligible amounts of plaque and gingivitis, virtually no deep pockets and minimal attachment loss; mean AL at the age of 30 years <1 mm Sri Lankan group: poor oral hygiene, abundant plaque and calculus, attachment loss present at the age of 16 years, increasing with age; mean AL at the age of 30 years ≈ 3 mm, a substantial number of teeth with AL of >10 mm
Baelum *et al*. (1988a) Kenya	A stratified random sample of 1131 subjects, 15–65 years; full-mouth assessments of tooth mobility, plaque, calculus, bleeding on probing (BoP), PD, and AL	Plaque in 75–95% and calculus in 10–85% of all surfaces PD ≥4 mm in <20% of sites AL of ≥1 mm in 10–85% of sites Percentage of sites/subjects with PD or AL of ≥4 mm or ≥7 mm conspicuously skewed
Brown *et al*. (1990) USA	A sample of 15 132 subjects, stratified by geographic region, representing 100 million employed adults aged 18–64 years; probing assessments at mesial and buccal sites in one upper and one lower quadrant; mesial assessments performed from the buccal aspect of the teeth; assessments of gingivitis, PD, AL, and gingival recession	44% of all subjects had gingivitis at an average of 2.7 sites/subject and at <6% of all sites assessed Pockets 4–6 mm were observed in 13.4% of subjects at an average of 0.6 sites/person and at 1.3% of all sites assessed; corresponding figures for pockets ≥7 mm were 0.6%, 0.01, and 0.03% AL ≥3 mm was prevalent in 44% of subjects (increasing with age from 16% to 80%) affecting an average of 3.4 sites/subject; corresponding figures for AL ≥5 mm were 13% (2–35%) and 0.7 sites/subject
Salonen *et al*. (1991) Sweden	A random sample of 732 subjects, 20–80+ years, representing 0.8% of the population of a southern geographic region; full-mouth radiographic examination; alveolar bone level expressed as a percentage of the root length (B:R ratio); B:R of ≥80% represents intact periodontal bone support	Age group of 20–29 years: 38% of subjects had no sites with a B:R of <80% and 8% of subjects had ≥5 sites below this threshold Corresponding figures for the age group 50–59 years: 5% and 75%; after the age of 40, women displayed more favorable B:R ratios than men
Hugoson *et al*. (1998) Sweden	Three random samples of 600, 597, and 584 subjects aged 20–70 years, examined in 1973, 1983, and 1993, respectively; full-mouth clinical and radiographic examination; based on clinical and radiographic findings, the subjects were classified according to severity of periodontal disease in five groups, where group 1 (G1) included subjects with close to faultless periodontal tissues and group 5 (G5) subjects with severe disease	Edentulism decreased over the 20-year period from 11% to 8% to 5%; percentage distribution of the subjects in the five groups in 1973, 1983, and 1993 respectively was: G1 8%, 23%, 22%; G2 41%, 22%, 38%; G3 47%, 41%, 27%; G4 2%, 11%, 10%; G5 1%, 2%, 3%; the increase in the prevalence of subjects with severe disease was apparently due to the increased number of dentate subjects at the older ages
Albandar *et al*. (1999) USA	A nationally representative, multistage probability sample comprising 9689 subjects, 30–90 years old (NHANES III study); probing assessments at mesial and buccal sites in one upper and one lower quadrant; mesial assessments performed on the buccal aspect of the teeth; assessments of gingivitis, PD, and location of the gingival margin in relation to the CEJ	Pockets ≥5 mm were found in 8.9% of all subjects (7.6% in non-Hispanic Caucasians, 18.4% in non-Hispanic Blacks, and 14.4% in Mexican Americans) AL ≥5 mm occurred in 19.9% of all subjects (19.9% in non-Hispanic Caucasians, 27.9% in non-Hispanic Blacks, and 28.34% in Mexican Americans)
Schürch & Lang (2004) Switzerland	A total of 1318 subjects, randomly selected based on community rosters in seven regions, aged 20–89 years; probing assessments of PD and AL for all teeth present; assessments of plaque and gingivitis for index teeth	7.1% of subjects were edentulous; mean number of teeth present in dentate subjects was 21.6 Mean values of PD reached a plateau of 3 mm by the age of 49 years AL increased dramatically after the age of 50 years and paralleled a marked loss of teeth
Susin *et al*. (2004a) Brazil	A sample of 853 dentate individuals, selected by multistage probability sampling, aged 30–103 years; full-mouth examination of AL at six sites/tooth	Moderate AL (≥5 mm) and advanced AL (≥7 mm) occurred in 70% and 52% of the subjects, affecting an average of 36% and 16% of their teeth, respectively; in comparison to 30–39 year olds, 40–49 year olds had 3x increased risk for moderate and 7.4x increased risk for advanced AL; corresponding figures for ≥50 year olds were 5.9x and 25.4x, respectively

Table 7-1 *Continued.*

Authors/country	Sample/methodology	Findings
Dye *et al*. (2007) USA	NHANES 1999–2004 study, nationally representative sample comprising 10 312 individuals in four age cohorts (35–49, 50–64, 65–74, and 75+ years; partial-mouth examination in two randomly selected quadrants (one maxillary and one mandibular) at the mesio-facial and mid-facial sites of all fully erupted teeth excluding third molars	Prevalence of AL ≥3 mm in the four age cohorts was 36.1%, 53.4%, 67.2%, and 75.5% respectively Corresponding figures for PD ≥4 mm were 11.9%, 13.2%, 11.3%, and 12.1% respectively
Wang *et al*. (2007) China	A sample of 1590 dentate subjects with ≥14 teeth present, aged >25 years, from four geographic regions, equally farmers and urban professionals; partial-mouth examination at six sites in each of six index teeth	Average of 40% of sites bled on probing in the rural group as compared to 35% in the urban group Prevalence of AL ≥4 mm was approximately 10% in ages 25–34 years, increasing to 31%, 53%, and 70% in ages 35–44, 45–59, and >60 years, respectively, in the rural group; corresponding figures were 18%, 38%, and 57% in the urban group
Holtfreter *et al*. (2010) Germany	The fourth German Dental Health Survey examined a total of 1965 individuals aged 35–44 years (adult sample) and 65–74 years (senior sample); partial-mouth examination of PD and AL at three sites in each of 12 index teeth	AL ≥3 mm was prevalent in 95% of the adults and 99.2% of the seniors (68.7% and 91.4% of teeth affected, respectively) PD ≥4 mm was prevalent in 70.9% and 87.4% of the adult and senor cohorts, respectively
Eke *et al*. (2012) USA	NHANES 2009–2010 study, nationally representative sample comprising 3742 individuals in four age cohorts (30–34, 35–49, 50–64, 65+ years); full-mouth examination at six sites per tooth at all fully erupted teeth excluding third molars	Prevalence of AL ≥3 mm in the four age cohorts was 64.1%, 83.1%, 92.0%, and 96.7%, respectively Corresponding figures for PD ≥4 mm were 29.6%, 35.5%, 47.5%, and 49.3%, respectively Prevalence of severe periodontitis, according to the CDC/AAP definition (Page & Eke 2007) was 1.9% in ages 30–34 years, 6.7% in ages 35–49 years, 11.7% in ages 50–64 years, and 11.2% in ages 65 years and above

PD, probing depth; AL, attachment level; CEJ, cemento-enamel junction; NHANES, National Health and Nutrition Examinations Surveys; CDC/AAP, Centers for Disease Control/American Academy of Periodontology.

Table 7-1 summarizes the design and main findings from a number of cross-sectional studies in adults from geographically divergent areas and involving samples of a relatively large size. Several included studies focused on assessments of prevalence of "advanced periodontitis", the definition of which is, however, far from identical across the different reports, rendering comparisons difficult. Nevertheless, it appears that severe forms of periodontitis affect a relatively limited portion of the population in the industrialized countries, usually not exceeding 10–15%. This fraction increases considerably with age and appears to reach its peak at the age of 50–60 years. The increased loss of periodontally affected teeth occurring after this age appears to account for the subsequent decline in prevalence. It is worth pointing out that studies employing full-mouth examination protocols generally generate higher prevalence estimates, underscoring the decisive impact of the methodology. An interesting issue is also the apparent disparity in the extent and severity of periodontitis across different populations. In an earlier report by Baelum *et al*. (1996), the authors recalculated their own data from a Kenyan (Baelum *et al*. 1988a) and a Chinese (Baelum *et al*. 1988b) adult population to conform with the examination methodology and data presentation utilized in each of six other surveys: from Japan (Yoneyama *et al*. 1988), Norway (Löe *et al*. 1978), New Mexico (Ismail *et al*. 1987), Sri Lanka (Löe *et al*. 1978), and two South Pacific islands (Cutress *et al*. 1982). Among the samples included in this analysis, only the Sri Lankan and the South Pacific island subjects appeared to suffer severe periodontal tissue breakdown, while the distribution of advanced disease was strikingly similar in six of the eight samples, despite marked differences in oral hygiene conditions. Hence, the data failed to corroborate the traditional generalization that the prevalence and severity of periodontitis is markedly increased in African and Asian populations. On the other hand, data from the National Health and Nutrition Examinations Surveys (NHANES) (Albandar *et al*. 1999; Dye *et al*. 2007; Eke *et al*. 2012), which examined large nationally representative, stratified, multistage probability samples in the US, clearly showed that the prevalence of deep pockets and advanced attachment loss was more pronounced in non-Hispanic black than in non-Hispanic white subjects. This observation was consistent even when several alternative thresholds defining advanced disease were employed. Thus, current evidence suggests that the prevalence of severe periodontitis is not

Table 7-2 Selected prevalence studies of periodontitis in elderly subjects.

Authors/country	Sample/methodology	Findings
Baelum *et al*. (1988b) China	544 persons, aged 60+ years, from two urban and one rural area of the Beijing area; assessments of plaque, calculus, gingivitis, loss of attachment, pocket depth and tooth mobility	0–29% edentulous; mean number of teeth 6.9–23.9, depending on age and sex ≈50% of all surfaces with plaque and calculus 50% of all sites with AL of ≥4 mm <15% with PD ≥4 mm Conspicuously skewed percentage of sites/persons with AL of ≥7 mm and PD ≥4 mm
Locker & Leake, (1993a) Canada	907 subjects, aged 50–75+ years, living independently in four communities; probing assessments at mesio-buccal and mid-buccal aspects of all teeth; mid-palatal and mesio-palatal probing assessments in upper molars; 23% of subjects edentulous; calculation of Extent and Severity Index (ESI) with AL threshold set at ≥2 mm; "severe disease": >4 sites with AL ≥5 mm and PD ≥4 mm at ≥1 of those sites	59% of subjects with PD of ≥4 mm, 16% with ≥6 mm, and 3% with ≥8 mm 86% of subjects with AL of ≥4 mm, 42% with ≥6 mm, and 16% with ≥8 mm; 20% of the subjects with a mean PAL of ≥4 mm Severe disease in 22% of subjects; mean ESI: 77, 2.44
Beck *et al*. (1990) USA	690 community dwelling adults, aged 65+ years; probing assessments at mesio-buccal and mid-buccal surfaces, all teeth; "advanced disease": ≥4 sites with AL of ≥5 mm and PD ≥4 mm at ≥1 of those sites	Mean ESI in Blacks: 78, 4; in Caucasians: 65, 3.1 Advanced disease in 46% of Blacks and 16% of Caucasians
Gilbert & Heft (1992) USA	671 dentate subjects, aged 65–97 years, attending senior activity centers; probing assessments at mesial and buccal surfaces of one upper and one lower quadrant; questionnaire data; calculation of ESI	Average of 17.0 teeth/subject 50.7% of subjects with most severe mesial PD of 4–6 mm and 3.4% with PD of ≥7 mm 61.6% with most severe AL of 4.6 mm and 24.2% with AL of ≥7 mm ESI increased with age: 84.8, 3.6 (65–69 years); 88.7, 3.8 (75–79 years); 91.2, 3.9 (85+ years)
Douglass *et al*. (1993) USA	1151 community-dwelling elders, aged 70+ years; probing assessments at ≥3 sites/tooth, all teeth; 57% of the sample female, predominantly Caucasian (95%); 37.6% edentulous; mean number of teeth present between 21.5 and 17.9, depending on age	85% of subjects with BOP 66% with 4–6-mm deep pockets affecting an average of 5.3 teeth/subject; 21% with pockets of >6 mm affecting an average of 2.2 teeth 39% with AL of 4–6 mm at 6.7 sites/subject and 56% with AL of >6 mm at 2.7 teeth/subject
Kiyak *et al*. (1993) USA	1063 residents in 31 nursing homes, aged 72–98 years; visual inspection of the oral cavity; periodontal status assessed indirectly through registration of intraoral swelling or suppuration, sore or bleeding gums, increased tooth mobility, and poor oral hygiene	42% of subjects with remaining natural teeth; 43% had sore or bleeding gums, 18% with significant tooth mobility, 6% with intraoral swelling or suppuration, and 72% with poor oral hygiene
Weyant *et al*. (1993) USA	650 long-term residents of nursing home care units, mean age 72 years; probing assessments at mesial and buccal surfaces, all teeth; demographic, oral and general health data recorded; sample predominantly male and Caucasian; calculation of ESI scores	42% edentulous 60% of subjects with PD of >3 mm at an average of 5.8 sites/person; 3.7% with PD of ≥6 mm at <1 site/person Overall mean mesial ESI of 74, 2.91
Bourgeois *et al*. (1999) France	603 non-institutionalized elderly, aged 65–74 years; stratified sample with respect to gender, place of residence and socioeconomic group; periodontal conditions assessed by CPITN	16.3% edentulous 31.5% of subjects had pockets ≥4 mm; 2.3% had pockets ≥6 mm
Levy *et al*. (2003) USA	From a sample of 449 community dwelling elders, mean age 85 years, 342 (76%) were dentate and 236 were examined with respect to PD and AL at four sites/tooth in all teeth present	91% of ubjects had ≥1 site with ≥4 mm AL, 45% ≥1 site with ≥6 mm AL, and 15% ≥1 site with ≥8 mm AL
Mack *et al*. (2004) Germany	1446 randomly selected subjects aged 60–79 years; half-mouth examination of PD and AL at four sites/ tooth; plaque calculus and BoP were assessed at index teeth	16% of the 60–65-year olds and 30% of the 75–79-year olds were edentulous Among the 70–79-year olds, median BoP was 37.5% in men and 50% in women Prevalence of PD ≥6 mm was 31.8% and 28.5% in men and women, respectively Prevalence of AL ≥5 mm was 71.9% and 66.9% in men and women, respectively
Syrjälä *et al*. (2010) Finland	1460 individuals aged ≥65 years, participants in the nationally representative Health 2000 Survey; full-mouth examination at four sites/tooth at all erupted teeth except third molars	44.3% edentulous 31% of dentate participants had no pockets >3 mm; 28% had 1–3 teeth with ≥4 mm pockets, 15% had 4–6 and 26% ≥7 affected teeth 73% showed BoP at ≥1 sextant

PD, probing depth; AL, attachment level; BoP, bleeding on probing; CEJ, cemento-enamel junction; ESI, Extent and Severity Index; CPITN, Community Periodontal Index of Treatment Needs.

uniformly distributed among various races, ethnicities or socioeconomic groups.

The limitations of the findings from studies using the CPITN system were discussed earlier. However, a substantial part of the available information from developing countries has been collected using this particular system. An article providing a summary of almost 100 CPITN surveys from >50 countries performed over the period 1981–89 for the age group 35–44 years was published by Miyazaki *et al*. (1991b). These studies indicate a huge variation in the percentage of subjects with one or several deep (≥6 mm) pockets, both between and within different geographic areas. The percentage of subjects with such deep pockets ranged between 1% and 74% in Africa (data from 17 surveys), 8% and 22% in North and South America (four surveys), 2% and 36% in the Eastern Mediterranean (six surveys), 2% and 40% in Europe (38 surveys), 2% and 64% in South-East Asia, and 1% and 22% in the Western Pacific area (17 surveys). The average number of sextants per subject with ≥6-mm deep pockets also varied considerably and ranged between 0 and 2.1 in Africa, 0.1 and 0.4 in North and South America, 0.1 and 0.6 in the Eastern Mediterranean, 0.1 and 0.8 in Europe, 0.1 and 2.1 in South-East Asia, and 0 and 0.4 in the Western Pacific area. However, it is difficult to assess the extent to which these values reflect true differences in the periodontal conditions given the methodologic limitations of the CPITN system.

Table 7-2 summarizes a number of prevalence studies of periodontal disease in elderly subjects. In four studies (Beck *et al*. 1990; Gilbert & Heft 1992; Locker & Leake 1993b; Weyant *et al*. 1993), data on attachment loss were used to calculate ESI scores, which appear to be relatively consistent between the surveys. It is evident that attachment loss of moderate magnitude was frequent and widespread in these subject samples; however, severe disease was again found to affect relatively limited proportions of the samples and usually only a few teeth per subject. It must be realized, however, that (1) edentulism is high in elderly subjects, and (2) the remaining teeth in elderly individuals are likely those least affected by periodontitis. As discussed later, tooth loss results in an underestimation of the "true" extent and severity of periodontitis in elderly individuals.

Periodontitis in children and adolescents

The form of periodontal disease that affects the *primary* dentition, the condition formerly termed *prepubertal periodontitis*, has been reported to appear in both a generalized and a localized form (Page *et al*. 1983). Information about this disease has mainly been provided by clinical case reports and no data on the prevalence and the distribution of the disease in the general population are available. However, a small number of studies involving samples of children have provided limited data on the frequency with which deciduous teeth may be affected by attachment loss. The criteria used in these studies are by no means uniform; hence the prevalence data vary significantly. In an early study, Jamison (1963) examined the "prevalence of destructive periodontal disease" (indicated by PDI scores >3) in a sample of 159 children in Michigan, USA and reported prevalences of 27% for 5–7-year-old children, 25% for 8–10-year olds, and 21% for 11–14-year olds. Shlossman *et al*. (1986) used an attachment level value of ≥2 mm as a cut-off point and reported prevalences of 7.7% in 5–9-year olds and 6.1% in 10–14-year olds in a sample of Pima Indians. Sweeney *et al*. (1987) examined radiographs obtained from 2264 children, aged 5–11 years, who were referred to a university clinic for routine dental treatment, and reported that a distinct radiographic bone loss was evident at one or more primary molars in 19 children (0.8%), 16 of whom were black, two Caucasian, and one Asian.

In contrast, relatively uniform criteria have been used in epidemiologic studies of periodontitis in teenagers and young adults, although, as discussed earlier, the vast majority of studies have not employed the diagnostic criteria of the current classification. Nevertheless, the clinical phenotype of *localized aggressive periodontitis* (LAP) in young individuals, the condition formerly termed *localized juvenile periodontitis* (LJP), that is the severe and disproportionate involvement of incisors and first molars, has facilitated more standardized detection methodologies. Typically, a two-stage approach has been adopted in these studies: first, bitewing radiographs are used to screen for bone loss adjacent to molars and incisors, and then a clinical examination is performed to verify the diagnosis. As illustrated by the data in Table 7-3, the prevalence of LAP varies in geographically and/or racially different populations. In Caucasians, the disease appears to affect females more frequently than males and the prevalence is low (approximately 0.1%). In other races, and in particular in Blacks, the disease is more prevalent, probably at levels over 1%, and the sex ratio appears to be reversed, since males are affected more frequently than females. Smoking and low socioeconomic status have been confirmed to be associated with *aggressive periodontitis* in various populations (Lopez *et al*. 2001; Susin & Albandar 2005; Levin *et al*. 2006).

Epidemiologic studies of periodontal conditions in adolescents have been also carried out using the CPITN system. Miyazaki *et al*. (1991a) presented an overview of 103 CPITN surveys of subjects aged 15–19 years from over 60 countries. The most frequent finding in these groups was the presence of calculus, which was much more prevalent in subjects from non-industrialized than industrialized countries. Probing pocket depths of 4-5 mm were present in about two-thirds of the populations examined. However, the occurrence of deep pockets (≥6 mm) was relatively infrequent: score 4 quadrants were

Table 7-3 Selected prevalence studies of periodontitis in adolescents and young adults.

Authors/Country	Sample/methodology	Findings
Saxén (1980) Finland	A random sample of 8096 16-year olds; radiographic and clinical criteria (bone loss adjacent to first molars without any obvious iatrogenic factors and presence of pathologic pockets)	Prevalence of LAP 0.1% (8 subjects, 5 of whom were females)
Kronauer *et al*. (1986) Switzerland	A representative sample of 7604 16-year olds; two step examination (radiographic detection of bone lesion on bite-wing radiographs, clinical verification of presence of pathologic pockets)	Prevalence of LAP of 0.1%; 1:1 gender ratio
Saxby (1987) UK	A sample of 7266 schoolchildren; initial screening by probing assessments around incisors and first molars; LAP cases diagnosed definitively by full-mouth clinical and radiographic examination	Overall prevalence of LAP of 0.1%, 1:1 gender ratio; however, prevalence varied in different ethnic groups (0.02% in Caucasians, 0.2% in Asians, and 0.8% in Afro-Caribbeans)
Neely (1992) USA	1038 schoolchildren 10–12 years old, volunteers in a dentifrice trial; three-stage examination including radiographic and clinical assessments; bite-wing radiographs screened for possible cases; bone loss measurements of the CEJ–bone crest distance of ≥2 mm used to identify probable cases; LAP diagnosed clinically as PD of ≥3 mm at ≥1 first permanent molars in the absence of local irritants	117 possible and 103 probable cases identified in steps 1 and 2, respectively; of 99 probable cases contacted, 43 were examined clinically; 2 cases of LAP confirmed in stage 3, yielding a prevalence rate of 0.46%
Cogen *et al*. (1992) USA	4757 children, aged <15 years, from the pool of a children's hospital; retrospective radiographic examination of two sets of bite-wings; LAP diagnosed in case of arc-shaped alveolar bone loss in molars and/or incisors	Caucasianss: LAP prevalence 0.3%, female:male ratio 4:1 Blacks: LAP prevalence 1.5%, female:male ratio ≈ 1:1 Among Black LAP cases with available radiographs from earlier examinations, 85.7% showed evidence of bone loss in the mixed dentition and 71.4% in the deciduous dentition
Löe & Brown (1991) USA	National Survey of US children, multistage probability sampling representing 45 million schoolchildren; 40 694 subjects, 14–17 years old examined; probing assessments at mesial and buccal sites, all teeth; LAP: ≥1 first molar and ≥1 incisor or second molar and ≤2 cuspids or premolars with ≥3 mm AL; GAP: if LAP criteria not met and ≥4 teeth (of which ≥2 were second molars, cuspids or premolars) with ≥3 mm AL; incidental loss of attachment (ILA): if neither LAP nor GAP criteria met but ≥1 teeth with ≥3 mm AL; bivariate and multivariate analysis	Population estimates: LAP 0.53%; GAP 0.13%; ILA 1.61%; all 2.27% representing almost 300 000 adolescents; Blacks at much higher risk for all forms of early-onset disease than Caucasians Males more likely (4.3:1) to have GAP than females, after adjusting for other variables; Black males 2.9 times as likely to have LAP than Black females; Caucasian females more likely to have LAP than Caucasian males by the same odds
Bhat (1991) USA	A sample of 11 111 schoolchildren, 14–17 years old; probing assessments at mesial and buccal surfaces of all teeth; multistage cluster sampling stratified by age, sex, seven geographic regions, and rural or urban residence; not stratified by race or ethnicity	22% of children with ≥1 site with AL of ≥2 mm, 0.72% of ≥4 mm, and 0.04% of ≥6 mm Supra- and sub-gingival calculus in 34% and 23% of children, respectively
van der Velden *et al*. (1989) The Netherlands	4565 subjects, 14–17 years old examined; randomization among high school students; probing assessments at the mesio- and disto-facial surfaces of first molars and incisors; one bacterial sample from the dorsum of the tongue and one subgingival plaque sample from the site with maximal attachment loss obtained from 103 of the 230 subjects with AL and cultured for identification of *Aggregatibacter actinomycetemcomitans*	Overall, AL occurred in 5% of the sample and was more frequent in males; 16 subjects (0.3%) had ≥1 site with AL of 5–8 mm; female:male ratio in this group 1.3:1 *A. actinomycetemcomitans* identified in 17% of the sampled subjects with AL
Lopez *et al*. (1991) Chile	2500 schoolchildren in Santiago (1318 male, 1182 female), aged 15–19 years; clinical and radiographic assessments; three-stage screening: (1) clinical assessments of PD at incisors and molars, (2) children with ≥2 teeth with PD of ≥5.5 mm subjected to a limited radiographic examination, and (3) children with alveolar bone loss of ≥2 mm invited for a full-mouth clinical and radiographic examination	After screening, 27 subjects had a tentative diagnosis of LAP, of which 8 were confirmed (7 female, 1 male); overall prevalence of LAP 0.32%, 95% CI 0.22– 0.42%; LAP significantly more frequent in the low socioeconomic group

Table 7-3 *Continued.*

Authors/Country	Sample/methodology	Findings
Ben Yehouda *et al*. (1991) Israel	1160 male Israeli army recruits, aged 18–19 years; panoramic radiography; JP diagnosed on the basis of bone loss involving ≥30% of the root length adjacent to first molars or incisors	10 recruits (0.86%, 95% CI 0.84–0.88%) had a bone loss pattern consistent with localized juvenile periodontitis
Melvin *et al*. (1991) USA	5013 military recruits, aged 17–26 years; panoramic radiography followed by full-mouth clinical examination; diagnosis of JP if bone loss and attachment loss was greater at first molars and/or incisors than at other teeth	Overall prevalence of JP 0.76%, female:male ratio 1.1:1 Prevalence in Blacks: 2.1%, female:male ratio 0.52:1 Prevalence in whites: 0.09%, female:male ratio 4.3:1
Tinoco *et al*. (1997) Brazil	7843 schoolchildren, aged 12–19 years; two-stage screening: (1) clinical assessment of PD at first molars, (2) children with ≥1 tooth with PD ≥5 mm examined further; LAP diagnosed if a person with no systemic disease presented with AL >2 mm at ≥1 sites with radiographic evidence of bone loss and ≥1 infrabony defects at molars/incisors	119 subjects identified at initial screening; 25 confirmed cases of LAP; overall prevalence 0.3% Ethnic origins and gender ratios not reported
Lopez *et al*. (2001) Chile	A random sample of 9162 high school students, aged 12–21 years; probing assessments of AL at six sites/tooth at all incisors and molars	Prevalence of AL of ≥1 mm was 69.2%, of ≥2 mm was 16%, and of ≥3 mm was 4.5%. AL was associated with older age, female gender, poor oral hygiene, and lower socioeconomic status
Levin *et al*. (2006) Israel	642 army recruits (87.5% men), aged 18–30 years (mean 19.6 years); radiographic and clinical examination of first molars and incisors	AP prevalence was 5.9% (4.3% LAP, 1.6% GAP); current smoking and north African origin were significantly related to AP
Taylor & Borgnakke (2007) USA	105 young adults aged 18–25 years, living in housing units in Detroit, Michigan; full-mouth examination at four sites/tooth at all teeth present	9% and 2% of sample were found to suffer from "moderate"' or "severe" periodontitis, respectively, according to the CDC/AAP criteria (Page & Eke 2007)
Holtfreter *et al*. (2009) Germany	587 young adults, aged 20–29 years, participants in the Study of Health in Pomerania (SHIP); half-mouth examination of an upper and lower quadrant at four sites/tooth with respect to PD and AL	12% and 1% of sample were found to suffer from "moderate" or "severe" periodontitis, respectively, according to the CDC/AAP criteria, as above 5% of sample exhibited AL ≥4 mm, 2% ≥5 mm and 1% ≥6 mm

Terms used in all but Levin *et al.* (2006): "localized juvenile periodontitis (JP)" instead of "localized aggressive periodontitis (LAP)", and "generalized juvenile periodontitis" instead of "generalized aggressive periodontitis (GAP)".
PD, probing depth; AL, attachment level; CEJ, cemento-enamel junction; AP, aggressive periodontitis; CDC/AAP, Centers for Disease Control/American Academy of Periodontology; CI, confidence interval.

reported to occur in only ten of the examined populations (in four of the nine examined American samples, one of 16 African samples, one of ten Eastern Mediterranean samples, two of 35 European samples, two of 15 South-East Asian samples, and none of 18 Western Pacific samples).

The progression pattern of periodontitis in a sample of 167 adolescents in the UK was studied in a 5-year longitudinal study by Clerehugh *et al*. (1990). In this study, 3% of the initially 14-year olds had attachment loss of ≥1 mm affecting >1% of sites. However, at age 19 years, 77% showed a similar level of attachment loss and 31% of sites were affected. Presence of subgingival calculus at baseline was significantly associated with disease progression. In a study involving a larger sample size in the US, Brown *et al*. (1996) studied a nationally representative sample comprising 14 013 adolescents with respect to the pattern of progression of the disease entity formerly termed *early-onset periodontitis*, that is the type of periodontitis that occurs in individuals of a young age. Subjects were diagnosed at baseline as free from periodontitis, or suffering from LAP, *generalized aggressive periodontitis* (GAP), or incidental attachment loss (IAL). Of the individuals diagnosed with LAP at baseline, 62% continued to display localized periodontitis lesions 6 years later, but 35% developed a generalized disease pattern. Among the group initially diagnosed as suffering from IAL, 28% developed LAP or GAP, while 30% were reclassified in the no attachment loss group. Molars and incisors were the teeth most often affected in all three affected groups. Thus, the study indicated that these three forms of periodontitis may progress in a similar fashion, and that certain cases of LAP may develop into a more generalized form of *aggressive periodontitis*.

The possibility that LAP and *prepubertal periodontitis* are associated conditions, that is the former is a

development of the latter, has also attracted attention. In an early study, Sjödin *et al*. (1989) retrospectively examined radiographs of the primary dentition of 17 subjects with LAP and reported that 16 of these subjects showed a CEJ–bone crest distance of ≥3 mm in at least one tooth site in their deciduous dentition. The same research group (Sjödin & Matsson 1992) examined the CEJ–bone crest distance on radiographs from 128 periodontally healthy children aged 7–9 years, in order to define a threshold value that, if exceeded, would indicate a high probability of periodontal pathology around the deciduous teeth. Having set this threshold value at 2 mm, Sjödin *et al*. (1993) retrospectively examined radiographs of the deciduous dentition from 118 patients with *aggressive periodontitis* and 168 age- and sex-matched periodontally healthy controls. The patients were divided in two groups, one comprising those with only one affected site (45 subjects) and another (73 subjects) including those with 2–15 sites with bone loss in their permanent dentition. It was found that 52% of the patients in the latter group, 20% of those in the former group, and only 5% of the controls exhibited at least one site with bone loss in their primary dentition. The authors concluded that, at least in some young subjects with *aggressive periodontitis*, the onset of the disease may manifest in the primary dentition. Similar results were reported by Cogen *et al*. (1992) from a study in the US. Among systemically healthy young Black subjects with *aggressive periodontitis* and available radiographs of the primary dentition, 71% showed alveolar bone loss adjacent to one or several primary teeth. Finally, an interesting radiographic study of the mixed dentition in Australian children aged 5–12 years by Darby *et al*. (2005) investigated the prevalence of alveolar bone loss around first permanent molars, and first and second deciduous molars. Based on radiographs of 542 children, 13% were found to display definite bone loss, that is bone levels >3.0 mm from the CEJ. Half of all sites with definite bone loss were on the second deciduous molars and, in the vast majority, on distal tooth surfaces. In other words, this study showed that the tooth surface of the deciduous dentition most frequently affected by bone loss was the one in close proximity to the most frequent localization of *aggressive periodontitis* in older children with permanent dentition, that is the mesial surface of the first permanent molar.

Periodontitis and tooth loss

Tooth loss may be the ultimate consequence of destructive periodontal disease. Teeth lost due to the sequelae of the disease are obviously not amenable to registration in epidemiologic surveys and may, hence, lead to an underestimation of the prevalence and the severity of the disease. The well-established epidemiologic concept of *selection bias* (also referred to as the *healthy survivor effect*, indicating that the comparatively healthier subjects will present for an examination while the more severely affected may refuse participation or fail to present because of the morbidity itself) is in this context applicable at the individual tooth level, since the severely affected teeth may have already been extracted/lost. Aspects related to tooth loss on a population basis have been addressed in numerous publications. Important questions that were analyzed included the relative contribution of periodontitis to edentulism (Eklund & Burt 1994; Takala *et al*. 1994) or to tooth extractions in subjects retaining a natural dentition (Reich & Hiller 1993; McCaul *et al*. 2001; Susin *et al*. 2005b; Thorstensson & Johansson 2010; Hirotomi *et al*. 2011).

Typically, surveys addressing the first topic have utilized questionnaire data obtained from general practitioners instructed to document the reasons why teeth were extracted over a certain time period. The results indicate that the reason underlying the vast majority of extractions in ages up to 40–45 years is dental caries. However, in older age cohorts, periodontal disease is about equally responsible for tooth loss. Overall, periodontitis is thought to account for 30–35% of all tooth extractions, while caries and its sequelae for up to 50%. In addition, caries appears to be the principal reason for extractions in cases of total tooth clearance. Finally, identified risk factors for tooth loss include smoking, poor dental health, poverty and other socio-behavioral traits, and poor periodontal status.

Obviously, it is not feasible to "translate" tooth loss data into prevalence figures of periodontal disease. An evaluation, however, of the periodontal status at the population level, and in particular in older age cohorts, must weigh the information provided by tooth loss data; otherwise underestimation of the occurrence and the sequelae of the disease is inevitable (Gilbert *et al*. 2005).

Risk factors for periodontitis

Introduction: Definitions

There is an abundance of both empirical evidence and substantial theoretical justification for accepting the widespread belief that many diseases have more than one cause, in other words they have a *multifactorial etiology* (Kleinbaum *et al*. 1982). Consequently, in any particular instance when a *causal relationship* is investigated, the specificity of the relation between exposure to an etiologic agent and effect (the *necessity* or the *sufficiency* of the condition) may be challenged. In the case of most infectious diseases for example, it is known that the presence of the microbial agent (which is defined as the necessary condition) is not always accompanied by signs or symptoms characteristic of that disorder. Thus, the agent itself is not sufficient to cause any pathologic occurrence; rather, the disease development may be dependent on multiple and diverse additional factors, including specific host responses, toxic exposures, nutritional deficiencies, emotional stress, and the complex

impact of social influences. In non-infectious diseases (except for genetic abnormalities), there is usually no factor known to be present in every single case of the disease. For example, smoking is not necessary for the development of lung cancer, and no degree of coronary atherosclerosis is a necessary condition for myocardial infarction.

The *causal inference*, in other words the process of drawing conclusions related to the cause(s) of a disease, is a particularly complex issue in epidemiologic research. Four decades ago, Hill (1971) formalized the criteria that have to be fulfilled in order to accept a causal relation. These included:

1. *Strength of the association.* The stronger the association between the potential (*putative*) risk factor and disease presence, the more likely it is that the anticipated causal relation is valid.
2. *Dose–response effect.* An observation that the frequency of the disease increases with the dose or level of exposure to a certain factor supports a causal interpretation.
3. *Temporal consistency.* It is important to establish that the exposure to the anticipated causative factor occurred prior to the onset of the disease. This may be difficult in cases of diseases with long latent periods or factors that change over time.
4. *Consistency of the findings.* If several studies investigating a given relationship generate similar results, the causal interpretation is strengthened.
5. *Biologic plausibility.* The anticipated relationship should make sense in the context of current biologic knowledge. However, it must be realized that the less that is known about the etiology of a given disease, the more difficult it becomes to satisfy this particular criterion.
6. *Specificity of the association.* If the factor under investigation is found to be associated with only one disease, or if the disease is found to be associated with only one factor among a multitude of factors tested, the causal relation is strengthened. However, this criterion can by no means be used to reject a causal relation, since many factors have multiple effects and most diseases have multiple causes.

It is important to realize that the criteria described above are meant as guidelines for the establishment of a causal inference. None of them, however, is either necessary or sufficient for a causal interpretation. Strict adherence to any of them without concomitant consideration of the others may result in incorrect conclusions.

A distinction has to be drawn between a *causal* factor, assessed as above, and a *risk* factor. In a broad sense, the term risk factor may indicate an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is known to be associated with disease-related conditions, based on epidemiologic evidence. Such an attribute or exposure may be associated with an increased probability of occurrence of a particular disease without necessarily being a causal factor. A risk factor may be modified by intervention, thereby reducing the likelihood that the particular disease will occur.

The principles of the *risk assessment process* were discussed by Beck (1994) and consists of the following four steps:

1. The *identification* of one or several individual factors that appear to be associated with the disease.
2. In case of multiple factors, a *multivariate risk assessment model* must be developed that discloses which combination of factors most effectively discriminates between health and disease.
3. The *assessment* step, in which new populations are screened for this particular combination of factors, with a subsequent comparison of the level of the disease assessed with the one predicted by the model.
4. The *targeting* step, in which exposure to the identified factors is reduced by prevention or intervention and the effectiveness of the approach in suppressing the *incidence* of the disease is evaluated.

Thus, according to this process, *potential* or *putative risk factors* (often also referred to as *risk indicators*) are first identified and thereafter tested until their significance as *true risk factors* is proven or rejected.

Finally, distinction must be made between *prognostic* factors (or *disease predictors*), that is characteristics related to the progression of *pre-existing* disease, and *true risk factors*, that is exposures related to the *onset* of the disease. For example, it is established in longitudinal studies of periodontal disease progression (Papapanou *et al*. 1989), that the amount of alveolar bone loss or the number of teeth present at baseline may be used to predict further progression of the disease. These variables are, in fact, alternative measures of the disease itself and express the level of susceptibility of a given subject to periodontal disease. Although they may be excellent predictors for further disease progression, they clearly cannot be considered as risk factors.

There are several ways to study the relation between exposure to a certain factor and the occurrence of a particular disease, as required under step 1. One of these is described in Fig. 7-3, which illustrates a hypothetical situation where exposure to the potential risk factor Z is studied in a cross-sectional study of 1000 subjects, 180 of whom are found to suffer from the disease D (“diseased”), while 820 are disease-free (“healthy”). In this particular setting, it was observed that 155 of the 180 diseased subjects had been exposed to factor Z, but this was also the case for 340 non-diseased subjects. In this example, the association between exposure and disease is expressed by the *odds ratio* (OR), which is the ratio of

	Exposed	Non-exposed	
Diseased	155	25	180
Healthy	340	480	820
	495	505	1000

Fig. 7-3 Contingency table describing the distribution of a group of 1000 subjects according to exposure to a particular factor and disease status.

exposure among the diseased and the healthy. For the data in Fig. 7-3, the OR is calculated as (155/25) over (340/480) = (155 × 480)/(340 × 25) = 8.75. This indicates that diseased individuals were 8.75 times more likely to be exposed to factor Z than healthy individuals. Note that the OR is frequently misinterpreted to describe the risk of an exposed subject developing the disease, something that is only correctly assessed in a prospective cohort rather than a cross-sectional study and is described by the *relative risk*. In the example of Fig. 7-3, if a sample of 495 subjects exposed to factor Z and 505 subjects not exposed to factor Z are prospectively followed over a given time period, and 155 among the exposed and 25 among the non-exposed develop disease D over this period, then the relative risk is calculated as (155/495) over (25/505) = 6.4. In other words, an individual exposed to factor Z is 6.4 times more likely to develop disease D than a non-exposed subject.

In a study of the association between an exposure and the occurrence of a disease, *confounding* can occur when an additional factor is associated with both the exposure and the disease under study. For instance, when examining the association between alcohol consumption and cancer, smoking may act as a confounder, because smokers are frequently alcohol consumers and smoking also has carcinogenic effects.

There are various ways to assess simultaneously the effect of the several putative risk factors identified in step 1 and to generate the *multivariate model* required for step 2. For example, the association between exposure and disease may, for reasons of simplicity, have the form of the following linear equation:

$$y = a - b_1x_1 + b_2x_2 + b_3x_3 + \ldots b_nx_n$$

where y represents occurrence or severity of the disease, a is the intercept (a constant value), x_1, x_2, … x_n describe the different exposures (putative risk factors), and b_1, b_2, … b_n are *estimates* defining the relative importance of each individual exposure as a determinant of disease, after taking all other factors into account. Such an approach will help to identify factors with statistically and biologically significant effects and may minimize the effect of confounders.

In the third step (*assessment step*), a new population sample that is independent of the one used in the construction of the multivariate model is screened for occurrence of disease and presence of the relevant factors included in the multivariate model of step 2. Alternatively, in the case of a prospective cohort study, exposure to the relevant factors is assessed among the subjects of the new sample, and disease incidence, that is the number of new cases of disease, is determined over a time period after a longitudinal follow-up of the subjects. Subsequently, disease occurrence predicted from the model is compared to the actual disease occurrence, and the *external validity* of the model (i.e. the "behavior" or "fitness" of the model in the new population) is evaluated.

Lastly, during the fourth step (*targeting*), aspects of causality or risk are verified if disease occurrence is suppressed when exposure is impeded. Ideally, such studies should be designed as randomized clinical trials, in which treatment is randomly assigned to one of two groups and the effectiveness of the intervention is assessed in direct comparison to outcomes in an untreated, control group. Additionally, an evaluation of the particular preventive/therapeutic strategy from a "cost–benefit" point of view is also facilitated in such studies. Note that successful fulfillment of the targeting step requires that (1) the factor is amenable to intervention and (2) the intervention is delivered at the appropriate time point. Genetic traits are examples of risk factors not amenable to intervention. Likewise, in cases where a single exposure to a factor results in detrimental and/or irreversible biologic damage (e.g. exposure to a high dose of radiation), interventions protecting against subsequent exposure to the factor (radiation) may not lower the incidence of disease (e.g. cancer).

In the context of periodontitis, it should be realized that few of the putative risk factors for disease development have been subjected to the scrutiny of all four steps. In fact, risk assessment studies in dental research in general have been frequently confined to the first two steps. Numerous cross-sectional studies identifying potential risk factors are available, but a relatively limited number of longitudinal studies involve a multivariate approach to the identification of exposures of interest while simultaneously controlling for the effect of possible confounders. Intervention studies in the form of randomized clinical trials are sparse. In the following text, the issue of risk factors is addressed according to the principles described above. Results from cross-sectional studies are considered to provide evidence for putative risk factors that may be further enhanced if corroborated by longitudinal studies involving multivariate techniques, or prospective intervention studies. As reviewed by Borrell and Papapanou (2005), distinction is also made between putative factors that are not amenable to intervention (non-modifiable background factors) and modifiable factors (environmental, acquired, and behavioral).

Non-modifiable background factors

Age

The relationship between age and periodontitis is complex. Although it is clear that both the prevalence and the severity of periodontitis increase with age (Burt 1994; Albandar *et al*. 1999; Dye *et al*. 2007), the concept of periodontitis as an inevitable consequence of aging has been challenged over the years (Papapanou *et al*. 1991; Papapanou & Lindhe 1992) and the alleged "age effect" largely represents the cumulative effect of prolonged exposure to true risk factors. Notably, the association between age and periodontitis appears to be different for pocket depth and amount of clinical attachment loss. While there is a pronounced effect of increasing attachment loss with age, the effect on pocket depth appears to be minimal (Albandar 2002a, b). Interestingly, the effect of age on attachment loss was found to be attenuated after adjustment for co-variates, such as oral hygiene levels or access to dental care services (Albandar, 2002a). In addition, epidemiologic studies have often failed to adjust for important co-variates such as presence of systemic diseases, consumption of multiple medications, and co-morbidities related to nutritional disturbances in the older population, all of which could partly account for the increased prevalence and severity of periodontitis in the elderly. On the other hand, age-associated molecular alterations in key phagocytic cells involved in both the protective and destructive immune responses have been shown to affect their ability to carry out efficient antimicrobial functions and to result in a dysregulation of the inflammatory response (Hajishengallis 2010). Since periodontitis is a microbially-induced inflammatory disorder, these alterations in innate immunity likely contribute to more pronounced periodontal pathology in elderly individuals. An age-related, rather than an age-dependent, increased susceptibility to periodontitis in older people is therefore biologically plausible.

Sex

There is no established, inherent difference between men and women in their susceptibility to periodontal disease, although men have been shown to exhibit worse periodontal conditions than women in multiple studies from different populations (Brown *et al*. 1989; Albandar 2002a; Susin *et al*. 2004a; Dye *et al*. 2007). This difference has been traditionally considered to reflect the documented better oral hygiene practices (Hugoson *et al*. 1998b; Christensen *et al*. 2003) and/or increased utilization of oral health care services among women (Yu *et al*. 2001; Dunlop *et al*. 2002; Roberts-Thomson & Stewart, 2003). On the other hand, there is evidence for sexual dimorphism in elements of both the innate and the acquired immunity that may lead to enhanced pro-inflammatory responses in men (Shiau & Reynolds 2010), which are in line with the epidemiologic evidence of gender-associated disparities in prevalence, extent, and severity of periodontitis.

Race/ethnicity

Differences in the prevalence of periodontitis between countries and across continents have been demonstrated (Baelum *et al*. 1996; Albandar, 2002a; Dye 2012), but no consistent patterns across racial/ethnic groups have been documented when co-variates such as age and oral hygiene were accounted for (Burt & Eklund 1999). National surveys in the US consistently show a racial/ethnic differential pattern in the prevalence of periodontitis, with African–Americans exhibiting the highest prevalence followed by Mexican Americans and non-Hispanic Caucasians; these findings are fairly consistent regardless of the case definition used (Albandar *et al*. 1999; Arbes *et al*. 2001; Borrell *et al*. 2002; Hyman & Reid 2003; Dye *et al*. 2007; Borrell & Crawford 2008). However, race/ethnicity is usually a social construct that determines an array of opportunities related to access, status, and resources (Williams 1997, 1999). As a result, race/ethnicity and socioeconomic status (SES) are strongly intertwined, suggesting that the observed racial/ethnic effect may be partially attributed to confounding by SES due to the unequal meaning of SES indicators across racial/ethnic groups (Williams 1996; Kaufman *et al*. 1997; Krieger *et al*. 1997; Lynch & Kaplan 2000). Corroborating this point, a study reported that African–Americans demonstrated a lower benefit from education and income in terms of periodontal health status than their Mexican American and Caucasian peers (Borrell *et al*. 2004). These findings confirm that socioeconomic

indicators across racial/ethnic groups are not commensurable but, probably, reflect the broad implications of historical unequal opportunities among certain racial groups (Borrell & Crawford 2012).

Gene polymorphisms

Evidence that genetic predispositions are significant determinants of periodontitis phenotype was first documented in a number of classical twin (Michalowicz *et al*. 1991) and family studies (Boughman *et al*. 1992; Marazita *et al*. 1994). The association of *single nucleotide polymorphisms* (SNPs), that is specific variations at defined locations of the genome that occur in at least 1% of the population, with different forms of periodontitis has been studied extensively (Kinane & Hart 2003; Laine *et al*. 2012). Following the report by Kornman *et al*. (1997) of an association between a composite genotype based on specific polymorphisms in the interleukin-1 (*IL-1*) gene cluster and severe periodontitis in non-smokers, there has been an exponential increase in publications examining a plethora of gene polymorphisms as severity markers of periodontitis. These include additional investigations of the particular composite *IL-1* gene polymorphism in cross-sectional and case–control studies (e.g. Diehl *et al*. 1999; Armitage *et al*. 2000; Papapanou *et al*. 2001; Meisel *et al*. 2004; Li *et al*. 2004), longitudinal studies (Ehmke *et al*. 1999; De Sanctis & Zucchelli 2000; Lang *et al*. 2000; Cullinan *et al*. 2001; Christgau *et al*. 2003; Jepsen *et al*. 2003), as well as studies in which polymorphisms in particular loci of the *IL1A* gene (Fiebig *et al*. 2008; Struch *et al*. 2008), the *IL1B* gene (Lopez *et al*. 2005; Ferreira *et al*. 2008), and the IL-1 receptor antagonist (Tai *et al*. 2002; Berdeli *et al*. 2006; Fiebig *et al*. 2008) were studied independently of each other.

Similar work has investigated polymorphisms in additional inflammatory genes, including the tumor necrosis factor (*TNF*) gene (Endo *et al*. 2001; Shapira *et al*. 2001; Craandijk *et al*. 2002; Fassmann *et al*. 2003; Shimada *et al*. 2004); the *IL-6* gene (Anusaksathien *et al*. 2003; Holla *et al*. 2004; Nibali *et al*. 2009); the *IL-4* gene (Kang *et al*. 2003; Holla *et al*. 2008; Kobayashi *et al*. 2009); and the *IL-10* gene (Brett *et al*. 2005; Kobayashi *et al*. 2009). A substantial body of data has accumulated on polymorphisms in genes coding for various receptors, including the leukocyte receptors for the constant part (Fc) of immunoglobulin G (Kobayashi *et al*. 1997; Sugita *et al*. 1999; Kobayashi *et al*, 2000a, b, 2001; Meisel *et al*. 2001; Loos *et al*. 2003; Yamamoto *et al*. 2004; Wolf et al. 2006; Nibali *et al*. 2006); pattern recognition receptors such as CD14 (Holla *et al*. 2002; James *et al*. 2007; Tervonen *et al*. 2007) and Toll-like receptors (TLRs) 2 and 4 (Folwaczny *et al*. 2004, Brett *et al*. 2005; Fukusaki *et al*. 2007; Noack *et al*. 2008); and the vitamin D receptor (Park *et al*. 2006; Nibali *et al*. 2008; Wang *et al*. 2009). Additional polymorphisms studied in single studies or a few cohorts have been discussed in a recent comprehensive review (Laine *et al*. 2012) and a meta-analysis of 53 studies collectively including 4178 cases and 4590 controls (Nikolopoulos *et al*. 2008).

Typically, the majority of these cross-sectional studies report positive associations between the investigated polymorphisms and the extent or the severity of periodontitis. The results, however, are not unequivocal, as the strength of the reported associations is not uniformly consistent across populations, the frequency of occurrence of these polymorphisms appears to vary extensively between ethnic groups, the subject samples involved are generally of limited size, the definitions of the outcome variable (periodontitis) vary considerably, and adequate adjustments for other important co-variates and risk factors have frequently not been carried out. Importantly, there appear to be differences in the impact of these polymorphisms on early-onset versus adult forms of periodontitis. For example, in the case of IL-1 polymorphisms, while it is the rare allele (allele 2) that has been linked with severe disease in adults, it is allele 1 that has been found to be more prevalent in subjects with early-onset periodontitis (Diehl *et al*. 1999; Parkhill *et al*. 2000).

The results of the relatively few longitudinal studies that have studied specific gene polymorphisms as exposures are also conflicting. Ehmke *et al*. (1999) reported no bearing of the *IL-1* gene polymorphism on the prognosis of periodontal disease progression following non-surgical periodontal therapy. Jepsen *et al*. (2003) failed to provide evidence that the *IL-1* risk genotype was associated with higher gingival crevicular fluid (GCF) volume and percentage of bleeding on probing (BoP) sites during the development of experimental gingivitis (Löe *et al*. 1965). In contrast, Lang *et al*. (2000) concluded that *IL-1* genotype-positive subjects have a genetically determined hyper-inflammatory response that is expressed clinically in the periodontal tissues as increased prevalence and incidence of BoP during maintenance. Three treatment studies examined the impact of this particular polymorphism in regenerative therapy: De Sanctis and Zucchelli (2000) reported that the *IL-1*-positive genotype was associated with an inferior long-term outcome for regenerative therapy of intrabony defects. In contrast, Christgau *et al*. (2003) and Weiss *et al*. (2004) failed to document such an association in similar studies. Finally, in a 5-year prospective study of 295 subjects, Cullinan *et al*. (2001) reported an interaction between the positive genotype, age, smoking, and colonization by *Porphyromonas gingivalis*, concluding that the positive genotype is a contributory but non-essential factor for the progression of periodontal disease. A systematic review of longitudinal studies that examined the composite *IL-1* genotype as a predictor of periodontitis progression or of periodontal treatment outcomes failed to establish a significant association (Huynh-Ba *et al*. 2007).

In conclusion, there is insufficient epidemiologic evidence that convincingly establishes any of the above polymorphisms as true risk factors for

periodontitis. Studies employing larger cohorts, strict classification criteria for periodontitis, and refined analytical methods will enhance our understanding of the role of genetic influences in the pathobiology of periodontitis.

Environmental, acquired, and behavioral factors

Specific microbiota

The microbial etiology of experimental gingivitis (Löe *et al*. 1965; Theilade *et al*. 1966) and periodontitis (Lindhe *et al*. 1973) has been established for several decades. Yet, epidemiologic studies that systematically investigated the role of specific microbiota as putative risk factors for periodontitis were undertaken only fairly recently. In a classic paper, Haffajee and Socransky (1994) adapted Koch's postulates for use in the identification of periodontal pathogens and proposed the following criteria:

1. Association, that is elevated ORs in disease
2. Elimination, that is conversion of periodontal disease to health when bacteria are eliminated (or suppressed beyond detection)
3. Development of a host response, typically manifested by a serum antibody titer to the infecting agent
4. Presence of virulence factors that can account for the microbe's ability to inflict tissue damage
5. Evidence from animal studies that corroborate the observations in humans and demonstrate development of periodontal pathology after infection by the microorganism.

Based on these criteria, the consensus report of the 1996 World Workshop in Periodontics identified three species, *Actinobacillus actinomycetemcomitans, P. gingivalis,* and *Bacteroides forsythus*, as causative factors for periodontitis [since then, two of these three causative species have been renamed: *A. actinomycetemcomitans* to *Aggregatibacter actinomycetemcomitans* (Norskov-Lauritsen & Kilian 2006) and *B. forsythus* to *Tannerella forsythia* (Sakamoto *et al*. 2002; Maiden *et al*. 2003)]. However, given that only approximately 50% of the bacteria of the oral cavity are currently recognized (Paster *et al*. 2001), it is clear that these three species cannot be considered to be the only causative pathogens, but are rather the ones for which sufficient data have accumulated.

Over the last decade, interesting data have emerged on the prevalence of these causative bacteria in different populations, including periodontally healthy as well as diseased subjects. Studies performed in children (Yang *et al*. 2002; Tanner *et al*. 2002) analyzed plaque from the gingival crevice, tooth surface, and dorsum of the tongue, and revealed that sizeable proportions of subjects harbored *P. gingivalis*, *T. forsythia*, and *A. actinomycetemcomitans* despite absence of overt gingival inflammation. A comparably high carrier state was documented in studies that sampled infants, children, adolescents, and adults with apparently healthy periodontal conditions (Könönen 1993; McClellan *et al*. 1996; Kamma *et al*. 2000; Lamell *et al*. 2000). Thus, contrary to the conclusions of earlier, culture-based studies suggesting that these bacteria occur infrequently in periodontally healthy oral cavities and behave as exogenous pathogens, use of contemporary molecular techniques for bacterial identification have demonstrated that this is not the case. However, both the prevalence and the level of colonization by these pathogens have been shown to vary significantly between populations of different racial or geographic origin (Ali *et al*. 1994; Sanz *et al*. 2000; Lopez *et al*. 2004; Haffajee *et al*. 2004; Rylev & Kilian 2008).

Several epidemiologic studies have examined the prevalence of the established periodontal pathogens and its relation to clinical periodontal status in population samples from both developed and developing countries. Griffen *et al*. (1998) examined a convenience sample recruited from a university clinic, and reported that 79% of the diseased and 25% of the healthy subjects were positive for *P. gingivalis*. Interestingly, the prevalence of *P. gingivalis* in the periodontally healthy group varied substantially with race/ethnicity, occurring in 22% of Caucasians, 53% of African–Americans, and 60% of Asian–Americans. In a case–control study of periodontitis patients and age- and sex-matched controls with no or only minimal attachment loss in Sweden, Papapanou *et al*. (2000) reported a high prevalence of *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia*, and *Treponema denticola* in periodontitis patients (95%, 83%, 97%, and 93%, respectively), but also similarly high prevalence rates among control subjects (82%, 90%, 82%, and 94%, respectively). However, in a quantitative analysis of bacterial load, substantial differences in colonization at high levels (i.e. at an average count of $\geq 10^5$ bacterial cells/plaque sample) were observed between patients and controls for three of the four bacteria: 19% versus 3% for *P. gingivalis*; 54% versus 12% for *T. forsythia*, and 46% versus 19% for *T. denticola*. In contrast, corresponding percentages were similar for *A. actinomycetemcomitans* (1% in both cases and controls). Substantially different prevalence data were reported in a study of blue- and white-collar university employees in Australia (Hamlet *et al*. 2001). These authors detected *A. actinomycetemcomitans* in 23% and *P. gingivalis* in 15% of the subjects.

A number of studies investigated the epidemiology of periodontal pathogens in Asian populations. Timmerman *et al*. (1998) examined a sample of adolescents in rural Indonesia, and detected *P. gingivalis* in 87% and *A. actinomycetemcomitans* in 57%. Mombelli *et al*. (1998) examined young factory workers in China and detected *A. actinomycetemcomitans* in 62% and *P. gingivalis* in 55%. In contrast, an almost ubiquitous presence of *P. gingivalis* and *T. forsythia* was reported

in rural subject samples in China (Papapanou *et al*. 1997) and Thailand (Papapanou *et al*. 2002), while *A. actinomycetemcomitans* was detected in 83% and 93% of the subjects in the Chinese and Thai samples, respectively. Despite this high prevalence, a quantitative analysis of bacterial load correlated well with periodontal status in both studies. For example, a discriminant analysis performed on the data from the Thai study (Papapanou *et al*. 2002) identified threshold levels of average bacterial load which, when exceeded, conferred increased ORs for the presence of three or more sites with a pocket depth of ≥5 mm. For three species [*P. gingivalis*, *T. forsythia*, and *T. denticola;* the "red complex" bacteria (Socransky *et al*. 1998)], colonization above these calculated thresholds resulted in statistically significant, elevated ORs for periodontitis. In addition, an analysis of the association between colonization at high levels by the "red complex" bacteria and specific periodontal conditions, defined in this particular study by the presence of three or more sites with a pocket depth of ≥5 mm and by two different extents of clinical attachment loss (≥10 and ≥30 sites with ≥5 mm attachment loss, respectively), revealed statistically significant ORs ranging between 3.7 and 4.3 for the "red complex" bacteria and all three disease definitions. Similar cross-sectional associations of statistically significant ORs for severe periodontitis conferred by specific bacteria have been also observed in several other studies involving subject samples from the Western world (Grossi *et al*. 1994, 1995; Alpagot *et al*. 1996; Craig *et al*. 2001).

Importantly, the association between high levels of colonization by specific periodontal pathogens and the progression of periodontal disease has been corroborated by longitudinal data in untreated populations. For example, in the study by Papapanou *et al*. (1997), a discriminant analysis based on quantitative assessments of subgingival bacterial load classified correctly the substantial majority of the subjects with progression of periodontitis over a preceding 10-year period. Indeed, bacterial profiles classified correctly 75% of the subjects with ten or more sites with longitudinal attachment loss of ≥3 mm, and 85% of those that remained stable over the observation period. In a 7-year follow-up study of Indonesian adolescents (Timmerman *et al*. 2000, 2001), and in a subsequent 15-year follow-up of the same cohort (van der Velden *et al*. 2006), it was shown that the subgingival presence of *A. actinomycetemcomitans* was associated with disease progression, defined as presence of longitudinal attachment loss of ≥2 mm. In a follow-up of 2–5 years' duration, Machtei *et al*. (1999) reported that subjects colonized by *T. forsythia* at baseline exhibited greater alveolar bone loss, a larger proportion of "loser" sites, that is sites exhibiting progressive attachment loss, and twice as high longitudinal tooth loss than non-colonized subjects. In a 3-year study, Hamlet *et al*. (2004) reported ORs of 8.2 for attachment loss in adolescents with persistent colonization with *T. forsythia*.

An important observation was made in a 2-year prospective study of clinical periodontal status in adolescents in Morocco (Haubek *et al*. 2008). These investigators reported that colonization by a specific clone of *A. actinomycetemcomitans*, namely the highly-leukotoxic JP2 clone, conferred a much higher risk for the onset of aggressive periodontitis in periodontally healthy schoolchildren than concomitant colonization by a variety of clones of the same species, or the total absence of colonization by *A. actinomycetemcomitans*. Indeed, in comparison to schoolchildren who were not colonized by *A. actinomycetemcomitans*, the relative risk for incident disease in those colonized exclusively by JP2 clones was 18.0 (95% CI 7.8–41.2), as compared to 12.4 (95% CI 5.2–29.9) in those colonized by both JP2 and non-JP2 clones, and 3.0 (95% CI 1.3–7.1) in those colonized exclusively by non-JP2 clones of *A. actinomycetemcomitans*. This study underscored the important role of this particular periodontal pathogen in the etiology of aggressive periodontitis, but also demonstrated that within-species variation in virulence is associated with differences in the clinical presentation of the disease.

Collectively, data generated in the past 20 years have enhanced our knowledge of the role of specific periodontal bacteria as risk factors for periodontitis (Table 7-4), and have clarified that (1) the intensity of the exposure to the specific microbiota ("*pathogen burden*") rather than the mere presence of the pathogen is an important determinant of the clinical phenotype; (2) the virulence of the pathogen, and thus its ability to cause periodontal tissue damage and confer risk for disease progression may be entirely different among various clonal types within a single species; and (3) pathogen elimination from the subgingival microbiota (or more correctly, suppression of its levels beyond detection) results in improvements in clinical periodontal status. This last "targeting" criterion of the risk assessment process described earlier has been abundantly fulfilled in the case of microbial risk factors. As demonstrated in systematic reviews, an antimicrobial approach, including removal of subgingival plaque with or without adjunctive antiseptics or antibiotics followed by adequate maintenance care, is the single most successful and consistent strategy in the treatment of periodontitis (Herrera *et al*. 2002; Heitz-Mayfield *et al*. 2002; Tonetti & Chapple 2011).

Cigarette smoking

The biologic plausibility of an association between tobacco smoking and periodontitis was founded on the broad effects of multiple tobacco-related substances on cellular structure and function. Smoking has been shown to affect the vasculature, the humoral and cellular immune responses, cell signaling processes, and tissue homeostasis [for review see Kinane and Chestnutt (2000) and Palmer *et al*. (2005)]. A substantial number of studies, a selection of which is

Table 7-4 Selected studies using bacteria as exposures of significance for periodontitis.

Authors/country[a]	Sample/methodology	Findings
Beck *et al*. (1990) USA	690 community dwelling adults, aged 65+ years; probing assessments at mesio- and mid-buccal surfaces, all teeth; logistic regression for advanced AL and deep pocketing; "advanced disease": ≥4 sites with AL of ≥5 mm and ≥1 of these sites with PD of ≥4 mm	Blacks: 78% of sites with attachment loss, mean AL on these sites 4 mm Caucasians: 65%, 3.1 mm OR in Blacks: tobacco use 2.9; *Porphyromonas gingivalis* >2% 2.4; *Prevotella intermedia* >2% 1.9; last dental visit >3 years 2.3; bleeding gums 3.9 OR in Caucasians: tobacco use 6.2; presence of *P. gingivalis* (+) 2.4; no dental visits for >3 years plus BANA (+) 16.8
Haffajee *et al*. (1991b) USA	38 subjects, aged 14–71 years, with prior evidence of attachment loss; 2-month follow-up; probing assessments at six sites/tooth, all teeth; 28 subgingival samples per subject at baseline, DNA probe analysis with respect to 14 bacterial species; progression threshold: ≥3 mm of longitudinal AL; the mean percentage of the total cultivable microbiota was averaged across active and inactive sites; OR computed at different thresholds for each species	Significant odds ratios for new disease: *P. gingivalis* 5.6, *Campylobacter rectus* 3.8, *Veillonela parvula* 0.16 and *Capnocytophaga ochracea* 0.08 Discriminant analysis using the significantly related species was useful in predicting subjects at risk for new attachment loss
Grossi *et al*. (1994) USA	Random sample of 1426 subjects, aged 25–74 years, in a metropolitan community; full-mouth probing assessments; multivariate analysis of risk indicators for attachment loss. Exposures: (1) clinical – supragingival plaque, gingival bleeding, subgingival calculus, PD, CAL; (2) microbial – *A. actinomycetemcomitans, T. forsythia, C. rectus, Eubacterium saburreum, Fusobacterium nucleatum, P. gingivalis, Capnocytophaga* spp and *P. intermedia*; (3) co-variates – age, gender, race, education, income, smoking and numbers of packs/year, exposure to occupational hazards, systemic diseases	In a multivariable logistic regression model, *P. gingivalis* (OR = 1.59; 95% CI 1.11–2.25) and *T. forsythia* (OR = 2.45; 95% CI 1.87–3.24) were positively associated with severity of AL, while *Capnocytophaga* spp. (OR = 0.60; 95% CI 0.43–0.84) were protective against AL
Grossi *et al*. (1995) USA	Same sample as in Grossi *et al*. (1994); 1361 subjects, aged 25–74 years; assessments of interproximal bone loss from full-mouth radiographs; the degree of association between bone loss and explanatory variables was analyzed by stepwise logistic regression	In a multivariable logistic regression model, *P. gingivalis* (OR = 1.73; 95% CI 1.27–2.37) and *T. forsythia* (OR = 2.52; 95% CI 1.98–3.17) were significantly associated with increasing severity of bone loss
Beck *et al*. (1997) USA (L)	540 dentate adults, aged 65+ years, examined at baseline, 18, 36 and 60 months; incidence of AL was defined as additional AL ≥3 mm; microbial variables included presence of *A. actinomycetemcomitans, P. intermedia*, and *P. gingivalis,* and the BANA test; co-variates included age, gender, missing teeth, education, smoking, dental visits	BANA (+), and presence of *P. gingivalis* were significantly associated with incident disease
Papapanou *et al*. (1997) China (L)	148 subjects, aged 30–39 and 50–59 years in a rural area examined 10 years apart; Full-mouth assessments of PD and AL at six sites/tooth; 14 subgingival plaque samples were obtained from each subject at the follow-up examination (1864 in total) and analyzed with respect to 18 bacterial species	Ubiquitous prevalence for the majority of the investigated species at the subject level. Bacterial colonization at high levels by *P. gingivalis, P. intermedia, Provotella nigrescens, T. forsythia, F. nucleatum, Treponema denticola, Parvimonas micra,* and *C. rectus* conferred statistically significant OR for being classified as "downhill" (≥10 sites with longitudinal AL loss of ≥3 mm)
Machtei *et al*. (1999) USA (L)	A sample of 415 subjects, aged 25–75 years, followed for a period of 2–4 years; full-mouth examination at six sites/tooth at all teeth present; full-mouth intraoral radiographs; bacterial samples obtained from 12 index teeth analyzed with respect to *A. actinomycetemcomitans, T. forsythia, C. rectus, P. intermedia, Capnocytophaga* spp*, P. gingivalis, E. saburreum,* and *F. nucleatum*; co-variates included age, gender, smoking (current smokers 15.4%), education, income	Subjects harboring *T. forsythia* at baseline showed significantly higher longitudinal bone loss, greater proportion of "loser'sites" (sites with additional AL of ≥2 mm) and twice as high tooth mortality

(*Continued*)

Table 7-4 *Continued*

Authors/country[a]	Sample/methodology	Findings
Timmerman *et al*. (2000) Indonesia (L)	A sample of 255 subjects, aged 15–25 years, in a rural area, examined 7 years apart; assessments of PD and AL at vestibular surfaces of all teeth; bacterial samples harvested from a variety of intraoral sites and analyzed with respect to *A. actinomycetemcomitans, P. gingivalis, P. intermedia,* spirochetes and motile microorganisms	Progressive disease (PDS) was defined as ≥1 site with longitudinal AL ≥2 mm Subgingival presence of *A. actinomycetemcomitans* (OR 4.2; 95% CI: 1.4–12.7), *P. gingivalis* (OR 2.3; 95% CI 1.0–5.2), and motile microorganisms (OR 2.2; 95% CI 1.0–5.0) were associated with PDS In a multivariable logistic model, including age and subgingival calculus, subgingival presence of *A. actinomycetemcomitans* (OR = 4.61, *P* = 0.01) was associated with PDS
Papapanou *et al*. (2002) Thailand	Random sample of 356 subjects aged 30–39 and 50–59 years, in a rural area; PD and CAL were assessed at six sites/tooth, at all teeth apart from third molars; subjects were grouped according to different levels of pocketing/attachment loss: subjects with ≥3 sites with PD ≥5 mm (59%, G1); ≥10 sites with CAL ≥5 mm (50%, G2); and ≥30 sites with CAL ≥5 mm (24%, G3) Subgingival plaque samples were obtained maximally at 14 sites/subject; checkerboard hybridizations were used to analyze a total of 4343 samples with respect to 27 bacterial species	OR for heavy colonization by "red complex" species (*P. gingivalis, T. forsythia, T. denticola*) were 3.7 (95% CI 2.3–5.9) for G1; 4.0 (95% CI 2.5–6.6) for G2; and 4.3 (95% CI 2.6–7.1) for G3 OR for heavy colonization by selected "orange complex" species (*F. nucleatum, P. intermedia, P. nigrescens, P. micros, E. nodatum, C. rectus*, and *Campylobacter showae*) were 1.5 (95% CI 0.8–2.9) for G1; 1.5 (95% CI 0.8–2.9) for G2; and 1.5 (95% CI 0.8–3.1) for G3
van der Velden *et al*. (2006) Indonesia (L)	15-year follow-up of 128 subjects from the cohort originally described by Timmerman *et al*. (2000)	In a multivariable logistic model, subgingival presence of *A. actinomycetemcomitans* (OR 4.3; 95% CI 1.2–15.7) was confirmed as a risk factor for the onset of the disease, i.e. longitudinal AL during the first 7-year period, but not for progression of disease during the subsequent 8-year period
Fine *et al*. (2007) USA (L)	1075 primarily African–American and Hispanic children aged 11–17 years were examined periodontally and with respect to oral colonization by *A. actinomycetemcomitans*; 96 children were followed up at 6-month intervals for at least 2.5 years; 38 were *A. actinomycetemcomitans*-positive at baseline (36 periodontally healthy and 2 with pathologic periodontal pockets) and 58 were *A. actinomycetemcomitans*-negative and periodontally healthy at baseline	In the cross-sectional cohort, 4% of the children had signs of periodontal pathology (≥1 pocket with ≥6 mm PD and >2 mm AL; 67% of those were *A. actinomycetemcomitans*-positive, as compared with 14% of the entire cohort In the longitudinal cohort, 21% of the *A. actinomycetemcomitans*-positive and 0% of the *A. actinomycetemcomitans*-negative children developed bone loss over the follow-up period
Haubek *et al*. (2008) Morocco (L)	700 adolescents form public schools in Rabat were examined for clinical periodontal status and presence of *A. actinomycetemcomitans* assessed by PCR; 682 were periodontally healthy; of these, 428 returned for a follow-up exam 2 years later	Individuals who carried the high leukotoxic JP2 clone of *A. actinomycetemcomitans* alone (RR 18.0; 95% CI 7.8–41.2) or together with non-JP2 clones (RR 12.4; 95% CI 5.2–29.9) had a significantly increased risk of developing periodontitis Risk for those carrying non-JP-2 clones alone was less pronounced (RR 3.0; 95% CI 1.3–7.1)

[a] **L** indicates a longitudinal study.
PD, probing depth; AL, attachment level; CAL, clinical attachment level; CEJ, cemento-enamel junction; CPITN, Community Periodontal Index of Treatment Needs; BANA: N-benzoyl-DL-arginine-2-naphthylamide; a substrate hydrolyzed in the presence of *T. denticola, Porphyromonas gingivalis*, and *Tannerella forsythia*;CI, confidenc interval; OR, odds ratio; RR, risk ratio; PCR, polymerase chain reaction.

summarized in Table 7-5, established the association of smoking with poor periodontal status. Importantly, the inferior periodontal status of smokers cannot be attributed to poorer plaque control or more severe gingivitis (Bergström 1989). While earlier reports suggested a rather similar composition of the subgingival microflora in smokers and non-smokers (Stoltenberg *et al*. 1993), recent studies demonstrated that smoking contributes to the formation of a dysbiotic biofilm. It affects bacterial acquisition and colonization (Brook 2011; Kumar *et al*. 2011), bacterial aggregation (Bagaitkar *et al*. 2011), and results in higher levels of colonization by key periodontal pathogens (Haffajee & Socransky 2001; Shchipkova *et al*. 2010; Kubota *et al*. 2011). In an attempt to quantitate the effects of smoking on the periodontal conditions, Haber *et al*. (1993) suggested that the excess prevalence of periodontal disease in the population attributed solely to

Table 7-5 Selected studies using smoking as exposure of significance for periodontitis.

Authors/country[a]	Sample/methodology	Findings
Bergström (1989) Sweden	Patients referred for periodontal therapy (155 subjects, aged 30, 40 and 50 years); a random sample of the Stockholm population served as controls; full-mouth probing assessments; sites with PD ≥4 mm considered diseased; recording of plaque and gingivitis scores	56% of the patients and 34% of the controls were smokers (OR 2.5); significantly higher frequency of periodontally-involved teeth in smokers; no notable difference between smokers and non-smokers with respect to plaque and gingivitis
Haber & Kent (1992) USA	196 patients with periodontitis in a periodontal practice and 209 patients from five general practices; probing assessments at six sites/tooth and full-mouth radiographs; questionnaire on smoking habits; patients with negative history of periodontal therapy from the general practices included as controls; comparison of (1) the prevalence of smoking among the two patient groups and (2) periodontitisdisease severity among current and never smokers	Overall smoking history in the periodontal practice 75%; in the general practice 54% Summary OR for positive smoking history in periodontal versus general practice patients was 2.6; in the periodontal group, frequency of current smoking increased with increasing severity of peridontitis
Locker (1992) Canada	907 adults, aged ≥50 years, living independently in four Ontario communities; partial, probing assessments; half of the participants reported a positive history of smoking and 20% were current smokers	Current smokers had fewer teeth, were more likely to have lost all their natural teeth, and had higher extent and severity of periodontitisthan those who had never smoked
Haber *et al*. (1993) USA	132 diabetics and 95 non-diabetics, aged 19–40 years; probing assessments at six sites/tooth, all teeth; questionnaire on smoking habits; calculation of the population attributable risk percent (PAR%), as an estimate of the excess prevalence of periodontitis in the study population that is associated with smoking	Prevalence of periodontitis was markedly higher among smokers than non-smokers within both the diabetic and non-diabetic groups; PAR% among non-diabetics was 51% in those aged 19–30 years and 32% in those aged 31–40 years
Stoltenberg *et al*. (1993) USA	Of 615 medically healthy adults, aged 28–73 years, attending a health maintenance organization, selection of 63 smokers and 126 non-smokers of similar age, sex, plaque and calculus scores; probing assessments at the proximal surfaces of premolars and molars in a randomly selected posterior sextant; detection of *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Eubacterium saburreum*, and *Fusobacterium nucleatum.* by a semiquantitative fluorescence immunoassay, in one buccal and one lingual sample per tooth examined; logistic regression to determine if any of the bacteria or smoking were indicators of mean posterior probing depth of ≥3.5 mm	OR for a smoker having a mean PD of ≥3.5 mm was 5.3 (95% CI 2.0–13.8) No statistically significant difference between smokers and non-smokers with respect to prevalence of the bacteria examined Logistic model revealed that a mean PD of ≥3.5 mm was significantly associated with the presence of *A. actinomycetemcomitans., P. intermedia, E. saburreum.,* and smoking; smoking was a stronger indicator than any of the bacteria examined
Jette *et al*. (1993) USA	1156 community dwellers, aged 70+ years; probing assessments at four sites/tooth, all teeth; evaluation of lifelong tobacco use as a modifiable risk factor for poor dental health; multiple regression analysis	18.1% of men and 7.9% of women were tobacco users (overall 12.3%; including 1% smokeless tobacco users) Years of exposure to tobacco products was a statistically significant factor for tooth loss, coronal root caries, and periodontal disease, regardless of other social and behavioral factors Periodontal disease (number of affected teeth) was predicted by longer duration of tobacco use, male sex, and more infrequent practice of oral hygiene
Martinez Canut *et al*. (1995) Spain	889 periodontitis patients, aged 21–76 years; probing assessments at six sites/tooth, all teeth; analysis of variance to examine the role of smoking on the severity of periodontitis	Smoking was statistically related to increased severity of periodontitis in multivariate analysis; a dose–response effect was demonstrated, with subjects smoking >20 cigarettes/day showing significantly higher attachment loss
Kaldahl *et al*. (1996) USA (L)	74 patients with moderate to advanced periodontitis, including 31 heavy smokers (≥20 cigarettes/day); the effects of cigarette consumption and smoking history on the response to active periodontal treatment and to up to 7 years of supportive periodontal treatment was evaluated Full-mouth examinations performed at baseline, 4 weeks after mechanical plaque control, 10 weeks following periodontal surgery, and yearly during 7 years of supportive periodontal treatment	Past and never smokers consistently exhibited a significantly greater reduction in PD and greater gains in AL than heavy and light smokers All groups experienced a similar decrease in the prevalence of BoP following active therapy

(*Continued*)

Table 7-5 *Continued.*

Authors/country[a]	Sample/methodology	Findings
Grossi *et al*. (1997) USA (L)	143 subjects aged 35–65 years with established periodontitis, including 60 current, 55 former, and 28 non-smokers, examined at baseline and 3 months after non-surgical periodontal therapy	Current smokers showed less reduction in PD and less AL gain than former- and non-smokers Fewer smokers harbored no *P. gingivalis* or *Tannerella forsythia* after treatment, compared to former and non-smokers
Axelsson *et al*. (1998) Sweden	A random sample of 1093 subjects, aged 35, 50, 65, and 75 years; prevalence of smoking in the four age groups was 35%, 35%, 24%, and 12%, respectively; recordings included AL, CPITN scores, DMF surfaces, plaque, and stimulated salivary secretion rate (SSSR)	In the oldest age group, 41% of the smokers and 35% of the non-smokers were edentulous In every age group, mean AL was statistically significantly increased in smokers by 0.37, 0.88, 0.85, and 1.33 mm, respectively Smokers had higher CPITN and DMF scores, increased SSSR, but similar plaque levels
Tomar & Asma (2000) USA	12 329 subjects, aged ≥18 years, participants in the NHANES III study; probing assessments at mesial and buccal sites in one upper and one lower quadrant; mesial assessments performed from the buccal aspect of the teeth; assessments of gingivitis, PD, and location of the gingival margin in relation to the CEJ; "periodontitis" was defined as ≥1 site with AL ≥ 4 mm and PD ≥4 mm	27.9% of participants were current smokers and 9.2% met the definition for periodontitis Current smokers were four times as likely to suffer from periodontitis than never smokers, after adjustments for age, gender, race/ethnicity, education, and income:poverty ratio Among current smokers, there was a dose–response relationship between cigarettes/day and periodontitis 41.9% of periodontitis cases were attributable to current smoking and 10.9% to former smoking
Bergström *et al*. (2000b) Sweden	257 subjects, aged 20–69 years, including 50 current smokers, 61 former smokers, and 133 non-smokers; full-mouth clinical and radiographic assessments of the periodontal tissues; smoking exposure defined in terms of consumption (number of cigarettes/day), duration (number of years of smoking) and lifetime exposure (product of daily consumption and years of duration – cigarettes/year); threshold levels used: heavy versus light consumption: ≥10 cigarettes/day versus <10 cigarettes/day; duration: ≥15 years versus <15 years; lifetime exposure: ≥200 cigarettes/year versus <200 cigarettes/year	Compared to former and non-smokers, current smokers had the highest prevalence of diseased sites (AL ≥4 mm) 40–69-year-old current smokers showed a significantly higher prevalence than 20–39-year-old current smokers (27% versus 4%) The same pattern emerged when comparing heavy versus light smokers according to consumption, duration, and lifetime exposure; in multiple regression, lifetime exposure was highly associated with the frequency of diseased sites and periodontal bone height after adjusting for age, gingival bleeding, and plaque index
Albandar *et al*. (2000) USA	705 subjects, aged 21–92 years, 52% males and 87% Caucasian; full-mouth examination of PD and AL at six sites; periodontitis was classified as advanced, moderate, or mild; cigar, pipe, and cigarette smoking were classified as current, former, and never	In multiple linear regression, current and former smoking, regardless of type, was associated with increased percentage of subjects with moderate/advanced periodontitis after adjusting for age, gender, race, and number of years of cigarette, cigar, and pipe smoking; current smoking was also associated with higher number of missing teeth
Bergström *et al*. (2000a) Sweden (L)	10-year follow-up of a sample of 84 dentally aware musicians, including16 current, 28 former, and 40 non-smokers; full-mouth clinical and radiographic assessments of periodontal status	Prevalence of PD ≥4 mm ("diseased" sites) was 18.7% for current, 11.1% for former, and 8.7% for non-smokers at baseline. At 10 years, these figures were 41.6%, 7.8%, and 6.6%, respectively; a similar pattern was observed for alveolar bone levels After adjusting for age, gingival bleeding, plaque index, and frequency of diseased sites at baseline, current smoking was a significant predictor of the increase in diseased sites at 10 years
Susin *et al*. (2004b) Brazil	974 subjects, aged 30–103 years; full-mouth examination of PD and AL; severe attachment loss was defined as AL ≥5 mm in ≥30% of the teeth; exposure to smoking classified as current/former, heavy/moderate/light/none, and quantified as lifetime consumption	Heavy and moderate smokers had significantly higher prevalence of AL ≥5 mm than non-smokers; in multivariate analysis heavy (OR = 3.6; 95% CI 2.2–6.0) and moderate smoking (OR = 2.0; 95% CI 1.4–2.9) conferred higher OR for AL; the attributable fraction of AL due to smoking was 37.7% and 15.6% among heavy and moderate smokers, respectively

(*Continued*)

Table 7-5 *Continued*

Authors/country[a]	Sample/methodology	Findings
Phipps *et al.* (2009) USA	1210 dentate men aged ≥65 years; random half-mouth assessments of PD and AL at six sites/tooth; "periodontitis" was defined as (1) presence of interproximal attachment loss ≥5 mm in ≥30% of the teeth present (5th European Workshop definition), or (2) according to the CDC/AAP definition; information on smoking habits collected through self-administered questionnaires and converted to pack-years	Prevalence of periodontitis according to the 5th European workshop definition was 30.4% among never smokers, 35.3% among smokers with <20 pack-years, and 50.3% among smokers with ≥20 pack-years (P <0.001); corresponding prevalence figures according to the CDC/AAP definition were 22.0%, 19.2%, and 36.4%, respectively (P <0.001) In multivariate analysis adjusted for age, race, and dental visit attendance, ≥20 pack-years were significantly associated with periodontitis OR 2.11 (95% CI 1.64–2.72) and 2.38 (95% CI 1.79–3.13), according to the two definitions, respectively

[a] **L** indicates a longitudinal study
PD, probing depth; AL, attachment level; BoP, bleeding on probing; CEJ, cemento-enamel junction; CPITN, Community Periodontal Index of Treatment Needs; NHANES, National Health and Nutrition Examination Survey; DMF, decayed, missing, filled; CI, confidence interval, OR, odds ratio.

smoking is much greater than that due to other systemic predispositions, such as diabetes mellitus. Data derived from the NHANES III study (Tomar & Asma 2000) suggested that as many as 42% of periodontitis cases in the US can be attributed to current smoking and another 11% to former smoking. Similarly, a study from Brazil (Susin *et al*. 2004b) reported that the attributable fraction of clinical attachment loss due to cigarette smoking was 37.7% and 15.6% among heavy and moderate smokers, respectively. In longitudinal studies, smoking has been found to confer a statistically significant increased risk for periodontitis progression after adjustment for other co-variates (Beck *et al*. 1995, 1997; Machtei *et al*. 1999; Norderyd *et al*. 1999; Chen *et al*. 2001; Ogawa *et al*. 2002; Paulander *et al*. 2004b).

Figure 7-4 shows an early *meta-analysis* of data from studies reporting on the association between smoking and periodontal conditions. In essence, meta-analysis is a statistical method which combines results from different studies of similar design, in order to achieve increased *power* to detect epidemiologic associations that may be difficult to identify in smaller, individual studies (Oakes 1993; Chalmers 1993; Proskin & Volpe 1994). This analysis, initially published as part of the 1996 World Workshop in Periodontics (Papapanou 1996), incorporated data from six studies, including a total of 2361 subjects with known smoking habits and periodontal status (Bergström & Eliasson 1989; Haber & Kent 1992; Locker 1992; Haber *et al*. 1993; Stoltenberg *et al*. 1993; Grossi *et al*. 1994). It can be observed that smoking was an overall increased, statistically and clinically, significant risk for severe disease (estimated overall OR of 2.82; 95% CI 2.36–3.39).

Studies examining the effects of smoking on the outcome of periodontal treatment have demonstrated that treatment responses are modified by cigarette consumption, with current smokers exhibiting poorer responses than former or never smokers (e.g. Ah *et al*.

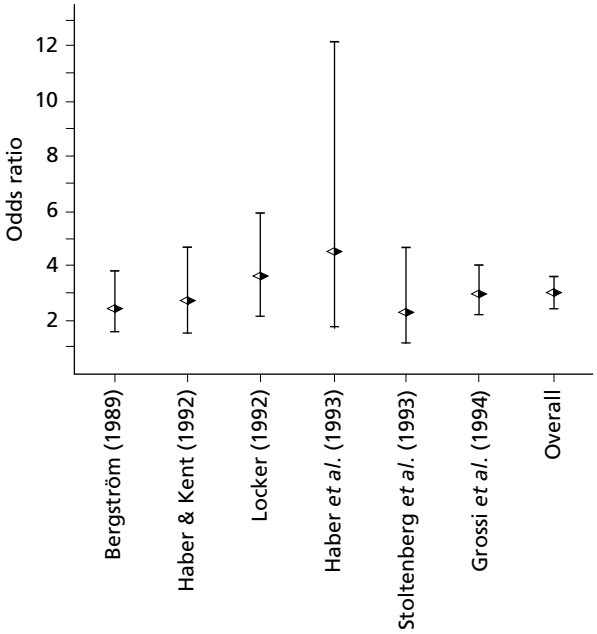

Fig. 7-4 Meta-analysis of smoking as a risk factor for periodontal disease. The studies included are: Bergström (1989), Haber & Kent (1992), Locker (1992), Haber *et al*. (1993), Stoltenberg *et al*. (1993), and Grossi *et al*. (1994). Bars indicate the 95% confidence limits for the depicted odds ratios. (Source: Papapanou 1996. Reproduced from American Academy of Periodontology.)

1994; Kaldahl *et al*. 1996; Grossi *et al*. 1997; Kinane & Radvar 1997; Tonetti *et al*. 1998; Trombelli *et al*. 2003, Stavropoulos *et al*. 2004; Paulander *et al*. 2004a; Rieder *et al*. 2004; Sculean *et al*. 2005; Wan *et al*., 2009). Notably, these studies have confirmed the negative effect of smoking on the outcome of several periodontal treatment modalities, including non-surgical, surgical, and regenerative periodontal therapy. Meta-analyses of the effects of smoking on the outcome of periodontal therapy (Garcia 2005; Labriola *et al*. 2005; Patel *et al*. 2012) support the above conclusions.

In contrast, smoking cessation was shown to have beneficial effects on periodontal status. In a

longitudinal study (Bolin *et al*. 1993), 349 subjects with ≥20 remaining teeth were examined on two occasions 10 years apart (1970 and 1980). Progression of periodontal disease was assessed on radiographs at all approximal tooth surfaces and was shown to be almost twice as rapid in smokers as in non-smokers. It was also observed that subjects who quit smoking at some time point within the observation period had a significantly retarded progression of bone loss compared to that in smokers. Similar observations were made by Krall *et al*. (1997) who reported that, over a mean follow-up period of 6 years, subjects who continued to smoke had a 2.4–3.5-fold risk of tooth loss when compared to individuals who quit smoking. In a 10-year follow-up study, Bergström *et al*. (2000a) observed an increase of periodontally diseased sites concomitant with loss of periodontal bone height in current smokers, as compared to non-smokers whose periodontal health condition remained unaltered throughout the period of investigation. The periodontal health condition in former smokers was similarly stable to that of non-smokers, underscoring the beneficial effects of smoking cessation. In a shorter (12-month) follow-up study evaluating the adjunctive effect of smoking cessation on the outcome of non-surgical periodontal therapy, Rosa *et al*. (2011) showed enhanced gain in clinical attachment in chronic periodontitis patients who quit smoking when compared to their smoking counterparts. Importantly, smoking cessation alone or in conjunction with non-surgical periodontal therapy appears to result in a composition of subgingival microbiota that comprises higher levels of health-associated species and lower levels of periodontal pathogens (Fullmer *et al*. 2009; Delima *et al*. 2010).

In conclusion, cigarette smoking appears to fulfill the majority of the required steps of the risk assessment process stipulated by Beck (1994) and is considered one of the major risk factors for periodontitis.

Diabetes mellitus

The role of diabetes mellitus (DM) as a risk factor for periodontitis has been debated for decades (Genco & Löe 1993), but several biologically plausible mechanisms by which the disease may contribute to impaired periodontal conditions have been identified over the past decade [for reviews see Lalla *et al*. (2000), Mealey & Oates (2006), and Lalla and Papapanou (2011)]. Table 7-6 summarizes the epidemiologic evidence based on a number of case–control and prospective cohort studies that examined the periodontal status of patients with diabetes. A recent meta-analysis including 49 cross-sectional and eight longitudinal studies confirmed a strong association between type 2 DM and periodontitis, but concluded that the evidence for type 1 DM is weaker (Chávarry *et al*. 2009). The adverse effects of DM on periodontal status appear to be particularly pronounced in subjects with a long duration of DM and poor metabolic control (Grossi & Genco 1998; Taylor *et al*. 1996, 1998a; Lalla *et al*. 2004). Indeed, studies have provided evidence of a dose–response relationship between poor metabolic control and the severity as well as the progression of periodontitis (Seppälä *et al*. 1993; Tervonen & Oliver 1993; Taylor *et al*. 1998a; Tervonen & Karjalainen 1997; Guzman *et al*. 2003; Bandyopadhyay *et al*. 2010). Expanding this observed dose–response relationship to the prediabetic state, the level of glucose intolerance in non-diabetic individuals was also correlated with the severity of periodontal disease (Saito *et al*. 2004). In line with the above observations, the outcome of periodontal treatment in well-controlled diabetic patients is similar to that of non-diabetic subjects (Westfelt *et al*. 1996; Christgau *et al*. 1998; Faria-Almeida *et al*. 2006), while patients with poorly controlled DM display an inferior treatment outcome (Tervonen & Karjalainen 1997).

The age of onset of DM manifestations in the periodontal tissues has been addressed in studies examining children and adolescents with type 1 DM (de Pommereau *et al*. 1992; Pinson *et al*. 1995) and both type 1 and type 2 DM (Lalla *et al*. 2006). All three studies documented more pronounced gingival inflammation in subjects with diabetes aged between 6 and 18 years. The case-control study by Lalla *et al*. (2006) further reported that clinical attachment loss was more pronounced in young patients with diabetes after adjustment for age, gender, ethnicity, gingival bleeding, and frequency of dental visits. In a subsequent publication, Lalla *et al*. (2007b) reported data on 350 children with either type 1 or type 2 DM and found a strong positive association between mean HbA1c levels over the 2 years preceding the dental examination and periodontitis. In a report including a total of 700 children, 350 with diabetes and 350 non-diabetic controls, Lalla *et al*. (2007a) documented a statistically increased periodontal destruction in children with diabetes across all disease definitions tested and in both age subgroups of 6–11 and 12–18 years.

Several studies suggest a two-way relationship between DM and periodontitis. Beyond the observed increased severity of periodontal tissue destruction in subjects with DM, studies indicate a higher incidence of DM complications and poorer metabolic control of diabetes in periodontitis patients [for review see Lalla & Papapanou (2011)]. These findings are discussed in more detail in Chapter 14.

Obesity

The biologic plausibility of a potential link between obesity and periodontitis has been suggested to involve a hyper-inflammatory state and an aberrant lipid metabolism prevalent in obesity, as well as the pathway of insulin resistance (Saito *et al*. 1998; Nishimura & Murayama 2001), all of which may collectively result in an accelerated breakdown of the

Table 7-6 Selected studies using diabetes mellitus as exposure of significance for periodontitis.

Authors/country[a]	Sample/methodology	Findings
Hugoson *et al*. (1989) Sweden	82 subjects with long and 72 with short duration IDDM; 77 non-diabetic individuals (aged 20–70 years); full-mouth, probing assessments at four sites/tooth; radiographs of lower molar–premolar regions; subjects assigned into five groups according to increasing severity of periodontal disease; no multivariate analysis	No notable difference in plaque, calculus, and number of teeth between individuals with and without DM Long duration DM patients were more frequently classified in groups 4 and 5 and had significantly more tooth surfaces with PD of ≥6 mm than non-diabetic controls Significantly more extensive alveolar bone loss in individuals with long duration DM aged 40–49 years old
Shlossman *et al*. (1990) USA	3219 Pima Indians, aged ≥5 years; prevalence of NIDDM 23% (20% in men, 25% in women); probing assessments at six sites/tooth for six index teeth; alveolar bone loss from panoramic radiographs; 2878 subjects with available radiographic data, probing assessments or both; comparison between diabetic and non-diabetic individuals with respect to AL and alveolar bone loss	Median attachment loss and alveolar bone loss higher in DM for all age groups and both genders
Emrich *et al*. (1991) USA	Sample and methodology same as above (Shlossman *et al*. 1990); 1342 Pima Indians, aged 15 years and older, with natural teeth; 19% (254) with diabetes and 12% (158) with impaired glucose tolerance; linear logistic models to predict prevalence and severity of periodontal disease; prevalence: ≥1 sites with AL of ≥5 mm or alveolar bone los ≥25% of the root length; severity: square root of average AL or alveolar bone loss	Diabetes, age, and calculus were significant risk markers for periodontitis OR for an individual with DM to have PD was 2.8 (clinically assessed) and 3.4 (radiographically)
de Pommereau *et al.* (1992) France	85 adolescents with IDDM,aged 12–18 years, and 38 healthy ag- matched controls; probing assessments at six sites/tooth, all teeth; bite-wing radiographs at molars and sites with AL >2 mm; patients divided according to disease duration (> or <6 years); sexual maturation according to Tanner's classification; metabolic control expressed through glycosylated hemoglobin (HbA1c); non-parametric pair-wise analysis	None of the subjects had sites with AL ≥3 mm or radiographic signs of periodontitis Despite similar plaque scores, diabetic children had significantly more gingival inflammation No significant relation between gingival condition and age, Tanner's index, HbA1c level or disease duration
Oliver & Tervonen (1993) USA	114 diabetic patients,aged 20–64 years (60% with IDDM and 40% with NIDDM); half-mouth, probing assessments at four sites/tooth; data from the 1985–86 National Survey served as controls	Tooth loss was similar among diabetic and non-diabetic US employed adults 60% of individuals with DM and 16% of controls had ≥1 site with PD ≥4 mm AL data were comparable in both groups
Thorstensson & Hugoson (1993) Sweden	83 IDDM patients and 99 age- and sex-matched non-diabetic controls, aged 40–70 years; full-mouth, probing assessments at four sites/tooth; radiographs of lower molar–premolar regions; subjects assigned to five groups according to increasing severity of periodontal disease; univariate analysis	DM patients aged 40–49 years (mean disease duration 25.6 years) had more periodontal pockets ≥6 mm and more extensive alveolar bone loss than non-diabetic controls, but this was not the case for subjects aged 50–59 or 60–69 years (mean disease duration 20.5 and 18.6 years, respectively) Disease duration appeared to be a significant determinant of development of periodontitis
Pinson *et al*. (1995) USA	26 IDDM children, aged 7–18 years, and 24 controls, 20 of whom were siblings of the diabetic patients; full-mouth, probing assessments at six sites/tooth; metabolic control assessed through HbA1c; analysis of co-variance	Overall, no statistically significant differences between cases and controls No association between levels of HbA1c and clinical variables After correcting for plaque, diabetics showed more severe gingival inflammation in specific tooth regions
Bridges *et al*. (1996) USA	A samples of 233 men, aged 24–78 years, including 118 diabetic (46 type 1 and 72 type 2) and 115 non-diabetic subjects, matched for age and BMI	Plaque and gingivitis, bleeding scores, PD, AL and missing teeth were significantly higher in diabetic than non-diabetic men

(*Continued*)

Table 7-6 *Continued*

Authors/country[a]	Sample/methodology	Findings
Tervonen & Karjalainen (1997) Finland (L)	36 patients with type 1 diabetes and 10 controls, aged 24–36 years, received non-surgical periodontal therapy and were followed at 4 weeks, 6 and 12 months; patient with diabetes were further grouped according to diabetic status as: D1 (n = 13) with no diabetic complications and good long-term metabolic control; D2 (n = 15) moderate metabolic control with/without retinopathy; D3 (n = 8) severe diabetes with poor metabolic control and/or multiple complications; periodontal status was monitored radiographically	The periodontal status of the diabetic patients with good control and no complications (D1) and those with moderate control (D2) was similar to non-diabetic controls Diabetic subjects with poor metabolic control and/or multiple complications (D3) exhibited higher extent of AL ≥2 mm at baseline and higher recurrence of PD ≥4 mm during follow up
Taylor *et al*. (1998a) USA (L)	2-year study of 21 patients with type 2 diabetes, including 14 with poor and 7 with better metabolic control, and 338 controls, aged 15–57 years, Native Americans; progression of bone loss was assessed on radiographs; co-variates included age, calculus, gingival and plaque indices, time to follow-up, alcohol consumption, smoking, obesity (BMI >27), coronary heart disease, and gender	In multiple logistic regression, poorly controlled diabetic subjects were 11 times more likely (95% CI 2.5–53.3) to have more pronounced bone loss progression than non-diabetic subjects; no such differences were found between better controlled and non-diabetic controls Age, time to follow-up, pronounced bone loss at baseline, and calculus index were significant predictors of bone loss progression.
Taylor *et al*. (1998b) USA (L)	2-year study of 24 subjects with NIDDM and 362 subjects without diabetes, aged 15–57 years; degree of bone loss on panoramic radiographs was assessed on a scale of 0–4	A regression model having progression of bone loss as the dependent variable revealed a cumulative OR for NIDDM of 4.23 (95% CI 1.8–9.9); the association was modified by age, with younger adults exhibiting higher risk for alveolar bone loss progression
Lalla *et al*. (2007) USA	Case–control study of 350 children and adolescents, aged 6–18 years, with diabetes (325 with type 1 diabetes; 25 with type 2 diabetes) and 350 non-diabetic controls; half-mouth examination at four sites/tooth in all fully erupted teeth with respect to PD and AL; three different definitions of periodontitis were used	Children with diabetes had significantly more plaque and gingival inflammation than controls and a higher number of teeth with AL Regression analysis controlling for age, gender, ethnicity, gingival bleeding, and frequency of dental visits revealed that diabetes was statistically related to periodontal destruction across all disease definitions (OR 1.84–3.72)

[a] **L** indicates a longitudinal study.
PD, probing depth; AL, attachment level; ; BMI, body mass index; OR, odds ratio; CI, confidence interval.
DM: diabetes mellitus.
IDDM and NIDDM, insulin-dependent and non-insulin dependent diabetes mellitus, respectively; these diagnostic terms are no longer used and have been replaced by type 1 and type 2 diabetes.

periodontal tissues. Indeed, a number of studies have indicated a positive association between obesity, defined as body mass index (BMI) ≥30 kg/m^2, and periodontitis. Four publications have documented such an association in the NHANES III database. Wood *et al*. (2003), using a subset including Caucasian subjects aged 18 years and older, reported that BMI, waist-to-hip ratio, visceral fat, and fat-free mass were associated with periodontitis after adjusting for age, sex, history of diabetes, current smoking, and socio-economic status. Al-Zahrani *et al*. (2003) reported a significant association between both BMI and waist-to-hip ratio and periodontitis in younger adults, but no association in middle-aged or older adults. Genco *et al*. (2005) reported that overweight subjects in the upper quartile of the insulin resistance index were 1.5 times more likely to have periodontitis compared to their counterparts with a high BMI but a low insulin resistance index. Finally, Andriankaja *et al*. (2010) demonstrated an association between *metabolic syndrome* (i.e. a combination of hypertension, impaired fasting glucose, large waist circumference, and dyslipidemia) and periodontitis in women, and between abdominal obesity and periodontitis in both women and men.

In a longitudinal study of 1038 healthy, Caucasian US male veterans, obesity conferred a 41–72% increased risk for progression of periodontitis, after adjustment for several co-variates (Gorman *et al*. 2012).

Corroborating data have been reported also from countries other than the US. In a sample of 643 apparently healthy Japanese adults, Saito *et al*. (2001) reported that waist-to-hip ratio, BMI, and body fat were significant risk indicators for periodontitis after adjustments for known risk factors. In a recent longitudinal study from Japan involving a sample of 3590

individuals, the 5-year incidence of periodontitis was statistically higher for both those with a BMI between 25 and 30 kg/m^2 and those with a BMI of ≥30 kg/m^2, when compared to individuals with a BMI of ≤22 kg/m^2 (Morita *et al*. 2011), establishing a dose–response relationship between overweight/obesity and risk for periodontitis. Finally, in a study involving a nationally representative sample of 7188 subjects in Korea, *metabolic syndrome* was associated with periodontitis (Kwon *et al*. 2011). In contrast, an inverse association between obesity and clinical attachment loss was observed in a study involving 1579 men and women in Denmark (Kongstad *et al*. 2009).

Given that (1) the majority of the above publications are cross-sectional, and thus do not facilitate inferences on temporality or mechanisms, and (2) the available epidemiologic data are limited and not universally consistent, additional research on the role of obesity in periodontitis is warranted.

Osteopenia/osteoporosis

Several early cross-sectional studies, of limited sample size and largely confined to post-menopausal women, have suggested that women with low bone mineral density are more likely to have gingival recession and/or pronounced gingival inflammation and clinical attachment loss (von Wowern *et al*. 1994; Mohammad *et al*. 1996, 1997; Tezal *et al*. 2000). In a radiographic study of 1084 subjects aged 60–75 years, Persson *et al*. (2002) reported a positive association between osteoporosis and periodontitis with an OR of 1.8 (95% CI 1.2–2.5). However, studies that have failed to report such an association have also been published (Weyant *et al*. 1999; Lundström *et al*. 2001).

Based on these observations, it has been hypothesized that the systemic loss of bone density in osteoporosis may, in combination with hormone action, heredity, and other host factors, provide a host system that is increasingly susceptible to inflammation-associated destruction of the periodontal tissues (Wactawski-Wende 2001). In a cross-sectional study of 1329 post-menopausal women in the US, systemic bone density was positively associated with clinical attachment loss in women with subgingival calculus, but negatively associated in women without calculus (Brennan *et al*. 2007). The data from longitudinal studies are apparently conflicting. Payne *et al*. (1999, 2000) reported an enhanced longitudinal alveolar bone loss in osteoporotic women versus women with normal mineral bone density, Yoshihara *et al*. (2004) found, after adjustments, a significant association between bone mineral density and 3-year longitudinal attachment loss in Japanese subjects aged ≥70 years. In contrast, Reinhardt *et al*. (1999) reported no significant impact of serum estradiol levels on longitudinal attachment loss over a 2-year period. Recent systematic reviews of the available studies on osteoporosis and periodontitis (Martinez-Maestre *et al*. 2010; Megson *et al*. 2010) concluded that the relationship between the two conditions remains unclear. Additional prospective studies are warranted to clarify the inter-relationship between the two diseases and its clinical implications.

Human immunodeficiency virus infection

Studies published in the late 1980s seemed to indicate that both the prevalence and the severity of periodontitis were exceptionally high in patients with acquired immunodeficiency syndrome (AIDS) (Winkler & Murray 1987), but a more tempered picture emerged in subsequent publications. While it cannot be ruled out that the initial reports included biased samples, it is also possible that the successful control of immunosuppression in human immunodeficiency virus (HIV)-positive subjects by means of high activity antiretroviral therapy (HAART) and other continuously evolving drugs has influenced the incidence of periodontal disease progression in HIV-seropositive subjects and has resulted in less severe periodontal manifestations of HIV infection (Chapple & Hamburger 2000). For example, a cross-sectional study of 326 HIV-infected adults (McKaig *et al*. 1998) revealed that, after adjustments for CD4 counts, persons taking HIV antiretroviral medication were five times less likely to suffer from periodontitis than those not taking such medication, underscoring the importance of the host's immunologic competency in this context.

Nevertheless, publications continue to generate conflicting results. Thus, although a number of studies (Smith *et al*. 1995a; Robinson *et al*. 1996; Ndiaye *et al*. 1997; McKaig *et al*. 1998; Nittayananta *et al*. 2010; Stojkovic *et al*. 2011) have indicated higher prevalence and severity of periodontitis in HIV-positive subjects when compared to controls, other studies have either not supported this notion or have indicated that the differences in periodontal status between HIV-seropositive and -seronegative subjects are limited (Cross & Smith 1995; Lamster *et al*. 1997; Scheutz *et al*. 1997; Lamster *et al*. 1998; Vastardis *et al*. 2003). Studies investigating the pathobiology of periodontitis in HIV-infected subjects suggested that specific IgG subclass responses to periodontopathic bacteria were similar in HIV-positive and HIV-negative subjects (Yeung *et al*. 2002), while CD4 count levels were not found to correlate with the severity of periodontitis (Martinez Canut *et al*. 1996; Vastardis *et al*. 2003).

The few available longitudinal studies are equally conflicting. Two companion publications, from a short-term follow-up study (Smith *et al*. 1995b; Cross & Smith 1995) involving a group of 29 HIV-seropositive subjects who were examined at baseline and at 3 months, reported a low prevalence and incidence of clinical attachment loss. The subgingival microbial profiles of the seropositive subjects resembled those of non-systemically affected subjects, and did not correlate with their CD4 and CD8 lymphocyte counts. Similarly, in a small follow-up study of 12 months' duration, Robinson *et al*. (2000) found no difference in the

progression of periodontitis between HIV-positive and HIV-negative subjects. Hofer *et al*. (2002) demonstrated that compliant HIV-positive subjects can be successfully maintained in a manner similar to non-infected controls. However, a 20-month follow-up study of 114 homosexual or bisexual men (Barr *et al*. 1992) revealed a clear relationship between incidence of clinical attachment loss and immunosuppression, expressed through CD4 cell counts. The authors suggested that seropositivity in combination with older age confers an increased risk for attachment loss. Similar observations were reported by Lamster *et al*. (1997), who concluded that periodontitis in the presence of HIV infection is dependent upon the immunologic competency of the host as well as the local inflammatory response to the subgingival microbiota.

It appears therefore that there is no consensus in the literature on the association of HIV/AIDS and periodontitis. Variation in the severity of oral pathologic conditions due to ongoing advancements in HIV/AIDS therapy will likely further contribute to the diversity of the findings (Freed *et al*. 2005).

Psychosocial factors

The mechanisms by which psychosocial stress may affect the periodontal status are complex. It has been suggested that one of the plausible pathways may involve behavioral changes leading to smoking and poor oral hygiene that, in turn, may affect periodontal health (Genco *et al*. 1998). In the absence of an unequivocal biologic measure of stress, a limited number of studies have used proxy measures of stress to study its association with periodontitis. In a study of 1426 subjects in Erie County, NY, USA, Genco *et al*. (1999) reported that adults who were under financial strain and exhibited poor coping behaviors were at increased risk of severe periodontitis when compared with subjects who demonstrated good coping behavior patterns under similar financial strain, or with controls under no financial strain. In a sample of 1089 adults in rural Japan, job- and health-related stress was positively associated with clinical attachment loss after adjustments for common risk factors (Akhter *et al*. 2005). War-related stress was found to be associated with poor periodontal conditions in Croatia (Spalj *et al*. 2008). Similar observations were made in a study of an immigrant population from Ethiopia, in which psychological distress was positively associated with deep periodontal pockets (Vered *et al*. 2011). In contrast, a study of 681 subjects carried out in Lithuania (Aleksejuniene *et al*. 2002) could not document an association between psychosocial stress and periodontitis, although it reported that the disease did correlate with lifestyle factors. In a small prospective study based on 23 employed adults, Linden *et al*. (1996) reported that longitudinal attachment loss was significantly predicted by increasing age, lower socioeconomic status, lower job satisfaction, and type A personality, characterized by aggressive, impatient, and irritable behavior.

Clearly, the role of stress in periodontitis has not been fully explored and multiple gaps in our knowledge exist. Nevertheless, given the established role of the sympathetic, parasympathetic, and peptidergic/sensory nervous systems, as well as that of the hypothalamic–pituitary–adrenal axis on brain-to-immune regulatory pathways, such a role is clearly biologically plausible. Experimental animal studies have begun to shed light on basic mechanisms that may explain the link between psychosocial factors and periodontitis. For example, a study by Breivik *et al*. (2006) demonstrated that experimentally-induced depression accelerated tissue breakdown in a ligature-induced periodontitis rat model and that pharmacologic treatment of depression attenuated this breakdown. In a study in humans, salivary cortisol levels (indicative of psychological stress) were positively associated with the extent and severity of periodontitis (Hilgert *et al*. 2006).

Additional basic and epidemiologic research is needed to fully elucidate a possible relationship between psychological factors and periodontal disease.

Concluding remarks

The analytical epidemiologic studies described in this chapter are obviously diverse with respect to important elements of design and methodology, such as definitions of disease, sample size, use of full-mouth or partial-mouth recording protocols, length of follow-up in longitudinal studies, adjustment for potential confounders, etc. Nevertheless, despite these apparent shortcomings, a number of conclusions can be made with reasonable certainty:

1. Specific bacteria, cigarette smoking, and diabetes mellitus are the major established risk factors for periodontitis. A number of biologically plausible, potentially important additional factors are in need of further investigation in future studies.
2. There is a need to introduce uniform definitions of periodontitis to be used in analytical epidemiologic studies. This will facilitate valid comparisons, establish whether seemingly conflicting data reflect true biologic variation or are exclusively owed to methodologic inconsistencies, and contribute to the correct identification of risk factors. The definitions proposed by the Consensus Report of the 5th European Workshop in Periodontology (Tonetti & Claffey 2005), the CDC/APP definition (Page & Eke 2007), and the definition for *aggressive periodontitis* in epidemiologic studies (Demmer & Papapanou 2010) may serve such a purpose. Obviously, no definition is devoid of shortcomings and the above proposals are no exception. In the absence of a universally accepted consensus definition, data presentation using several of the above definitions should be encouraged.

3. Studies need to distinguish clearly between risk factors and disease predictors. Although the use of the latter as explanatory variables in multivariate models may increase the coefficient of determination (i.e. the proportion of the variance explained by means of the models), it may also obscure the significance of true etiologic factors. For example, as shown by Ismail *et al*. (1990), factors with biologically plausible etiologic potential (such as dental plaque) may not retain their significance in multivariate models that include alternative expressions of disease such as tooth mobility. It has been demonstrated that baseline levels of disease and morphologic features such as angular bony defects are powerful predictors of future disease progression (Papapanou *et al*. 1989; Papapanou & Wennström 1991). Haffajee *et al*. (1991a) showed that age, plaque, and bleeding on probing are related to baseline disease levels as well as to incident disease. In the search for true exposures of significance for disease onset or progression, inclusion of a factor in a model may thus erroneously discredit another co-varying, biologically significant factor.

An interesting observation was made in a longitudinal study by Beck *et al*. (1995), in which characteristics of patients experiencing clinical attachment loss at previously non-diseased sites were compared with those of patients suffering progression of already established disease. While low income and medication with drugs associated with soft tissue reactions were features common to both groups of patients, new sites with attachment loss were more frequent in patients who used smokeless tobacco and had a history of oral pain. Risk for progression of established disease was higher in cigarette smokers, subjects with high levels of subgingival *P. gingivalis*, and individuals with worsening financial problems. These data suggest that periodontitis may be like other diseases for which the factors associated with the initiation of the disease may be different from the ones involved in its progression. Such a distinction between factors associated with initiation and with progression may have implications for future assessment strategies and may improve the accuracy of the risk/prediction models.

One of the issues related to the descriptive epidemiology of periodontal infections that is still under debate is whether their worldwide prevalence has been decreasing over the last decades. Unfortunately, the data do not allow a clear answer for a number of reasons. First, no universal conclusion is possible, since the prevalence of periodontal disease appears to vary with race and geographic region. Second, the quality of the data available from developing and developed countries is clearly not comparable. While some well-conducted epidemiologic surveys that provide detailed information have been carried out in a number of countries, the majority of the studies in the developing world have used the CPITN system, which produced data of inadequate detail. Moreover, studies using the exact same methodology to evaluate random samples drawn from the same population over time are sparse. Among the few exceptions, data available from some parts of the world, notably the US, are suggestive of such a trend for decreasing prevalence of periodontitis (Dye *et al*. 2007). A series of studies from Sweden (Hugoson *et al*. 1992, 1998b, 2005) that documented, by clinical and radiographic means, the frequency distribution of various levels of severity of periodontitis in four cross-sectional studies over a 30-year period (in 1973, 1983, 1993, and 2003). In these studies, subjects were grouped according to the severity of their periodontal conditions into five groups: groups 1 and 2 included subjects who were periodontally healthy or only had gingivitis; group 3 included subjects with moderate periodontitis, that is whose loss of periodontal tissues support did not extend beyond one-third of the root length; and groups 4 and 5 included subjects with more severe destructive disease. As shown in Fig. 7-5, a clear increase in the frequency of subjects in groups 1 and 2 was noted over the 30-year period, from 49% in 1973 to 60% in 1993 to almost 62% in 2003. This increase occurred primarily at the expense of group 3, which declined from 38% in 1973 to 27% in 1993 and apparently reached a plateau at 28% in 2003. Nevertheless, the frequency of subjects in groups 4 and 5 was virtually stable over the 30-year period: 13% in 1973, 13% in 1993, and 10.5% in 2003. Based on these data derived from a population with arguably the best access to and utilization of oral health care in the world, it may be concluded that the fraction of the population which is most susceptible to severe periodontitis is apparently not declining in frequency. Instead, the main beneficiaries of the improved oral health awareness, access to care, and increased utilization of therapeutic resources that has occurred over the last decades are likely the individuals with

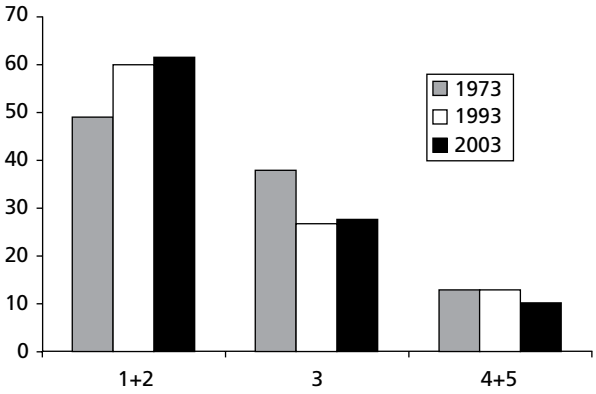

Fig. 7-5 Frequency distribution of subjects with healthy periodontal conditions or gingivitis (groups 1 + 2), moderate periodontitis (group 3), and advanced and severe periodontal disease (groups 4 + 5), in a Swedish cohort in 1973, 1993, and 2003. For definitions see text. (Adapted after personal communication with Anders Hugoson, based on data from Hugoson *et al*. 1992, 1998, 2006).

moderate levels of periodontitis whose prevalence is clearly lower.

It has also been well-documented in these and other studies that the rate of edentulism has decreased substantially over the past 30 years, with elderly groups retaining their natural dentition and higher mean numbers of teeth than their counterparts a generation ago (Kassebaum *et al*. 2014). This fact *per se* should contribute to an increased prevalence of periodontal disease in older age cohorts, since retained teeth in the elderly are more likely to experience substantial cumulative attachment loss which forms the basis of the assessment of prevalence (Douglass & Fox 1993). It has been argued, however, that such a potential increase may not necessarily result in increased need for periodontal therapy (Oliver *et al*. 1989). Additional research is clearly required to further elucidate these issues, and an adequate and consistent epidemiologic methodology is essential for generating valid comparative data. Arguably, the principle task of future epidemiologic research is to elucidate the determinants of susceptibility to severe periodontitis, prior to the development of irreversible tissue damage (Papapanou 2012, 2014). Although several risk factors have been established and a wide array of disease markers has been recognized, the impact of intervention addressing such factors on the state of periodontal health on a population level has yet to be documented. To assess the magnitude of the clinical benefit achieved by such modulation, prospective, long-term epidemiologic surveys have to be conducted.

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Part 3: Microbiology

Chapter 8

Dental Biofilms

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Introduction

Humans have evolved to have an intimate and dynamic relationship with microorganisms; this includes those that make up the resident microbiota of all environmentally-exposed surfaces of the body as well as those that cause disease. Contemporary studies are demonstrating that the relationship with the resident microbiota is highly interactive, and makes a major contribution to the health of the host. This relationship is dynamic and fragile, and a number of intrinsic and extrinsic factors can perturb this exquisite balance. An understanding of the relationship between host and oral microbiota is critical for the effective clinical management of dental patients both during health and when treating disease.

A remarkable statistic is that the human body is estimated to be composed of $>10^{14}$ cells, of which only 10% are mammalian (Sanders & Sanders 1984; Wilson 2005). The majority are the microorganisms that make up the resident microbiotas that colonize all accessible surfaces of the body and which, as will be discussed later, confer significant benefits to the host. These microbiotas have a diverse composition, and function as interactive microbial communities in which their combined properties are greater than the sum of the activities of the constituent species (see later). The microbiotas of the skin, mouth, digestive and reproductive tracts are distinct from each other despite the frequent transfer of organisms between these sites; their characteristic composition is a consequence of significant differences in the biologic and physical properties of each habitat (Wilson, 2005). These properties determine which microorganisms are able to colonize successfully, and which will predominate or be only a minor component of the established microbial community.

The mouth as a microbial habitat

The mouth is similar to other habitats within the body in having a characteristic microbial community that provides benefits for the host. The mouth is warm and moist, and is able to support the growth of a wide range of microorganisms, including viruses, mycoplasma, bacteria, Archaea, fungi, and protozoa (Wilson 2005; Marsh & Martin 2009). These microorganisms colonize mucosal and dental surfaces in the mouth to form three-dimensional, structurally-organized multispecies communities that are termed biofilms. The biofilms that form on teeth are referred to as dental plaque. In general, desquamation ensures that the microbial load on mucosal surfaces is kept relatively low. In contrast, the mouth is a unique site in the body in that it provides non-shedding surfaces (teeth, dentures) for microbial colonization. This can result in the accumulation of large numbers of microorganisms, particularly at stagnant and hard-to-reach sites, unless patients practice effective oral hygiene. The main focus of this chapter is to describe the properties of biofilms that develop on teeth (dental biofilms).

A number of environmental factors will influence the distribution and metabolic activity of the resident oral microbiota (Fig. 8-1a) (Marsh & Devine 2011).

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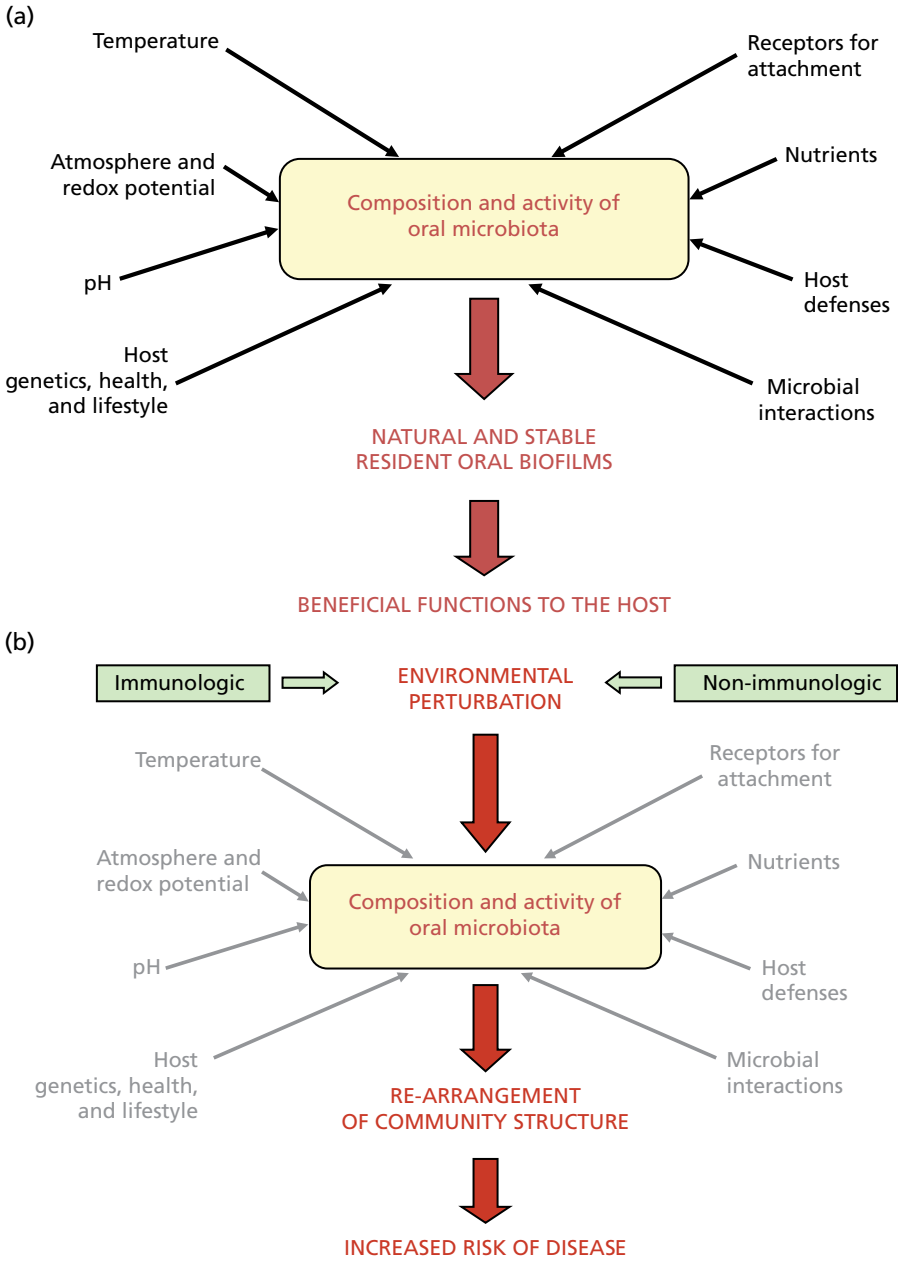

Fig. 8-1 Host factors that influence the microbial composition, activity, and stability of the resident oral microbiota. (a) A number of host factors help to determine the composition and activity of the natural oral microbiota, which provides benefits to the host. (b). Perturbation in a key environmental factor can disrupt the natural stability (microbial homeostasis) of the resident microbiota at a site and result in a rearrangement of the composition and activity of the resident microbial community; such a change might predispose the site to disease. (Source: Adapted from Marsh & Devine 2011, from John Wiley & Sons.)

The mouth is maintained at a temperature of around 35–37 °C, which is suitable for the growth of a broad range of microbes. Temperature does increase at subgingival sites during inflammation, and this can alter bacterial gene expression, which in turn can alter the competitiveness of bacteria within the microbial community, and favor growth and protease activity of some putative periodontal pathogens. Although the mouth is overtly aerobic, the majority of oral bacteria are facultatively or obligately anaerobic. The distribution of these anaerobes in the mouth is generally related to the redox potential (Eh), the measure of the degree of oxidation–reduction at a site. The gingival crevice has the lowest Eh in the healthy mouth, and harbors the largest numbers of obligate anaerobes (Kenney & Ash 1969). As oral bacteria exist as members of microbial communities, some anaerobic species survive in more aerobic habitats by existing in close partnership with oxygen-consuming species. Bacterial metabolism in mature oral biofilms results in sharp gradients of oxygen and Eh, thereby generating a mosaic of microenvironments suitable for the growth of bacteria with a range of oxygen tolerances. Many oral anaerobes also express a range of enzymes whose function is to scavenge low levels of oxygen in the environment to enable them to survive.

In the mouth, pH is a major determinant of bacterial distribution and metabolism. The buffering activity

of saliva plays a major role in maintaining the intraoral pH at around neutrality, which again is suitable for the growth of members of the resident oral microbiota. Changes in environmental pH frequently occur, and when they do they drive major shifts in the proportions of bacteria within dental plaque biofilms. After sugar consumption, the pH in plaque can fall rapidly to below 5.0 by the production of acidic fermentation products (Marsh & Martin 2009). Depending on the frequency of sugar intake, the bacteria in plaque will be exposed to varying challenges of low pH. Many of the predominant plaque bacteria that are associated with healthy sites can tolerate brief conditions of low pH, but are inhibited or killed by more frequent or prolonged exposures to acidic conditions (Svensater *et al*. 1997). This can result in the enrichment of acid-tolerant (aciduric) species, especially mutans streptococci, bifidobacteria, and lactobacilli, which are normally absent or only minor components in dental plaque at healthy sites. Such shifts in the bacterial composition of plaque predispose a surface to dental caries. The pH of the healthy gingival crevice is approximately 6.9, but this rises to between pH7.2 and 7.4 during inflammation, with a few patients having pockets with a mean pH of around 7.8 (Eggert *et al*. 1991). Inflammation results in the increased flow of gingival crevicular fluid (GCF) in the subgingival habitat, and the rise in pH is a consequence of increased bacterial proteolysis of host proteins and glycoproteins in GCF. Even a small change in pH can alter the growth rate and pattern of gene expression in subgingival bacteria, and increase the competitiveness of some of the putative Gram-negative anaerobic pathogens at the expense of species associated with periodontal health (McDermid *et al.* 1988).

Saliva and GCF also have a major influence on bacterial distribution because they provide an array of host molecules that are potential nutrients for microorganisms. Primary nutrients, such as amino acids, proteins, and glycoproteins, are obtained from saliva and GCF; diet has only a minor role on the resident microbiota, mainly via the change in pH from sugar catabolism, as discussed earlier. The metabolism of complex host molecules requires the sequential or concerted action of consortia of bacteria (see later) in order to achieve their complete breakdown (ter Steeg & van der Hoeven 1989; Homer & Beighton 1992a, b; Bradshaw *et al*. 1994; Palmer *et al.* 2006; Periasamy & Kolenbrander 2009).

The mouth is richly endowed with components of both the innate (e.g. lysozyme, lactoferrin, sialoperoxidase, host defense peptides, neutrophils, etc.) and adaptive (secretory IgA, IgG, etc.) immune response (Marsh & Martin 2009). Complement, which bridges both the innate and adaptive immune responses, is also present. An area of considerable research activity at present concerns the relationship between the resident microbiota at any site and the host defenses, and how these microbial communities persist without triggering an undesirable and unwanted detrimental host response, while the host retains the ability to respond to a genuine microbial challenge. Evidence is accumulating that some members of the resident oral microbiota are involved in active cross-talk with the host to down-regulate potential pro-inflammatory responses (Hasegawa *et al*. 2007; Cosseau *et al*. 2008).

The lifestyle of an individual can affect the distribution and metabolism of the oral microbiota (Marsh & Devine 2011). The impact of a diet with a high frequency of intake of fermentable carbohydrates has been discussed already. Smoking may select for potential periodontal pathogens in dental biofilms, and individuals with diabetes have a higher frequency of certain Gram-negative periodontal pathogens in plaque. The composition of the oral microbiota can also change with age as a consequence of a number of host-related events, including tooth eruption in early life or the waning of the immune response in old age. The influence of female hormones in GCF during pregnancy on the prevalence of some periodontal pathogens is controversial (Adriaens *et al*. 2009), although correlations have been found between maternal hormone levels and the increased proportions of black pigmented anaerobes, such as *Porphyromonas gingivalis* and *Prevotella intermedia*, in dental biofilms (Carrillo-de-Albornoz *et al*. 2010).

In general, once established, the microbial composition of the biofilm at a site remains stable over time, unless a major perturbation occurs in a key environmental determinant, such as a major change in diet or an alteration to the immune status of the host. Such perturbations can drive shifts in the balance of the microbiota, which can increase the risk of disease (Fig. 8-1b).

Significance of a biofilm and community lifestyle for microorganisms

The vast majority of microorganisms in nature, including those in the mouth, are found attached to surfaces as biofilms. Biofilms have been defined as matrix-embedded microbial populations, adherent to each other and/or to surfaces or interfaces (Costerton *et al*. 1995). The ability to attach to and be retained at a surface is a fundamental survival strategy for most prokaryotic organisms. Microorganisms would be lost from the mouth if they did not firmly attach to an oral surface and form a biofilm. The microbes found in multispecies biofilms are not randomly distributed but are spatially and functionally organized, and many natural biofilms have a highly diverse microbiota.

There would be little scientific or clinical interest if the properties of biofilms were simply those of planktonic (liquid culture) cells attached to a surface, and if the properties of microbial communities were merely the sum of those of the constituent species. However, studies have established that bacterial gene expression can alter markedly when cells form

a biofilm, resulting in many organisms having a radically different phenotype following attachment to a surface (Marsh 2005). Furthermore, the binding of bacteria to specific host receptors can also trigger significant changes in patterns of host cell gene expression. Most natural biofilms contain multiple species that engage in a wide range of physical, metabolic, and molecular interactions, and are termed microbial communities. This community lifestyle provides several potential benefits to the participating organisms (Caldwell *et al*. 1997; Shapiro 1998; Marsh & Bowden 2000) including:

- *Broader habitat range for growth*. For example, the metabolism of early colonizers alters the local environment, making conditions suitable for attachment and growth of later (and sometimes more fastidious) species.
- *Increased metabolic diversity and efficiency*. Molecules that are normally recalcitrant to catabolism by individual organisms can often be broken down by microbial consortia.
- *Enhanced tolerance of environmental stress, antimicrobial agents, and the host defenses*. Neighboring cells of a different species can produce neutralizing enzymes (β-lactamase, IgA protease, catalase, etc.) that protect inherently susceptible organisms from inhibitors (Brook 1989). Horizontal gene transfer is also more efficient in multispecies biofilms (Molin & Tolker-Nielsen 2003; Wilson & Salyers 2003). Microbial communities can also give physical protection from phagocytosis to cells deep within a spatially-organized consortium (Costerton *et al.* 1987; Fux *et al*. 2005).
- *Enhanced ability to cause disease*. Abscesses are examples of polymicrobial infections whereby organisms that individually cannot cause disease are able to do so when they are present as a consortium (pathogenic synergism) (van Steenbergen *et al.* 1984).

Thus, microbial communities display emergent properties, in other words the properties of the community are more than the sum of its component populations.

An important clinical consequence of both the structural and functional organization of multispecies biofilms is their reduced susceptibility to antimicrobial agents (Gilbert *et al.* 1997; Ceri *et al*. 1999; Stewart & Costerton, 2001; Gilbert *et al*. 2002). Conventionally, the sensitivity of bacteria to antimicrobial agents is determined by growing them in liquid culture and measuring the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC). The MIC of an organism growing on a surface can be from 2- to 1000-fold greater than that of the same cells grown planktonically (Stewart & Costerton 2001), with older biofilms being most recalcitrant.

The mechanisms behind the increased tolerance of biofilms to antimicrobial agents are still the subject of much research (Stewart & Costerton 2001; Gilbert *et al.* 2002). Resistance conventionally develops due to mutations affecting the drug target, to the presence of efflux pumps or to the production of modifying enzymes, etc., but even sensitive bacteria become less susceptible when growing on a surface. The structure of a biofilm may restrict the penetration of the antimicrobial agent; charged inhibitors can bind to oppositely-charged polymers that make up the biofilm matrix (diffusion–reaction theory). The agent may also adsorb to and inhibit the organisms at the surface of the biofilm, leaving cells in the depths of the biofilm relatively unaffected. The matrix in biofilms can also bind and retain neutralizing enzymes (e.g. β-lactamase) at concentrations that could inactivate an antibiotic or inhibitor (Allison 2003). As stated earlier, bacteria growing on a surface display a novel phenotype, and this can result in a reduced sensitivity to inhibitors, because the drug target may be modified or not expressed, or the organism may use alternative metabolic strategies. Bacteria grow only slowly under nutrient-depleted conditions in an established biofilm and, as a consequence, are much less susceptible than faster dividing cells. In addition, it has also been proposed that the environment in the depths of a biofilm may be unfavorable for the optimal action of some drugs (Gilbert *et al.* 2002). One hypothesis suggests that the increased tolerance of some biofilms to antibiotics is due largely to the presence of a subpopulation of "persister" organisms that are specialized survivor cells (Keren *et al*. 2004).

The most diverse collections of oral microorganisms are found in the biofilms on teeth (dental plaque) (Aas *et al*. 2005; Marsh & Martin 2009; Papaioannou *et al*. 2009; Dewhirst *et al*. 2010). It is now very common to see the term "dental biofilm" used instead of the original descriptor "dental plaque". This does not mean that the original work performed on "dental plaque" is now invalid or irrelevant; rather it emphasizes the point that the broader principles derived from work on biofilms from across the spectrum of microbiologic habitats are directly relevant to dental biofilms, and *vice versa*.

Formation of dental biofilms

Dental biofilms form via an ordered sequence of events, resulting in a structurally- and functionally-organized, species-rich microbial biofilm (Socransky & Haffajee 2002; Marsh 2005; Kolenbrander *et al*. 2006; Marsh *et al.* 2011) (Fig. 8-2). The distinct stages in dental biofilm formation include:

1. Adsorption of a conditioning film (acquired pellicle)
2. Reversible adhesion between the microbial cell surface and the conditioning film
3. More permanent attachment involving interactions between specific molecules on the microbial cell surface (adhesins) and complementary molecules (receptors) present in the conditioning film
4. Co-adhesion, in which secondary colonizers adhere to receptors on already attached bacteria

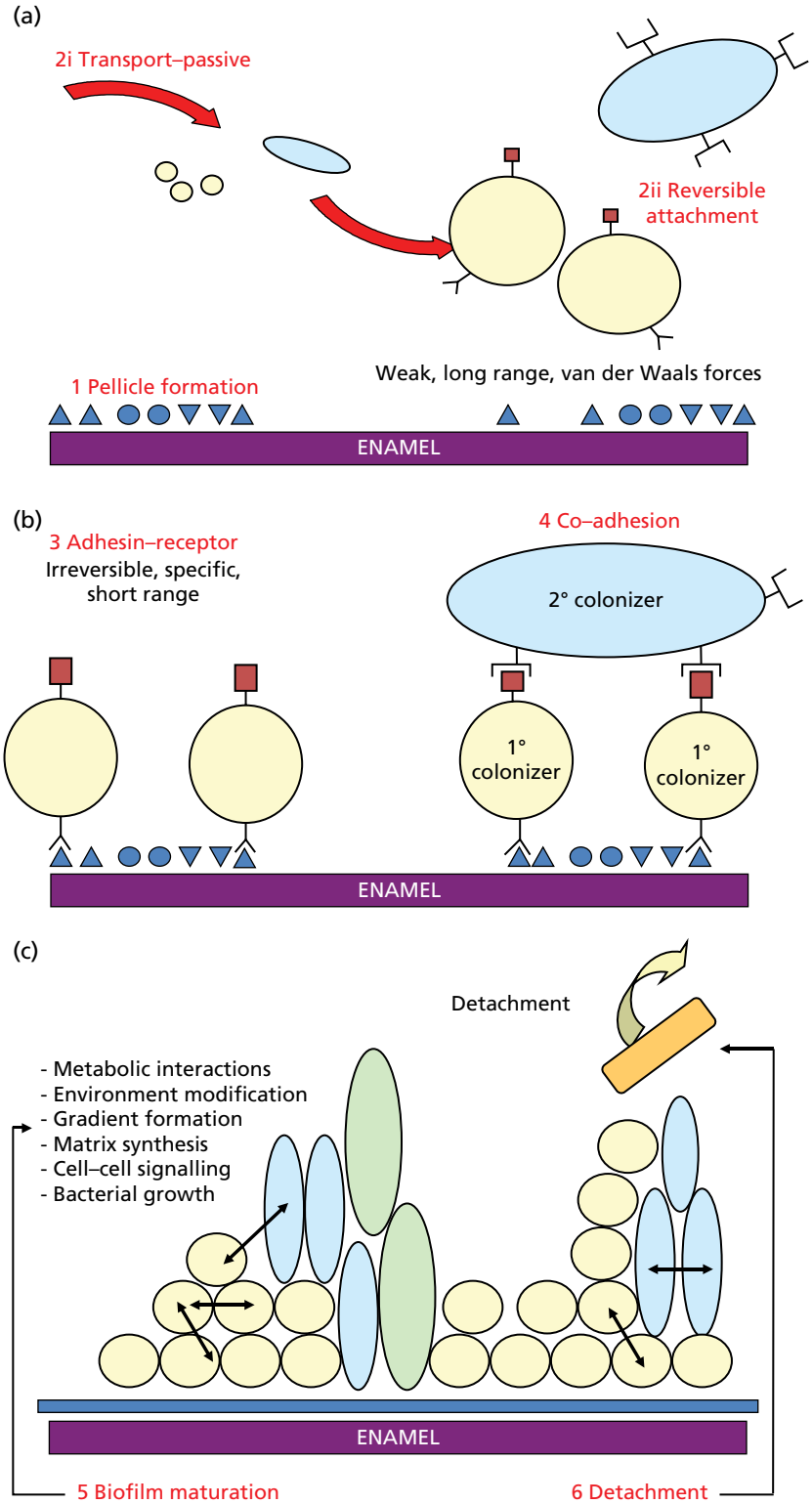

Fig. 8-2 Schematic representation of the different stages in the formation of dental biofilms. (a) Pellicle forms on a clean tooth surface (1). Bacteria are transported passively to the tooth surfaces (2i), where they may be held reversibly by weak, long-range forces of attraction (2ii). (b) Attachment becomes more permanent through specific stereochemical molecular interactions between adhesins on the bacterium and complementary receptors in the pellicle (3), and secondary colonizers attach to the already attached primary colonizers by molecular interactions (co-adhesion) (4). (c) Growth results in biofilm maturation, facilitating a wide range of intermicrobial interactions (synergistic and antagonistic) (5). On occasions, cells can detach to colonize elsewhere (6). (Source: Marsh & Martin 2009. Reproduced with permission from Elsevier.)

(Kolenbrander *et al*. 2010), leading to an increase in microbial diversity

5. Multiplication of the attached cells, leading to an increase in biomass and synthesis of exopolymers to form the biofilm matrix (plaque maturation)
6. Detachment of attached cells to promote colonization elsewhere.

These stages will now be described in more detail.

Conditioning film formation

Bacteria rarely colonize clean enamel. Within seconds of eruption, or following cleaning, tooth surfaces become coated with a conditioning film of molecules (biologically-active proteins, phosphoproteins, and glycoproteins) derived mainly from saliva (but also from GCF and from the bacteria themselves) (Hannig *et al.* 2005). The conditioning film alters the biologic and chemical properties of the surface, and the composition of the pellicle directly influences the pattern of subsequent microbial colonization. Microorganisms interact directly with this conditioning film (Fig. 8-3).

Reversible and more permanent attachment

Initially, only a limited number of bacterial species are able to attach to the conditioning film. Bacteria can be held reversibly near to the surface by weak, long range, physicochemical forces between the electrical charge of the molecules on the pellicle-coated surface and those on the cell surface (Bos *et al.* 1999). This reversible adhesion creates the opportunity for stronger and more permanent attachment to be established. Molecules (adhesins) on these early bacterial colonizers (mainly streptococci, e.g. *Streptococcus mitis*, *Streptococcus oralis*) can bind to complementary receptors in the acquired pellicle to make the attachment stronger (Busscher *et al.* 2008; Nobbs *et al.* 2011). Individual species can deploy multiple adhesins (Nobbs *et al.* 2011); in Gram-positive bacteria, several families of surface proteins can act as adhesins, including serine-rich repeat, antigen I/II, and pilus families. In Gram-negative bacteria, auto-transporters, extracellular matrix-binding proteins, and pili function as adhesins (Nobbs *et al.* 2011).

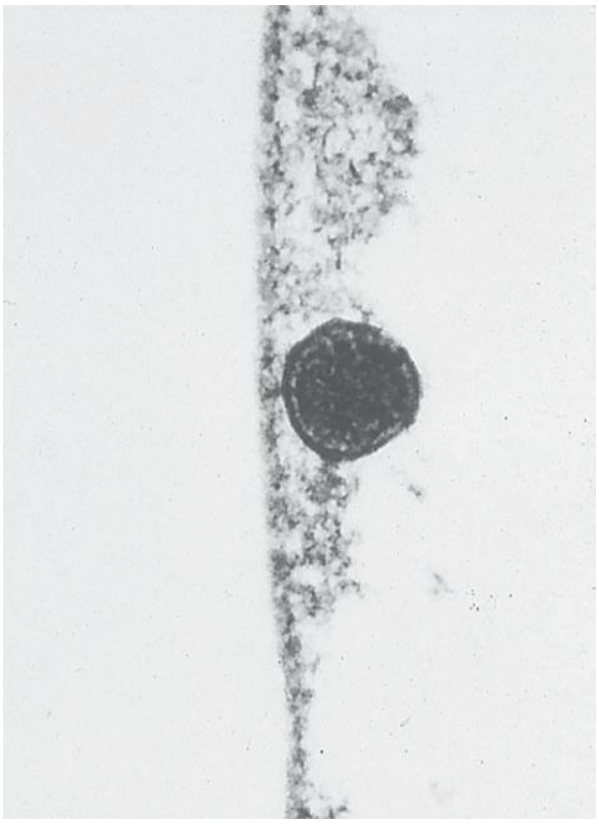

Fig. 8-3 Electron micrograph illustrating a 4-hour pellicle with a single bacterial cell attached. (Source: Brecx *et al.* 1981. Reproduced with permission from John Wiley & Sons.)

Co-adhesion

Once attached, the pioneer colonizers start to multiply. The metabolism of these bacteria that attach early modifies the local environment, for example by making it more anaerobic following their consumption of oxygen and the production of reduced end products of metabolism. As the biofilm develops, adhesins on the cell surface of more fastidious secondary colonizers, such as obligate anaerobes, bind to receptors on bacteria that are already attached by a process termed co-adhesion or co-aggregation, and the composition of the biofilm becomes more diverse (a process termed microbial succession) (Kolenbrander *et al.* 2006) (Figs. 8-4, 8-5). A key organism in plaque biofilm

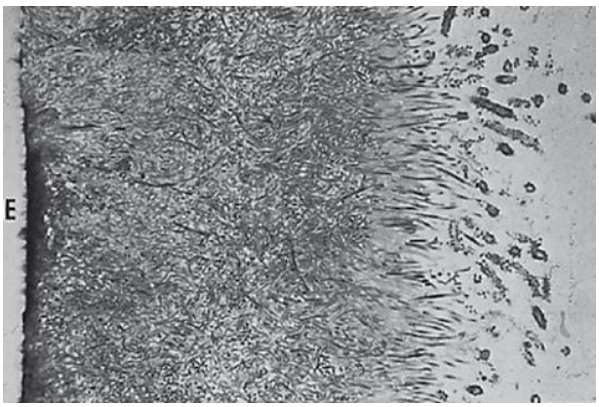

Fig. 8-4 Semi-thin section of a supragingival biofilm on enamel (E) which has been dissolved prior to sectioning. Magnification ×750. (Source: Listgarten 1976. Reproduced with permission from the American Academy of Periodontology.)

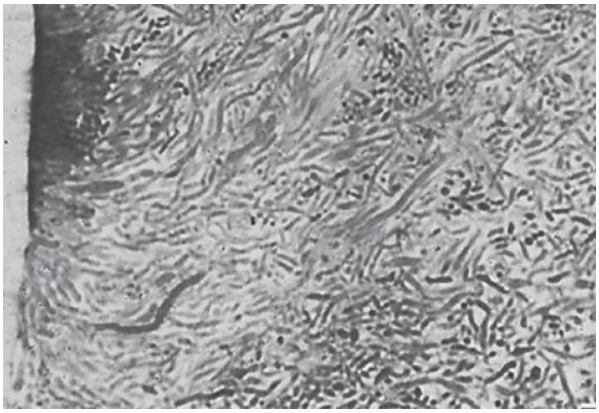

Fig. 8-5 Semi-thin section of supragingival biofilm. Filamentous organisms predominate. At the surface, some of these organisms are surrounded by cocci; the configuration resembles a corn-cob. Magnification ×1400. (Source: Listgarten 1976. Reproduced with permission from the American Academy of Periodontology.)

development is *Fusobacterium nucleatum*. This species can co-adhere to most oral bacteria, and acts as an important bridging organism between early and late colonizing species. Co-adhesion may help ensure that bacteria co-locate with other organisms with complementary metabolic functions.

Plaque maturation

Some of the attached bacteria synthesize extracellular polymers (the plaque matrix) that can consolidate attachment of the biofilm. The matrix is more than a mere scaffold for the biofilm; it can bind and retain molecules, including enzymes, and also retard the penetration of charged molecules into the biofilm (Allison 2003; Vu *et al*. 2009; Marsh *et al.* 2011). Biofilms are spatially- and functionally-organized, and the heterogeneous conditions within the biofilm induce novel patterns of bacterial gene expression, while the close proximity of different species provides the opportunity for interactions (Kuramitsu *et al*. 2007; Hojo *et al*. 2009; Marsh *et al*. 2011). Examples of these interactions include:

- Development of food chains (in which the end product of metabolism of one organism is used as a primary nutrient by secondary feeders) and metabolic cooperation among species to catabolize structurally-complex host macromolecules. These interactions increase the metabolic efficiency of the microbial community (Periasamy & Kolenbrander 2010; Marsh *et al.* 2011).
- Cell–cell signaling. Plaque bacteria have been shown to communicate with one another in a cell density-dependent manner via small diffusible molecules, using strategies similar to those described for other biofilms, for example by the secretion of small peptides by Gram-positive bacteria to coordinate gene expression among cells of a similar species (Suntharalingam & Cvitkovitch 2005). In *Streptococcus mutans*, quorum sensing is mediated by a competence stimulating peptide (CSP) (Li *et al*. 2002). This peptide also induces genetic competence in *S. mutans* so that the transformation frequency of biofilm-grown *S. mutans* was 10–600-fold greater than for planktonic cells. Lysed cells in biofilms could then act as donors of DNA, thereby increasing the opportunity for horizontal gene transfer in dental plaque. This quorum sensing system also functions to regulate acid tolerance in *S. mutans* biofilms. It has been proposed that *S. mutans*, upon exposure to low pH, could release CSP, and initiate a coordinated "protective" response among neighboring cells to this potentially lethal stress.

Other communication systems may function between different oral species (Kolenbrander *et al.* 2002). *LuxS* genes encode for autoinducer-2 (AI-2), and have been detected in several genera of oral Gram-positive and Gram-negative bacteria, implying that AI-2 may signal across a broader species range. Several putative periodontal pathogens (*F. nucleatum*, *P. intermedia*, *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*) secrete a signal related to AI-2 (Fong *et al*. 2001; Frias *et al.* 2001).

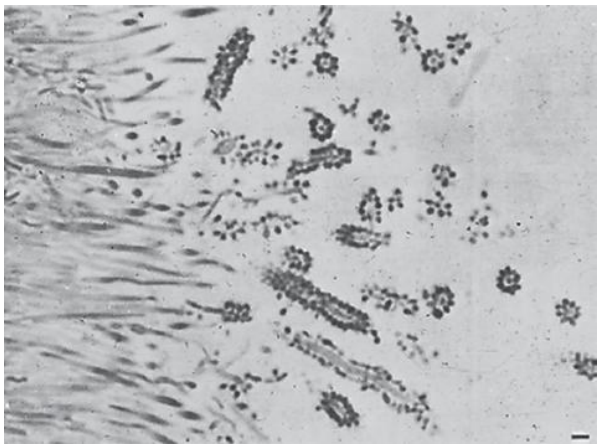

Fig. 8-6 "Corn-cob" formations seen at the biofilm surface shown in Figs. 8-4 and 8-5. Magnification ×1300.Bar 1 μm (Source: Listgarten 1976. Reproduced with permission from the American Academy of Periodontology.)

Characteristic cell associations can be seen in mature dental plaque, such as "corn-cob" (in which coccal-shaped cells attach along the tip of filamentous organisms; Fig. 8-6) and "test-tube brush" (rod-shaped bacteria sticking out perpendicularly from bacterial filaments) formations (Zijnge *et al*. 2010). These will be discussed further in the next section.

The structure of biofilms facilitates the likelihood of successful horizontal gene transfer. As discussed above, signaling molecules such as CSP markedly increase the ability of recipient cells in biofilms to take up DNA. The transfer of conjugative transposons encoding tetracycline resistance between streptococci has been demonstrated in model biofilms. The recovery from the nasopharynx of resident (*S. mitis*, *S. oralis*) and pathogenic (*S. pneumoniae*) bacteria with penicillin resistance genes showing a common mosaic structure confirms that gene transfer can occur *in vivo* (Dowson *et al*. 1990; Hakenbeck *et al*. 1998). Similar evidence suggests sharing of genes responsible for penicillin-binding proteins among commensal and pathogenic *Neisseria* (Bowler *et al*. 1994).

Structure of dental biofilms

Early studies using electron microscopy (EM) gave important insights into the structure of dental plaque from different sites, and demonstrated the presence of biofilms containing a range of morphologic types of microorganism, often as a compacted structure. More recently, confocal laser scanning microscopy has been used, which does not require the type of sample processing as for EM, and so samples can be seen in their natural, hydrated state. In confocal

microscopy, biofilms are optically sectioned and reconstructed as three-dimensional structures using appropriate software. The use of confocal microscopy has confirmed that dental plaque can also have an open architecture similar to that of biofilms from other habitats. Channels have been observed within biofilms, although they may also contain exopolymers (Wood *et al*., 2000; Auschill *et al*. 2001). Various microscopy techniques can also be combined with new staining methods to give more detail about the composition and organization of these biofilms. For example, the use of live/dead stains has indicated that bacterial vitality varies throughout the biofilm, with the most viable bacteria present in the central part of plaque, and lining the voids and channels (Auschill *et al.* 2001). This more open architecture should enable molecules to readily move in and out of plaque, but the presence of a matrix comprised of a diverse range of exopolymers creates a complex environment for accurately predicting the penetration and distribution of molecules within plaque (Robinson *et al*. 1997; Thurnheer *et al*. 2003; Marcotte *et al*. 2004), including the delivery of oral care and therapeutic agents. Fluorescent *in situ* hybridization (FISH), in which a fluorescent probe is combined with an oligonucleotide probe specific for a particular organism, can show the location of these microbes, including unculturable species, within the biofilm (Marsh *et al.* 2011; Zijnge *et al.* 2010) (Fig. 8-7).

Supragingival plaque biofilms appear to be quite heterogeneous in structure when viewed using FISH probes designed against a range of bacterial species (Zijnge *et al.* 2010). Subgingival plaque has an even more complex architecture. Initial studies using conventional light microscopy identified distinct tooth-associated and epithelial cell-associated biofilms, with the possibility of a less dense zone of organisms between the two (Socransky & Haffajee 2002). Co-adhesion is considered to be important in the temporal and spatial development of subgingival biofilms. Many of the putative pathogens that can be found in subgingival dental plaque in health are present in low numbers, and persist by attaching to the early streptococcal and actinomyces colonizers (Kuboniwa & Lamont 2010). These developing complex microbial communities engage in numerous metabolic interactions in order to survive.

Recently, subgingival biofilms were observed directly on extracted teeth, and the identification and location of bacteria was investigated using FISH (Zijnge *et al.* 2010). The architecture of subgingival biofilms was shown to be complex, with four layers being identified. The basal layer was composed of rod-shaped bacteria (*Actinomyces* spp.) attached perpendicularly to the tooth surface, above which was an intermediate layer composed of many spindle-shaped cells, including *F. nucleatum* and *Tannerella forsythia*. In the top layer were many putative periodontal pathogens, such as *P. gingivalis*, *Porphyromonas endodontalis*, *P. intermedia*, and *Parvimonas micra*. A fourth layer of unattached cells mainly consisted of spirochetes. Also, *Synergistetes* spp. formed a palisade-like layer along the outer edge of the biofilm, and were in direct contact with host immune cells. These bacteria are very difficult to grow in pure culture (most are currently "unculturable"), but can make up a sizeable proportion of subgingival plaque, and their location may indicate an important role in modulating host–biofilm interactions (Zijnge *et al.* 2010). The FISH studies allowed the identification of the species involved in the characteristic aggregates seen in subgingival biofilms. Lactobacilli formed the central axis of some of the "test-tube brushes", with organisms such as *Tannerella*, *F. nucleatum*, and

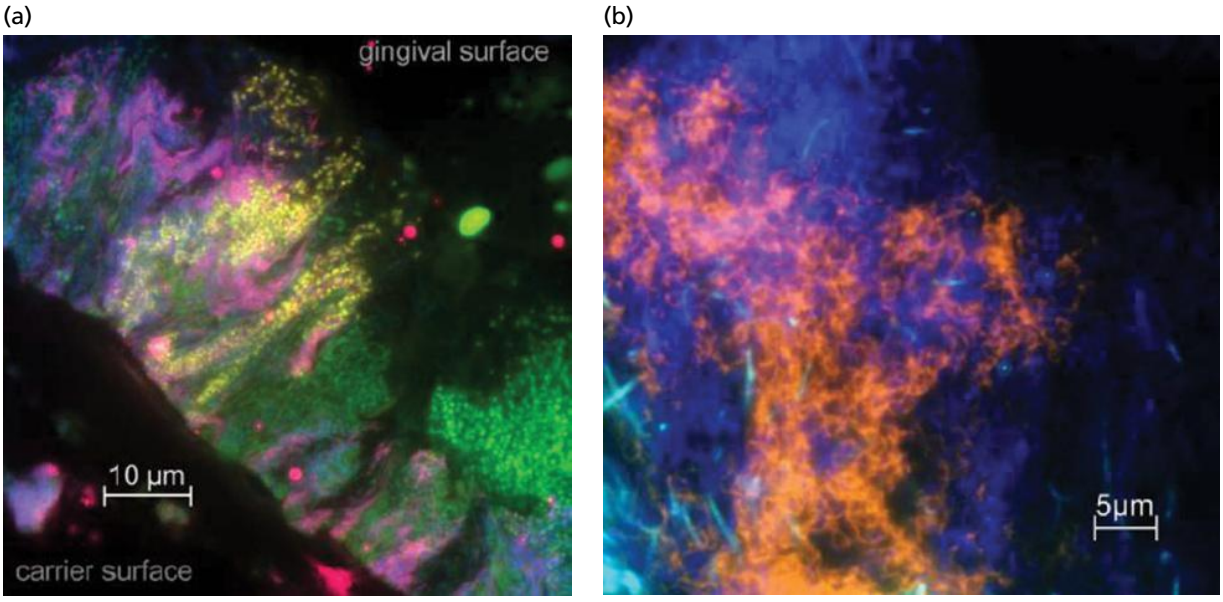

Fig. 8-7 Samples of subgingival biofilms with various oral species detected by fluorescence *in situ* hybridization (FISH). (a) Clusters of *Fusobacterium* spp. (magenta) and *Prevotella intermedia* (yellow). (b) Unculturable spirochetes (orange) and *Fusobacterium* spp. (light blue). (Source: Marsh & Moter 2011a. Reproduced with permission from John Wiley & Sons.)

Synergistetes spp. radiating from this central cell. Corn-cobs consisting of streptococci adhering to a central axis of yeast cells or hyphae were observed by FISH (Zijnge *et al.* 2010). Corn-cobs formed between streptococci and *Corynebacterium matruchotii*, and between *Veillonella* spp. and *Eubacterium* spp. have also been reported.

Bacterial metabolism in plaque results in the development of gradients within dental biofilms in parameters that are critical to microbial growth (nutrients, pH, oxygen, etc.). These gradients are not necessarily linear; the use of two-photon excitation microscopy coupled with fluorescent lifetime imaging demonstrated considerable heterogeneity in pH over relatively short distances in model mixed culture oral biofilms (Vroom *et al*. 1999). Such environmental heterogeneity will allow fastidious bacteria to survive in plaque, and enable microorganisms to coexist that would be incompatible with one another in a more homogeneous environment. This explains how organisms with apparently contradictory metabolic and growth needs (e.g. in terms of atmospheric and nutritional requirements) are able to persist at the same site.

Microbial composition of dental biofilms

As discussed earlier, the mouth supports the growth of a characteristic microbiota which includes viruses, mycoplasma, bacteria, Archaea, fungi, and protozoa (Marsh & Martin 2009). Bacteria are the most numerous group and, initially, they were characterized using traditional cultural approaches. Over time, it became apparent that there was a large discrepancy between the number of bacteria in a sample that could be grown by these conventional approaches and those that were observed directly by microscopy (Choi *et al*. 1994; Paster *et al*. 2001). It is estimated that only about 50% of the resident oral microbiota can currently be cultivated in pure culture in the laboratory (Wade 1999, 2002). This may be due to our ignorance of the growth requirements of some species, but probably also reflects our naïvety in attempting to isolate microbes in pure culture that have evolved over millennia to grow with other species as part of a community (Vartoukian *et al.* 2010a, b).

Our knowledge of the richness and diversity of the resident oral microbiota has been enhanced by the recent application of culture-independent, molecular approaches (Pozhitkov *et al*. 2011; Wade 2011). The accumulated data from numerous studies of different surfaces and sites based around amplification, cloning, and sequencing of the *16S rRNA* gene have identified around 900 species in the mouth. Most sites (mucosal or plaque) yielded 20–30 different predominant species, while the number of species per individual mouth can range from 34 to 72 (Aas *et al.* 2005). However, these figures may still be an underestimate and the use of more powerful, high throughput, next-generation sequencing platforms will better detect low abundance species.

Underway is the "Human Oral Microbiome" project, which aims to identify and characterize all members of the resident oral microbiota found in health and disease (Dewhirst *et al.* 2010). Data are being placed in the publically accessible web-based Human Oral Microbiome Database (http://www.homd.org), which also feeds information into the larger Human Microbiome Project. It is beyond the scope of this chapter to describe the properties of members of the resident oral microbiota, and the reader is recommended to refer to this website or to other specialist texts for more detail (Marsh & Martin 2009).

Biofilms develop on mucosal and dental surfaces, and the microbial composition of the biofilm varies at distinct sites on a tooth (fissures, approximal surfaces, gingival crevices), reflecting the inherent differences in their anatomy and biology (Fig. 8-8) (Aas *et al.* 2005; Sachdeo *et al.* 2008; Marsh & Martin 2009; Papaioannou *et al.* 2009). The properties of each habitat will select for those organisms that are best adapted to the prevailing conditions, and are able to persist. This also means that any changes to the environment will directly impact on the composition and activity of the biofilm. The remainder of this chapter will focus on the properties of dental biofilms.

The normal microbiota of *fissures* is relatively sparse and the organisms present have a saccharolytic metabolism (i.e. their energy is derived from sugar catabolism), and are either aerobic or facultatively anaerobic. The predominant bacteria are streptococci, many of which produce extracellular polysaccharides, and there are few Gram-negative or anaerobic organisms (Theilade *et al*. 1982). The properties of this site are strongly influenced by saliva.

In contrast, the *gingival crevice* has a more diverse microbiota, including many Gram-negative anaerobic and proteolytic species; this is due to the lower Eh at this site and the delivery of a distinct set of proteins and glycoproteins by the GCF (Slots 1977). The black pigmented anaerobes have an absolute requirement for hemin for growth, and these organisms can obtain this co-factor from the degradation of heme-containing host molecules present in GCF. Molecular studies using culture-independent approaches have emphasized the fact that the gingival crevice supports the most diverse microbial communities in the healthy mouth, with 40% of the amplified clones representing novel phylotypes. Many currently unculturable species can be detected at this site (Figs. 8-7b, 8-8).

Approximal surfaces have a microbiota that is intermediate in composition between that of fissures and gingival crevices, and also harbors many anaerobic species. These sites have high proportions of *Actinomyces* spp. (Bowden *et al.* 1975).

As discussed earlier, once established, the composition of the resident microbiota at any site remains relatively stable over time, unless there are marked changes to the habitat. Importantly, this stability,

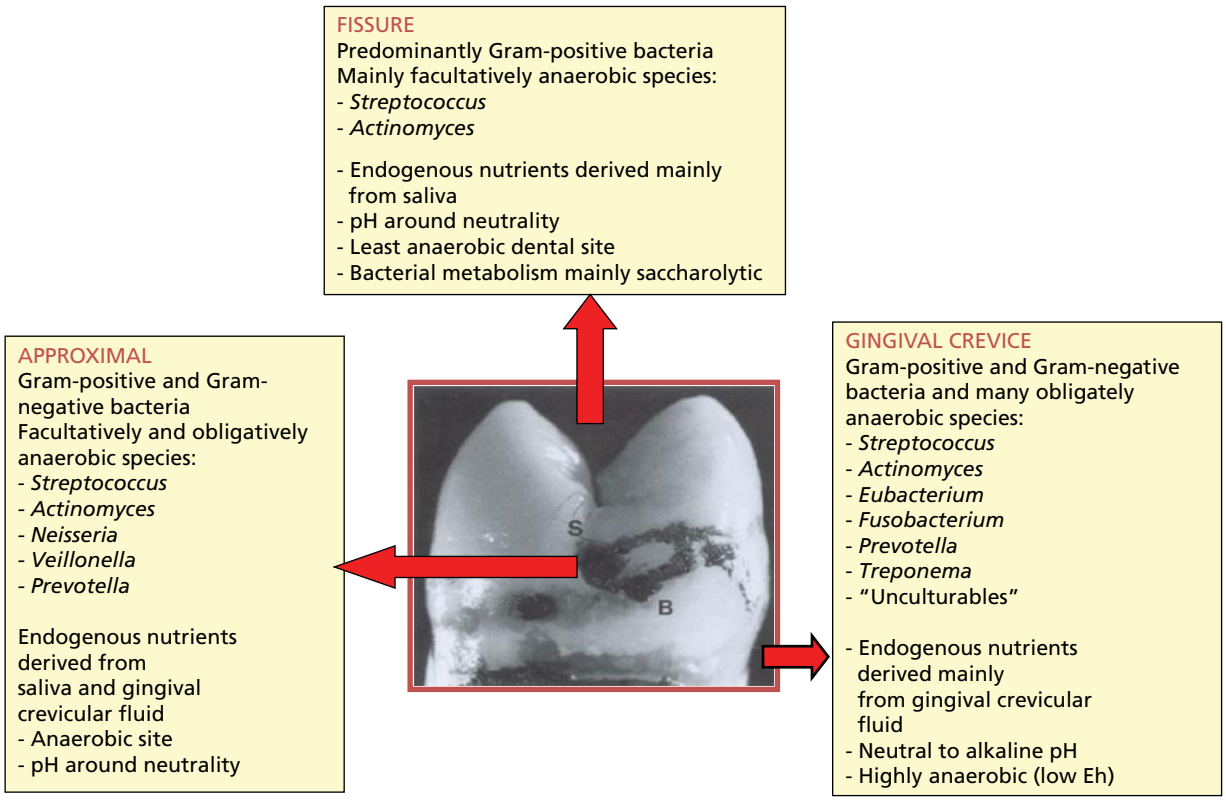

Fig. 8-8 Predominant groups of bacteria found at distinct sites on the tooth surface, and key features of each habitat.

termed microbial homeostasis, stems not from any metabolic indifference by the resident microbiota, but reflects a highly dynamic state in which the relative proportions of individual species are held in balance due to the numerous interactions, both synergistic and antagonistic, described earlier (Marsh 1989). This natural balance is maintained despite continual surveillance by the host defenses and the regular exposure of the mouth to a variety of modest environmental stresses, such as via the diet, changes in saliva flow, and oral hygiene (see Fig. 8-1a). However, microbial homeostasis can break down on occasions if one of the key parameters affecting growth is perturbed and this perturbation is sufficiently robust or regular to result in the reorganization of the composition of the biofilm, with the outgrowth of previously minor components (see Fig. 8-1b). Such perturbations can be due to immunologic (e.g. neutrophil dysfunction, immune suppression, etc.) or non-immunologic (e.g. xerostomia, diet change, etc.) factors, and can predispose a site to disease (Marsh & Martin 2009; Marsh *et al.* 2011b), and forms the basis of the "ecological plaque hypothesis" (Marsh 2003) that describes the dynamic relationship between the oral microbiota and the host in health and disease.

Benefits to the host of a resident oral microbiota

The host has a sophisticated array of host defenses provided by both the innate and adaptive arms of the immune system, the primary function of which is to protect tissues against microbial colonization and invasion. Despite these host defenses, the host has evolved over millennia to support a complex resident microbiota and, at first sight, this might appear paradoxical (the "commensal paradox") (Henderson & Wilson 1998). It is now apparent that the resident microbiota confers considerable benefit to the host, and that these natural microbial residents are essential for the normal development of the physiology, nutrition, and defenses of the host (Marsh 2000; Wilks 2007) (Fig. 8-9).

The biologic mechanisms that permit a constructive coexistence between the host and the resident microbiota, while enabling the host to retain the capacity to respond to exogenous microbial insults, are now being dissected. The host is not indifferent to the presence of the diverse microbial communities that reside on its surfaces. It is actively engaged in cross-talk with its resident microbiota in order to effectively maintain a constructive relationship. The host is able to detect microorganisms, and has evolved systems to enable it to tolerate resident microorganisms without initiating a damaging inflammatory response, while also being able to mount an efficient defense against pathogens. Pathogenic and non-pathogenic bacteria may initiate different intracellular signaling pathways and innate immune responses in epithelial cells (Canny & McCormick 2008; Hooper 2009; Neish 2009). Certain oral streptococci have been shown to suppress epithelial cell cytokine expression (Hasegawa *et al.* 2007; Peyret-Lacombe *et al.* 2009). *Streptococcus salivarius* K12 not only down-regulated epithelial cell inflammatory responses by inhibiting the NF-κB pathway,

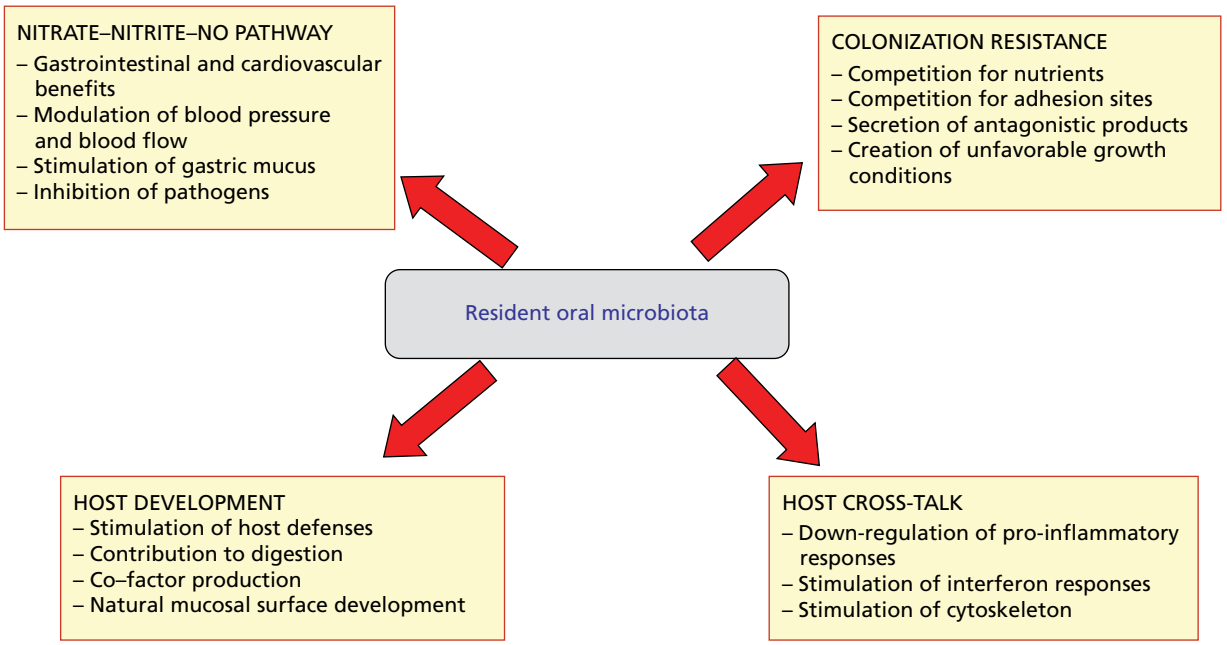

Fig. 8-9 Beneficial functions of the resident oral microbiota.

but also actively stimulated beneficial pathways, including type I and II interferon responses, and exerted significant effects on the cytoskeleton and adhesive properties of the host cell (Cosseau *et al.* 2008). The "commensal communism" paradigm proposes that our oral microbiota and mucosa form a unified "tissue" in which host–microbe "cross-talk" is finely balanced to ensure microbial survival and prevent the induction of damaging inflammation (Henderson & Wilson 1998).

One of the principal benefits emanating from the existence of a resident microbiota at a site is the ability to prevent colonization by exogenous (and often pathogenic) microorganisms. This property, termed "colonization resistance" (Van der Waaij *et al.* 1971), is due to various properties of resident microbes, including more effective (1) attachment to host receptors, (2) competition for endogenous nutrients, (3) creation of unfavorable growth conditions to discourage attachment and multiplication of invading organisms, and (4) production of antagonistic substances (hydrogen peroxide, bacteriocins, etc.). Colonization resistance can be impaired by factors that compromise the integrity of the host defenses or perturb the stability of the resident microbiota, such as the side effects of cytotoxic therapy or the long-term use of broad-spectrum antibiotics (Johnston & Bodley 1972). For example, the latter can suppress the resident bacterial oral microbiota, permitting overgrowth by previously minor populations of oral yeasts. Attempts to boost colonization resistance using replacement therapy (in which resident organisms are deliberately re-implanted), for example after periodontal therapy (Teughels *et al.* 2007) or by the use of probiotics (Devine & Marsh 2009), are being explored, although the evidence for benefits from oral probiotics is still equivocal.

The resident oral bacteria play an important role in maintaining many important aspects of the gastrointestinal and cardiovascular systems, via the metabolism of dietary nitrate. Approximately 25% of ingested nitrate is secreted in saliva where facultatively anaerobic oral resident bacteria reduce nitrate to nitrite. Nitrite affects a number of key physiologic processes, including the regulation of blood flow, blood pressure, gastric integrity, and tissue protection against ischemic injury. Nitrite can be further converted to nitric oxide in the acidified stomach. This has antimicrobial properties and contributes to defense against enteropathogens and in the regulation of gastric mucosal blood flow and mucus formation. Significantly, studies have shown that the use of an antimicrobial mouthwash (Govoni *et al.* 2008; Petersson *et al.* 2009) or a broad-spectrum antibiotic (Dougall *et al.* 1995) reduced the microbial conversion of nitrate to nitrite with a loss of the biologic benefits of nitrite, including reduced gastric mucus thickness and loss of an expected fall in blood pressure.

Concluding remarks

The mouth supports the establishment of diverse communities of microorganisms. These communities, and those present at other habitats in the body, play an active and critical role in the normal development of the host and in the maintenance of health. Clinicians need to be aware of the beneficial functions of the resident oral microbiota, so that treatment strategies are focused on the control rather than the elimination of these natural biofilms. In conclusion, oral care practices should attempt to maintain plaque at levels compatible with health in order to retain the beneficial properties of the resident oral microbiota, while preventing microbial excesses that increase the risk of dental diseases.

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Chapter 9

Dental Calculus

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Dental calculus or tartar represents mineralized bacterial plaque, although calculus formation can be induced in germ-free animals as a result of precipitation of mineral salts originating from saliva (Theilade 1964). Supragingival calculus is located coronal to the gingival margin (Fig. 9-1a), whereas subgingival calculus is found apical to the gingival margin (Fig. 9-1b). Supra- and sub-gingival calculus has characteristic features. It should be noted that calculus continually harbors viable bacterial plaque (Zander *et al*. 1960; Theilade 1964; Schroeder 1969).

Clinical appearance and distribution

Supragingivally, calculus can be recognized as a creamy-whitish to dark yellow or even brownish mass of moderate hardness (Fig. 9-2). The degree of calculus formation is not only dependent on the amount of bacterial plaque present, but also on the secretion of the salivary glands. Hence, supragingival calculus is predominantly found adjacent to the excretion ducts of the major salivary glands, such as the lingual aspect of the mandibular anterior teeth and the buccal aspect of the maxillary first molars, where the parotid gland ducts open into the oral vestibule. The duct openings of the submandibular glands are located in the former region.

Subgingivally, calculus may be found by tactile exploration only, since its formation occurs apical to the gingival margin and, hence, it is usually not visible to the naked eye. Occasionally, subgingival calculus may be visible on dental radiographs provided that the deposits are of sufficient mass (Fig. 9-3). Small deposits or residual deposits following root instrumentation may barely be visualized radiographically. If the gingival margin is pushed open by a blast of air or retracted by a dental instrument, a brownish-to-black calcified hard mass with a rough surface may become visible (Fig. 9-4). Again, this mineralized mass reflects predominantly bacterial accumulations mixed with products from gingival crevicular fluid (GCF) and blood. Consequently, subgingival calculus is found in most periodontal pockets, usually extending from the cementoenamel junction to close to the bottom of the pocket. However, a band of approximately 0.5 mm is usually found coronal to the apical extension of the periodontal pocket (Fig. 9-5). This zone appears to be free of mineralized deposits owing to the fact that GCF is exuding from the periodontal soft tissues and acting as a gradient against the microbial accumulation. This calculus-free zone can also be seen in histologic sections (see Fig. 9-1a, b). Like supragingival calculus, subgingival calculus also provides an ideal substrate for bacterial adhesion (Zander *et al*. 1960; Schroeder 1969).

Plaque mineralization varies greatly between and within individuals and, as indicated earlier, also within the different regions of the oral cavity. Not only the formation rate for bacterial plaque (amount of bacterial plaque per time and tooth surface), but also the formation rate for dental calculus (time period during which newly deposited supragingival plaque with an ash weight of 5–10% becomes calcified and yields an ash weight of approximately 80%) is subject to great variability. In some subjects, the time required for the formation of supragingival

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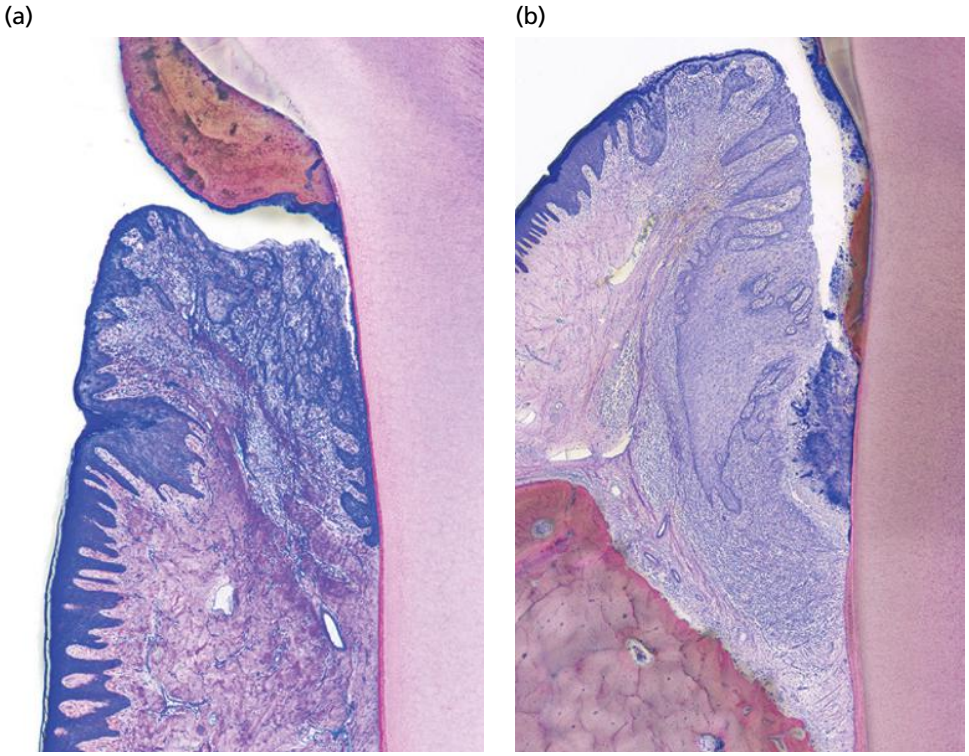


Fig. 9-1 (a) Supragingival calculus adhering to enamel and the root surface of a dog tooth. An initial gingival pocket and a slight gingival inflammation has developed. (b) Subgingival calculus on the root of a dog tooth with a periodontal pocket. Note the inflamed gingival tissue and bone loss. For both supra- and sub-gingival calculus, uncalcified dental plaque extends apically and forms a calculus-free zone between the apical termination of calculus and the apical extension of the pockets. Undecalcified ground sections stained with toluidine blue and basic fuchsin.

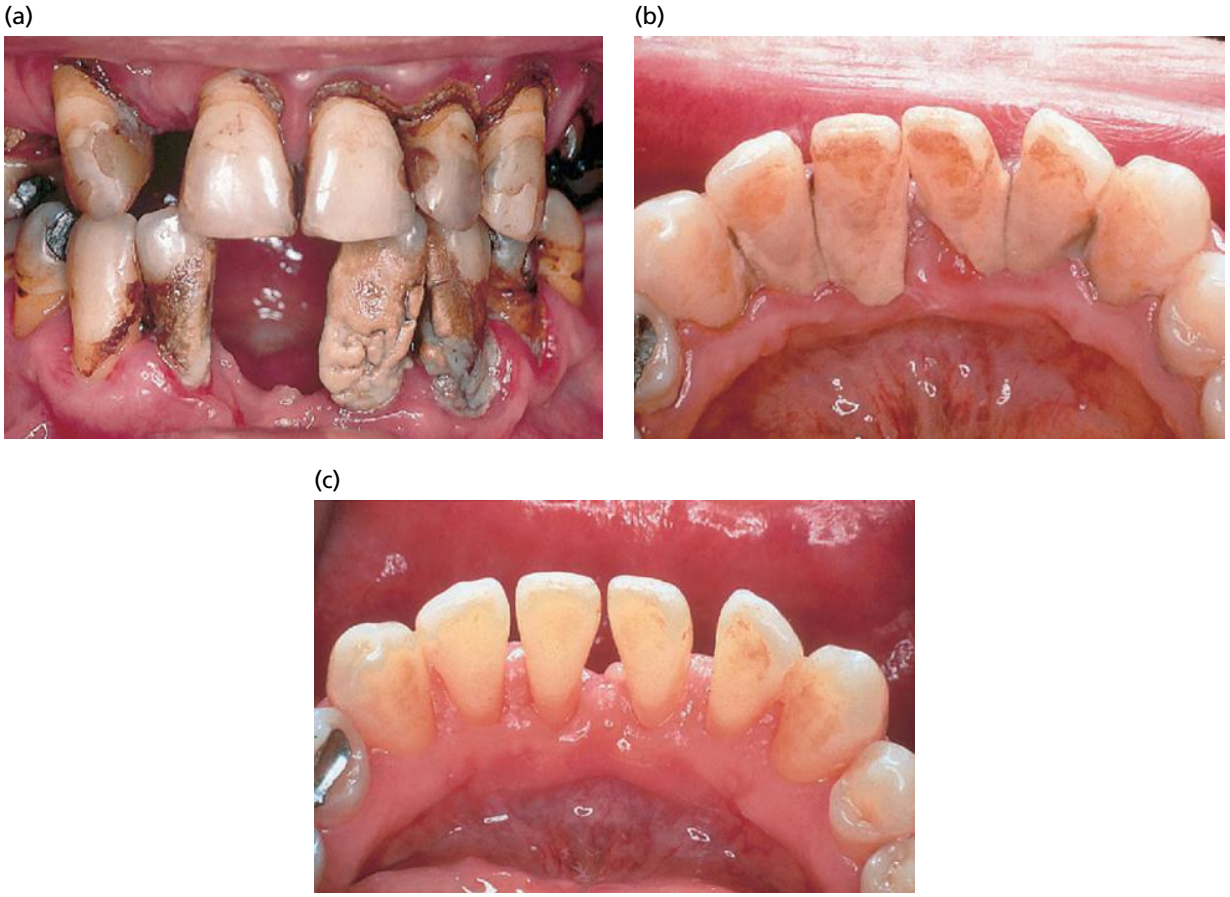


Fig. 9-2 Abundance of supragingival calculus deposits. (a) Gross deposits as a result of long-term neglect of oral hygiene. Two mandibular incisors have been exfoliated. (b) Supragingival plaque usually covering the lingual aspect of mandibular incisors. Note the intense inflammatory reaction adjacent to the deposits. (c) Same patient and region as in (b) following removal of the calculus. The gingival tissues demonstrate healing.

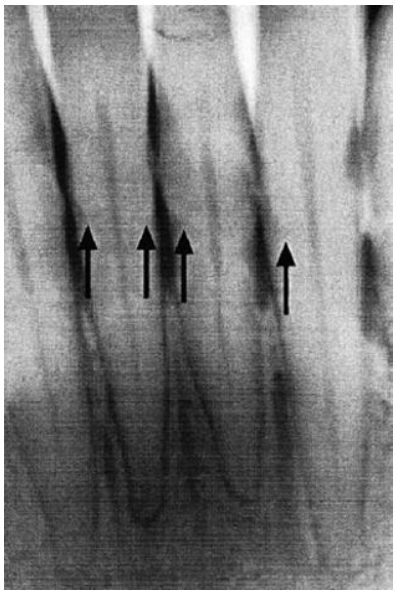
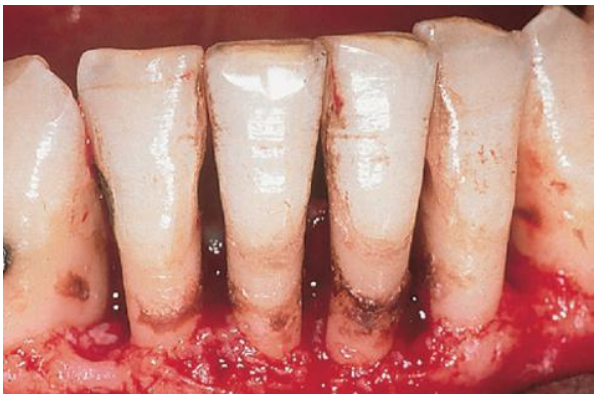


Fig. 9-3 Subgingival calculus may be visible (arrows) on radiographs if abundant deposits are present.

(a)



(b)

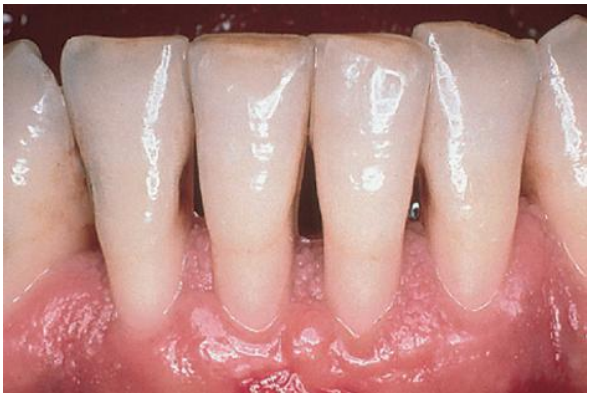


Fig. 9-4 (a) Subgingival calculus presents as a black–brownish hard mass if the gingival margin is retracted or reflected during a surgical procedures. (b) Healing of the site following removal of all hard deposits.

calculus is 2 weeks, at which time the deposit may already contain approximately 80% of the inorganic material found in mature calculus (Fig. 9-6) (Mühlemann & Schneider 1959; Mandel 1963; Mühlemann & Schroeder 1964). In fact, evidence of

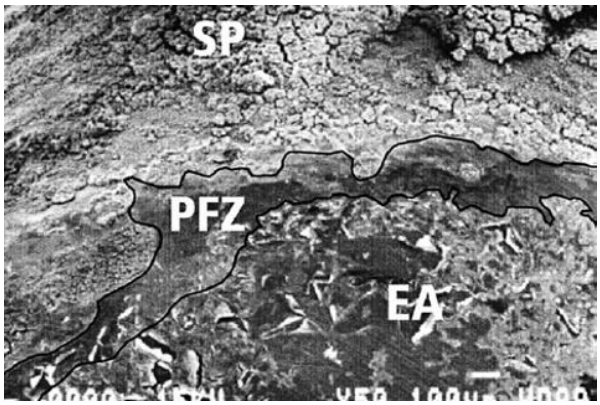


Fig. 9-5 Plaque- and calculus-free zone coronal to the epithelial attachment. (SP, subgingival plaque bacteria; PFZ, plaque-free zone; EA, remnants of junctional epithelium.)

Fig. 9-6 Seven-day-old calcified plaque. Observe the isolated calcification centers indicated by the black areas (van Kossa stain).

mineralization may already be present after a few days (Theilade 1964). Nevertheless, the formation of dental calculus with the mature crystalline composition of old calculus may require months to years (Schroeder & Baumbauer 1966).

Calculus formation and structure

In humans, the formation of calculus is always preceded by the development of a bacterial biofilm (see Chapter 8). The intermicrobial matrix and the bacteria themselves provide the matrix for calcification, which is driven by the precipitation of mineral salts. Supragingival plaque becomes mineralized due to the precipitation of mineral salts present in saliva, whereas subgingival plaque mineralizes due to the presence of mineral salts in the inflammatory exudate passing through the pocket. It is, therefore, evident that subgingival calculus represents a secondary product of infection and not a primary cause of periodontitis.

Mineralization starts at crystallization foci in the intermicrobial (intercellular) matrix and on the bacterial walls (Fig. 9-7), and eventually proceeds inside the bacteria (Fig. 9-8) (Zander *et al*. 1960). The detection of lactate dehydrogenase, alkaline and acid phosphatase activities, and various extracellular matrix proteins in plaque suggests that calculus formation is not merely

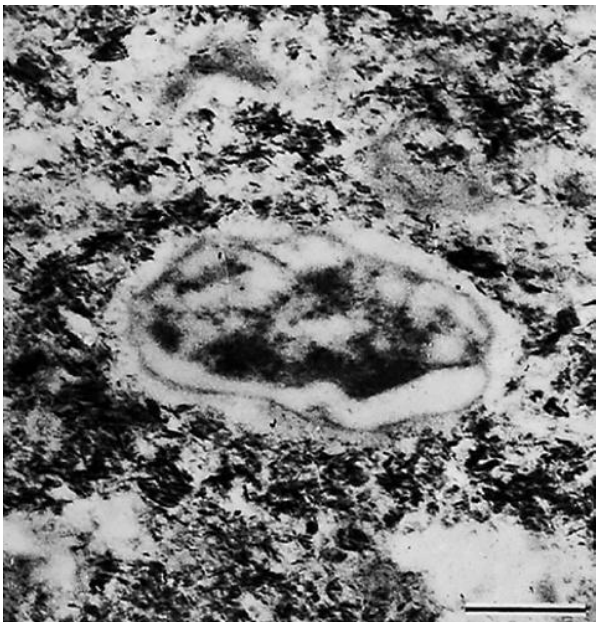


Fig. 9-7 Thin section of old plaque. A degenerating organism is surrounded by intermicrobial matrix in which initial mineralization has begun with the deposition of small needle-shaped electron-dense apatite crystals. ×26 500. Bar: 0.5 μm. (Source: Zander *et al*. 1960. Reproduced with permission from Sage.)

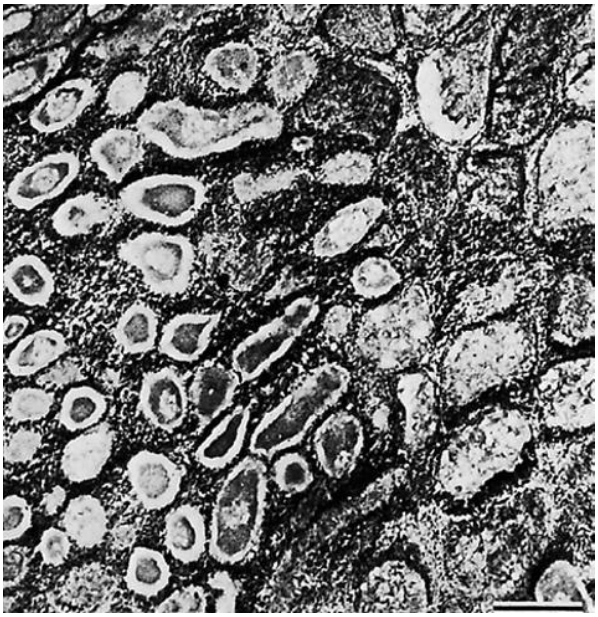


Fig. 9-8 Thin section of old mineralizing plaque. The intermicrobial matrix is totally calcified, and many microorganisms show intracellular crystal deposition. ×9500. Bar: 1 μm. (Source: Theilade 1964.)

a passive mineralization process. Bacterial enzymes (Friskopp & Hammarström 1982), calcium phosphate supersaturation, cell membrane-associated constituents, and inactivation of nucleation inhibitors (Jin & Yip 2002) may all be involved in the initiation and regulation of plaque calcification. Osteopontin and bone sialoprotein (Fig. 9-9), two non-collagenous extracellular matrix proteins involved in the mineralization of bone and cementum, have indeed been immunodetected in human calculus, but not in the unmineralized dental plaque. Osteopontin and bone sialoprotein are present in blood plasma and osteopontin has been identified in GCF and calculus. Their presence in the intermicrobial matrix and at the surface of bacteria suggests an involvement in the regulation of mineralization.

The progression of mineralization in an incremental pattern from the inner zones of the bacterial plaque outward may produce concentric rings, called Liesegang rings, that reflect successive phases of mineralization. Furthermore, the presence of numerous mineralization foci, from which mineralization spreads and which partially coalesce, may leave some unmineralized areas and thus account for the porous nature of calculus whose cavities and channels are filled with uncalcified plaque (see Fig. 9-6).

Attachment to tooth surfaces and implants

Dental calculus generally adheres tenaciously to tooth surfaces. Hence, the removal of subgingival calculus may be expected to be rather difficult. The reason for this firm attachment to the tooth surface is the fact that the pellicle beneath the bacterial plaque also calcifies. This, in turn, results in an intimate contact with enamel (Fig. 9-10), cementum (Fig. 9-11) or dentin crystals (Fig. 9-12) (Kopczyk & Conroy 1968; Selvig 1970). In addition, the surface irregularities are also penetrated by calculus crystals and, hence, calculus is virtually locked onto the tooth. This is particularly the case on exposed root cementum, where small pits and irregularities occur at the sites of the previous insertion of Sharpey's fibers (Bercy & Frank 1980). Uneven root surfaces may be the result of carious lesions and small areas of cementum may have been lost due to resorption, when the periodontal ligament was still invested into the root surface (Moskow 1969). Under such conditions it may become extremely difficult to remove all calculus deposits without sacrificing some hard tissues of the root.

Although some irregularities may also be encountered on oral implant surfaces, the attachment to commercially pure titanium generally is less intimate than to root surface structures. This in turn means that calculus may be chipped from oral implants (Fig. 9-13) without detriment to the implant surface (Matarasso *et al*. 1996). Excess cement at the crown–abutment interface has been associated with peri-implant disease (Pauletto *et al*. 1999; Gabski *et al*. 2008; Wilson 2009). The rough surface of the cement may provide a plaque/calculus retention site, which can lead to peri-implant disease (Lang *et al*. 2004). Overhang at such sites (Fig. 9-14) may impede calculus removal. It has been shown that clinical and endoscopic signs of peri-implant disease were absent in the majority of cases after removal of excess cement (Wilson 2009).

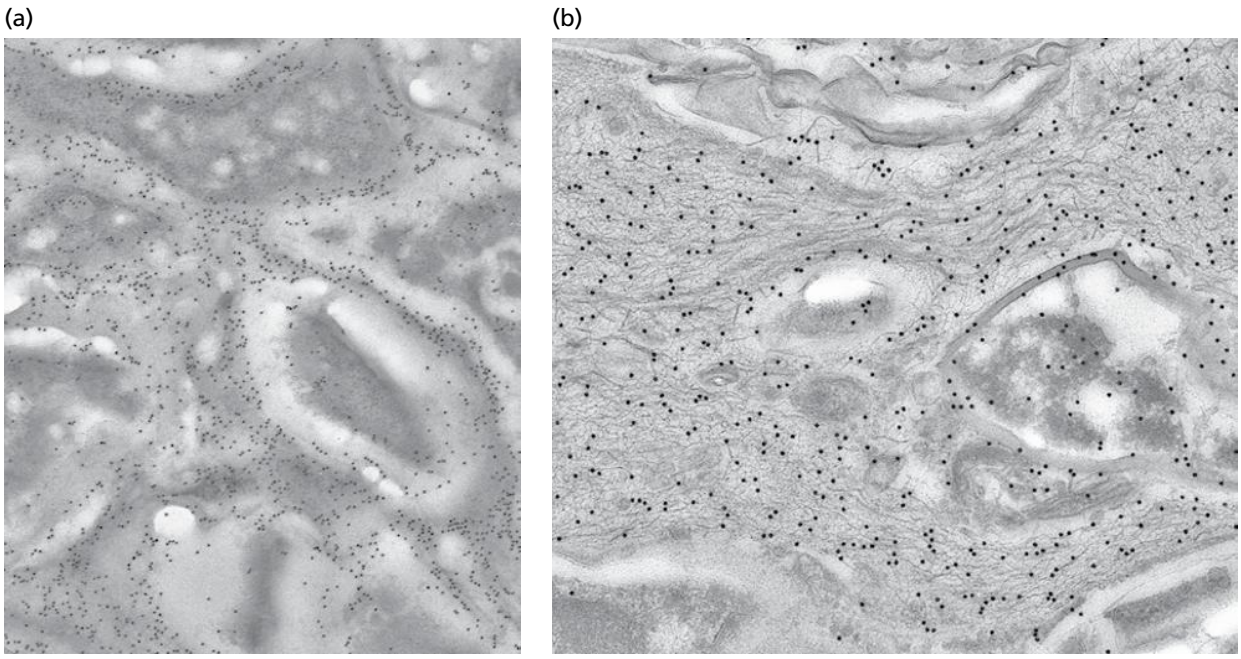


Fig. 9-9 Immunolabeling of calculus on a human tooth root with an antibody against bone sialoprotein. (a) Predominant gold particle labeling of the bacterial cell walls in the inner portion of calculus. (b) Labeling over extensive intermicrobial filamentous matrix. Ultrathin sections viewed under the transmission electron microscope.

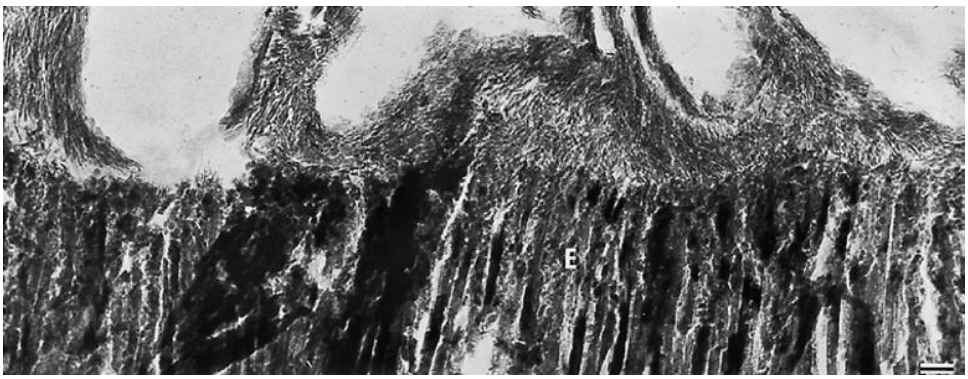


Fig. 9-10 Thin section of enamel surface (E) with overlying calculus. The enamel and calculus crystals are in intimate contact, and the latter extends into the minute irregularities of the enamel. ×37 500. Bar: 0.1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

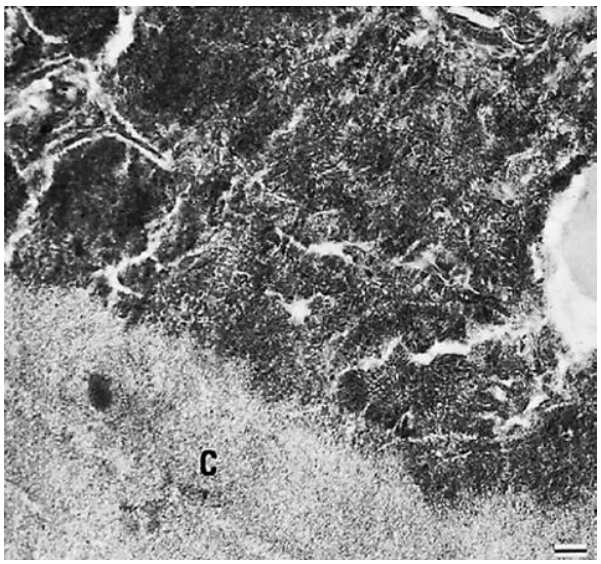


Fig. 9-11 Thin section of cementum surface (C) with overlying calculus. The calculus is closely adapted to the irregular cementum and is more electron dense and therefore harder than the adjacent cementum. To the right, part of an uncalcified microorganism. ×32 000. Bar: 0.1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

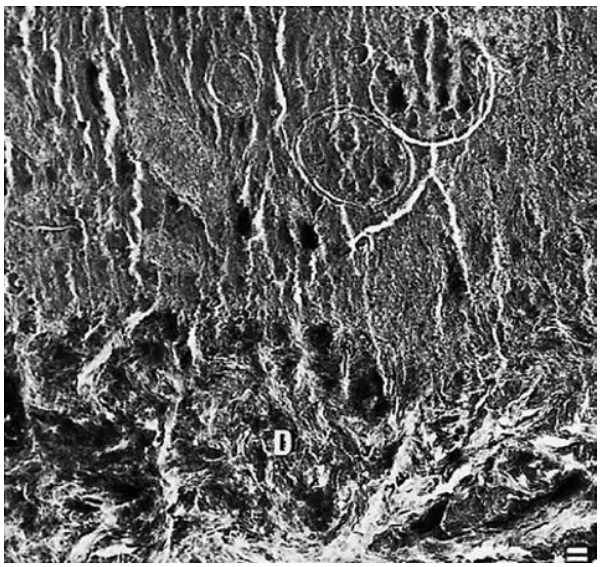


Fig. 9-12 Thin section of dentin (D) surface with overlying calculus. The interface between the calculus and dentin cannot be precisely determined because the calculus crystals fill the irregularities of the dentin surface, which is devoid of cementum as a result of a previous scaling of the root surface. The circular profiles in the calculus completely surround calcified bacteria. ×19 000. Bar: 1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

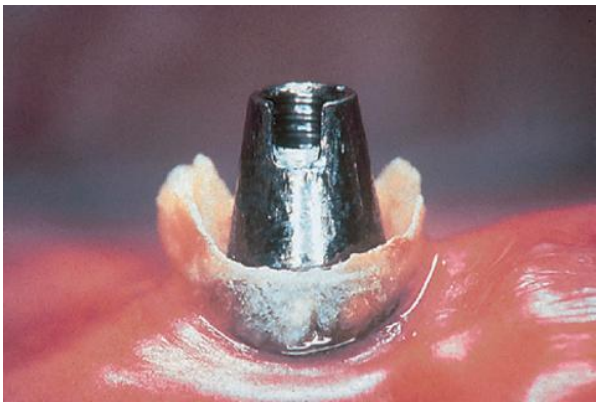


Fig. 9-13 Calculus deposit on an oral implant in a patient without regular maintenance care.

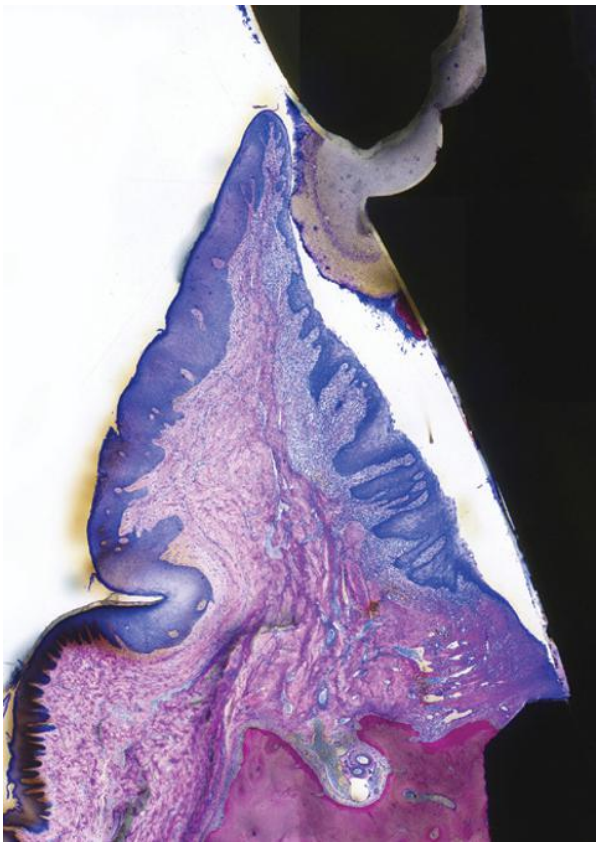


Fig. 9-14 Excess cement at the abutment–crown interface provides an ideal substrate for plaque and calculus deposition and retention. Bacterial plaque covers the entire surface of the cement, whereas calculus is present apical to the cement overhang. Detachment of the epithelium indicates pocket formation. The detachment of the apical-most portion of the epithelium, however, may represent an artifact due to histologic processing. Undecalcified ground section stained with toluidine blue and basic fuchsin.

Calculus composition

Recent and old calculus consists of four different crystals of calcium phosphate [for review see Schroeder (1969) and Jepsen *et al*. (2011)]:

1. $CaH(PO_4) \times 2H_2O$ = brushite (B)
2. $Ca_4H(PO_4)_3 \times 2H_2O$ = octa calcium phosphate (OCP)
3. $Ca_5(PO_4)_3 \times OH$ = hydroxyapatite (HA)
4. $\beta\text{-}Ca_3(PO_4)_2$ = whitlockite (W).

X-ray diffraction studies suggest that mineralization begins with the deposition of OCP and dicalcium phosphate dehydrate (DCPD), followed by less soluble HA and W (Rowles 1964; White 1997).

Supragingival calculus is clearly built up in layers and shows a great heterogeneity from one layer to another with regard to mineral content. On average, the mineral content is 37%, but ranges from 16% to 51%, with some exceptional layers having a maximal density of minerals of up to 80% (Kani *et al*. 1983; Friskopp & Isacsson 1984). The predominant mineral in exterior layers is OCP, while HA is dominant in the inner layers of old calculus. W is only found in small proportions (Sundberg & Friskopp 1985). B is identified in recent calculus, not older than 2 weeks, and appears to form the basis for supragingival calculus formation. Each type of crystal has a characteristic appearance: OCP forming platelet-like crystals for OCP; HA forming sandgrain or rod-like crystals, and W forming hexagonal (cuboidal, rhomboidal) crystals for W (Kodaka *et al*. 1988).

Subgingival calculus appears somewhat more homogeneous since it is built up in layers of equally high mineral density. On average, the density is 58% and ranges from 32% to 78%. Maximal values of 60–80% have been found (Kani *et al*. 1983; Friskopp & Isacsson 1984). The predominant mineral is always W, although HA has been found (Sundberg & Friskopp 1985). W contains small proportions (3%) of magnesia (McDougall 1985).

In the presence of a relatively low plaque pH and a concomitant high Ca/P ratio in saliva, B is formed and this may later develop into HA and W. When supragingival plaque mineralizes, OCP forms and is gradually changed into HA. In the presence of alkaline and anaerobic conditions and concomitant presence of magnesia (or Zn and CO_3), large amounts of W are formed in a stable form of mineralization.

Clinical implications

Although strong associations between calculus deposits and periodontitis have been demonstrated in experimental (Wærhaug 1952, 1955) and epidemiologic studies (Lövdal *et al*. 1958), it has to be realized that calculus is always covered by an unmineralized layer of viable bacterial plaque. It has been debated whether or not calculus may exert a detrimental effect on the soft tissues owing to its rough surface. However, it has clearly been established that surface roughness alone does not initiate gingivitis (Wærhaug 1956). In monkeys a normal epithelial attachment with the junctional epithelial cells forming hemidesmosomes and a basement membrane on calculus could be observed if the calculus surface was disinfected using chlorhexidine (Fig. 9-15) (Listgarten & Ellegaard 1973). Furthermore, it has been demonstrated that autoclaved calculus may be encapsulated in connective tissue without inducing marked inflammation or abscess formation (Allen & Kerr 1965).

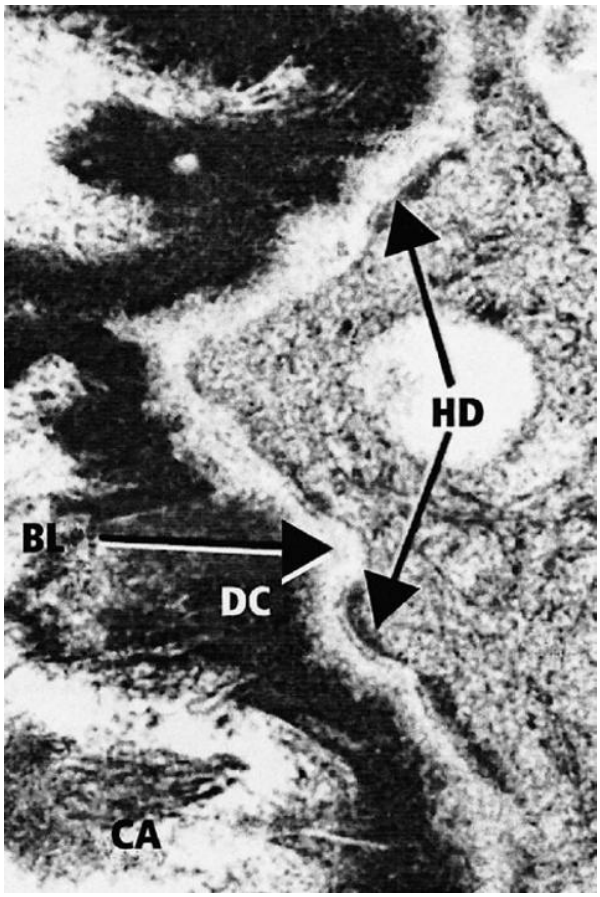


Fig. 9-15 Hemidesmosomal attachment of junctional epithelium on dental calculus in the absence of bacteria following application of chlorhexidine. (CA, calculus; HD, hemidesmosomes; BL, basement lamina; DC, dental cuticle.) ×32 000. (Data from Listgarten & Ellegaard 1973).

These studies clearly exclude the possibility of dental calculus being a primary cause of periodontal diseases. Calculus seems to have a secondary effect by providing a surface configuration conducive to further plaque accumulation and subsequent mineralization.

Nevertheless, calculus deposits may develop in areas that are difficult to access for oral hygiene or may, depending on their size, jeopardize proper oral hygiene practices. Calculus may also amplify the effects of bacterial plaque by keeping the bacterial deposits in close contact with the tissue surface, thereby influencing both bacterial ecology and tissue response (Friskopp & Hammarström 1980).

Well-controlled animal (Nyman *et al*. 1986) and clinical (Nyman *et al*. 1988; Mombelli *et al*. 1995) studies have shown that the removal of subgingival plaque on top of subgingival calculus results in healing of periodontal lesions and the maintenance of healthy gingival and periodontal tissues, provided that the removal is meticulous and done on a regular basis. One of these studies (Mombelli *et al*. 1995) clearly demonstrated that microbiota composition and clinical parameters following the diligent and complete removal of subgingival plaque on top of mineralized deposits after chipping off gross amounts of calculus were almost identical to those obtained with routine removal of subgingival calculus by root surface instrumentation. Again, it has to be realized that meticulous supragingival plaque control guarantees the depletion of the supragingival bacterial reservoir for subgingival recolonization. These studies have clearly elucidated the role of subgingival calculus as a plaque-retaining factor.

The presently available techniques used to remove deposits on the root surface cannot completely eliminate all calculus from diseased root surfaces. Factors such as anatomy, probing depth, instruments, and operator experience influence the efficacy of subgingival calculus removal (Jepsen *et al*. 2011). Some agents have been proven to reduce calculus formation (Jepsen *et al*. 2011). However, their effects appear to be limited to supragingival calculus and complete prevention cannot be achieved with them.

Conclusion

Dental calculus represents mineralized bacterial plaque. It is always covered by unmineralized viable bacterial plaque, and hence, does not directly come into contact with the gingival tissues. Calculus, therefore, is a secondary etiologic factor for periodontitis. Its presence, however, makes adequate plaque removal impossible and prevents patients from performing proper plaque control. It is the most prominent plaque-retentive factor that has to be removed as a basis for adequate periodontal therapy and prophylactic activities.

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Chapter 10

Periodontal Infections

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Introduction

Our mucosal surfaces are colonized by complex communities of microorganisms, or microbiotas, which are uniquely adapted to the different environmental niches in the human body. These microbiotas are composed of distinct and specialized microorganisms which are characteristic of the respective niche, for example the mouth, the gastrointestinal or the genitourinary tract (Fig. 10-1). Collectively the microbiotas on our mucosal surfaces and other anatomic locations in the body comprise the human microbiome, which has become an area of intensive investigation in recent years because of the recognition that the balance between these organisms and the human host plays a fundamental role in our biology, the maintenance of our health, and the development of disease.

The intestinal microbiota, for example, has a profound impact on human physiology, metabolism, local tissue organization, and the development of the immune system. Its composition is heavily influenced by the host genotype and is also dynamic and subject to variation due to environmental factors, including diet, antibiotic usage, and the introduction of pathogenic microorganisms. In some instances, changes in the ecologic balance of the microbiota lead to changes in the bacterial diversity, outgrowth of potentially pathogenic bacteria, and loss of bacterial species normally beneficial to the host (Round & Mazmanian 2009). An unfavorable alteration of the microbiota composition is called *dysbiosis* (Hill & Artis 2010). It has become increasingly evident that alterations to the normally balanced microbial populations at different sites of the human body may have a profound effect on human health (Frank *et al.* 2011). Diseases and conditions which have been linked to dysbiosis of the commensal microbiota include antibiotic-associated diarrhea (Young & Schmidt 2004; Chang *et al.* 2008), bacterial vaginosis (Fredricks *et al.* 2005; Oakley *et al.* 2008), celiac disease (De Palma *et al.* 2011), esophageal disease (Pei *et al.*, 2005), Crohn's disease and ulcerative colitis (Frank *et al.* 2007; Packey & Sartor 2009; Willing *et al.*, 2009, 2010), irritable bowel syndrome (Mättö *et al.* 2005; Kassinen *et al.* 2007; Codling *et al.* 2010), necrotizing enterocolitis (Wang *et al.* 2009), and psoriasis (Paulino *et al.* 2006). More surprisingly however, dysbiosis of the commensal microbiota has also been linked to obesity (Ley *et al.* 2005, 2006; Zhang *et al.* 2009), colorectal cancer (Scanlan *et al.* 2008; Sobhani *et al.* 2011), and metabolic syndrome. Moreover, the *functional* importance of dysbiosis of a mucosal microbiota is now becoming clearer through studies which have demonstrated that several diseases, including obesity, metabolic disorders, and inflammatory bowel conditions, can be transmitted via the transfer of dysbiotic microbiota in animal model systems (Garrett *et al.* 2010).

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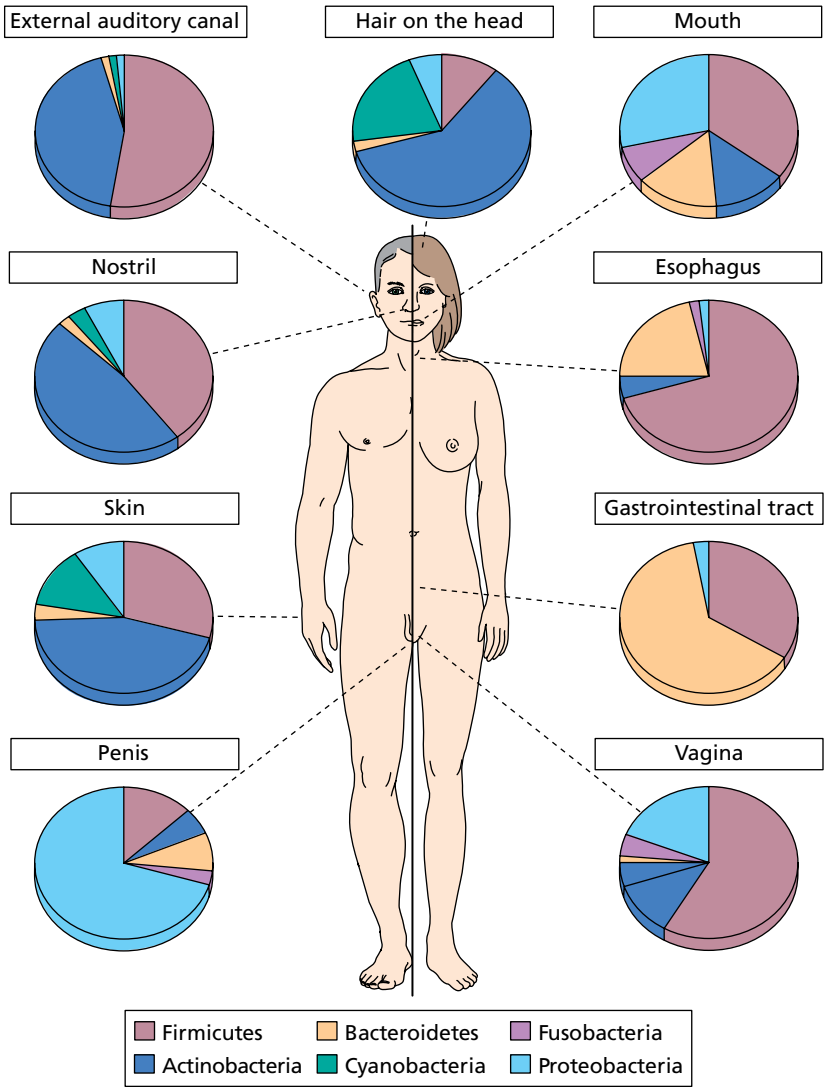


Fig. 10-1 Relative abundances of the six dominant bacterial phyla in each of the different body sites: the external auditory canal, the hair on the head, the mouth, the esophagus, the gastrointestinal tract, the vagina, the penis, the skin, and the nostril. (Source: Spor *et al*. 2011. Reproduced with permission from Macmillan Publishers Ltd.)

Of all the environmental niches in the human body, the oral cavity provides an optimal habitat for the growth of bacteria: a stable temperature, constant moisture, an abundant supply of nutrients, and, uniquely, the hard surfaces of the teeth. The evolutionary forces which shaped the development of a calcified dentition of animals, including humans, have introduced a developmental weak spot from the perspective of infectious disease: nowhere else in the human body is the normally contiguous epithelial barrier of the mucosal surfaces breached by a solid, non-shedding structure which permits the development of a microbial biofilm in direct contact with the adjacent soft tissues. The defense against this challenge, which has co-evolved with the development of calcified tissues protruding through the mucosal barrier, is a sophisticated set of specialized anatomic features, innate immune and inflammatory responses. Furthermore, this site in the human body actively promotes the selection of a unique microbiota which normally is both tolerated by the adjacent tissues and provides protection from microorganisms deleterious to the healthy status of the tooth-supporting apparatus. Disease of the periodontal tissues can therefore be viewed as a breakdown of this balanced homeostasis between the host tissues and the resident microbiota.

Analysis of the human oral microbiome extends back through history to the very first microscopic observations of bacteria by Antonie van Leeuwenhoek in 1665 and continues apace to this day through the application of high throughput DNA sequencing techniques which are beginning to yield a description of this microbiota in extraordinary detail. This centuries-old tradition of oral microbiologic analysis has placed our knowledge of the bacterial communities of the mouth at the very leading edge of our understanding of the human microbiome. From these investigations, it is clear that the phenomenon of dysbiosis, or a deleterious alteration to the microbiota, is a fundamental characteristic of periodontal disease.

In addition to dysbiosis, several other characteristics of this microbiota need to be considered to properly appreciate the role of bacteria in periodontal disease. First, the growth of these organisms in a subgingival biofilm leads to a number of characteristics which define the biology of these organisms and can present a unique challenge to the adjacent tissues. These include: inter-bacterial nutritional dependencies and communication; the development of specific consortia of different bacterial species which may act cooperatively in the presentation of a microbial challenge; an optimal environment for genetic exchange between different species; and resistance to the immune and inflammatory clearance mechanisms of the host and to chemical antimicrobial agents. A more detailed description of the consequences of the biofilm lifestyle adopted by dental plaque bacteria is given in Chapter 8.

Second, analysis of the population structure of some of the bacterial species associated with periodontal disease reveals significant genetic differences which, in some instances, have a defining role in the pathogenic variation within an individual species. Third, analysis of the properties of bacterial species frequently present in a dysbiotic periodontal microbiota has demonstrated that the ability to successfully manipulate elements of the innate and inflammatory response is a common characteristic of these microorganisms and may indeed represent an overriding principle of periodontal virulence.

Analysis of the microbiology of periodontal disease has been undertaken by very many investigators, beginning with the very first microscopic identification of bacteria as unicellular organisms over 300 years ago. Examination of the medical publication databases reveals that over 10 000 research papers have been written on the subject of periodontal infections over the last 50 years and hence the current chapter can only be a highly selective representation of this literature. The aim is to present an overview of our current understanding of the composition and properties of the periodontal microbiota, and to provide a conceptual framework to understand the mechanisms and consequences of dysbiosis of this microbial community and the influence that this process has on the development of periodontal disease.

Dysbiosis of the oral microbiota in periodontal disease

The underlying principles of infectious disease, first enunciated by Louis Pasteur and subsequently proven by Robert Koch, provided the essential framework for the identification of microorganisms responsible for diseases of a monospecific etiology. Koch's postulates provide four criteria which should be met in order to identify an infectious agent as a disease causing agent: (1) found in abundance in all organisms suffering from the disease, but not found in healthy organisms; (2) isolated from a diseased organism and grown in pure culture; (3) causes disease when the cultured microorganism is introduced into a healthy organism; and (4) re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. Whilst these principles have undergone significant revisions since their introduction and have been updated into a molecular interpretation by Falkow (1988), they underpinned the discovery of the causative agents of very many medically important infections throughout the mid-19th and early 20th centuries. Koch himself applied these criteria to the discovery of *Mycobacterium tuberculosis* and *Bacillus anthracis* – the causative agents of tuberculosis and anthrax, respectively.

However, in the case of diseases involving a complex microbial etiology, where the fundamental basis is one of dysbiosis, or perturbation of a normal commensal microbiota, the description of the infectious challenge is more demanding. Here, the accuracy of the description is intimately linked to the effectiveness of the technology available to quantitatively and qualitatively determine the composition of a complex microbial mixture. In that sense, our understanding of the periodontal microbiota has undergone sequential stepwise changes over time following the introduction and application of increasingly more sophisticated and higher throughput methods for bacterial characterization and identification (Fig. 10-2).

These studies extend back over three centuries to the very first description of bacterial cells by Antonie van Leeuwenhoek, who in 1676 using the newly invented microscope described the "animacules" in the biofilms from human teeth. In the intervening period, our understanding of the complexity, site specificity, and environmentally driven nature of these microbial communities has expanded with each technological advance in microbial identification and classification. Advances have accompanied the introduction of standardized cultural techniques on solid media, the development of anaerobic culture systems, the introduction of non-cultural techniques for bacterial identification, and the use of molecular phylogeny through nucleic acid analyses using DNA–DNA hybridization, the polymerase chain reaction (PCR), Sanger DNA sequencing, and the more recent developments in high throughput pyro-sequencing and metagenomics (Wade 2011). These cultural and non-cultural investigations have now culminated in the development of the Human Oral Microbiome Database (http://www.homd.org), which lists all bacterial species found in the human mouth (Dewhirst *et al.*, 2010), and more recently CORE (http://microbiome.osu.edu) (Griffen *et al.*, 2011), a phylogenetically curated 16S rDNA database of the core oral microbiome representative of the bacteria which regularly reside in the human oral cavity.

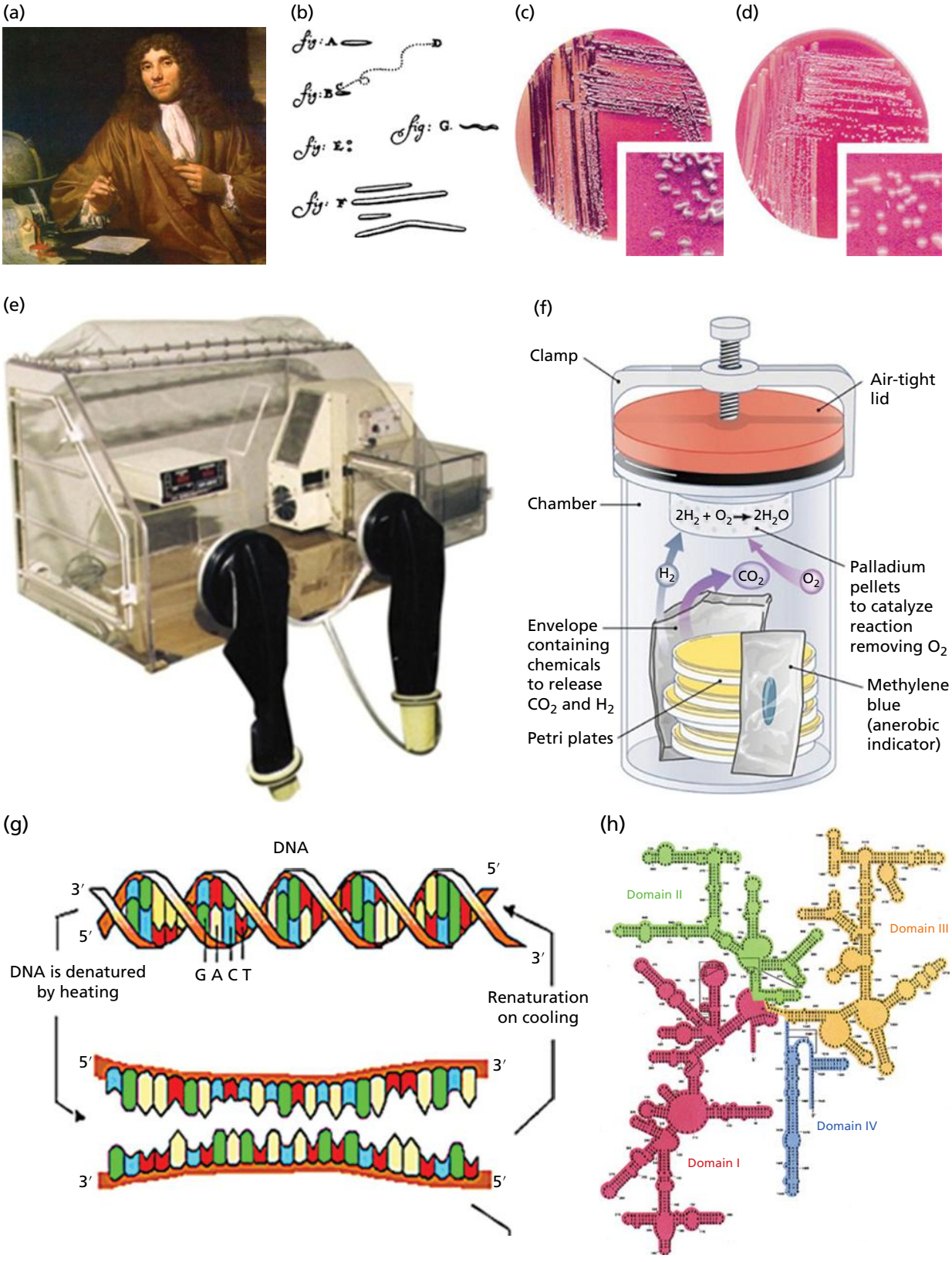


Fig. 10-2 Technological advances linked to increased understanding of the oral microbiota. Appreciation of the complexity of the oral microbiota has increased with the development of technology. Microscopy: (a) Antonie van Leeuwenhoek who used the first microscopes to characterize dental plaque bacteria (b). Bacterial culture on solid media: (c) *Porphyromonas gingivalis* grown on blood agar and (d) a non-pigmenting mutant of *P. gingvalis*. *Anaerobic microbiology:* (e) Anaerobic chambers and (f) anaerobic jars enabled the culture of bacteria whose growth is inhibited by oxygen. *Molecular techniques for bacterial identification*: (g) DNA–DNA hybridization and (h) sequence analysis of the variable regions of the *16S rRNA* gene allow for the identification and quantitation of bacteria in the absence of culture.

Early microscopic and cultural microbiology investigations

The progress made in describing the etiologic agents of infectious diseases in the late 19th and early 20th century naturally led to a search for the causative organisms involved in periodontal infections. These investigations were restricted by the techniques available for visual inspection of subgingival samples or by the relatively primitive cultural techniques that had been developed at this early stage of the discipline of microbiology. Socransky and Haffajee (1994) summarized the findings of these early investigations into the description of four potential groups of etiologic agents.

First, on the basis of cultural microbiologic studies, the streptococci were proposed to be important microorganisms in the disease process. This was perhaps an inevitable conclusion given that the cultural techniques in common use during this period were limited in terms of the diversity of organisms capable of being detected and the streptococci were most probably the only group which was reliably grown. As an indication of the relatively primitive status of bacterial taxonomy at the time, it is worth noting that in the early part of the 20th century there was still significant debate about whether or not "the streptococci" represented just a single bacterial species. Only upon the development of more discriminatory techniques did the heterogeneity within the streptococci, which is now a hallmark of this genus, become apparent. For example, Gordon (1905) stated that "the differential tests which I have recommended in previous reports and applied in recent years to the careful study of "strepto-biology" of milk, saliva, water, excremental matters, and morbid and other materials afford in my opinion a definite basis (hitherto lacking) upon which to classify streptococci. Briefly, the doctrine of the unity of streptococci has arisen chiefly from inability of the use of older laboratory tests to discriminate between species."

The other three groups of organisms which were considered to be potential agents of periodontal disease were all described on the basis of microscopy. Stained smears of dental plaque revealed the presence of ameba, and it was reported that there were higher levels of these organisms in samples taken from periodontal lesions compared to those taken from healthy mouths or those with gingivitis. Wet mount preparations or specific staining techniques enabled the visualization of spirochetes and it was suggested that the levels of these bacteria were positively associated with periodontal disease. Finally, fusiform bacteria, readily detectable because of their characteristic large, spindle-like cellular morphology by light microscopy, were also implicated in the disease process, in particular in acute necrotizing ulcerative gingivitis, which appeared to be a relatively common disease in the early part of the 20th century, particularly among troops in World War I, referred to as "trench mouth".

For each of these agent types however, further investigations – based on comparable studies in other patient groups or the use of treatment regimens designed to specifically target these organisms – failed to reliably support the contention that these organisms explained the microbiologic basis of the disease. This may have reflected the fact that the microbial etiology of periodontal disease varies between individuals and is multifactorial within an individual, as well as the problem that these early investigations were so highly dependent on the analytical tools available at that time. Probably as a result of the inability to accurately define the etiologic agent(s) of the disease, in contrast to the great strides being made elsewhere in describing the causative organisms in the major, monospecific infectious diseases, there was a loss of impetus in microbiologic research into periodontal infections in the early decades of the 20th century.

Nonetheless, it was apparent to the clinicians treating the disease that control of dental plaque was of critical importance both to treatment and to prevention. As a consequence, the notion of a non-specific etiology came to the forefront. The "non-specific" plaque hypothesis suggested that accumulations of microorganisms at or below the gingival margin would produce irritants leading to inflammation, which in turn would lead to periodontal tissue destruction. In this scenario, although bacteria were recognized to be important in the etiology of the disease, the critical factor was their total number, and the resultant magnitude of the challenge they presented to the host tissues, rather than the precise species of bacteria that were present. Alternative hypotheses which describe a more specific etiology will be described in the final section of this chapter.

Advent of anaerobic microbiologic techniques

A major breakthrough in our understanding of the complexity of the periodontal microbiota was achieved through the introduction of methods which allowed the laboratory culture of anaerobic microorganisms. The low oxygen levels in the subgingival biofilm are highly permissive for the growth of obligately anaerobic bacteria and hence a significant fraction of the total periodontal microbiota would have been largely undetected in previous microbiologic investigations conducted under aerobic conditions. This technological advance included the use of anaerobic roll tubes and anaerobic jars which could be flushed with oxygen-free gases and then sealed to prevent the access of air. More latterly, anaerobic chambers were developed which enabled the culture of anaerobic bacteria on both solid and liquid media in a relatively spacious, low oxygen environment periodically flushed with a mixture of nitrogen, carbon dioxide, and hydrogen.

These studies were pioneered by several oral microbiology laboratories throughout the 1970s and 1980s (Socransky *et al.* 1963; Socransky 1970; Slots 1976, 1977; Tanner *et al.* 1979; Slots & Rosling 1983; Haffajee *et al.* 1984; Christersson *et al.* 1985; Dzink *et al.* 1985; Loesche *et al.* 1985; Dzink *et al.* 1988; Haffajee *et al.* 1988; van Winkelhoff *et al.* 1988; Zambon *et al.* 1988; Tanner & Bouldin 1989; Zambon *et al.* 1990; Slots *et al.* 1991; Socransky & Haffajee 1994).The highly labor intensive nature of the methodology meant these studies were usually limited to the analysis of relatively few periodontal subjects. Importantly, however, these investigations began to put clear definition to the very significant qualitative differences in the overall microbiota present at periodontally diseased sites compared to control healthy sites and to identify some of the key, characteristic organisms which were frequently associated with disease. The exhaustive investigations conducted in the Virginia Polytechnic Institute laboratories of Holdeman and Moore (Moore *et al.* 1983, 1985; Moore 1987) were typical of these investigations and are among the most influential studies of the total, cultivatable, anaerobic microbiota. These authors brought the techniques developed in their investigations of the anaerobic microbiota of the intestine to the study of the periodontal microbiota. In a series of publications, throughout the 1980s in particular, they described the bacteriology of chronic and severe periodontal disease in adults, the bacteriology of experimental gingivitis and juvenile periodontitis in young adults, and the stability of the periodontal microbiota over time. Typically these investigations involved sampling the subgingival microbiota at one or more diseased sites in an individual as well as at adjacent control supragingival sites, followed by culture on selective and non-selective media in anerobic roll tubes or jars and, later, in anerobic chambers. Discrete colonies were then isolated and the identity of the resultant pure isolate was established on the basis of a variety of morphologic, serologic, and biochemical techniques. A single study would frequently involve the isolation and characterization of literally thousands of isolates in order to build a complete picture of the total cultivatable microbiota. These were heroic investigations involving laborious and time-consuming methodologies. For example, in their investigation of the bacteriology of severe generalized periodontitis in 21 individuals, they described the isolation and characterization using biochemical techniques of 2723 individual isolates representing 190 bacterial species, subspecies, or serotypes (Moore *et al.* 1982). Of these, 11 species exceeded 1% of the subgingival flora and were most closely associated with the diseased sulci and 11 others were also sufficiently frequently isolated to be suspected as agents of tissue destruction.

An example of the outcome of these investigations can be seen in Table 10-1, which shows the types of cultivatable bacteria that were more numerous in subgingival compared to supragingival plaque samples in young adults with advanced periodontal disease, and conversely those which were more numerous in supragingival samples. This study highlights the marked difference between the overall microbiota in periodontally diseased, subgingival sites compared to the adjacent supragingival microbiota. Whilst the supragingival microbiota is dominated by the actinomyces, streptococci, and veillonella, which comprise some 40% of the total cultivatable bacteria, the same genera represent only approximately 10% of the subgingival organisms. Conversely, members of the bacteroides and fusobacteria represent approximately 20% of the subgingival microbiota, but only approximately 5% of the supragingival microbiota.

Studies of this kind began to convincingly reveal the sheer complexity of the microbiota in periodontal disease to a level that had hitherto been unseen. A reference catalog of bacterial taxa began to develop and this would prove invaluable for later investigations. Furthermore, there were some important additional messages. First, as is evident in Table 10-1, frequently those bacteria which are significant components of the subgingival plaque from diseased sites are also present, albeit at reduced levels, in supragingival samples, and *vice versa*. Indeed, other studies demonstrated that many of the bacteria positively associated with the microbiota at a diseased subgingival site were also present in healthy subgingival sites.

These investigations indicated that a specific etiology for the periodontal disease process could only be explained on the basis of a quantitative rather than solely qualitative perspective. To gain sufficient power to address the nature of the etiology it would be necessary to perform studies involving significantly more samples/subjects than was feasible by this total microbiologic analysis approach, which was typically restricted to investigations on relatively small numbers of individuals. However, these large-scale anaerobic microbiologic analyses on a relatively few samples had provided several valuable, potential "specific periodontal pathogens" for future studies in which it would be possible to increase the sample size through a more targeted analytical approach (Table 10-2). In addition, it is also evident from the data in Table 10-1 that there was a very significant shortfall in the understanding of the taxonomic classification of many of these newly described bacterial taxa, not least in the case of the *Bacteroides*. Clarification of the taxonomy of the periodontal microbiota was therefore a priority.

Significant effort was therefore placed on a systematic analysis of a number of these organisms using biochemical, physiologic, and immunologic approaches. As a result, gradually the underlying diversity within some of the organisms previously characterized as a single bacterial species became apparent (Fig. 10-3). This reclassification was accelerated to a new level by the application of molecular

Table 10-1 Selected taxa as a % of microbiota that were more numerous in (A) the supragingival microbiota and (B) the subgingival microbiota of young adults with severe generalized periodontitis.[a]

A)	Taxa	Supragingival	Subgingival	Taxa	Supragingival	Subgingival
	Actinomyces			*Leptotrichia D-35*	0.26	0.06
	A. israelii I	1.54	0.82	***Propionibacterium***		
	A. israelii II	1.20	0.47	*P. acnes*	2.40	1.29
	A. israelii X	0.17	0.06	***Peptostreptococcus***		
	A. naeslundii I	2.49	1.40	*P. anaerobius*	1.63	0.70
	A. naeslundii I	3.26	0.41	***Selenomonas***		
	A. naeslundii I II	3.18	1.76	*Selenomonas D-1*	0.60	0.12
	A. "naeslundii-viscosus"	4.03	0.58	*Selenomonas D-2*	0.60	0.12
	A. odontolyticus I	0.86	0.18	*Selenomonas D-3*	0.43	–
	A. viscosus II	2.40	1.52	*Selenomonas D4*	1.03	–
	Actinomyces D-8	0.26	0.12	*Selenomonas D-1 1*	0.52	0.06
	Bacteroides			***Staphylococcus***		
	B. disiens	0.09	0.06	*S. haemolyticus*	0.26	0.12
	B. gingivalis	0.43	0.23	*S. aureus*	0.09	0.06
	B. gracilis	1.89	1.17	*S. hominis*	0.09	0.06
	B. loescheii	0.43	0.29	***Streptococcus***		
	B. melaninogenicus	0.26	0.06	*S. constellatus*	0.77	0.64
	B. oris	1.54	1.23	*S. intermedius III*	0.52	0.12
	B. denticola	2.75	1.46	*S. mitis*	0.86	0.53
	Bacteroides D-19	0.09	0.06	*S. mutans*	0.34	0.23
	Capnocytophaga			*S. sanguis I*	1.89	0.18
	C. ochracea	4.21	1.17	*S. sanguis II*	3.43	0.29
	C. sputigena	0.34	0.12	*Streptococcus D-6*	0.17	0.12
	Eubacterium			*Streptococcus D-7*	0.60	0.12
	E. saburreum	0.69	0.06	*Streptococcus D-39*	4.64	1.76
	Fusobacterium			*Streptococcus SA*	0.09	0.06
	F. naviforme	0.52	0.06	*Streptococcus SM*	0.60	0.12
	Fusobacterium D-10	0.26	0.12	***Veillonella***		
	Leptotrichia			*V. atypica*	0.60	0.06
	L. buccalis	0.26	0.18	*V. dispar*	0.26	0.12
	Leptotrichia D-16	0.34	0.12	*V. parvula*	5.84	1.52

B)	Taxa	Supragingival	Subgingival	Taxa	Supragingival	Subgingival
	Actinomyces			*Fusobacterium D-2*	0.34	0.76
	A. meyeri	0.26	0.53	*Fusobacterium D-5*	–	0.29
	Bacteroides			*Fusobacterium D-7*	–	0.29
	B. buccae	0.09	0.64	*Fusobacterium D-9*	0.17	0.41
	B. capillosus	0.09	0.12	*Fusobacterium RD*	–	0.29
	B. intermedius 4197	0.52	3.92	***Lactobacillus***		
	B. intermedius 8944	0.34	0.82	*L. catenaforme*	0.17	0.29
	B. oralis	0.26	0.35	*L. minutus*	0.94	5.21
	B. pneumosintes	–	0.70	*Lactobacillus D-2*	1.63	1.87
	B. zoogleoformans	–	0.41	*Lactobacillus D-8*	0.26	0.29
	Bacteroides D-10	0.09	0.18	*Lactobacillus D-10*	0.17	0.41
	Bacteroides D-12	0.09	0.12	*Lactobacillus D-12*	0.09	0.35
	Bacteroides D-22	–	0.18	***Peptostreptococcus***		
	Bacteroides D-23	–	0.47	*P. micros*	2.32	4.45
	Bacteroides D-25	0.17	0.29	*Peptostreptococcus A2*	0.26	0.35
	Bacteroides D-28	0.26	0.88	***Propionibacterium***		
	Bacteroides D-32	0.09	0.18	*P. avidum*	–	0.94
	Bacteroides D41	–	0.23	***Selenomonas***		
	Bacteroides D42	–	0.82	*S. sputigena*	0.60	0.82
	Bifidobacterium			*Selenomonas D-12*	1.20	1.23
	B. dentium	0.17	0.53	*Selenomonas D-14*	0.17	0.23
	Eubacterium			***Staphylococcus***		
	E. alactolyticum	–	0.88	*S. epidermidis*	0.26	0.29
	E. brachy	0.17	1.52	***Streptococcus***		
	E. nodatum	0.69	8.31	*S. anginosus*	0.94	3.28
	E. timidum	1.37	6.21	*S. intermedius IV*	0.17	0.23
	Eubacterium D4	0.09	0.70	*S. sangius III*	0.34	0.47
	Eubacterium D-6	0.09	1.58	***Wolinella***		
	Eubacterium D-8	0.34	2.69	*W. recta*	0.17	0.76
	Eubacterium D-12	–	0.23	*Wolinella HVS*	0.34	0.58
	Fusobacterium			*Wolinella X*	0.34	0.58
	F. nucleatum	4.38	7.55			

[a] Adapted from Moore *et al*. (1982), from the American Society for Microbiology.

Table 10-2 Some of the bacteria which emerged as putative periodontal pathogens from cultural investigations of the subgingival microbiota.

Initial description	Reclassification
Bacteriodes melaninogenica	*Porphyromonas gingivalis, Prevotella intermedia*
Actinobacillus actinomycetemcomitans	*Aggregatibacter actinomycetemcomitans*
Tannerella forsythia	
Fusobacterium nucleatum	
Treponema denticola	
Peptostreptococcus micros	
Eikenella corrodens	
Selenomonas spp.	
Eubacteria spp.	

DNA analysis of these bacteria, in particular through comparative analysis of the *16S rRNA* gene (see later), which facilitated the differentiation of individual species. This process was essential in order to guide the identification of those bacterial species most closely associated with the periodontal disease process. A case in point is the evolution of the taxonomy of the black-pigmented bacteroides and the taxonomic changes to the classification of *Bacteroides melaninogenica* shown in Fig. 10-4. Through the application of successively higher definition identification schemes, what was previously a single entity is now appreciated to contain two different genera (*Porphyromonas* and *Prevotella*) and multiple species within each of these genera. Importantly, whilst the relevance of the black-pigmented organisms to periodontal infection had been evident through cultural investigations for several decades, the taxonomic definition of this group of organisms made it possible to determine which species were most closely associated with disease. Hence, it has become apparent that whereas *Porphyromonas gingivalis* is a critically important bacterium in disease, and is indeed now classified as one the red complex group of bacteria most closely associated with periodontal disease, this group of organisms also contains species which are frequently associated with periodontal health.

Targeted microbiologic analyses: Rise of specificity

Cultural and immunochemical studies

Having developed a candidate list of putative periodontal pathogens, it became possible to perform rather more targeted investigations that aimed to

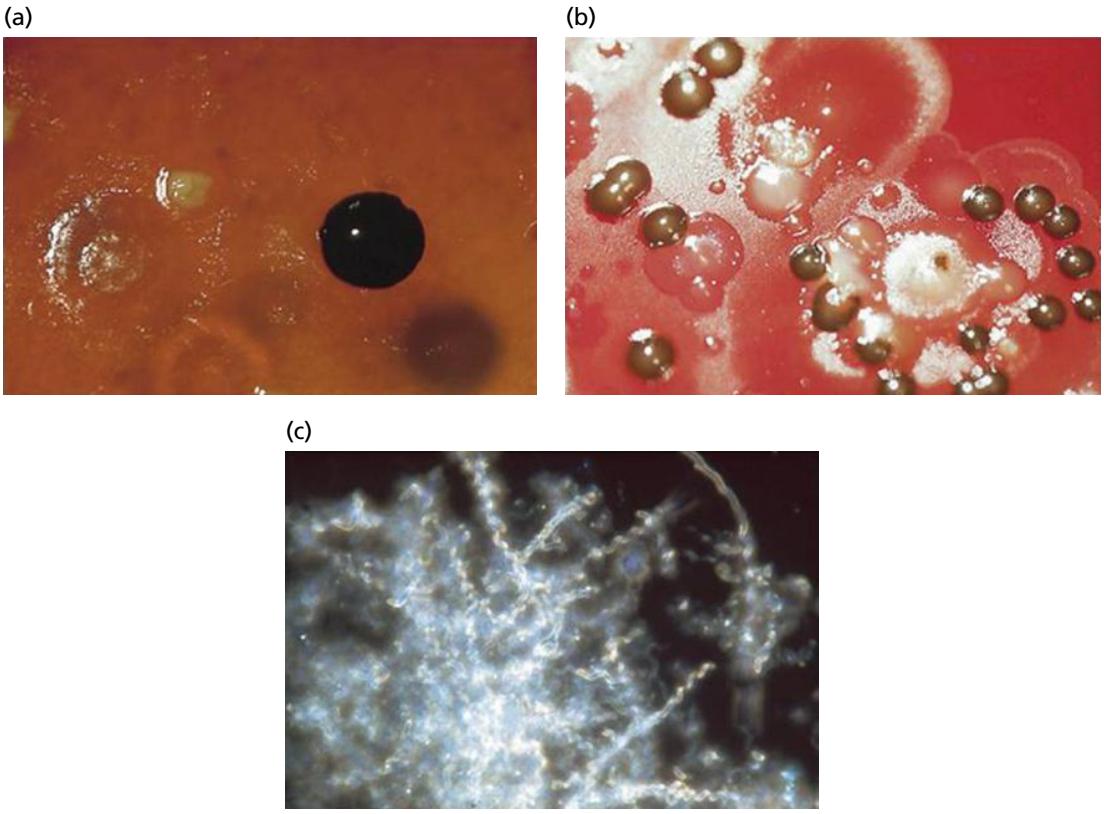


Fig. 10-3 Culture and microscopy analysis of dental plaque. Primary isolation plates of (a) a subgingival plaque sample from a subject with chronic periodontitis – the black-pigmented colony was an isolate of *Porphyromonas gingivalis*; (b) a subject with chronic periodontitis. In the latter case the dark-pigmented colonies were isolates of *Prevotella intermedia*. (c) Photomicrograph of a sample of subgingival plaque from a subject with advanced chronic periodontitis viewed by darkfield microscopy. The sample was dominated by large spirochetes with the typical corkscrew appearance. (Source: Socransky & Haffajee 2008. Reproduced with permission from John Wiley & Sons.)

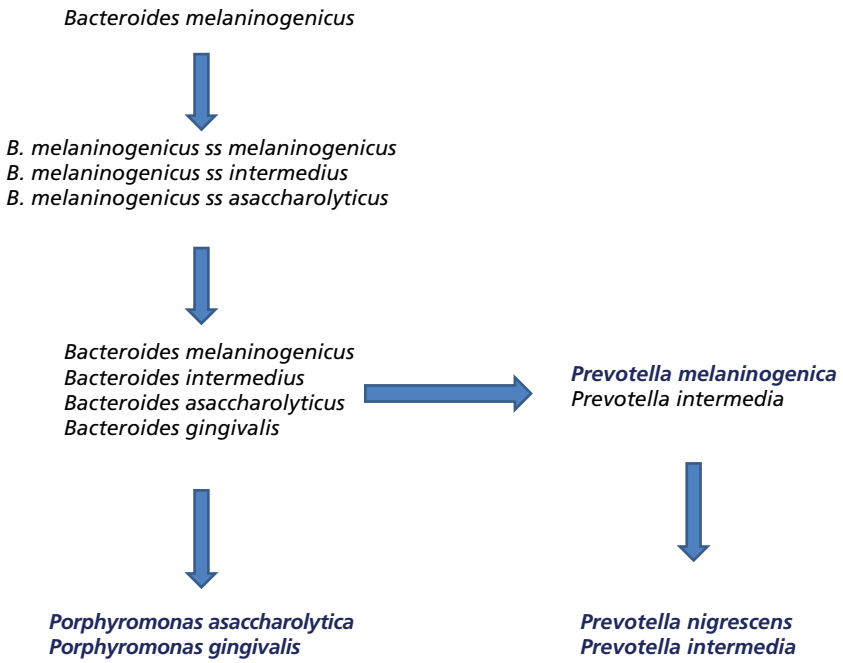


Fig. 10-4 Evolution of the taxonomy of the black-pigmented bacteroides. Organisms in bold are the current designations whilst those not in bold represent intermediate classifications during the reclassification of the taxonomy of this group of bacteria.

focus on detection of this group of bacteria in larger numbers of clinical samples than it was feasible to process when the entire cultivatable microbiota was examined. These investigations relied upon the application of a combination of identification approaches: novel selective media for the enrichment or selective culture of specific bacteria; immunologic techniques using newly developed monoclonal antibodies or polyvalent sera to individual species; or microscopy for the identification of spirochetes. For example, Bragd *et al.* (1987) used a selective media approach to evaluate the association of *Actinobacillus* (now *Aggregatibacter*) *actinomycetemcomitans*, *Bacteroides* (now *Porphyromonas*) *gingivalis*, and *Bacteroides (Prevotella) intermedia* in over 200 samples from progressing and non-progressing periodontal sites. Similarly, Slots *et al.* (1990) employed a cultural approach to examine the influence of subject age on the prevalence and recovery of *A. actinomycetemcomitans* and *B. intermedius* in 1624 patients aged between 15 and 89 years. Grossi *et al.* (1995) used an immunochemical approach to assess the presence of eight candidate periodontal pathogens in a study involving 1361 subjects to identify risk markers for periodontal bone loss. Suda *et al.* (2002) used an indirect immunofluorescence approach to enumerate the levels of *Eikenella corrodens* in samples from over 250 periodontal and control samples, and Riviere *et al.* (1997) a similar antibody- and microscopy-based investigation to determine the levels of different spirochetes in an analysis of the development of periodontal disease using over 1000 samples from 65 subjects.

By focusing on a small group of candidate organisms using relatively high throughput approachesm, it became possible to design appropriately statistically powered investigations to address a number of key issues relevant to the etiology and treatment of periodontal disease. These included studies of the presence of these candidate periodontal pathogens in different global populations (van Winkelhoff *et al.* 1999); of the association between different organisms such as *Bacteroides forsythus* and *Bacteroides gingivalis* (Gmur *et al.* 1989), and their spatial distribution in plaque (Kigure *et al.* 1995); the association with disease of different morphotypes of the same species, such as the smooth and rough colony types of *Peptostreptococcus micros* (van Dalen *et al.* 1998; Kremer *et al.* 2000); and the effect of treatment on persistence/eradication of these key organisms (Mandell *et al.* 1986; Rodenburg *et al.*, 1990; Mombelli *et al.* 2000). Furthermore, when isolation and identification of a specific organism was coupled to more detailed characterization of the individual strain (e.g. by restriction digestion of the isolates' DNA followed by separation by agarose electrophoresis), it became feasible to perform transmission studies. Notably, Petit *et al.* (1993a, b) and Van Steenbergen *et al.* (1993) used this approach to demonstrate that *P. gingivalis* was transmitted between spouses and that intrafamilial transmission of individual strains of *P. intermedia* and *Prevotella nigrescens* also occurred.

Other investigations utilized these selective methodologies to examine the association of alternative bacterial species with periodontal disease in addition to the, by now, well- established, periodontal bacteria mentioned earlier. In so doing the list of bacterial species positively associated with periodontal disease, in particular adult disease, was extended to include, for example, *Wolinella* (now *Campylobacter*) *recta* (Lai *et al.* 1992; Rams *et al.* 1993), *Enterococci* (Rams *et al.* 1992), *Peptostreptococcus micros* (van Dalen *et al.* 1998), eubacterial species (Grossi *et al.* 1995), *E. corrodens* (Suda *et al.* 2002), and *Fusobacterium*

nucleatum (van Winkelhoff *et al.* 2002). Hence, whilst a specific microbial etiology for periodontal disease was still considered by many to be the most reasonable interpretation of the accumulated data, there was an acceptance that the nature of the microbial challenge, particularly in the case of chronic adult periodontitis, was highly complex and likely to vary significantly between individuals and potentially within an individual at different sites and at different times (Maiden *et al.* 1990).

In contrast to adult-type chronic periodontitis, in one particular instance of aggressive periodontitis affecting adolescents of African descent, there is evidence to suggest that a single specific microbial etiology may be responsible for the development of disease. *A. actinomycetemcomitans* is a Gram-negative rod that produces a leukotoxin that specifically lyses human neutrophils. The organism displays significant genetic diversity, but one particular clone, referred to as JP2, has a number of genetic variations that distinguish it from other clonal types, including a 530-base pair deletion in the promoter region of the leukotoxin gene *operon*. As a result, the JP2 clone produces significantly enhanced levels of leukotoxin compared to the other lineages of this bacterium: this could theoretically lead to an enhanced potential to disrupt the immune defenses of the periodontium. Population genetic analysis by multilocus sequencing of *A. actinomycetemcomitans* strains from geographically dispersed individuals suggest that the JP2 clone originally emerged as a distinct genotype in the Mediterranean part of Africa over 2000 years ago and subsequently spread to West Africa, from where it was transferred to North and South America by the trans-Atlantic slave trade in the 16th–18th centuries. Remarkably, despite its now global dissemination, the JP2 clone remains exclusively associated with individuals of West African descent, indicating a strong host tropism effect (Haubek *et al.* 2008). While the prevalence of aggressive periodontitis in adolescents is normally <1%, it is far higher in individuals of North and West African descent. In a longitudinal study of the disease in Moroccan adolescents, 61 of 428 (14.3%) individuals who were periodontally healthy at baseline had developed disease after 2 years. Moreover, in this population, individuals who carried the JP2 clone at baseline were far more at risk of developing disease than those who carried non-JP2 clones of this bacterium (relative risk 18.0 versus 3.0) (Haubek *et al*. 2008). Hence, the JP2 clone of *A. actinomycetemcomitans* has the characteristics of a traditional bacterial pathogen, albeit in a host-restricted background.

Nucleic acid-based techniques for bacterial identification

With the development of a catalog of the major cultivatable species in the periodontal microbiota through these cultural microbiologic analyses came the need to develop more rapid, less time-consuming and laborious methods for larger sale epidemiologic analyses of the association of these organisms with health and disease. This was accomplished through the introduction of techniques that were not reliant on culture immediately following sample collection. The most commonly used of these were analyses based on nucleic acid approaches – PCR amplification of specific regions of the chromosome of the target organism, usually the *16S rRNA* gene, followed by quantitation of the product and DNA–DNA hybridization techniques.

Use of the DNA–DNA checkerboard methodology

A step change in the potential throughput of microbiologic analyses of periodontal plaque samples arrived with the introduction and application of DNA–DNA hybridization technology. The development of the checkerboard assay allowed the simultaneous hybridization of 45 individual DNA samples extracted from periodontal plaque against 30 different DNA probes on a single membrane. The DNA probes can either be prepared from whole genomic DNA extracted from the relevant target bacterium or alternatively from PCR amplicons of bacterial species-specific regions of the *16S ribosomal RNA (rRNA)* gene. Hybridization of the sample DNA with the probe DNA is then visualized via a chemifluorescent signal, the intensity of which is proportionate to the amount of the target organism DNA present in each sample (Fig. 10-5).

Whilst there are some limitations to the accuracy of identification of individual bacterial species due to potential cross-hybridization of DNA from closely related bacterial species in the same clinical samples, this technology has revolutionized the analysis of clinical samples and the ability to make definitive bacterial associations with periodontal health and disease. Now it was possible to perform qualitative and quantitative analysis of the bacterial composition of far, far greater numbers of clinical samples than with the previous culture-based methodologies. For example, in a landmark investigation, Socransky *et al*. (1998) analyzed approximately 13000 plaque samples from 185 subjects using whole genomic DNA probes to 40 bacterial species. Associations were sought among species using cluster analysis and community ordination techniques. One of the key and fundamental findings of this study, which has shaped our understanding of periodontal infections, was the definition of bacterial complexes, as opposed to individual bacterial species, that were associated with either periodontal health or periodontal disease (Fig. 10-6).

This finding led to the concept that there may be a co-dependency or synergy between different bacterial species acting in concert as a specific complex. The complex most strongly associated with periodontal disease became the focus of intense investigation. The "red complex" is composed

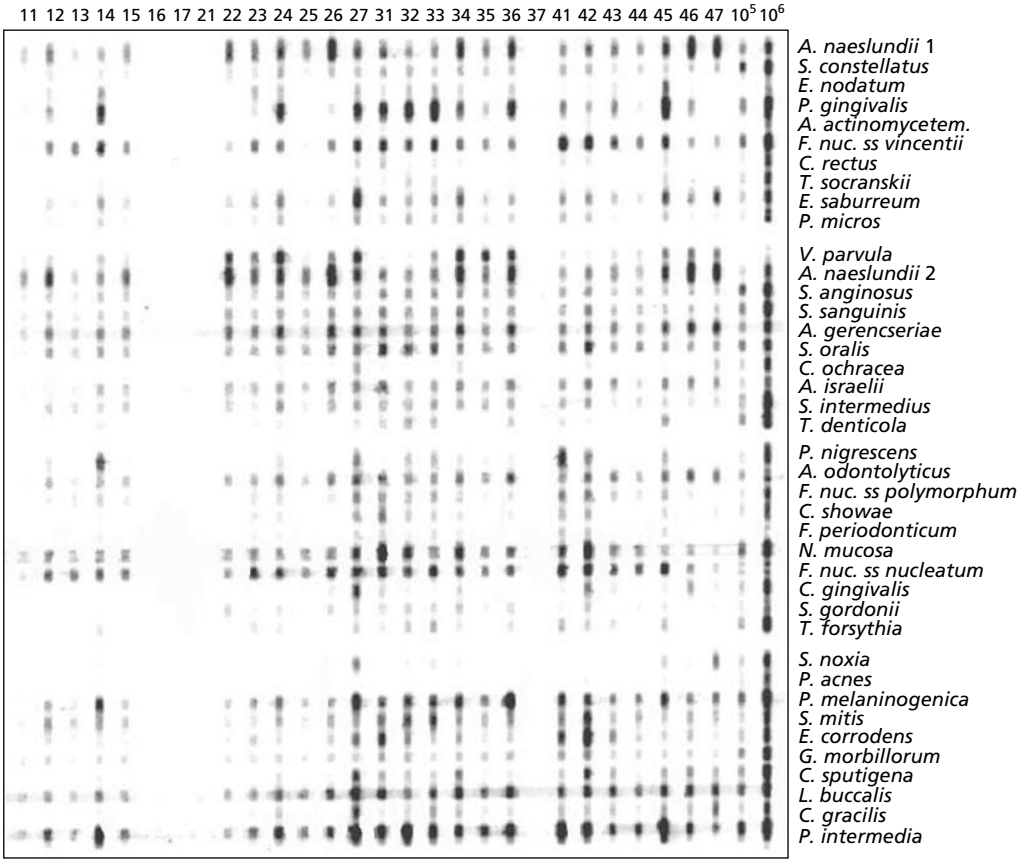


Fig. 10-5 DNA–DNA checkerboard analysis. The vertical lanes are the plaque samples numbered 11–47 and the two lanes of standards on the far right contain either 10^5 or 10^6 cells of each test bacterial species. The horizontal lanes contain whole genomic DNA probes labeled with digoxygenin to each represented bacterium. A signal at the intersection of the vertical and horizontal lanes indicates the presence of a bacterial species and the intensity of the signal is related to the number of bacterial cells present. The methodology enables the simultaneous and rapid analysis of 40 different bacterial species in 28 different plaque samples. (Source: Socransky & Haffajee 2008. Reproduced with permission from John Wiley & Sons.)

of three bacterial species: *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia.* Other complexes, for example the *yellow complex* which comprises predominantly different *Streptococcus* species, and the green complex which comprises a preponderance of *Capnocytophaga* species, represent early colonizers of dental plaque which were more closely associated with health. The orange complex contains those organisms generally considered to colonize dental plaque later: *Fusobacteria*, *Prevotella*, and *Campylobacter* species. The presence of these organisms is now thought to facilitate colonization of mature dental plaque by the red complex organisms either through the presentation of appropriate binding sites or by the creation of a suitable environment for the growth of these more fastidious species.

It is noteworthy that *A. actinomycetemcomitans*, the bacterium associated with rapidly progressive disease in individuals of West African descent, does not cluster with the most disease-associated red complex organisms. This probably reflects the very large effect of the host genetic background on the disease associated with this bacterium, as described previously.

Use of the checkerboard technology enabled a range of questions to be addressed concerning, for example, the sequential changes that occur in the composition of supragingival and subgingival plaque during development, and the qualitative and quantitative influence of tooth cleaning on the microbiology of supragingival and subgingival plaque. An example of this kind of study is shown in Fig. 10-6b, which demonstrates the significant qualitative and quantitative differences associated with disease not only in subgingival but also supragingival plaque.

Furthermore, the sensitivity of the checkerboard assay meant it was possible to examine site-to-site variations both between and within individuals and to correlate the differences with periodontal disease experience. For example, Fig. 10-7 demonstrates the changes in 40 bacterial species before and 12 months following therapy at sites which showed improvement in attachment level of >2 mm, sites that showed loss of attachment of >2 mm, and sites where the change in attachment level was intermediate between the two extremes. The data are an excellent representation of the community-wide compositional changes that occur in periodontal samples at sites of different disease outcome. Whilst a major reduction is observed in the red complex group of organisms in those periodontal sites where a gain in attachment level is observed, it is also evident that significant changes also occur in many of

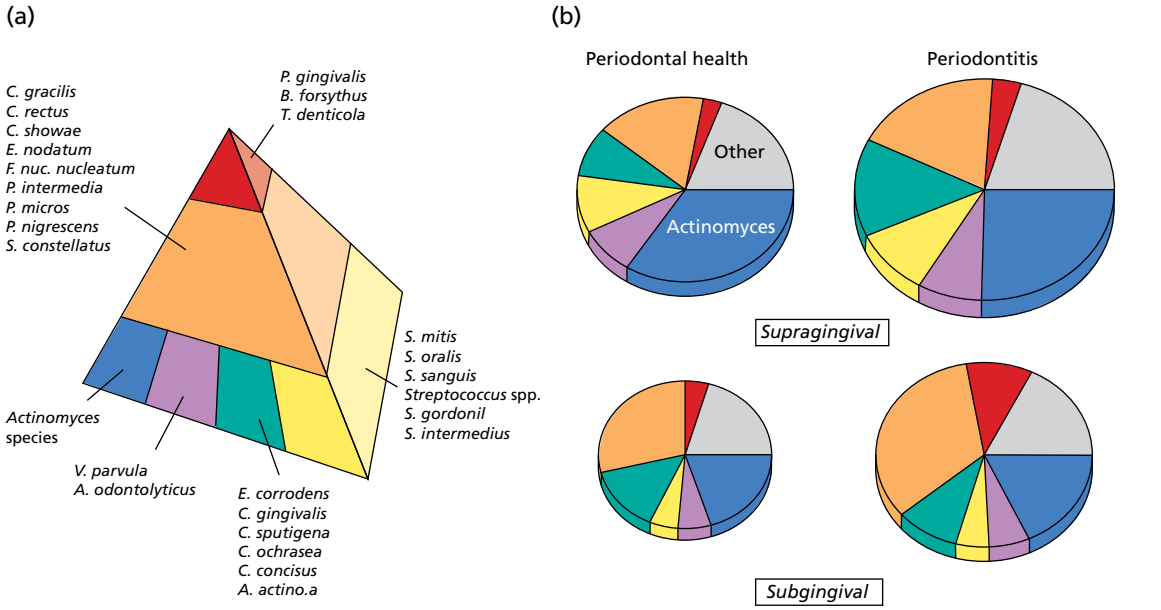


Fig. 10-6 (a) Association among subgingival species. The different colors in the pyramid represent different bacterial complexes which are frequently detected in association with one another. The base of the pyramid represents the early stage of plaque development, whereas the apex contains those organisms thought to be the last species to become established in the microbiota. The red complex of bacteria includes those organisms frequently associated with sites of periodontal disease. (Source: Socransky & Haffajee 2002. Reproduced with permission from John Wiley & Sons.) (b) Pie charts of the mean percentage DNA probe count of microbial groups in supragingival plaque. Plaque samples from periodontally healthy (58) and periodontitis (136) subjects and subgingival plaque samples from periodontally healthy (189) and periodontitis subjects (635). The species were grouped into seven microbial groups based on the description of Socransky *et al.* (1998) and described in more detail in (a). The "other" category represents probes to species that did fall into a complex as well as probes to new species whose relationships with other species has not yet been ascertained. The areas of the pie charts were adjusted to reflect the mean total DNA probe counts at each of the sample locations. The significance of differences in mean percentages of the supra- and sub-gingival complexes in health and disease was tested using the Kruskal Wallis test. All complexes differed significantly among groups (P <0.001 after adjusting for seven comparisons. (Source: Socransky & Haffajee 2008. Reproduced with permission from John Wiley & Sons.)

the other species. Thus, even in this snap shot of 40 microorganisms, it is evident that the overall population structure of the bacteria in a periodontal site may strongly influence disease outcome.

PCR amplification of the *16S rRNA* gene of periodontal bacteria

16S rRNA is a component of the 30S small subunit of all bacterial ribosomes. The genes coding for it are referred to as *16S rDNA*. Although the sequences of *16S rDNA* are highly conserved between different bacteria, they also contain hypervariable regions that can provide species-specific signature sequences useful for bacterial identification. Therefore, once the sequence of a *16S rDNA* gene from a bacterium has been determined, it is possible to design a PCR, using primers which will anneal to sequences within the hypervariable regions, which will specifically amplify only the *16S rDNA* from the target bacterium. The great advantages of the application of this methodology in the detection of periodontal bacteria in clinical samples is the high sensitivity of detection, the high throughput, the assay speed, and the multiple bacterial species that can be detected in the same reaction – multiplex PCR. As a result, this technology has been used extensively for the detection of putative periodontal pathogens. Typically, these studies have focused on the detection of only a few bacterial species, including the well-established periodontal bacteria *P. gingivalis, T. forsythia, T. denticola*, and *A. actinomycetemcomitans* (Leys *et al.* 2002; de Lillo *et al.* 2004; Sanz *et al.* 2004; Tanner *et al.* 2006). However, studies involving PCR amplification of the *16S rDNA* gene have also been used to confirm the presence of novel bacterial species whose presence was originally identified by cloning and sequence analysis of the *16S rDNA* gene in periodontal samples. These investigations confirmed that several additional species, including those that have not yet been grown *in vitro*, were associated with oral health or periodontitis.

The initial studies in this area were largely qualitative in nature in that they only determined whether an organism was present or absent (or more correctly below the limits of detection of the assay – typically 100 bacterial cells). More recently, real-time PCR, also referred to as qPCR or qRT-PCR, has been introduced: it quantifies the numbers of copies of the gene of interest in a given sample. Real-time PCR has been used to detect and quantify several periodontal pathogens, including *A. actinomycetemcomitans*, *P. gingivalis*, and *Prevotella intermedia*, and total bacteria in clinical samples (Lyons *et al.* 2000; Maeda *et al.* 2003; Boutaga *et al.* 2007; Atieh 2008).

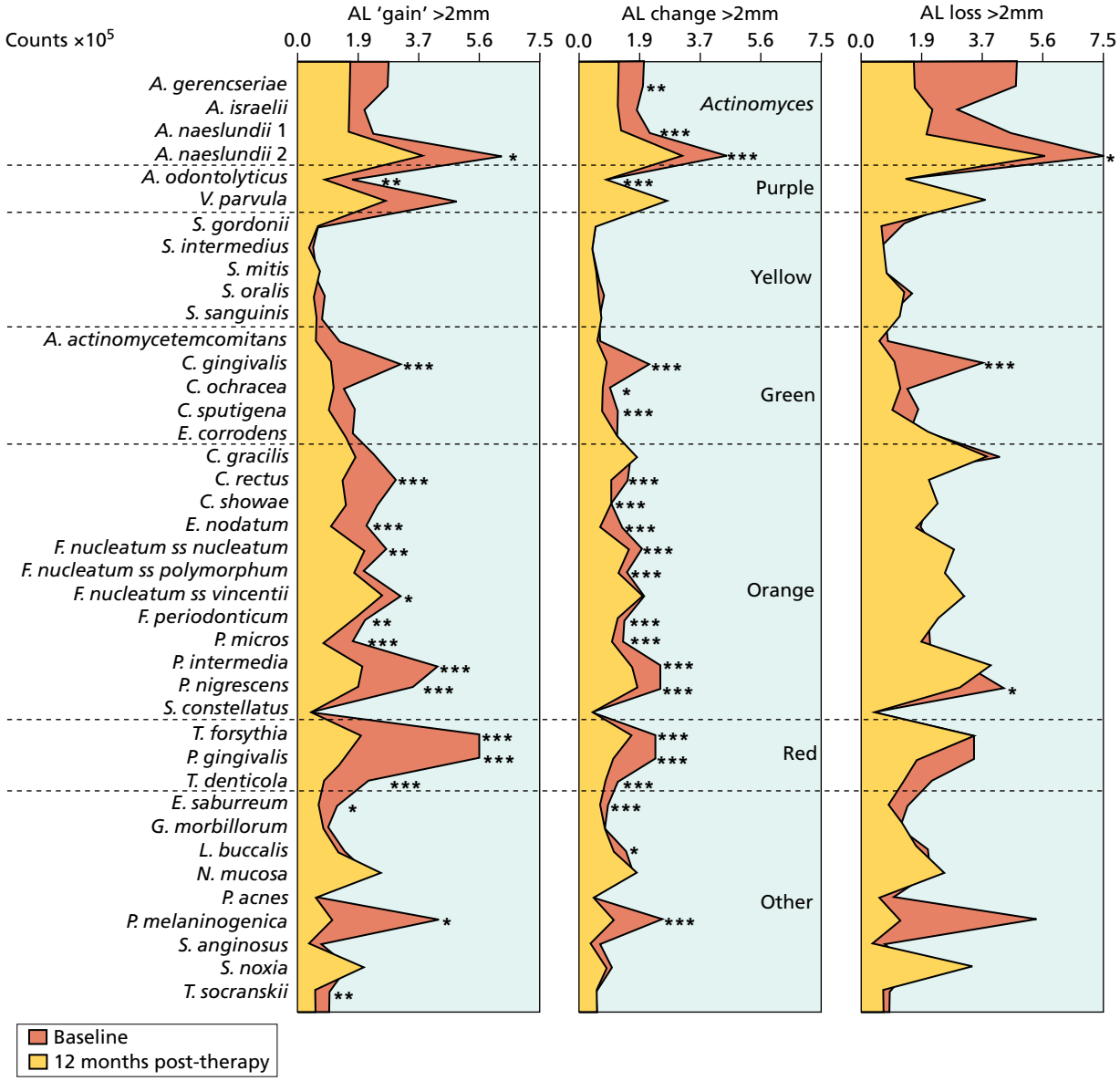


Fig. 10-7 Plots of mean counts (×10[5]) of 40 taxa in subgingival plaque samples at baseline and 12 months following therapy from sites that exhibited attachment level (AL) "gain" of >2 mm, (left panel), change of ≤2 mm (middle panel) or loss of >2 mm (right panel). Counts of each species at sites in each of the three attachment level change categories were determined, averaged within a subject, and then averaged across subjects in the three site categories separately at baseline and 12 months post therapy. Significance of differences between counts at baseline and 12 months was determined using the Wilcoxon signed ranks test and adjusted for multiple comparisons (*P <0.05; **P <0.01; ***P <0.001). Species were ordered according to microbial complexes. (Source: Haffajee *et al*. 2006. Reproduced with permission from John Wiley & Sons.)

Serologic analyses

The largely culture-based investigations which identified a relatively small group of bacteria as potentially key agents in periodontal disease were reinforced by serologic analyses of the antibody response of periodontal patients. These studies have tended to rely upon analysis of the serum IgG antibody response to whole cells of the candidate bacterium in periodontal patients compared to that in healthy age-matched control individuals. They have demonstrated unequivocally that patients with a history of periodontal disease quite frequently display elevated serum IgG antibody titers to several of the candidate periodontal pathogens (Ebersole *et al*. 1982, 1987; Taubman *et al*. 1992; Colombo *et al*. 1998). Hence, it is reasonable to assume that these bacteria, as well as being associated with the disease, also interact with the immune system of periodontitis patients.

The majority of these studies have focused upon a limited number of periodontal organisms, most notably *P. gingivalis* and *A. actinomycetemcomitans*. In the case of the former bacterium, the overwhelming evidence from these investigations indicates a very significant positive association between elevated levels of serum IgG antibodies to this organism and various forms of periodontal disease. In the case of *A. actinomycetemcomitans*, a similar relationship exists, although in this instance the association is most pronounced in the case of localized aggressive

periodontal disease – the form of the periodontitis most closely associated with colonization by this bacterium. Furthermore, multiple investigations indicate that titers to important periodontal pathogens are substantially reduced after successful periodontal therapy (Aukhil *et al.* 1988; Johnson *et al.* 1993; Darby *et al.* 2001). One can therefore conclude that many, although not all, patients experiencing periodontal attachment loss exhibit elevated levels of antibodies to antigens of candidate periodontal pathogen organisms, suggesting that these species gain access to underlying tissues, directly interact with the immune system of the colonized host, and may therefore initiate or at least contribute to the observed pathology.

However, it is also clear that diseased subjects exhibit elevated serum antibody to numerous other oral microorganisms. For example, Ebersole *et al.* (1992) examined the serum antibody response to a panel of organisms including *P. intermedia*, *E. corrodens*, *W. recta*, *F. nucleatum*, and *Capnocytophaga* species, and demonstrated elevated levels of antibody to this panel of organisms in adult periodontitis patients, primarily to *P. gingivalis, E. corrodens,* and *W. recta*. Similarly, elevated serum antibodies to multiple periodontal species have been reported in individuals with chronic periodontitis (Haffajee *et al.* 1995), early-onset periodontitis (Albandar *et al.* 2001), and refractory periodontitis (Hernichel-Gorbach *et al.* 1994; Colombo *et al.* 1998). In a longitudinal study, Papapanou *et al.* (2004) determined the serum IgG antibody reactivity to a range of oral bacteria in 89 patients with chronic periodontitis and 42 control subjects with no deep periodontal pockets and no or minimal attachment loss. In addition to the anticipated elevated antibody responses in the patients compared to the controls to the established periodontal organisms, *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythensis*, and *T. denticola*, there was clear evidence for elevated immune recognition of multiple other species. These included *P. intermedia*, *P. nigrescens*, *Micromonas micros*, *Campylobacter rectus, F. nucleatum*, *Streptococcus intermedius*, *Eubacterium nodatum*, *Streptococcus oralis*, *Capnocytophaga ochracea*, and *E. corrodens.* Conversely, the controls displayed statistically significantly higher titers against *Prevotella melaninogenica* and *Actinomyces naeslundii*, while no statistically significant differences could be detected in titers to *Porphyromonas endodontalis* and *Veillonella parvula.* Hence, similar to the cultural microbiologic findings, the patterns of the serologic response in periodontal disease are consistent with global shifts in the microbial composition of the microbiota in disease, wherein some species become more predominant whilst others are reduced as a proportion of the total population.

In a variation of these studies, rather than using whole bacterial cells in these assays, which could present a potentially wide range of different surface antigens, preparations of individual cellular constituents, such as the outer membranes in the case of Gram-negative bacteria or selected surface or extracellular antigens, were used as the target antigens. These studies enabled some definition of the specificity of the immune response to periodontal organisms and a start to the identification of the cellular location of the immunodominant antigens. In turn, this led to the characterization of these dominant antigens by more detailed immunochemical analysis, such as Western blotting, as a means to identify putative virulence factors produced by these organisms. For example, in one study of the serum IgG antibody response to outer membrane proteins of *P. gingivalis* (Curtis *et al.* 1991), immunodominant antigens with molecular weights of approximately 105 kDa, 55 kDa, and 47 kDa were identified that were strongly recognized by periodontal patient serum samples, but poorly reactive with sera from age-matched control individuals. Subsequent characterization of the identity and functions of these outer membrane constituents of *P. gingivalis* revealed that the 47-kDa protein represented a component of one of the potent proteolytic enzymes of this bacterium, Arg gingipain (Curtis *et al.* 1999), whilst the other two antigens, RagA and RagB, were components of a cell surface complex involved in outer membrane transport (Hanley *et al.* 1999). These antigens, initially revealed by serologic analysis of the outer membranes, have become recognized as important colonization and virulence determinants of *P. gingivalis*.

Hence, serologic investigations have played an important role both in confirming the association of different bacteria with the disease process, consistent with dysbiosis of the resident microbiota, and in facilitating the discovery of some of the important bacterial factors which are likely to be involved in the interaction of the bacterium with the host. It should be remembered however, that there are some limitations to the methodology: the approach can only be readily applied to those bacteria which can be cultured; growth of a bacterium *in vitro* will not necessarily lead to the expression of the proteins and other cell surface components which the bacterium produces when growing *in vivo*; there may be cross-reacting antibodies present in the serum of periodontal patients which were originally produced by another organism, for example in the gut, unrelated to the periodontal bacterium under study.

Challenge of the unculturable bacteria

As in other environments, a significant proportion of the total oral microbiota remains as yet unculturable and hence non-cultural methods are required to describe the overall species richness of the oral microbiome. Sequence analysis of *16S rRNA* has been the method of choice because of its universal presence in all organisms and because, through PCR primer design, it is possible to describe either all the species present in a given sample or target-specific genera. Application of this approach led to the description of 13 phyla in the domain Bacteria in the human oral microbiome: Actinobacteria, Bacteroidetes,

Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochetes, SR1, Synergistetes, Tenericutes, and TM7, in addition to methanogenic species of the Methanobrevibacter genus from the domain Archaea. Several hundred distinct species are contained within these divisions, representing the highly diverse microbial communities of the mouth. The periodontal microbiota is particularly heterogeneous and in excess of 400 species have been described in this habitat alone using a *16S rRNA* amplification, cloning, and Sanger sequencing approach (Dewhirst *et al.* 2010). These molecular studies have significantly extended the number of potential periodontal pathogens. For example, based on their *16S rDNA* analysis of subgingival plaque samples from healthy subjects and subjects with refractory periodontitis, adult periodontitis, human immunodeficiency virus periodontitis, and acute necrotizing ulcerative gingivitis, Paster *et al.* (2001) described several new candidates. Species or phylotypes commonly detected in disease but rarely in health included *Eubacterium saphenum, Filifactor alocis* (formerly *Fusobacterium alocis*), *Catonella morbi, Megasphaera* spp., *Dialister* spp., and *Selenomonas sputigena*, and several of these organisms, in particular *F. alocis*, have subsequently been confirmed in other studies to be positively associated with disease.

The Human Oral Microbe Identification Microarray

Recognition of this increased and substantial microbial diversity through the identification of lower abundance species and organisms not amenable to routine laboratory culture has led to the development of a new diagnostic methodology capable of the rapid identification of greater numbers of bacterial phylotypes in periodontal infections (Paster & Dewhirst 2009). The Human Oral Microbe Identification Microarray (HOMIM) was developed in order to examine the complex oral microbial diversity in a single hybridization on glass slides (Paster *et al.* 2006; Preza *et al.* 2008, 2009b). This high sample-throughput, *16S rRNA*-based technology allows the simultaneous detection of approximately 300 key and predominant bacterial species, including species that have not yet been cultivated. *16S rRNA*-based, oligonucleotide probes are printed onto glass slides. The *16S rRNA* genes in clinical samples are PCR amplified using *16S rRNA* universal forward and reverse primers, fluorescently labeled and then hybridized to the probes on the slides. In order to analyze the large datasets from HOMIM arrays, individual signals are translated into a "bar code" format in which the bands correspond to the presence or absence of a particular organism and band intensities reflect the organism's abundance. Figure 10-8 illustrates the bar code format of HOMIMs comparing the microbial profiles of approximately 300 bacterial species from subjects with periodontal health and periodontitis. These data can be analyzed further to determine specific bacterial associations (Colombo *et al.* 2009; Preza *et al.* 2009a, b) or the relationships of *entire* microbial populations with respect to health and disease using correspondence analysis, as shown in Fig. 10-9. The dramatic difference in the overall bacterial population structure of these two sets of data vividly reinforces the findings of the total cultural microbiology studies performed some 30 years ago and is consistent with dysbiosis of the microbiota as a defining characteristic of periodontal disease.

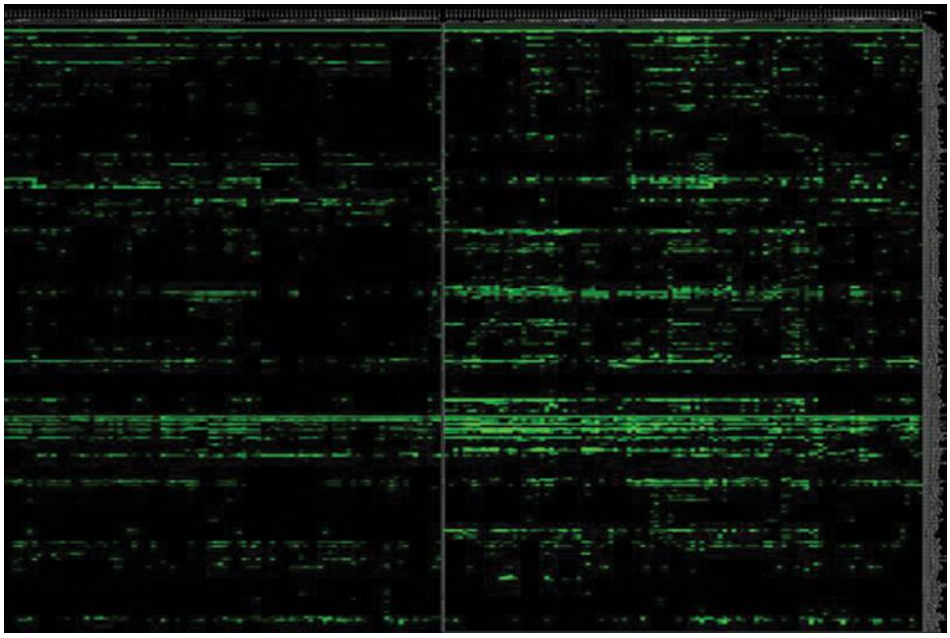


Fig. 10-8 Bacterial profiles of 461 bacterial taxa (representing approximately 300 species) comparing subgingival plaque from 105 healthy sites in periodontally healthy subjects (n = 20) (left panel) to 154 diseased sites from periodontally diseased subjects (n = 47) (right panel). (Source: Paster & Dewhirst 2009. Reproduced with permission from John Wiley & Sons and courtesy of A.P. Colombo.)

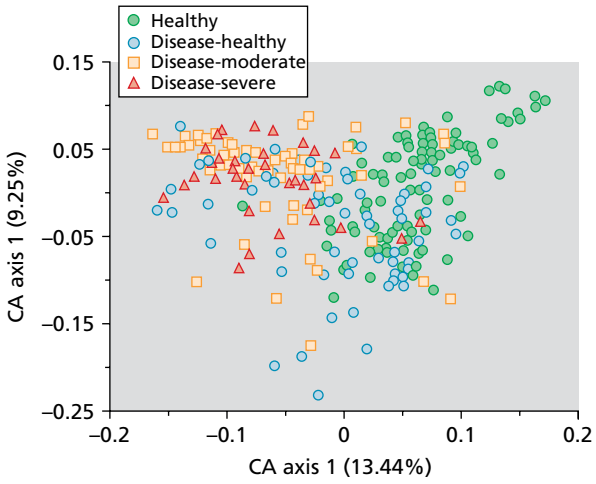


Fig 10-9 Correspondence analysis (CA) of subgingival plaque bacterial communities in health and disease. Each symbol represents one community from one site. Communities that are closer together have more similar HOMIM profiles. In this plot, the healthy sites from healthy subjects (green circles) are distinct from healthy and diseased sites in diseased subjects (red symbols). (Courtesy of Dr Vanja Klepac-Ceraj, Forsyth Dental.)

Whilst these findings have significantly enhanced our understanding of the oral microbiome, they have also highlighted the likelihood that there may be an additional large number of low abundance species which have remained undetected using this standard methodologic approach, largely because of the relatively time-consuming and laborious nature of the techniques. This issue is now being addressed through the application of deep sequencing methods, in particular pyro-sequencing technologies which enable a more comprehensive coverage of the *16S rRNA* sequences in large numbers of samples.

High throughput sequencing revolution

Application of next-generation DNA sequencing to the oral and periodontal microbiota in health and disease is the newest technological advance in our study of these consortia. Although relatively few large-scale studies have been undertaken, there are indications that it may be necessary to revise our estimates of the species richness of the oral microbiome, perhaps by a factor of 10. For example, in a study of the microbiota of saliva and supragingival plaque from 71 and 98 healthy adults, respectively, amplicons from the V6 hypervariable region of the small-subunit *rRNA* gene were generated by PCR and sequenced by means of 454 technology. The 197 600 sequences analyzed were suggested to represent 22 phyla comprising 3621 and 6888 species-level phylotypes in saliva and plaque, respectively (Keijser *et al.* 2008). However, these early data need to be viewed with some caution as it is well recognized that the errors inherent in pyrosequencing, particularly of homopolymeric tracts, may lead to over estimation of the total number of unique sequences in a given sample. The development of increasingly sophisticated software to minimize these problems should lead to increasingly accurate estimates of the species diversity of the oral microbiome and indeed more recent investigations have tended to suggest more conservative phylotype numbers (Zaura *et al.* 2009). Nonetheless, the application of high throughout sequencing approaches, particularly to comparative analyses of health and disease, are likely to lead to increasing insights into the range of bacterial species associated with the development of pathology. For example, this technology has been applied to compare the total oral, gut, and atherosclerotic plaque microbiota in patients with atherosclerosis (Koren *et al.* 2011). This comprehensive analysis indicated that bacteria from the oral cavity, and perhaps even the gut, may correlate with disease markers of atherosclerosis (Fig. 10-10). A significant challenge in this area will be the analysis and interpretation of these high volumes of data: whilst the frequent condensation of high granularity phylotype information to the phylum or genus level, which is evident in much of the published literature on human microbiomes, enables ready comparison of different datasets, this practice does not maximize the value of these high throughput approaches.

Genetic variation

A further layer of complexity to the microbial diversity of the periodontal microbiota derives from the genetic variation between different isolates of the same bacterial species caused by changes to the bacterial chromosome over time. These changes can result from random point mutations during chromosomal replication, and internal genome rearrangement and duplications during recombination events. Furthermore, it is clear that genetic exchange between different bacterial species may be a very significant force in bacterial genome evolution. For example, it is well established that bacterial pathogenicity factors may be encoded by transmissible genetic elements, including plasmids, bacteriophages or transposons, which have the capacity to spread between different bacterial populations. Furthermore, the study of bacterial genomes in the last decade has revealed that bacterial virulence determinants are frequently encoded in regions of the genome which appear to have arisen via horizontal gene transfer from a separate organism. These pathogenicity islands are specific chromosomal elements which can occupy quite large regions often flanked by mobility genes such as insertion sequences. Mutations during replication and acquisition of additional genetic loci through horizontal gene transfer both increase the flexibility of a bacterial species and can contribute to the spread and evolution of virulence.

These intraspecies chromosomal variations result in the generation of a population structure for each species. In some instances, this variation leads to

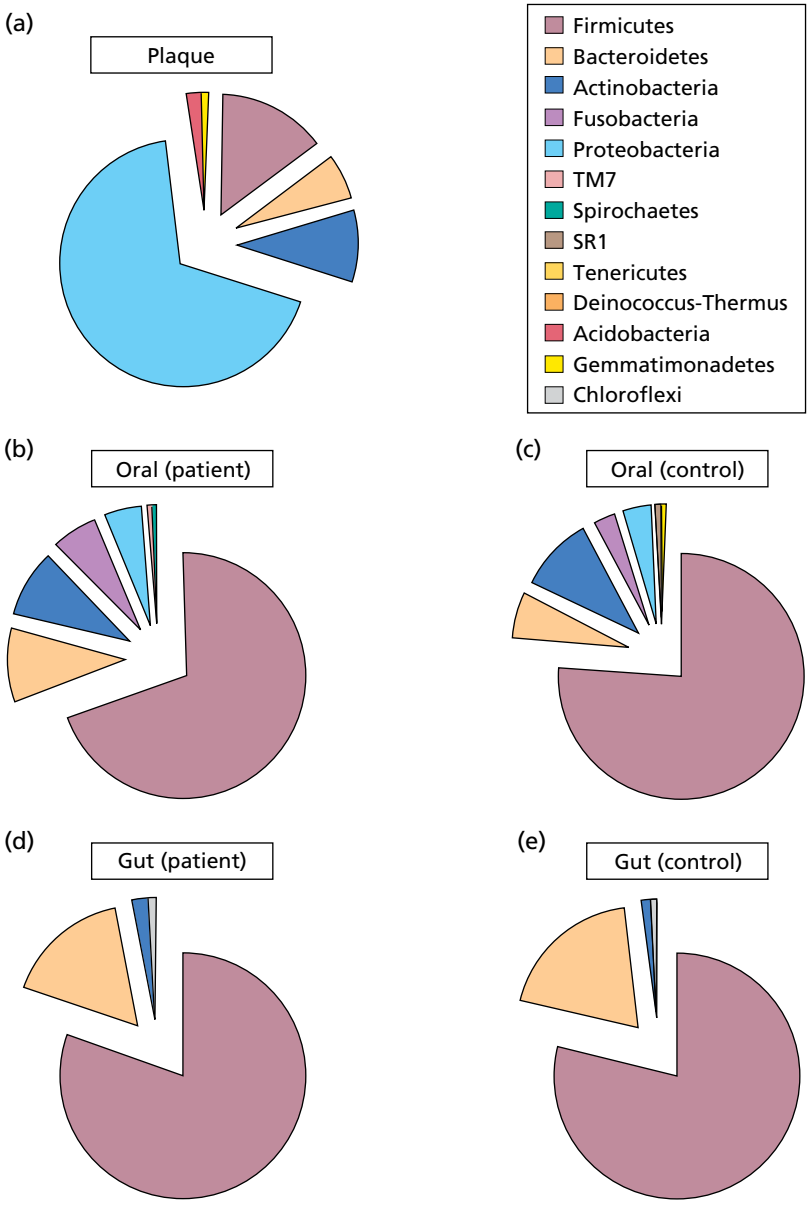
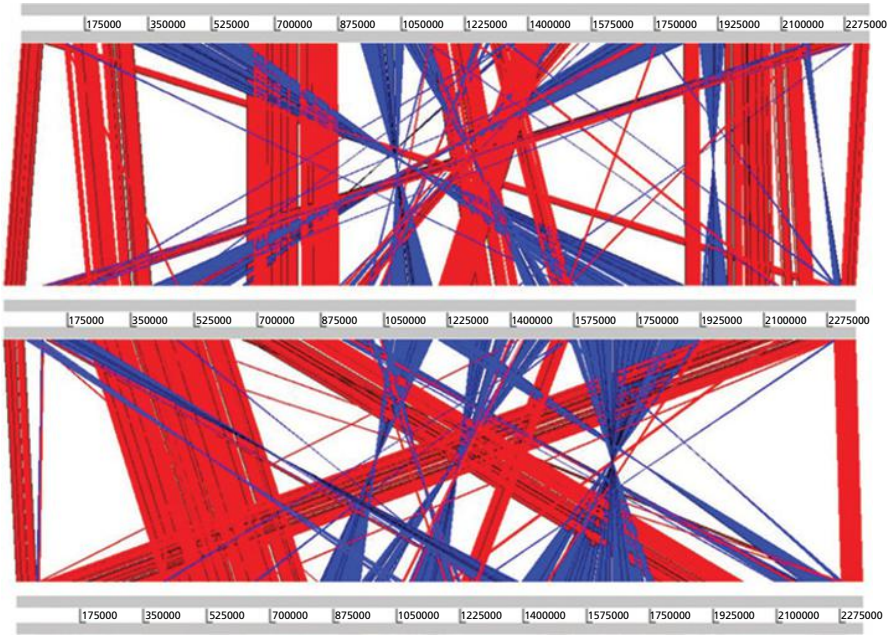


Fig. 10-10 Composition of the microbiota at different body sites in patients with atherosclerosis and controls determined by pyrosequencing. Plotted values are mean sequence abundances in each phylum for 1700 randomly selected sequences per sample. (a) Atherosclerotic plaque; (b) oral cavity, patient; (c) oral cavity, control; (d) gut, patient; (e) gut, control. (Source: Koren *et al*. 2011. Reproduced with permission from PNAS and R.E. Ley and F. Bäckhed.)

the generation of distinct clonal types, some of which may have properties which cause them to be responsible for the majority of the disease caused by that particular bacterial species. A good example of this in the periodontal microbial field *A. actinomycetemcomitans*, an organism which is strongly implicated in periodontal disease in individuals of West African descent, most especially through a specific clonal type, referred to as JP2. In this instance, as previously described, the chromosomal change which has resulted in a more clinically deleterious phenotype involves a small genetic deletion upstream of the leukotoxin gene of this organism. This has placed the transcription at this locus under a stronger promoter than in the original locus, leading to elevated synthesis of this virulence determinant.

At present, the JP2 clone of *A. actinomycetemcomitans* remains the most persuasive example of how genetic variation within a periodontal bacterial species can lead to the generation of a more virulent clonal type and consequent variation in the disease potential within the species. However, good evidence from the *in vitro* assessment of other periodontal organisms suggests that intraspecies genetic variation will also play a role in the disease potential of these bacteria. For example, the virulence potential of different isolates of *P. gingivalis* has been examined using a number of *in vivo* animal models and *in vitro* systems. It is clear from these experiments that there is highly significant variation within this species, for example in its capacity to cause disease in murine infection models, suggesting that genetic variation between different strains may have a significant



P. gingivalis strain	Genome size (bp)	% Guanosine-cytosine	Genes encoded	Strain specific genes	Reference
W83	2 343 476	48.30	1,990	415	(Nelson *et al.* 2003)
ATCC33277	2 354 886	48.40	2,090	461	(Naito *et al.* 2008)
TDC60	2 339 898	48.34	2,220	382	(Watanabe *et al.* 2011)

Fig. 10-11 Comparison of the genome organization of three strains of *P. gingivalis:* W83, ATCC33277, and TDC60. Each genome is shown as a numbered gray bar representing the forward and reverse strands. Top: *P. gingivalis* W83; middle: *P. gingivalis* ATCC 33277; bottom *P. gingivalis* TDC60. The red lines between the genomes represent DNA–DNA homologies between the two forward sequences. The blue lines represent homologies between the forward strand of the upper sequence and the reverse complement of the lower sequence. The analysis demonstrates very extensive rearrangements of the genetic material in these three strains which will contribute to the interstrain variation in their biologic properties.

influence on their role in periodontal disease in human populations.

An example of the genetic diversity within *P. gingivalis* is shown in Fig. 10-11, which compares the genomes of three isolates of this species which have been sequenced in recent years. Figure 10-11 demonstrates that while the total genome size of all three isolates is approximately the same (2.3 Mb), each strain contains several hundred strain-specific genes (i.e. genes which are not present in the other two strains) and there has been extensive rearrangements of the bacterial chromosomes over time; these could also have an influence on gene expression in the different isolates and consequent properties in an infection. Hence, whilst routine diagnostic microbiology may indicate that a clinical sample contains a given bacterial species such as *P. gingivalis*, the genetic variation within that species suggests that different isolates may present quite different challenges to the periodontal tissues.

Influence of a biofilm lifestyle

Microbial biofilms consist of one or more communities of microorganisms, embedded in a largely carbohydrate matrix, that are attached to a solid surface. The biofilm allows microorganisms to adhere to and multiply on surfaces. Thus, attached sessile bacteria growing in a biofilm display a wide range of characteristics that provide a number of advantages over single-cell, planktonic bacteria. The interactions among bacterial species living in biofilms take place at several levels, including physical contact, metabolic exchange, small signal molecule-mediated communication, otherwise known as quorum sensing, and exchange of genetic information (Kolenbrander *et al.* 2006; Newman & Wilson 1999; Socransky & Haffajee 2002; Marsh 2005). A more detailed description of dental plaque as a biofilm is given in Chapter 8.

The key characteristic of a biofilm is that the microcolonies within the biofilm attach to a solid surface. Thus, adhesion to a surface is the essential first step in the development of a biofilm. In the mouth, there is a wide variety of surfaces to which bacteria can attach, including the oral soft tissues, the salivary pellicle-coated teeth, other bacteria, as well as prosthetic replacements such dentures and implants. Many bacterial species possess surface structures such as fimbriae and fibrils that aid in their attachment to different surfaces. Fimbriae have been detected on a number of oral species, including *A. naeslundii, P. gingivalis, A. actinomycetemcomitans*, and some strains of streptococci, such as *Streptococcus salivarius, Streptococcus parasanguinis*, and members of the *Streptococcus mitis* group.

Fibrils can be found on a number of oral bacterial species. They are morphologically different and shorter than fimbriae, and may be densely or sparsely distributed on the cell surface. Oral species that possess fibrils include *S. salivarius*, the *S. mitis group*, *P. intermedia*, *P. nigrescens*, and *Streptococcus mutans*.

In the case of dental plaque, it is clear from the extensive microscopic analysis undertaken over the last 50 years on *ex vivo* samples, that there is a very ordered structure to the biofilms adherent to the tooth surface. A section of human supragingival dental plaque grown on an epon crown in a human volunteer is shown in Fig. 10-12a (Listgarten *et al.* 1975; Listgarten 1976, 1999). The section demonstrates many of the characteristic features of biofilms outlined earlier. Bacterial cells have adhered to the solid surface, multiplied, and, in this section, formed columnar microcolonies. The heterogeneity of colonizing species is evident even at a morphologic level and yet there is a clear pattern of organizational structure to these bacterial masses. The surface layers of the biofilm exhibit morphotypes that are not evident in deeper layers, perhaps indicative of the role of bacterial succession in the development of the complex microbiota and potentially of the role that co-aggregation plays in the development of biofilms. Not evident in this section are the water channels in biofilms which are thought to be features common to most biofilms in nature. This might be due to preparation or fixation artifacts (Costerton *et al.* 1999). Water channels have been observed in plaque grown in the human oral cavity by confocal microscopy (Wood *et al.* 2000). This dental biofilm has all of the properties of biofilms in other habitats in nature. It has a solid substratum, in this case an epon crown but more typically a tooth, mixed microcolonies growing in a glycocalyx, and the bulk–fluid interface provided by saliva.

A second biofilm ecosystem, this time of human subgingival plaque is shown in Fig. 10-12b. The section is at lower magnification than that shown in Fig. 10-12a to permit visualization of regions within the biofilm. The plaque attached to the tooth surface is evident in the upper left portion of the section. This tooth-associated biofilm is an extension of the biofilm found above the gingival margin and may be quite similar in microbial composition. A second, possibly epithelial cell-associated biofilm may be observed lining the epithelial surface of the pocket. This biofilm contains primarily spirochetes and Gram-negative bacterial species (Listgarten *et al.* 1975; Listgarten 1976, 1999). *P. gingivalis* and *T. denticola* have been detected, by immunocytochemistry, in large numbers in the epithelial cell-associated biofilms within the periodontal pocket (Kigure *et al*. 1995). *T. forsythia* might also be numerous in this zone, since high levels of this species have been detected, using DNA probes, in association with the epithelial cells lining the periodontal pocket (Dibart *et al*. 1998). Between the tooth-associated and epithelial cell-associated biofilms, a less dense zone of organisms may be observed. These organisms may be "loosely attached" or they may be in a planktonic state. The critical feature of Fig. 10-12b is that there appear to be tooth-associated and epithelial cell-associated regions in subgingival plaque as well as a possible third weakly attached or

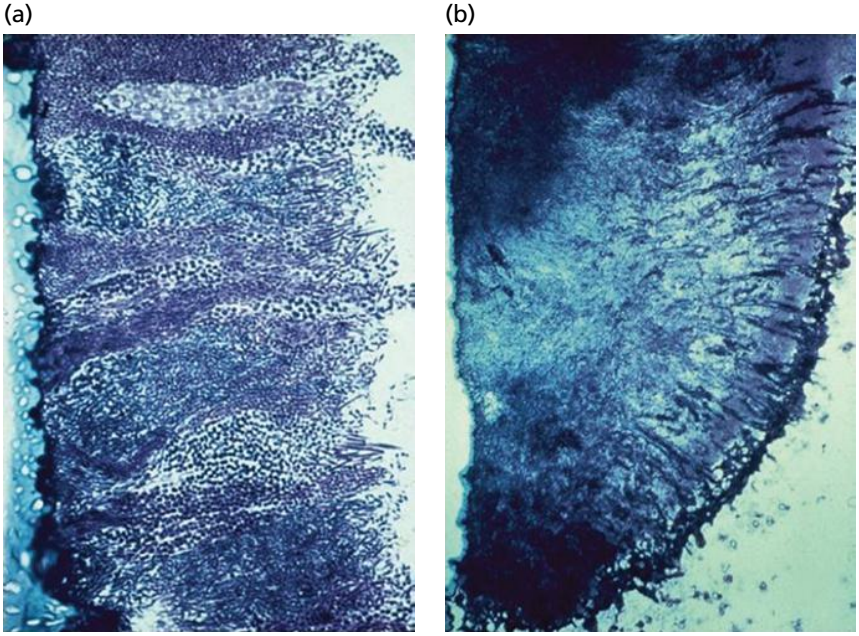


Fig. 10-12 (a) Histologic section of human supragingival plaque stained with toluidine blue–methylene blue. The supragingival plaque was allowed to develop for 3 days on an epon crown in a human volunteer. The crown surface is on the left and the saliva interface is towards the right. (b) Histologic section of human subgingival dental plaque stained with toluidine blue–methylene blue. The tooth surface is on the left and the epithelial lining of the periodontal pocket is on the right. Bacterial plaque attached to the tooth surface is evident towards the upper left of the section, while a second zone of organisms can be observed lining the periodontal pocket wall. (Courtesy of M. Listgarten, University of Pennsylvania.)

unattached zone of microorganisms. It is highly likely that these regions differ markedly in microbial composition, physiologic state, and their response to different therapies.

The markedly different environmental conditions prevailing within a biofilm compared to a free-living planktonic state have a significant influence on the properties of the resident organisms. Changes to, for example, the availability of nutrients, local conditions of pH and redox potential (Eh), and the presence of bacteria producing bacteriocidal agents to other species and signaling molecules from the same and different species are all considered to be pivotal to alterations in gene expression of bacteria in sessile versus planktonic conditions. Such altered patterns of gene expression and the resultant influence on the phenotype of periodontal bacteria growing in biofilms have been demonstrated in several studies. For example, Lo *et al.* (2009) compared the overall transcription of genes of *P. gingivalis* in either the planktonic or biofilm state grown in continuous culture. Approximately 18% of the *P. gingivalis* genome was differentially expressed when the bacterium was grown as a biofilm. This included genes involved in the formation of the cell envelope, DNA replication, energy production, and biosynthesis of co-factors, prosthetic groups which were all down-regulated in biofilm cells. Conversely, genes encoding transport and binding proteins were up-regulated. The study also demonstrated that several genes predicted to encode proteins involved in signal transduction and transcriptional regulation were differentially regulated and may be important in the regulation of biofilm growth. Analysis of the total proteome of *P. gingivalis* cells grown under similar conditions confirmed the widespread changes to the phenotype of the bacterium when grown in a biofilm (Ang *et al.* 2008). Similar studies are now being performed on mixed cultures of periodontal organisms grown together in biofilms to determine the influence that intimate association between these organisms will have on the patterns of gene and protein expression (Zainal-Abidin *et al.* 2012).

The recognition that growth in a biofilm leads to profound changes in the properties of bacteria has led to the development of experimental systems to study the growth and biologic features of bacterial populations grown under sessile conditions. An example of one such system, in this case using a mixture of supragingival and subgingival microorganism, is shown in Fig. 10-13. The formation of organized structures of microcolonies of different organisms with discrete spatial localization and the presence of channels through these structures mimics the patterns of microbial organization observed in the *ex vivo* dental plaque samples in Fig. 10-12. Models of this kind therefore have great utility for the study of the growth of periodontal bacteria in mixed culture in a biofilm state in order to address issues pertinent to dental plaque development and accumulation, and control using antiseptic and host-derived antimicrobial systems. Furthermore, when grown under conditions mimicking the *in vivo* state, they provide experimentally important bacteria and bacterial products for further phenotypic analysis and use in *in vitro* systems of virulence.

Periodontal bacteria and virulence

The virulence of a microbial pathogen is generally defined as the degree of pathogenicity or ability of the organism to cause disease as measured by an experimental procedure. It represents a combination of highly complex parameters and depends upon both the relative infectivity of the organism and the severity of the disease produced. However, in all cases, these two parameters of infectivity and disease severity are profoundly influenced by the nature and status of the host organism or the site of colonization in that host. Thus, a breach in the normal defensive barriers of the host through, for example, trauma, immunosuppression/dysfunction or co-infection by another organism, can dramatically increase the virulence of a given organism. Hence, any description of microbial virulence is fundamentally reliant on an understanding of the relative susceptibility of the colonized host.

The requisite stages in the life cycle and spread of one organism which parasitizes another are presented in Fig. 10-14. The key steps are: initial colonization and attachment; multiplication and nutrition; evasion of the host defenses; (in some cases) invasion; and, lastly, exit in order to disseminate to a new host. Specific gene products (presumptive virulence factors) are required to facilitate each of these processes, and these products will vary from organism to organism dependent upon the particular strategy employed to satisfy each element of the life cycle. The gene products or traits associated with each step in the life cycle presented in Fig. 10-14 represent examples drawn from multiple organisms. Disease can be defined as the unfavorable outcome in the host from the application of these life cycle stages of the pathogen in a *susceptible* host background.

The virulence determinants of a pathogen can simply be defined as those gene products which facilitate colonization, growth, and survival within the diseased host organism and spread to a new host. Examples of the virulence properties of some key periodontal organisms, *P. gingivalis, A. actinomycetemcomitans, T. forsythia*, and *T. denticola*, are given in Table 10-3. In most cases, the rationale for considering these determinants to be important determinants of the virulence of these organisms is derived from a wealth of *in vitro* investigations and/or animal models employing isogenic mutants of the gene of interest. Further details of the properties of these organisms in relation to the pathogenesis of disease can be found in recent reviews on this subject (Hajishengallis 2009; Henderson *et al.* 2010; Sharma 2010; Dashper *et al.* 2011; Bostanci & Belibasakis 2012). However, an emerging key

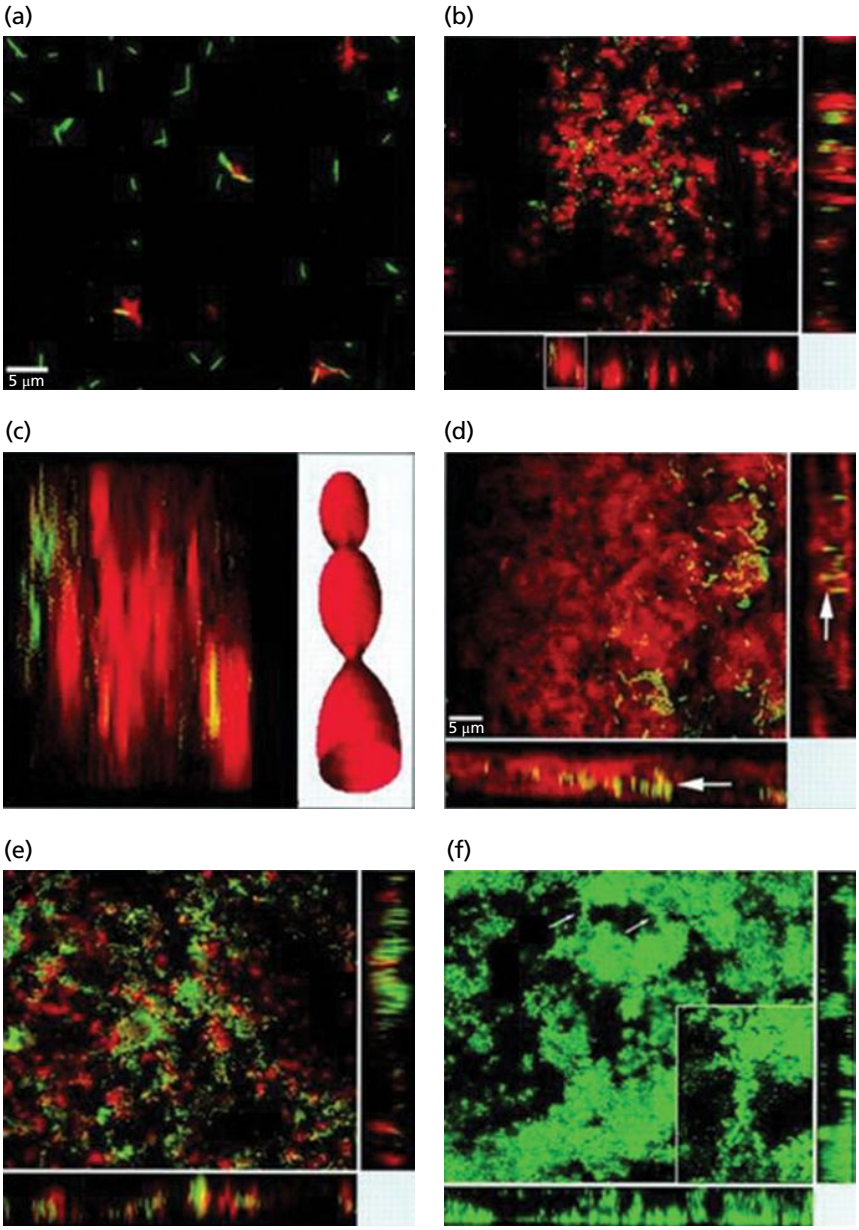


Fig. 10-13 *In vitro* models of biofilm formation. Confocal laser scanning microcopy images of *in vitro* biofilms stained with pairs of species-specific antibodies. (a) *F. nucleatum* (green) plus *A. naeslundii* (red) after 15 minutes' Growth; (b) *V. dispar* (green) plus *A. naeslundii* (red) after 16 hours. (c) Sagittal section (the boxed area in b) showing stacked microcolonies of *A. naeslundii*; the image has been stretched by a factor of 1.5 along the x–z axis. The drawing to the right is an idealized representation of the stacked microcolonies' unduloid appearance. (d) *S. sobrinus* (green) plus *F. nucleatum* (red) after 64 hours; the arrows indicate the z-plane of the main image. (e) *V. dispar* (green) plus *S. sobrinus* (red) after 40 hours. (f) *S. oralis* after 40 hours. The arrows indicate cellular bridges linking microcolonies; the box lower right is an enlargement of an intermicrocolony bridge (the accompanying labeled partner species is not shown). (Source: Guggenheim *et al*. 2001. Reproduced with permission from the American Society for Microbiology.)

property of several of these organisms concerns the strategies they appear to employ in order to evade the host defenses operative in the periodontium.

It is becoming increasingly evident that microbial organisms, having co-evolved with the innate defense systems of their respective hosts, have developed strategies not only to overcome protective host barriers but also to manipulate these systems to their own advantage. One example of this phenomenon is the ability of cell surface proteins of both Gram-negative and Gram-positive bacteria, including *A. actinomycetemcomitans* and *P. gingivalis*, to influence the pattern of cytokine expression by host cells. The term "bacterial modulins" was introduced by Henderson, Poole, and Wilson to describe these bacterial cytokine-inducing molecules because of their ability to modulate eukaryotic cell behavior (Henderson *et al.* 1996). More recently, a sophisticated manipulation of the host response by *P. gingivalis* has been described as a consequence of the biologic properties of different molecular species of the lipid A portion of the lipopolysaccharide (LPS) of this bacterium (Darveau *et al.* 2004). Some of these lipid A species are able to act as agonists of the host response through Toll-like receptor signaling, and thus have similar biologic properties to the hexa-acylated lipid A species of enteric

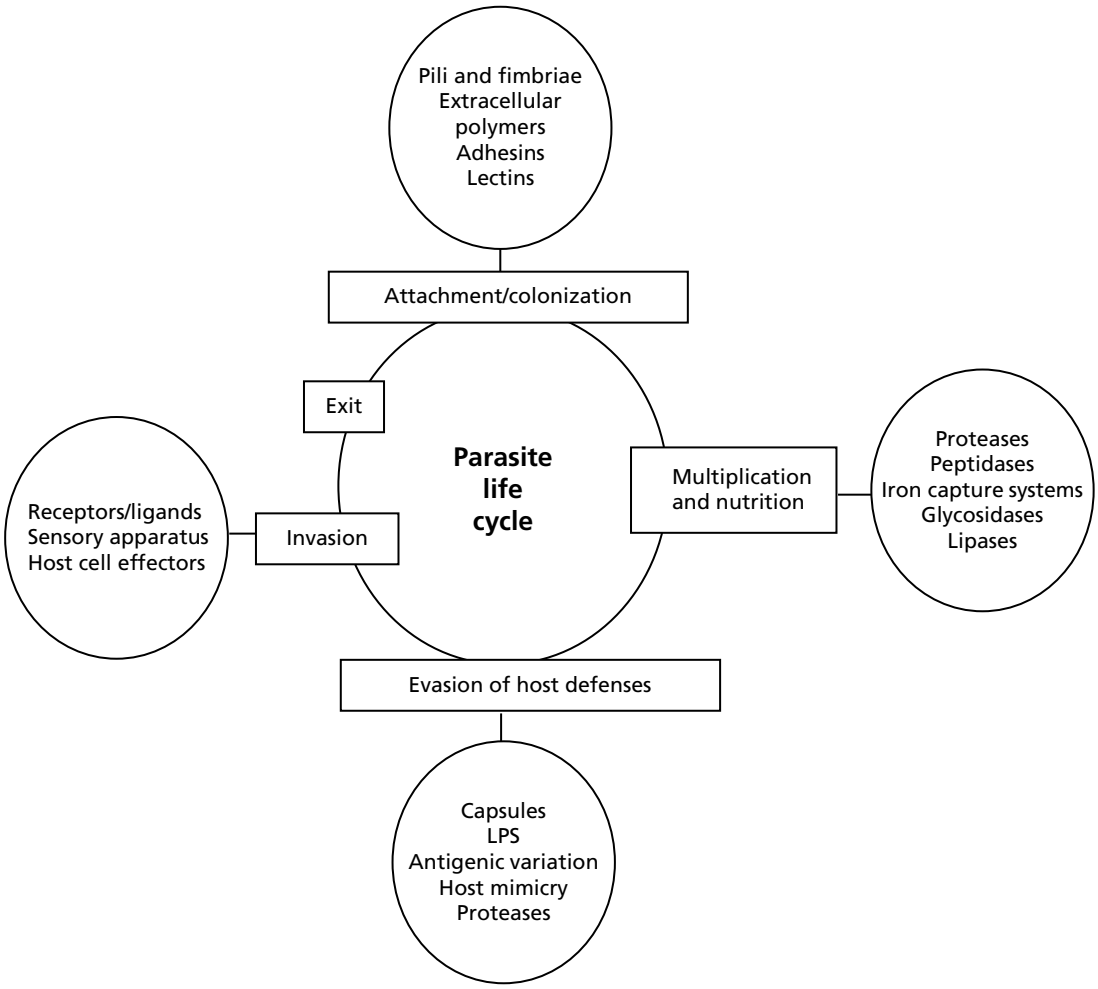


Fig. 10-14 Essential components of the parasite life cycle. Successful colonization and transmission of a parasite is dependent upon the ability to attach, multiply, evade host defenses, invade and exit the host. These processes each require specialized gene products and processes. (LPS, lipopolysaccharide.) (Adapted from Curtis *et al*. 2005, from John Wiley & Sons.)

organisms. Conversely, other lipid A moieties produced by *P. gingivalis* act as antagonists of this signaling pathway and are able to block the activity of the pro-inflammatory lipid A forms. This has led to the suggestion that by altering the proportions of the different lipid A components, *P. gingivalis* may be able to manipulate the innate response in order, for example, to down-regulate the inflammatory response as a defensive measure.

An additional evasive measure practiced by some of the better characterized periodontal bacteria, a component of the so-called "stealth technology", involves entry into other host cells, primarily epithelial cells, to gain access to an immune-privileged site (Lamont & Jenkinson 1998; Fives-Taylor *et al.* 1999; Meyer *et al.* 1999). Verification of this process *in vivo* is now emerging from the detection of these and other species using fluorescent labeling within buccal epithelial cells taken directly from the mouth (Fig. 10-15) (Rudney *et al.* 2005). In the case of *P. gingivalis*, the organism has been shown to rapidly invade epithelial cells derived from the human gingiva and accumulate and persist in high numbers with a perinuclear localization (Lamont & Jenkinson 2000).This positioning is similar to the localization observed for purified preparations of RgpA, which is able to translocate the plasma membrane of epithelial cells (Scragg *et al.* 2002). While the precise mechanism is still under investigation, FimA, a major fimbriae, and the gingipain proteinases are required for the attachment and internalization of the bacterial cells. In the case of *A. actinomycetemcomitans*, while the precise details of the mechanism are unknown, there is a suggestion that the invasion process may be augmented by soluble CD14 derived from saliva (Takayama *et al.* 2003).

The recognition that the virulence properties of some of the key organisms involved in periodontal disease may be more directed towards an anti-inflammatory or subversive phenotype is leading to a new appreciation of the etiopathogenesis of the disease process and this is presented in the final section of this chapter.

Microbial pathogenesis of periodontal disease

The extensive microbiologic analyses of periodontal infections over the last 100 years have led to the formulation of a number of hypotheses on the fundamental nature of the pathogenesis of the disease. In each

Table 10-3 Selected virulence determinants of some periodontal bacteria.

Organism	Product/activity	Comment	References
Porphyromonas gingivalis	Arginine gingipains: RgpA RgpB	Deregulation of host immune and inflammatory response: Complement inactivation Degradation of host protease inhibitors	Curtis *et al.* (2001)
	Lysine gingipain: Kgp	Hemoglobin breakdown/hemin acquisition	Lewis *et al.* (1999)
	Lipid A	Low inflammatory potential Antagonism of bacterial lipid A recognition by TLR4	Reife *et al.* (2006)
	Chemokine paralysis: SerB	Inhibition of chemokine IL-8 biosynthesis	Darveau *et al*. (1998), Hasegawa *et al*. (2008)
	Fimbrillin FimA	Adherence to epithelial cells Signaling	Sojar *et al*. (1999), Amano (2003)
	Capsule production	Evasion of phagocytosis	Aduse-Opoku *et al.*, 2006), Singh *et al*. (2011)
	Outer membrane vesicles	Infiltration of host tissues; decoy function	Grenier & Mayrand (1987), Furata *et al*. (2009)
	Epithelial cell invasion	Evasion of immune response, deregulation of epithelial cell function	Madianos *et al.* (1996), Tribble *et al*. (2006)
Aggregatibacter actinomycetemcomitans	Leukotoxin: LtxA	Killing of leukocytes	Lally *et al*. (1989)
	Cytolethal distending toxin: Cdt	Cell–cycle-mediated growth arrest	Sugai *et al*. (2004)
	Epithelial cell invasion	Evasion of immune response, deregulation of epithelial cell function	Meyer *et al.* (1996)
	Attachment: EmaA	Collagen binding	Ruiz *et al.* (2004)
Tannerella forsythia	Surface associated glycoproteins (S-layer) TfsA, TfsB	Attachment to epithelial cells	Lee *et al.* (2006), Higuchi *et al.* (2000)
	BspA surface protein	Leucine-rich repeat protein Potential role in adherence and invasion Interaction with the innate host response via TLR2 and 3.	Sharma *et al.* (1998)
	Sialidases: SiaHI NanH	Degradation of host oligosaccharides	Ishikura *et al.* (2003), Thompson *et al.* (2009), Stafford *et al.* (2012)
	Protease: PrtH	Epithelial barrier disturbance	Saito *et al*. (1997)
Treponema denticola	Major sheath protein: Msp	Cell surface porin associated with adherence	Fenno & McBride, (1998), Ellen (2006)
	Leucine rich protein: Lrr	Bacterial and epithelial cell adherence	Ikegami *et al.* (2004), Rosen *et al*. (2008)
	Dentilisin: PrtP	Degradation of host cell matrix proteins and signaling molecules	Uitto *et al.* (1988), Okuda *et al.* (2007)
	Trypsin-like protease: OpdB	Protein and peptide degradation	Lee & Fenno (2004)

TLR, Toll-like receptor; IL-8, interleukin-8.

case, bacteria in dental plaque are acknowledged to be the critically important agent in driving an inflammatory response in the periodontal tissues, which can ultimately lead to destructive disease. Hence, whilst the processes of irreversible destruction of the soft tissues of the periodontium and the bony support structures of the teeth occur through host-mediated mechanisms, these are dependent upon stimulation by a bacterial challenge. However, the underlying principles of each of these hypotheses differ significantly.

It was first believed that periodontal disease was the cumulative effect of all the bacterial species found

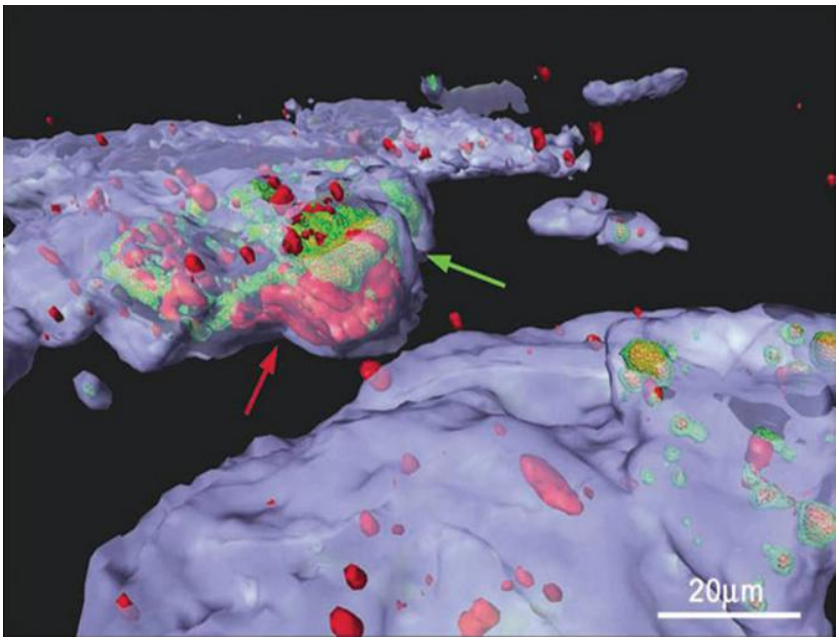


Fig. 10-15 Intracellular bacteria in buccal epithelial cells. A three-dimensional reconstruction of buccal epithelial cells stained using a specific probe for *A. actinomycetemcomitans* (green) and a universal probe for all bacteria (red). Bacteria recognized only by the universal probe are shown in solid red, while co-localization of the *A. actinomycetemcomitans* and universal probes is depicted by a green wireframe over a red interior. Reconstructed buccal epithelial cell surfaces are presented in blue. The red and green colors are muted when bacterial masses are intracellular, and brighter when bacteria appear to project out of the surface. The large mass which appeared to have a lobular structure was seen to be a cohesive unit containing *A. actinomycetemcomitans* in direct proximity to other species (red and green arrows). (Adapted from Rudney *et al*. 2005, from Sage.)

in dental plaque. This *non-specific plaque hypothesis* held that the precise microbial composition of dental plaque was not the critical determinant of disease, rather it was the magnitude of the total bacterial challenge, or the amount of dental plaque, in juxtaposition with the periodontal tissues, that was the overriding factor determining the balance between health and disease. The origins of this hypothesis extend as far back as the end of the 19th century when bacterial isolation and identification techniques were still in their infancy. Gradually, this non-specific view of the etiology came under increasing scrutiny. First, it was clear that the presence of large accumulations of dental plaque in some individuals did not lead to destructive disease or, in some instances, even mild symptoms of inflammation. Furthermore, the increased sophistication of clinical microbiology was beginning to demonstrate that there were very marked differences in the microbial composition of dental plaque taken from sites in patients with disease in comparison to healthy sites in the same patient or indeed from healthy individuals. Hence, the prevailing view altered to one in which the presence and potential overgrowth of specific bacteria, or periodontal pathogens, was decisive.

The *specific plaque hypothesis* (Loesche 1979) has since provided the conceptual framework for much of the investigation of the microbial etiology of periodontal disease. More detailed investigations of the microbiota has led to the identification of increasing numbers of bacterial species which appear to be more associated with disease than health. Patterns in the association between different bacterial species in different clinical conditions were observed and encouraged the view that there may be specific combinations or complexes of species that are the most critical in the development of disease. Importantly, the pathogenic potential of some of these candidate species, either singly or in combination, came under investigation in both animal models and *in vitro* systems. This led to the development of plausible biologic mechanisms by which these specific organisms could contribute to the promotion or deregulation of an inflammatory response and/or impaired immune defense of the periodontal tissues.

The diagnostic and treatment implications of the specific plaque hypothesis are self-evident. If specific bacterial species are the driving force of the disease, then identification of the presence of these organisms in an individual ought to be helpful in predicting clinical outcome. Furthermore, targeted treatment strategies which aim to eliminate or at least control these particular organisms, rather than necessarily attempting to eliminate the entire microbial population, should be clinically beneficial. The specific plaque hypothesis also raises the issue of where and how these organisms are acquired. If they are acquired exogenously, that is transmitted from another individual rather than being component members of the oral microbiota acquired early in life, then strategies which prevent or limit transmission in the human population could be considered beneficial in the same way as prevention of transmission of more well-known medically important human pathogens is an accepted and successful public health measure.

This latter issue has been subsequently addressed by an alternative hypothesis – the *ecological plaque hypothesis* (Marsh 2003). In this thesis, the contribution of the environment in which the bacteria of dental plaque reside is paramount. The varying abilities of different bacteria to grow and proliferate under different environmental conditions will dictate the balance of microbial communities at any given site on the tooth surface. For example, in a periodontal pocket where the pH can rise to well over 7, those bacteria most well suited to grow at alkaline pH will be able to out compete those bacteria most suited to more acidic conditions. Similarly, organisms able to withstand the antimicrobial properties of the host's inflammatory response will be more predominant at inflamed sites in the periodontium than those bacteria ill-equipped for this injurious environment. Hence, the composition of microbial communities in disease will be intimately linked to the environmental conditions prevalent at a diseased site.

Shifts in the environmental conditions due to, for example, the introduction of different nutrients with the arrival of a plasma exudate in the form of gingival crevicular fluid (GSF), will lead to concomitant shifts in the microbial community. Organisms previously limited in their growth due to, for example, only very low concentrations of the iron source, hemin, will have the nutritional capacity to increase in number and potentially out compete those bacteria most frequently found in health where low or no GCF is present. Those bacteria able to withstand the killing effects of migratory phagocytic cells will be able to increase in number at the expense of those organisms susceptible to these killing mechanisms. In so doing, the newly selected microbial community will present a different and potentially more injurious challenge to the periodontal tissues and hence the escalation of increasing inflammation coupled to frustrated bacterial clearance will continue. Importantly, the ecological plaque hypothesis allows for the fact that potential periodontal pathogens may be present in health, albeit in relatively low numbers, but with the capacity to become more dominant members of the community when the environmental conditions favor their competitiveness over the other, more health-associated, members of the microbiota. Thus, this hypothesis can explain the microbial specificity of the disease without the requirement for the acquisition of these periodontal pathogens via an exogenous route of transmission in order to initiate the disease.

This evolving view of the pathogenesis of periodontal disease now has a further modification which incorporates elements of all the preceding views, both specific and non-specific, and acknowledges the fundamental importance of dysbiosis of the normally benign microbial populations of the tooth surface in the development of disease (Darveau *et al.* 2012). The essence of this more recent concept of pathogenesis comes primarily from the recognition of the global population changes that occur to the microbiota in periodontal disease. However, it is significantly reinforced by observations in the mouse model of periodontal disease showing that one of the presumed key specific agents of the disease, *P. gingivalis* – a member of the "red complex" of periodontal bacteria, contributes to disease by altering the normal oral microbiota to a dysbiotic state (Hajishengallis *et al.*, 2011). These studies demonstrated that the oral commensal microbiota is responsible for the tissue and bone destruction associated with periodontitis when just low numbers of *P. gingivalis* are present.

This finding helps explain an apparent paradox associated with *P. gingivalis* being regarded as a key specific agent in periodontal disease when several lines of investigation have demonstrated that this bacterium is not a potent inducer of inflammation (Curtis *et al.* 2011). For example, as described earlier in this chapter, the LPS of *P. gingivalis* has an unusually low inflammatory potency and furthermore this bacterium is able to synthesize a lipid A structure that inhibits rather than promotes inflammation through antagonism of one of the innate immune receptors for LPS, Toll-like receptor 4. This is in stark contrast to the highly inflammatory properties of the LPS produced by most other bacteria and challenges the view that exacerbation of the inflammatory response by *P. gingivalis* is a driving force in the development of periodontal disease. In addition, *P. gingivalis* is unusual in that it does not induce secretion of interleukin-8 (IL-8) by gingival epithelial cells, unlike a variety of other oral bacteria. Instead, it actually inhibits the secretion of this potent chemokine for neutrophil recruitment through a phenomenon termed local chemokine paralysis (Darveau *et al.* 1998). Once again, such an anti-inflammatory property, in this case down-regulation of phagocytic cell trafficking into the periodontium, is contrary to the properties one would anticipate to be a prerequisite of an organism which drives the disease process through up-regulation of the inflammatory response. These apparent paradoxes can however be explained if periodontitis is viewed as a community disease reliant upon an entire dysfunctional microbiota as opposed to the traditional view of a conventional infectious disease caused by a single, multiple or indeed complexes of periodontal pathogens.

The evidence that the commensal microbiota may significantly contribute to periodontitis was obtained when the disease experience of germ-free mice, which are not colonized with any bacteria, was compared to that of the well-established *P. gingivalis* murine model of periodontal disease with an intact commensal microbiota. Although both groups of mice were colonized in the oral cavity to the same extent with *P. gingivalis*, only the mice with a commensal microbiota developed bone loss. Furthermore, in the conventional animals, there was a very significant change in the commensal microbiota. First, the total load of the commensal organisms rose by approximately 2 log10 units. Second, there was a qualitative shift in the

population structure of this commensal microbiota, leading to loss of detection of some organisms and the appearance of others. The demonstration that *P. gingivalis* colonized both germ-free and conventional animals, yet only the conventional mice developed disease, and the very significant changes in the oral commensal community in these animals, indicated that the commensal bacteria themselves are necessary for and directly contribute to the bone loss observed in this model. In addition, and based upon the fact that *P. gingivalis* was present in very low abundance yet had such a profound effect on both the amount and composition of the oral microbiota and resulted in periodontal disease, this bacterium was designated a "keystone" species in this work. The concept of a keystone species derives from ecologic studies and is defined as a species that is present in low abundance yet provides a major supporting role for an entire ecologic community (Hajishengallis *et al.* 2012).

Hence, admittedly only in a model of the disease, *P. gingivalis* contributes to destructive periodontitis in an indirect fashion. Rather than a direct effect on host tissue function, its presence, even at low abundance, alters the total commensal microbial load and composition which overwhelms normal host tissue protective mechanisms and results in disease. The qualitative changes in the microbiota may include an increase in the numbers of more harmful bacteria and/or a shift in the balance of the microbiota away from organisms which are potentially protective. The mechanisms through which *P. gingivalis* accomplishes this significant microbial change are still only partially understood, but are probably related to inhibition of key features of the normal host protective mechanisms in the periodontium, as shown in Fig. 10-16. Consistent with a keystone contribution of *P. gingivalis* to disease, studies in humans have shown that *P. gingivalis* is frequently present in low abundance when compared to the total oral microbiota in diseased sites (Kumar *et al.* 2006). It remains to be determined whether other members of the oral microbiota designated as periodontal pathogens in Table 10-3 share similar "keystone species"-like properties to *P. gingivalis* in being able to shape the quantity and qualitative nature of the entire microbial community; this model leaves open that possibility. However, the key features of this model are consistent with many of the microbiologic observations of periodontal infections and combine elements of both the non-specific hypothesis, through Acknowledgment of the fundamental importance of the total microbial load of the entire microbiota, and of the specific plaque hypothesis, through acknowledging the role of individual bacterial species.

Conclusion

Our understanding of the microbial pathogenesis of periodontal disease has undergone significant changes over the last century and continues to be

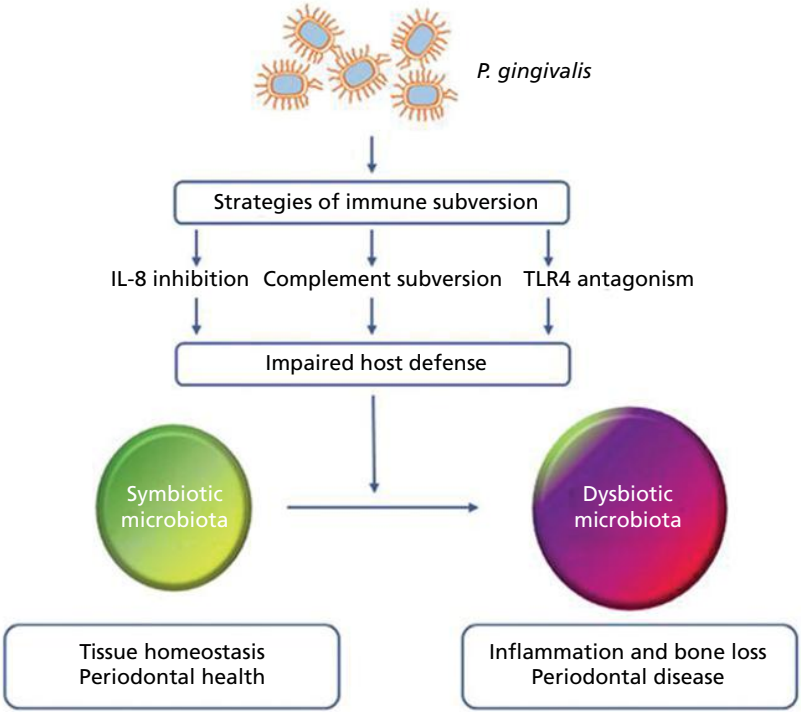


Fig. 10-16 Red complex bacterium *P. gingivalis* causes inflammation and bone loss by remodeling the oral commensal microbiota. *P. gingivalis* modulates innate host defense functions that can have global effects on the oral commensal community. Immune subversion of interleukin-8 (IL-8) secretion, complement activity, or Toll-like receptor 4 (TLR4) activation can result in an impaired host defense. The inability of the host to control the oral commensal microbial community in turn results in an altered oral microbial composition and an increased microbial load. This alteration from a symbiotic to a dysbiotic microbiota is responsible for pathologic inflammation and bone loss. (Source: Darveau *et al.* 2012. Reproduced with permission from SAGE Publications.)

refined to this day through more detailed analyses of clinical samples, improved understanding of the biology of the component organisms of this microbiota, and application of experimental model systems. In this chapter, the central role of a dysbiotic microbiota has been highlighted, similar to our understanding of the etiology of diseases with a complex microbial etiology at other sites of the human body. In all of these cases, disease is a consequence of a breakdown in the normally homeostatic balance between the commensal microbiota and the immune and inflammatory systems of the tissues. In this regard, periodontal infections and the response to them represent an excellent, accessible, and tractable system to understand the underlying principles of a wide range of inflammatory diseases of humans characterized by a dysbiotic commensal microbiome.

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Chapter 11

Peri-implant Infections

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Introduction

With a large and increasing number of implants being placed worldwide, it is expected that there will be an increase in the number of patients diagnosed with peri-implant infections. Peri-implant infections or peri-implant diseases are defined as either (1) peri-implant mucositis, where there are clinical signs of inflammation (bleeding on gentle probing, 0.25 N) of the peri-implant mucosa without loss of supporting bone, or (2) peri-implantitis, where there is concomitant loss of supporting bone. In the case of peri-implantitis, probing depths ≥5 mm and suppuration are frequently present (Lang & Berglundh 2011) (Fig. 11-1). This chapter addresses the etiology of peri-implant infections, describing the microbiota associated with healthy and diseased peri-implant tissues in both partially dentate and edentulous subjects. Factors influencing peri-implant biofilm formation and risks for peri-implant infection, including material surface characteristics, local environment, and reconstruction design, are discussed. Similarities and differences in the microbiota associated with periodontal and peri-implant infections are outlined, and the clinical implications discussed. Finally, effects on the microbiota of an anti-infective approach in the management of peri-implant infections are described.

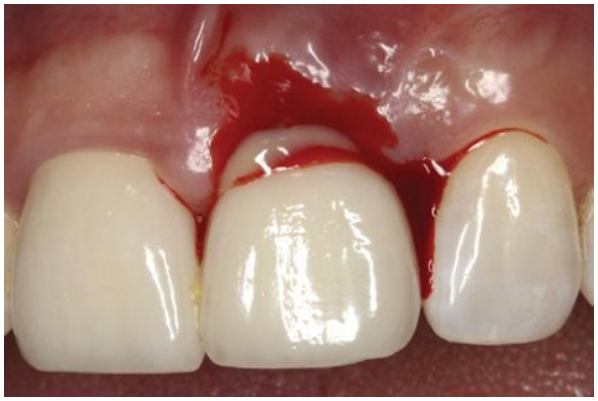

Fig. 11-1 Clinical appearance of a peri-implant infection with suppuration and bleeding following probing of the deep (>6 mm) peri-implant pocket.

Peri-implant biofilm formation

When a dental implant is placed, the endosseous part of the implant should ideally be surrounded by bone and is, therefore, usually not exposed to biofilm formation. In contrast, the transmucosal part of the implant/abutment, once exposed to the oral cavity, becomes rapidly colonized by microorganisms (Fürst *et al*. 2007), which attach to salivary proteins and peptides constituting the pellicle. The pellicle provides receptors for adhesins present on the cell surface of all

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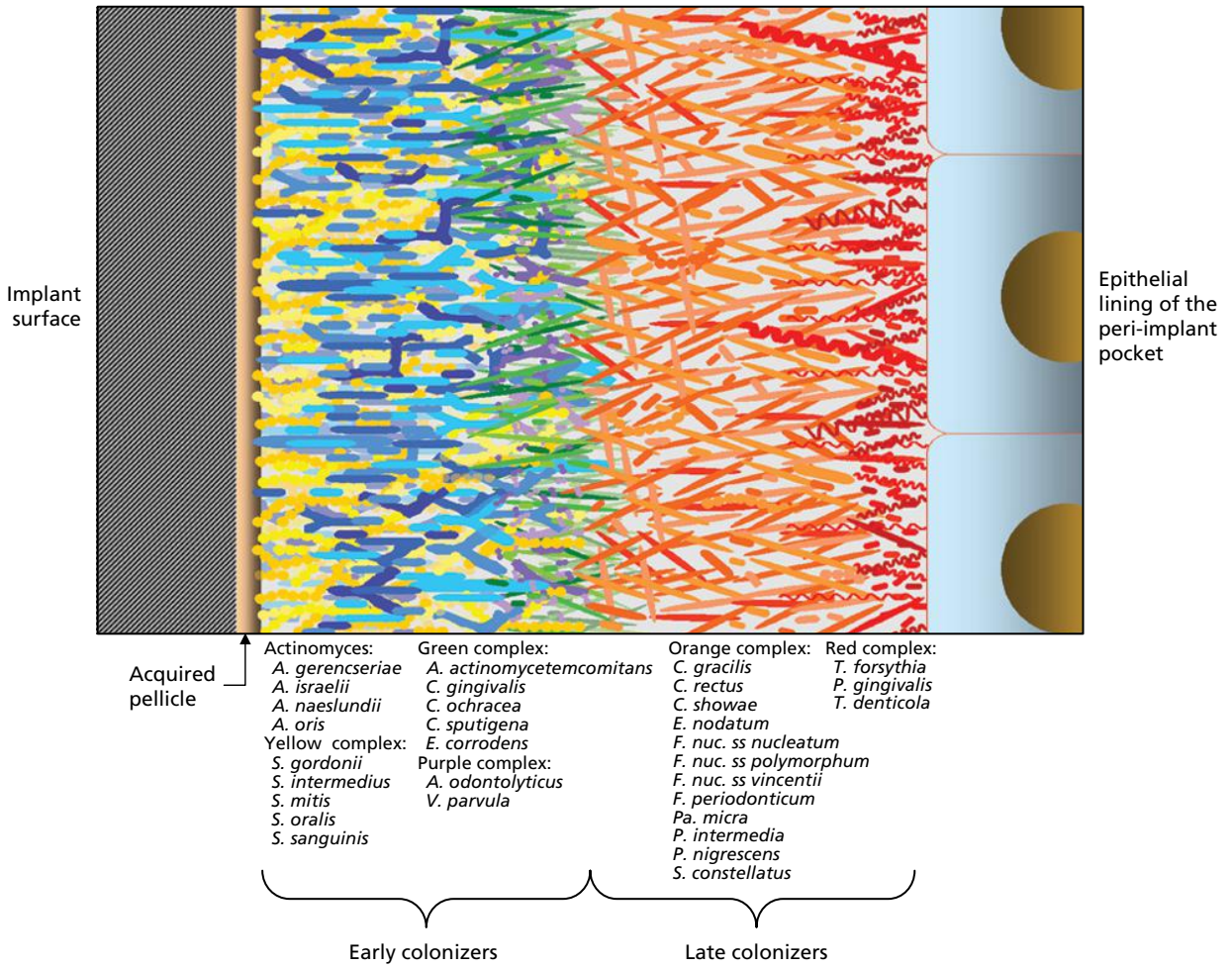


Fig. 11-2 Simplified schematic representation of the microbial succession that may take place on an implant surface exposed to the oral environment. Microbial species are colored according to the microbial complexes described by Socransky *et al*. (1998).

oral bacterial species. Enamel pellicles and titanium pellicles are not identical. Salivary pellicles formed on titanium surfaces *in vitro* have been found to include molecules such as high molecular weight mucins, α-amylase, secretory IgA, and proline-rich proteins, while molecules commonly found on tooth enamel (cystatins and low molecular weight mucins) were not detected (Edgerton *et al*. 1996). Although the salivary pellicle that forms on titanium surfaces might differ from that forming on enamel surfaces, the differences do not seem to influence the bacterial composition of the biofilm formation (Leonhardt *et al*. 1995).

Due to a common ecologic environment, the principles and sequence of biofilm formation at teeth and implants are similar (Lang & Berglundh 2011). Biofilm formation is initiated by adhesion of early colonizers such as *Streptococcus sanguinis* and *Actinomyces naeslundii*, through interactions with the salivary pellicle. The early colonizers grow, modify the environment, and promote the adhesion of secondary colonizers via co-aggregation (Fig.11-2). The biofilm with its diverse community of interacting organisms, glycocalyx matrix, and complex structure becomes stable over time, affording a protective environment from host defenses and antimicrobial agents (Marsh 2005; Socransky & Haffajee 2005; Kolenbrander *et al*. 2006). Figure 11-3 shows a series of scanning electron micrographs illustrating different stages of biofilm formation on a titanium implant surface.

Factors which may influence microbial colonization include the surface characteristics of the implant/abutment, local environment, resident oral microbiota, and implant prosthesis design and its accessibility for oral hygiene.

Surface characteristics of the implant/abutment

Surface characteristics of the implant/abutment and restorative components, including chemical composition, surface free energy (SFE; wettability), and surface roughness, may impact biofilm formation. Both *in vitro* and *in vivo* studies have indicated that increasing the surface roughness of titanium results in greater bacterial adhesion and biofilm accumulation (Teughels *et al*. 2006; Subramani *et al*. 2009; Burgers *et al*. 2010; Fröjd *et al*. 2011). An *in vitro* scanning electron microscope study investigating attachment of oral species to titanium disks with various surface characteristics, demonstrated an increased bacterial attachment to rough surfaces (Wu-Yuan *et al*. 1995). In a series of split-mouth studies, it was

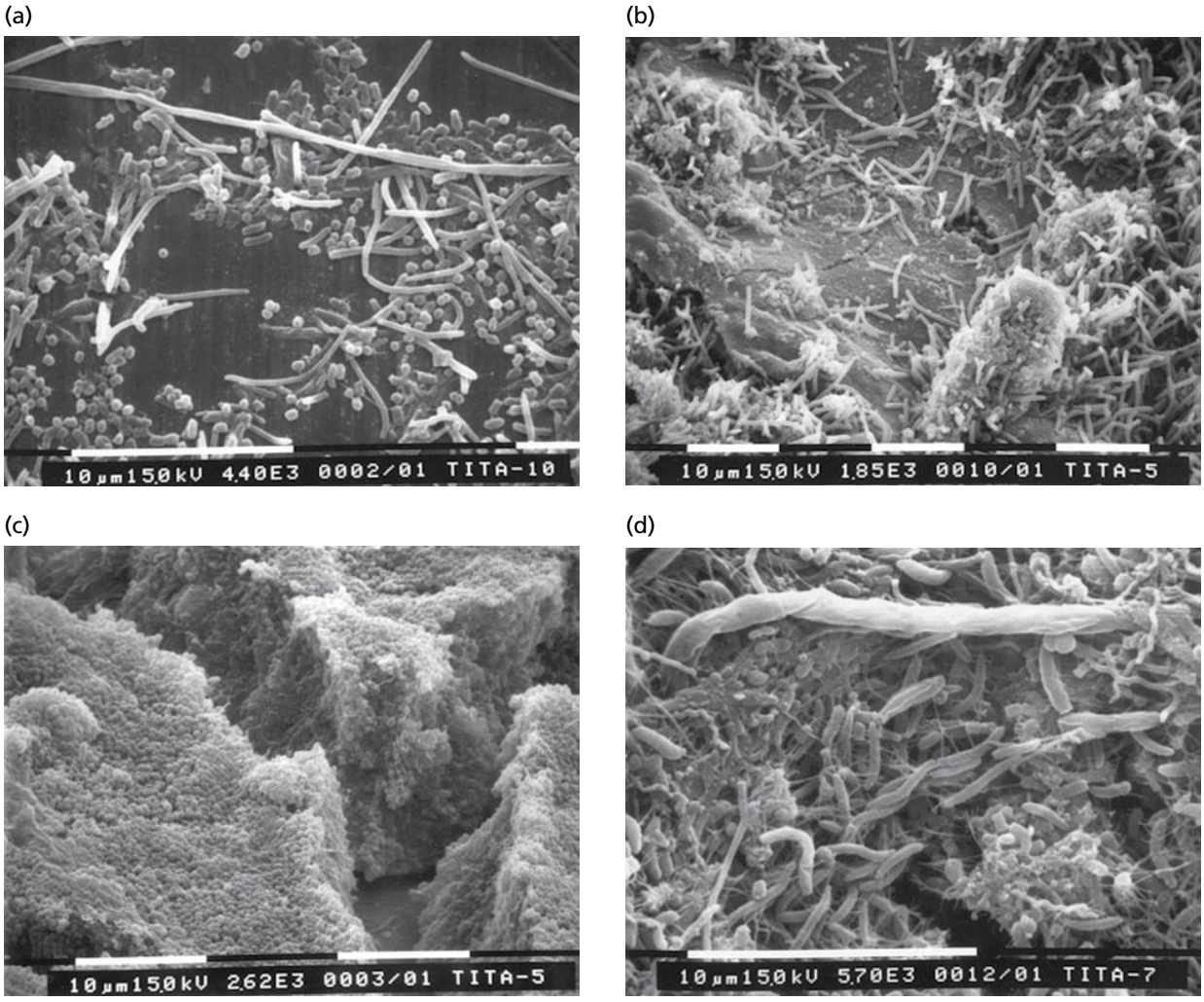


Fig. 11-3 Scanning electron micrographs showing different stages of biofilm formation on a titanium implant surface. One can observe the initial colonization by a small number of cells and a limited variety of bacterial morphotypes (a, b), followed by an increase in the biomass due to the proliferation of early colonizers (c) and the subsequent establishment of a complex climax community (d). (Courtesy of C. Cobb.)

demonstrated that an increase in the surface roughness (Ra) above a threshold of 0.2 μm and/or an increase in the SFE facilitated biofilm formation on restorative materials (Teughels *et al*. 2006). The effect of SFE on supra- and sub-mucosal plaque maturation around implants was investigated by comparing plaque from abutments with either a high (titanium) or a low (teflon coating) SFE (Quirynen *et al*. 1993). The teflon-coated titanium abutments harbored a less mature biofilm characterized by a higher proportion of cocci and a lower proportion of motile organisms and spirochetes than the uncoated titanium abutments (Quirynen *et al*. 1993). When both surface characteristics interact with each other, surface roughness was found to be predominant (Teughels *et al*. 2006). The impact of surface roughness on biofilm formation can be explained by several factors, including the protection from shear forces, increased area for adhesion, and difficulty in cleaning rough surfaces which enables rapid regrowth of the biofilm by multiplication of resident bacterial species (Quirynen & Bollen 1995).

Quantitative analysis of 14-day supra- and submucosal biofilm formation on titanium healing abutments in 10 subjects, showed that biofilm formation was significantly increased by higher surface roughness in supramucosal areas, with no influence of increased surface roughness in the submucosal environment (Elter *et al*. 2008).

An *in vitro* study examined the effect of surface characteristics on biofilm formation, using two and three-species biofilm models, 16S ribosomal RNA (rRNA) fluorescence, and confocal scanning laser microscopy (CSLM) (Fröjd *et al*. 2011). After 2 hours, surfaces with increased surface roughness had higher bacterial adhesion, most likely the result of protection of bacteria from shear forces. However, after 14 hours the volume of biofilm was similar on all surfaces, indicating that the influence of surface characteristics on adhesion was surpassed by biofilm development (Fröjd *et al*. 2011).

A range of restorative materials is available for fabrication of implant components, including titanium, gold, ceramics, and zirconium. Due to an increased demand for tooth-colored restorations, zirconium oxide ceramics (zirconia) have become more widely used as materials for implant abutments and transmucosal components of implant prostheses. In an *in vivo* study using CSLM to investigate the formation

of oral biofilm on various dental ceramics, zirconia was shown to exhibit low biofilm accumulation when used intraorally (Bremer *et al*. 2011). Several randomized controlled studies have compared the early bacterial colonization of periodontal pathogens at zirconium oxide abutments to titanium alloy abutments. While zirconium oxide abutments showed lower SFE than titanium abutments, there was no difference in the adhesion of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, 5 weeks after abutment connection (Salihoglu *et al*. 2011). This lack of difference between zirconium and titanium was confirmed in a similar study evaluating bacterial counts of seven bacterial species 2 weeks and 3 months following abutment connection (van Brakel *et al*. 2011).

Based on the surface roughness value Sa (average 3D height deviation), a proposal to categorize the surfaces of titanium implants as smooth (Sa <0.5 μm), minimally rough (Sa 0.5–1.0 μm), moderately rough (Sa 1.1–2.0 μm), and rough (Sa >2.0 μm) was made (Albrektsson & Wennerberg 2004). The original Brånemark turned machined surface was a minimally rough surface. More recently, the surfaces of commercially available titanium implants have been modified to promote osseointegration and are moderately rough or rough. If these implant surfaces become exposed to the oral environment, due to loss of supporting peri-implant marginal bone, the roughened surface may enhance biofilm formation and contamination of the implant surface. While there is no evidence that surface roughness of a properly placed and integrated implant influences the development of peri-implant infection, it has been documented that rough surface implants [titanium plasma sprayed (TPS)] are more likely to develop peri-implantitis than minimally rough implant surfaces if the implant surface becomes exposed to the oral environment (Lang & Berglundh 2011).

Local oral environment

Peri-implant colonization has been studied in both edentulous and partially dentate patients. A cause and effect relationship between biofilm formation on implants and peri-implant mucositis has been demonstrated in humans (Pontoriero *et al*. 1994; Zitzmann *et al*. 2001; Salvi *et al*. 2012). In these studies, when oral hygiene was discontinued in order to allow undisturbed plaque accumulation, clinical signs of peri-implant inflammation appeared after a few days and resolved when oral hygiene was reinstated. Not surprisingly, the composition of peri-implant biofilms associated with this inflammation, which may lead to further peri-implant infection in a susceptible host, is influenced by the local environment and the microbiota on the remaining teeth in partially dentate subjects. Cross-sectional studies have shown that the microbiota identified in the peri-implant sulci are nearly identical to those found at neighboring teeth (Quirynen & Listgarten 1990; Leonhardt *et al*. 1993; Mombelli *et al*. 1995b; Lee *et al*. 1999; Hultin *et al*. 2000; Agerbaek *et al*. 2006). It has been shown that deeper periodontal pockets harbor a greater number and proportion of periodontal pathogens (Socransky *et al*. 1991), serving as a potential reservoir for recolonization.

Transmission of bacteria from periodontal pockets to the peri-implant region of newly placed implants has been suggested in longitudinal studies (Mombelli *et al*. 1995a; Quirynen *et al*. 1996). A number of studies have used techniques to identify individual strains of bacteria in order to determine if transmission from a periodontal site to an implant site can occur in a patient (Sumida *et al*. 2002; Takanashi *et al*. 2004). Using pulsed field gel electrophoresis (PFGE), chromosomal DNA segmentation patterns of isolates of *P. gingivalis* and *Prevotella intermedia* obtained from implants and natural teeth in the same subjects were found to be identical, while PFGE patterns differed among samples from different subjects (Sumida *et al*. 2002). Similarly, it was found that 75% of the *P. gingivalis* isolates in samples from teeth and implants were the same in one subject, while 100% of the *P. intermedia* strains within a subject were a perfect match, clearly demonstrating transmission from the natural teeth to the implant sites (Takanashi *et al*. 2004). Although the remaining dentition seems to be the primary source of bacteria for the colonization of implant surfaces in partially dentate subjects, the potential role of soft tissue surfaces, crypts of the tongue or tonsils, and saliva as reservoirs for implant colonization should also be considered. A comprehensive assessment of the microbiota associated with oral mucosal surfaces in edentulous subjects wearing complete dentures, outlined the numerous habitats colonized by biofilms of differing complexities, unique to each individual (Sachdeo *et al*. 2008). Biofilm samples were taken from the dentures, the dorsal, lateral, and ventral surfaces of the tongue, the floor of the mouth, buccal mucosa, hard palate, vestibule/lip, and saliva. Checkerboard DNA–DNA hybridization was used to analyze the levels and proportions of 41 different species. Distinct patterns of microbial colonization were seen on different soft tissue surfaces and in saliva. One of the more important findings of this investigation was the detection of the periodontal pathogens *A. actinomycetemcomitans* and *P. gingivalis* in these edentulous subjects, as it was previously thought that these species would not be present following removal of all teeth (Sachdeo *et al*. 2008). Other studies have also reported the presence of periodontal pathogens in edentulous subjects (Danser *et al*. 1998; Cortelli *et al*. 2008) and in edentulous subjects in an elderly population who had never worn dentures but had a history of periodontitis (Fernandes *et al*. 2010).

These findings have clinical implications for the prevention of peri-implant infections. Pathologic conditions in the oral environment, such as the persistence of untreated periodontal disease, could induce changes in the ecosystem that may favor the colonization of pathogenic microorganisms at implant sites (Lang & Berglundh 2011). Treatment of

periodontal disease prior to implant placement, and provision of adequate supportive periodontal/peri-implant maintenance care in order to reduce the reservoir of potential periodontal pathogens, may reduce the risk of peri-implant infections.

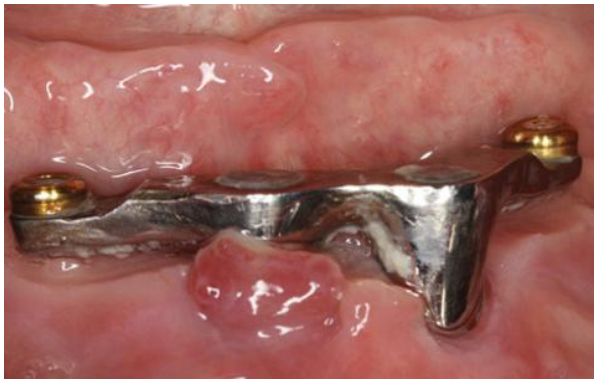
Oral hygiene and accessibility

The importance of maintenance care in the prevention of peri-implant infections has been demonstrated in several studies where subjects who did not follow a structured maintenance care program had a greater incidence of peri-implant infections than those who followed a maintenance care program (Roccuzzo *et al*. 2010; Costa *et al*. 2012). The importance of good compliance following treatment [adhering to the recommended prophylaxis/supportive periodontal therapy (SPT) interval, and maintaining a full-mouth plaque score of <20% (O'Leary *et al*. 1972)] was also highlighted in a cross-sectional study where the prevalence of peri-implantitis was associated with poor compliance (Rinke *et al*. 2011).

Peri-implant infection has been linked with poor oral hygiene (Lindquist *et al*. 1997; Ferreira *et al*. 2006) (Fig. 11-4). Higher plaque scores, assessed using the modified Plaque Index (mPI) (Mombelli *et al*. 1987), were significantly associated with peri-implant infection in a cross-sectional study evaluating 212 partially dentate subjects with implant-supported prostheses (Ferreira *et al*. 2006). One pertinent study underlined the importance of designing implant prostheses with adequate access for cleaning (Serino & Ström 2009). Subjects who were referred for treatment of peri-implantitis at one or more of their implants were found to have no access for appropriate oral hygiene measures in a high proportion of the implants diagnosed with peri-implantitis, while good access for oral hygiene was rarely associated with peri-implantitis (Serino & Ström 2009). Implant reconstructions should be designed to enable access for regular self-performed biofilm removal, and for early detection of clinical signs of peri-implant infection (Fig. 11-5).

Cemented prostheses should be designed with accessible cement margins. Peri-implant infection was associated with the presence of excess luting cement, acting as a foreign body, in the peri-implant sulcus of 81% of 39 cases following cementation of prostheses (Wilson 2009). Once the excess cement was removed, the clinical signs of infection resolved in 74% of cases (Wilson 2009).

(a)



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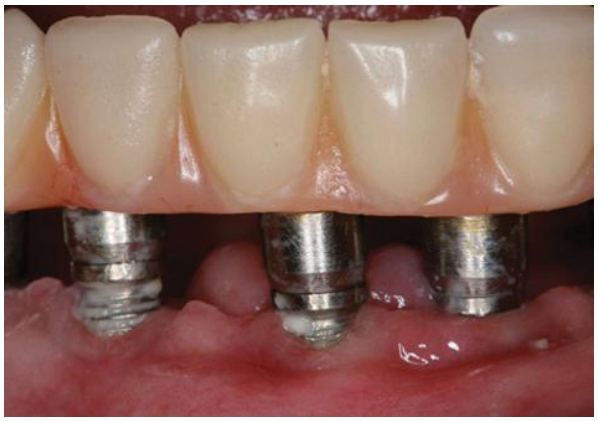
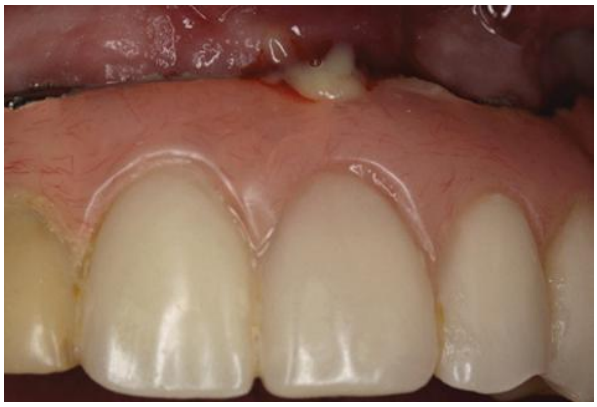


Fig. 11-4 Supramucosal peri-implant biofilm accumulation and associated peri-implant infections. (a) Biofilm present on the implant supported bar and implant abutments. (b) Biofilm present on the titanium abutment surfaces and exposed implant threads due to poor oral hygiene.

(a)



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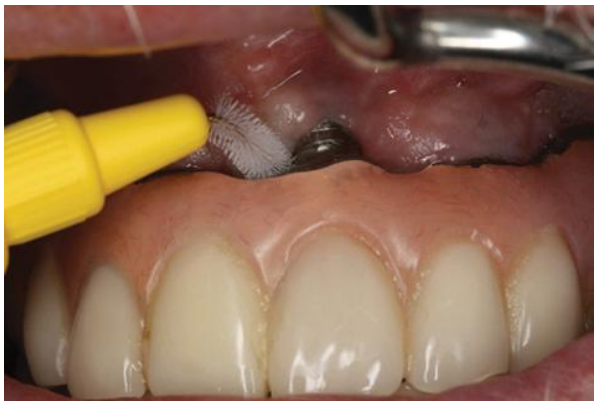

Fig. 11-5 (a) Clinical photograph showing an implant-supported prosthesis where there is inadequate access for plaque removal and an associated peri-implant infection (suppuration and bleeding). (b) Clinical photograph after remodeling of the implant-supported prosthesis to enable access for plaque removal.

Microbiota associated with peri-implant mucosal health

An understanding of the nature and composition of biofilms associated with peri-implant health and disease is important in order to develop targeted and effective preventive and treatment strategies for the management of peri-implant infections.

A peri-implant biofilm is formed within minutes of exposure to the oral cavity, and a multispecies supra- and sub-mucosal complex community develops within weeks to months of exposure to the oral cavity (Quirynen *et al*. 2005; Fürst *et al*. 2007). This is similar to the dynamics of biofilm formation at teeth (Socransky & Haffajee 1997; Li *et al*. 2004; Kolenbrander *et al*. 2006), although it has been suggested that it may take longer for a mature biofilm to develop at implant sites (Papaioannou *et al*. 1995; Sbordone *et al*. 1999). Figures 11-6 and 11-7 illustrate the similarity of the microbiota colonizing tooth and implant sites within the same subject (Quirynen *et al*. 2006). Figure 11-8 illustrates the increase in detection frequency of *P. gingivalis* and *Tannerella forsythia* over time after non-submerged implant placement in 22 partially dentate subjects with a history of treated aggressive periodontitis (De Boever & De Boever 2006).

Early investigations characterized the peri-implant microbiota using darkfield microscopy and culture analyses to examine samples taken from the peri-implant sulci of newly placed implants in edentulous subjects (Mombelli *et al*. 1987, 1988; Mombelli & Mericske-Stern 1990). The microbiota associated with peri-implant health was described as predominantly Gram-positive facultative cocci, with high levels of *Actinomyces* and *Veillonella* spp., low total anaerobic counts, low levels of Gram-negative anaerobic rods, and low proportions of *Fusobacterium* spp., spirochetes, fusiforms, motile and curved rods. Thus, the microbiota appeared similar to that associated with healthy periodontal sites in healthy periodontal subjects (Socransky & Haffajee 2005).

As previously discussed, the lack of detection of species such as *P. gingivalis* in edentulous patients (Mombelli *et al*. 1987; Danser *et al*. 1994, 1995, 1997) and edentulous patients with implants (Mombelli *et al*. 1987; Ong *et al*. 1992) led to the suggestion that periodontal pathogens do not colonize dental implants placed in edentulous individuals. However, subsequent investigations incorporating more sensitive molecular techniques for analyses [including polymerase chain reaction (PCR), DNA–DNA checkerboard hybridization] have shown this

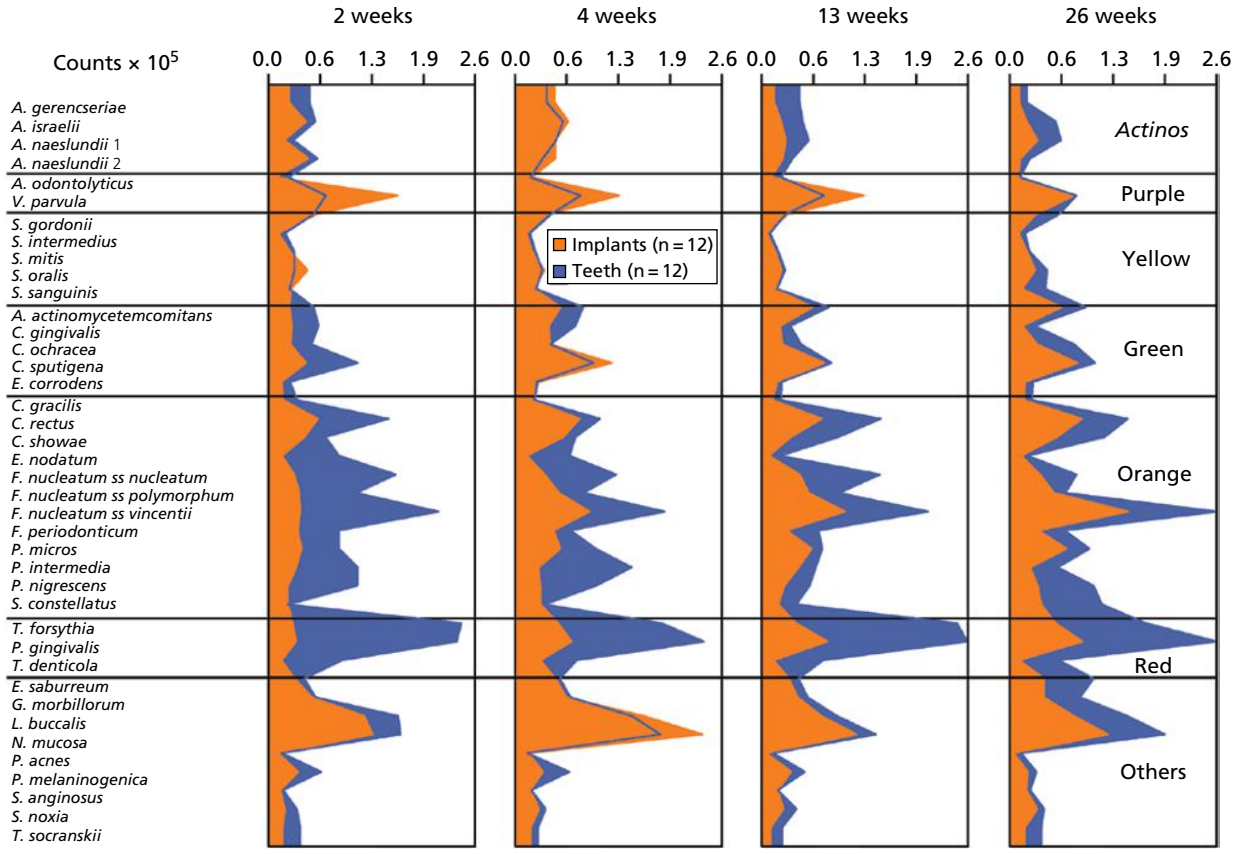

Fig. 11-6 Mean counts (×10[5]) of 40 species in samples from 48 implants and 48 teeth in 12 subjects at 2, 4, 13, and 26 weeks after exposure of the implant to the oral environment. Mean counts of each species were computed by averaging the data for each site category separately in each subject, and then averaging across subjects at each time point separately. Significance of differences between site categories was sought using the Mann–Whitney test. No significant differences were found after adjusting for multiple comparisons (Socransky *et al*. 1991). The species were ordered and grouped according to the complexes described by Socransky *et al*. (1998). (Data adapted from Quirynen *et al*. (2006).)

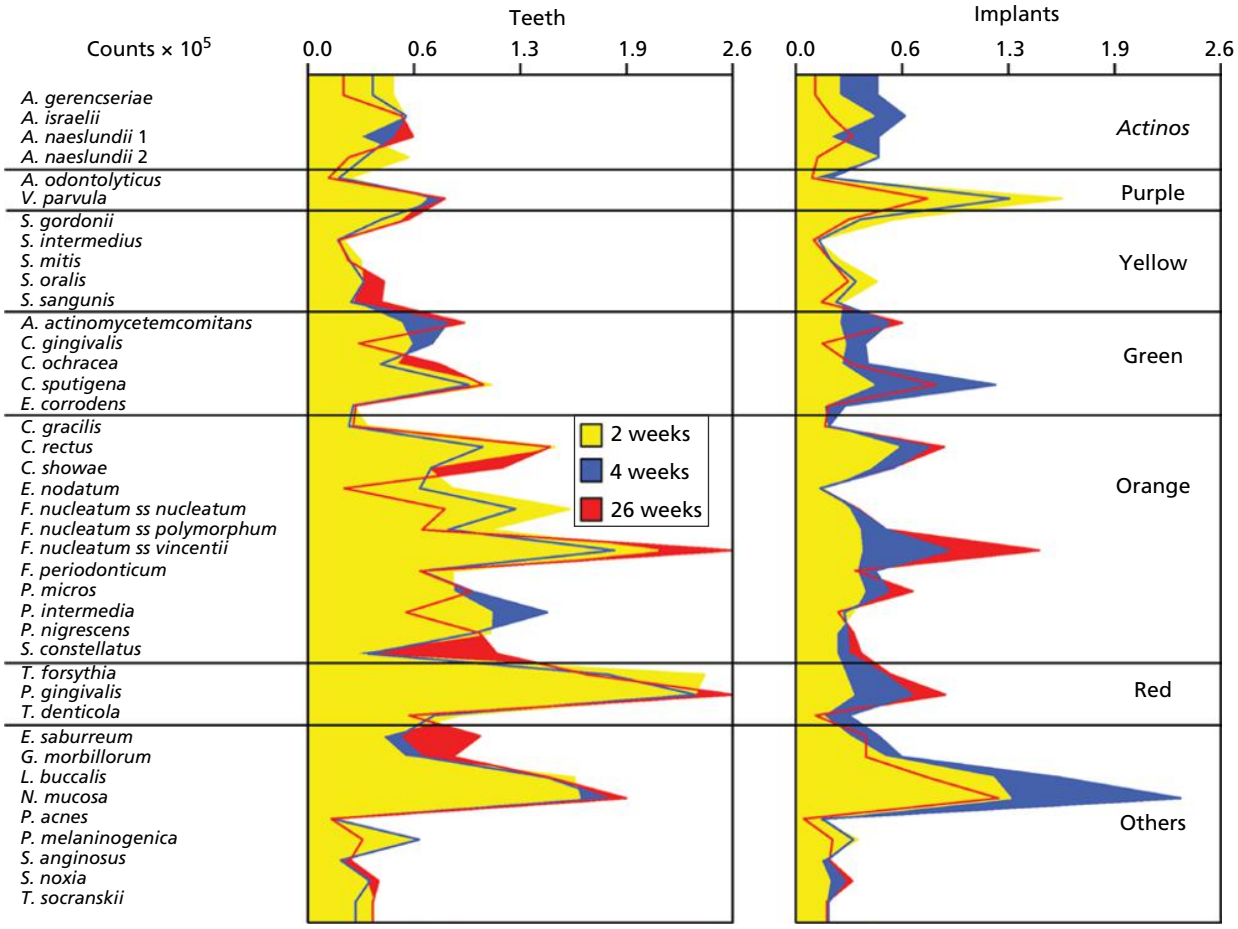

Fig. 11-7 Mean counts (×10[5]) of 40 species at 2, 4, and 26 weeks after implant exposure in samples from 48 teeth (left panel) and 48 implants (right panel) from 12 subjects. Mean counts of each species were computed by averaging the data for each site category separately in each subject, and then averaging across subjects at each time point separately. Significance of differences over time was sought using the Friedman test. No significant differences were detected after adjusting for multiple comparisons (Socransky *et al*. 1991). The species were ordered and grouped according to the complexes described by Socransky *et al*. (1998). (Data adapted from Quirynen *et al*. (2006).)

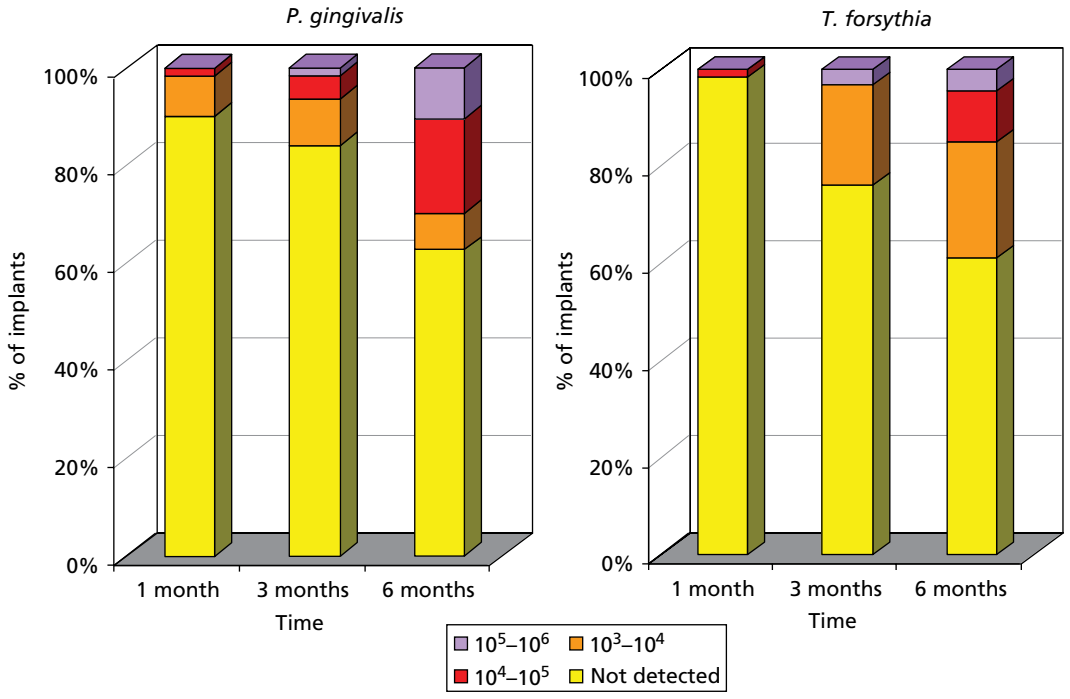

Fig. 11-8 Stacked bar charts of the frequency of detection of *Porphyromonas gingivalis* (left panel) and *Tannerella forsythia* (right panel) at different levels on 68 implants inserted in 22 subjects with a history of treated aggressive periodontitis at different time points. The bar colors indicate the different levels of detection of *P. gingivalis* and *T. forsythia* using DNA probes. (Data adapted from De Boever & De Boever (2006).)

not to be the case. Using molecular techniques, the presence of periodontal pathogens (including *P. gingivalis, T. forsythia, A. actinomycetemcomitans, Treponema denticola, Parvimonas micra, Streptococcus intermedius*) in low proportions and levels were demonstrated in healthy peri-implant sulci in fully edentulous subjects (Lee *et al*. 1999; Hultin *et al*. 2002; Quirynen *et al*. 2005; Devides & Franco 2006; Van Assche *et al*. 2009; Fernandes *et al*. 2010; Quirynen & Van Assche 2011) and partially dentate subjects (Lee *et al*. 1999; Casado *et al*. 2011; Van Assche *et al*. 2011). It should be emphasized that in patients with good oral hygiene and a stable periodontal condition, implants can maintain a successful treatment outcome without peri-implant infection despite the presence of periodontal pathogens (Van Assche *et al*. 2011).

Microbiota associated with peri-implant infections

The characteristics of biofilms associated with peri-implant disease (peri-implant mucositis and peri-implantitis) have been studied using various microbiologic techniques and sampling methods, most of which disrupt the three-dimensional structure of the biofilm. While the majority of studies have found the composition of the submucosal microbiota to be similar to that in chronic periodontitis, with a mixed anaerobic infection dominated by Gram-negative bacteria, some studies have found high numbers of other microorganisms not commonly associated with periodontal diseases, including enteric rods and yeasts, or microorganisms associated with extraoral infections such as staphylococci (i.e. *Staphylococcus aureus* and *Staphylococcus epidermidis*) or peptostreptococci (Leonhardt *et al*. 2003; Fürst *et al*. 2007; Persson *et al*. 2010).

Numerous studies have documented the presence of periodontal pathogens at peri-implantitis sites (Rams & Link 1983; Rams *et al*. 1984; Mombelli *et al*. 1987, 1988; Becker *et al*. 1990; Sanz *et al*. 1990; Alcoforado *et al*. 1991; Rams *et al*. 1991; Rosenberg *et al*. 1991; Mombelli & Lang 1992; Augthun & Conrads 1997; Danser *et al*. 1997; Salcetti *et al*. 1997; Kalykakis *et al*. 1998; Muller *et al*. 1999; Hultin *et al*. 2000; Mombelli *et al*. 2001; Rutar *et al*. 2001; Leonhardt *et al*. 2003; Botero *et al*. 2005; Covani *et al*. 2006; Persson *et al*. 2006; Shibli *et al*. 2008; Emrani *et al*. 2009; Maximo *et al*. 2009; Tabanella *et al*. 2009; Persson *et al*. 2010). Figure 11-9 illustrates the microbial complexity of a submucosal biofilm associated with a peri-implantitis lesion. Some studies have examined the microbiota of healthy peri-implant sites, comparing that found in the context of an otherwise healthy mouth versus that found when peri-implantitis was present at some implants, noting an increased level of pathogens even in healthy sites in patients with peri-implantitis (Fig. 11-10). The findings of the mentioned studies outline the similarities in microbiota found at sites with peri-implant infection and periodontitis.

Fig. 11-9 Scanning electron micrograph showing the complexity of the microbial composition of a submucosal biofilm associated with a peri-implantitis lesion. (Courtesy of C. Cobb.)

The microbiota associated with peri-implant mucositis appears to be similar to that associated with peri-implantitis (Maximo *et al*. 2009; Casado *et al*. 2011), suggesting that supramucosal plaque formation and development of peri-implant mucositis is the precursor to peri-implantitis. Plaque samples, analyzed using checkerboard DNA–DNA hybridization for 40 bacterial species, from 13 subjects with peri-implantitis and 12 subjects with peri-implant mucositis found similar levels of all species with the exception of three species (*T. forsythia*: higher levels in peri-implantitis; *Actinomyces gerencseriae* and *Campylobacter ochracea*: lower levels in peri-implantitis) (Maximo *et al*. 2009) (Fig. 11-11).

In another study evaluating the presence and levels of 36 species by DNA–DNA hybridization, there were no significant differences observed in supra- and sub-mucosal microbial profiles from the same implant site, in 22 subjects with peri-implantitis (Shibli *et al*. 2008) (Fig. 11-12). Deeper peri-implant pockets harbor greater total anaerobic counts and presence of *P. gingivalis* compared to shallower peri-implant pockets (Rutar *et al*. 2001). Human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) have also been associated with peri-implant infection, suggesting a possible etiologic role via local immune suppression allowing overgrowth of periodontal pathogens (Jankovic *et al*. 2011). HCMV was detected in 65% and EBV in 45% of the 20 peri-implantitis sites evaluated, while co-infection was reported in 33% of peri-implantitis sites. In healthy and peri-implant mucositis sites, no co-infection was detected (Jankovic *et al*. 2011).

There is no histologic documentation of bacterial invasion of the peri-implant tissues, although it has been suggested that this may occur due to the epithelial ulceration and disruption of connective tissue

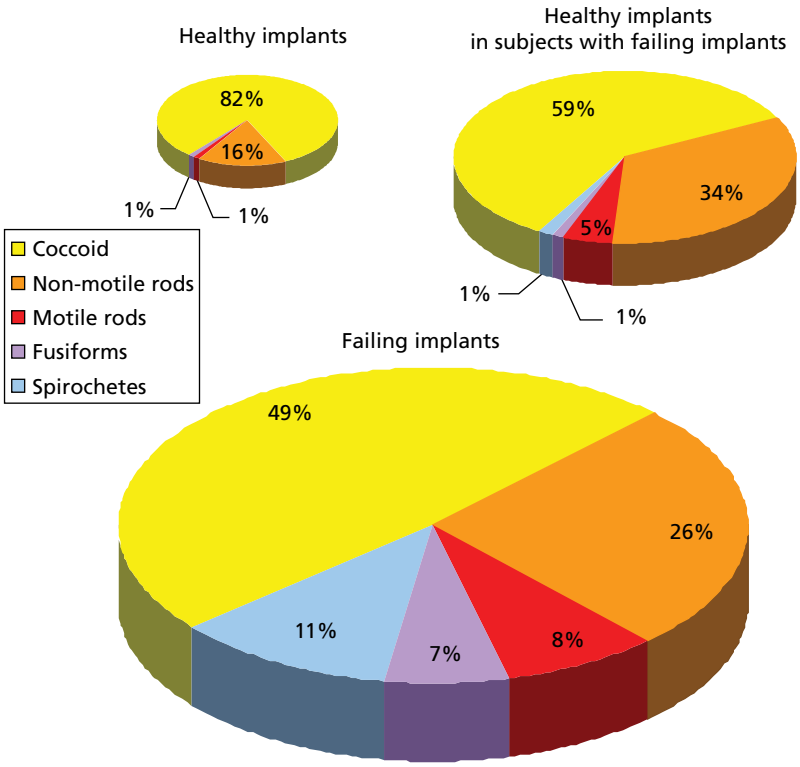

Fig. 11-10 Pie charts of the mean percentage of different morphotypes in the microbiota of samples from 10 healthy implant sites in subjects with only successful implants, samples from six healthy implant sites and from eight peri-implantitis sites in subjects with peri-implantitis. The numbers correspond to the mean percentage of each morphotype within the microbiota. The areas of the pie charts have been adjusted to reflect mean total counts of each site category. (Data adapted from Mombelli *et al*. (1987).)

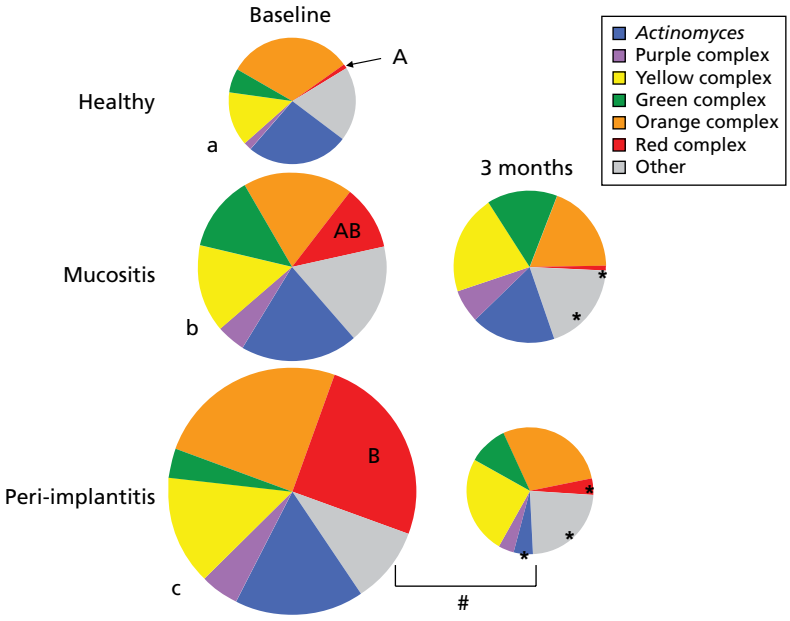

Fig. 11-11 Pie charts of the mean percentage DNA probe count of subgingival microbial complexes (Socransky *et al*. 1998) from samples of submucosal biofilms obtained from healthy implants (n = 10), implants with mucositis (n = 12), and implants with peri-implantitis (n = 13) at baseline and 3 months after mechanical therapy (diseased implants only). The areas of the pie charts were adjusted to reflect the mean total counts of each clinical group. Significance of differences between the two time points for the total DNA probe counts ($^{\#}P$ <0.05) and the proportions of each complex ($^{*}P$ <0.05) was tested using the Wilcoxon signed-rank test. Different uppercase letters indicate differences in proportions of microbial complexes among groups at baseline using the Kruskal–Wallis and Dunn *post-hoc* tests. Different lowercase letters indicate differences in the mean total DNA probe counts at baseline using the Kruskal–Wallis and Dunn *post-hoc* tests. (Data adapted from Maximo *et al*. (2009).)

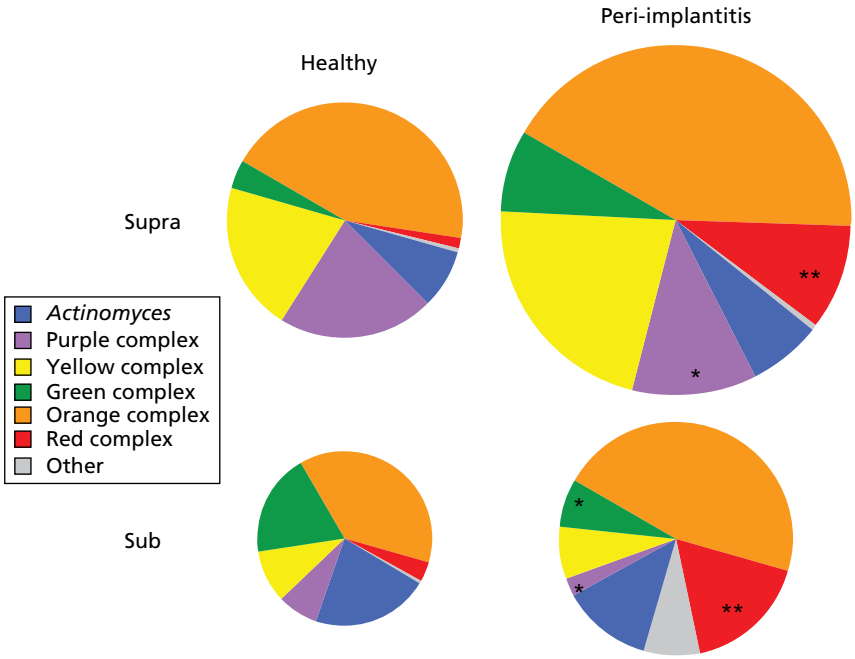

Fig. 11-12 Pie charts of the mean percentage DNA probe count of microbial complexes (Socransky *et al*. 1998) in samples of supra- and sub-mucosal biofilms obtained from healthy implants (n = 22) and implants with peri-implantitis (n = 22). Areas of the pie charts were adjusted to reflect the mean total DNA probe counts of each sample type. Significance of differences between the two clinical groups for the proportions of each complex was tested for supra- and sub-mucosal samples separately using the Mann–Whitney U-test ($^{*}P$ <0.05; $^{**}P$ <0.01). (Data adapted from Shibli *et al*. (2008).)

adhesion observed in experimental peri-implantitis studies (Lang & Berglundh 2011).

Molecular techniques, including *16S rRNA* gene sequencing, have led to the identification and discovery of previously unrecognized microorganisms in the oral cavity (Faveri *et al*. 2008; Ahn *et al*. 2011; Wade 2011). Due to these advances, researchers are now recognizing the diversity of both the periodontal and peri-implant microbiota. Phyla including Chloroflexi, Tenericutis, and Synergistes, and species including *P. micra*, *Peptostreptococcus stomatis*, *Pseudoramibacter alactolyticus*, and *Solobacterium moorei*, have been identified from peri-implantitis sites (Koyanagi *et al*. 2010) (Fig. 11-13). Furthermore, Archaea, a distinct group of single-cell microorganisms that produce methane gas and have been associated with periodontal disease severity (Lepp *et al*. 2004) have also been identified using *16S rRNA* clonal analyses at peri-implantitis sites, suggesting a role in the etiology of peri-implant infection (Faveri *et al*. 2011). Subgingival/submucosal samples were obtained from 50 periodontally healthy sites, 50 healthy peri-implant sites, and 25 peri-implantitis sites. The prevalence of Archaea (*Methanobrevibacter oralis*) was significantly higher at peri-implantitis sites compared to healthy sites at implants and teeth (Faveri *et al*. 2011).

The true nature, role, and diversity of the microbiota associated with peri-implant infections may only be realized as future investigations focus on the study of non-cultivable organisms, using techniques which do not disrupt the three-dimensional structure of the biofilm.

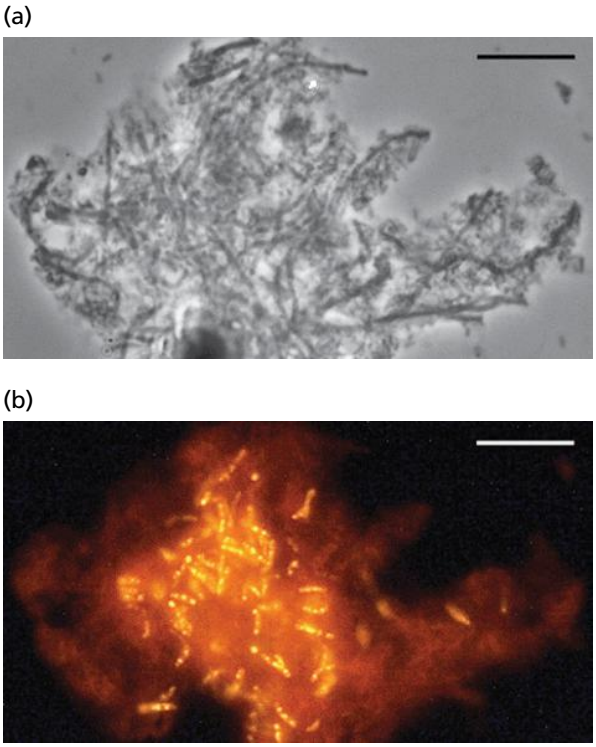

Fig. 11-13 (a) Inverted light microscopy of a subgingival biofilm obtained from a peri-implantitis site. (b) Fluorescent image of the same field stained specifically by fluorescence *in situ* hybridization (FISH) for Synergistes group A2. Bars correspond to 10 µm. (Courtesy of G.N. Belimpasakis and Helga Lüthi-Schaller, University of Zürich.)

Patients at risk for peri-implant infections

There is emerging evidence that patients who have a history of treated periodontitis have an increased risk for peri-implant infections (Hardt *et al*. 2002; Karoussis *et al*. 2003, 2004; Heitz-Mayfield 2008; Ong *et al*. 2008; Roccuzzo *et al*. 2010). This is perhaps not surprising considering the two diseases share common risk factors, and patients with a host susceptibility to periodontitis will still be susceptible to biofilm infections at implant sites if periodontal pathogens colonize these sites.

This consideration is supported by findings that in patients diagnosed with advanced periodontitis, the persistence of periodontal pathogens was observed following full-mouth extraction and implant placement (Quirynen & Van Assche 2011). Ten patients with advanced periodontitis had all their teeth extracted and 6 months after tooth extraction, implants were placed. Abutment connection was completed 3–6 months later. Plaque samples were collected from the tongue dorsum, saliva, and subgingival/mucosal area (teeth/implants) before extraction and up to 1 year after abutment connection, and analyzed by culture, quantitative PCR, and checkerboard technology. A reduction in the total number of aerobic and anaerobic colony-forming units (CFU)/mL was observed, and there was a reduction in the detection of *P. gingivalis* and *T. forsythia* in the saliva and on the dorsum of the tongue. However, the submucosal areas of the peri-implant sulci were rapidly colonized by these key pathogens, and no changes could be detected for *A. actinomycetemcomitans.* Thus, while the extraction of the remaining periodontally involved teeth resulted in a significant reduction of bacteria related to periodontitis and peri-implantitis, they were not eliminated. The pathogens could then colonize the peri-implant regions and detection frequencies remained high (Quirynen & Van Assche 2011). While it may take many years, peri-implant infections may develop if periodontal pathogens become established in the peri-implant biofilm in a susceptible host.

Furthermore, periodontal patients with residual probing depths of ≥6 mm at remaining teeth were found to have a greater prevalence of peri-implantitis (bone loss and peri-implant probing depth ≥5 mm with bleeding on probing) compared to periodontal patients with no residual pockets, or periodontally healthy subjects (Lee *et al*. 2012). Moreover, a study including patients in maintenance care, with an average follow-up of 8 years, reported that periodontitis-susceptible patients with implants who developed peri-implantitis had significantly more residual periodontal pockets (≥5 mm) at the end of active periodontal therapy than patients who did not develop peri-implantitis (Pjetursson *et al*. 2012). This highlights the maintenance of periodontal health as a critical factor in reducing risk for peri-implant infection. Clinicians should inform patients with a history of periodontitis of their increased risk for peri-implant infections, and of the importance of optimal oral hygiene and regular supportive periodontal/peri-implant care.

Few studies have investigated the presence of specific bacterial species as a risk for the initiation or progression of peri-implantitis. One study found that the addition of a positive DNA test (which determined the presence of *A. actinomycetemcomitans, P. gingivalis, P. intermedia or T. denticola*) enhanced the diagnostic power of the presence of bleeding on gentle probing (0.25 N) to predict progression of peri-implant disease (Luterbacher *et al*. 2000).

Anti-infective treatment and microbiologic effects

Treatment protocols for peri-implant infections have empirically been based on treatment philosophies for the management of periodontal infections, and are aimed at the suppression of the total bacterial load and reduction of the presence and levels of periodontal pathogens. The majority of studies investigating the microbiologic outcomes following peri-implant mucositis/peri-implantitis treatment have incorporated mechanical debridement with or without adjunctive antiseptics and/or antimicrobial agents.

Most studies have reported a reduction in the total bacterial counts and levels of periodontal pathogens in the first 3 months following treatment. However, those with longer follow-up periods have observed a gradual return to baseline levels of the microbiota analyzed.

Non-surgical mechanical therapy

While non-surgical mechanical therapy alone seems to be effective in the treatment of peri-implant mucositis (Heitz-Mayfield & Lang 2004; Maximo *et al.* 2009; Heitz-Mayfield *et al*. 2011), the improvements using this approach at peri-implantitis sites have so far shown limited and unpredictable results (Lindhe & Meyle 2008; Renvert *et al*. 2008b, 2009; Persson *et al*. 2010). Mechanical debridement at peri-implantitis sites using either titanium hand-instruments or ultrasonic devices resulted in transient changes in only a few microbial species, with a return to baseline microbial levels 6 months following treatment (Persson *et al*. 2010). No clinical improvement was observed 6 months following non-surgical mechanical treatment in this study (Persson *et al*. 2010). In a subsequent study, the same group of researchers reported limited microbiologic and clinical improvements following peri-implantitis treatment using either a erbium-doped:yttrium, aluminum, and garnet (Er:YAG) laser or an air-abrasive polishing device (Persson *et al*. 2011). The limited clinical and microbiologic improvements

observed following non-surgical therapy in deep peri-implant pockets can be attributed to the difficulty in gaining access to the biofilm adhering to the implant surface, due to the topography of the implant and its surface characteristics.

Non-surgical mechanical therapy and adjunctive antimicrobial agents

As a result of the inability to resolve peri-implant infections using mechanical means alone, treatment protocols using adjunctive antimicrobial agents have been proposed. However, few studies have evaluated both clinical and microbiologic outcomes following non-surgical mechanical debridement and adjunctive systemic antimicrobials (Mombelli & Lang 1992) or local antimicrobial agents (Mombelli *et al*. 2001; Persson *et al*. 2006; Renvert *et al*. 2006). A case series reported the clinical and microbiologic outcomes of an anti-infective protocol incorporating mechanical debridement, irrigation with 0.5% chlorhexidine, and the systemic administration of ornidazole at 100 mg/day for 10 days (Mombelli & Lang 1992). Microbiologic samples taken at various time points after therapy were examined using anaerobic culture techniques and darkfield microscopy. At 10 days post therapy, there was a dramatic reduction in the total anaerobic microbiota from 3.45×10^6 CFU/mL to 0.04×10^6 CFU/mL. The post-treatment microbiota consisted mainly of Gram-positive facultative cocci (95% of the microbiota). Spirochetes and selected species including *P. intermedia*, *P. gingivalis*, *Fusobacterium* spp., *Actinomyces odontolyticus*, *Selenomonas* spp., *Veillonella* spp., *Campylobacter* spp., *A. naeslundii*, and *Actinomyces oris* (formerly *A. naeslundii* genospecies 1 and 2), could not be recovered in the day 10 samples, despite being present at baseline. After 12 months, the frequency of detection of *P. intermedia*, *Fusobacterium* spp., *A. odontolyticus*, and *Campylobacter* spp. was significantly lower than at baseline and the proportion of Gram-negative anaerobic rods shifted from 39.8% to 15.2% of the total cultivable microbiota. The beneficial changes in the composition of the peri-implant microbiota were accompanied by clinical improvements, including a reduction in bleeding on probing and mean pocket depth over 12 months (Mombelli & Lang 1992).

Clinical improvements accompanied by significant reductions in total bacterial load and levels of putative pathogens (including *A. actinomycetemcomitans*, *P. gingivalis, T. forsythia, T. denticola, P. intermedia, Fusobacterium* spp., *Campylobacter rectus*, and spirochetes) have also been documented following the local delivery of antimicrobials (Mombelli *et al*. 2001; Persson *et al*. 2006). Studies evaluating local delivery devices including non-resorbable tetracycline fibers (Actisite®) (Mombelli *et al*. 2001) and minocycline hydrochloride microspheres (Arestin®) (Renvert *et al*. 2004; Persson *et al*. 2006; Renvert *et al*. 2006; Salvi *et al*. 2007; Renvert *et al*. 2008a) have shown microbiologic improvements for up to 12 months in the majority of patients. However, as previously mentioned, the initial suppression of the microflora was followed by a gradual recolonization, and in some sites recurrent peri-implantitis, requiring further treatment.

Surgical access and implant surface decontamination

The challenge of obtaining access to the implant surface for biofilm removal in non-surgical therapy can be overcome by access flap therapy. Following debridement of the lesion and removal of inflammatory tissue to expose the implant surface and bone defect, an attempt to decontaminate the implant surface is made. Implant surface decontamination methods have been investigated in *in vitro*, experimental, and clinical studies (Kolonidis *et al*. 2003; Schou *et al*. 2003) evaluating a range of chemicals (including citric acid, hydrogen peroxide, saline, chlorhexidine), lasers (including Nd:YAG, CO_2, Er:YAG) (Schwarz *et al*. 2006), photodynamic therapy, and mechanical approaches (including carbon fiber, titanium, and plastic curettes, and ultrasonic and air-abrasive polishing devices). Microbiologic effects following these decontamination procedures have scarcely been evaluated, with the focus of the investigations being on defect fill. Photodynamic therapy, where a photosensitive dye (toluidine blue) was applied to the implant surface following access flap elevation, and activated using a diode laser (wavelength 905 nm), showed promising results in reducing total bacterial counts and levels of specific periodontal pathogens (*A. actinomycetemcomitans, P. gingivalis,* and *P. intermedia*) (Dörtbudak *et al*. 2001). However, no particular implant surface decontamination protocol has been found to be superior in terms of clinical or microbiologic outcomes.

The few studies evaluating the clinical and microbiologic effects of surgical peri-implantitis therapy have included adjunctive systemic antimicrobials, with the exception of one short-term study which documented 3-month microbiologic and clinical improvements following surgical access and debridement without adjunctive systemic antimicrobials (Maximo *et al*. 2009). In this study positive qualitative and quantitative changes were observed, with levels of *T. denticola, T. forsythia, P. micra, Fusobacterium nucleatum ss nucleatum*, *P. gingivalis*, and *Treponema socranskii* significantly reduced 3 months after therapy (Maximo *et al*. 2009) (see Fig. 11-11).

The rationale for combining systemic antimicrobials with surgical interventions is the infectious nature of the disease. A study of nine patients, with 26 implants with peri-implantitis, treated by surgical access and debridement with adjunctive antimicrobials, followed by 3–6-monthly maintenance care, reported clinical and microbiologic findings over a 5-year period (Leonhardt *et al*. 2003). One of six

different systemic antimicrobial agents, based on the results of individual bacterial susceptibility testing, was administered. Seven implants in four patients were lost, and four implants continued to lose bone. *A. actinomycetemcomitans* was present in six of the nine patients prior to treatment, while at 6 months and 5 years this species was not found. *S. aureus* and enteric rods were detected in one and three patients, respectively, prior to treatment, but were not detected in any patients 5 years following treatment. The presence of *P. intermedia* and *Prevotella nigrescens* was not altered following treatment. Therefore, some bacterial species were either not completely removed during debridement or recolonized the peri-implant sites (Leonhardt *et al*. 2003).

In a retrospective study of 245 patients who had received a wide range of peri-implantitis treatments, most involving surgical access with various systemic antimicrobial agents, baseline microbial sampling showed 27% of patients had moderately heavy to heavy levels of *P. intermedia/P. nigrescens* and 19% had moderately heavy to heavy levels of anaerobic Gram-negative bacilli. Success of treatment (absence of bleeding on probing and/or suppuration in conjunction with periodontal depth of <5 mm and stable bone levels) was observed in 45% of all cases. The type and regimens of antimicrobials used during treatment varied greatly, but the majority of cases received a combination of amoxicillin and metronidazole (47%). Baseline microbial data did not correlate with the outcome of treatment (Charalampakis *et al*. 2012).

Treatment of peri-implant infection is challenging and the optimal protocol for successful treatment remains to be elucidated. Once an effective protocol is established, it can be implemented as a control to test other protocols in randomized controlled trials. However, it is obvious that an anti-infective approach is indicated, with the goals being biofilm control, and the establishment of a local environment and peri-implant biofilm compatible with healthy peri-implant tissues. Strategies for preventing peri-implant infection include the identification of high-risk individuals, treatment of periodontitis prior to implant placement, establishment of good oral hygiene practices, implant-supported prostheses designed to give adequate access for self-performed plaque removal, avoidance of iatrogenic problems such as excess restorative cement, and provision of supportive periodontal/peri-implant care.

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Part 4: Host–Parasite Interactions

Chapter 12

Pathogenesis of Gingivitis

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Introduction

The experimental gingivitis studies of the 1960s (Löe *et al*. 1965) elegantly demonstrated that there is a one-to-one relationship between the development of dental plaque and the development of gingivitis (Figs. 12-1, 12-2). These studies, together with those of more recent times (Trombelli *et al*. 2004a, 2008), also show that there is variation in this response, with some individuals manifesting disease to a greater or lesser degree and at different time periods compared with others. So, while it has been known for many years that plaque is the etiologic agent, the factors contributing to patient susceptibility are still not fully understood. While all individuals with periodontitis will have had, at one stage, gingivitis, not all patients with gingivitis, nor all gingivitis lesions, will necessarily progress to periodontitis. The difficulty arises in identifying those lesions with gingivitis which will progress to periodontitis.

Development of gingival inflammation

The development of gingivitis and periodontitis was loosely classified into the "initial", "early", "established", and "advanced" lesions by Page and Schroeder (1976). The initial and early lesions will be described here, while the established and advanced lesions will be described in Chapter 13.

The initial lesion

The "initial" lesion occurs 2–4 days following the beginning of plaque accumulation. The lesion is subclinical and can only be seen histologically. It is characterized by the formation of edema [manifesting as an increase in gingival crevicular fluid (GCF) flow], an accumulation of polymorphonuclear neutrophils (PMNs), and loss of connective tissue (Fig. 12-3). Streptococci are among the first organisms to colonize the acquired pellicle as plaque develops. These organisms produce a range of enzymes and metabolic end products which increase the permeability of the junctional epithelium, allowing both the ingress of further bacterial products and at the same time the outflow of GCF. At this early stage, the GCF is essentially the same as interstitial fluid, but nevertheless contains many serum proteins, including all the components necessary for the activation of complement.

Lipoteichoic acid and peptidoglycans, which are components of the cell wall of these early colonizers, are capable of activating complement via the so-called "alternative pathway". This occurs in the gingival sulcus and results in the production of the "anaphylatoxins" C3a and C5a, which in turn flow back into the tissues, establishing a concentration gradient from the gingival sulcus into the tissues. Once in the tissue, these anaphylatoxins lead to the release of vasoactive amines from resident mast

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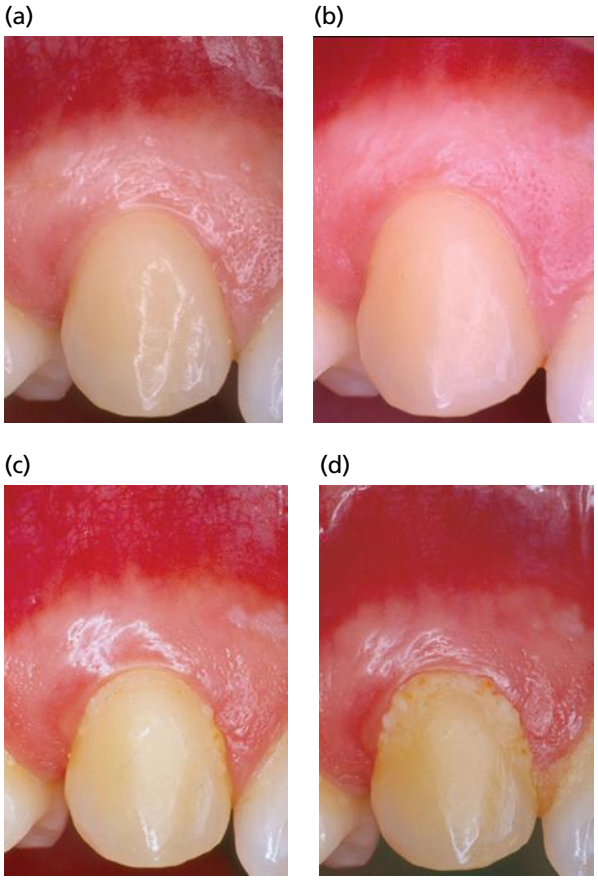

Fig. 12-1 Experimentally-induced gingivitis lesion (Trombelli *et al*. 2004a). (a) Clinically healthy state; (b) after 7 days of plaque accumulation, dental biofilm is visible and a slight inflammation of the gingival margin is present; (c) at day 14, a substantial amount of plaque deposit is associated with an increasingly evident gingival inflammation; (d) at day 21, large deposits of plaque are present along the gingival margin (buccally and interproximally) in association with severe edema and erythema of the gingiva. (Source: Trombelli *et al*. 2004a. Reproduced with permission from John Wiley & Sons.)

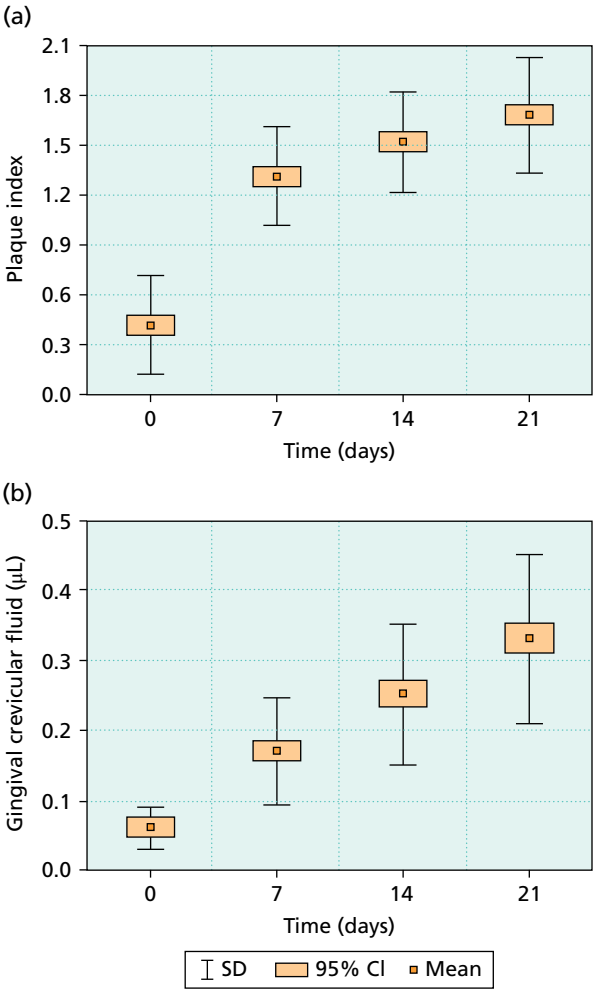

Fig. 12-2 Descriptive statistics (box and whisker plot) for (a) plaque index and (b) gingival crevicular fluid volume over experimental gingivitis period (0, 7, 14, and 21 days of undisturbed plaque accumulation). (Source: Trombelli *et al*. 2004. Reproduced with permission from John Wiley & Sons.)

cells. In turn, these vasoactive amines lead to an increase in vascular permeability and the formation of edema, one of the hallmarks of inflammation. Mast cells also release preformed cytokines, including tumor necrosis factor-alpha (TNF-α), which results in the expression of adhesion molecules by endothelial cells and the subsequent sticking and migration of PMNs into the gingival tissues. While activation of the alternative complement pathway is essential for the vascular responses, bacterially-derived chemotactic substances together with C5a are responsible for the migration of PMNs into the gingival sulcus. Once in the gingival sulcus however, the PMNs are unable to phagocytose the bacteria, which are beginning to form a biofilm and as such are firmly adherent to the tooth surface. In this situation, the PMNs disgorge their lysosomal contents into the gingival sulcus in what has been termed "abortive phagocytosis". These lysosomal enzymes can then return into the tissues and contribute to the local destruction of connective tissues. In addition, PMNs release structures called neutrophil extracellular traps (NETs) which

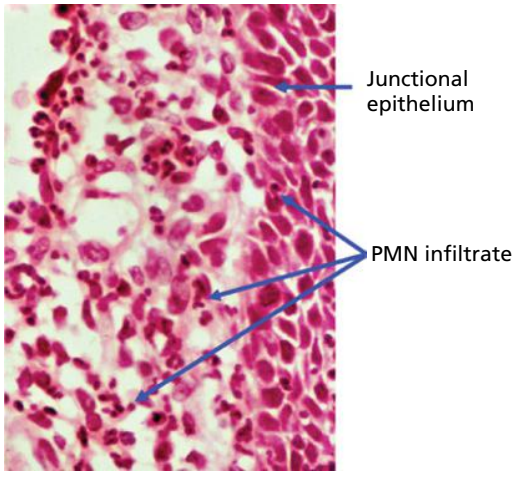

Fig. 12-3 Polymorphonuclear neutrophil (PMN) infiltration with destruction of the infiltrated connective tissue in the initial lesion.

can trap and kill microbial pathogens. These were first described by Brinkman *et al*. (2004) and consist of chromatin structures, nuclear histones, and many granular antimicrobial proteins. NETs are released

during a form of pathogen-induced cell death, recently called NETosis, that differs from apoptosis and necrosis (Steinberg & Grinstein 2007) and represents one of the first lines of defense against pathogens. *In vivo* both dead and viable PMNs can release NETs, which in turn can be associated with severe tissue damage. In addition, a variety of pro-inflammatory stimuli, all of which can be found in the gingival sulcus, such as lipopolysaccharide (LPS), interleukin-8 (IL-8), TNF, as well as the streptococcal M protein can all induce NET formation [ror review, see Remijsen *et al*. (2011)].

While NETs have been described in periodontitis, it is likely that they are also formed in this initial lesion stage of gingivitis and then persist through all stages of gingivitis and periodontitis. Evidence for this however, is at present lacking.

Other cell types, such as eosinophils and mast cells, are also able to release extracellular traps (von Kockritz-Blickwede *et al*. 2008). These mast cell extracellular traps (MCETs) appear to be released in response to the same factors that lead to NET release from PMNs. MCETs are also composed of nuclear histones together with the antimicrobial cathelicidin LL37, as well as tryptase, a granular mast cell marker, and their formation in the tissues would not only limit the ingress of bacteria but also of bacterial vesicles. They may however, contribute to localized tissue destruction. Again, while highly likely, evidence for the formation of both NETs and MCETs in the tissues is lacking. Indeed, the role of mast cells in periodontal disease is largely unknown.

Within the gingival sulcus, PMNs also produce and release a variety of cytokines including IL-1, the IL-1 receptor antagonist (IL-1RA), and high levels of IL-17. IL-17 in turn induces the production of IL-8 by sulcus epithelial cells. IL-8 is not only a very strong chemoattractant for PMNs, but as stated earlier, is also a strong stimulus for NET formation, thus establishing a positive feedback loop in an attempt to contain the developing bacterial infection. Indeed, it is highly likely that the role of IL-17 in periodontal disease is a protective one in that it maintains the PMN barrier in the gingival sulcus. It is well established that loss of this barrier, either due to an absence of PMNs (such as agranulocytosis or cyclic neutropenia) or a defect in their function (either chemotactic or phagocytic), leads to severe and rapid progression of periodontal destruction.

At this initial stage however, the lesion occupies no more than 5–10% of the connective tissues, and is still not evident clinically.

The early lesion

The so-called "early" lesion develops after approximately 4–7 days of plaque accumulation. At this stage the nature of the developing lesion changes from one consisting primarily of PMNs to one with increased numbers of lymphocytes and macrophages

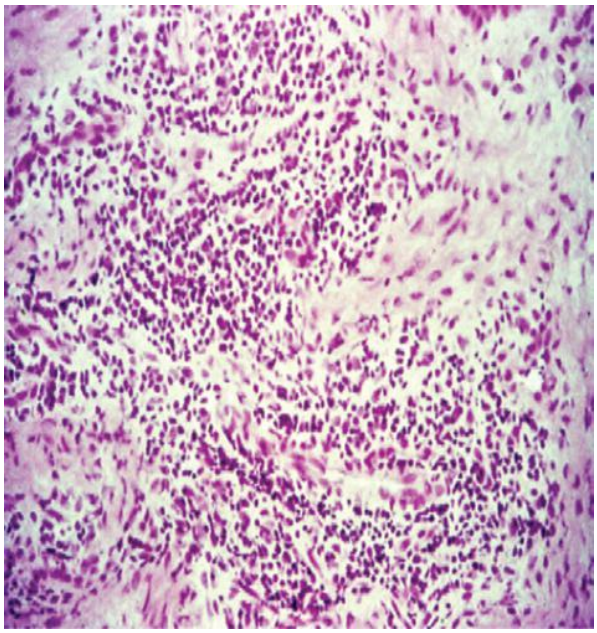

Fig. 12-4 Perivascular lymphocyte/macrophage infiltrate seen in a 21-day experimental gingivitis lesion.

(Fig. 12-4). Vascular changes become more pronounced with the opening of previously dormant capillary beds, the formation of post-capillary venules, increased vascular permeability, and the development of perivascular inflammatory infiltrates. As a result, there is a net increase in the flow of fluid into the affected gingival tissues, and a subsequent increase in the flow of GCF. The nature of the GCF at this stage changes from that of interstitial fluid to that of an inflammatory exudate, in other words edema. An increase in the permeability of the sulcular and junctional epithelia, as a result of widening of the intercellular spaces between the epithelial cells, allows increased ingress of bacterial products into the gingival tissues and escalation of the inflammatory response.

Initially, the lesion develops as small perivascular infiltrates which progressively increase in size and coalesce such that at around day 12–21 following the beginning of plaque accumulation the lesion becomes clinically evident. By day 21, lymphocytes make up 70% of the infiltrate and although there is a four-fold increase in PMN numbers within the junctional epithelium (Lindhe & Rylander 1975). PMNs and plasma cells make up <10% of the total infiltrate (Seymour *et al*. 1983). As with the initial lesion, the release of cytokines such as TNF-α and IL-17 from mast cells and PMNs undergoing NETosis leads to an increase in cell adhesion molecules, such as endothelial cell leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1), which together with an increase in IL-8 production by the epithelial cells help to establish a fast flow of PMNs through the junctional epithelium and into the gingival sulcus (Moughal *et al*. 1992), where they form a barrier against plaque microorganisms (Attstrom

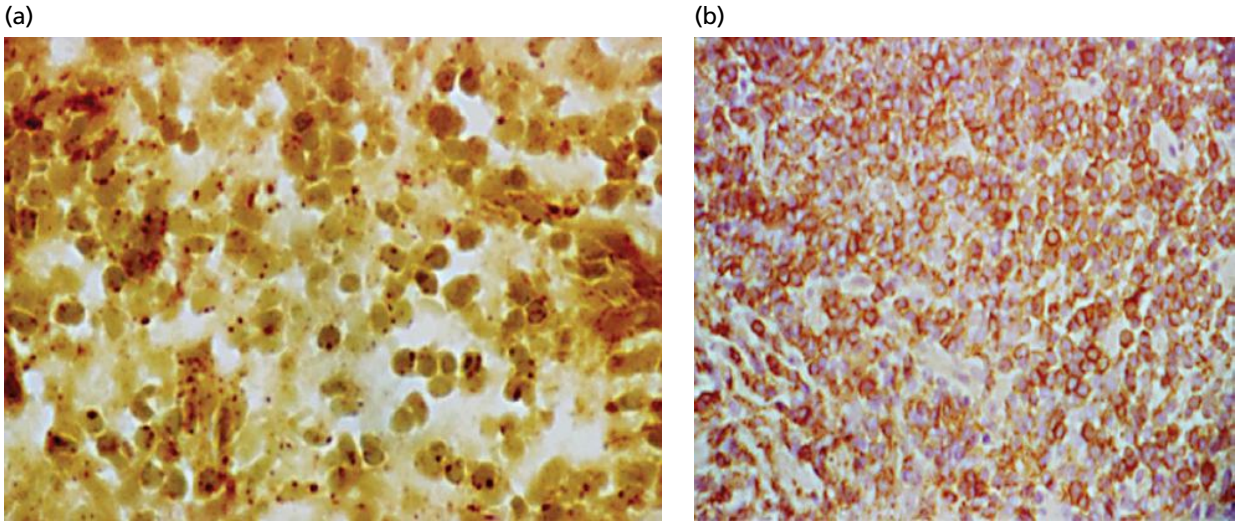

Fig. 12-5 21-Day experimental gingivitis lesion showing the predominance of (a) non-specific esterase-positive and (b) CD3-positive T cells.

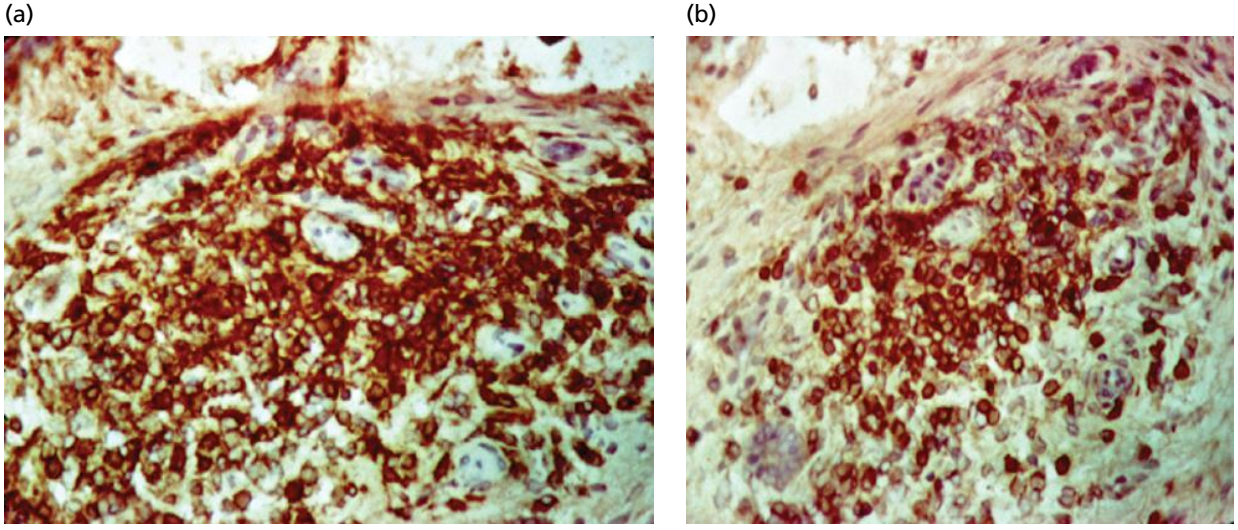

Fig. 12-6 21-Day experimental gingivitis lesion showing a (a) CD4 to (b) CD8 ratio of 2:1.

1971). Although the infiltrated area remains fairly localized at this stage, up to 60–70% of collagen within the infiltrated zone is degraded (Page & Schroeder 1976).

The immunologic events occurring during the development of gingivitis have been described (Seymour *et al*. 1988). These events are identical to the development of delayed-type hypersensitivity (DTH) and involve the formation of perivascular lymphocyte/macrophage infiltrates (Fig. 12-4) which, as they increase in size, coalesce and merge, eventually becoming clinically evident. The infiltrates consist predominantly of T cells (Fig. 12-5), with a CD4:CD8 ratio of around 2:1(Fig. 12-6), together with both dendritic antigen-presenting cells (APCs) and infiltrating phagocytic macrophages. These activated T cells, along with the sulcular epithelial cells, express high levels of MHC class II antigens (HLA-DR and HLA-DQ) (Fig. 12-7). Langerhans cells are seen in increased numbers in both the oral as well as the oral sulcular epithelium (Fig. 12-8a). Less than 5% of the T cells express the IL-2 receptor CD25 (Fig. 12-8b), suggesting that these cells are not proliferating locally. As soluble antigen enters the tissues, it is taken up by the resident Langerhans cells and carried to the regional lymph nodes where antigen-specific T cells are sensitized. These sensitized cells then travel back to the site of original antigen challenge (i.e. the gingival tissues). Once there, following further antigen presentation by dendritic cells, they become activated and together with the infiltrating phagocytic macrophages, they control the ingress of antigen and achieve a balance with the plaque biofilm. While dendritic APCs can be found in the perivascular spaces, the majority of macrophages in the developing lesion are phagocytic cells. The production of interferon gamma (IFN-γ) by the activated CD4 T cells further activates the PMNs and macrophages. Although

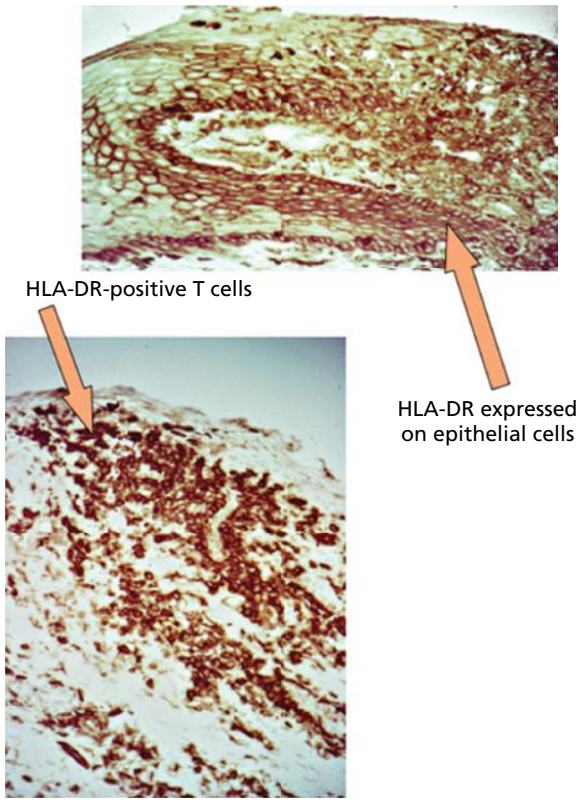

Fig. 12-7 21-Day experimental gingivitis lesion showing HLA-DR-positive activated T cells and HLA-DR-positive epithelial cells.

these cannot eliminate the bacterial challenge, they, via the production of NET in the gingival sulcus and the production of cytokines within the tissues, are able to control the infection. As noted earlier, this sequence of events is identical to that seen in the development of DTH (Poulter *et al*. 1982). The development of DTH is a well-controlled immunologic response which develops in 12–24 hours, peaks within 48 hours, and is gone within a week. In this context, gingivitis can also be considered to be a well-controlled immunologic response but, as noted earlier, because of the persistence of the plaque biofilm, the immunologic response persists rather than resolving. The subsequent, prolonged nature of the inflammatory response results in gingivitis becoming chronic in nature. While in most people the immune response is able to contain the microbial challenge, it is only with mechanical cleaning that the microbial challenge can be cleared. Collagen is degraded in the stable lesion but does not result in any loss of attachment. When the plaque is removed, gingival tissues repair and remodel, and there is no permanent damage to or alteration of tissue architecture.

The end stage of gingivitis is the so-called established lesion, which is distinguished from the early lesion by its increased proportions of B cells and plasma cells. The established gingivitis lesion may be differentiated from the considerably larger

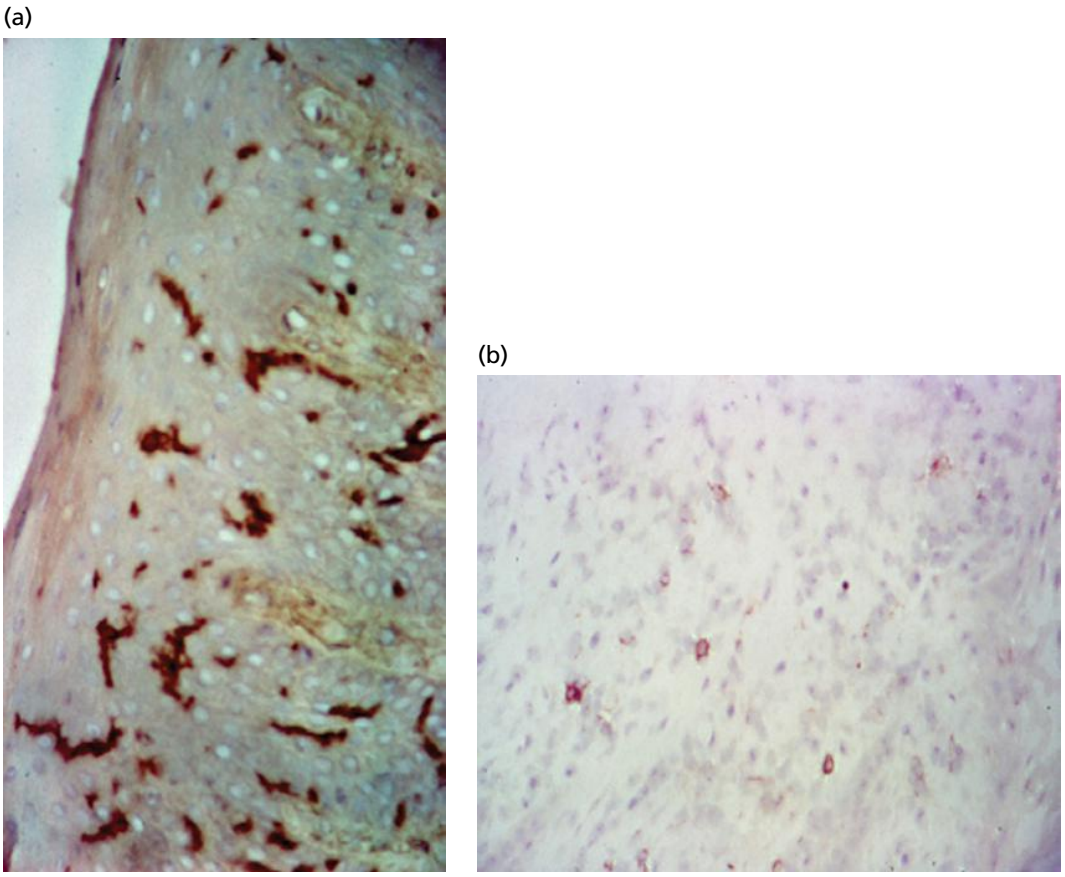

Fig. 12-8 21-Day experimental gingivitis lesion showing (a) increased CD1a-positive Langerhans cells in the oral epithelium and (b) relatively few CD25 (IL-2 receptor)-positive T cells in the infiltrate.

and plasma cell-dominated established periodontitis and advanced periodontitis lesions described in Chapter 13. Clinically it is not yet possible to determine disease activity; hence, it is not possible to say if the increased proportions of B cells and plasma cells in the established gingivitis lesion represent a stable gingivitis lesion or indeed are the beginning of a progressive periodontitis lesion. In this context, and in terms of the development of periodontal disease (gingivitis and periodontitis), it is probably better to consider the established gingivitis lesion and the increasing numbers of plasma cells as a possible transitional lesion between gingivitis and periodontitis.

Individual variations in the development of gingivitis

While experimental gingivitis studies clearly demonstrate that gingivitis is the response of the body to the build-up of dental plaque, there can also be a significant degree of variation between individuals even when there appears to be no quantitative or qualitative difference in plaque accumulation (Abbas *et al*. 1986; Trombelli *et al*. 2004a). It has repeatedly been shown that during a 3-week experimental gingivitis trial, the majority of subjects develop inflammation within the 3-week period (see Figs. 12-1, 12-2); however, some subjects may not develop clinically evident gingivitis despite plaque accumulation, while others may exhibit substantial gingival inflammation within 2 weeks (Wiedemann *et al*. 1979). Whether or not those who exhibit greater than average gingival inflammation in a short period of time represent a "susceptible" group, and those with a consistently below average level of inflammation represent a "resistant" group (Van der Weijden *et al*. 1994), remains to be determined. Two distinct subpopulations of individuals presenting a substantially different gingival inflammatory response to plaque have, however, been identified in a large cohort 21-day experimental gingivitis trial. These individuals showed significantly different severity of gingivitis arising from similar amounts of plaque and similar times of exposure (Trombelli *et al*. 2004a) (Table 12-1). Interestingly, these individuals could be identified after only 7 days of plaque exposure and the differences could still be observed even when oral hygiene and control of supragingival plaque was re-established (Trombelli *et al*. 2004b).

Whether these differences in the gingival inflammatory response under quantitatively and/or qualitatively almost identical bacterial challenge represent normal biologic variation or are an early indication of an individual's responsiveness to plaque bacteria, is not yet known (Tatakis & Trombelli 2004; Scapoli *et al*.

Table 12-1 Descriptive statistics and comparisons for (a) plaque index (mean ± SD) and (b) gingival crevicular fluid volume (in μL; mean ± SD) in test and control quadrants of "low-responder" (LR) and "high-responder" (HR) subjects.

(a)	LR		HR		*t*-test (*P* value)
	n	Mean ± SD	n	Mean ± SD	
Test quadrant					
Day 0	24	0.34 ± 0.25	24	0.42 ± 0.32	0.32
Day 7	24	1.28 ± 0.25	24	1.25 ± 0.39	0.77
Day 14	24	1.55 ± 0.30	24	1.55 ± 0.33	1.00
Day 21	24	1.65 ± 0.37	24	1.73 ± 0.33	0.41
Control quadrant					
Day 0	24	0.35 ± 0.24	24	0.47 ± 0.37	0.23
Day 7	24	0.40 ± 0.31	24	0.41 ± 0.33	0.94
Day 14	24	0.42 ± 0.33	24	0.47 ± 0.35	0.62
Day 21	24	0.42 ± 0.30	24	0.49 ± 0.37	0.48

(b)	LR		HR		*t*-test (*P*-value)
	n	Mean ± SD	n	Mean ± SD	
Test quadrant					
Day 0	24	0.06 ± 0.02	24	0.08 ± 0.04	0.025
Day 7	24	0.15 ± 0.06	24	0.21 ± 0.09	0.018
Day 14	24	0.21 ± 0.07	24	0.30 ± 0.12	0.002
Day 21	24	0.22 ± 0.07	24	0.46 ± 0.13	<0.001
Control quadrant					
Day 0	24	0.05 ± 0.03	24	0.08 ± 0.05	0.015
Day 7	24	0.06 ± 0.03	24	0.09 ± 0.05	0.014
Day 14	24	0.07 ± 0.04	24	0.10 ± 0.06	0.038
Day 21	24	0.08 ± 0.03	24	0.11 ± 0.05	0.006

Source: Trombelli *et al*. 2004a. Reproduced with permission from John Wiley & Sons.

2005, 2007). While some studies report that a percentage of repeatedly tested participants shows consistently high or low inflammatory responses to *de novo* plaque accumulation (van der Weijden *et al*. 1994; Watts 1978; Trombelli *et al*. 2008), others showed that there is little, if any, agreement between individual responses in repeated trials (Shearer *et al*. 2005). Clearly, further work needs to be done in this context.

Further, differences in the composition of the lesions between young and old individuals has been shown using the 3-week experimental gingivitis design. As discussed earlier, in young subjects gingivitis is a lymphocyte/macrophage-dominated lesion and its development is identical to that of DTH (Brecx *et al*. 1988; Seymour *et al*. 1988). In older subjects however, Fransson *et al*. (1996) found that plasma cells tended to dominate in some lesions after the 3-week experimental period. Similar differences were demonstrated between young and old dogs (Berglundh & Lindhe 1993). This difference may reflect the fact that older individuals (or animals) are more likely to have experienced one or more episodes of progressive periodontitis and hence may have a greater tendency to develop another progressive periodontitis lesion within the 3-week experimental period compared with young individuals, although this remains to be determined.

Factors influencing the development of gingivitis

Microbiologic factors

While variations in the development of gingivitis were observed in the initial experimental gingivitis studies (Löe *et al*. 1965; Theilade *et al*. 1966), they have usually been ascribed to differences in plaque accumulation rates (quantitative plaque differences) and/or to differences in the species of bacteria present in the plaque (qualitative plaque differences) (Löe *et al*. 1965; Theilade *et al*. 1966). Under experimental gingivitis conditions, it has long been known that phylogenetic shifts occur in the composition of the plaque microbiota, which parallel the amount of plaque accumulated over time (Theilade *et al*. 1966; Oliver *et al*. 1989). A higher prevalence of specific bacterial species, such as *Porphyromonas gingivalis, Treponema denticola, Parvimonas micra, Fusobacterium nucleatum*, and *Prevotella intermedia,* has been observed at sites where rapid plaque accumulation and severe gingival inflammation occur. However, the prevalence of several of these species (*Tannerella forsythia*, *T. denticola*, *Campylobacter rectus*, *P. micra*, *P. intermedia*, and *F. nucleatum*) was lower than observed in sites presenting with naturally occurring gingivitis (Table 12-2) (Farina *et al*. 2012). It is also interesting to note that there are changes in the bacterial profile of the microbiota of sites associated with gingival bleeding (Löe *et al*. 1965; Theilade *et al*. 1966; Bosman & Powell 1977; Oliver *et al*. 1989; Moritz *et al*. 1998). However, it is not known whether these differences are a cause of the gingival bleeding or are a result of the gingival bleeding and the altered environment.

Predisposing factors

Predisposing factors are defined as those factors which retain or hinder the removal of plaque and therefore are associated with both the maintenance and severity of gingival inflammation. Predisposing factors are largely local with the most common being the formation of dental calculus. Other predisposing factors include developmental or anatomic tooth variations [palatogingival groove (Hou & Tsai 1993), enamel pearls (Goldstein 1979)], pathologic tooth conditions [fractures (Polson 1977), caries (Albandar *et al*. 1995)], gingival anatomic conditions [recession defects (Smukler & Machtei 1987; Goutoudi *et al*. 1997), frenal positions (Addy *et al*. 1987)], crowding (Chung *et al*. 2000), and iatrogenic factors such as subgingival restoration margins (Waerhaug 1975; Bader *et al*. 1991), overhangs (Rodriguez-Ferrer *et al*. 1980; Lang *et al*. 1983), partial dentures (Bissada *et al*. 1974; Yeung *et al*. 2000), and orthodontic appliances (Boyd & Baumrind 1992). Maxillofacial anatomic variants (e.g. inadequate upper lip coverage) and/or upper respiratory obstructions (e.g. epipharyngeal adenoids, deviated nasal septum) may lead to mouth breathing, which has been shown to lead to changes in plaque accumulation and gingivitis expression, particularly in the maxillary anterior segment of the dentition (Jacobson 1973; Addy *et al*. 1987; Wagaiyu & Ashley 1991; Gulati *et al*. 1998), and hence should be considered as a predisposing factor.

In addition, the frequent intake of sucrose, acting at a local level, is well established as being responsible for increased plaque accumulation and concomitantly increased gingival inflammation (Jalil *et al*. 1983; Sidi & Ashley 1984).

Finally, the role of incisor crown form, which relates to periodontal biotype, has been used to explain subject variations in gingivitis expression. Subjects with "long narrow" incisors tend to have significantly higher bleeding scores compared with subjects with "short wide" incisors, irrespective of the amount of plaque accumulation (Trombelli *et al*. 2004c).

Modifying factors

Modifying factors are defined as those factors which alter the nature or course of the inflammatory response. As chronic inflammation can be considered to be comprised of a vascular response and a cellular response together with the simultaneous presence of destruction and repair, anything which alters the vascular response, the cellular response or the repair potential of the tissues can be considered a modifying factor.

Table 12-2 Microbiologic profiles of test and control quadrants in naturally occurring (N-O) and experimentally induced (E-I) gingivitis (Farina *et al*. 2012).

		N-O gingivitis									E-I gingivitis								
		Pg	**Tf**	**Td**	**Aa**	**Pi**	**Ec**	**Cr**	**Fn**	**Pm**	**Pg**	**Tf**	**Td**	**Aa**	**Pi**	**Ec**	**Cr**	**Fn**	**Pm**
Test quadrant	Positive	21	31	29	2	7	31	33	31	30	23	17	8	3	3	29	8	24	12
	Negative	12	5	7	34	29	5	3	5	6	12	18	27	32	32	5	27	11	23
	Not available	3	0	0	0	0	0	0	0	0	1	1	1	1	1	2	1	1	1
	% Positive	63.3	86.1	80.6	5.6	19.4	86.1	91.7	86.1	83.3	65.7	48.6[a]	22.9[a]	8.6	8.6[b]	85.3	22.9[a]	68.6[b]	34.3[a]
Control quadrant	Positive	32	28	5	30	33	30	22	32	18	3	13	1	2	1	23	10	15	3
	Negative	2	6	29	4	1	4	11	2	16	29	19	31	30	31	8	22	17	29
	Not available	2	2	2	2	2	2	3	2	2	4	4	4	4	4	5	4	4	4
	% Positive	94.1	82.4	14.7	88.2	97.1	88.2	66.7	94.1	52.9	9.4[a]	40.6[a]	3.1	6.3[a]	3.1[a]	74.2[b]	31.3[a]	46.9[a]	9.4[a]
	P valve	<0.001	0.485	<0.001	<0.001	<0.001	0.595	0.001	0.033	<0.001	<0.001	0.257	<0.001	0.426	0.044	0.101	0.215	0.006	<0.001

Pg, *P. gingivalis*; Tf, *T. forsythia*; Td, *T. denticola*; Aa, *A. actinomycetemcomitans*; Pi, *P. intermedia*; Ec, *E. corrodens*; Cr, *C. rectus*; Fn, *F. nucleatum*; Pm, *P. micra*.

[a] Significantly different from the same quadrant as assessed in N-O gingivitis ($P<0.001$).

[b] Significantly different from the same quadrant as assessed in N-O gingivitis ($P<0.05$).

Source: Farina *et al*. 2012. Reproduced with permission from Springer Science and Business Media.

Vascular response

Sex hormones

Physiologic and pathologic endocrine changes have long been established as significant modifying factors in the expression of gingivitis (Sooriyamoorthy & Gower 1989; Mariotti 1999; Tatakis & Trombelli 2004).

The variation in sex hormone levels during puberty (Mombelli *et al*. 1989; Bimstein & Matsson 1999), pregnancy (Hugoson 1971), and menstruation (Koreeda *et al*. 2005) has been shown to alter the plaque–gingivitis relationship, resulting in increased levels of inflammation. Gingival and periodontal tissues contain receptors for sex steroid hormones and their physiology is regulated, at least in part, by serum and salivary hormonal levels (Soory 2000). In particular, estrogen has a stimulatory effect on both the metabolism of collagen and on angiogenesis, and at the same time it leads to a decrease in keratinization of the gingival epithelium. However, it is progesterone which is thought to have the major effect in the gingival tissues, both in terms of its effect on the levels of pro-inflammatory mediators (Lapp *et al*. 1995; Markou *et al*. 2011) and on the gingival vasculature. It has been known for many years that progesterone not only increases vascularity of the gingival tissues but also increases their permeability, thus resulting in a highly vascular edematous inflammatory response (Hugoson 1970; Lundgren *et al*. 1973).

Pregnancy

Pregnancy was one of the first conditions identified as having an impact on the expression of gingivitis (Ziskin *et al*. 1946; Löe & Silness 1963; Silness & Löe 1964). In particular, increases in both the prevalence and severity of gingivitis were reported during the second and third trimester of pregnancy (Löe & Silness 1963; Löe 1965; Hugoson 1971; Arafat 1974). While the selective growth of specific bacterial species, including some periodontal pathogens, has been reported during pregnancy (Jensen *et al*. 1981; Muramatsu & Takaesu 1994; Di Placido *et al*. 1998), a number of case–control and experimental gingivitis studies have failed to show a correlation between increased gingival inflammation and quantitative variations in plaque levels (Raber-Durlacher *et al*. 1994; Gürsoy *et al*. 2008; Figuero *et al*. 2010). In this context, the generally accepted mechanisms leading to the exaggerated inflammatory response seen in pregnancy are related to the increased levels of progesterone, which lead to increased permeability and dilatation of gingival capillary vessels, resulting in increased vascular flow and exudation (Hugoson 1970; Lundgren *et al*. 1973). These effects are partly mediated by an increased synthesis of prostaglandin (Miyagi *et al*. 1993).

Puberty

With the onset of puberty, an increase in gingival inflammation not associated with a concomitant increase in plaque levels has been reported for both males and females (Parfitt 1957; Sutcliffe 1972; Hefti *et al*. 1981; Mombelli *et al*. 1989). In addition, variations in the severity of gingival inflammation have been described during the menstrual cycle, particularly during the ovulation period, despite unvarying levels of plaque (Koreeda *et al*. 2005). Fluctuation of sex steroid hormones, especially progesterone, is thought to alter the host response, leading to the observed increase in the clinical signs of gingival inflammation (Baser *et al*. 2009; Becerik *et al*. 2010). Sex steroid hormones may affect blood volume, flow rate, and vascular permeability in young females (Lindhe & Attsfrom 1967; Mariotti 1994), leading to the observed increase in gingival exudate during ovulation (Hugoson 1971). The evidence, however, suggests that hormonal variations during the cycle do not affect clinically normal gingiva, but do exacerbate existing chronic gingivitis (Holm-Pedersen & Löe 1967; Kovar *et al*. 1985; Niemi *et al*. 1986; Becerik *et al*. 2010).

Contraceptives

Early clinical studies reported a higher incidence of gingival inflammation in women taking hormonal contraceptives compared with women not taking these agents (Lindhe & Bjorn 1967; El-Ashiry *et al*. 1970; Pankhurst *et al*. 1981). Effects similar to the ones associated with changes in hormone levels during pregnancy have been reported for contraceptives (Lindhe *et al*. 1969; Kalkwarf 1978). Since 1976, however, formulations of oral contraceptives have changed dramatically, resulting in substantially lower concentrations of hormones. More recent studies suggest that the effect of newer contraceptive pills on gingivitis is practically nil (Preshaw *et al*. 2001). Consistently, a comprehensive evaluation of data from two large surveys (National Health and Nutrition Examination Survey I and III) failed to find a strong association between oral contraceptives (either for earlier/high or current/low dosages) and occurrence of plaque-induced gingivitis (Taichman & Eklund 2005). Recently, the periodontal condition of women using contraceptive pills for at least 2 years was compared with that of matched controls not taking an oral contraceptive. In contrast with the above results, current oral contraceptive pill users had higher levels of gingival inflammation and bleeding on probing despite similar amounts of supragingival plaque (Haerian-Ardakani *et al*. 2010).

Diabetes

Diabetes is an endocrine condition with a well-characterized effect on gingivitis. Clinically, subjects with diabetes, whether insulin-dependent or non-insulin dependent, have significantly higher gingival inflammation compared with those who do not have diabetes with similar plaque levels (Bernick *et al*. 1975; Cutler *et al*. 1999; Salvi *et al*. 2005). Data from experimental gingivitis studies support these findings, with individuals with type 1 diabetes showing

more severe inflammation in response to a comparable bacterial challenge than that of subjects without diabetes (Salvi *et al*. 2005, 2010).

At the vascular level, the accumulation of advanced glycation end products (AGEs) alters the function of several intercellular matrix components, including vascular wall collagen, resulting in thickening of the capillary basement membrane and loss of vascular elasticity (Ulrich & Cerami 2001). Results from controlled histologic studies in animals showed that diabetes was associated with changes of the gingival vascular apparatus, such as the formation of new vessels with variable wall thickness, hyperemia, localized moderate-to-severe vasculitis (Tesseromatis *et al*. 2009), increased vascular permeability accompanied by increased leukocyte adhesion molecule expression, and enhanced leukocyte rolling (Sima *et al*. 2010).

Smoking

The effect of smoking on the expression of plaque-induced gingival inflammation is controversial. A number of studies have shown that smokers, when compared with non-smokers, accumulate plaque at the same rate but exhibit significantly less gingival inflammation in experimental gingivitis studies, albeit with similar plaque levels (Bergstrom & Preber 1986; Danielsen *et al*. 1990; Lie *et al*. 1998; Müller *et al*. 2002). In addition, significantly lower GCF volumes were detected at periodontally healthy or slightly inflamed sites in young regular smokers compared with non-smokers (Persson *et al*. 1999). At the same time, a single episode of smoking has been shown to produce a transient increase in GCF volume (McLaughlin *et al*. 1993).

The biologic mechanisms underlying the suppressive effect of smoking on clinical parameters of gingival inflammation are poorly understood. A structural and/or functional impairment of the gingival and periodontal microcirculatory system however, has been put forward (Scott & Singer 2004). In one, albeit small, study, the periodontal vascular system in smokers was found to be composed of smaller numbers of large vessels, but larger numbers of small vessels, compared with non-smokers, with no differences in terms of mean vascular density between smokers and non-smokers (Mirbod *et al*. 2001). This, together with the well-established nicotine-induced peripheral vasoconstriction as well as the reduction in GCF, is consistent with the effect of smoking being mediated, at least in part, by modulation of the local vascular response.

In contrast, Bergstrom *et al*. (1988) showed that after 28 days of experimentally-induced plaque accumulation, smokers had 50% more gingival blood vessels compared with non-smoking controls in spite of similar levels of plaque accumulation.

Further, Baab and Öberg (1987) found that a single episode of cigarette smoking was associated with a transient increase in gingival blood flow compared with sham-smoking in young smokers. Consistently, a modest increase in gingival blood flow was noted during the smoking episode, as well as over the following 10 minutes (Mavropoulos *et al*. 2003). When periodontally healthy sites were compared in terms of gingival blood flow between non-smokers performing sham-smoking, light smokers, and heavy smokers, however, no differences in gingival blood flow were observed between the groups either before, during or after smoking (Meekin *et al*. 2000).

At the present time, there is insufficient data to determine whether and to what extent the suppressive effect of smoking on the plaque-induced gingival inflammatory response may be ascribed to a modulatory effect of smoking on the vascular response.

Cellular response

Blood dyscrasias

The systemic conditions usually identified as affecting the cellular response in gingivitis are the blood dyscrasias, including neutropenias (Andrews *et al*. 1965; Rylander *et al*. 1975; Reichart & Dornow 1978), leukemias (Levin & Kennedy 1973; Bergmann *et al*. 1992), and human immunodeficiency virus/acquired immune deficiency syndrome (AIDS) (Glick *et al*. 1990). These conditions are characterized either by low numbers of functional PMNs (neutropenias) or large numbers of immature dysfunctional leukocytes (leukemias) infiltrating the gingival tissues or, as in the case of AIDS, by a very low CD4-positive T-cell count and the inability to mount an effective T-cell response. Other conditions which are characterized by defective PMN function, either phagocytic (Chédiak–Higashi syndrome) or chemotactic (Down's syndrome) (Izumi *et al*. 1989), also display severe gingival inflammation. These conditions highlight the fact that abnormalities in cell numbers or function can modify the inflammatory response to plaque and manifest as severe gingival inflammation.

Diabetes

As noted earlier, the development of gingivitis involves an initial innate immune response to the formation of plaque. In the presence of a poor innate response and the relative lack of PMNs in the gingival sulcus, a more severe inflammatory response occurs in an attempt to contain the developing infection. In addition to the vascular response noted earlier, hyperglycemia also leads to an impairment of immune cell function (Gugliucci 2000). In this respect, individuals with uncontrolled diabetes show reduced PMN function (Marhoffer *et al*. 1992), defective chemotaxis (Ueta *et al*. 1993), and significantly more severe gingival inflammation compared with those without diabetes with similar plaque levels (Gislen *et al*. 1980; Cianciola *et al*. 1982; Rylander *et al*. 1987; Salvi *et al*. 2005).

Chronic hyperglycemia leads to the accumulation of AGEs, which bind to macrophages and monocytes (Brownlee 1994), resulting in an increased release of

pro-inflammatory mediators (Iacopino 1995) and more severe gingival inflammation with higher levels of IL-1β and matrix metalloproteinase-8 (MMP-8) (Salvi *et al*. 2010).

Smoking

Smoking also has a profound effect on the immune and inflammatory system (Barbour *et al*. 1997; Palmer *et al*. 2005), including reduced migration (Eichel & Shahrik 1969) and phagocytic capacity of PMNs (Kenney *et al*. 1977) and increased numbers of circulating T and B lymphocytes (Sopori & Kozak 1998). However, the relevance of these mechanisms in altering the gingival inflammatory response to the dental biofilm needs to be determined.

Repair potential

The final feature of a chronic inflammatory response is the ability of the tissue to repair itself, such that anything which affects this ability will modify the gingival response to plaque and will either manifest as an enlargement (over response) or loss of connective tissue (impaired response) and progression to periodontitis.

Over response

Several drugs (Seymour 1993), including anticonvulsants such as phenytoin (Angelopoulos 1975a, b), antihypertensive calcium channel blockers such as nifedipine (Nery *et al*. 1995; O'Valle *et al*. 1995), and the immunosuppressant cyclosporine (Seymour & Jacobs 1992; O'Valle *et al*. 1995) cause severe gingival enlargement, a reaction related to the plaque-induced gingival inflammation (Seymour *et al*. 1996). Although these drugs have different pharmacologic mechanisms, a common denominator appears to be their effect on calcium metabolism which has been hypothesized to result in gingival enlargement (Hassell & Hefti 1991). Consistent with this concept is the fact that the clinical and histologic features of gingival enlargements induced by phenytoin, cyclosporine, or nifedipine are all similar (Hassell & Hefti 1991; Seymour *et al*. 1996). Histologic studies have shown that accumulation of extracellular matrix within the gingival connective tissue is the main feature of the overgrown tissues (Rostock *et al*. 1986; Mariani *et al*. 1993).

It is well established that the severity of the gingival enlargement is related to the level of plaque control and the presence of gingivitis (Steinberg & Steinberg 1982; Addy *et al*. 1983; Hassell *et al*. 1984; Tyldesley & Rotter 1984; Daley *et al*. 1986; McGaw *et al*. 1987; Modeer & Dahllof 1987; Yahia *et al*. 1988; Barclay *et al*. 1992; Lin & Yang 2010), which supports the concept that the enlargement reflects an over response of the repair component of the inflammatory reaction. Further, a high concentration of tissue plasminogen activator (t-PA) (Buduneli *et al*. 2004) and plasminogen activator inhibitor type 2 (PAI-2) has been demonstrated in GCF from enlarged sites, which suggests that the enlargement itself may act as a predisposing factor and lead to the aggravation of gingival inflammation (Kinnby *et al*. 1996). However, whether and to what extent the drugs associated with gingival enlargement may intimately modulate the complex host–bacteria interaction leading to gingival inflammation remains to be determined.

Impaired response

An example of how an impaired repair potential can influence the expression of gingivitis can be seen in vitamin C deficiency where an impairment of collagen metabolism results in highly inflamed, friable gingivae in the presence of plaque. Indeed, in both humans (Leggott *et al*. 1986, 1991) and non-human primates (Alvares *et al*. 1981) a subclinical deficiency of ascorbic acid results in increased gingivitis relative to non-deficient controls with similar plaque levels and the same type of microbiota.

Other studies, although preliminary and limited in number, suggest that other nutritional factors, including vitamin E (Cohen & Meyer 1993; Offenbacher *et al*. 1990; Asman *et al*. 1994), riboflavin, calcium, and frequency of fiber intake (Petti *et al*. 2000) may influence the incidence and severity of plaque-induced gingivitis, but their mechanisms are unknown.

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Chapter 13

Pathogenesis of Periodontitis

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Introduction

An understanding of the etiology and pathogenesis of periodontitis is essential for treatment planning. In this context, it is clear that the bacteria in dental plaque are the cause of both gingivitis and periodontitis; however, not all individuals with gingivitis will progress to periodontitis, and not all individuals with periodontitis will progress to tooth loss. The development of gingivitis can be considered to be a well-controlled immunologic response, as outlined in Chapter 12. However, in some people, due to environmental factors, their own innate susceptibility or both, there is loss of connective tissue and bone, apical migration of the junctional epithelium, and development of periodontitis.

The aim of this chapter is to present an understanding of the pathogenesis of periodontitis, which will provide a basis for treatment planning and future risk assessment.

Over the past two decades it has become established that periodontitis results from the interaction of the host's defense mechanisms with biofilms containing complexes including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (Socransky *et al.* 1998). Although present in a large proportion of the normal population (Cullinan *et al*. 2003), *Aggregatibacter actinomycetemcomitans* has been implicated in so-called aggressive periodontitis in some populations. Notwithstanding these observations, it has also been shown that there is a high degree of volatility with respect to the presence and/or absence of these organisms over time, such that it would appear that they are more widespread in the community than previously thought. Indeed, it is now recognized that many people carry the organisms without manifesting disease progression (Cullinan *et al*. 2003). In this context, it is clear that most people are in balance with their biofilm for most of the time and it is only when this balance is disturbed that disease results. Such disturbances may occur as a result of environmental influences leading to an opportunistic increase in the numbers of organisms, or a depression of the host's defense mechanisms or indeed both. Disease expression and progression therefore reflects the interplay between the bacteria, the host's immune system, and environmental factors (Cullinan *et al*. 2001;

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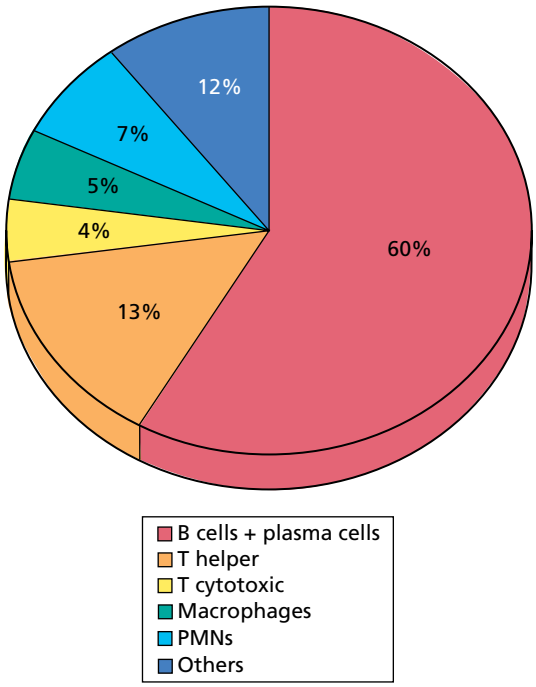

Fig. 13-1 Distribution of cells in periodontitis lesions. (Adapted from Berglundh *et al*. 2011, from John Wiley & Sons.)

Seymour & Taylor 2004), with tissue destruction being due to the response to the patient's specific individual pathogenic microbiota.

In 1965, Brandtzaeg and Kraus (1965) demonstrated the presence of immunoglobulin-producing plasma cells in the gingival tissues of patients with periodontitis. This was the first direct evidence that adaptive immune mechanisms play a role in the pathogenesis of periodontal inflammation. It was not until 1970 however, that Ivanyi and Lehner (1970), using peripheral blood lymphocyte transformation assays, highlighted a role for cell-mediated immunity. However, subsequent studies demonstrated that the periodontitis lesion itself involves predominantly B cells and plasma cells (Fig. 13-1) (Mackler *et al*. 1977; Seymour *et al*. 1978; Seymour & Greenspan 1979; Berglundh *et al*. 2011) and in this context it has been proposed that the development of periodontitis involves a switch from a predominantly T-cell gingivitis lesion to one involving large numbers of B cells and plasma cells (Seymour *et al*. 1979)

Histopathology of periodontitis

As described in Chapter 12, the development of gingivitis and periodontitis can be loosely divided into a series of stages, as described by Page and Schroeder (1976). These authors classified the development of the disease into the "initial", "early", "established", and "advanced"' lesions. The initial and early lesions have been described in Chapter 12. The established and advanced lesions are described here and while they are histopathologically similar, they differ in their clinical expression and degree of destruction.

Established or progressive lesion

The established/progressive lesion is primarily a lymphocyte/plasma cell lesion with the main identifying feature being the predominance of plasma cells within the periodontal connective tissues (Mackler *et al*. 1977; Seymour *et al*. 1978; Seymour & Greenspan 1979). The majority of lymphocytes are immunoglobulin-bearing B cells, although up to 30% of the lymphocytes may be T cells. While the gingivally confined T-cell lesion remains relatively stable, this B-cell/plasma cell lesion progresses and leads to the development of a periodontal pocket. Connective tissue breakdown leads to loss of the connective tissue attachment to the tooth and as a result the junctional epithelium migrates in an apical direction, thus forming a periodontal pocket (Fig. 13-2). This in turn becomes lined by pocket epithelium with in-growth of rete pegs into the surrounding connective tissue (Fig. 13-3). Polymorphonuclear neutrophils (PMNs) continue to migrate through this pocket lining epithelium and into the periodontal pocket where they form a barrier between the tissues and plaque biofilm. Increased permeability and ulceration of the pocket epithelium allows further ingress of microbial products, leading to the continued production of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and prostaglandin E_2 (PGE_2) [for review, see Gemmell *et al*. (1997)], and perpetuation of the inflammatory process resulting in destruction of both connective tissue and bone (Reynolds & Meikle 1997). Surrounding the inflammatory infiltrate is a fibrous tissue band. This is common to all chronic inflammatory lesions and is an attempt by the lesion to wall off from the surrounding tissues. Indeed, in periodontitis, irrespective of the depth of the pocket, the underlying alveolar bone and periodontal ligament do not become inflamed (Fig. 13-4).

Advanced lesion

The advanced lesion has essentially the same cellular make-up and features as the established lesion. The main difference lies in the overt loss of attachment that is evident clinically and histologically (Figs. 13-5, 13-6). It is now generally accepted that the mechanism of tissue destruction is via the effects of the immune response (Birkedal-Hansen 1993) and is not a direct consequence of the bacteria *per se*. Macrophages are not a dominant feature of the advanced lesion, comprising fewer than 5% of the cells. Fibroblasts, however, when stimulated by the inflammatory cytokines IL-1, IL-6, TNF-α, and

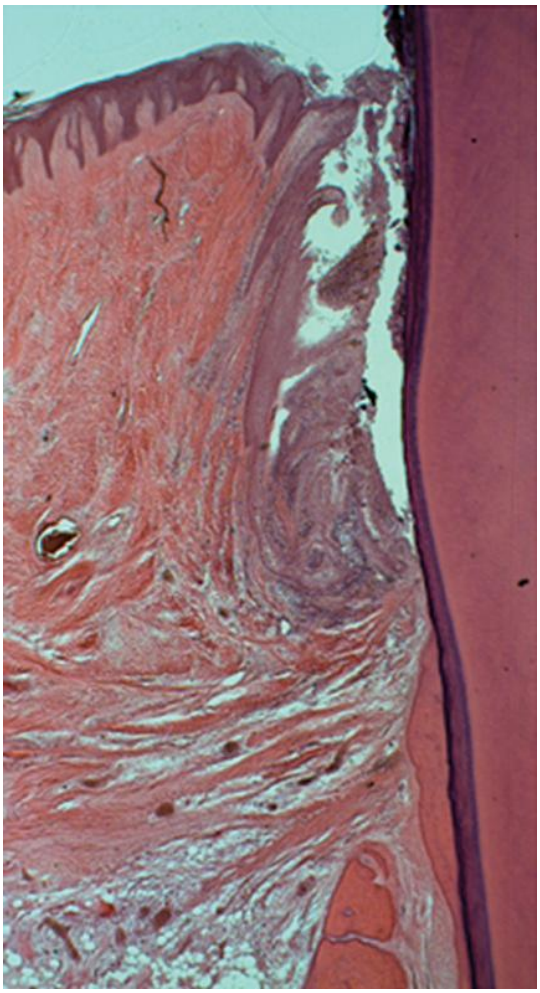

Fig. 13-2 Autopsy specimen showing a human periodontitis lesion. Calculus and biofilm in the pocket. Note the infiltrated connective tissue lateral and apical of the pocket epithelium.

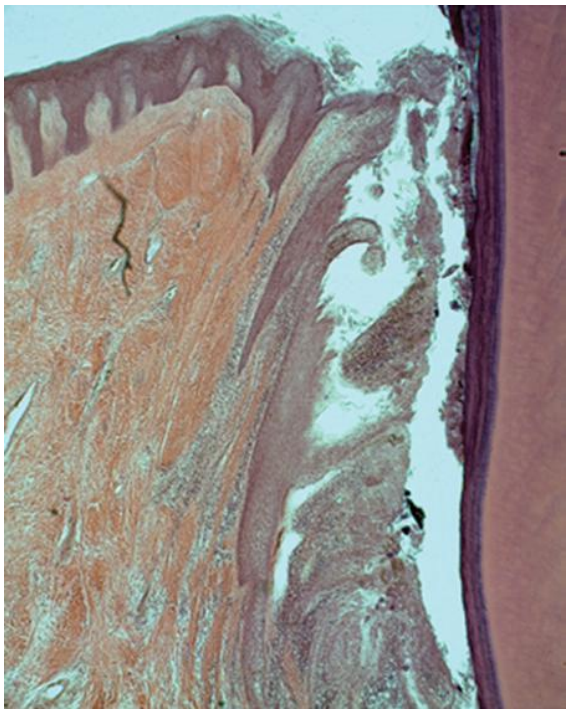

Fig. 13-3 Detail of Fig. 13-2. Note the ulcerated pocket epithelium with rete pegs into the connective tissue.

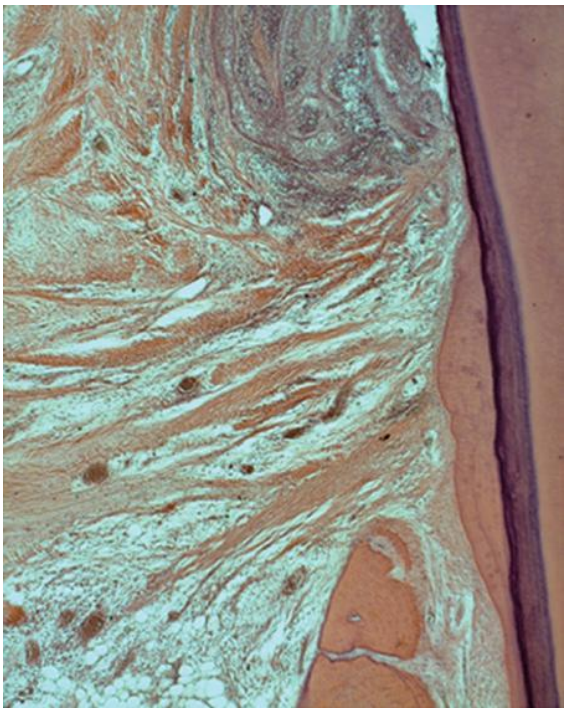

Fig. 13-4 Detail of Fig. 13-2. A band of non-infiltrated connective tissue is interposed between the infiltrated connective tissue and the alveolar bone.

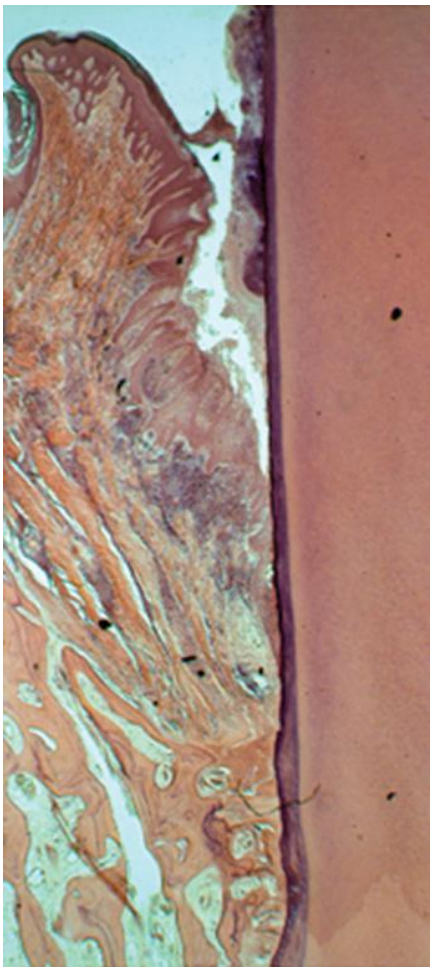

Fig. 13-5 Autopsy specimen showing a human periodontitis lesion. The overt loss of attachment and bone is characteristic for the advanced lesion.

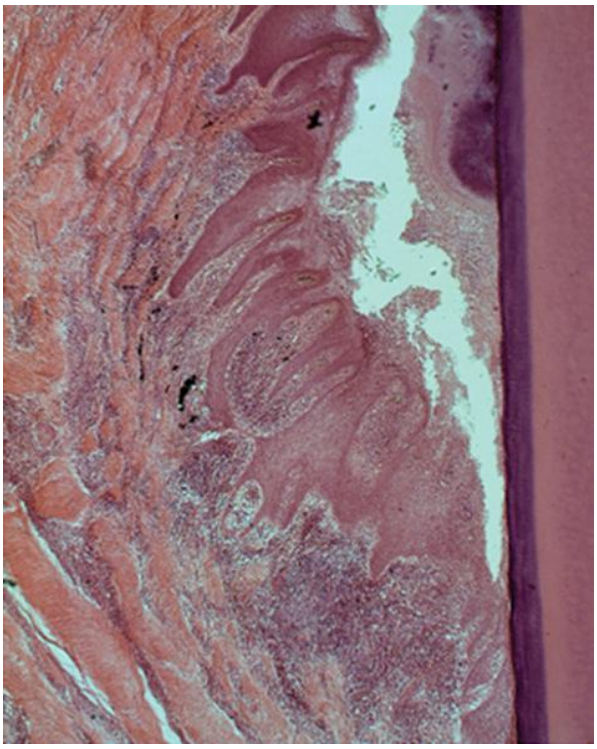

Fig. 13-6 Detail of Fig. 13-5. Pocket epithelium walling off calculus and biofilm in the pocket.

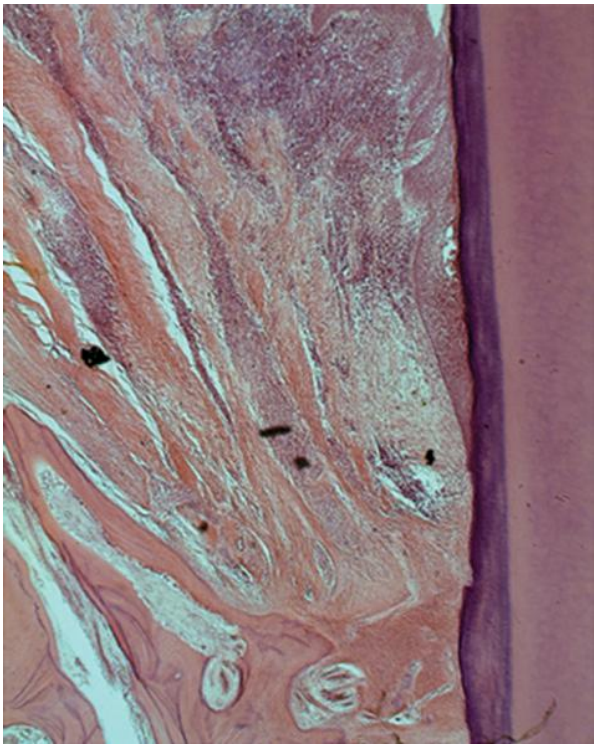

Fig. 13-7 Detail of Fig. 13-5. Note the non-infiltrated fibrous band between the infiltrated connective tissue and the bone.

PGE_2, produce matrix metalloproteinases (MMPs), which are a family of proteinases whose primary purpose is the degradation of the extracellular matrix. Collagen molecules are cleaved into smaller fragments, which then become denatured in the extracellular environment or are phagocytosed by surrounding fibroblasts. As the lesion advances, alveolar bone loss becomes apparent. However, the non-infiltrated fibrous band remains adjacent to the crestal bone, effectively encapsulating the progressing lesion and walling it off from the surrounding tissues. It should be noted again that the underlying bone and periodontal ligament remain non-inflamed (Fig. 13-7).

B cells in periodontitis

As noted above, the periodontitis lesion is characterized by large numbers of B cells and plasma cells. Immunoglobulin-bearing B cells in a periodontitis lesion are illustrated in Fig. 13-8. B cells can be activated either by specific antigens or by polyclonal activators. Indeed, a number of the putative periodontal pathogens, including *P. gingivalis*, *A. actinomycetemcomitans*, and *Fusobacterium nucleatum* have been shown to have profound polyclonal B-cell activation properties (Bick *et al*. 1981; Mangan *et al*. 1983; Carpenter *et al*. 1984; Ito *et al*. 1988). However, polyclonal activators do not activate all B cells. Approximately 30% of B cells may be stimulated by a single polyclonal activator, with different activators acting on different B-cell subpopulations. Further, the antibodies produced as a result of this polyclonal activation are likely to be of low affinity and the memory component may not be induced (Tew *et al*. 1989). At the same time, a degree of antigen-specific induction of sensitized B cells is also likely to occur. The principal immunoglobulin class produced in the periodontal tissues is IgG, followed by IgM and some IgA.

The role of specific antibodies in the pathogenesis of chronic periodontitis is poorly understood. High titers of specific antibodies to *P. gingivalis* and *A. actinomycetemcomitans* have been demonstrated in the serum and gingival crevicular fluid (GCF) of subjects with periodontal disease; however, the reports are still conflicting with respect to disease activity (Baranowska *et al*. 1989; Ebersole *et al*. 1995; Nakagawa *et al*. 1994). Immunodominant antigens of *P. gingivalis* and *A. actinomycetemcomitans* have also shown different patterns of immunoreactivity, while anti-*P. gingivalis* antibodies with different avidities have been demonstrated in various forms of periodontal disease (Mooney & Kinane 1994). It has been suggested that antibodies with high avidity confer resistance to continued or repeated infection, whereas non-protective low-avidity antibodies may be incapable of effectively mediating a variety of immune responses (Lopatin & Blackburn 1992; Kinane *et al*. 2008).

While a strong antibody response has been suggested to be generally protective, facilitating

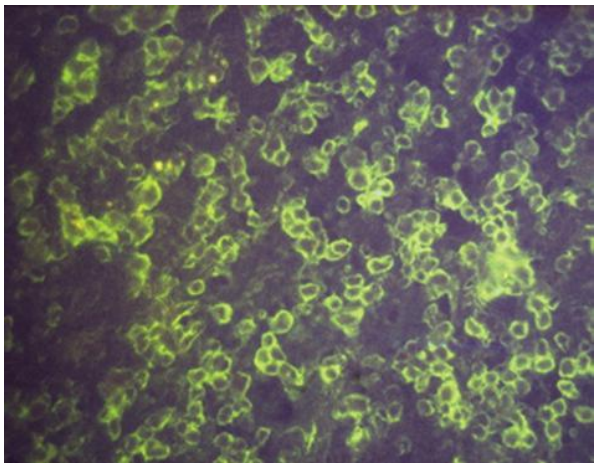

Fig. 13-8 Immunoglobulin-bearing B cells in a periodontitis lesion.

bacterial clearance and arresting disease progression (Offenbacher 1996; Kinane *et al*. 2008), the mechanism by which this is achieved is unclear. Antibodies, by virtue of their molecular size, are unlikely to penetrate the biofilm and hence their ability to clear the subgingival infection is questionable. Equally, PMNs do not penetrate the biofilm, again limiting their ability to clear the infection. Nevertheless, an increased capacity of serum to opsonize *P. gingivalis* has been shown to be a distinctive feature in patients with past destructive periodontal disease (Wilton *et al*. 1993). However, this high level of opsonizing antibody is more likely to be related to past bacteremias and the ability to clear the serum, than an ability to clear the subgingival infection. On the other hand, repeated infection with *A. actinomycetemcomitans* in an animal model has been shown to elicit an anti-leukotoxin antibody which protects PMNs from the leukocidal activity of the leukotoxin (Underwood *et al*. 1993). In this context, specific antibodies to bacterial products may be involved in controlling disease expression rather than clearing the organism from the subgingival biofilm. On the other hand, polyclonal B-cell activation by periodontopathic bacteria and the production of non-specific and/or low-avidity antibodies may not be capable of controlling the disease.

As well as producing immunoglobulins/antibodies, continued B-cell activation leads to the production of high levels of cytokines, including IL-1 and IL-10, which may contribute to subsequent tissue destruction. However, while *P. gingivalis* depresses the gene for IL-1β in T cells, it has been shown to induce an increased percentage of peripheral blood B cells from periodontitis patients to produce IL-1β (Gemmell & Seymour 1998). Since macrophages are not a dominant feature of the advanced lesion (Chapple *et al*. 1998) and suppressed cell-mediated immunity is associated with advanced periodontitis, it may be that B cells are the major source of IL-1 in periodontitis.

T cells in periodontitis: The Th1/Th2 paradigm

The fact that the development of gingivitis is identical to the development of delayed-type hypersensitivity (DTH) and that progressive chronic periodontitis is fundamentally a B-cell lesion, led to the concept that gingivitis and hence the stable periodontal lesion is mediated by Th1 cells, while periodontitis is mediated by Th2 cells (Seymour *et al*. 1993). In this concept it is proposed that a strong innate immune response leads to the production of high levels of IL-12 by both PMNs and macrophages, which in turn leads to a Th1 response, cell-mediated immunity, protective antibody, and a stable periodontal lesion. In contrast, a poor innate immune response with polyclonal B-cell activation leads to a Th2 response, non-protective antibody, and a progressive periodontal lesion. Since being put forward over 20 years ago, this hypothesis has attracted a lot of attention with a number of studies supporting the hypothesis by showing either depressed Th1 responses or increased Th2 responses in periodontitis. In contrast, other studies (primarily in animal models) have implicated increased Th1 responses in periodontitis, while others have highlighted a role for Th0 cells. Nevertheless, it is now generally agreed that periodontitis in humans is mediated by a balance in Th1 and Th2 cells with a shift towards a Th2 profile (Berglundh & Donati 2005; Kinane & Bartold 2007).

Suppression of cell-mediated immunity

The first study to report a possible suppression of cell-mediated immunity in advanced periodontitis subjects was by Ivanyi and Lehner (1970). Subsequently, a number studies have shown that periodontopathic bacteria, including *P. gingivalis*, *A. actinomyetemcomitans*, *T. denticola*, *Capnocytophaga ochracea*, and *F. nucleatum* (Shenker *et al*. 1982; Shenker & Slots 1989; Shenker & Datar 1995) could induce lymphocyte suppression *in vitro*. In addition, T cells extracted from periodontitis lesions not only have a reduced ability to respond in an autologous mixed lymphocyte reaction (AMLR), but also fail to produce IL-2, suggesting that this suppression of cell-mediated responses in periodontitis may also occur *in vivo* (Seymour *et al*. 1985) The fact that the AMLR returns to normal following periodontal therapy (Evans *et al*. 1989) also supports the concept that the suppressive effect of plaque bacteria on cell-mediated immunity (i.e. Th1 responses) may be fundamental in the conversion of a stable to a progressive lesion.

T cells and homeostasis

T cells are involved in nearly all immunoregulatory interactions both *in vivo* and *in vitro*, and a delicate

balance between effector and regulatory subsets is required for immune homeostasis. Th1 cells not only mediate DTH but also increase the ability of macrophages to kill intracellular and extracellular pathogens (Romagnani 1992). Further, there is evidence that T cells are involved in the recruitment and activation of PMNs at the site of infection (Campbell 1990), suggesting that in the stable lesion, activation of PMNs may be crucial in keeping the infection under control. Indeed, a strong innate immune response in the gingival tissues and the production of IL-12 could be critical in the establishment of a Th1 response. The presence of natural killer (NK) cells in gingival tissues has also been demonstrated (Wynne *et al*. 1986) and may also be significant in the establishment of a Th1 response. The production of interferon gamma (IFN-γ) enhances the phagocytic activity of both PMNs and macrophages, and hence containment of the infection.

In contrast, the B-cell nature of the progressive periodontitis lesion suggests either an increase in production of Th2 cytokines or a decline in the production of Th1 cytokines, in other words a shift in the balance towards Th2.

Cytokine profiles

Studies over the past decade have supported the hypothesis that Th1 cells are associated with the stable lesion and Th2 cells with disease progression [for review, see Gemmell *et al*. (2007)]. However, other studies have reported a predominance of Th1-type cells or reduced Th2 responses in diseased tissues (Ebersole & Taubman 1994; Salvi *et al*. 1998; Takeichi *et al*. 2000). More recently, the involvement of both Th1 and Th2 cells in periodontal disease in humans [for review, see Gemmell *et al*. (2007)] has been suggested. However, although cytokine patterns reflecting both subsets can be found in periodontitis tissues (Yamamoto *et al*. 1997), as noted above, it is now agreed (Berglundh & Donati 2005; Kinane & Bartold 2007) that periodontitis in humans is associated with a shift towards a Th2 response. Further circumstantial evidence for this concept is seen in the fact that *P. gingivalis* cysteine proteases (gingipains) hydrolyze IL-12, thereby having the capacity to reduce IL-12–induced IFN-γ production by CD4 cells and so favor a shift to a Th2 response and subsequent disease progression (Yun *et al*. 2001). Also, peripheral blood cells from periodontitis patients produce significantly lower levels of IL-12 (Fokkema *et al*. 2002) and the numbers of IgG4-positive B cells in the gingival tissues have been shown to increase relative to IgG2-positive cells with increasing inflammation, indicating the influence of IL-4 and Th2 responses and a corresponding decrease in IFN-γ and Th1 responses in large infiltrates in periodontitis.

CD8 T cells

The CD4:CD8 ratio in gingivitis is approximately 2:1 (Berglundh *et al*. 2002a; Zitzmann *et al*. 2005). This is consistent with the ratio seen in peripheral blood, in secondary lymphoid organs, and in the development of DTH (Seymour *et al*. 1988) In contrast, early studies on cells extracted from periodontitis lesions (Cole *et al*. 1987; Stoufi *et al*. 1987) reported the CD4:CD8 ratio in periodontitis to be around 1:1. Despite this obvious increase in CD8-positive T-cells, their functional activity in the context of periodontitis is poorly understood. While the majority of CD4 clones established from periodontitis tissues have Th2 phenotypes producing high levels of IL-4 and low levels of IFN-γ, the majority of CD8 clones produce equal amounts of IL-4 and IFN-γ, that is they have a Th0 phenotype (Wassenaar *et al*. 1995). Similar to CD4 cells, two subsets of CD8 clones exist. One, whose primary function is to mediate cytolytic activity, produces high levels of IFN-γ, but no IL-4 or IL-5. These are the classic CD8-positive cytotoxic T cells. The secondary function of this subset is to suppress B cells. The other subset of CD8 cells, whose primary function is to suppress the proliferative response of cytotoxic CD8 T-cell clones and to suppress cell-mediated immunity, produce high levels of IL-4 together with IL-5. These are the classic CD8-positive suppressor cells. The secondary effect of these cells is to provide help to B cells. It has been shown that peripheral blood CD8 cells from highly susceptible patients with severe periodontitis produce high levels of intracellular IL-4. If these cells also occur locally within the periodontal tissues of these susceptible patients, they may participate in the local response by suppressing IFN-γ–producing cells and favoring humoral immune responses (Wassenaar *et al*. 1995), and hence a shift towards a type 2 function. Teng (2003), however, has played down a role for CD8 cells in periodontal disease by concluding that this subset does not participate directly in the destruction during disease progression. Although they may not play a direct role in tissue destruction, CD8-positive T cells do produce cytokines which play a role in both innate and adaptive immune responses and are important in the lysis of bacteria-infected or bacteria-damaged tissues and cells. Overall, the role of CD8-positive T cells in the pathogenesis of periodontitis has been largely overlooked. However, determination of the functions of this subset is paramount in fully understanding the pathogenesis of periodontal disease.

Immunoregulation in periodontitis

While the Th1/Th2 paradigm provides a possible mechanism by which periodontal lesions become progressive or remain stable, an important question that remains is, what causes some lesions to show Th1 characteristics while others show Th2 characteristics? The answers may lie in the nature of the microbial challenge, as well as particular genetic and environmental susceptibility factors. Importantly, some of these factors may be clinically identifiable and modifiable.

It is likely that different T-cell subsets predominate at different phases of disease and the inability to determine disease activity clinically has been a major limitation in all studies. However, it remains clear that the balance of cytokines in inflamed periodontal tissues is what determines whether the disease remains stable or leads to progression and tissue destruction (Seymour & Gemmell 2001). In this context, the control of Th1 and/or Th2 expression is therefore fundamental in understanding the immunoregulatory mechanisms in chronic periodontitis (Fig. 13-9). Factors that control Th1 and Th2 expression include:

- Genetics
- Innate immune response
- Nature of the antigen
- Nature of the antigen-presenting cell (APC)
- Hypothalamic–pituitary–adrenal axis and the sympathetic nervous system
- Treg/Th17 axis.

Genetics

Study of identical twins who were raised apart indicates that between 38% and 80% of the variation in periodontal disease is due to genetics [for review,

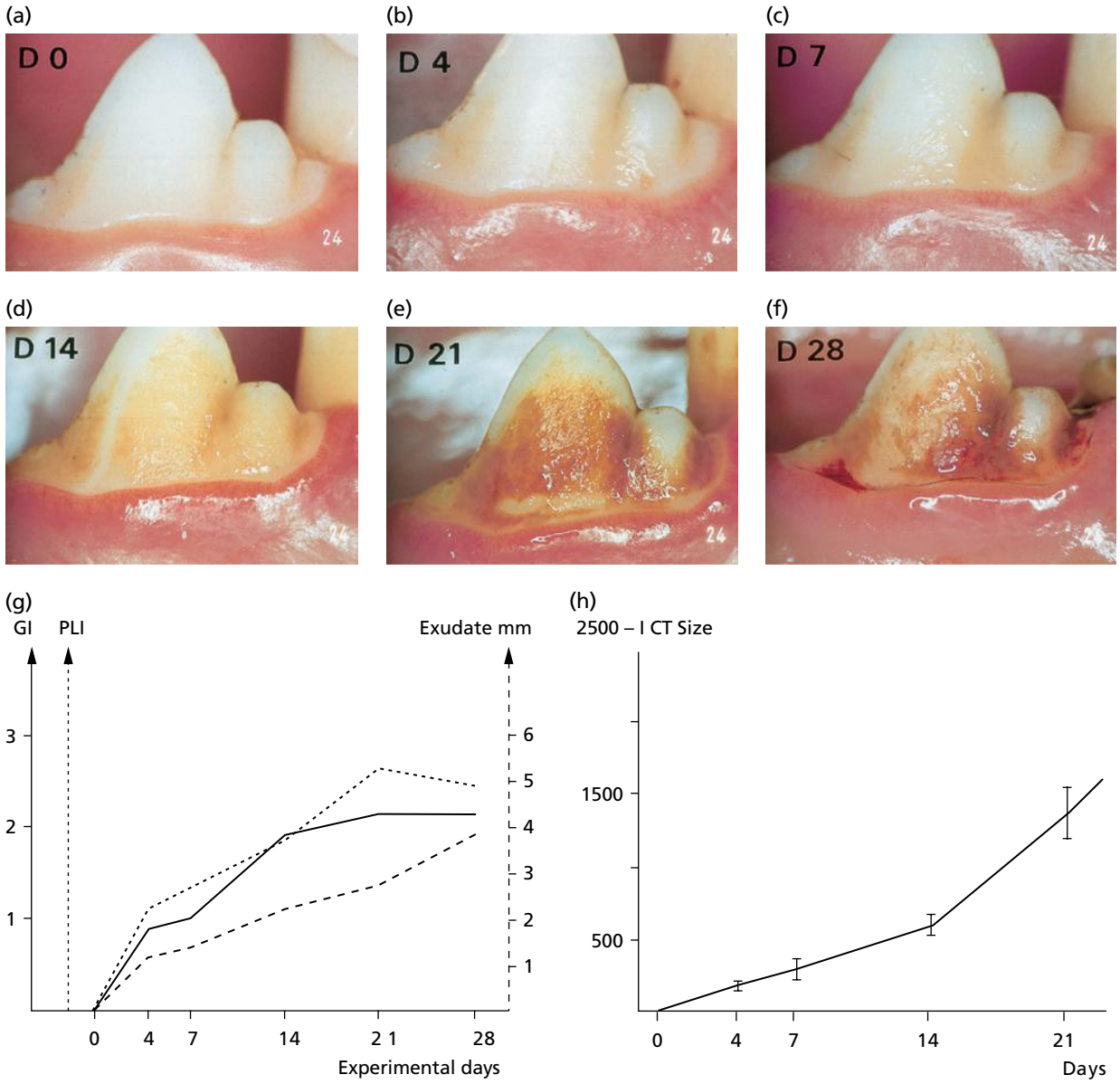

Fig. 13-9 Components involved in immune regulation in periodontitis. APC, antigen-presenting cell; IL, interleukin; IFN, interferon; Pc, plasma cells; TNF, tumor necrosis factor; Treg, regulatory T cell; TCR, T-cell receptor.

see Michalowicz (1994)]. Susceptibility to *P. gingivalis* infection in mice is also genetically determined (Gemmell *et al*. 2002b), although the relevance of this to human periodontal disease remains to be ascertained. However, it is interesting to note that the susceptible strains of mice show low Th1 responses, while the resistant strains show moderate-to-high Th1 responses to *P. gingivalis*.

Innate immune response

It is generally stated that there are two distinct arms of the immune response; the non-specific natural or innate response and the specific or adaptive immune response. In recent years, however, the distinction between these has become blurred with the discovery that, in many respects, the innate immune response determines the nature of the subsequent adaptive response and at the same time aspects of the adaptive response control the effectiveness of the innate response.

IL-12

As noted earlier, PMNs are a consistent feature of the periodontal lesion in both gingivitis and periodontitis, and deficiencies in PMN function are associated with severe and rapidly progressive periodontitis. A strong innate immune response will result in high levels of IL-12 and is therefore associated with a Th1 response, while a poor innate immune response and relatively low levels of IL-12 favor a Th2 response. Support for the concept of a Th1 response in gingivitis came from a study demonstrating significantly higher levels of IL-12 in the GCF from gingivitis sites in both gingivitis and periodontitis patients compared with periodontitis sites from the same periodontitis patients (Orozco *et al*. 2006).

Toll-like receptors

The discovery of toll-like receptors (TLRs) has led to a far greater understanding of innate immunity and the induction of adaptive immunity. TLRs are found on dendritic cells, PMNs, and macrophages among others, and have the ability to recognize structures known as pathogen-associated molecular patterns (PAMPs) that are highly conserved across a wide variety of pathogens. Such PAMPs include lipopolysaccharide (LPS), peptidoglycan, bacterial DNA, double-stranded RNA, and lipoprotein.

Given their role in innate immunity, it is likely that TLRs are important in determining the nature of the host response to plaque. TLR-2 and TLR-4, upon stimulation, may induce markedly different immune responses as determined by the resulting cytokine profiles. When stimulated, TLR-4 has been shown to promote expression of IL-12 and INF-γ–inducible protein-10 (IP-10), which is indicative of a Th1 response. Conversely, TLR-2 promotes the inhibitory IL-12p40, which is characteristic of a Th2 response (Re & Strominger 2001). These differences are reflected in differential cytokine expression by *Escherichia coli*-derived LPS and *P. gingivalis*-derived LPS. *E. coli*-derived LPS, which activates TLR-4, induces a strong Th1 response, while *P. gingivalis*-derived LPS, which activates TLR-2 (Hirschfeld *et al.* 2001), induces a strong Th2 response (Pulendran *et al*. 2001). These findings may indicate a further mechanism of susceptibility to periodontitis.

Nature of the antigen

As noted earlier, biofilms containing complexes of bacteria including *P. gingivalis, T. forsythia,* and *T. denticola* have been related to periodontitis, such that it is unlikely that a single antigen or a single organism is responsible for the disease. Further, there is the possibility that different people may have individually specific pathogenic complexes such that any single complex may not be pathogenic in all people. Indeed, little is actually known of the biofilm-specific antigens involved in periodontal disease and of the immune response to them. T-cell clones derived from mice immunized with *P. gingivalis* alone were found to have a Th1 profile, whereas T-cell clones derived from mice immunized with *F. nucleatum* followed by *P. gingivalis* demonstrated a Th2 profile (Choi *et al*. 2000). This may be due to the fact that *F. nucleatum* is a polyclonal B-cell activator such that B cells subsequently present the *P. gingivalis* antigen. Further, mice immunized with *F. nucleatum* were subsequently unable to make antibody to *P. gingivalis* (Gemmell *et al*. 2002a, 2004). This was not the case if bacteria were injected in the reverse order. These findings, albeit preliminary, nevertheless show that it is possible for co-infection with multiple organisms to modulate the immune response. The level and relevance of this modulation to human periodontal disease however, remains to be demonstrated but it is likely to involve the Th1/Th2 balance.

Nature of the antigen-presenting cell

It has been suggested (Kelso 1995) that Th1 and Th2 cells actually represent a spectrum of cells and, depending upon the conditions, can produce either Th1 or Th2 cytokines. In this context, Th0 cells may represent cells midway in the spectrum as well as naïve or non-committed cells.

The predominant APC in gingivitis tissues is a CD14-positive, CD83-positive dendritic cell (Gemmell *et al*. 2002c). In periodontitis tissues, the predominant APC is a CD19-positive, CD83-positive B cell, although a large number of CD83-positive endothelial cells are also present, suggesting that these cells may also be involved in antigen presentation. The cytokine profile of *P. gingivalis*-specific CD4 T-cell lines can be modified by changing the APC. When

autologous peripheral blood mononuclear cells are used as APCs, the cell lines are predominantly IFN-γ producing with a Th1 profile, but if autologous Epstein–Barr virus (EBV)-transformed B cells are used, the same cell lines become predominantly IL-4 producing, that is they have a Th2 profile (Gemmell & Seymour 1998). These findings suggest that it is possible to modulate the Th1/Th2 profile by varying the nature of the APC. In gingivitis, the predominant APC is a dendritic cell, whereas in periodontitis it is primarily a B cell.

Hypothalamic–pituitary–adrenal axis and the sympathetic nervous system

It is well accepted that stress, or at least the inability to cope with stressful situations, results in rapid progression of periodontitis. Stimulation of the sympathetic nervous system (SNS) as well as hypothalamic–pituitary–adrenal axis (HPA) activation leads to a selective suppression of Th1 responses, a shift towards Th2 dominance, and an increase in periodontitis (Breivik *et al*. 2000; Elenkov 2002).

Treg/Th17 axis

Regulatory T cells

Increased numbers of regulatory T cells (Tregs) have been demonstrated in periodontitis lesions where there are increased proportions of B cells. Foxp3, the forkhead/winged helix transcription factor and a characteristic marker of Tregs, was also shown to be more highly expressed in periodontitis compared with gingivitis tissues (Nakajima *et al.* 2005). The role of these cells in periodontal disease in humans however, is still speculative although they have an important function in the control of autoimmunity and as part of a regulatory axis with the so-called Th17 cells.

Th17 cells

Over the past two decades most attention has focused on Th1 and Th2 cells; however, in recent years a third lineage of T cells has been described, the so-called Th17 cells which selectively produce IL-17. IL-17 induces the secretion of IL-6, IL-8, and PGE_2; hence, these cells are thought to play a crucial role in regulating inflammation. IL-17 is also thought to affect osteoclast activity and thereby mediate bone resorption.

In the mouse, naïve T cells when incubated with TGF-β and IL-2 up-regulate the transcription factor Foxp3 and develop into the so-called Tregs which have an important function in suppressing autoimmune responses. In contrast, when incubated in the presence of transforming growth factor beta (TGF-β) and IL-6, CD4-positive T cells express the transcription factor RORγt and become Th17 cells. While these cells are thought to have a protective role against bacterial infections, they may on the other hand contribute to autoimmune disease. There are however, some important differences between mouse and human Th17 cells. In the human for example, TGF-β is not necessary for Th17 differentiation and there is some doubt over the role of IL-23, with some studies showing that IL-23 is a potent inducer of Th17 cells and others showing that IL-23 alone is relatively ineffective. Activation of monocytes via TLR-2 is an effective stimulus for Th17 differentiation and, while IL-2 initially inhibits Th17 differentiation, ultimately it leads to Th17 expansion [for review, see Laurence & O'Shea (2007)].

P. gingivalis leads to the down-regulation of the IL-17 receptor (*IL-17r*) gene in mice (Gemmell *et al*, 2006). *IL-17r*-deficient mice have a defect or display a significant delay in neutrophil recruitment into infected sites, resulting in susceptibility to infection (Kelly *et al*. 2005). This may account partly for the reported inhibition of entry of PMN into *P. gingivalis*-induced lesions in mice (Gemmell *et al*. 1997). These studies seem to suggest that IL-17 and its ability to enhance PMN activity would have a protective effect in periodontal disease. In contrast to this mouse study, IL-17 expression in human periodontitis tissue is controversial. In periodontitis patients, 51% of gingival T-cell clones were found to express IL-17 compared with only 11% of peripheral blood T-cell clones (Ito *et al*. 2005). Also, stimulation of peripheral blood mononuclear cells by *P. gingivalis* antigen enhanced not only transcription but also translation of the *IL-17* gene (Oda *et al*. 2003). On the other hand, immunohistologic and gene expression studies on diseased human tissue suggest low levels of IL-17 and low expression of IL-17 pathway genes (Okui *et al*. 2012). In addition, Th17 cells show enormous plasticity and are easily converted to Th2 cells *in vivo*: their role and that of the Treg/Th17 axis in human periodontal disease remains to be determined. Recently, a small number of IL-17-positive/Foxp3-positive cells have been identified in periodontal disease tissues (Okui *et al*. 2012), but other preliminary studies (Culshaw *et al*. 2011) seem to question a role for these cells in human periodontitis and suggest that mast cells may be the major source of IL-17 in human periodontitis. Parachuru *et al*. (2014) have also shown very few IL-17-positive cells (<1%) in B-cell/plasma cell-dominated periodontal lesions in humans, but a statistically significant correlation between the numbers of Foxp3-positive cells and the B-cell/plasma cell-to-T-cell ratio in these lesions. They further showed that the majority of IL-17-positive cells present had an ovoid/plasmacytoid morphology and were larger than the surrounding inflammatory cells, suggesting that these cells may be mast cells. In view of the latter findings, the role of IL-17 and especially of Th17 cells in human periodontal disease still remains to be determined.

Autoimmunity

NK T cells

Autoimmunity has been suggested to be a feature of periodontal disease. Cross-reactivity of human heat shock protein (HSP) 60 and *P. gingivalis* GroEL, a bacterial homolog, has been observed in periodontal disease (Tabeta *et al*. 2000; Ford *et al.* 2005). HSP60-specific as well as *P. gingivalis* cross-reactive T cells have also been demonstrated to accumulate in periodontitis lesions (Yamazaki *et al*. 2002). Taken together, these data suggest that both a humoral and a cell-mediated specific immune response to HSP60 may be important in the disease process. Additionally, anticollagen type l and lll antibodies have been demonstrated in the gingivae of periodontitis patients (Hirsch *et al.* 1988) and collagen type I-specific T-cell clones have been identified in inflamed tissues of periodontitis patients (Wassenaar *et al*. 1995).

A subset of T cells that express NK surface receptors are thought to play an important autoimmune immunoregulatory role. An immunohistologic study found that NK T cells were more numerous in periodontitis lesions compared with gingivitis tissues or peripheral blood. These NK T cells also appeared to associate with CD1d-positive cells and it was suggested that they play a regulatory role in periodontal disease (Yamazaki *et al*. 2001).

The role of autoimmunity in chronic inflammation is still not clear. It is possible that autoimmunity is a feature of all chronic inflammatory processes. In this context, it has been known for many years that gingival fibroblasts are able to phagocytose collagen such that anticollagen antibodies may facilitate this phagocytosis and hence the removal of the broken down collagen. At the same time, an anti-HSP response may enhance the removal of dead and dying cells such that these autoimmune responses may be a natural part of chronic inflammation. Control of these responses would therefore be essential. This concept further illustrates that the role of T cells in periodontal disease may be one of immune homeostasis. Further studies are clearly needed to test this hypothesis and to determine the role of regulatory T cells in periodontal inflammation.

B-cell subsets

There are two major subsets of B cells: B-1 and B-2 cells. B-2 cells are recognized as conventional B cells and represent the traditional group of B cells that take an active part in the adaptive host response. They interact with T cells and develop into memory cells and long-lived plasma cells that produce antibodies with high affinity.

B-1 cells, on the other hand, may either be T-cell independent and responsible for early antibody responses with low affinity, or interact with T cells and undergo class switching and produce IgG autoantibodies with high affinity. A specific subset of B-1 cells is the B-1a cell, which expresses the surface marker CD5. B-1a cells produce autoantibodies and are found in large proportions in subjects with autoimmune diseases and periodontitis (Afar *et al*. 1992; Berglundh *et al*. 2002b). The proportions of B-1a cells in peripheral blood are reported to be five to six times greater in subjects with periodontitis than in controls, and up to 40–50% of circulating B cells were positive for the B-1a cell marker CD5 in periodontitis (Berglundh *et al*. 2002b). B-1a cells also occur in large proportions in the gingival lesions of periodontitis patients such that the abundance of plasma cells seen in periodontitis lesions may be the result of both B-2 and B-1a proliferation and differentiation (Donati *et al*. 2009a). A study on experimental gingivitis in periodontitis patients has also demonstrated that B-1a cells are involved in the host response to microbial challenge (Donati *et al*. 2009b).

The large proportion of B-1a cells in periodontitis has also been associated with elevated levels of IL-10. B cells are one source of this cytokine and although IL-10 was previously regarded to play mainly anti-inflammatory roles, it also exhibits several pro-inflammatory functions, including activation of B cells, and serves as an autocrine growth factor for B-1a cells.

Connective tissue matrix destruction

Connective tissue remodeling is regulated by the interplay of cell–cell and cell–matrix interactions involving the production of enzymes, activators and inhibitors, and cytokines and growth factors (Reynolds & Meikle 1997). Proteinases such as the MMPs are key enzymes in tissue degradation. They are produced by resident cells, including fibroblasts, macrophages, and epithelial cells, and are regulated by tissue inhibitors of metalloproteinases (TIMPs).

It has been suggested that tissue destruction in disease processes may be due to an imbalance of MMPs over tissue inhibitors. Greater collagenase activity, which was demonstrated to derive mostly from PMNs, has been found in the GCF of periodontitis patients compared with the GCF of control subjects (Villela *et al*. 1987). MMP-9, which is produced by PMNs, was shown to be prominent not only in the GCF but also in gingival tissue samples from patients with periodontitis. Latent MMP-2 and MMP-9 have been shown to be expressed in the gingival tissues of patients with periodontitis, with the active forms being detected only in tissues associated with clinical disease (Korostoff *et al*. 2000; Seguier *et al*. 2001). Increases in the amounts of MMP-1, -2, -3, and -9, and the active form of MMP-9 have in fact been correlated with the number of CD22-positive B cells. This again suggests a possible mechanism by which B cells contribute to tissue destruction in periodontitis.

Up to 97–99% of the collagen in normal gingiva is made up of collagen types I and III. Collagen type III

represents a minor fraction (about 10%). All other types (IV, V, VI, and VII) are related to basement membranes and together do not exceed 1–3%. Transmission electron microscopy of biopsies from periodontitis patients demonstrated the almost complete destruction of collagen types l and lll in areas with leukocyte infiltration, while the basement membrane-associated collagen types V and Vl seem to remain and are related to the increased vascularity and epithelial proliferation in the inflamed tissue.

Bone loss

Bone resorption in periodontitis is regulated by the interplay between osteoblasts and the activation of osteoclasts. Osteoclasts share a common origin with cells of the macrophage/monocyte lineage and respond to and produce cytokines that regulate cells of this lineage. Osteoblasts originate from bone marrow stromal stem cells of mesenchymal origin and also have the capacity to produce factors which influence lineage development. Upon stimulation, osteoblasts produce a molecule known as receptor activator of nuclear factor-kappa B (NF-κB) ligand (RANKL), also known as osteoprotegerin-L (OPG-L), which regulates osteoclast differentiation and functions via its receptor (RANK). These activated osteoclasts then produce a number of acids and acid hydrolases which decalcify the mineral content of the bone and break down the organic matrix. The osteoclasts further phagocytose the broken down organic matrix, thus resorbing the bone. A variety of cells produce a decoy receptor osteoprotegerin (OPG), which when released binds RANKL to prevent activation of RANK and hence osteoclasts (Simonet *et al.* 1997).

While these factors have potent effects on osteoclast development, they also have regulatory effects on immune cell function (Lorenzo 2000), being critical for T-cell maturation and the production of cytokines such as IFN-γ, IL-2, and IL-4 (Kong *et al*. 1999).

Studies have reported increased concentrations of RANKL and decreased concentrations of OPG in the GCF and tissues from periodontitis patients (Mogi *et al*. 2004; Vernal *et al*. 2004). However, the relationship between this observation and the progression of periodontitis is speculative. Interestingly, human gingival fibroblasts stimulated with bacterial LPS have been shown to express OPG and OPG mRNA rather than RANKL. Supernatants of LPS-stimulated fibroblasts reduced the numbers of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts generated by monocytes cultured in the presence of RANKL and macrophage colony-stimulating factor (M-CSF), suggesting the inhibition of monocyte-derived osteoclasts via the OPG pathway (Nagasawa *et al*., 2002). RANKL and RANKL mRNA are expressed by inflammatory lymphocytes and macrophages as well as by proliferating epithelium in the vicinity of inflammatory cells. Thus, the high levels of RANKL seen in the GCF of periodontitis patients may be a reflection of the degree of inflammation rather than of bone loss and disease progression *per se*. Although both soluble and membrane-bound RANKL can be produced by activated T cells (Kong *et al*. 1999) and B cells (Taubman *et al*. 2005; Horowitz *et al*. 2010), it is the coupling of osteoblast-produced RANKL with osteoclast-expressed RANK that results in bone loss in periodontitis.

As already stated, IL-1 has a major role in bone resorption in periodontal disease, and both IL-1 and TNF-α have been reported to regulate the balance of RANKL and OPG (Hofbauer *et al*. 1999). Increased IL-1β production by B cells in periodontitis may therefore provide the link between increasing numbers of B cells and alveolar bone destruction in human periodontitis.

Conclusion

While there is no doubt that patient susceptibility determines periodontal disease expression and that this involves the interaction of bacterial, host, and environmental factors, determination of risk in individuals with periodontitis has proven elusive.

Despite over 40 years of research into the immunology of periodontal disease, the precise mechanisms and the role of many cell types remain an enigma. It is clear from the data obtained from a number of *in vitro* human studies and a recent microarray study, albeit in mice (Gemmel *et al.* 2006), that *P. gingivalis* has the ability to down-regulate both CD4 and CD8 cells *in vitro* and *in vivo*. These results, together with the plethora of data on human disease, have led to the development of the hypothesis that the function of the immune response in periodontal disease is to maintain homeostasis in the presence of the plaque biofilm. In this context, it can be seen that a balance between the biofilm and the host is reached. The T-cell response can therefore be considered to be the default response that balances activation with suppression. It is when this balance is disturbed that disease progression occurs.

This hypothesis is based in part on findings using a mouse model of *P. gingivalis* infection. However, mice do not develop periodontal disease and the *P. gingivalis*-induced immune response is a simple response to a single periodontopathic bacterium. In humans, dental plaque is a complex biofilm and the role of and response to biofilm-specific antigens has yet to be established.

The role of autoimmunity in chronic inflammation is also of major interest. In this context it can by postulated that autoimmunity is a critical and integral part of chronic inflammation in that it enhances the removal of collagen by enhancing fibroblast phagocytosis of protease-digested collagen fragments, as well as the removal of destroyed or dying cells. Control of this process by regulatory T cells (Tregs/Th17/NK T) then becomes fundamental and, again, if there is a disturbance in this homeostatic mechanism, enhanced tissue destruction could result.

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Chapter 14

Modifying Factors

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Introduction

This chapter discusses factors that may modify the host's susceptibility to periodontitis and the disease's clinical phenotype, including its extent, severity, progression, and response to therapy. The emphasis is on the two major modifying factors, diabetes mellitus and tobacco smoking. Aspects related to the epidemiologic evidence for the effect of these factors on periodontitis are reviewed in Chapter 7; thus, here we focus on underlying mechanisms, clinical presentation of affected individuals, and treatment considerations. A list of potential modifiers of periodontal health is shown in Table 14-1. Among these, factors such as puberty, menstruation, pregnancy, and medications that affect only the gingival status are discussed in Chapter 19, and the impact of HIV/AIDS on the periodontium is covered in Chapter 22.

Table 14-1 Potential modifiers of periodontal health.

- Diabetes mellitus
- Tobacco smoking
- Obesity and nutrition
- Osteoporosis and osteopenia
- Psychosocial stress
- Menstrual cycle
- Pregnancy
- Medications
  - Oral contraceptives
  - Anticonvulsants
  - Immunosuppressants
  - Calcium channel blockers
- HIV/AIDS
- Hematologic and genetic disorders and syndromes associated with diagnostic category IV "periodontitis as a manifestation of systemic diseases" (Armitage 1999)

Diabetes mellitus

Diabetes mellitus is a common, chronic condition with serious health implications. It comprises a group of metabolic disorders characterized by defects in insulin production, insulin action, or both, leading to abnormal glucose metabolism. The resulting hyperglycemia that characterizes both major types of diabetes (type 1 and type 2) is associated with a range of acute and chronic complications, and may eventually affect all organs of the body, including the periodontal tissues. Indeed, diabetes is established as a major risk factor for periodontitis.

Mechanisms underlying the effect of diabetes on periodontitis

Early studies exploring the mechanisms that may contribute to the increased prevalence and severity of periodontal destruction observed in patients with diabetes suggested the existence of distinct subgingival microbial profiles or antibody response patterns (Zambon *et al*. 1988). Subsequent reports concluded that the nature of the bacterial challenge in patients with diabetes and periodontitis does not appear to differ from that in those without diabetes (Feitosa *et al*. 1992; Thorstensson *et al*. 1995; Novaes *et al*. 1997;

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Sbordone *et al*. 1998). However, many of these studies included small numbers of individuals, assessed only a handful of bacterial species, and most importantly compared patients with diabetes and periodontitis to controls without diabetes who were periodontally healthy. Taking these limitations into consideration, the subgingival microbial challenge in diabetes was later revisited using a cohort of subjects with type 1 diabetes and a control group of age- and gender-matched individuals without diabetes but with similar levels of periodontitis (Lalla *et al*. 2006b). Bacterial profiles, based on 12 species, as well as the homologous serum antibody responses were found to be comparable between the two groups. Yet, microbial studies to date are restricted to known biofilm species. Future global analyses of the periodontal microbiome may shed further light on this issue. For now, it appears that it is the host response to the bacterial challenge that drives the enhanced susceptibility to periodontal disease in diabetes. Indeed, it was proposed early on that impairment of neutrophil function may facilitate bacterial persistence and increase periodontal destruction (Manouchehr-Pour *et al*. 1981a, b; McMullen *et al*. 1981). Subsequently, neutrophil priming in moderately and poorly controlled patients with diabetes, caused by increased levels and activity of protein kinase, was demonstrated (Karima *et al*. 2005). Other studies suggested a hyperinflammatory monocytic phenotype in diabetes characterized by enhanced levels of pro-inflammatory mediators in gingival crevicular fluid (GCF) or following challenge with lipopolysaccharide (LPS) in culture (Salvi *et al*., 1997, 1998; Yalda *et al*. 1994). In a study employing the experimental gingivitis model approach (i.e. 3-week cessation of oral hygiene resulting in gingivitis, followed by 2 weeks of optimal plaque control resulting in resolution of gingival inflammation), individuals with diabetes were found to develop accelerated and exaggerated gingival inflammation compared to controls without diabetes, despite a similar bacterial challenge (Salvi *et al*. 2005). Effects on other relevant cell types have also been reported, such as decreased collagen production and increased collagenolytic activity by gingival and periodontal ligament fibroblasts (Ramamurthy & Golub 1983; Sasaki *et al.* 1992; Yu *et al*. 2012), and hyperinflammatory response by oral epithelial cells (Amir *et al*. 2011).

Consistent with the evidence in humans, a number of animal studies have demonstrated that diabetes may increase the inflammatory response to bacteria. *Porphyromonas gingivalis* injection into the calvariae of diabetic mice was shown to stimulate an exaggerated cytokine expression and inflammatory infiltrate compared to the response observed in non-diabetic mice (Naguib *et al*. 2004; Graves *et al*. 2005; Nishihara *et al*. 2009). Reduction of inflammation and lesion size by specific inhibition of tumor necrosis factor-alpha (TNF-α) in these studies suggested that cytokine dysregulation represents a mechanism through which diabetes alters the host response to the bacterial challenge (Naguib *et al*. 2004; Takano *et al*. 2010).

A number of other reports, including human studies, have focused on osteoclastogenesis-related factors and explored the role of the receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin (OPG) in diabetes associated periodontal infections (Mahamed *et al*. 2005; Duarte *et al*. 2007; Lappin *et al*. 2009; Santos *et al*. 2010). These studies have suggested that hyperglycemia in diabetes may modulate the RANKL:OPG ratio in periodontal tissues and thus contribute to alveolar bone destruction. Along this line, the cycle of bone loss and subsequent bone formation was examined in a model of ligature-induced alveolar bone loss in rats (Liu *et al*. 2006b). Osseous repair was significantly limited by diabetes and the level of apoptosis of bone-lining cells was higher. In the calvarial model, diabetic mice also displayed increased fibroblast apoptosis and reduced fibroblast density following *P. gingivalis*-induced injury (Liu *et al*. 2004). Healing was significantly improved by blocking apoptosis with a caspase inhibitor (Al-Mashat *et al*. 2006) or by anti-TNF-α treatment (Liu *et al*. 2006a). These results were confirmed in diabetic mice with intraoral wounds (Desta *et al*. 2010; Siqueira *et al*. 2010). TNF-α inhibition in diabetic rats with ligature-induced periodontitis was also shown to impair expression of growth factors that control proliferation, differentiation or apoptosis of osteoblasts, to restore the bone coupling process, and to increase the capacity of the animals to form new bone (Pacios *et al*. 2012).

The first attempt to explore more upstream changes induced by diabetes that may explain the observed hyperinflammatory response to infection, focused on the role of the receptor for advanced glycation end products (RAGE), a multiligand signaling receptor and member of the immunoglobulin superfamily of cell-surface molecules. RAGE expression is increased in diabetes and its activation through ligand interaction has an established role in the development and progression of other diabetic complications (Yan *et al*. 2009). First, expression of AGE ligands and of markers of oxidative stress was demonstrated in gingival tissues of patients with diabetes and periodontitis (Schmidt *et al*. 1996). Subsequently, levels of serum AGEs were shown to be significantly associated with the extent of periodontitis in type 2 diabetic adults (Takeda *et al*. 2006) and increased RAGE expression was reported in gingival tissues of individuals with diabetes and periodontitis (Katz *et al*. 2005; Abbass *et al*. 2012; Yu *et al*. 2012,).

In a model of oral infection and diabetes in mice, *P. gingivalis*-induced alveolar bone loss was increased in diabetic animals compared to non-diabetic controls and was accompanied by enhanced expression of RAGE, inflammatory AGEs, and tissue destructive matrix metalloproteinases (MMPs) in the gingival tissues (Lalla *et al*. 1998). In subsequent studies, treatment with soluble RAGE (sRAGE), the

extracellular ligand-binding domain of RAGE which antagonizes interaction of ligands with the whole receptor, decreased levels of TNF-α, interleukin-6 (IL-6), and MMPs in gingival tissues and suppressed alveolar bone loss in a dose-dependent manner in diabetic animals (Lalla *et al*. 2000). Importantly, the beneficial effects of RAGE blockade were paralleled by suppressed expression of the receptor and its ligands in gingival tissues and were independent of the level of glycemia. These findings demonstrated that AGE–RAGE interaction leads to the exaggerated inflammatory response to the bacterial challenge and subsequent tissue destruction seen in diabetes-associated periodontitis. Accumulation of AGEs and their interaction with RAGE have been also suggested to contribute to osteoclastogenesis via increased RANKL expression and OPG down-regulation in various cell types (Ding *et al*. 2006; Yoshida *et al*. 2009).

Moreover, RAGE may contribute to impaired repair following injury, as shown in studies of excisional dermal wounds in diabetic mice, where inhibition of RAGE signaling enhanced the rate of wound closure and repair, and down-regulated MMP activity (Goova *et al*. 2001). Studies of osteoblast cultures and craniotomy defects in mice in the absence of infection have demonstrated the role of RAGE and its interaction with the AGE ligand carboxymethyllysine (CML)–albumin in delayed bone healing (Santana *et al*. 2003). Using the same experimental approach, the apoptotic effect of CML–collagen on osteoblasts was shown to be mediated through RAGE (Alikhani *et al*. 2007).

The basic mechanisms involved in the pathogenesis of diabetes-associated periodontitis are summarized in Fig. 14-1: the hyperglycemia that characterizes diabetes drives the formation of AGEs and leads to increased expression and activation of their chief receptor RAGE. AGEs can impact cellular phenotype directly via receptor-independent pathways but, importantly, the AGE–RAGE interaction negatively affects cellular phenotype and function, leading to enhanced inflammation, production of reactive oxygen species or oxidative stress, and compromised tissue repair. Hyperglycemia also promotes oxidative stress directly, and both inflammation and oxidative stress can contribute to further AGE formation. These mechanisms coupled with the impact of the periodontal pathogens perpetuate this vicious cycle of inflammatory stress and impaired repair in the diabetic periodontium. Of note, there are several links between the various elements shown in Fig. 14-1, but they cannot all be demonstrated in a single diagram. For example, inflammation and oxidative stress amplify one another and can also promote shifts in the subgingival biofilm. The net result of all these complex pathways is the accelerated periodontal tissue destruction observed in diabetes.

Clinical presentation of the periodontal patient with diabetes

Patients with diabetes will often present with pronounced clinical and radiographic signs of periodontitis, including gingival inflammation, increased pocketing, and increased attachment, bone, and tooth

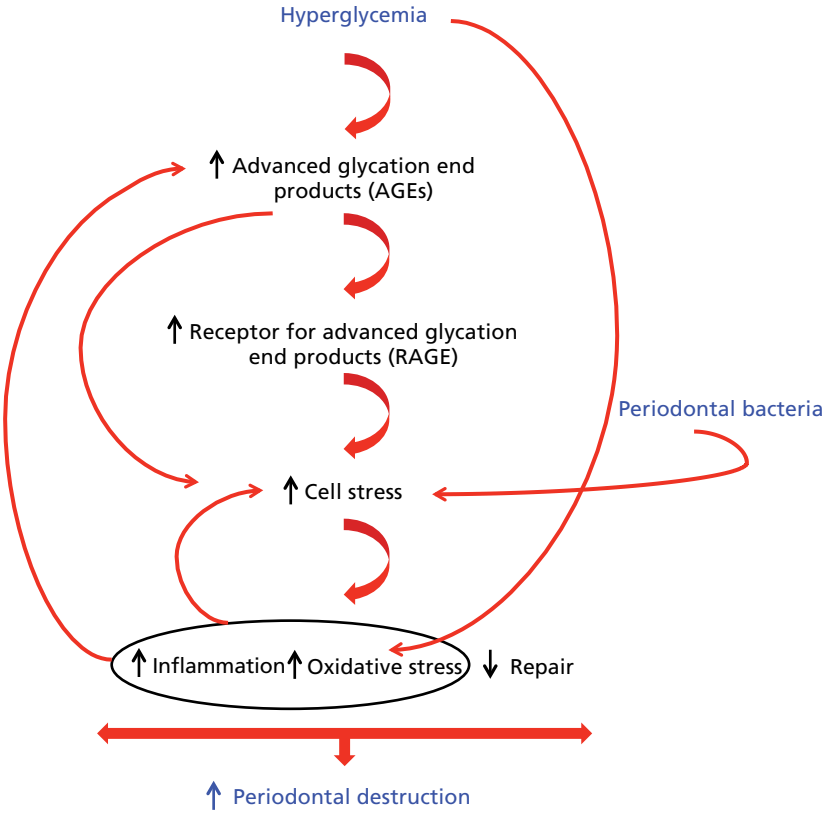

Fig. 14-1 Potential mechanisms in the pathogenesis of diabetes-associated periodontitis (see text).

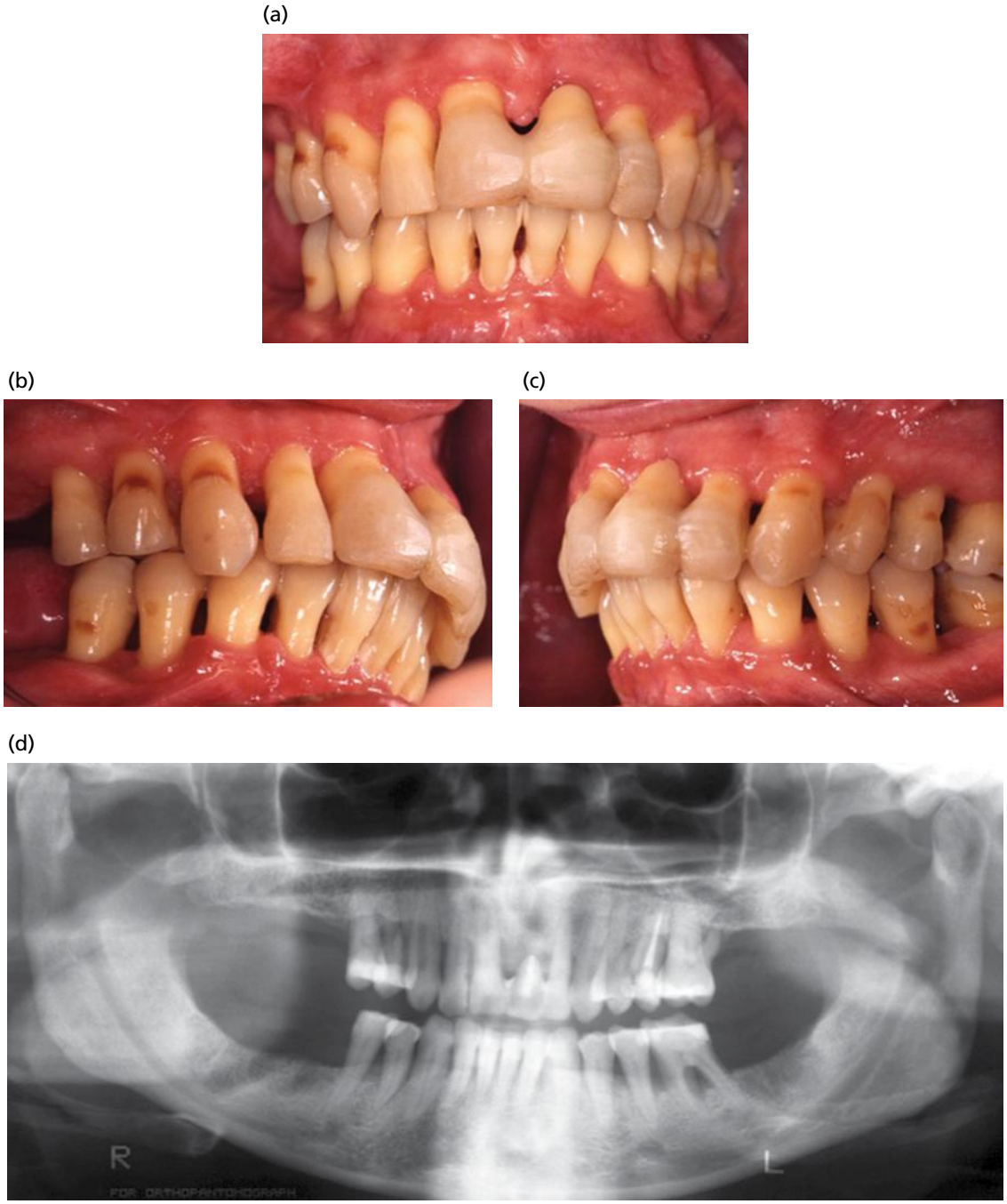

Fig. 14-2 (a–c) Clinical and (d) radiographic presentation of a 38-year-old female patient with type 1 diabetes and severe periodontitis. The patient was diagnosed with diabetes at the age of 10 years, has poor glycemic control, and is also a smoker. (Courtesy of T. Tervonen.)

loss (Figs. 14-2, 14-3, 14-4, 14-5). It is recognized that among those affected by diabetes, patients with poor glycemic control are at a higher risk for presenting with severe periodontitis (Tsai *et al*. 2002). In addition, clinical and radiographic signs of periodontitis progression may be evident (Figs. 14-6, 14-7), especially in periods when glycemic control deteriorates over time (Westfelt *et al.* 1996). Given that many of the effects of hyperglycemia discussed in the section above are irreversible and may have long-lasting effects, poor periodontal status may even be present in patients with adequate current glycemic levels, but past periods of poor metabolic control. Beyond the typical appearance of amplified gingival inflammation and bone or attachment loss, poorly controlled or undiagnosed/untreated patients with diabetes may present with or experience recurrent periodontal abscesses (Harrison *et al*. 1983; Ueta et al. 1993).

Importantly, even children and adolescents with diabetes may present with significant periodontal changes (Cianciola *et al*. 1982). A series of reports in 6–18-year-old individuals (Lalla *et al*. 2006a, 2007a, b) has demonstrated that increased attachment loss manifests much earlier in life in diabetes than previously recognized and is associated with poor glycemic control. Therefore, a thorough periodontal

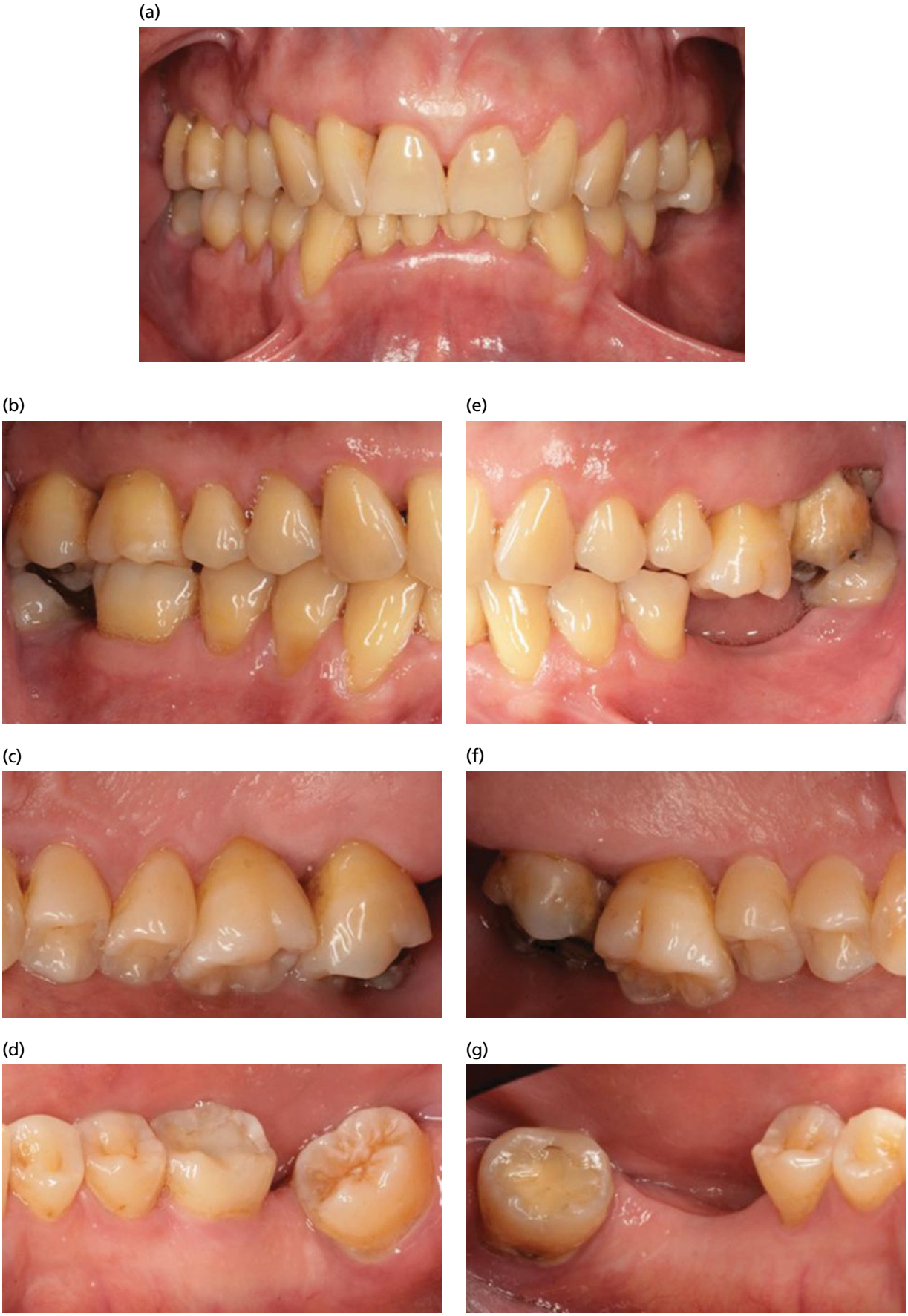

Fig. 14-3 Clinical presentation of a 50-year old male patient with type 2 diabetes. (a) Anterior view; (b–d) right side view; (e–g) left side view. The patient was diagnosed with diabetes 8 years earlier, is poorly controlled, and is a former smoker. Periodontal examination revealed probing depths of up to 10 mm and multiple sites with gingival recession. (Courtesy of T. Spinell.)

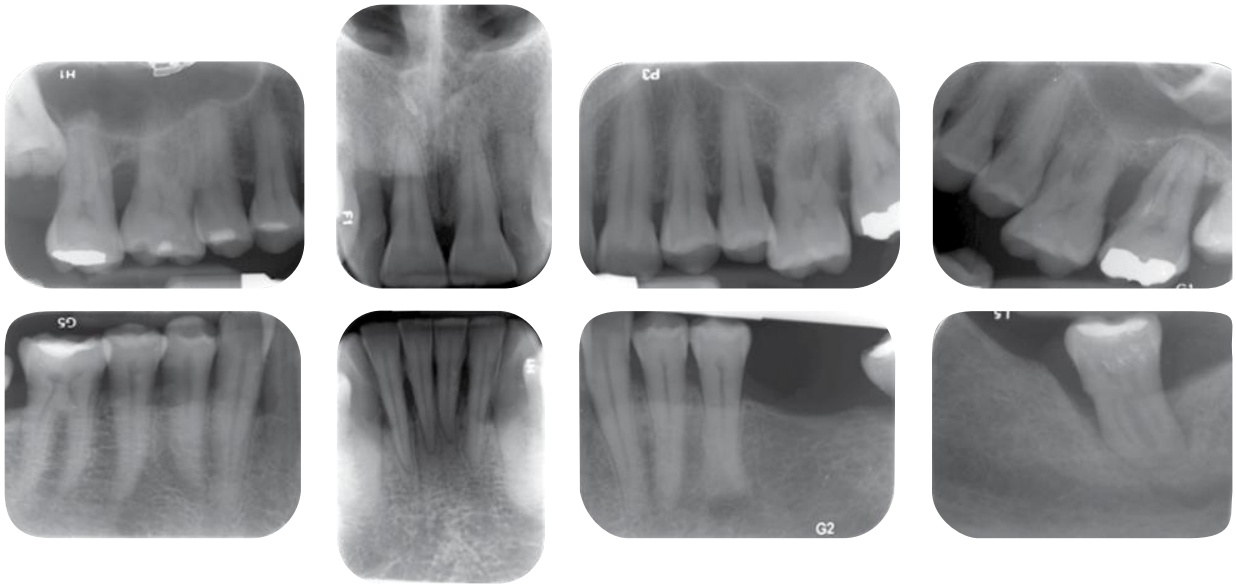

Fig 14-4 Periapical radiographs of the patient shown in Fig. 14-3 reveal areas of severe bone loss. (Coutesy of T. Spinell.)

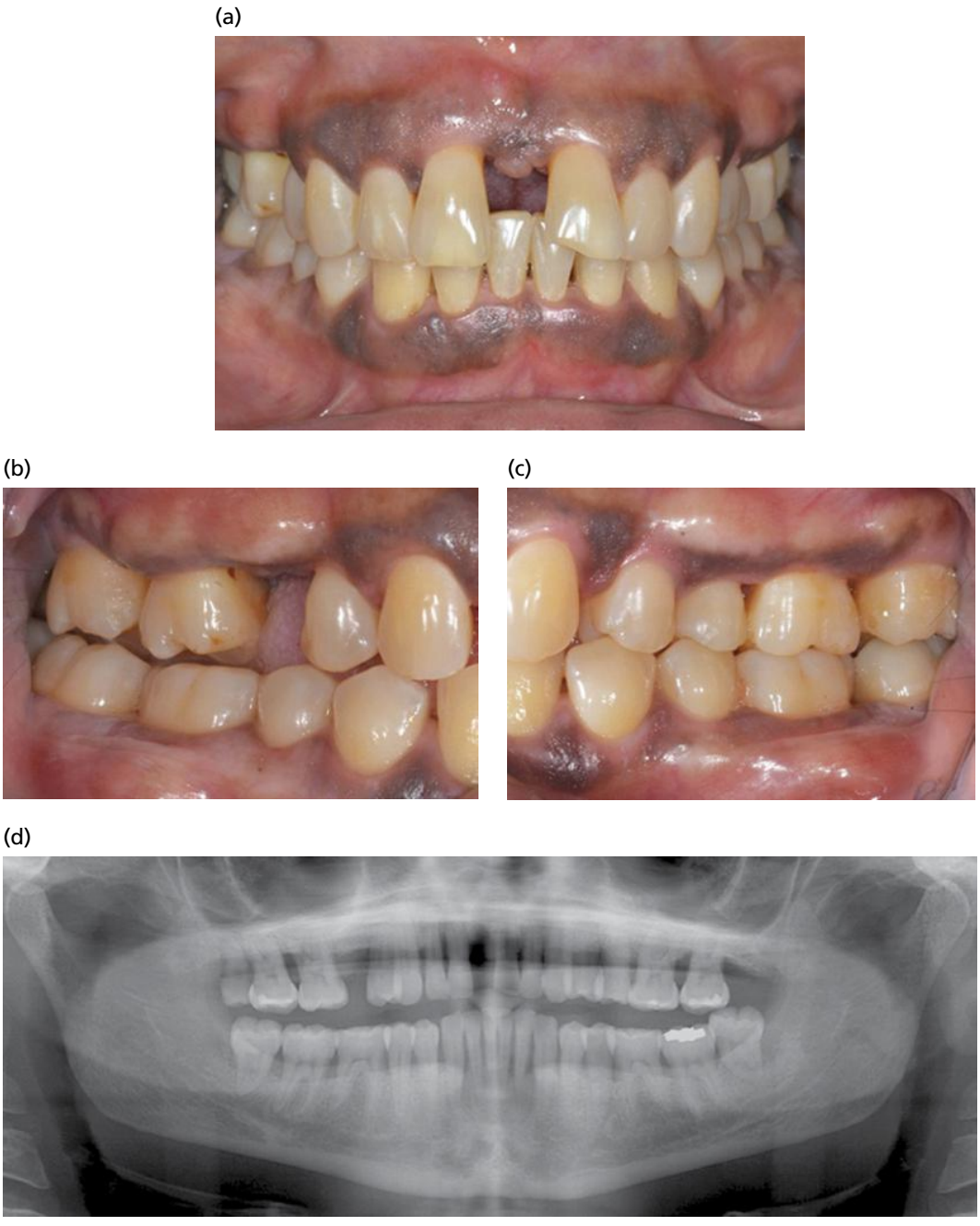

Fig. 14-5 (a–c) Clinical and (d) radiographic presentation of a 41-year-old female patient with type 1 diabetes. The patient was diagnosed with diabetes at the age of 26 years, has poor glycemic control, and is a former smoker. Periodontal examination revealed generalized severe periodontitis with probing depths ranging between 5 and 9 mm on most teeth. (Courtesy of S. Tsuji.)

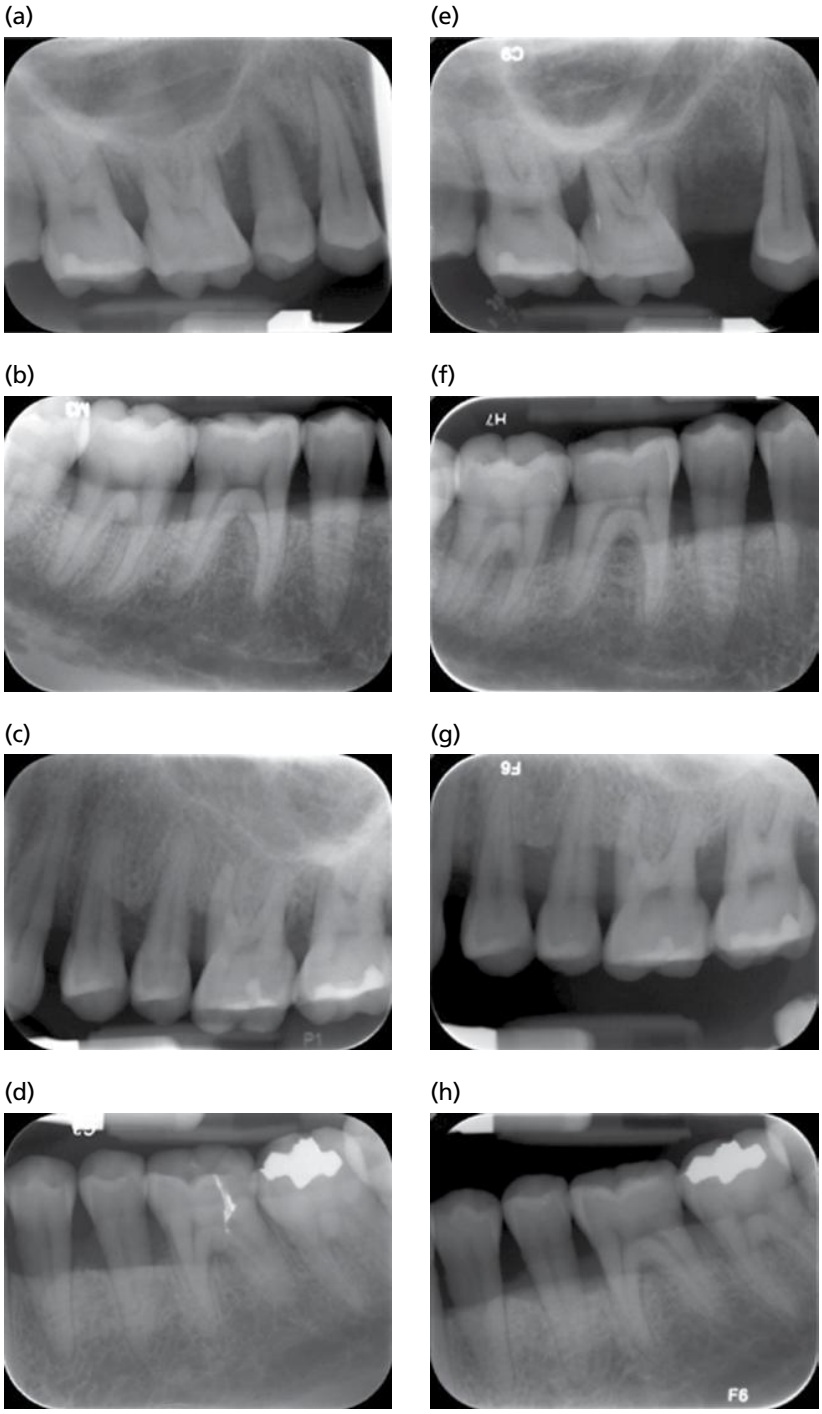

Fig. 14-6 Same patient as in Fig. 14-5. Posterior periapical radiographs at presentation (e–h), and corresponding radiographs taken 17 months earlier (a–d). Comparison reveals progression of bone loss and loss of the upper right second premolar within this short time period, during which glycemic control was poor (HbA1c values of 9–10%). (Courtesy of S. Tsuji.)

evaluation is needed in patients with diabetes across all age groups.

With respect to non-surgical periodontal therapy outcomes, patients with adequately controlled diabetes can respond well and achieve reduced probing depths and attachment gain (Christgau *et al*. 1998). In such patients, periodontal status can remain stable over time following surgical therapy and appropriate maintenance (Westfelt *et al*. 1996). However, in patients with poor glycemic control, long diabetes duration, and other diabetic complications, response to periodontal therapy appears to be unpredictable as tissue repair and wound healing are compromised (Tervonen & Karjalainen 1997). There is little available evidence to date on specific responses to different types of surgical therapy in patients with diabetes. Clinicians may use early responses to non-surgical therapy, especially at the more "predictable" sites (e.g. shallow–moderate pockets, accessible sites, single-rooted teeth), in order to identify potential non-responders early, properly inform/advise such patients, and plan further treatment accordingly.

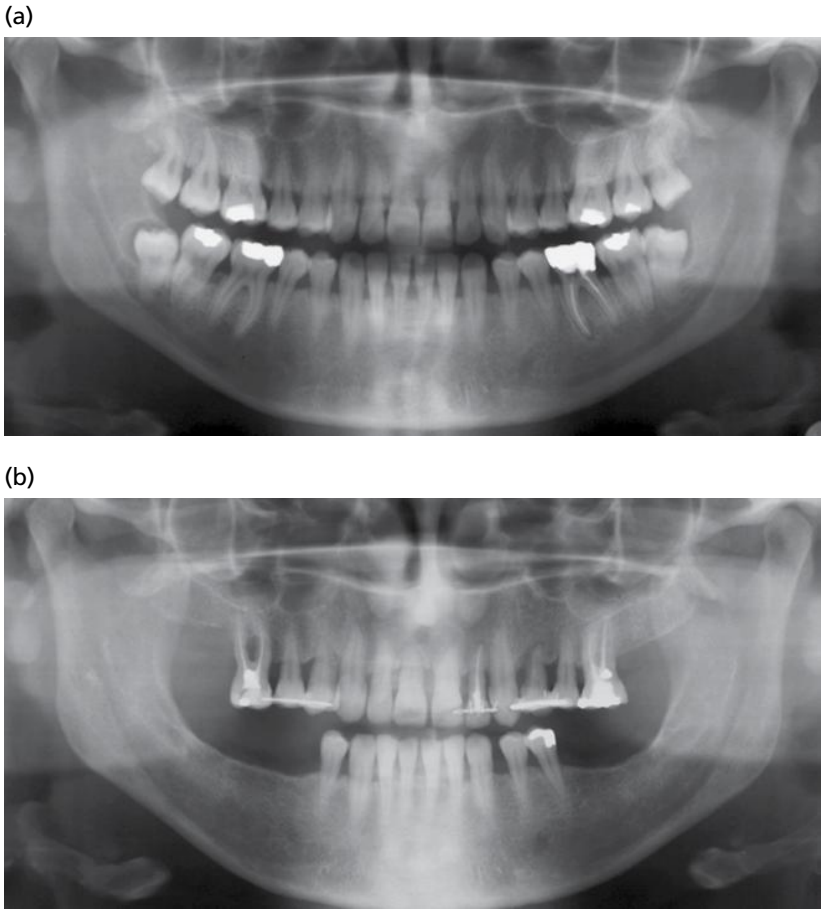

Fig. 14-7 Panoramic radiographs of a female patient with type 1 diabetes (a) at presentation at the age of 29 years and (b) 12 years later. The patient had been diagnosed with diabetes at the age of 12 years, was poorly controlled, and a smoker. She developed nephropathy and was on peritoneal dialysis. Despite comprehensive periodontal therapy, her periodontal status deteriorated significantly. The patient died of a myocardial infarction at age 41. (Courtesy of T. Tervonen.)

Concepts related to patient management

Studies suggest that oral disease awareness among individuals with diabetes is low (Moore *et al*. 2000; Tomar & Lester 2000; Sandberg *et al*. 2001; Jansson *et al*. 2006; Allen *et al*. 2008; Al Habashneh *et al*. 2010). Therefore, dental professionals need to educate their patients with diabetes, young and old, about the link between diabetes and periodontitis, and stress that the two conditions may amplify one another.

Managing the periodontal patient with diabetes who is under good medical care and maintains adequate glycemic control should not generally be difficult. However, as the concepts discussed earlier suggest, patients with poor metabolic control and those who present with other complications and co-morbidities may present a challenge when treated for periodontal conditions. Therefore, special considerations must be taken into account to ensure that the oral care provided is safe and that it leads to predictable outcomes. These considerations include: (1) taking a thorough medical history with a focus on understanding the patient's metabolic profile; (2) establishing communication with the treating physician; (3) performing a careful intraoral evaluation and a comprehensive periodontal examination; (4) addressing other risk factors present, such as smoking or overweight/obesity; and (5) considering co-morbidities and other complications, such as hypertension, vascular or kidney disease.

Initial therapy should focus on the control of acute infections, if present, as these may also have a direct adverse effect on the level of the patient's glycemic control. Good oral and overall health behaviors along with lifestyle changes, as needed, must be promoted. Recommendations for proper home care are very important and a less complex, stepwise periodontal therapy plan should be offered whenever possible. Clinical protocols should be in place for determining frequency of maintenance care (to reinforce oral hygiene and prevent, monitor, and treat any disease reactivation), the need for referral to a periodontist, and the need for medical consultation, referral, and follow-up. An interdisciplinary approach and collaboration beyond professional boundaries is often essential.

Furthermore, extreme glycemic variability is a relatively common medical emergency in a dental care setting. Prevention, early recognition, and proper management of potential hypo- and hyperglycemic episodes are very important. Dental professionals need to remember that, for all people with type 1 and many with advanced type 2 diabetes,

episodes of hypoglycemia are very common and can be precipitated by several factors, including missed or delayed meals, excessive physical activity, stress, or alcohol consumption. Acute hyperglycemic episodes are less common, but also serious. They can be precipitated by pain and stress, that antagonize insulin action, or by under-dosing of diabetic medications prior to the dental appointment. Therefore, consideration must be given to the appropriate timing and duration of appointments: early mornings are preferable, as patients can tolerate stress better due to higher levels of endogenous corticosteroids. Likewise, procedures should preferably be brief and as atraumatic and pain free as possible, requiring profound anesthesia and adequate post-treatment analgesic coverage. In addition, since the patient's ability to eat may be affected by a periodontal procedure, a change in diabetic regimen may be necessary and should be explored in consultation with the treating physician.

A preoperative determination of glucose levels using the patient's glucometer can be very helpful in prevention and/or early identification of episodes of extreme glycemic variability. Early signs of hypoglycemia (glucose levels <70 mg/dL) include shakiness, weakness, hunger, cold and clammy skin, and nausea, and later symptoms include increasingly bizarre behavior, mental confusion, hypotension, and loss of consciousness. If the patient is conscious, 15–20 g of simple carbohydrates should be given orally (e.g. glucose tablets or gel, ½ cup of fruit juice, 1 tablespoon of table sugar). The patient should respond in about 15 minutes and should be then given a snack with complex carbohydrates and protein. If the patient does not respond, treatment can be repeated. If the patient becomes unconscious, glucagon (available as a kit with a 1-mg ampule, diluents, and syringe) can be injected into the upper arm or thigh muscle and medical emergency services must be called. When the patient responds to the glucagon injection and is able to swallow, the oral carbohydrate administration steps described above can be followed until the patient is stabilized. A patient with an acute hyperglycemic emergency (glucose levels >250–300 mg/dL) can present disoriented, thirsty, fatigued or nauseated, with rapid and deep breathing, hot and dry skin, and fruity breath, and can progress to hypotension and loss of consciousness. Such patients require transfer to an emergency room/hospital setting and immediate medical intervention. Again, having a glucometer at hand is very helpful; glucose levels can be assessed when symptoms arise to confirm whether the episode is because of hypo- or hyper-glycemia, and in the case of a hypoglycemic episode, to reassess levels following initial treatment. If a glucometer is not available and the dental professional is unable to differentiate whether the patient is hypo- or hyper-glycemic, treatment for hypoglycemia should be initiated. The patient's treating physician should always be informed of extreme glycemic emergencies that occurred in the dental setting and provided with all related information.

Finally, another concern relates to the large number of people worldwide who have diabetes, but remain undiagnosed, and the even larger number of individuals at risk for diabetes who are unaware of it. Since diabetes has early oral effects and many patients visit a dentist annually, often returning for multiple non-emergent visits, dental care settings are ideal healthcare sites that can be used for the early identification of undiagnosed diabetes. Dental professionals can assess risk factors, refer for testing or "formally" screen, and follow-up on outcomes. Studies based on national data in the US explored the ability of clinical periodontal parameters to identify patients with undiagnosed diabetes and findings suggested that such an approach is promising (Borrell *et al*. 2007; Strauss *et al*. 2010, Li *et al*. 2011, 2013). The first study to prospectively collect data in a clinical setting in order to discern a simple and efficient protocol to identify people with undiagnosed prediabetes or diabetes revealed that two dental parameters (number of missing teeth and percent of teeth with deep periodontal pockets) were effective in correctly identifying the majority of cases of unrecognized dysglycemia (Lalla *et al*. 2011). The addition of a point-of-care HbA1c test result was found to significantly improve the performance of the screening algorithm in the population under investigation. As the performance of this and any similar approaches is tested in diverse populations in the future, we can expect that assessment for undiagnosed dysglycemia may be incorporated into the periodontal evaluation of each patient at risk.

Tobacco smoking

Tobacco smoking is a prevalent behavior with widespread and severe health consequences. Although tobacco use was once classified as a habit, it is now considered an addiction to nicotine and a chronic relapsing medical condition. Smoking has several effects on the oral cavity ranging from simple tooth staining to oral cancer.

As reviewed in Chapter 7, smoking is recognized as an important risk factor for periodontitis, and a multitude of epidemiologic and clinical studies have established its detrimental effects on the periodontium. These effects have been shown to be dose-dependent and can be particularly evident in younger individuals (Stabholz *et al*. 2010). There is also evidence for a link between passive, also termed environmental or second-hand, smoking and periodontal disease (Arbes *et al*. 2001; Nishida *et al*. 2008). Tobacco smoke contains thousands of different substances and most of its harmful effects result through systemic exposure following lung absorption, in addition to the obvious absorption in the oral cavity (Palmer *et al*. 1999).

Mechanisms underlying the effect of smoking on periodontitis

The pathways by which cigarette smoking affects periodontal status are not fully understood; however, various potential mechanisms have been discussed in the literature, including effects on the oral microbiota, the gingival tissues, the inflammatory and immune response, and the healing capacity of the periodontium.

Early reports suggested that the amount of plaque in smokers is higher compared to non-smokers (Preber *et al*. 1980), but studies controlling for confounding factors revealed that smoking does not appear to affect plaque scores, and indeed, in experimental gingivitis models the rate of plaque formation was similar between smokers and non-smokers (Bergstrom 1981; Preber & Bergstrom 1986, Lie *et al*. 1998). Further, certain studies focused on smoking and qualitative changes in subgingival plaque. Zambon *et al*. (1996) found higher prevalence of *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *P. gingivalis* in current and former smokers compared with never-smokers. Similarly, Haffajee and Socransky (2001) found a higher prevalence of eight bacterial species in current smokers compared with past smokers and non-smokers. In subsequent reports, tobacco smoking has been shown to affect bacterial acquisition and colonization (Brook 2011; Kumar *et al.* 2011) and bacterial aggregation (Bagaitkar *et al*. 2011), and to promote colonization with key periodontal pathogens (Shchipkova *et al*. 2010; Kubota *et al.* 2011). Based on these studies, it appears that microbiologic differences exist between smokers and non-smokers, but they primarily concern the composition rather than the amount of subgingival plaque.

Importantly, it is well accepted that smoking has the potential to impair several aspects of the innate and immune response and, in the setting of periodontitis, this can tip the balance towards an exaggerated tissue breakdown and impaired repair. To this end, it has been reported that neutrophil migration and chemotaxis in the periodontal tissues are negatively affected in smokers (Pabst *et al*. 1995; Persson *et al*. 2001; Soder *et al*. 2002). Interestingly, neutrophils express functional receptors for many tobacco smoke components and, for example, the numbers of nicotine receptors are increased in smokers and have been shown to decrease following smoking cessation (Ackermann *et al*. 1989; Lebargy *et al.* 1996). Not all data on neutrophil effects are consistent, but overall cigarette smoke appears to shift the balance of neutrophil activities in the more destructive direction (Palmer *et al*. 2005; Matthews *et al*. 2012). The effects of tobacco smoking on T- and B-cell numbers and function are more complex and less consistent across studies, as both immunosuppressive and inhibitory processes have been described (Palmer *et al*. 1999; Loos *et al*. 2004). There is also, mostly *in vitro*, evidence suggesting that gingival and periodontal ligament fibroblast recruitment and adhesion may be negatively affected in smokers, and that collagen production is decreased while collagenolytic activity is increased (Tipton & Dabbous 1995; James *et al*. 1999; Gamal & Bayomy, 2002; Poggi *et al*. 2002). Finally, the reported suppressed gingival inflammation in smokers as evidenced by clinical signs of reduced gingival bleeding and bleeding on probing (Preber & Bergstrom 1985, 1986; Bergstrom *et al*. 1988; Bergstrom & Bostrom 2001) appears to be related to fewer gingival vessels (Rezavandi *et al*. 2002; Palmer *et al.* 2005), rather than to vasoconstriction as originally speculated. The above effects of smoking on the inflammatory response, vasculature, and fibroblast function can also explain its well-described negative effects on healing following non-surgical and surgical periodontal therapy (Kinane & Chestnutt 2000).

Much less is known about the mechanisms underlying the effects of passive smoking on the periodontium. However, there is evidence for increased levels of salivary cotinine (a nicotine metabolite), higher levels of a number of inflammatory mediators, and an increased proportion of phagocytic cells in gingival lesions of individuals exposed to second-hand smoking, possibly indicating an altered host response to the bacterial challenge (Walter *et al*. 2012).

Clinical presentation of the periodontal patient who smokes

The oral effects of smoking become evident relatively early in the course of tobacco use, and smokers often present clinically and radiographically with signs of increased bone, attachment, and tooth loss (Figs. 14-8, 14-9). Deeper pockets in anterior and maxillary palatal sites may often be seen. At the same time, however, smoking masks some other important clinical signs of gingivitis and periodontitis, complicating the usual approach to recognizing these conditions. Indeed, smokers often present with fibrotic gingiva and limited gingival erythema and edema relative to the amount of plaque and the severity of the underlying bone loss (Scott & Singer 2004). Bleeding on probing is reduced in a dose-dependent manner in smokers compared to non-smokers with similar levels of plaque (Bergstrom & Bostrom 2001; Dietrich *et al*. 2004), and it can re-emerge within weeks in patients who quit, even in the presence of improved plaque control (Nair *et al*. 2003).

Moreover, and as described in detail in Chapter 7, multiple studies examining the effects of smoking on periodontal treatment outcomes have demonstrated that response to therapy is compromised in smokers, with current smokers exhibiting less probing depth reduction and/or attachment gain compared to former or never smokers (Heasman *et al*. 2006). Meta-analyses of the effects of smoking on the outcomes of periodontal therapy corroborate these conclusions (Garcia, 2005a, b; Labriola *et al*. 2005a, b; Patel *et al*. 2012a, b) and suggest that a smoker's post-treatment

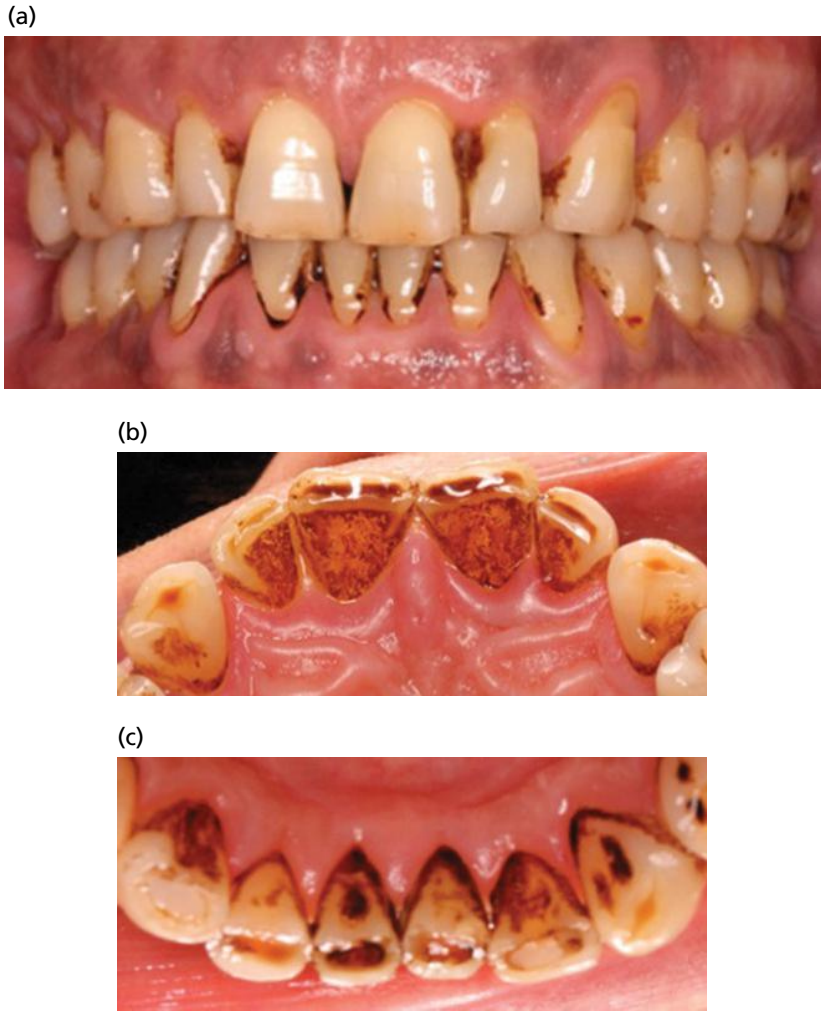

Fig. 14-8 Clinical appearance of a 53-year-old male patient who reports smoking one pack a day for 35 years. (a) Anterior view; (b) palatal view of the maxillary anterior teeth, and (c) lingual view of the mandibular anterior teeth. Note the heavy staining. Periodontal examination revealed probing depths of up to 9 mm, gingival recessions, and furcation involvements at all molars. (Courtesy of M. Hickin.)

clinical presentation may not be compatible with the expected profile of a treated patient.

Concepts related to patient management

The evidence reviewed above has direct patient management implications, especially when surgical and/or regenerative therapy is under consideration. Patients who smoke need to be informed of their enhanced risk for limited or delayed treatment responses and this may actually provide an opportunity to further motivate a patient to consider smoking cessation.

Dental professionals are healthcare providers and, as such, they have the responsibility to advocate smoking cessation among their patients. In doing so, they can contribute to improved patient oral health, overall health, and quality of life. Smoking cessation has been shown in longitudinal studies to have beneficial effects on the periodontal status (Bolin *et al*. 1993; Krall *et al*. 1997; Bergstrom *et al*. 2000; Rosa *et al*. 2011), and smoking cessation alone or in conjunction with non-surgical periodontal therapy appears to result in a subgingival microbiota that comprises higher levels of health-associated species and lower levels of pathogens (Fullmer *et al*. 2009; Delima *et al*. 2010).

There are multiple opportunities to interact with patients and provide tobacco use intervention, especially after initial periodontal evaluation of a new patient and during the long-term maintenance phase of periodontal therapy. Different approaches can be used. Asking every patient about tobacco use, documenting smoking status and motivation to quit, and advising patients to stop are the minimum obligations. A more comprehensive intervention that includes offering smoking cessation counseling with pharmacologic therapy and supportive follow-up is ideal. Complex patients such as those suffering from psychiatric illness or medical co-morbidities should be referred to smoking cessation specialists/clinics where comprehensive treatment can be offered.

Some of the different approaches to smoking cessation that can be considered in the dental setting are briefly discussed below. In general, evidence to date suggests that dental professionals tend to ask their

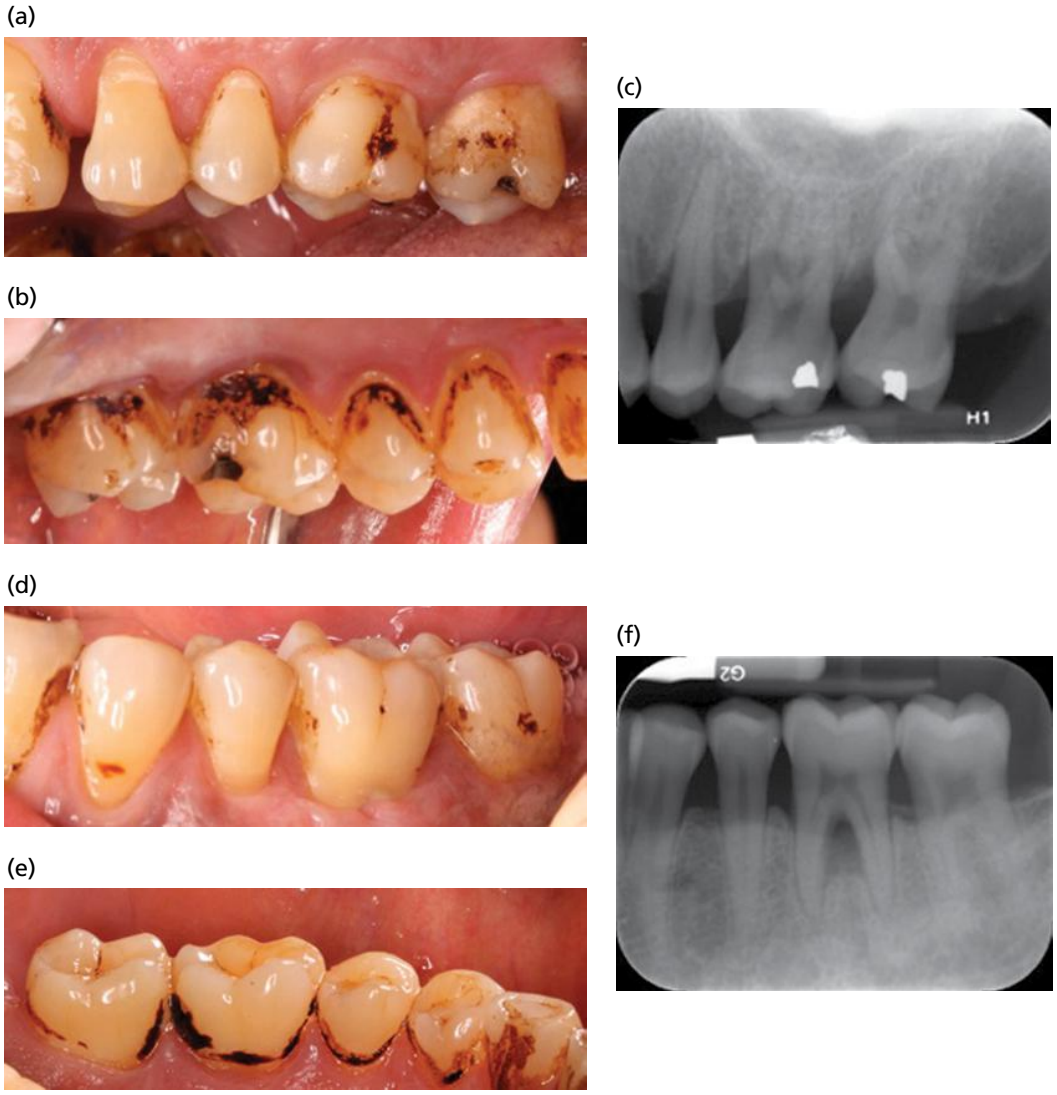

Fig. 14-9 Same patient as in Fig. 14-8. (a, b) Maxillary left buccal and palatal views and (c) corresponding radiograph; (d, e) mandibular left buccal and lingual views and (f) corresponding radiograph. Heavy staining and advanced bone loss are apparent. (Courtesy of M. Hickin.)

patients about smoking, but do not provide help regarding cessation, and several barriers to delivering smoking cessation intervention by dental professionals have been reported (Albert *et al*. 2005; Kunzel *et al*. 2006; Patel *et al*. 2011). For those providers who identify lack of time or expertise/confidence as barriers, a "brief intervention" approach may be a useful model. The dental team can give patients educational brochures to take home and also provide some encouragement and support by relating tobacco use to medical and oral health risks. This strategy is often effective as the advice of a trusted healthcare provider is always valuable.

If the dental team is willing to be more proactive and the patient is motivated, a more extensive behavioral program can be introduced. The "five A's", from the United States Public Health Service (U.S. Public Health Service 2008), has become the model program:

Ask: Ask about smoking behavior directly and document status (current, former, or never smoker; duration and number of cigarettes per day). Tobacco use status indicators on paper charts or electronic records can make screening easier.

Advise: Advise patient to quit. The message should be clear, strong, and tailored. A good time to do this is after the periodontal examination is completed and when findings, etiology, risk factors, and prognosis are discussed. Several health organizations and internet sites that provide valuable information are available.

Assess: Assess the patient's readiness and motivation to quit. If the patient is willing to attempt cessation, provide assistance as described below. If the patient is clearly unwilling to attempt quitting at this time, offer written materials about quitting and re-assess at future appointments. Improving the patient's interest and readiness level is a successful intervention, even if cessation is not immediately contemplated.

Assist: Assist the patient willing to make a quit attempt by providing a structured plan for quitting. Decide

on a quit date and encourage the patient to seek support from family and friends. Consider the use of pharmacotherapies that have proven effective and are briefly described below. Anticipate challenges that might threaten smoking cessation and decide in advance on a plan of action if/when those arise.

Arrange: Arrange follow-up, including behavioral support and telephone contact/counseling. The first week of cessation is especially critical.

Pharmacologic treatment options include nicotine replacement therapy, sustained-release bupropion, and varenicline (Aubin *et al*. 2011). Nicotine replacement therapy involves the use of products that provide low doses of nicotine, but do not contain the toxins found in smoke. The goal of therapy is to relieve cravings for nicotine and ease the withdrawal symptoms. Nicotine supplements come in different forms: transdermal patch, gum, lozenges, nasal spray, and inhaler. The different forms of replacement therapy can be used alone or in combination, and all work well if they are used correctly. The choice depends on the patient's smoking habits and preferences, and initial treatment lasts for 2–3 months. Side effects include headaches, nausea, and insomnia in the first few days, especially with the patch. Sustained-release bupropion inhibits the neuronal uptake of norepinephrine and dopamine. It can therefore control nicotine withdrawal symptoms and may also help patients manage associated anxiety and depression. Treatment with bupropion should be initiated 1–2 weeks before the quit date, since 1 week is necessary to achieve steady-state blood levels; treatment usually lasts for 2–3 months, but it can continue safely for maintenance for up to 6 months. The use of bupropion is contraindicated for patients with a history of seizures, eating disorders, and those who are on certain antidepressants. Common side effects of bupropion include insomnia and dry mouth, and patients should be monitored closely for unusual changes in behavior, such as agitation, depression, and attempted suicide (Hays & Ebbert 2010). Varenicline is the newest drug for smoking cessation. It has a structure similar to that of nicotine and thus it can antagonize nicotine binding to its receptor sites. As with buproprion, varenicline treatment starts 1 week before the quit date and continues for 3 months; maintenance treatment, if needed, may be for up to 6 months. Common side effects include nausea, trouble sleeping, and abnormal or vivid dreams (Garrison & Dugan 2009; Hays & Ebbert 2010). Patients taking varenicline should be monitored closely for any changes in mood and behavior.

Unfortunately, nicotine dependence is chronic and strong, and therefore the possibility of relapse is high. Smokers often must experience many attempts at cessation before they can remain totally tobacco free. They are certainly more likely to be successful if they have support with quitting. Providing encouragement at every appointment with the dentist and hygienist is key in helping patients to stay smoke free.

Obesity and nutrition

Obesity, a condition characterized by accumulation of excess body fat, is defined in adults as a body mass index (BMI) of ≥30 kg/m^2, while a BMI between 25 and 29.9 kg/m^2 indicates an overweight individual. In the past few decades, many countries in both the industrialized and the developing world have experienced a substantial increase in the prevalence of obesity, which is known to be a major contributor to morbidity. Concomitant occurrence of obesity, insulin resistance, dyslipidemia, and hypertension constitute the metabolic syndrome, a precursor condition to type 2 diabetes and incident cardiovascular disease.

As discussed in Chapter 7, several studies have demonstrated a positive association between obesity/metabolic syndrome and periodontitis. Indeed, a systematic review and meta-analysis (Chaffee & Weston, 2010) confirmed a higher prevalence and severity of periodontitis among obese adults. Although the limited number of longitudinal studies of adequate quality does not facilitate the exact delineation of the temporality of this association at the present time, it is biologically plausible that obesity may contribute to a higher risk for periodontitis.

The function of the adipose tissue as essentially an endocrine organ is central to its role in the association between obesity and periodontitis. Adipocytes secrete a variety of metabolically and immunologically active molecules, termed adipokines, among which leptin, adiponectin, and resistin have been studied the most. The primary function of leptin is to negatively regulate appetite and weight, but it also interacts with other hormones, including insulin (Margetic *et al*. 2002; Guzik *et al*. 2006). Interestingly, there is a negative correlation between GCF and serum levels of leptin in periodontitis, and this association was reported to become stronger with increasing levels of attachment loss (Karthikeyan & Pradeep 2007a, b). In contrast, serum levels of adiponectin are decreased in obesity, insulin resistance, diabetes, and cardiovascular disease (Matsuzawa *et al*. 2004). Adiponectin has been shown to be a potent negative regulator of osteoclast formation in response to challenge by LPS by *A. actinomycetemcomitans* (Yamaguchi *et al*. 2007). However, there is no clear association between its serum levels and periodontal status (Furugen *et al*. 2008; Saito *et al*. 2008), and its levels in GCF have not been studied. In contrast, levels of resistin were found to be higher in patients with periodontitis than in periodontally healthy individuals, and to correlate with the extent of bleeding on probing (Furugen *et al*. 2008; Saito *et al*. 2008). Thus, adipokine action and oxidative stress have been proposed to serve as the common link in the pathobiology of obesity and periodontitis (Bullon *et al*. 2009). Indeed, there is evidence of higher serum levels of markers of oxidative stress and of decreased antioxidant capacity in individuals with periodontitis when compared to periodontally healthy controls (Chapple & Matthews 2007).

Finally, there has been an increased interest in the role of nutritional exposures in the etiology and therapeutic management of periodontitis. The effect of ascorbic acid (vitamin C) deficiency on the gingival tissues has been known since the 18th century, when an association between scurvy and bleeding gums and tooth loss was first observed in sailors who did not have access to fresh fruit and vegetables over prolonged time periods. Vitamin C is a powerful antioxidant radical scavenger (Da Costa *et al*. 2012) that is distributed in many cell types, including polymorphonuclear leukocytes, platelets, and endothelial cells (Evans *et al*. 1982), and which has been shown to exercise effects on osteoclasts and periodontal ligament fibroblasts (Mimori *et al*. 2007). Likewise, while it has long been known that vitamin D and calcium are important for skeletal development and maintenance of bone mass, vitamin D has emerged as an important regulator of innate immune responses in infectious diseases (Adams & Hewison 2008). Additional micronutrients that have been investigated with respect to their association with periodontal status include both antioxidant (vitamin E, carotenoids, polyphenols, glutathione) and non-antioxidant molecules (vitamin B, omega-3 polyunsaturated fatty acids). In general, epidemiologic studies reveal that periodontitis is associated with low serum/plasma micronutrient levels (Van der Velden *et al.* 2011), while early evidence from interventional studies (Campan *et al*. 1997; Staudte *et al*. 2005; Jenzsch *et al*. 2009; Chapple *et al*. 2012) suggests that adjunctive nutritional supplementation may result in improved periodontal therapy outcomes. Additional research from randomized placebo-controlled trials is needed to further document these effects and to facilitate the development of nutritional recommendations in the prevention and control of periodontal diseases.

Osteoporosis and osteopenia

Osteoporosis is a disease characterized by loss of bone mineral density that can lead to bone fragility and increased susceptibility to fractures (Eastell 1998). Female gender, advanced age, family history of osteoporosis, ethnicity (Caucasian or Asian), history of a low-impact bone fracture, thin skeletal frame, and early menopause are non-modifiable risk factors for osteoporosis. High alcohol intake, smoking, low BMI, vitamin D deficiency, and physical inactivity are other important modifiable risk factors. The femur and spine are most commonly affected and bone density at these sites can be quantified using dual-energy X-ray absorptiometry (DXA) scans to define a diagnostic T-score. The T-score compares bone density for a given patient to the mean peak bone density for an individual of the same gender, and is reported as the number of standard deviations below that mean. A T-score of −1 or above is considered normal and a score of −2.5 or lower signifies osteoporosis. Scores <-1.0 and >-2.5 indicate osteopenia, an intermediate state between health and osteoporosis.

Several clinical studies have drawn attention to the possible link between osteoporosis and periodontal disease, as both conditions involve bone loss and may potentially share common risk factors and pathogenic mechanisms (Otomo-Corgel 2012). However, and as reviewed in Chapter 7, many of the clinical studies thus far were uncontrolled, cross-sectional, had small sample sizes, and were restricted to post-menopausal women (von Wowern *et al*. 1994; Mohammad *et al*. 1996, 1997; Tezal *et al*. 2000). Further data from longitudinal studies appear conflicting, and two systematic reviews concluded that the relationship between osteoporosis and periodontitis remains unclear (Martinez-Maestre *et al*. 2010; Megson *et al*. 2010).

It has been proposed that low bone mineral density in the maxilla and mandible as a result of osteoporosis may contribute to periodontal pathology by accelerating alveolar bone resorption that is initiated by the periodontal infection (Wactawski-Wende 2001). In addition, factors affecting systemic bone remodeling (e.g. heredity, estrogen, vitamin D, RANKL, and OPG) may also modify the local tissue response to periodontal infection, increase the release of pro-inflammatory mediators, and lead to enhanced destruction of the periodontal tissues. Studies exploring the potential underlying mechanisms are extremely scarce (Jabbar *et al*. 2011) and although these hypothetical pathways are biologically possible, they are only speculative at present.

Skeletal bone loss in those affected by osteoporosis is usually gradual and painless. Often, there are no obvious symptoms until a fracture occurs and thus early identification of those affected by or at risk for osteoporosis is of importance. Dental professionals may be able to recognize clinical risk factors for osteoporosis among their patients and see radiographic changes, such as thinning and porosity of the inferior border of the mandible in available panoramic radiographs or cone-beam computed tomographs (Horner *et al*. 2010; Koh & Kim 2011). Discussion of such findings and referral for further investigation by a medical colleague of those identified as potentially at risk for osteoporosis can be beneficial in the prevention of osteoporotic fractures.

Finally, it is important for dental professionals to remember that, with increasing longevity, osteoporosis prevalence is on the rise and that many female, and also male, dental patients may be affected and be under lifelong antiresorptive medications. Dentists need to review medications, including method of delivery, duration, and dosages, and consult with the patient's physician if there are concerns regarding necessary periodontal treatment. For those patients on bisphosphonates, careful planning and consultation with the treating physician is important, especially when periodontal therapy may involve extractions or other extensive surgical procedures

and the patient has been on the medication for >2–3 years. Such patients should be informed of the risks and possible effects of bisphosphonates on dental treatment outcomes. Any acute lesions must be treated immediately, oral hygiene instruction must be thorough, and the periodontal condition carefully controlled. Systemic use of antibiotics and use of antimicrobial mouth rinses can be considered. The potential complication that needs to be prevented is osteonecrosis of the jaw (ONJ), defined as an exposure of bone in the mandible or maxilla persisting for >8 weeks in a patient who previously received, or is currently under, treatment with a bisphosphonate and who has no history of radiation therapy to the jaws (Khosla *et al*. 2007). Clinically, ONJ may present as exposed alveolar bone occurring spontaneously or after dental surgery that caused bone trauma. The sites are usually painful, have soft tissue swelling or ulceration, mobile teeth, and induration with drainage. Radiographically, if teeth are present, there may be sclerosis of the alveolar lamina dura, loss of the alveolar lamina dura, and/or widening of the periodontal ligament space. Depending on the severity of ONJ, treatment strategies may include antibacterial mouth rinses, symptomatic treatment with oral antibiotics and analgesics, superficial debridement, and in severe cases, surgical debridement/resection. The patient's treating physician must always be contacted and informed.

Psychosocial stress

Stress results from interactions between individuals and their environment. It has been defined as a state of mental or bodily tension resulting from factors that tend to alter an existent equilibrium, or as a condition or feeling experienced when a person perceives that demands exceed the personal and social resources he/she is able to mobilize. There are numerous emotional and physical disorders that have been linked to stress, including depression, hypertension, cardiovascular and cerebrovascular events, obesity, immune system disturbances that increase susceptibility to infections, viral disorders ranging from the common cold and herpes to AIDS, certain cancers, as well as autoimmune diseases like multiple sclerosis (Spiegel & Giese-Davis 2003; Ziemssen & Kern 2007; Chida *et al*. 2008; Chida & Mao 2009; Falagas *et al*. 2010; Puder & Munsch 2010; Artemiadis *et al*. 2011; Bender & Alloy 2011; Blashill *et al*. 2011; Proietti *et al*. 2011; Wardle *et al*. 2011; Rosenthal & Alter 2012). Stress can also have direct effects on the skin and the gastrointestinal tract, and can contribute to sleep disturbances (Kim & Dimsdale 2007; Basavaraj *et al*. 2011; O'Malley *et al*. 2011).

As expected, psychosocial stress can also affect the periodontium. This concept is not new; stress has been reported as an important risk factor for necrotizing ulcerative gingivitis for many decades. The effects of stress on the periodontium can be described as indirect or direct. Indirect effects are those mediated through lifestyle changes that can exacerbate periodontal destruction, such as compromised oral hygiene, inattention to dental visits for prevention/care, deterioration of metabolic control in diabetes, increase in smoking, and inability to maintain healthy eating habits. Direct effects may be mediated both via modification of the composition of the subgingival biofilm and exaggeration of the host inflammatory response.

In response to stressful events, the hypothalamus–pituitary–adrenal axis is stimulated, leading eventually to increased production and secretion of cortisol, a hormone that can stimulate the immune system. Further, the autonomic nervous system is stimulated, leading to secretion of catecholamine and substance P that can also regulate the immune/inflammatory response and affect bacterial adherence and growth. Indeed, several stress markers have been reported in the blood, saliva, and GCF of periodontitis patients, and may mediate the potential detrimental effects of stress on the periodontal tissues (Axtelius *et al*. 1998; Hilgert *et al*. 2006; Johannsen *et al*. 2006; Ishisaka *et al*. 2007, 2008; Rai *et al*. 2011)

In the first large-scale study aiming to explore the link between stress and periodontal status, 1426 adults in the US were evaluated (Genco *et al*. 1999). Subjects under high levels of financial stress and with poor coping responses were reported to have significantly more severe alveolar bone loss and attachment loss than those with low levels of stress within the same coping group, after adjustment for age, gender, and cigarette smoking. Many other studies in subjects with different types of psychosocial stress, such as academic or job related, and poor coping behaviors have provided similar results (Moss et al. 1996; Croucher *et al*. 1997; Deinzer *et al*. 1998, 1999; Mengel *et al*. 2002; Giannopoulou *et al*. 2003; Kamma *et al*. 2004; Ishisaka *et al*. 2007, 2008; Johannsen *et al*. 2007; Furugen *et al*. 2008, Johannsen *et al*. 2010). Of interest is the fact that adequate coping behaviors, as evidenced by high levels of problem-based coping, may reduce the stress-associated risk.

The variability associated with self-reported measures of psychological stress and the use of different periodontal parameters as outcomes across studies investigating the link between stress and periodontitis make comparisons of such studies and the interpretation or generalizability of results difficult. However, it is fair to conclude that accumulating evidence to date is in the direction of a positive association between psychosocial stressors and poor periodontal status.

Further, experimental studies using animal models and cell culture systems have provided evidence for a link between markers of stress and the severity of periodontal inflammation/destruction, mediated at least in part through pro-inflammatory molecules (Shapira *et al*. 2000; Kim *et al*. 2009; Huang *et al*. 2011; Semenoff-Segundo *et al*. 2012). Similarly, in human

studies, salivary and serum stress marker levels were positively associated with the extent and severity of periodontitis (Hilgert *et al*. 2006; Ishisaka *et al*. 2007, 2008; Rai *et al*. 2011). The potential effect of stress on bacterial growth and virulence, although biologically plausible, is less studied and understood.

Unequivocally, stress is part of human life, is commonly present to varying degrees, and although it may have different consequences in different individuals, its potential effect on periodontal disease presentation and the response to therapy should not be underestimated. The dental team needs to remember that periodontal disease prevention, meticulous monitoring, and careful maintenance strategies are important for patients under stress, especially those who appear to cope inadequately.

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Chapter 15

Genetic Susceptibility to Periodontal Disease: New Insights and Challenges

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Introduction

Periodontitis is a chronic inflammatory disease of the supporting tissues of the teeth. In subjects susceptible to destructive periodontal disease, there is an imbalance between the host's immune system and the oral bacteria. In these individuals, certain microbial pathogens can proliferate and this leads to the induction of inflammatory reactions in the periodontal tissues. These inflammatory reactions slowly destroy the periodontium. If left untreated, the teeth lose their ligamentous support to the alveolar bone and alveolar bone is resorbed, with the consequence that the affected teeth become mobile and are eventually lost.

The oral cavity is one of the most complex ecosystems of the human body and contains myriads of different bacterial species. These species co-evolved with the human organism and the oral microbiota adapted to the environmental conditions provided by the host. The evolution of this ecosystem was subjected to strong selection pressures in a biologically active environment and it is considered to have largely developed for mutual benefit. The normal oral microbiota protects the host from extrinsic pathogens and the immune system controls bacterial proliferation to maintain homeostasis. The complex interplay between environmental factors, that is pathogens in the oral cavity, the immune system, and consequences of lifestyle factors is largely regulated by genes. Genes encode immune receptors as well as molecules, which influence receptor specificity and sensitivity to bacterial species. They regulate and influence the intensity of the inflammatory response by encoding and adapting the signal transduction pathways up- and down-stream of the inflammatory signals, and allow a flexible response of the organism to external and internal stimuli.

The interplay of the microbiota, the immune system, and lifestyle habits (smoking, stress, diet, etc.) underlie the constant changes to which the host's physiology must adapt to maintain health: the bacterial species change in number and proportions, and may also change in characteristics, for example by horizontal gene transfer or mutation. The host's immune system changes over time and can be

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positively or negatively influenced by lifestyle factors, other diseases, or age. Additionally, the genetic constitution of the host may change during life, for example by epigenetic effects or somatic mutations. As a result, periodontitis is considered to be a complex disease.

Genetic research can improve the understanding of the factors that mediate the immune response and explain why this response often greatly differs between individuals who have the same environmental context and comparable lifestyle habits. An important objective of genetic research is to identify the genes underlying disease and to estimate the genetic effects of potential risk variants within these loci. Genetic variation most often affects the regulatory regions of the genes, which lead to subtle changes in their expression: in the quantity of the transcribed gene products, but also the tissue- and development-specific gene expression. It is important to identify these genetic elements and to characterize their modes of action to understand how the expression of target genes in a tissue is regulated, including their time-specific expression. This knowledge is indispensable for the understanding of the molecular biology of periodontitis.

The genetic basis of periodontitis was demonstrated by formal genetic studies, and many genetic variants were analyzed for their involvement in disease physiology. However, within recent years, there have been enormous developments in the tools for genetic analysis and, for many common, complex human diseases, in knowledge of the relevant genetic factors. In this chapter, instead of discussing a long list of earlier studies and their often ambiguous results, we will describe the underlying concepts and methodologic principles necessary for the understanding of the current genetic basis of periodontitis. We will comment on the limitations of and the progress achieved with recent studies, the different paths that are opening up in the efforts to identify the full spectrum of genetic risk factors for periodontitis, and how this newly acquired knowledge can be used to improve diagnosis and in an emerging personalized medical care. We will also illustrate the current state of genetic research in periodontitis and give an overview on the risk genes that are currently regarded as validated. Additionally, we will discuss the likely directions of genetic research in the field of periodontitis in the near future. We will provide an evaluation of the current predictive ability of genetic tests for monogenetic and complex diseases and give an outlook on future possibilities of personal genome testing.

Evidence for the role of genetics in periodontitis

Until the middle of the last century, it was thought that subjects with a longstanding history of poor oral hygiene develop periodontitis. This was mainly because all forms of periodontitis were largely shown to be associated with specific bacterial pathogens and many studies demonstrated immunologic responses within the oral cavity. In addition, the prevalence and proportions of periodontal pathogens were regarded to be higher in periodontitis patients compared to healthy controls (Griffen *et al*. 1998; Van Winkelhoff *et al*. 2002). It remained an open discussion whether or not periodontitis was solely caused by one or more specific periodontal pathogens. If it were, it should develop in most infected subjects. However, periodontal pathogens show a relatively high prevalence in healthy subjects as well as in subjects with gingivitis or minor periodontitis. For example, in a study of 222 healthy children aged 0–18 years from Ohio, USA, pathogenic strains of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* were detected in 48% and 36% of the children, respectively, and both species were detected in infants as young as 20 days old (Lamell *et al*. 2000). Interestingly, in a large group of subjects with gingivitis or minor periodontitis (mean age 52 years), *A. actinomycetemcomitans* and *P. gingivalis* were similarly prevalent (38% and 32%, respectively) (Wolff *et al*. 1993). In the last decades, epidemiologic studies as well as longitudinal clinical studies have shown that the presence of bacteria does not invariably induce periodontal attachment loss, but that host factors are also required for periodontitis. The concept of high-risk groups was added to the pathogenesis model, and was one of the factors that developed the hypothesis that periodontitis may have a genetic background.

A study from 1966 was one of the earliest to deduce that certain individuals are more at risk for periodontitis than others (Trott & Cross 1966). This study investigated the principal reasons for tooth loss in over 1800 subjects. The study showed that in each age category, many teeth are lost in relatively few patients. This phenomenon was confirmed in a 28-year longitudinal study of a dentate American population. It was found that 14.4% of this population who became edentulous accounted for 64% of all teeth lost in that period. Among those who lost teeth but remained partially dentate, 13.8% were responsible for 60.2% of all teeth lost in that group (Burt *et al*. 1990). The same phenomenon was found in two longitudinal studies, which evaluated the effect of periodontal therapy in periodontitis patients over >15 years (Hirschfeld & Wasserman 1978; McFall 1982). These studies showed that 20% of the patient populations accounted for about 75% of all lost teeth.

The concept of high risk for the development of periodontitis was further confirmed in longitudinal studies investigating the natural history of periodontal disease. In a population in Sri Lanka without access to dental care and absence of oral hygiene, Löe *et al*. (1986) were able to identify three subpopulations: a group with no progression (11%), a group with moderate progression (81%), and a group with

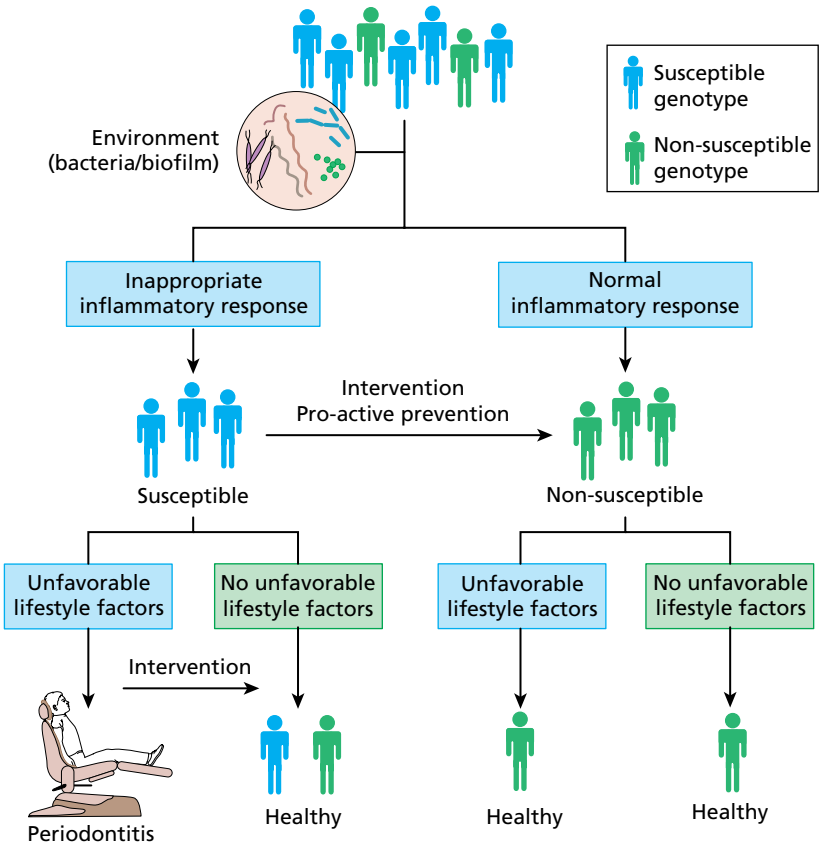

Figure 15-1 Variations in the antimicrobial response of the host may be important features of the pathogenesis of complex diseases such as periodontitis. In this model, the population, consisting of non-susceptible and susceptible hosts, is exposed to prevalent oral bacteria. Non-susceptible individuals with a normal, effective antibacterial response do not develop the disease, whereas susceptible individuals are at risk of developing the disease if key environmental factors are present. An understanding of the immune system alterations that make individuals susceptible may allow for interventions that aim to render the individual insensitive to the environmental stimuli that induce disease (proactive prevention), or that can alleviate or cure the disease after it has become manifest. This model suggests that it is critical to learn more about the factors that influence host–microbial homeostasis. (Adapted from Foxman & Iwasaki 2011, with permission from Macmillan Publishers.)

rapid progression of periodontal breakdown (8%). In a more recent study, the initiation and progression of periodontal breakdown was studied in a remote village in West Java that was deprived of regular dental care (Van der Velden *et al*. 2006). The authors found that 20% of the subjects developed severe breakdown, whereas the remaining population developed minor-to-moderate breakdown, and suggested that not everybody is equally susceptible to periodontitis. This shaped the hypothesis that host susceptibility may have a genetic background: the antimicrobial response of the host is defined in part by genes and can vary across the population. Genetic variants in the genes which encode the pathways of the host's antibacterial response, but also in the bacterial factors that are targeted by the host's immune system, have the potential to deleteriously affect the interplay of the immune system, environment, and lifestyle factors. In some cases they can lead to disease development. Figure 15.1 illustrates this hypothesis and shows how an almost continual exposure to bacteria may or may not cause disease symptoms. It also shows how interventions may be effective before disease manifestation. The individual's immune response, which determines the extent of periodontal destruction, is additionally challenged by other internal and external factors, like systemic diseases (e.g. diabetes), smoking, stress, and age (Kinane *et al*. 2006), which are again determined by the individual's genetic constitution. This interplay between the oral microbiota, internal and external factors which influence the immune system, and the host's general genetic constitution forms the individual susceptibility of a subject to periodontitis.

Heritability

Heritability measures the proportion of phenotypic variation that can be attributed to genetic variation. For example, members of a family may have a large variation of body weight that can be expressed by the body mass index (BMI). The observed variation can be due to different dietary habits among the family members. However, genetic factors can also influence the BMI independent of diet and can be shared between some of the related family members (Schousboe *et al*. 2003; Speliotes *et al*. 2010). Heritability measures the fraction of the phenotype variability that is due to genetic variation between the individuals of the sample. Heritability is also

Table 15-1 Heritability estimates of various complex traits and diseases.

Trait or disease	Heritability (%)	Reference
Eye color	>99	Zhu *et al*. (2004)
Type 1 diabetes	88	Hyttinen *et al*. (2003)
Schizophrenia	81	Sullivan *et al*. (2003)
Alzheimer's disease	79	Gatz *et al*. 2006)
Height	70–87 (M), 68–85 (F)	Silventoinen *et al*. (2003)
Obesity	65–84 (M), 64–79 (F)	Schousboe *et al*. (2003)
Smoking persistence	59 (M), 46 (F)	Li *et al*. (2003a)
Rheumatoid arthritis	53–65	MacGregor *et al*. (2000)
Periodontitis	50	Michalowicz *et al*. (2000)
Prostate cancer	42	Lichtenstein *et al*. (2000)
Migraine	40–50	Ligthart *et al*. (2006)
Heart attack	38 (M), 57 (F)	Zdravkovic *et al*. (2002)
Depression	37	Sullivan et al. (2000)
Type 2 diabetes	26	Poulsen *et al*. (1999)
Happiness	22 (M), 41 (F)	Bartels *et al*. (2010)

Heritability estimates and frequencies were obtained from published studies and meta-analyses.
M, male; F, female.
Adapted from Janssens *et al*. (2006), from Macmillan Publishing.

always specific to a particular population in particular surroundings. If, for example, a family shows uniformity in dietary habits, the heritability will be higher than if the family shows high variation in dietary habits. In the context of oral health, in a sample that shows uniformity in oral hygiene habits, the heritability will be higher compared to a sample that has strong variation in oral hygiene. Table 15-1 shows the wide range of heritability estimates observed for complex diseases and traits, ranging from 22% for happiness to >99% for eye color.

Heritability of aggressive periodontitis (early-onset periodontitis)

Siblings of patients with juvenile periodontitis (JP) frequently also suffer from periodontitis. This observation was based on family studies as well as on reports of single cases. The largest JP family study included 227 probands with aggressive periodontitis (Marazita *et al*. 1994). Of the 227 probands, 104 had at least one first-degree relative who was clinically examined. A segregation analysis was carried out on 100 families, which included 527 cases and healthy subjects. A segregation analysis is a method of formal genetic analysis employed to determine whether or not a phenotype is inherited. It tests whether the transmission pattern in human families over different generations is consistent with the expectations derived from Mendel's first law of segregation. This method also allows the mode of inheritance to be determined, for example if the genetic factor has a dominant or a recessive effect on the phenotype. The authors concluded that the most likely mode of inheritance in the examined families was autosomal dominant (see Box 15-1), with a penetrance of the causative genetic factors of about 70%.

Familial segregation of cases indicates that genetic factors may be important in the susceptibility to periodontitis, but results from segregation analyses need to be interpreted with caution as they may also reflect exposure to common lifestyle factors like oral hygiene, diet, and smoking. Certain infectious agents may also cluster in families. Additionally, segregation studies with human families are hampered by various methodologic factors, which often are the lack of adequate statistical power due to small numbers of families, too small or incomplete families, and a high heterogeneity between families.

A preferred alternative method to determine the evidence for genetic factors in the familial aggregation is the study on monozygotic twins. Twins arise in two ways. The parallel fertilization of two ova by two different spermatozoa results in dizygotic (DZ) twins. These comparatively common cases have the same genetic relationship as siblings. However, infrequently after fertilization by a single spermatozoon, the ovum divides in two, resulting in a pair of monozygotic (MZ) twins who are genetically identical. Severe, early-onset forms of periodontitis,

Box 15-1 Human genes, genetic variation, and useful definitions.

Genes direct the production of proteins with the assistance of enzymes and messenger molecules. In humans, the genes are located on 23 pairs of chromosomes: 22 pairs of *autosomal* chromosomes (autosomes) and one pair of *sex chromosomes* (the gonosomes, XX for females and XY for males). From each pair, one chromosome is inherited from the father and one from the mother. The complete set of chromosomes is called the *genome*. Each chromosome contains a long duplex of deoxyribonucleic acid (DNA). DNA consists of sequences of nucleotides, which are chemically linked by a sugar–phosphate backbone. The nucleotides are the "building blocks" of the DNA and are made up of nitrogenous bases. Four nitrogenous bases exist: adenine (A), guanine (G), cytosine (C), and thymine (T).

In the chromosomes, DNA is arranged in a double helix: two polynucleotide chains are associated together by hydrogen bonding between the nitrogenous bases. The pairing of the two single-stranded nucleotide chains is complementary: G pairs only with C, and A pairs only with T; these are called base pairs (bp). The order of these four nucleotides determines the meaning of the information encoded in that part of the DNA molecule, just as the order of letters determines the meaning of a word. Virtually every single cell in the body contains a complete copy of the approximately 3 milliard (US; English 3 billion) DNA base pairs that make up the genome [National Human Genome Research Institute (NHGRI), National Institute of Health (NIH), www.genome.gov). The genetic code is read in groups of three nucleotides; each trinucleotide sequence (triplet) is called a *codon*, which encodes a specific amino acid.

A gene usually consists of various parts. The *promoter region* is a specific sequence of nucleotides upstream of the coding region that is essential for the regulation and initiation of the transcription of the coding region. *Introns* are sequences of non-protein coding nucleotides and surround the *exons*, which code for the sequence of amino acids of a protein (Fig. 15-2). The collection of known exons in the genome is called the *exome*.

Genes can be transcribed in alternative ways, such that each of the estimated 20 000–25 000 genes in the human genome codes for an average of four proteins (ENCODE-Project-Consortium 2012). Proteins make up body structures like organs and tissues, carry signals between cells, and are the enzymes that control biochemical reactions. If a cell's DNA is mutated, an abnormal protein or abnormal protein quantities may be produced, which can disrupt the body's usual processes and lead to a disease.

For translating the information contained in the DNA into cellular function, the DNA must be transcribed into corresponding molecules of ribonucleic acid (RNA), referred to as transcripts. There are various kinds of RNA transcripts. The type that carries the information that codes the amino acid sequence of the proteins is called messenger RNA (mRNA) and is transcribed from the exons. Non-protein coding RNAs, such as *microRNAs* or long non-coding RNAs (ncRNA), largely function in the regulation of gene expression. The collection of all transcripts present in a given cell is called the *transciptome*.

Sequencing technologies determine the exact order of the nucleotides in a strand of DNA. The international *Human Genome Project* completed the first working draft sequence of the entire human genome in 2000 (Baltimore 2001; Venter *et al*. 2001) and the first high-quality reference sequence in 2003. In May 2006, the finished high-quality version of the sequences of all human chromosomes was published. It showed that >99% of the genomes of any two people are identical, but variations between the individual genomes exist and on average about one in every 1200 bp is different. Differences in individual bases are by far the most common type of genetic variation, and are known as *single nucleotide polymorphisms* (SNPs). Approximately 10 million SNPs are estimated to occur regularly in the human genome (Fig. 15-3) and that in each new generation >30

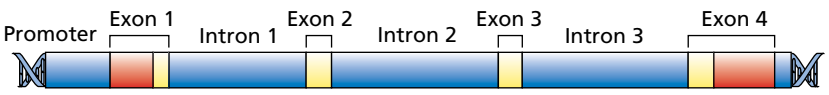

Fig 15-2 Schematic structure of a gene. This gene has four exons (yellow bands), but in reality genes can have many more exons. The first exon is preceded by an untranslated region, the 5′-UTR (left red band), and the last exon is followed by another untranslated region, the 3′-UTR (right red band).

```
CCTCGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGACACCAC    A/GCCCGGCGGATAGAGAGAATTT
TGACAGGTGAGGAGGTATTCCAATGCAAAAGAATAATAGGAGCAAAAGCACAGTGGTGAGAAATTGGA
GGGGAACTGTGAAAATTGCCACATAGATTAGAGGCAGGAAAATAAAGGAC    A/GGCT
```

Fig 15-3 Single nucleotide polymorphisms (SNPs) in a randomly selected segment of the transcribed region of the gene *ANRIL*. The two alternative nucleotides (alleles) in this sequence stretch are depicted in red. The allele common in the Northern European population is given first and the rarer allele second.

Box 15-1 *Continued*.

de novo mutations arise per individual (Abecasis *et al*. 2010). The great majority of known SNPs are listed in the catalog of common genetic variation, the *HapMap*, which was generated by the HapMap project and first published in 2005 (The-International-HapMap-Consortium 2005; www.hapmap.org). It describes the characteristics of the variants, where they occur in the DNA, and how they are distributed within populations and between populations.

The alternative variants at a specific chromosomal region (*locus*) of the DNA are called *alleles,* and the collection of alleles in an individual's chromosomes is termed the *genotype*. Two or more alleles for a given locus may exist in nature and occur with different frequencies. The *minor allele frequency* (MAF) is the proportion of the least frequent allele in a population and can range from 0–50%. Variants with a MAF of >5% are termed *common variants*. If the MAF of a variant ranges between 1% and 5% it is called a *rare variant*. Genetic variants with frequencies of <1% are called *mutations*.

A mutation or a genetic variant may have no effects or may have moderate to strong effects. For example, if a mutation occurs within the coding region of a gene, it may result in an amino acid substitution and therefore an altered protein structure, which may affect the protein's function (non-synonymous SNP). Or, when such a mutation occurs in a regulatory region of a gene (e.g. the promoter or an enhancer element), it may alter the gene's expression level. Accordingly, genotypic differences among individuals can contribute to phenotypic variation, termed *genetic variance*. The strength with which a genetic variant affects the susceptibility to a disease is defined as the *genotype relative risk* (GRR), the ratio of the risk of disease between individuals with and without the genotype. A ratio of 1.1 equates to a 10% increase in risk and is often expressed as the odds ratio (OR). However, carriership of a genetic variant or mutation does not inevitably lead to disease, as only a proportion of individuals with a mutation or risk variant will develop the disease. This proportion is described as the *penetrance*. The severity of the disease in individuals who have the risk variant and the disease is described as the *expressivity* of the variant.

Despite the existence of many genetic variants, only a fraction of the genotypic differences contributes to phenotypic variation. Where in the chromosomes the causative variants are located and how they interact is mostly unknown. Testing all of the several millions of common and rare SNPs in a person's chromosomes would be extremely expensive. Variants that are near each other tend to be inherited together; for example, individuals who have an A rather than a G at a particular location in the chromosome can have identical genetic variants at other SNPs in the chromosomal region surrounding the A. This non-random association between alleles at different loci is termed *linkage disequilibrium* (LD) and the regions of linked variants are known as *haplotypes* (www.hapmap.ncbi.nlm.nih.gov). Determining the identity of a common SNP on a haplotype, the *tag SNP*, uniquely identifies all other linked variants on the same haplotype. Identifying an individual's tag SNPs, a process known as *genotyping*, enables the haplotypes in the chromosomes to be identified. If patients with the same disease tend to share a particular haplotype, variants contributing to the disease might be somewhere within or near that haplotype. The number of tag SNPs that contain most of the information about the patterns of genetic variation of a genome is estimated to be 300 000–600 000, which is far fewer than 10 million common SNPs, and much less expensive to genotype. Thus, the information from the HapMap has been instrumental in mapping variants contributing to the disease.

such as aggressive periodontitis, for which it is believed that genetic factors are particularly important in influencing disease susceptibility, have a comparatively low prevalence in the general population and it is very difficult to identify enough affected MZ twins to provide sufficient statistical power to test the concordance of this disease phenotype. Nevertheless, the most conclusive indication of whether or not the disease has a genetic cause is obtained by a comparison of the presence of the same disease phenotype in both members of a pair of twins. This is expressed by a comparison of the concordance rate of MZ and DZ twins. For example, twins are concordant when both have or both lack a given phenotype. There are two alternative measures of twin concordance. The pair-wise concordance expresses the probability that both twins of a pair show the disease phenotype, if one of the twins already has the disease. The proband-wise concordance expresses the probability that one twin is diseased, given that the other twin is diseased. Geneticists and twin researchers have long debated the relative merits of the two methods of expressing twin concordance. It was shown that for most applications, the proband-wise rate is the more accurate in genetic twin studies (McGue 1992).

Ciancio *et al*. (1969) addressed the concordance of the periodontal condition in twins, but the study design and the low sample numbers (seven MZ and 19 DZ twin pairs ranging in age from 12 to 17 years) did not allow a clear conclusion on the concordance rate of early-onset periodontitis.

Table 15-2 Concordance rates for early-onset periodontitis in twins.

	n	Concordance rate
Monozygotic	116	0.38
Dizygotic	233	0.16

A twin pair was considered to be concordant if information was provided by one or both pair members and indicated that both pair members were affected.
Data from Corey *et al*. (1993).

Table 15-3 Heritability estimates for measures of chronic periodontitis.

	Age and gender adjusted	Fully adjusted[c]
Attachment loss[a] (%)	52	50
Deepened probing depth[b] (%)	50	50
Gingival index (%)	52	0

[a]Mean percentage of teeth with attachment loss of ≥3 mm.
[b]Mean percentage of teeth with probing depth of ≥4 mm.
[c]Adjustments for age, gender, and oral hygiene as described in Michalowicz *et al*. (2000).
Adapted from Michalowicz *et al*. (2000), with permission from the American Academy of Periodontology.

Pair-wise and proband-wise rates were used to estimate the degree of concordance of early-onset periodontitis in MZ and DZ twins (Corey *et al*. 1993). Information on periodontal disease was available for 4908 twin pairs. The mean age at diagnosis of periodontitis in these twins was 31 years. A total of 349 twins reported a history of periodontal disease in one or both pair members. Of these, 116 were MZ and 233 were DZ twins; 70 twins were concordant. The concordance rate for the history of periodontal disease in MZ and DZ twin pairs based on this study is given in Table 15-2. The proband-wise concordance rate showed more than a two-fold increased risk for early-onset periodontitis for the genetically identical MZ twins compared to the DZ twins. It also indicated that in a high proportion of cases factors other than genetic factors were important in triggering this disease phenotype. The mean age difference at diagnosis for the concordant MZ twin pairs was 1 year, while the corresponding difference in concordant DZ twin pairs was 5.4 years (information on age at diagnosis of periodontal disease was only available for both members in 34 of the 70 concordant twin pairs). This reduced mean difference of age at first diagnosis for the MZ twins may also point to an influence of heritable factors in periodontitis.

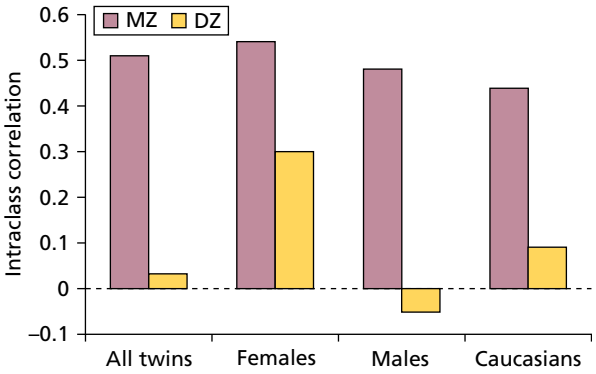

Fig 15-4 Twin intraclass correlations for mean attachment loss in subgroups of different gender and race. The monozygotic (MZ) correlations are remarkably stable among the subgroups. However, the dizygotic (DZ) correlations vary by gender. As indicated by Michalowicz *et al*. (2000), this variation may reflect sampling errors or, more unlikely, gender-specific genetic effects of the DZ twins. MZ = 82 females, 46 males; DZ = 64 females, 42 males. (Source: Michalowicz *et al*. 2000. Reproduced from the American Academy of Periodontology and with permission from K. Murphy.)

Heritability of chronic periodontitis

A few twin studies have assessed the heritability of a periodontal disease status in adults and almost all have reported a heritable component for chronic periodontitis (Corey *et al*. 1993; Michalowicz *et al*. 1991; Michalowicz 1994; Michalowicz *et al*. 2000). One of the first studies included 110 pairs of adult twins (mean age 40.3 years), including 63 MZ and 33 DZ twin pairs reared together, and 14 MZ twin pairs reared apart. The periodontal parameters probing depth, clinical attachment loss, gingivitis, and plaque were examined, and it was estimated that 38–82% of the variance in these measures could be attributed to genetic factors (Michalowicz *et al*. 1991). Another population-based twin study on 117 twin pairs (Michalowicz *et al*. 2000) assessed the heritability of the genetic and environmental variation in chronic periodontitis and gingivitis. It showed that the investigated MZ twins (64 pairs) were more similar than the DZ twins (53 pairs) for attachment loss and probing depth, and showed statistically significant genetic variance for the severity and extent of the disease. The heritability was estimated to be ~50%, which was unaltered following co-variate adjustments for smoking, dental hygiene, age, and gender (Table 15-3). It is noteworthy that this study showed no evidence of heritability for gingivitis and attributed this disease phenotype entirely to disease-related behaviors such as oral hygiene and smoking. This study also examined whether the concordance of the twins varied according to gender. It is conceivable that gender differences determine differential physiologic factors, caused by different hormonal, metabolic, and immunologic environments, as well as lifestyle, and possibly influence disease susceptibility and progression. Nevertheless, MZ twin

correlations did not significantly differ between the genders, indicating that potential gender-specific genetic effects may not contribute to the heritability of periodontitis (Fig. 15-4).

Gene mutation of major effect on human disease and its association with periodontitis

Complex diseases such as periodontitis are caused by an intricate interplay of many genetic and non-genetic factors. In contrast, monogenic diseases such as Huntington's disease and cystic fibrosis are fully heritable. People who carry a causative allele in a single specific gene will inevitably develop the disease. The Papillon–Lefèvre syndrome (PLS) is relatively unique in the group of monogenic diseases, in that severe aggressive periodontitis forms a significant component of the phenotype and is a defining clinical feature (Toomes *et al*. 1999). Both the deciduous and permanent dentitions are affected, resulting in prepubertal periodontitis and premature tooth loss. Additionally, palmoplantar keratosis, varying from mild psoriasiform scaly skin to overt hyperkeratosis, typically develops within the first 3 years of life. Keratosis also affects other sites such as the elbows and knees. Most PLS patients display both periodontitis and hyperkeratosis. Some patients have only one or the other, and rarely the periodontitis is mild or of late onset.

The causative mutations of PLS are located in the *CTSC* (cathepsin C) gene on chromosome 11; over 50 mutations in the gene are now recognized. The protein encoded by this gene is cathepsin C, a lysosomal cysteine proteinase, that appears to be a central coordinator for activation of various serine proteinases. It is expressed at high levels in polymorphonuclear leukocytes (PMNs) and alveolar macrophages and their precursors (Rao *et al*. 1997). It was proposed that minimal cathepsin C activity (~13%) was necessary to prevent the clinical features of PLS, but the exact mechanism by which an altered function of cathepsin C plays a role in the pathogenesis of PLS-associated prepubertal periodontitis is unknown (Hewitt *et al*. 2004). It is speculated that cathepsin C is essential for activation of many serine proteinases in immune-inflammatory cells, including cathepsin G, neutrophil serine proteases, proteinase 3, and elastase (Dalgic *et al*. 2011). The inactive forms of these neutrophil serine proteases result in dysregulation of the host immune response. Increased susceptibility to infections has been attributed to impaired neutrophil and T- and B-cell functions (Ryu *et al*. 2005). The impaired localized PMN response in inflamed periodontal tissues leads to aggressive periodontitis, most likely due to improper phagocytosis and digestion of Gram-negative periodontal pathogens. Likewise, the mutation in the *CTSC* gene seems to result in the incapacity of PMNs to kill *A. actinomycetemcomitans* in an anaerobic environment (de Haar *et al*. 2006).

Identification of genetic risk factors of periodontitis

What are the common genetic risk factors of periodontitis? Interestingly, despite tremendous efforts in the field of genetic association studies over the last decade, the causative gene polymorphisms of periodontitis and their pathophysiologic effects have remained mostly controversial. In this section, we will describe the focus and the limitations of recent studies that have been performed to identify the genetic risk factors underlying periodontitis. Additionally, we will summarize and discuss the current state of genetic research in periodontitis. To begin with, we will briefly look at what has been learned from research into other complex human diseases.

Similarly to periodontitis, many genetic risk factors were proposed for other complex diseases and also were controversial (Morgan *et al*. 2007). These genes were implicated as potential risk factors, but few of these candidate genes, if any, have definitively been established as such (Casas *et al*. 2006; Morgan *et al*. 2007). Several factors have undermined the validity of published reports, including inappropriately small sample sizes, multiple subgroup comparisons, and publication bias. Apparently, publication bias is a crucial stratification factor in the short-term advancement of research. It is explained by the simple fact that positive results are much easier to get published than negative findings, which results in publications biased towards the accumulation of false-positive findings in the scientific literature and under-representation of true negative findings. However, over time the true results usually achieve acceptance. These shortcomings have resulted in significant doubts about the collective panel of putative genetic risk factors for most complex diseases.

In 2007 there was an important turning point in the genetics of complex diseases. The era of genome-wide association studies (GWAS; Box 15-2) was ushered in by the milestone publication of the Wellcome Trust Case Control Consortium (WTCCC 2007). To begin this era, two paradigm shifts were necessary. First, it was realized that the literature-based hypotheses on candidate genes do not usually reflect the situation in nature, while technical advances allow the hypothesis-free approach of simultaneously testing 500 000 to several million polymorphisms spread across the genome in GWAS. Second, it was recognized that large case–control populations are an indispensable prerequisite to overcoming the inherent heterogeneity in populations, and that potential genetic risk factors have to be replicated in large, well-characterized patient populations to rule out stochastic chance observations (see Box 15-2) (Ioannidis *et al*. 2001). True positive as well as true negative associations can only reliably be identified if the statistical power of the population that is clinically analyzed is sufficient. The statistical power is determined, among other factors,

Box 15-2 Genetic association studies.

Studies designed to localize chromosomal regions (loci) that contribute to a disease susceptibility analyze the allele frequencies of variants in a study population and test their co-occurrence with the disease, in comparison to a study population not having the disease (control group). The intention of such *genetic association studies* (or association mapping) is to determine whether an individual carrying one or two copies of a high-risk variant is at increased risk of developing a disease. The principle of the commonly used case–control association study is illustrated in Fig. 15-5. This study is a powerful method to detect associations of certain alleles with a disease phenotype, and it has frequently been employed for the identification of the genetic risk factors in periodontitis.

An important prerequisite of case–control studies is to ensure a good match between the genetic background of cases and controls, so that any genetic difference between them is related to the disease under study and not to biased sampling. Therefore, cases and controls should have similar ethnical descent. A further prerequisite is a *case selection strategy* that is designed to enrich specific disease-predisposing alleles. This includes efforts to minimize phenotypic heterogeneity by stringent diagnosis criteria, and should focus on extreme cases, defined, for example, by a particularly early age of disease onset or severe disease or both.

In most circumstances, and particularly when the total sample size has financial or operational constraints, efforts to enrich case selection with the most severe phenotypes are very likely to improve the *statistical power* of a study due to an increase in the frequency of the risk genotype (McCarthy *et al*. 2008). Related to this and compulsory for the identification of a true genetic risk factor, are case–control analysis populations, which are large enough to provide the necessary statistical power for the initial explorative association study and the necessary subsequent replication of the finding. The statistical power increases with sample size and correlates with allele frequency and the genetic effect of the respective variant (Kathiresan *et al*. 2004). This is why common variants or variants with a high odds ratio (OR) are more likely to be detected in

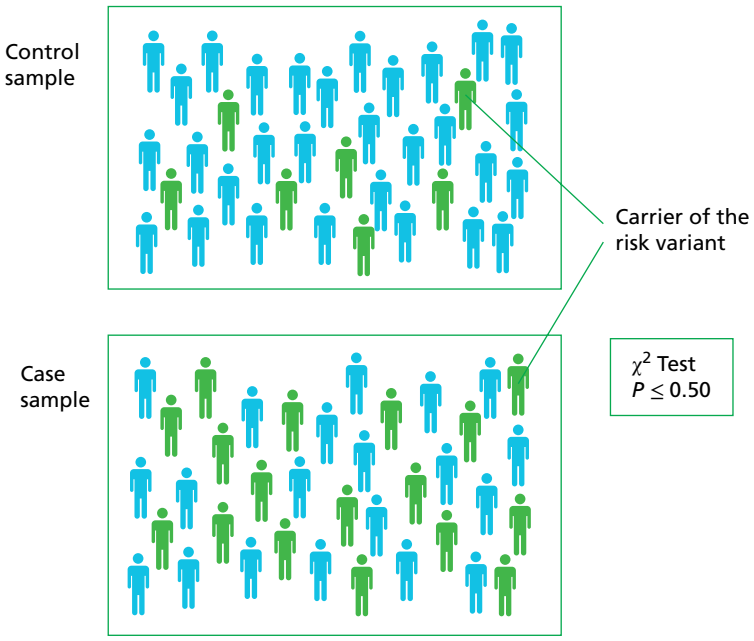

Fig 15-5 Case–control studies compare the frequency of single nucleotide polymorphism (SNP) alleles in two well-defined groups of non-related individuals: controls, who are either known to be unaffected or who have been randomly selected from the population, and cases who have been diagnosed with the disease under study. An increased frequency of an SNP allele or genotype in cases compared with controls indicates that the presence of the SNP allele may increase the disease risk. The potential association is a mere statistical association and always requires a replication in an independent sample. Significance can be assessed with various methods, but most often the χ^2 statistic is used in contingency table analyses, which provide an assessment of the departure from equal SNP allele frequencies in cases and controls (P value). Association studies can also be used to estimate the disease risk conferred by the SNP allele, which is expressed by the odds ratio (OR). The OR is the ratio of allele carriers to non-carriers in cases compared with that in controls, which gives the increase in disease risk for carriers compared to non-carriers (Lewis 2002).

Box 15-2 *Continued.*

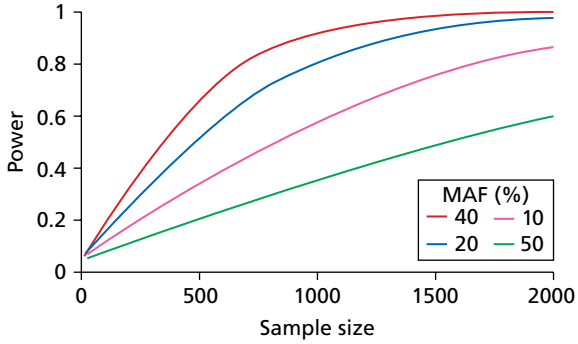

Fig 15-6 Statistical power in relation to the sample size, allele frequency, and odds ratio (OR). To identify a genetic risk variant with a minor allele frequency (MAF) of, for example, 20% in the general population, ≈1000 cases and 2000 controls are required to achieve the necessary statistical power of 0.8. [The statistical power was calculated as described by Dupont & Plummer (1998) for an average OR of 1.3, and twice as many controls as cases were considered. A power of 0.8 is regarded as statistically significant.]

genome-wide association studies (GWAS) than rare variants or variants with a small effect (Fig. 15-6). However, most disease-associated variants increase the susceptibility rather modestly and to identify a common variant with a modest genetic effect, often >1000 well-defined cases and at least the same number of controls are necessary to reach a sufficient statistical power.

The findings of case–control studies are mere statistical associations, which describe differences of allele frequencies between two independent samples; importantly, they should not be regarded as causative associations. By a preassigned significance threshold of 0.05, one in every 20 allelic variants tested will pass the commonly preassigned significance threshold of a *P* value of <0.05 by chance alone. Allele frequencies between independently sampled populations are also liable to stochastic fluctuations (random allele drifts across and between populations, without selection pressure). For these reasons, *replication* of the initial findings is the gold standard for genetic association studies. Notably, the replication needs to be performed in an independent case–control sample of the same phenotype (diagnosis criteria) and the same ethnic background. A repetition of the study with samples from different ethnic groups, with different diagnostic criteria or with independent cases but the same controls, cannot be considered as a replication and does not test the initial finding properly. Only after confirmation by replication is it useful to validate the initial finding of an association study in different sub-phenotypes or in different ethnicities.

As genes are usually patchworks of different haplotypes, being mostly in poor-to-moderate linkage disequilibrium (LD), the information on the potential association of one haplotype provides little to no information on the association or non-association with another haplotype within that gene (Slatkin 2008). Thus, association studies should capture the complete haplotype information of the gene of interest before drawing an unambiguous conclusion of the association findings for that gene, positive or negative (Slatkin 2008).

Candidate gene association studies

Until the middle of the last decade, investigations of selected candidate genes based on literature reviews and perceived pathophysiologic pathways was the most important strategy for the identification of risk genes that contribute to a disease. A major disadvantage of candidate gene studies is the requirement for an *a priori* hypothesis on the involvement of the gene in disease risk and on the presence of a functional variant within this particular gene (Wilkening *et al.* 2009). Essentially, there are two different selection strategies for a candidate gene, which depend on the question addressed. When it is of interest to ask whether or not specific loci within a regulatory signaling pathway are involved in the increase of the genetic risk of periodontitis, or there is functional evidence of the effect of a variant from the study of other diseases, it is reasonable to select genes from this pathway or the specific variants. This approach will determine whether or not the selected genes carry genetic variants which increase the risk of the disease.

Another question which addresses the classical objective of molecular genetics is more difficult to answer: which specific genes and pathways influence the disease risk? As the formulation of the hypothesis for the selection of the candidate gene is entirely dependent on the current knowledge of the molecular biologic mechanisms of the disease, hundreds of loci and/or genes which can have an influence on the disease will not be selected because their function might be unknown or their function lies within pathways that have not yet been implicated in the disease. As the knowledge on these genes is very incomplete, selection of candidate genes is necessarily arbitrary. Accordingly, most associations observed in these studies cannot be successfully replicated. Obviously, this does not rule out the finding of a true positive association if the correct candidate gene was selected *a priori*, but with this approach it is not possible to identify hitherto unknown genes that are disease relevant.

Genome-wide association studies

In contrast, GWAS provide an unbiased and hypothesis-free approach. A large number of SNPs (currently 500 000 to >1 000 000 markers) distributed

(*Continued*)

Box 15-2 *Continued.*

across the whole genome serve as proxies for multiple other SNPs in LD. Nevertheless, genome-wide testing of polymorphisms also entails problems. First, if by chance alone, one in every 20 markers tested gives a P value of <0.05, the probability of statistical errors rises with increasing number of single SNP association tests, so-called type 1 errors (false-positive association findings). If 500 000 markers or more are independently tested, the P value obtained from the χ^2 statistics must be corrected for multiple testing. This is addressed by setting a genome-wide significance threshold by correcting for the number of tests performed (Balding 2006). The current standard for declaring statistical significance at genome-wide level is a combined P value (including "initial discovery" GWAS and replication cohorts) of $<5 \times 10^{-8}$ (Manolio 2010). However, the sample sizes that are required to achieve such significance thresholds may be unrealistic for the study of less common diseases. The resulting lack of statistical power is the major factor that leads to type 1 and type 2 errors (false positive and false negatives), that is the failure to detect a true association.

Table 15-4 Number of identified risk diseases for a selection of inflammatory diseases. The total population size included in the explorative study and the replication is given for the largest of the current studies, which validated previous findings and reported new genetic susceptibility loci.

Disease	Number of risk genes	Population size	Reference
Atherosclerosis	46	64 000 cases	Deloukas *et al.* (2013)
		131 000 controls	
Type 2 diabetes	66	>35 000 cases	
		115 000 controls	Morris *et al.* (2012)
Rheumatoid arthritis	46	12 000 cases	Eyre *et al.* (2012)
		16 000 controls	
Systemic lupus erythematosis (SLE)	51	>8000 cases [e.g. Lessard *et al.* (2012)]	Various individual studies summarized in Boackle (2013)
		>8000 controls [e.g. Lessard *et al.* (2012)]	
Crohn's disease	163	38 000 cases	Jostins *et al.* (2012)
		38 000 controls	

to a large extent by the size of the population analyzed (see Box 15-2). Thus, thousands of well-defined cases and many more controls are needed to detect a genetic variant with a small effect that is observed commonly for complex diseases. This realization eventually resulted in the formation of extensive international consortia for the recruitment of the appropriate case and control numbers.

In a first wave of GWAS during 2007–2010, an era often referred to as the genetic gold rush of human genetics, many of the common genetic risk factors of complex human diseases (i.e. those genetic variants with a ≥5% prevalence in a given population) were identified. Although these studies proved highly successful in identifying the most common genetic susceptibility variants, they could explain only a fraction of the underlying genetic heritability (Maher 2008; Manolio *et al.* 2009). It turned out that the power of an individual study encompassing >1000 cases was still limited in terms of detecting small or modest effects of disease-associated variants. To detect such variants of moderate effect, but also rare variants with a large effect at the individual level, much larger analysis populations were required. To this end, the investigators of the first GWAS joined forces and combined data for GWAS meta-analysis, which eventually included over tens of thousands of cases and controls. Since then, it is considered that most of the common genetic risk factors for co-morbidities of periodontitis, like type 2 diabetes, coronary artery disease, or rheumatoid arthritis, have been unveiled. Table 15-4 gives a snapshot of the findings of recent years in terms of the numbers of identified genetic risk loci of the major complex inflammatory diseases, some of which are co-morbidities of periodontitis, and the numbers of cases and controls employed in these studies. Although the numbers of the identified risk loci for the various diseases are high, it is expected

that they will continue to rise in the coming years. Interestingly, most of the identified genes had not been thought of as likely candidate genes before. These findings confirm the polygenic character of complex diseases, and the pathogenic contribution of single nucleotide polymorphisms (SNPs) in individual genes to be low. We propose this is similarly valid for periodontitis.

Most of the genetic association studies which were designed for the elucidation of the genetic risk factors of periodontitis focused on a range of various candidate genes selected for their roles in the immune system (e.g. genes of the interleukin and Toll-like receptor families), tissue destructive processes (e.g. matrix metalloproteinases), or various metabolism mechanisms (Loos *et al*. 2005; Laine *et al*. 2010, 2012,). For reasons similar to those described for other complex diseases in the pre-GWAS era, despite many efforts in the field of genetic association studies, the genetic risk factors of periodontitis and their pathophysiologic effects had largely remained controversial. Few genes were established as conclusive. Significant doubts about the collective panel of the putative genetic risk factors were raised. In order to clarify the putative role of a comprehensive set of genes that had been the focus of recent genetic research in periodontitis, a large-scale replication study analyzed 23 genes in detail (*ABO, CCR5, FCGR2A, FCGR2C, FCGR3A, FCGR2B, FCGR3B, IL-1B, IL-2, IL-6, IL-10, LTA, MMP-9, NOD2, TLR-2, TLR-4, VDR, CD14, IL-1A, IL-1RN, TNFRSF11B, IFNGR1, L-selectin*) in 600 German patients with aggressive periodontitis and 1440 German population representative controls with an average SNP coverage of <5000 base pairs (bp) (Schäfer *et al*. 2013). Except for *IL-10*, this study showed no strong association between the tested genes and their regulatory regions with aggressive periodontitis, and the authors suggested that the positive associations with periodontitis that had previously been reported for these genes were most likely caused by type I errors. This non-validation of the classical candidate genes of periodontitis further emphasized the need for caution in the interpretation of genetic associations and for extensive validation of reported genetic risk factors.

Some genes can still be considered as true genetic susceptibility factors for periodontitis if evidence for this is replicated in repeated independent, reasonably large case–control populations.

ANRIL, CAMTA1/VAMP3, GLT6D1, COX-2, and *NPY* (Box 15-3)

ANRIL

The best-replicated evidence for conferring risk of periodontitis to date has been for the gene *ANRIL* ["antisense non-coding RNA in the *INK4* locus" (Pasmant *et al*. 2007); Genbank accession no.

Box 15-3 Genomic locations of genetic risk variants.

The recent discussion in genetic research on complex diseases, including periodontitis, suggests that common genetic risk variants are likely not to be found within the coding regions of the classical candidate genes, but rather within regulatory elements of unforeseen genes and chromosomal regions. Figure 15-7 shows that a majority of common human genomic variants that are strongly associated with over 400 common diseases and traits lie within regulatory active regions. This is also true for the location of the genetic risk variants of periodontitis, which is intronic for both *ANRIL* and *GLT6D1*, lying several kilobases up- and down-stream of the protein-coding regions of *COX-2* and *NPY*. Generally, disease- and trait-associated variants are significantly enriched within the sites of physiologically or pathogenetically relevant regulatory regions. Interestingly, they also cluster within known regulatory pathways and expose functional networks that are centered on specific transcriptional regulators. The results of recent GWAS point to the widespread involvement of regulatory DNA variation in common human diseases, and implicate numerous transcriptional regulators in disease susceptibility and pathogenesis.

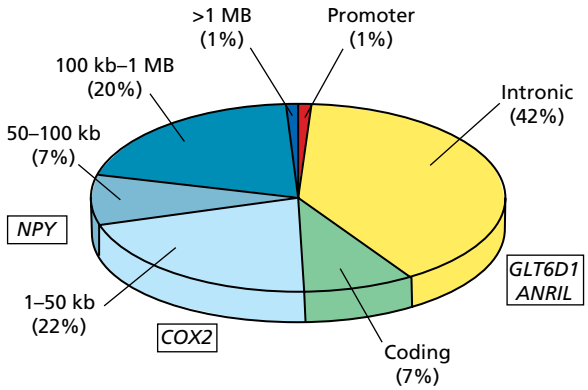

Fig 15-7 Chromosomal location of disease-associated single nucleotide polymorphisms (SNPs) of genome-wide significance from genome-wide association studies (GWAS) of various complex diseases. On average, 64% of disease-associated variants are located within the introns and 1–50 kb up- or down-stream of a gene. The location of the validated periodontitis-associated variants is in accordance with this observation (depicted in orange). (Courtesy of J. Stamatoyannopoulos, adapted from original.)

DQ485453; alias *CDKN2B-AS1* (*CDKN2B* antisense RNA 1) on chromosome 9p21.3], as shown in three independent North-West European populations with aggressive periodontitis (Schäfer *et al*. 2009; Ernst *et al*. 2010) and one Turkish population with aggressive periodontitis (Schäfer *et al*. 2013), as well as in one population with chronic periodontitis (Schäfer *et al*. 2011). Interestingly, *ANRIL* is also considered to be the most important genetic risk factor of myocardial infarction, as identified in various early GWAS on coronary artery disease (CAD) (McPherson *et al*. 2007; Samani *et al*. 2007; WTCCC 2007). This gene encodes a large antisense non-protein coding RNA molecule, a 126.6-kb full length transcript of 19 differentially spliced exons, yielding different RNA molecules of various lengths. Despite extensive research within the last few years, the molecular function of *ANRIL* has remained very poorly understood and the nature of the causative variants has not been clearly identified. It is still unknown how the genetic susceptibility for various diseases associated with this locus is transcribed into specific (patho)physiologic functions. It is agreed that *ANRIL* has a negative regulatory effect on the expression of the adjacent cycline-dependent kinase inhibitor genes *CDKN2A* and *CDKN2B* (Visel *et al*. 2010; Yap *et al*. 2010).

CAMTA1/VAMP3

In accordance with observations that lncRNAs often play a role in the transregulation of gene expression (Pandey *et al.* 2008; Mercer *et al.* 2009), it was shown that decreased expression of *ANRIL* is correlated with decreased expression levels of the distant genes *ADIPOR1* (adiponectin receptor 1; chromosome 1), *VAMP3* (vesicle-associated membrane protein 3; chromosome 1), and *C11ORF10* (chromosome 11 open reading frame 10; chromosome 11) (Bochenek *et al.* 2013). The protein VAMP3 belongs to the VAMP/synaptobrevin family and plays a role in phagocytosis, where VAMP3 mediates, for example, the delivery of tumor necrosis factor-alpha (TNF-α) to the cell surface (Murray *et al.* 2005). Located 2 kb upstream of *VAMP3* is the extremely large gene *CAMTA1* (calmodulin-binding transcription activator 1), spanning >1 Mb. In a GWAS on periodontal pathogen colonization, a large stretch of the *CAMTA1/VAMP3* region was reported to be strongly associated with increased quantities of pathogenic oral bacteria (Divaris *et al.* 2012). A search for potential periodontitis-associated variants within *CAMTA1/VAMP3* identified several SNP located at this pathogen-associated region to be significantly associated with aggressive periodontitis (Bochenek *et al.* 2013). Interestingly, this region was also shown to strongly increase the risk of CAD, a finding that was subsequently validated in a meta-analysis of 13 GWAS of CAD comprising 21 033 individuals with CAD and 44 065 controls of European descent (Bochenek *et al.* 2013). This makes the *CAMTA1/VAMP3* region the second validated shared genetic risk locus of periodontitis and CAD.

Further borderline associations with aggressive periodontitis were found at *C11ORF10* and the adjacent genes *FADS1* and *FADS2* (fatty acid desaturases 1 and 2). These alleles were identical to previously identified associations of genome-wide significance with the metabolic syndrome (Zabaneh & Balding 2010), type 2 diabetes (Dupuis *et al.* 2010), and the inflammatory bowel disease, Crohn's disease (Franke *et al.* 2010), indicating some genetic overlap between periodontitis and these conditions.

GLT6D1

Another risk gene of aggressive periodontitis, *GLT6D1*, also mapped to chromosome 9, at 9q34.3, was identified in the first GWAS on periodontitis (Schäfer *et al*. 2010b). It encodes an unknown protein belonging to a family of proteins that is characterized by a glycosyltransferase domain-1. *GLT6D1* was found to be predominantly expressed in the gingiva and T cells. The molecular function of this gene is still unknown, but sequencing and subsequent molecular biologic characterization of the main associated genetic polymorphisms suggest an impaired GATA3-transcription factor binding site as the causative variant for increased disease risk.

COX-2

The metabolic protein COX-2 converts arachidonic acid into prostaglandin H_2 (PGH_2), the precursor of prostaglandin E_2 (PGE_2). Prostaglandins (PGs) are a group of key inflammatory mediators of the immune response to infection. PGE_2 plays an important role in periodontitis by mediating pro-inflammatory reactions in the periodontal tissues, and is partly responsible for the resorption of the alveolar bone in the course of periodontal pathogenesis. *COX-2* (located on chromosome 1 at 1q24-25) expression is specifically induced by cytokines and specific *COX-2* expression has been reported for gingival tissues in periodontitis. In accordance with the central position of *COX-2* in the regulation of PGH_2 levels and the specificity of activation by cytokines, *COX-2* was subjected to various candidate–SNP association studies for different complex diseases, and polymorphisms within the *COX-2* gene were related to increased susceptibility to various inflammatory diseases. In Taiwanese and Chinese periodontitis case–control populations, the same genetic region was independently shown to be associated with severe periodontitis (Ho *et al*. 2008; Xie *et al*. 2009), and this association was subsequently validated in a European population with aggressive periodontitis (Schäfer *et al*. 2010a).

Therefore, these studies have provided strong evidence for a confined chromosomal region upstream to *COX-2* that possibly carries one or more risk variants of severe periodontitis in populations of different ethnic backgrounds.

NPY

NPY (neuropeptide Y) has immunomodulatory effects that are thought to alter the pro-inflammatory T-helper type 1 (Th1)-to-anti-inflammatory T-helper type 2 (Th2) balance. Binding of NPY to Y1 receptors on a variety of immune cells is thought to be responsible for promoting the anti-inflammatory Th2 response (Bedoui *et al*. 2003). NPY is therefore potentially important in the coordination of inflammation and bone metabolism, both of which are central to the pathogenesis of periodontitis (Lundy *et al*. 2009). Accordingly, the presence of NPY Y1 receptors was verified in human gingival tissue and of NPY in human gingival crevicular fluid (GCF), with significantly higher NPY levels in GCF in healthy compared with periodontitis-affected sites (Lundy *et al*. 2009). A GWAS first described an association with severe chronic periodontitis downstream of the coding region of *NPY* (chromosome 7) in a large sample of European–American individuals (Divaris *et al*. 2013). A second GWAS that systematically analyzed gene–sex interactions in German cases of aggressive periodontitis and controls observed that a sexually dimorphic role of genetic variants upstream of *NPY* was associated with aggressive periodontitis (Freitag-Wolf *et al*. 2014). Interestingly, sex-dependent effects of NPY had previously been described in mice. *NPY* loss-of-function mice showed different anxiogenic responses in behavioral tests in males and females, indicating a sexually dimorphic role of NPY in behavioral stress responses. Also, gastrointestinal inflammation, known to enhance anxiety in a sex-dependent manner, produced different behavioral responses to stress challenges in female and male *NPY* knockout mice (Painsipp *et al*. 2011). NPY activates the hypothalamic–pituitary–adrenal (HPA) axis and modulates the visceral stress responses mediated through corticotrophin-releasing hormone (CRH) pathways (Dimitrov *et al*. 2007). Additionally, NPY is potently anxiolytic (Karl *et al*. 2008), acting through NPY Y1 receptors in the amygdala to inhibit CRH signaling and terminate the behavioral stress and anxiety responses.

The genes *ANRIL*, *GLT6D1*, *COX-2*, and *NPY* are conclusive risk genes of periodontitis, (*ANRIL*, *COX-2*, and *NPY* for both aggressive and chronic periodontitis; *GLT6D1* for aggressive periodontitis only), because of repeated replication of evidence in independent large analysis populations. Obviously, they do not explain the complete heritability of periodontitis, and many more other genes, genetic elements, and variants are yet to be discovered (Boxes 15-4, 15-5).

Box 15-4 Current and future strategies for identifying the full range of genetic variance in periodontitis.

The basic paradigm used in the recently completed phase of genome-wide association studies (GWAS) into the genetics of frequently occurring inflammatory diseases was to catalog the common risk variants. These GWAS successfully represented variants with a frequency well above 5% in the general population. For the detection of less common variants, an extension of GWAS with a much increased coverage of rare variants is appropriate. This line of thought underlined the international consortium-driven "1000 Genomes Project" (www.1000genomes.org), which extended the catalog of known human variants with a frequency near 1%. A new wave of GWAS will catalog less common variants with allele frequencies of 1–5%, and will identify some new associations of rare variants. However, to capture rare variants with allele frequencies of <1%, entire genomes or the whole exome (see Box 15-1) of cases will have to be sequenced to provide sufficient coverage to read all DNA variations, including common and rare variants implicated in monogenic and complex diseases. Eventually, studies of the role of inherited variation in diseases will involve whole-genome sequencing of all enrolled subjects. Such studies will eventually be carried out in a manner similar to GWAS, with very large sample sizes that will provide sufficient statistical evidence to implicate variants on the basis of association evidence alone (Cirulli & Goldstein 2010; Janssens & van Duijn 2010). Several studies have already shown that whole exome sequencing can identify disease-causing variants (Choi *et al*. 2009; Ng *et al*. 2010a, b). However, until complete genomic sequencing is cheap enough to be generally used in large samples, various designs are likely to be the primary engines of discovery and will likely identify many common and rare causative variants:

1. Selecting families that have multiple affected individuals (family-based sequencing) and selecting individuals who are at the extreme ends of a trait distribution (extreme-trait designs)
2. Whole-exome sequencing or whole-exome genotyping arrays, which bundle the almost complete spectrum of known coding variants in the human exome (Cirulli & Goldstein 2010).

Epigenetic signatures

The above-described strategies for identifying genetic risk factors of periodontitis explore changes within the nucleotide sequence in the DNA. However, it is now becoming clear that a full understanding of the interactions of the environment and lifestyle factors with the genome will also require the consideration of epigenetic mechanisms. Epigenetics can be defined as the structural (mitotically or meiotically) heritable or reversible adaptation of chromosomal regions so as to register, signal or perpetuate altered gene activity states (Bird 2007), which refers to changes in gene expression that do not involve a change in the DNA nucleotide sequence, but encompass an array of molecular modifications to both DNA and chromatin (Li 2002; Klose & Bird 2006; Talbert & Henikoff, 2006). These modifications are conferred by methylation of cytosines in CpG dinucleotides, changes to chromatin and packaging of DNA by post-translational histone modifications, mechanisms that control the higher level organizations of chromatin within the nucleus, which have a range of effects on gene expression. In this context, the low concordance rates in MZ twins, who do not always show the same disease susceptibility, also raised the possibility of epigenetic differences arising during early development as well as with aging (Wong *et al*. 2005). Accordingly, it has been reported that young twins have similar amounts of DNA methylation, whereas older twins differ considerably in the amounts and patterns of this modification (Fraga *et al*. 2005). It is a subject of speculation whether the amounts and patterns of epigenetic alterations could give rise to the divergent disease predispositions of some MZ twins. However, unambiguous, reliable epigenetic data for twins and unrelated humans are scarce (Eckhardt *et al*. 2006), and generalizations and interpretations should be handled with prudence. Data from model organisms have suggested long-term and possibly even transgenerational epigenetic effects on gene expression (Morgan *et al*. 1999; Rakyan *et al*. 2003; Anway *et al*. 2005). Increasing evidence for potential mechanisms that modify the epigenome and link environmental and lifestyle influences to disease phenotypes (Jirtle & Skinner 2007) was reported for nutritional supplements (Wolff *et al*. 1998; Waterland & Jirtle 2003), xenobiotic chemicals (Li *et al*. 2003b; Anway *et al*. 2005; Ho *et al*. 2006), and even behaviors (Weaver *et al*. 2004).

Epigenetics has particularly caught the imagination because it is principally stable and inheritable, but is affected by the environment and lifestyle factors. The possibility that an acquired imprint can be kept through long periods of the lifetime or even passed from parents to children has drawn extensive public attention as it is perceived to be an alternative to genetic determinism (Bird 2007). How insights into epigenetics obtained from animal models can be extended to determine the importance of environmental influences on human disease susceptibility will be an exciting challenge in future research (Rakyan *et al*. 2011).

It has been speculated that epigenetic modifications can play a role in periodontitis (Barros & Offenbacher 2009). However, only a very few studies

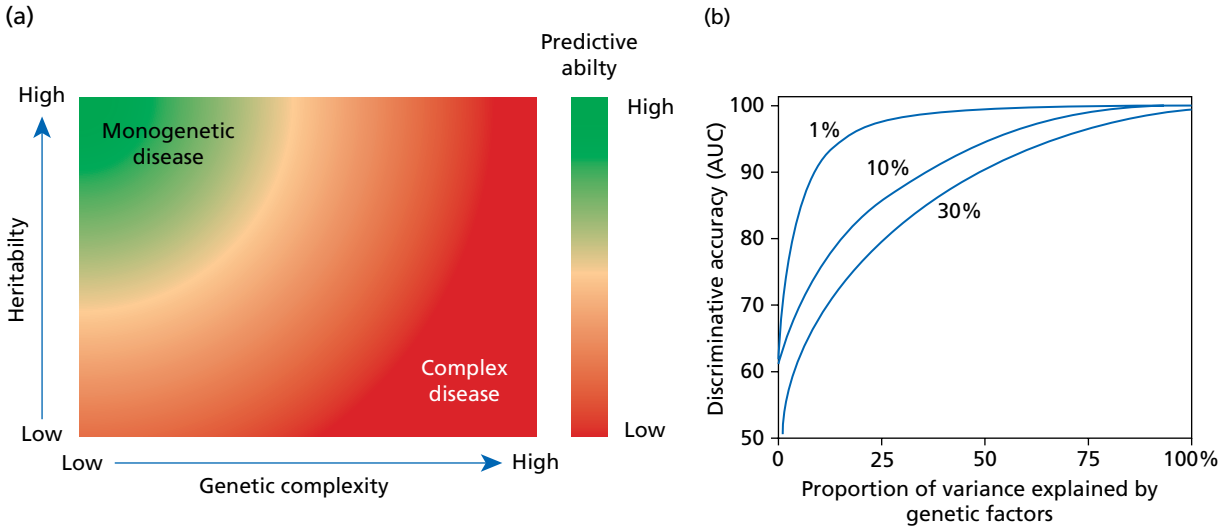

Fig 15-8 (a, b) Relationship between the heritability, genetic complexity, and predictive ability in personal genome testing. The predictive ability is highest if the heritability is high and the genetic complexity is low. The discriminative accuracy, assessed as the area under the operating characteristic curve (AUC), is the extent to which predicted risks can discriminate between individuals who will develop a disease of interest, like periodontitis, and those who will not. The AUC is the probability that the test correctly identifies the person who will develop the disease from a pair of whom one will be affected and one will remain unaffected, and ranges from 50% (complete lack of discrimination) to 100% (perfect discrimination). The percentages on the graph refer to the risk of disease prevalence in the population. Underlying this is the assumption that the total heritability can be explained, but whether or not this is realistic depends on the complexity of the genetic etiology. The discriminative accuracy for chronic periodontitis will always be low; however, for aggressive periodontitis the discriminative accuracy is expected to be higher. (Source: Janssens *et al*. 2006, from Macmillan Publishing.)

Box 15-5 Future perspectives.

Recent genome-wide association studies (GWAS) have provided valuable insight into the genetic basis of complex diseases and identified many genetic susceptibility genes. In 2014, the GWAS catalog of the US National Human Genome Resource Institute (NHGRI; http://www.genome.gov/gwastudies) included 14 769 SNPs with genome-wide associations in >600 traits (Welter *et al*. 2014). However, these variants only explain a small proportion of the heritability of these traits (Frazer *et al*. 2009). This is in part due to statistical limitations, which are inherent to GWAS and generally allow only the detection of common risk variants (see Box 15-2). Where the missing heritability is likely to lie and how research strategies might best be developed to uncover the missing genetic risk factors is currently debated (Eichler *et al*. 2010). When GWAS began some years ago, it was widely believed that complex disease is largely attributable to a moderate number of common variants, each of which explains several percent of the risk in a population (this was called the common disease–common variant hypothesis) (Pritchard & Cox 2002). This model is challenged by the so-called "missing heritability problem", which describes the observation that loci detected by GWAS almost without exception have only limited contribution to the disease (Maher 2008). In this context, Gibson (2011) stated that, "it was simply not the case, that a few dozen loci of moderate effect and intermediate frequency each explained several percent of disease risk in a population, as was typically observed in crosses or pedigrees". Therefore, the genetic variance has largely been attributed to one of two causal models of disease:

1. A large number of small-effect common variants across the entire allele frequency spectrum cause the genetic disease susceptibility. Underlying this hypothesis is the proposition that common genetic variants are among the major sources of genetic variance (see Box 15-1) or disease susceptibility, and hundreds or even thousands of different loci contribute to each case. The loci detected by GWAS are merely the largest effect sizes drawn from a Poisson or similar distribution (Gibson 2011). If ten common variants explain 10% of risk in a population, the remainder is attributable to a myriad of variants that each explain considerably <1% of risk and have a genotype relative risk of <1.1 (Gibson 2011). The disease is expressed as the subsequent combination of genetic, environmental, and lifestyle interactions (Feldman & Lewontin 1975; Eichler *et al*. 2010). Accordingly, this model is referred to as the "infinitesimal model" (Visscher *et al*. 2008).
2. Alternatively, in the "rare allele model", most of the genetic variance is due to highly penetrant variants with allele frequencies of <1%, but that strongly elevate the genetic risk. Many different rare variants have large effects on the phenotypic variation (Cirulli & Goldstein 2010). Each of these variants explains most of the risk in a subset of cases, but does not explain enough of the

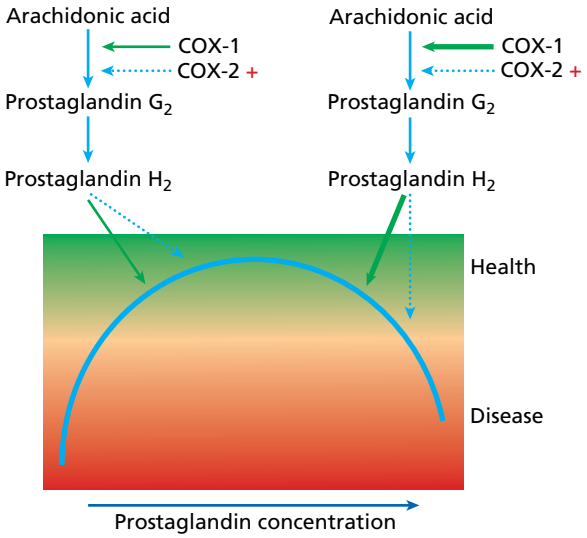

Fig 15-9 It is hypothesized that common variants influence the expression and activity of genes in pathways establishing the background susceptibility to disease that is then further modified by less common variants with larger effects. Prostaglandins are produced by a cascade of biochemical reactions following the sequential oxidation of arachidonic acid by the cyclooxygenases COX-1 and COX-2 and terminal prostaglandin synthases. Whereas COX-1 is responsible for the baseline levels of prostaglandins, COX-2 produces prostaglandins by specific stimulation in scenarios of periodontal inflammation. The half circle represents a range of prostaglandin concentrations in the lesion of a given population. The prostaglandin concentration is influenced by the interplay of the individual genetic constitutions, and the individual physiologic and environmental states. Prostaglandin concentrations at the low and high ends are associated with disease, while an intermediate concentration is physiologic and compatible with health. In this hypothetical illustration, genetic variation somewhere within the prostaglandin synthesis pathway results in some individuals having lower prostaglandin levels (left, normal COX-1 activity, indicated by the green horizontal arrow from COX-1) than others (right, genetic variation in COX-1 that establishes the background susceptibility to disease; indicated by the thick green horizontal arrow from COX-1). The variation in individuals with a background susceptibility is still within the healthy range. The effect of an additional variant that increases COX-2 synthesis (indicated by the "+" sign and blue dashed arrows) upon inflammatory stimulation is conditional on this liability, pushing those with a high concentration of prostaglandin that is genetically determined by the background susceptibility (those on the right) beyond the disease threshold and towards the development of periodontitis (into the red danger zone), whereas those with a low concentration of prostaglandin on the left can accommodate the genetic variation and remain in the green safe zone. (Adapted from Gibson 2011, from Macmillan Publishing.)

(*Continued*)

Box 15-5 *Continued.*

variance in the total population. Thus, they cannot be detected by standard GWAS. Although the severity of the disease is largely caused by the rare susceptibility genotype, it may be modified by the environment (which can lead to a change in penetrance of the genetic effects of rare as well as of common variants), epistasis or epigenetics (Bodmer & Bonilla 2008). However, a recent large-scale study showed that rare coding-region variants at known risk loci of autoimmune diseases have a negligible role in common autoimmune disease susceptibility (Hunt *et al*. 2013). An alternative study that used yeast as a model to study the missing heritability of complex traits, showed that interactions of known common genetic variants could explain almost the entire additive contribution to heritable variation (Bloom *et al*. 2013). These results are currently not in support of the rare-variant synthetic genome-wide association hypothesis.

In all likelihood, each of these genetic architectures contribute in various degrees to different diseases, but there is as yet insufficient data to resolve the debate, despite the many strong arguments in favor or against each of these two models (Gibson 2011). The debate on the contribution of genetic variation to disease over the coming years will center on how common and rare variants interact (Schork *et al*. 2009). A straightforward hypothesis states that common variation influences the expression and activity of genes in molecular pathways, establishing the background susceptibility to the disease that is then further modified by rare variants with larger effects (Fig. 15-9).

Figure 15-9 illustrates that disease is generally a threshold-dependent response that is superimposed on a continuous physiologic characteristic.

As only a proportion of the genetically predisposed and/or pathogen-exposed individuals develop a disease, simple genetic explanations for individual susceptibility to chronic inflammatory diseases such as periodontitis have not been forthcoming. The challenge for future research will be, apart from identifying as many true susceptibility factors as possible, to discern the relevant patterns within the generated data, in other words to model the effects of SNP–SNP interactions (Renz *et al*. 2011).

on epigenetic effects have been performed to date. Some have investigated epigenetic modifications in candidate genes that play a role in the pathophysiology of periodontitis or had been investigated in other diseases with reported positive results, and several studies suggest that bacteria or bacterial components are responsible for the epigenetic modifications. Similar to the earlier genetic association studies in periodontitis, these studies employed low sample sizes and were not replicated, so the reported epigenetic effects in periodontitis should be interpreted with caution. Modifications in *COX-2* were independently investigated in two studies (Loo *et al*. 2010; Zhang *et al*. 2010), with both showing increased hypermethylation of CpG dinucleotide sites in *COX-2* DNA extracted from periodontal inflamed gingival biopsies when compared with non-inflamed samples, but lacking clear functional evidence for the observations. Large-scale systematic studies of periodontitis-associated epigenetic variation will surely elucidate the role of epigenetic changes in the pathophysiology of periodontitis in the future.

From genetic disease susceptibility to improved oral care

Despite great breakthroughs in human genetics in recent years in a substantial number of inflammatory diseases, few direct improvements in clinical care have resulted to date. This is largely due to the complexity of most heritable diseases, as described earlier. Most of the identified common risk factors have only moderate effects and in most cases, the true causative variants that mediate the effect at the molecular biologic level, as well as the underlying mechanism, still await elucidation. Furthermore, only a relatively limited number of low-risk variants have been discovered so far. In this context it is of interest to look at the present potential of genetic health tests, which are offered in increasing numbers. Over time, these tests have evolved from testing a few variants for the prediction of a single disease, to testing hundreds of thousands of genetic variants genome-wide for multiple diseases simultaneously (Janssens & van Duijn 2010). The prediction ability of these tests is very imprecise and differs considerably between monogenic and complex diseases, which is explained by the different genetic complexities of these diseases (Hunter *et al*. 2008). Monogenic diseases such as cystic fibrosis or Huntington's disease are fully heritable and a mutation in a single specific gene is sufficient to cause these diseases. Testing for the absence or presence of these mutations gives an accurate estimate of future disease development. The effect of heritability and genetic complexity on the predictive ability of genetic tests for disease development is shown in Fig. 15-8a (Box 15-5). When diseases have a high heritability and a low genetic complexity, such as monogenetic disorders, genetic tests will be very accurate. In contrast, the predictive ability of tests for complex diseases is determined by the combined effect of all genetic, environmental, and lifestyle factors tested (Janssens & van Duijn 2010). Only when

diseases have a high heritability is the maximum discriminative accuracy reliable, assuming all variants are identified. Figure 15-8b (Wray *et al*. 2010) shows that a good predictive ability of a genetic test will theoretically be possible for a disease with a very high heritability and a low genetic complexity. Such diseases are commonly severe and have an early age of onset and a low frequency (<1%) in the population. Thus, accurate genetic testing may become possible for the juvenile and post-adolescent (early-onset) forms of aggressive periodontitis, which are the most severe phenotypes and have a particularly early age of onset, particularly if the genetic susceptibility factors are fully be identified. In contrast, late-onset diseases such as chronic periodontitis, with moderate and variable phenotypes and a high risk in the population, have many underlying low-risk variants, which may interact with each other and with other non-genetic risk factors in many different ways. Increased and decreased risks due to such very complex multidimensional interactions are still beyond our statistical and computational scope in predictive testing models (Janssens & van Duijn 2010). Nevertheless, the vision remains that, on the basis of comprehensive data that encompass the complete DNA sequence, biochemical data, and information on environmental and behavioral factors over a large time period in the life of a patient, this information can be turned into computational models that represent the patient and his/her health status and will enable the physician to devise a personalized therapy for the consenting patient. In order to make this information accessible, international pilot projects have begun, to assess the feasibility in scientific, technical, and financial terms, and to establish structures for integrating personal analytical and clinical data into an individualized model of the patient.

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Part 5: Trauma from Occlusion

Chapter 16

Trauma from Occlusion: Periodontal Tissues

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Definition and terminology

Trauma from occlusion is a term used to describe pathologic alterations or adaptive changes which develop in the periodontium as a result of undue force produced by the masticatory muscles. It is only one of many terms that have been used to describe such alterations in the periodontium. Other terms often used are: *traumatizing occlusion*, *occlusal trauma*, *traumatogenic occlusion*, *periodontal traumatism*, and *overload*. In addition to damaging the periodontal tissues, excessive occlusal force may also injure, for example, the temporomandibular joint, the masticatory muscles, and the pulp tissue. This chapter deals exclusively with the effects of trauma from occlusion on the periodontal tissues.

Trauma from occlusion was defined by Stillman (1917) as "a condition where injury results to the supporting structures of the teeth by the act of bringing the jaws into a closed position". The World Health Organization (WHO) in 1978 defined trauma from occlusion as "damage in the periodontium caused by stress on the teeth produced directly or indirectly by teeth of the opposing jaw". Occlusal trauma is an injury to the attachment apparatus that results from excessive occlusal force(s).

Traumatizing forces may act on an individual tooth or on groups of teeth in premature contact relationship; they may occur in conjunction with parafunctions such as clenching and bruxism, or in conjunction with loss or migration of premolar and molar teeth with an accompanying, gradual spread of the anterior teeth of the maxilla, etc.

In the literature, the tissue injury associated with trauma from occlusion is often divided into *primary* and *secondary*. The *primary* form includes tissue reactions (damage) elicited around a tooth with normal periodontium height, while the *secondary* form is related to situations in which occlusal forces cause injury to a periodontium of reduced height. The distinction between a primary and a secondary form of injury – primary and secondary occlusal trauma – serves no meaningful purpose, since the alterations which occur in the periodontium as a consequence of trauma from occlusion are similar and independent of the height of the target tissue, that is the periodontium. It is, however, important to understand that symptoms of trauma from occlusion may develop only in situations when the magnitude of the load elicited by occlusion is so high that the periodontium around the exposed tooth cannot properly withstand and distribute the resulting force without altering the position and stability of the tooth involved. This means that in cases of severely reduced height of the periodontium, even comparatively small forces may produce traumatic lesions or cause adaptive changes in the periodontium.

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Trauma from occlusion and plaque-associated periodontal disease

Ever since Karolyi (1901) postulated that an interaction may exist between "*trauma from occlusion*" and "*alveolar pyrrohea*", different opinions have been expressed regarding the validity of this claim. In the 1930s, Box (1935) and Stones (1938) reported experiments in sheep and monkeys, the results of which seemed to indicate that "trauma from occlusion is an etiologic factor in the production of that variety of periodontal disease in which there is vertical pocket formation associated with one or a varying number of teeth" (Stones 1938). The experiments by Box and Stones, however, have been criticized because they lacked proper controls and because their design did not justify the conclusions drawn.

The interaction between trauma from occlusion and plaque-associated periodontal disease in humans was frequently discussed in the period 1955–1970 in connection with "case reports", "in my opinion" statements, etc. Even if such anecdotal data may have some value in clinical dentistry, it is obvious that conclusions drawn from research findings are much more pertinent. The research-based conclusions are not always indisputable but they invite the reader to critique them, which anecdotal data do not. In this chapter, therefore, the presentation will be limited to findings from research endeavors involving (1) human autopsy material, (2) clinical trials, and (3) animal experiments.

Analysis of human autopsy material

Research data derived from studies of human autopsy material are not always easy to interpret. Histologic sections of the site involved may have been examined regarding (1) the dimension the lesions in the periodontium, as well as (2) the presence and apical extension of microbial deposits at adjacent root surfaces. In addition, comments may have been made regarding (3) the anticipated mobility of the teeth examined, and (4) "the occlusion" of the sites under scrutiny. It is obvious that assessments made of specimens from cadavers have a limited to questionable value when "cause–effect" relationships between occlusion, plaque, and periodontal lesions are to be described. It is not surprising, therefore, that *conclusions* drawn from this type of research are controversial. This can best be illustrated by comparing "Glickman's concept" with "Waerhaug's concept" of what autopsy studies may document regarding the role of trauma from occlusion in the pathogenesis of periodontal disease.

Glickman's concept

Glickman (1965, 1967) claimed that the pathway of the spread of a plaque-associated gingival lesion can be changed if forces of an abnormal magnitude are acting on the contaminated tooth. This implies that the character of the progressive tissue destruction of the periodontium at a "traumatized tooth" may be different from that characterizing a "non-traumatized" tooth. Instead of an even destruction of the periodontium and the alveolar bone (suprabony pockets and horizontal bone loss), which, according to Glickman, occurs at sites with uncomplicated plaque-associated lesions, sites which are also exposed to abnormal occlusal force will develop angular bony defects and infrabony pockets.

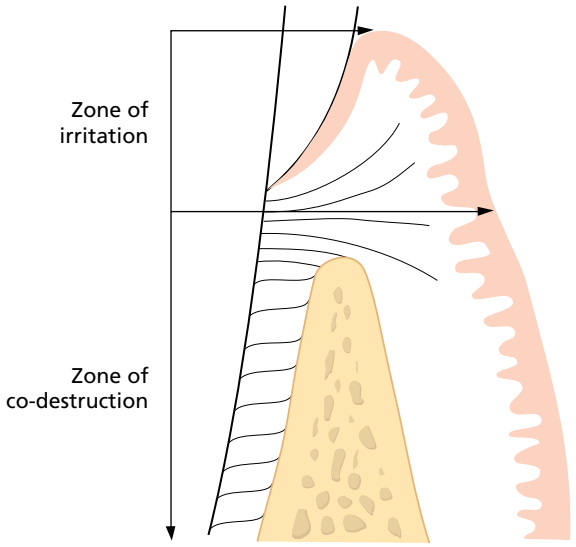

Fig. 16-1 Schematic drawing of the zone of irritation and the zone of co-destruction according to Glickman.

Since Glickman's concept regarding the effect of trauma from occlusion on the spread of the plaque-associated lesion is often cited, a more detailed presentation of his theory seems pertinent. The periodontal structures can be divided into two zones (Fig. 16-1):

1. Zone of irritation
2. Zone of co-destruction.

The *zone of irritation* includes the marginal and interdental gingiva. The soft tissue of this zone is bordered by hard tissue (the tooth) only on one side and cannot therefore be affected by forces of occlusion. Thus, the gingival lesion is the tissue response to products from microbial plaque. This gingival lesion at a "non-traumatized" tooth propagates, according to Glickman, in the apical direction by first involving the alveolar bone and only later the periodontal ligament area. The progression of this lesion results in an even (horizontal) bone destruction.

The *zone of co-destruction* includes the root cementum (mineralized tissue), the periodontal ligament, and the alveolar bone (mineralized tissue), and is coronally demarcated by the trans-septal (interdental) and the dentoalveolar collagen fiber bundles (Fig. 16-1). The tissues in this zone may become the seat of a lesion caused by trauma from occlusion.

It was claimed that the fiber bundles which separate the zone of co-destruction from the zone of irritation can be affected from two different directions:

1. From the inflammatory gingival lesion maintained in the *zone of irritation*
2. From trauma-induced changes in the *zone of co-destruction*.

Through this exposure from two different directions, the fiber bundles may become dissolved and/or orientated in a direction parallel to the root surface. The gingival lesion in the *zone of irritation* will spread directly into the "trauma-exposed" periodontal ligament (i.e. not via the bone) (Fig. 16-2). This alteration of the "normal" pathway of spread of the plaque-associated inflammatory lesion results in the development of angular bony defects. Glickman (1967) stated in a review paper that *trauma from occlusion* is an etiologic factor (co-destructive factor) of importance in situations where angular bony defects combined with infrabony pockets are found at one or several teeth (Fig. 16-3).

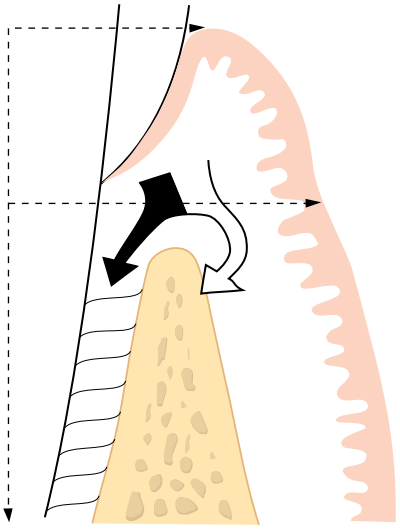

Fig. 16-2 Inflammatory lesion in the zone of irritation can, in teeth not subjected to trauma, propagate into the alveolar bone (open arrow), while in teeth also subjected to trauma from occlusion, the inflammatory infiltrate spreads directly into the periodontal ligament (filled arrow).

Waerhaug's concept

Waerhaug (1979) examined autopsy specimens (Fig. 16-4) similarly to Glickman, but in addition measured the distance between the microbial plaque and (1) the periphery of the associated inflammatory cell infiltrate and (2) the surface of the adjacent alveolar bone. He concluded from his measurements that angular bony defects and infrabony pockets occur equally, often at teeth which are not affected by trauma from occlusion. In other words, he refuted the hypothesis that trauma from occlusion plays a role in the spread of a gingival lesion into the zone of co-destruction.

The loss of connective attachment and bone around teeth is, according to Waerhaug, exclusively the result of inflammatory lesions associated with subgingival plaque. Waerhaug concluded that angular bony defects and infrabony pockets occur when the subgingival plaque of one tooth has reached a more apical level than the plaque on the neighboring tooth, and when the volume of the alveolar bone surrounding the roots is comparatively large. Waerhaug's observations support findings presented by Prichard (1965) and Manson (1976), which imply that the pattern of loss of supporting structures is the result of an interplay between the form and volume of the alveolar bone and the apical extension of the microbial plaque on the adjacent root surfaces.

Conclusion: It is obvious that examinations of autopsy material have a limited value when determining "cause–effect" relationships with respect to trauma

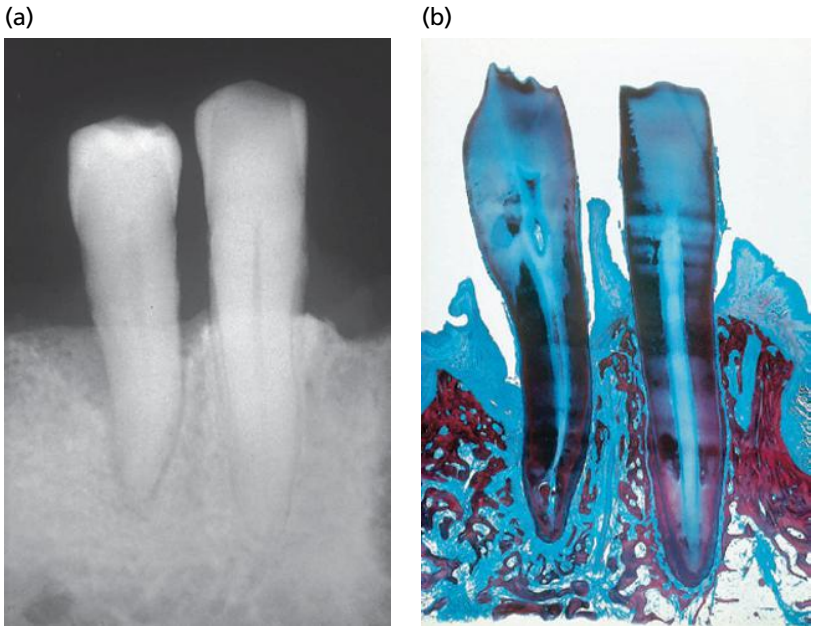

Fig. 16-3 (a) Radiograph of a mandibular premolar–canine region. Note the angular bony defect at the distal aspect of the premolar. (b) Histologic mesiodistal section of the specimen shown in (a). Note the infrabony pocket at the distal aspect of the premolar. (Source: Glickman & Smulow 1965. Reproduced from the American Academy of Periodontology.)

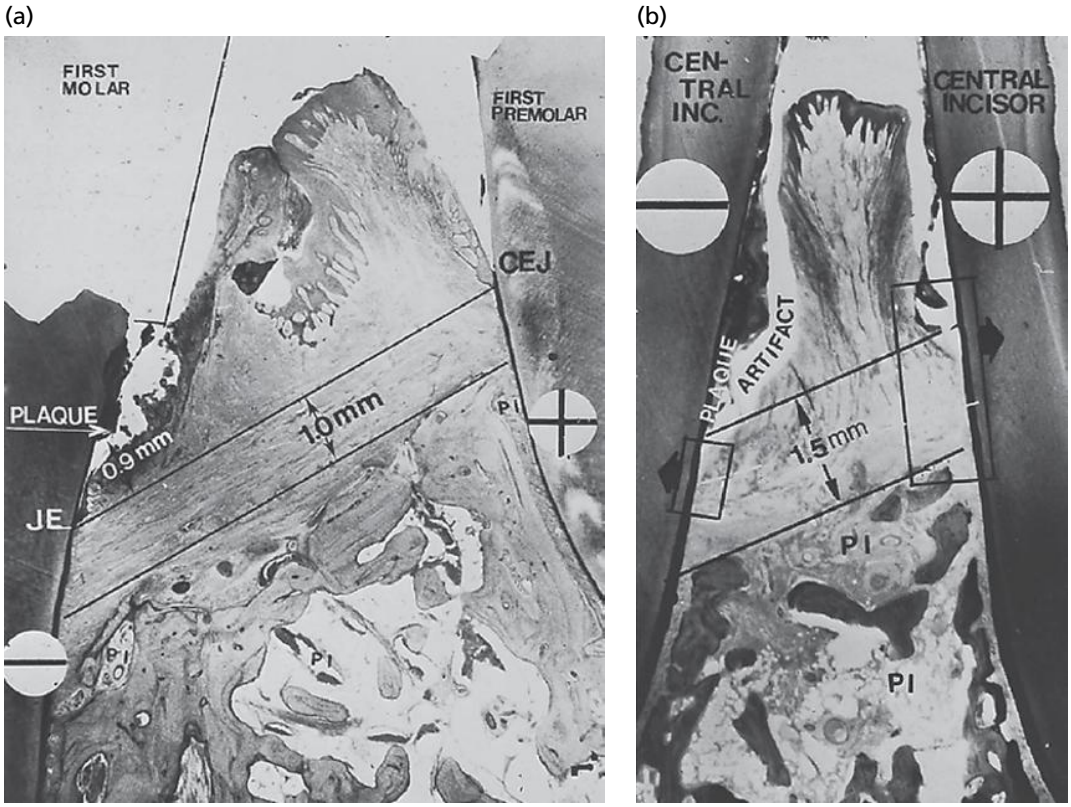

Fig. 16-4 (a, b) Microphotographs illustrating two interproximal areas with angular bony defects. "–" denotes a tooth not subjected and "+" denotes a tooth subjected to trauma from occlusion. In categories "–" and "+", the distance between the apical cells of the junctional epithelium (JE) and the supporting alveolar bone is about 1–1.5 mm, and the distance between the apical extension of plaque and the apical cells of the JE is about 1 mm. Since the apical cells of the JE and the subgingival plaque are located at different levels on the two adjacent teeth, the outline of the bone crest becomes oblique. A radiograph from such a site would disclose the presence of an angular bony defect at a non-traumatized ("–") tooth.

and progressive periodontitis. As a consequence, the conclusions drawn from this field of research have not been generally accepted. Some clinicians have tended to accept Glickman's conclusions that trauma from occlusion is an aggravating factor in periodontal disease (e.g. Macapanpan & Weinmann 1954; Posselt & Emslie 1959; Glickman & Smulow 1962, 1965), while others accept Waerhaug's concept that there is no relationship between occlusal trauma and the degree of periodontal tissue breakdown (e.g. Lovdahl *et al*. 1959; Belting & Gupta 1961; Baer *et al*. 1963; Waerhaug 1979).

Clinical trials

In addition to the presence of angular bony defects and infrabony pockets, *increased tooth mobility* is frequently listed as an important sign of occlusal trauma. For details regarding tooth mobility, see Chapter 52. Conflicting data have been reported regarding the periodontal condition of mobile teeth. In one clinical study by Rosling *et al*. (1976), patients with advanced periodontal disease associated with multiple angular bony defects and mobile teeth were exposed to antimicrobial therapy (i.e. subgingival scaling after flap elevation). Healing was evaluated by probing attachment level measurements and radiographic monitoring. The authors reported that "the infrabony pocket located at hypermobile teeth exhibited the same degree of healing as those adjacent to firm teeth". In another study, however, Fleszar *et al*. (1980) reported on the influence of tooth mobility on healing following periodontal therapy, including both antimicrobial therapy and occlusal adjustment. They concluded that "pockets of clinically mobile teeth do not respond as well to periodontal treatment" (including tooth debridement) "as do those of firm teeth exhibiting the same disease severity".

Pihlstrom *et al*. (1986) studied the association between trauma from occlusion and periodontitis by assessing a series of clinical and radiographic features at maxillary first molars: probing depth, probing attachment level, tooth mobility, wear facets, plaque and calculus, bone height, and widened periodontal space. The authors concluded from their examinations that teeth with increased mobility and widened periodontal ligament space had deeper pockets, more attachment loss, and less bone support than teeth without these symptoms.

In another clinical trial, Burgett *et al*. (1992) studied the effect of occlusal adjustment in the treatment of periodontitis. Fifty patients with periodontitis were examined at baseline and subsequently treated for their periodontal condition with root debridement ± flap surgery. Twenty-two of the 50 patients additionally received comprehensive occlusal adjustment. Re-examinations

performed 2 years later disclosed that probing attachment gain was on average about 0.5 mm greater in patients who received the combined treatment, that is debridement and occlusal adjustment, than in patients who did not receive occlusal adjustment.

Nunn and Harrel (2001) and Harrel and Nunn (2001) examined the relationship between occlusal discrepancies and periodontitis in two studies. Their sample included about 90 patients who had been referred for treatment of periodontal disease and who had at least two (≥1 year apart) complete periodontal records, including an analysis of their occlusion. The patients were examined with respect to probing pocket depth, tooth mobility, and furcation involvement (at multirooted teeth). In addition, occlusal contact relationships were studied, such as (1) discrepancies in centric relation and centric occlusion and (2) premature occlusal contacts in protrusive movements (lateral and frontal) of the mandible in working and non-working quadrants. A treatment plan, including both periodontal and occlusal measures, was subsequently designed for each patient. About one-third of the patients decided to abstain from treatment, about 20 accepted only a non-surgical approach to periodontal therapy (SRP), and about 50% accepted and received comprehensive treatment that included surgical pocket elimination (tooth debridement; SRP + surgery) as well as occlusal adjustment (if indicated). Some teeth in the SRP group received occlusal therapy, while other teeth with occlusal discrepancies were left untreated. It was observed that teeth with occlusal discrepancies had significantly deeper pocket depth values and higher mobility scores than teeth without occlusal "trauma", and also that teeth exposed to occlusal adjustment responded better (reduction in pocket depth) to SRP than teeth with remaining occlusal discrepancies.

The findings in some of the clinical studies referred to above lend some support to the concept that trauma from occlusion (and increased tooth mobility) may have a detrimental effect on the periodontium. Neiderud *et al*. (1992), however, in a Beagle dog study demonstrated that tissue alterations which occur at mobile teeth with clinically healthy gingivae (and normal height of the tissue attachment) may reduce the resistance offered by the periodontal tissues to probing. In other words, if the probing depth at two otherwise similar teeth – one non-mobile and one hypermobile – is recorded, the tip of the probe will penetrate 0.5 mm deeper at the mobile than at the non-mobile tooth. This finding must be taken into consideration when the above clinical data are interpreted.

Since neither analysis of autopsy material nor data from clinical trials can be used to properly determine the role trauma from occlusion may play in periodontal pathology, it was considered necessary to describe also the contributions from animal research in this particular field.

Animal experiments

Orthodontic-type trauma

In early experiments, the reaction of the periodontium was studied following the application of forces applied to teeth in one direction only. Biopsy specimens, including tooth and periodontium, were harvested after varying intervals and prepared for histologic examinations. Analysis of the sections (Häupl & Psansky 1938; Reitan 1951; Mühlemann & Herzog 1961; Ewen & Stahl 1962; Waerhaug & Hansen 1966; Karring *et al*. 1982) revealed that when a tooth is exposed to unilateral forces of a magnitude, frequency or duration that its periodontal tissues are unable to withstand and distribute while maintaining the stability of the tooth, certain well-defined reactions develop in the periodontal ligament, eventually resulting in an adaptation of the periodontal structures to the altered functional demand. If the crown of a tooth is affected by such horizontally directed forces, the tooth tends to tilt (tip) in the direction of the force (Fig. 16-5). The forces result in the development of *pressure* and *tension zones* within the marginal and apical parts of the periodontium. The tissue reactions which develop in the *pressure zone* are characteristic of a mild inflammation (increased number of vessels, increased vascular permeability, vascular thrombosis, and disorganization of cells and collagen fiber bundles). If the magnitude of forces is within certain limits, the vitality of the periodontal ligament cells is maintained and bone-resorbing osteoclasts soon appear on

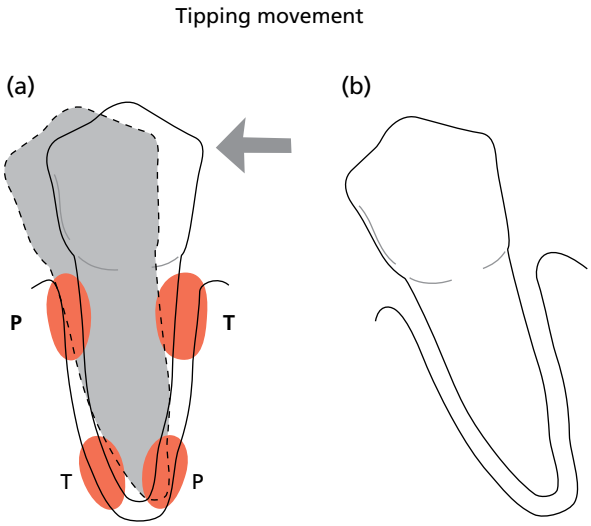

Fig. 16-5 (a) If the crown of a tooth is exposed to excessive, horizontally directed forces (arrow), pressure (P) and tension (T) zones will develop within the marginal and apical parts of the periodontium. The supra-alveolar connective tissue remains unaffected by force application. Within the pressure and tension zones, tissue alterations take place and eventually allow the tooth to tilt in the direction of the force. (b) When the tooth is no longer subjected to the trauma, complete regeneration of the periodontal tissues takes place. There is no apical down-growth of the dentogingival epithelium.

the bone surface of the alveolus in the *pressure zone*. A process of *direct bone resorption* is initiated.

If the force applied is of higher magnitude, the periodontal ligament tissue in the *pressure zone* may become necrotic and undergo *hyalinization*. "Direct bone resorption" therefore cannot occur. Instead, osteoclasts appear in marrow spaces within the adjacent bone tissue where the stress concentration is lower and a process of undermining or "*indirect bone resorption*" is initiated. Through this reaction the surrounding bone is resorbed until there is a breakthrough to the hyalinized tissue within the *pressure zone*. This breakthrough results in a reduction of the stress in this area, and cells from the neighboring bone or adjacent areas of the periodontal ligament can proliferate into the *pressure zone* and replace the previously hyalinized tissue, thereby re-establishing the prerequisites for "direct bone resorption". Irrespective of whether the bone resorption is of a direct or an indirect nature, the tooth moves (tilts) further in the direction of the force.

Concomitant with the tissue alterations in the *pressure zone*, apposition of bone occurs in the *tension zone* in order to maintain the normal width of the periodontal ligament in this area. Because of the tissue reactions in the *pressure* and *tension* zones, the tooth becomes hypermobile. When the tooth has moved (tilted) to a position where the effect of the forces is nullified, healing of the periodontal tissues takes place in both the *pressure* and the *tension zones*, and the tooth becomes stable in its new position. In orthodontic tilting (tipping) movements, neither gingival inflammation nor loss of connective tissue attachment will occur at teeth with a healthy periodontium.

These tissue reactions do not differ fundamentally from those which occur as a consequence of *bodily tooth movement* in orthodontic therapy (Reitan 1951). The main difference is that the *pressure* and *tension zones*, depending on the direction of the force, are more extended in an apicocoronal direction along the root surface than in conjunction with the tipping movement (Fig. 16-6). The supra-alveolar connective tissue is not affected by the force, either in conjunction with tipping or in conjunction with bodily movements of the tooth. Unilateral forces exerted on the crowns of teeth, therefore, will not induce inflammatory reactions in the gingiva or cause loss of connective tissue attachment.

Studies have demonstrated, however, that orthodontic forces producing bodily (or tipping) movement of teeth may result in gingival recession and loss of connective tissue attachment (Steiner *et al*. 1981; Wennström *et al*. 1987). This breakdown of the attachment apparatus occurred at sites with gingivitis when, in addition, the tooth was moved through the envelope of the alveolar process. At such sites bone dehiscence became established and, if the covering soft tissue was thin (in the direction of the movement of the tooth), recession (attachment loss) occurred.

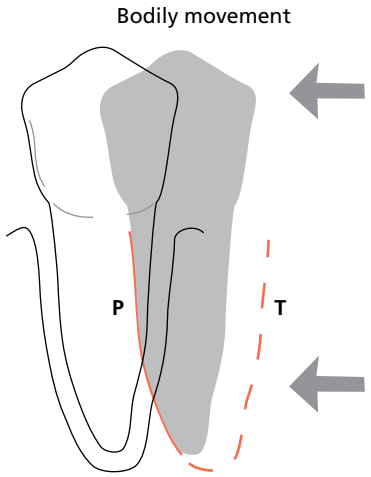

Fig. 16-6 When a tooth is exposed to forces which produce "bodily tooth movement", for example in orthodontic therapy, the pressure (P) and tension (T) zones, depending on the direction of the force, are extended over the entire tooth surface. The supra-alveolar connective tissue is not affected in conjunction either with tipping or with bodily movements of teeth. Forces of this kind, therefore, will not induce inflammatory reactions in the gingiva. No apical down-growth of the dentogingival epithelium occurs.

Criticism has been directed at experiments in which only unilateral trauma is exerted on teeth (Wentz *et al*. 1958). It has been suggested that in humans, unlike in the animal experiments described above, the occlusal forces act alternately in one and then in the opposite direction. Such forces have been termed *jiggling forces*.

Jiggling-type trauma

Healthy periodontium with normal height

Experiments have been reported in which traumatic forces were exerted on the crowns of the teeth, alternately in the buccal/lingual or mesial/distal directions, and the teeth were not allowed to move away from the force (e.g. Wentz *et al*. 1958; Glickman & Smulow 1968; Svanberg & Lindhe 1973; Meitner 1975; Ericsson & Lindhe 1982). In conjunction with "*jiggling-type trauma*" no clear-cut *pressure* and *tension zones* can be identified, but rather there is a combination of pressure and tension on both sides of the jiggled tooth (Fig. 16-7).

The tissue reactions in the periodontal ligament provoked by the combined *jiggling* forces were found to be rather similar to those reported to occur in the pressure zone at orthodontically moved teeth, but with one important difference. The periodontal ligament space at jiggled teeth gradually increased in width on both sides of the tooth. During the phase when the periodontal ligament gradually increased in width, (1) inflammatory changes were present in the ligament tissue, (2) active bone resorption

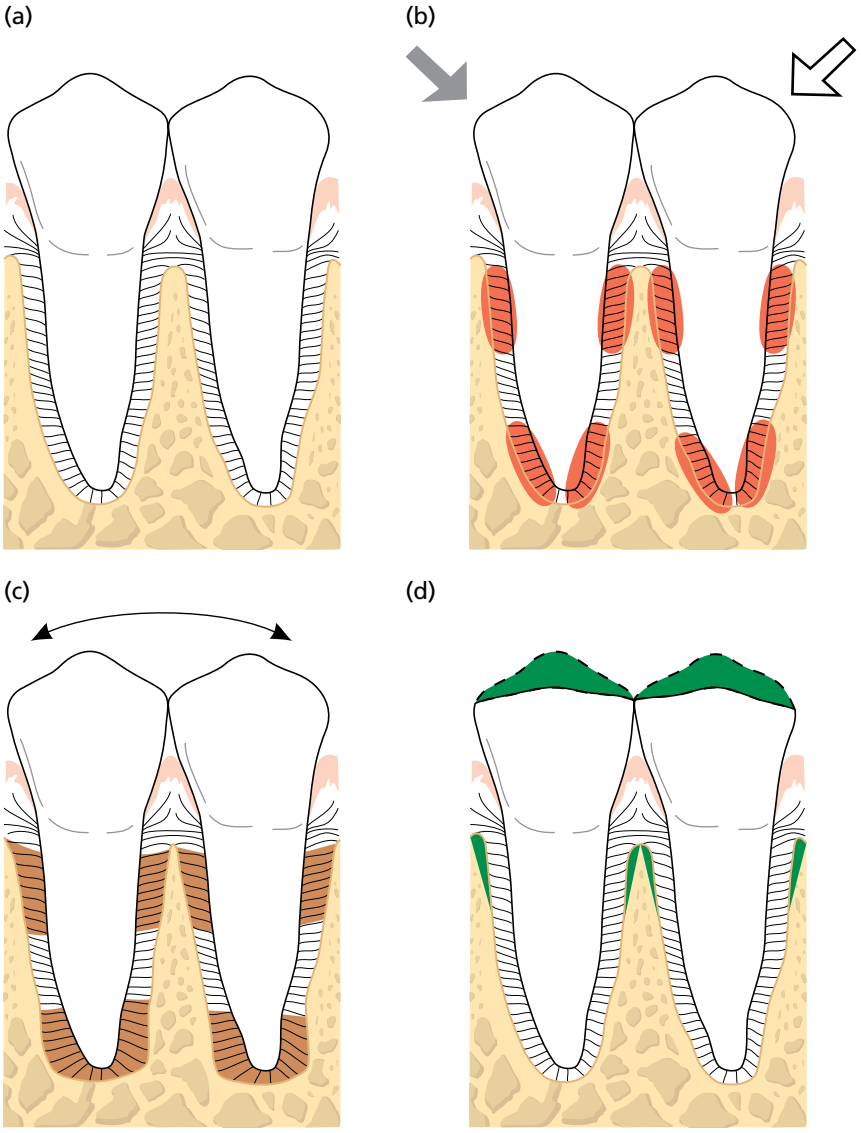

Fig. 16-7 Two mandibular premolars with normal periodontal tissues (a) are exposed to jiggling forces (b), as illustrated by the two arrows. The combined tension and pressure zones (encircled areas) are characterized by signs of acute inflammation, including collagen resorption, bone resorption, and cementum resorption. As a result of bone resorption, the periodontal ligament space gradually increases in size on both sides of the teeth as well as in the periapical region. (c) When the effect of the force applied has been compensated for by the increased width of the periodontal ligament space, the ligament tissue shows no signs of inflammation. The supra-alveolar connective tissue is not affected by the jiggling forces and there is no apical down-growth of the dentogingival epithelium. (d) After occlusal adjustment the width of the periodontal ligament becomes normalized and the teeth are stabilized.

occurred, and (3) the tooth displayed signs of gradually increasing (*progressive*) mobility. When the effect of the forces applied had been compensated for by the increased width of the periodontal ligament space, the ligament tissue showed no signs of increased vascularity or exudation. The tooth was hypermobile but the mobility was no longer *progressive* in character. Distinction should thus be made between *progressive* and *increased* tooth mobility.

In *jiggling-type trauma* experiments performed in animals with a normal periodontium, the supra-alveolar connective tissue was not influenced by the occlusal forces. This means that a gingiva which was healthy at the start of the experiment remained healthy. It was also observed that an overt gingival lesion was not aggravated by the jiggling forces.

Healthy periodontium with reduced height

Progressive periodontal disease is characterized by gingival inflammation and a gradually developing loss of connective tissue attachment and alveolar bone. Treatment of periodontal disease, that is removal of plaque and calculus and elimination of pathologically deepened pockets, will result in the re-establishment of a healthy periodontium but with reduced height. The question is whether a healthy periodontium with reduced height has a capacity similar to that of the normal periodontium to adapt

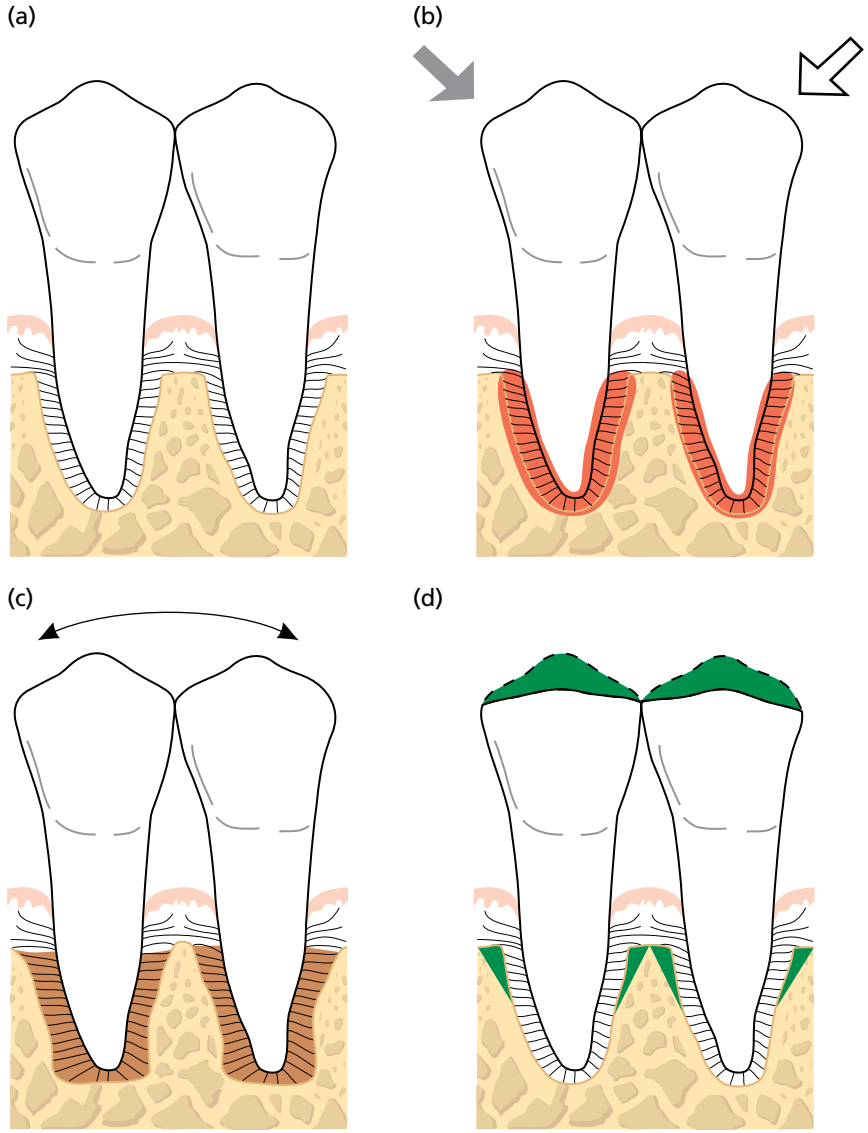

Fig. 16-8 (a) Two mandibular premolars are surrounded by a healthy periodontium with reduced height. (b) If such premolars are subjected to traumatizing forces of the jiggling type, a series of alterations occurs in the periodontal ligament tissue. (c) These alterations result in a widened periodontal ligament space and increased tooth mobility, but do not lead to further loss of connective tissue attachment. (d) After occlusal adjustment, the width of the periodontal ligament is normalized and the teeth are stabilized.

to traumatizing occlusal forces (secondary occlusal trauma).

This problem has also been examined in animal experiments (Ericsson & Lindhe 1977). Destructive periodontal disease was initiated in premolars of dogs by allowing the animals to accumulate plaque and calculus. When around 50% of the periodontal tissue support had been lost, the involved teeth were exposed to debridement and surgical pocket elimination. Following healing, these teeth had a reduced but healthy periodontium (Fig. 16-8a). During the subsequent months of continued plaque control, certain premolars were exposed to traumatizing jiggling forces (Fig. 16-8b). The periodontal tissues in the combined *pressure* and *tension zones* reacted to the application of forces with inflammation as well as by bone resorption. In the initial phase, the traumatized teeth displayed signs of *progressive* tooth mobility and a progressive increase of the size of the periodontal ligament. After several weeks of jiggling, there was no further increase in the mobility (Fig. 16-8c). The active bone resorption had ceased and the markedly widened periodontal ligament tissue had regained its normal composition. The teeth were hypermobile at this stage, but surrounded by a periodontal ligament which had adapted to the altered functional demands.

During the entire experimental period the supraalveolar connective tissue remained unaffected by the jiggling forces. There was no further loss of connective tissue attachment and no further downgrowth of dentogingival epithelium. The results from this study clearly revealed that, within certain limits, a healthy periodontium with reduced height has a capacity similar to that of a periodontium with

normal height to adapt to altered functional demands. Removal of the jiggling forces ("occlusal adjustment") will in this situation result in a normalization of the width of the periodontal ligament (Fig. 16-8d).

Plaque-associated periodontal disease

Experiments carried out on humans and animals have demonstrated that *trauma from occlusion* cannot induce pathologic alterations in the supra-alveolar connective tissue, in other words cannot produce inflammatory lesions in a normal gingiva or aggravate a gingival lesion and cannot induce loss of connective tissue attachment. The question remains whether or not abnormal occlusal forces can influence the spread of the plaque-associated lesion and enhance the rate of tissue destruction in periodontal disease. This has been studied in animal experiments (Lindhe & Svanberg 1974; Meitner 1975; Nyman *et al*. 1978; Ericsson & Lindhe 1982; Polson & Zander 1983) in which progressive and destructive periodontal disease was first initiated in dogs or monkeys by allowing the animals to accumulate plaque and calculus. Some of the premolars that were involved in a progressive periodontal disease process (periodontally involved) were also subjected to trauma from occlusion.

"Traumatizing" jiggling forces (Lindhe & Svanberg 1974) were exerted on periodontally involved premolars and were found to induce certain tissue reactions in the combined *pressure/tension zones*. Within a few days of the onset of the jiggling forces, the periodontal ligament tissue in these zones displayed signs of inflammation. On the adjacent bone surfaces a large number of osteoclasts were present. Since the teeth could not orthodontically move away from the jiggling forces, the periodontal ligament on both sides of the tooth gradually increased in width, the teeth became hypermobile (*progressive* tooth mobility), and angular bony defects could be detected on the radiographs. The effect of the forces were eventually nullified by the increased width of the periodontal ligament.

If the forces applied were of a magnitude to which the periodontal structures could adapt, the *progressive* increase of the tooth mobility terminated within a few weeks. The active bone resorption ceased, but the angular bone destruction persisted as well as the increased tooth mobility. The periodontal ligament had an increased width, but a normal tissue composition. Biopsy specimens including the periodontally involved teeth revealed that this process of adaptation had occurred with no further attachment loss (Fig. 16-9) (Meitner 1975). This means that occlusal forces which allow adaptive alterations to occur in

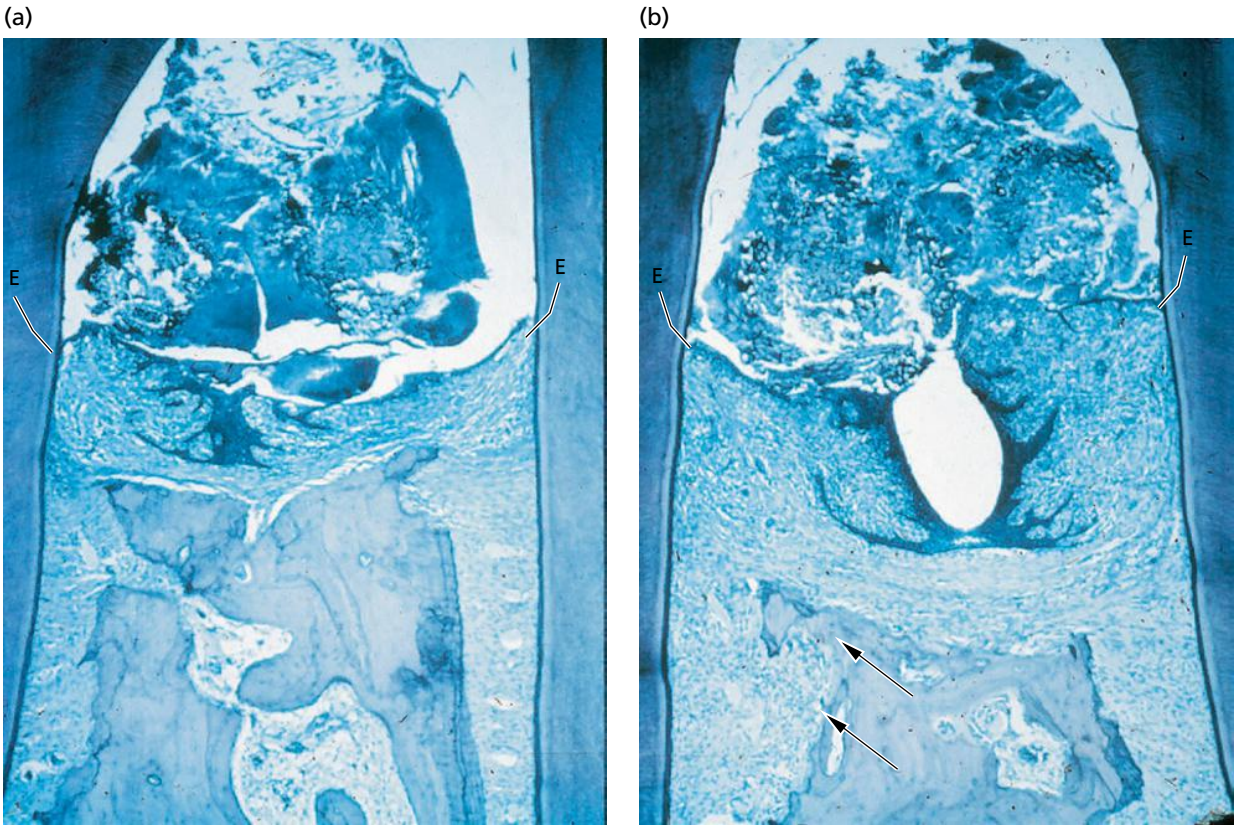

Fig. 16-9 (a) A composite photomicrograph illustrating the interdental space between two pairs of teeth. The teeth have been subjected to experimental, ligature-induced periodontitis and in (b) also to repetitive mechanical injury. In (b), there is considerable loss of alveolar bone and an angular widening of the periodontal ligament space (arrows). However, the apical down-growth of the dentogingival epithelium in the two areas in (a) and (b) is similar. E indicates the apical level of the dentogingival epithelium. (Courtesy of S.W. Meitner.)

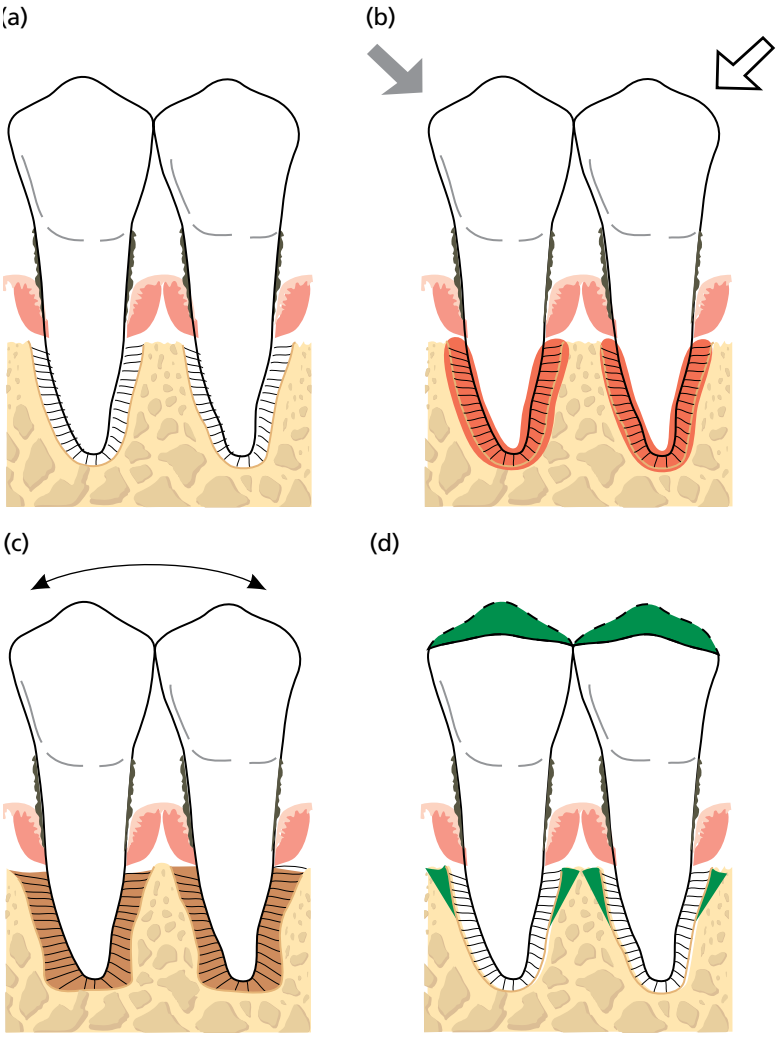

Fig. 16-10 (a) Two mandibular premolars with supra- and sub-gingival plaque, advanced bone loss, and periodontal pockets of a suprabony character. Note the connective tissue infiltrate (shadowed areas) and the uninflamed connective tissue between the alveolar bone and the apical portion of the infiltrate. (b) If these teeth are subjected to traumatizing forces of the jiggling type, pathologic and adaptive alterations occur within the periodontal ligament space. (c) These tissue alterations, which include bone resorption, result in a widened periodontal ligament space and increased tooth mobility, but no further loss of connective tissue attachment. (d) Occlusal adjustment results in a reduction of the width of the periodontal ligament and in less mobile teeth.

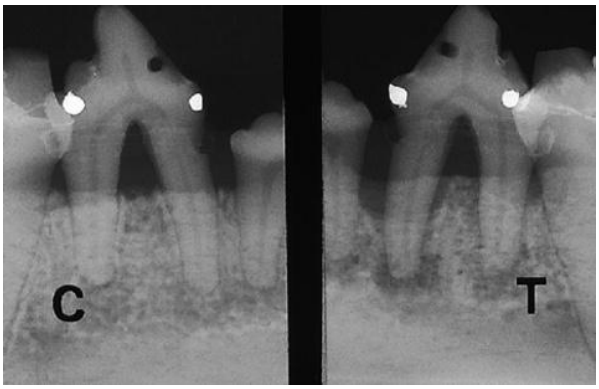

Fig. 16-11 Radiographic appearance of one test tooth (T) and one control tooth (C) at the termination of an experiment in which periodontitis was induced by ligature placement and plaque accumulation, and in which trauma of the jiggling type was induced. Note the angular bone loss particularly around the mesial root of the mandibular premolar (T) and the absence of such a defect at the mandibular premolar (C). (Source: Lindhe & Svanberg 1974. Reproduced with permission from John Wiley & Sons.)

the *pressure/tension* zones of the periodontal ligament will not aggravate a plaque-associated periodontal disease (Fig. 16-10).

If, however, the magnitude and direction of the jiggling forces were such that, during the course of the study, the tissues in the pressure/tension zones could not adapt, the injury in the *zones of co-destruction* had a more permanent character. For several months the periodontal ligament in the pressure/tension zones displayed signs of inflammation and osteoclastic bone resorption. This resulted in a gradual widening of the periodontal ligament (Fig. 16-11). As a consequence, the resulting angular bone destruction was continuous and the mobility of the teeth remained progressive. The plaque-associated lesion in the "zone of irritation" and the inflammatory lesion in the "zone of co-destruction" merged. In this dog model experiment, additional portions of the connective tissue attachment were lost and periodontal tissue destruction became more severe (Figs. 16-12, 16-13) (Lindhe & Svanberg 1974).

On the other hand, findings from more short-term experiments using a monkey model (Polson & Zander 1983), failed to support the observations of Lindhe and Svanberg (1974) and Ericsson and Lindhe (1982). Polson and Zander (1983) reported that trauma superimposed on periodontal lesions associated with angular bony defects caused increased loss of alveolar bone, but failed to produce additional loss of connective tissue attachment.

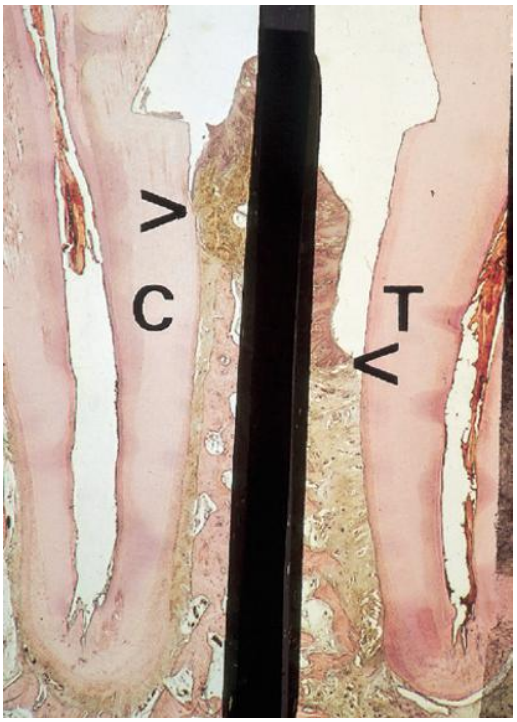

Fig. 16-12 Microphotographs from one control (C) and one test (T) tooth after 240 days of experimental periodontal tissue breakdown and 180 days of trauma from occlusion of the jiggling type (T). The arrowheads denote the apical position of the dentogingival epithelium. The attachment loss is more pronounced in T than in C. (Source: Lindhe & Svanberg 1974. Reproduced with permission from John Wiley & Sons.)

Conclusion

Experiments carried out in humans as well as in animals have produced convincing evidence that neither unilateral forces nor jiggling forces, applied to teeth with a healthy periodontium, result in pocket formation or in loss of connective tissue attachment. *Trauma from occlusion cannot induce periodontal tissue breakdown*. Trauma from occlusion does, however, result in resorption of alveolar bone, leading to an increased tooth mobility which can be of a transient or permanent character. This bone resorption with resulting increased tooth mobility should be regarded as a physiologic adaptation of the periodontal ligament and surrounding alveolar bone to the traumatizing forces, that is to altered functional demands.

In teeth involved in progressive, plaque-associated periodontal disease, trauma from occlusion may, under certain conditions, enhance the rate of progression of the disease, in other words act as a co-factor in the destructive process. It is important to realize that in such cases, treatment directed towards the trauma alone, that is occlusal adjustment or splinting, may reduce the mobility of the traumatized teeth and result in some regrowth of bone, but it will not influence the features of the plaque-associated lesion.

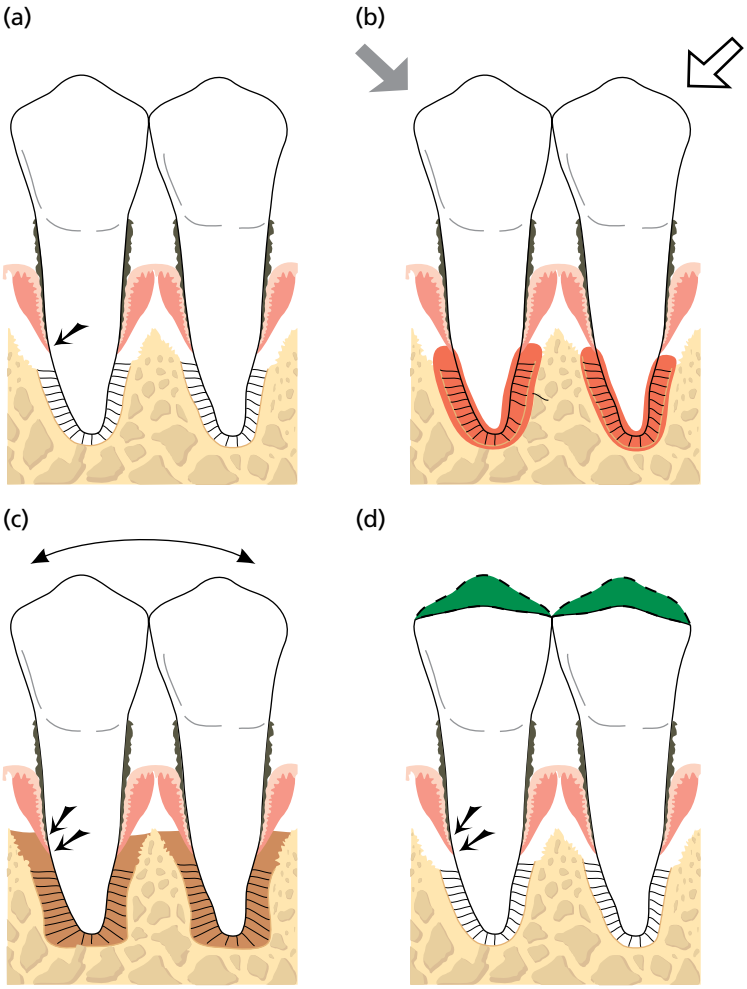

Fig. 16-13 (a) A tooth where subgingival plaque has mediated the development of an infiltrated soft tissue (shadowed area) and an infrabony pocket. (b) When trauma from occlusion of the jiggling type is inflicted (arrows) on the crown of this tooth, the associated pathologic alterations occur within a zone of the periodontium which is also occupied by the inflammatory cell infiltrate (shadowed area). In this situation, the increasing tooth mobility may also be associated with an enhanced loss of connective tissue attachment and further downgrowth of dentogingival epithelium; compare arrows in (c) and (d). Occlusal adjustment will result in a narrowing of the periodontal ligament, less tooth mobility, but no improvement of the attachment level (d). (Source: Lindhe & Ericsson 1982. Reproduced from the American Academy of Periodontology.)

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Chapter 17

Trauma from Occlusion: Peri-implant Tissues

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Introduction

Endosseous osseointegrated oral implants have been suggested to serve as anchorage for orthodontic appliances where the existing dentition does not provide sufficient anchorage (see Chapter 59). Both clinical (Turley *et al*. 1988; Ödman *et al*. 1988; Haanaes *et al*. 1991; Ödman *et al*. 1994) and experimental (Wehrbein & Diedrich 1993; Wehrbein *et al*. 1996) studies have demonstrated that osseointegrated implants were able to provide sufficient and stable anchorage for tooth movement during the time period of orthodontic therapy, thereby eliminating the need to observe Newton's third law according to which an applied force can be divided into an *action* component and an equal and opposite *reaction* moment.

In long-term clinical studies of various two-stage submerged implant systems, however, implant losses have been attributed to *overloading* or *excessive loading*. In patients with edentulous (Adell *et al*. 1981; Lindquist *et al*. 1988) and partially edentulous jaws (Jemt *et al*. 1989; Quirynen *et al*. 1992), most of the implants losses were considered to be the result of excessive occlusal loading. While it has been shown that early loading of oral implants may impede successful osseointegration (Sagara *et al*. 1993), the effect of excessive occlusal functional forces following successful osseointegration has not been documented so far. However, studies by Isidor (1996, 1997) have demonstrated that loading of implants through the creation of a massive supraocclusion, leading to excessive – and most likely non-physiologic – laterally directed occlusal forces, established a high risk for the loss of osseointegration. Nevertheless, in one of four experimental animals, even such excessive loading forces were unable to jeopardize the interfacial union of the alveolar bone with the implant surface.

The forces applied in the studies mentioned were characterized as being very high and of short duration. However, they could not be quantified. None of the experimental studies analyzed the direct relationship between changes in the stress and strain applied to oral implants during functional loading and the tissue reactions of the surrounding alveolar bone. For the evaluation of the etiology and pathogenesis of implant losses due to overload, such information would appear to be of crucial importance.

Orthodontic loading and alveolar bone

In order to evaluate the tissue reactions adjacent to oral implants following loading with well-defined forces and to relate these to the strain values applied on the trabecular surface of the alveolar bone, an animal study was performed using finite element analysis (FEA) to determine the cellular activity (Melsen & Lang 2001). In six adult monkeys, the lower first

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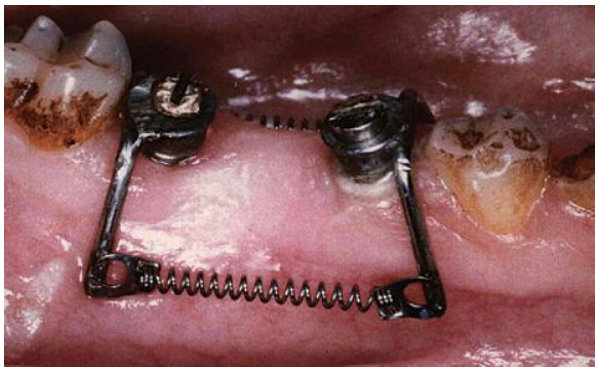

Fig. 17-1 Clinical image demonstrating the nickel–titanium coil springs applied for a continuous loading through the center of resistance.

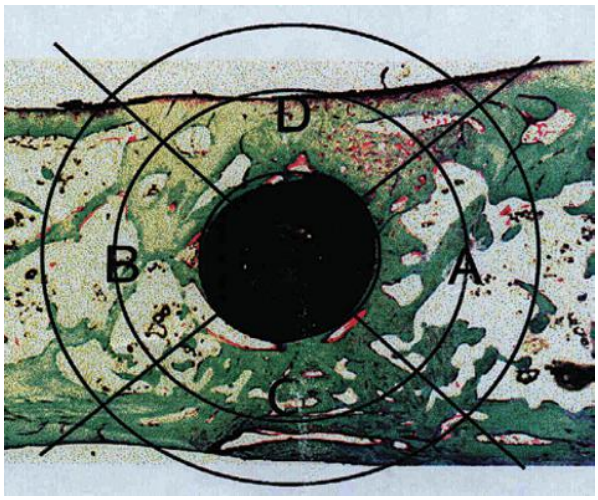

Fig. 17-2 Horizontal section of the implant with the projected grid used for the histomorphometric evaluation of different regions surrounding the implant. Region A is submitted to compression, region B to tension, and regions C and D to shearing forces.

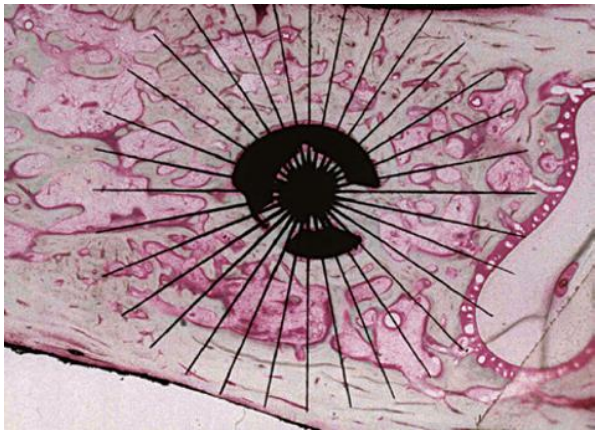

Fig. 17-3 Horizontal section of the implant onto which a grid with 32 radial lines was projected. The evaluation of the osseointegration included the determination of the percentage of direct bone–implant contact (×160).

and the second premolars as well as the second molars were removed. After 6 months, two specially designed screw implants were inserted in the region of the lower left second premolar and second molar. After a further 3 months, a square rod with three notches at different levels was inserted and tightened to the top of the implants. The notches served as a reference for the measurements of the implant displacement. A flat disk was placed between the implant and the rod. To this disk two extensions were welded buccally and lingually in a way that allowed a coil spring to be placed as close as possible to the estimated level of the center of resistance (Fig. 17-1). Immediately before the buccal and lingual springs were inserted, the extensions were placed on the occlusal surface of the implants. Impressions of each segment were taken. Subsequently, two measurements were performed with an electronic strain gauge-based measuring device. For anchorage of the device, a cast splint was fitted to the anterior segment of the dentition and each of the implant screws. One measurement was taken between the notches close to the implant connection, and another between the notches close to the top of the square rod extensions. These were repeated after 11 weeks, in other words at the termination of the orthodontic loading period. The direction and magnitude of the displacement of the implant as a result of loading could thus be calculated in the sagittal plane.

Following the baseline recordings, springs extending from the anterior to the posterior implant were attached to the power arms buccally and lingually (Fig. 17-1). Total load applied to each implant varied from 100 to 300 cN. One monkey served as a control with the implants in this animal not subjected to any loading.

At the end of the experiment, the monkeys were sacrificed. Subsequently, parallel horizontal tissue sections from the coronal to the apical end of the implants were cut and stained with fast green. A grid consisting of three concentric circular lines was projected onto the sections, with each of these lines intersected by four equidistant radial lines starting at the center of the grid and coinciding with the central axis of the implants. The four radial lines divided the circle into eight areas, two in the direction of the force (A: compression zone), two in the opposite direction (B: tension zone), and four lateral to the implants (C and D: shear zone) (Fig. 17-2).

At a magnification of ×160, the extent of resorption lacunae and the extent of the trabecular bone surfaces covered by osteoid as a fraction of the total were assessed. Also, using morphometry, bone density was evaluated within each quadrant. Furthermore, to measure the amount of osseointegration, the proportion of direct bone–implant contact was calculated by projecting a grid consisting of 32 radial lines extending from the center of the implants onto the section to be analyzed (Fig. 17-3).

None of the implants had lost osseointegration after 11 weeks of orthodontic loading, but loading significantly influenced the turnover of the alveolar bone in the vicinity of the implants. Bone apposition was most frequently found when the calculated strain varied between 3400 and 6600 μstrain. On the

other hand, when the strain exceeded 6700 μstrain, the remodeling of the bone resulted in a net loss of bone.

This study clearly supports the theory that apposition of bone around an oral implant is the biologic response to a mechanical stress below a certain threshold, whereas loss of marginal bone or complete loss of osseointegration may be the result of mechanical stress beyond this threshold. Hence, occlusal forces would have to substantially exceed the physiologic range before occlusal contacts could jeopardize the tissue integrity of an implant.

Several other studies of applied orthodontic forces have confirmed that the apposition or increase in bone density surrounding an oral implant, rather than loss of bone (Roberts *et al*. 1984; Wehrbein & Diedrich 1993; Asikainen *et al*. 1997; Akin-Nergiz *et al*. 1998).

Bone reactions to functional loading

A study addressed the reaction of peri-implant bone after longstanding functional loading compared to non-loaded controls (Berglundh *et al*. 2005). After extraction of all mandibular premolars, four AstraTech® implants were placed in one side of the mandible, and four Brånemark System® fixtures were installed in the contralateral side. Three months after abutment connection, fixed dental prostheses (FDPs) were fabricated in gold and cemented onto the maxillary canines and premolars (Fig. 17-4). FDPs were also installed onto three of the four mandibular implants in both sides. The fourth implant remained unloaded and served as a control (Fig. 17-5). Radiographs were obtained from each site following implant installation, abutment connection, and FDP placement. All radiographs were repeated after 10 months of functional loading. At this time, biopsies were obtained and analyzed histologically.

Radiographic analysis revealed that the largest amount of bone loss occurred following implant installation and abutment connection. This bone loss was more pronounced at the Brånemark® than at the AstraTech® implants. However, as a result of functional loading, bone loss was small and did not differ significantly from the unloaded control sites (Fig. 17-6).

Histologic analysis showed that implants subjected to 10 months of functional loading had more direct bone–implant contact than their unloaded counterparts. This was observed for both implant systems (Fig. 17-7).

Based on the radiographic and histologic results, this study demonstrated that *functional loading of implants may enhance osseointegration* (direct bone–implant contact) rather than induce marginal bone loss and hence, any bone loss should not be attributed to loading of implants. Whenever marginal bone loss is observed around implants in function, the most likely etiologic factor is bacterial in nature (see Chapter 26).

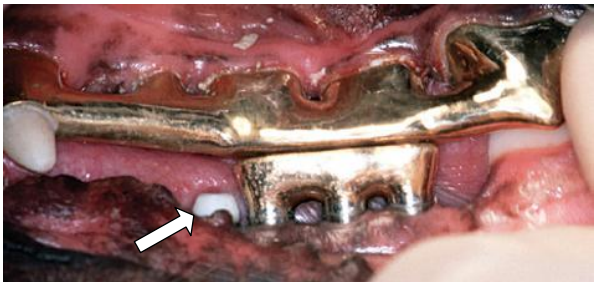

Fig. 17-4 Clinical image of the fixed dental prosthesis (FDP) supported by maxillary canines and premolars. The FDP is installed on implants in the mandible to provide masticatory function. The non-loaded control implant is mesial to the FDP (arrow). (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

Excessive occlusal load on implants

The effect of *excessive occlusal load* following placement of titanium implants in the presence of healthy peri-implant mucosal tissues was evaluated in an experimental dog study (Heitz-Mayfield *et al*. 2004). In six Labrador dogs, two titanium plasma-sprayed (TPS) implants and two sandblasted, large grit, acid-etched (SLA) implants were placed on each side of the mandible (Fig.17-8a). A total of 45 implants were evaluated. Following 6 months of healing (Fig. 17-8b), gold crowns were placed on implants on the test side of the mandible. The crowns were in supraocclusal contact with the opposing teeth in order to create an

(a) (b)

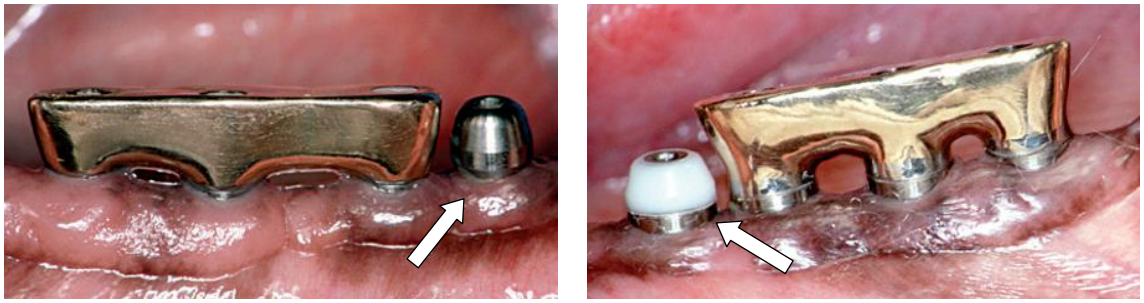

Fig. 17-5 Fixed dental prostheses fabricated of gold and installed on implants for functional loading. Unloaded implant as control (arrows). (a) AstraTech® implants and (b) Brånemark System®. (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

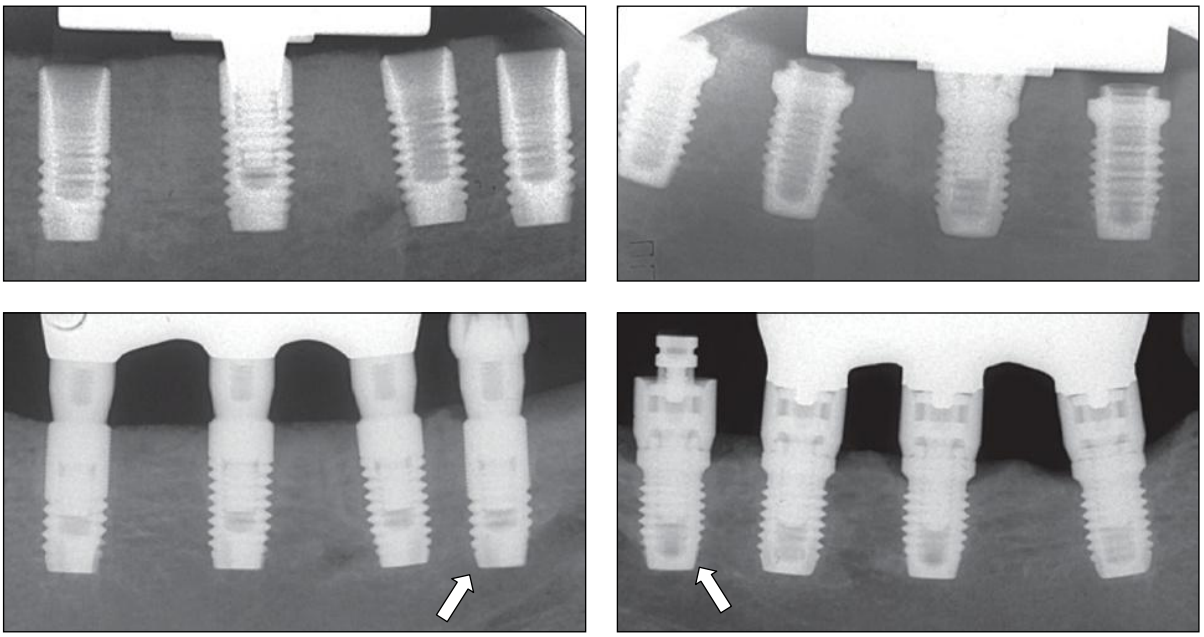

Fig. 17-6 Radiographs obtained for AstraTech® (left side) and Brånemark® (right side) implants immediately after implant installation (top row) and following 10 months of functional loading (bottom row). Unloaded control implants are indicated with arrows.

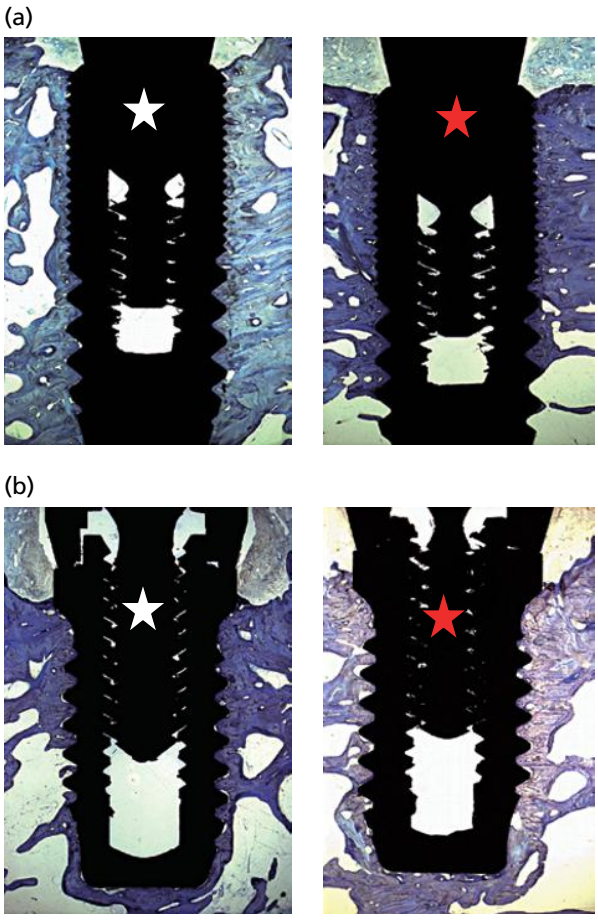

Fig. 17-7 (a) Non-loaded control AstraTech® implant after 10 months (white star) and functionally loaded AstraTech® implant (red star) after 10 months. (b) Non-loaded control Brånemark® implant after 10 months (white star) and functionally loaded Brånemark® implant (red star) after 10 months. (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

excessive occlusal load (Fig. 17-8c). Implants on the control side were not loaded. Plaque control was performed throughout the experimental period. Clinical measurements and standardized radiographs (Fig. 17-8d) were obtained at baseline and 1, 3, and 8 months after loading. At 8 months, all implants were osseointegrated, the dogs were sacrificed, and histologic analyses were performed.

The mean probing depth was 2.5 ± 0.3 and 2.6 ± 0.3 mm at the unloaded and loaded implants, respectively. Radiographically, the mean distance from the implant shoulder to the marginal bone level was 3.6 ± 0.4 mm in the control group and 3.7 ± 0.2 mm in the test group. There were no statistically significant changes in any of the parameters from baseline to 8 months in the loaded and unloaded implants.

Histologic evaluation (Fig. 17-9) showed a mean mineralized bone–implant contact of 73% in the control implants and 74% in the test implants, with no statistically significant difference between test and control implants.

Table 17-1 shows the level of osseointegration in relation to the total length of the implant after 8 months of excessive loading or non-loading. These values were generally slightly below those of the alveolar bone height (Table 17-2) for all sites and surfaces in both test and control implants. The differences varied between 1.1% and 3.7% and were not statistically significant.

Likewise, there were no statistically significant differences between the excessively loaded and the unloaded implants in terms of peri-implant bone density either at the implant–bone interface or at 1 mm from the implant surface (Fig. 17-9) after 8 months.

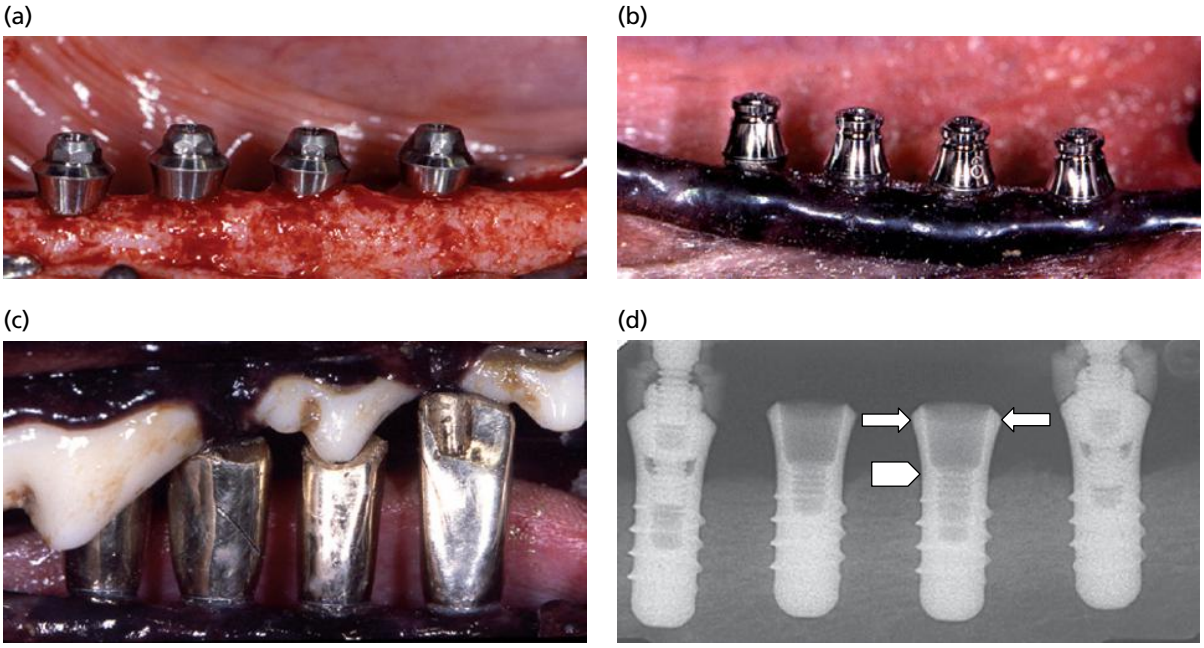

Fig. 17-8 (a) Clinical view of four ITI® implants at the time of placement in one side of the mandible. (b) Clinical view of the ITI® implants after 6 months of non-submerged healing. (c) Clinical view of the test side of the mandible in one dog. Note the four single gold crowns in supraocclusal contact with the opposing teeth. (d) Standardized radiograph showing the level of the implant shoulder (arrows), and the first bone–implant contact visible in the radiograph (arrowhead) at the mesial and distal surfaces of the implant.

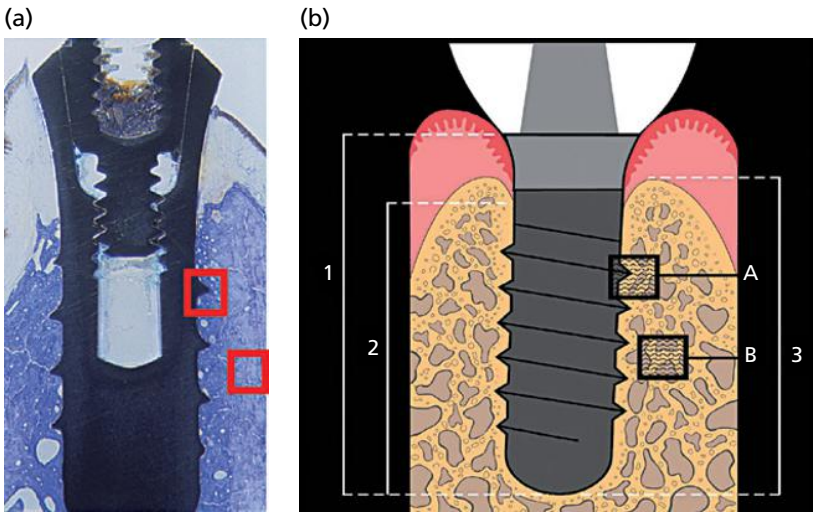

Fig. 17-9 Histologic and schematic representation of the histomorphometric measurements. 1, Implant length = distance from the base of the implant to the implant shoulder; 2, distance from the base of the implant to the most coronal point of bone–implant contact; 3, distance from the base of the implant to the alveolar bone crest. A, Percentage of mineralized bone density adjacent to the implant surface and B, 1 mm distant from the implant surface. Red frames in the histologic micrographs correspond to zones A and B in the schematic representation.

Table 17-1 Buccal and lingual percentages of the level of osseointegration (bone–implant contact) in relation to the total length of the implant for control and test implants with a titanium plasma-sprayed (TPS) or sandblasted, large grit, acid-etched (SLA) surface after 8 months.

	Buccal osseointegration		Lingual osseointegration	
	TPS	SLA	TPS	SLA
Number	12	11	12	11
Control (%)	57.9	60.4	67.5	66.7
Number	10	12	10	12
Test (%)	62.1	59.2	68	68

Table 17-2 Buccal and lingual percentages of alveolar bone height in relation to the total length of the implant for control and test implants with a titanium plasma-sprayed (TPS) or sandblasted, large grit, acid-etched (SLA) surface after 8 months.

	Buccal osseointegration		Lingual osseointegration	
	TPS	SLA	TPS	SLA
Number	12	11	12	11
Control (%)	61.1	63.8	69.5	68.7
Number	10	12	10	12
Test (%)	64.7	60.3	71.4	70.2

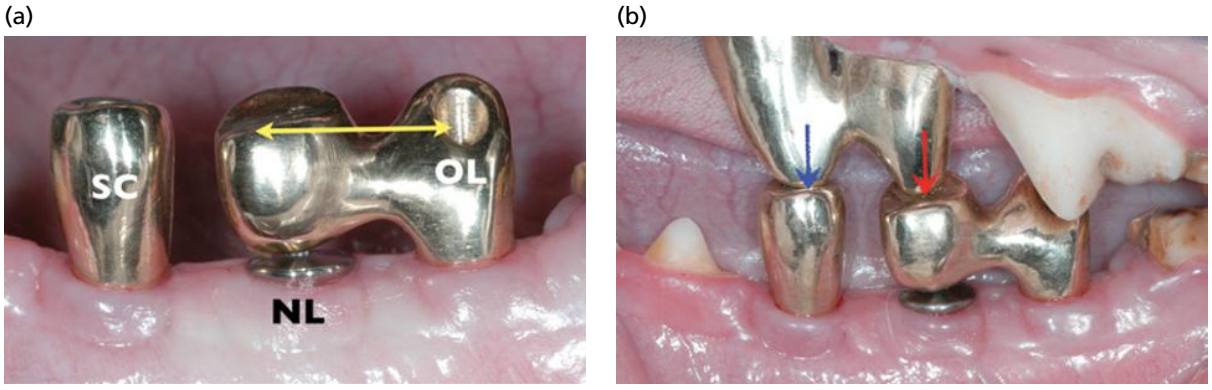

Fig. 17-10 Osseointegrated implants (a) not in occlusal contact and (b) in occlusal contact: a single crown unit with normal occlusal contacts and stable occlusion (SC) (blue arrow); a single non-loaded implant (NL) protected by a cantilever beam of 13.5 mm in length (yellow arrow); and an overloaded abutment (OL) with overt occlusal contacts through the cantilever beam (red arrow).

Since none of the clinical, radiographic, or histologic parameters yielded statistically significant differences between non-loaded and excessively loaded implants, the study clearly demonstrates that, in the presence of peri-implant mucosal health, a period of 8 months of *excessive occlusal load* on titanium implants does *not* result in loss of osseointegration or marginal bone loss when compared with non-loaded implants.

More recently, implants with both SLA and SLActive implant surfaces restored and overloaded by means of cantilever reconstructions were evaluated for implant stability over a period of 6 months using resonance frequency analysis (RFA) (Lima *et al*. 2010). In five Beagle dogs, all mandibular premolars were extracted bilaterally. After 3 months, full thickness flaps were raised, and six implants (Straumann®, length 8 mm, diameter 3.3 mm, three SLA and three SLActive) were installed in a block-randomized split-mouth design (d0). After 4 weeks, implants were restored on each side of the mandible as follows: one single crown with stable occlusal contacts (SC); one crown and a 13.5-mm cantilever unit with overt occlusal contacts (OL); and one non-loaded implant (NL) protected by the cantilever unit (Fig. 17-10). The vertical dimension was increased by 3 mm. RFA was evaluated on day 0 and weekly for 2–10 weeks after surgery, and at 12 weeks and 24 weeks after loading. Repeated measure MANOVA was used to test the significance of the interaction between three within-subject effects (i.e. implant surface, type of treatment, and follow-up) and their interaction with RFA values.

Mean implant stability quotient (ISQ) values (RFA) from 61 to 66 for SLA implants and 58–67 for SLActive implants immediately after placement, and then significantly increased to 74–77 and 76–78, respectively, 4 weeks later (P <0.001). Six months after loading, ISQ values were significantly greater for both SLA and SLActive implants, reaching levels of 77.90 (SLA/OL), 76.80 (SLA/NL), 77.75 (SLA/SC), 76.40 (SLActive/OL), 79.80 (SLActive/NL), and 74.30 (SLActive/SC), with no significant differences between units ($P = 0.30$).

It was evident that the application of early and excessive occlusal load on clinically stable implants restored with cantilever reconstructions did not cause significant changes in implant stability. Consequently, this study, again, provides evidence that *occlusal overload* does *not* result in loss of implant stability and hence, does not jeopardize the integrity of the implants even when under heavy function.

Static and cyclic loads on implants

While the study by Berglundh *et al.* (2005) addressed the possible influence of functional loading on the marginal bone levels of implants by applying a flat occlusal plane scheme and physiologic forces, many authors have studied the influence of loading forces exceeding physiologic functional conditions and impacting on the implants in a non-axial direction (Barbier & Schepers 1997; Gotfredsen *et al*. 2001a–c, 2002; Heitz-Mayfield *et al*. 2004).

The bone tissue reaction to axial loading was evaluated using conventional three-unit FDPs in the mandible of Beagle dogs, and compared with that to non-axial loading provoked by installing a distal cantilever of two implants (Barbier & Scheppers 1977). Bone remodeling was modest at the implant sites supporting conventional FDPs, while the non-axial load induced by the cantilever FDPs yielded a more pronounced bone response, including a higher activity of osteoclasts in the peri-implant bone. However, bone levels were not affected. This was interpreted as an adaptive phenomenon within the peri-implant bone as a result of non-axial loading.

The bone reactions around osseointegrated implants to static load were analyzed in three studies in dogs (Gotfredsen *et al*. 2001a–c, 2002). In the

first study (Gotfredsen *et al*. 2001a), a lateral static load was induced by an orthodontic expansion screw at eight ITI® TPS hollow-screw implants in each dog. After a loading period of 24 weeks, during which time the screws were activated every 4 weeks from 0.0, 0.2, 0.4, to 0.6 mm, histologic and histometric analysis revealed no marginal bone loss at loaded and unloaded implant sites. Peri-implant bone density and mineralized bone–implant contact was higher at the loaded than the unloaded implant sites. This, again, was interpreted as lateral static load resulting in an *adaptive remodeling of the peri-implant bone*.

In the second study (Gotfredsen *et al*. 2001b), two TPS and two turned ITI® hollow-screw implants were subjected to the 24-week loading period in each dog using orthodontic expansion screws. These were activated by 0.6 mm every 4 weeks. The histologic and histometric analysis showed higher marginal bone levels around TPS implants than around turned implants. Likewise, the peri-implant bone density and mineralized bone–implant contact was higher around the roughened TPS than the turned implants. Hence, it was concluded that surface roughness influences the bone reactions to the applied load. This in turn indicates that surface roughness may also be a determining factor in the remodeling process triggered by load at the bone–implant interface.

The third study (Gotfredsen *et al*. 2001c) analyzed the dynamics of applying a static load for various durations to ITI® implants in three Beagle dogs. After 24 weeks, the static load was maximally activated onto the implants of the right mandibular side, giving a total loading period of 46 weeks at sacrifice. At 60 weeks, maximal activation of static load was set onto the implants of the left mandibular side, giving a total loading period of 10 weeks at sacrifice.

Fluorochrome labeling was performed at weeks 62, 64, 66, and 68. The dogs were sacrificed at week 70. A similar distribution of bone markers, bone density, and bone–implant contact was observed at 10 and 46 weeks of static lateral loading. However, higher fluorochrome proportions were seen at 10 weeks compared to 46 weeks of lateral loading, suggesting higher adaptive activity at 10 weeks. Nevertheless, the structural adaptation appeared to be similar at the two observation periods.

In all three studies, greater bone–implant contact was identified at implants subjected to lateral static load application compared to non-loaded implants. Moreover, lateral static load failed to induce peri-implant bone loss or to enhance peri-implant bone loss. Hence, *lateral static load* does *not* appear to be detrimental to implants exhibiting peri-implant mucositis or peri-implantitis (Gotfredsen *et al*. 2001a–c).

In contrast to these findings are those from a study in dogs by Hoshaw *et al*. (1994). In this study, excessive cyclic axial forces were applied to implants [high cyclic (500 cycles/day) axial tension (10–300 N) for 5 consecutive days) placed in the tibiae of ten animals. Bone loss was observed to occur around the neck of the Brånemark implants after 1 year. Similar results were reported for a rabbit model (Duyck *et al*. 2001) in which dynamic load on implants resulted in the establishment of marginal crater defects, while no effects on osseointegration could be identified in other parts of the implants.

Load and loss of osseointegration

It has been reported (Isidor 1996, 1997) that excessive occlusal load may – under certain circumstances – lead to loss of osseointegration along the entire length of the implant, resulting in implant mobility. In this study, four monkeys received 18 self-tapping screw implants in the mandible after the first molars (n = 7), premolars (n = 8), and incisors (n = 3) had been extracted. Using an opposing maxillary splint in heavy supraocclusal contacts, *excessive occlusal load*, predominantly in the non-axial (lateral) direction, was applied to eight implants. Furthermore, cotton ligatures for increased plaque retention were placed around another 10 implants, resulting first in mucositis and later in peri-implantitis (Lindhe *et al*. 1992; Lang *et al*. 1993). After 18 months of excessive occlusal loading, two of the eight implants subjected to excessive occlusal load were lost. Two of the ten implants with the cotton ligatures revealed partial loss of osseointegration as a result of plaque-induced peri-implantitis (Fig. 17.11a). Of the retained six implants subjected to excessive load, two showed complete loss of osseointegration with a connective tissue capsule formed around the entire outline of the implants (Fig. 17.11b). Radiographically, the two implants showing complete loss of osseointegration and clinical mobility showed a peri-implant radiolucency after 18 months of excessive occlusal load. However, no loss of marginal bone height was evident.

Another two excessively loaded implants (in one monkey) showed no loss of osseointegration whatsoever. Instead, an increase in bone density and the highest percentage of bone–implant contact area was seen at these implants compared to the remaining implants. This monkey also did not develop ligature-induced peri-implantitis (at three implants). Two implants under excessive occlusal load revealed a reduced bone–implant contact.

Thus, the study demonstrated that excessive occlusal load can, indeed, result in loss of osseointegration characterized by a fibrous connective tissue capsule around the implant, in contrast to the marginal bone loss encountered at implants with ligature-induced peri-implantitis. It must be noted, however, that the bone trabecular structure

around the implant loosing osseointegration as a result of excessive occlusal load (Fig. 17.11b) was much less dense than that of, for example, the implants subjected to experimental peri-implantitis (Fig. 17.11a). Thus, this study does not support the concept that occlusal overload may lead to implant losses. Rather, it supports the fact that marginal bone loss at implants is associated with peri-implant disease.

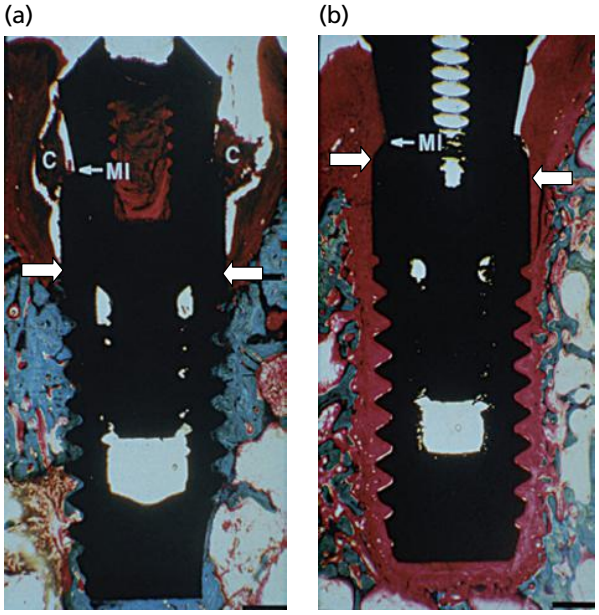

Fig. 17.11 (a) Osseointegrated implant with plaque accumulation. The marginal bone level is located apical to the margin of the implant. (b) Excessively loaded implant with complete loss of osseointegration. The marginal bone level is located near the margin of the implant. Narrow zone of fibrous tissue interposed between implant and bone. (MI, margin of implant; C, cotton ligature; arrows, apical extent of epithelium.) (Source: Isidor 1997. Reproduced with permission from John Wiley & Sons.)

Masticatory occlusal forces on implants

Closing and occlusal functional force distributions have been studied using one- (Lundgren *et al*. 1987, 1989; Falk *et al*. 1989, 1990) or three-dimensional piezoelectric force transducers (Mericske-Stern *et al*. 1996; Mericske-Stern 1997, 1998; Mericske-Stern *et al*. 2000).

Eight strain gauge transducers were mounted bilaterally in a maxillary complete denture to occlude with a mandibular implant-supported fixed cantilever prosthesis (Fig. 17-12a) (Lundgren *et al*. 1989). The study demonstrated that closing and chewing forces *increased* distally along the cantilever beams when occluding with complete dentures. Moreover, on both the preferred and non-preferred chewing sides, significantly larger closing and chewing forces were measured over the cantilever segments than over the implant-supported area (Fig. 15-12b). Also, the distally increasing force distribution pattern could be changed to a distally *decreasing* force distribution pattern by infra-occluding the second cantilever unit by as little as 100 µm. Such slight reductions in posterior occlusal contacts on cantilevers may need to be considered whenever the opposing masticatory unit is a complete removable dental prosthesis. However, maximal biting and chewing forces *decreased* distally along the cantilever beams when occluding with tooth-supported FDPs (Fig. 17-13) (Lundgren *et al*. 1987).

From this series of experimental clinical studies it was concluded that forces directed onto the implants *per se* are difficult to evaluate using the transducer methodology. Nevertheless, maximal closing forces were always substantially greater than chewing forces. In addition, each subject in these studies developed a preferred chewing side that was associated

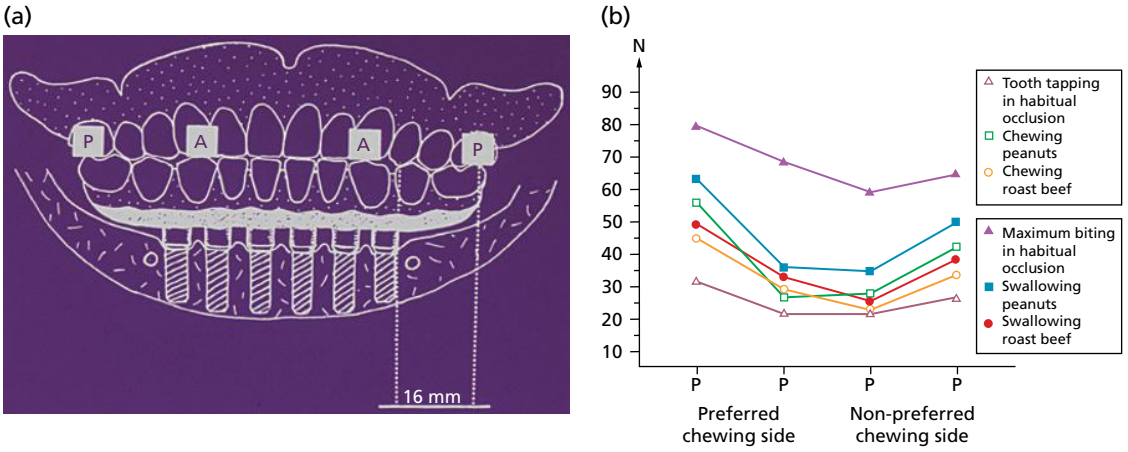

Fig. 17-12 (a) Eight strain gauge transducers placed into a maxillary completely removable prosthesis and occluding against an implant-supported fixed mandibular dental prosthesis with cantilever beams of 16 mm. (Source: Lundgren *et al*. 1989. Reproduced from Quintessence.) (b) Chewing forces amounting to a maximum biting force of 80 N on the preferred (right) chewing side and 64 N on the non-preferred (left) chewing side. While masticating, higher forces are applied to the cantilever beams than to the implant-supported part of the mandibular FDP. (Data from Lundgren *et al*. 1989. Courtesy of D. Lundgren, Gothenburg.)

with higher chewing forces than the non-preferred chewing side (Lundgren *et al*. 1987, 1989; Falk *et al*. 1989, 1990).

Occlusal force distribution patterns have been studied using three-dimensional piezoelectric transducers for mandibular overdentures that were mounted onto two mandibular implants in the canine region designed to support either a ball joint- or a bar-retained mandibular complete removable prosthesis. Rigid bars provided the best distribution of forces in a vertical direction onto the two mandibular implants (Mericske-Stern *et al*. 1996; Mericske-Stern 1998). Moreover, short distal bar extensions did not negatively influence the force pattern (Mericske-Stern 1997).

When ball joint anchors were used to retain the mandibular overdenture, rather low forces were measured on the implants, particularly in a vertical direction (Mericske-Stern 1998). Vertical forces amounted to 60–140 N, while horizontal forces were much smaller (15–60 N).

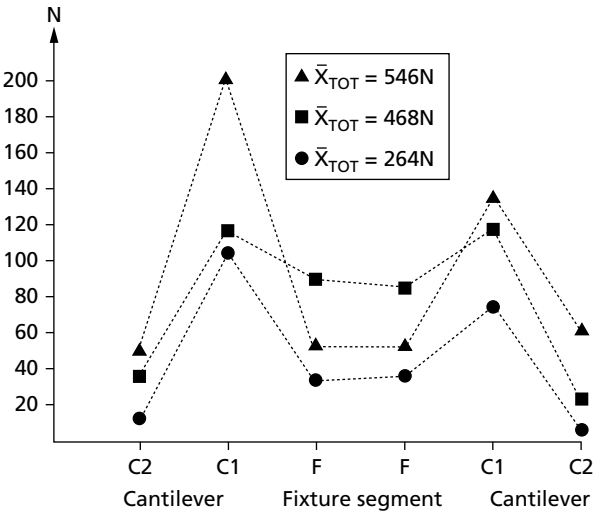

Fig. 17-13 Chewing force patterns in implant-supported fixed dental prosthesis (FDP) with cantilever beams occluding against the tooth-supported FDP. (Source: Lundgren *et al*. 1987. Reproduced with permission from Elsevier.)

Tooth–implant supported reconstructions

In reconstructing patients with inadequate masticatory function, oral implants are often used to increase the patients' chewing comfort (see Chapter 53) and provide additional chewing units in an edentulous posterior region. Occasionally, reconstruction of a chewing side may be contemplated, with the reconstruction supported by both a tooth and an implant (Fig. 17-14). In this way, problems with the location of the mental nerve in an area of a planned implant installation or lack of an adequate bone volume may be overcome.

Combined tooth–implant reconstructions have been associated with numerous clinical problems, including root intrusion as a potential clinical hazard of non-rigid connection. Hence, it has been claimed that natural teeth should not be connected to implants beneath a fixed prosthesis.

However, experimental studies have clearly established that no detrimental effects on the periodontium of abutment teeth can be demonstrated despite the different biomechanical condition mediated by a periodontal ligament as opposed to the ankylotic anchorage of an implant (Biancu *et al*. 1995).

In vivo measurements of vertical forces and bending moments during biting and chewing were carried out on ten three-unit prostheses in the posterior mandibles of five patients. Each patient had two prostheses, one supported by two implants and the other supported by one implant and one tooth. The results demonstrated no major difference in functional load magnitudes between the support types. Obviously, functional loads were shared between the teeth and the implants (Gunne *et al*. 1997; Rangert *et al*. 1991, 1995).

Further studies using FEA showed no increased risk of stress concentrations at the neck of the implant (Gross & Laufer 1997; Laufer & Gross 1998).

Clinical studies reporting life table statistics in combined implant and tooth restorations do not show adverse effects of splinting teeth to implants. No increased risk of tooth intrusion was reported if the

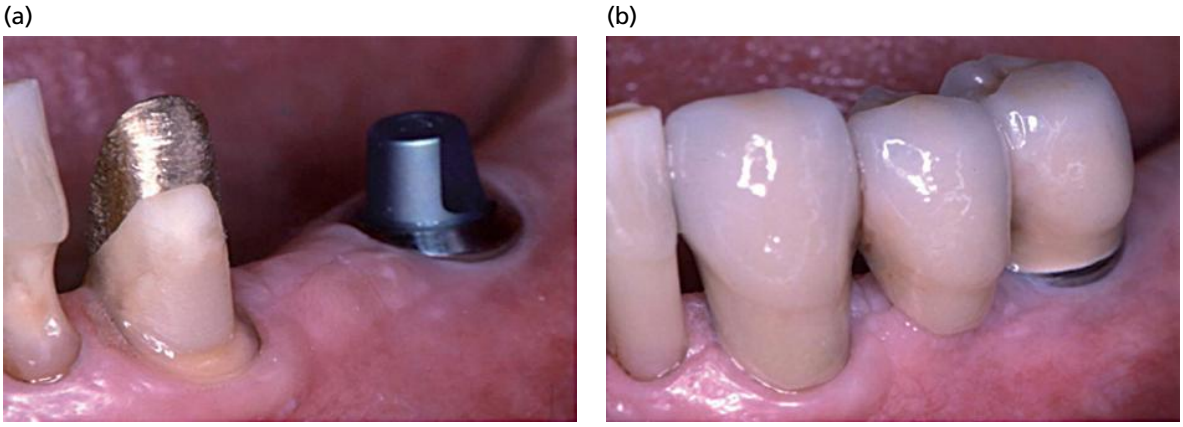

Fig. 17-14 Reconstruction of a chewing side in the left mandible using a fixed dental prosthesis (FDP). (a) Prepared abutment tooth 33 after having established adequate abutment height by the installation of a cast post and core prior to seating a three-unit FDP. (b) Tooth-implant supported three-unit FDP 10 years after placement.

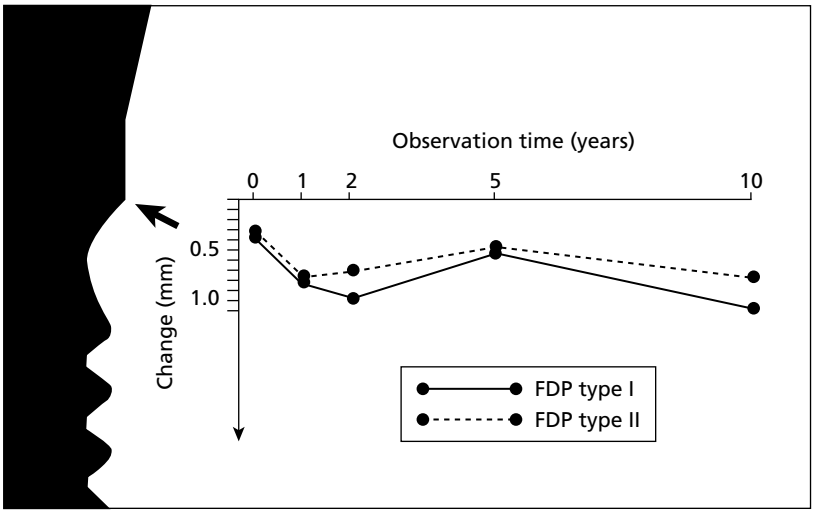

Fig. 17-15 Ten-year randomized controlled clinical trial of three-unit fixed dental prostheses, either implant–implant (type I) or tooth–implant (type II) supported. No differences in the crestal bone levels after 1, 2, 5, and 10 years in function. (Source: Lundgren *et al*. 1987. Reproduced with permission from Elsevier.)

implant was rigidly connected to the tooth (Fugazzotto *et al*. 1999; Lindh *et al*. 2001; Naert *et al*. 2001a, b).

For 843 consecutive patients treated in a private practice set-up (Fugazzotto *et al*. 1999) with 1206 natural tooth–implant supported prostheses utilizing 3096 screw-fixed attachments, after 3–14 years in function, only nine intrusion problems were noted. All problems were associated with fractured or lost screws.

Probably the most relevant clinical study is a 10-year randomized controlled prospective study of 23 patients with residual mandibular anterior teeth (Gunne *et al*. 1999). Each patient received two three-unit FDPs either supported by two implants or, on the contralateral side, by one implant and one tooth, thus permitting intraindividual comparison. The distribution of the two types of FPDs in each jaw was randomized. Implant success rates, marginal bone changes, and mechanical complications were studied. The tooth–implant connection did not demonstrate any negative influences on the overall success rates for the 10-year period when compared to the implant–implant supported FDPs (Fig. 17-15). Hence, it was suggested that a prosthetic construction supported by both a tooth and an implant may be recommended as a predictable and reliable treatment alternative in the posterior mandible (Gunne *et al*. 1999).

Based on the available evidence, it can be stated that a combination of implant and tooth support for FDP is acceptable (Belser *et al*. 2004).

While a systematic review (Lang *et al*. 2004) indicated that tooth–implant reconstructions have a 5-year survival rate of 94.1%, thus comparing very well with the 5-year survival rate of implant–implant reconstructions of 95.0% (Pjetursson *et al*. 2004), the 10-year survival rate of tooth–implant reconstructions (77.8%) appears to be significantly lower than the 10-year survival of implant–implant reconstructions (86.7%). However, owing to the fact that the former 10-year survival rate was based on only 60 (I–T) FDPs and the latter on only 219 (I–I) FDPs, the reliability of such 10-year survival rates has to be questioned.

The biomechanical aspects of implant–tooth-supported FDPs have been presented (Lundgren & Laurell 1994). As the implant is rigidly fixed within the alveolus and the tooth is surrounded by a periodontal ligament that allows minute movement, rigid FDP designs have been advocated.

The movement of the natural tooth abutment affects the load-bearing capacity of the FDP whenever a long-span FDP is constructed (e.g. a beam length of 24 mm or two premolar or molar pontics). Before the occlusal load is applied, the FDP acts as a cantilever construction. Upon loading, an angular deflection of the implant–crown unit of approximately 50 µm is noted. Along with bending of the long-span beam, an apical deflection of the tooth of approximately 50 µm is allowed, leading to bilateral (tooth and implant) support for the FDP.

If the tooth and implant only support a short-span FDP (e.g. a beam length of 12 mm or one premolar pontic only), however, the angular deflection of the implant–crown unit of approximately 50 µm and the bending of the short-span beam are insufficient to provide bilateral support for the bridge. Apical deflection of the tooth will not be achieved and the implant will bear the entire occlusal load applied to the FDP. As indicated above, there is no doubt that osseointegration will cope with such functional loads.

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Part 6: Periodontal Pathology

Chapter 18

Non–Plaque-Induced Inflammatory Gingival Lesions

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Gingival inflammation, clinically presenting as gingivitis, is not always due to accumulation of plaque on the tooth surface, and non–plaque-induced inflammatory gingival reactions often present with characteristic clinical features (Holmstrup 1999). They may have several causes, such as specific bacterial, viral or fungal infection. Inherited gingival lesions are seen in hereditary gingival fibromatosis, and several mucocutaneous disorders manifest as gingival inflammation. Typical examples of such disorders are lichen planus, pemphigoid, pemphigus vulgaris, and erythema multiforme. Allergic and traumatic lesions are other examples of non–plaque-induced gingival inflammation. Dentists, and especially specialists in periodontology, are the key healthcare providers in the diagnostic unraveling and treatment of patients affected by such lesions.

This chapter focuses on the most relevant non–plaque-induced inflammatory lesions of the gingival tissues, either because they are common or because they are important examples for the understanding of the variety of tissue reactions that take place in the periodontium. For further information, the reader is referred to oral medicine textbooks. The modifying factors of plaque-related gingivitis such as smoking, sex hormones, and metabolic anomalies (diabetes) are dealt with in Chapters 12 and 14.

Gingival diseases of specific bacterial origin

Infective gingivitis and stomatitis may occur on rare occasions in both immunocompromised and non-immunocompromised individuals, when the homeostasis between innate host resistance and non–plaque-related pathogens is not maintained (Rivera-Hidalgo & Stanford 1999). The lesions may be due to bacteria and oral lesions may be the primary presentation of the infection. Typical examples of such lesions are due to infections with *Neisseria gonorrhea* (Scully 1995; Siegel 1996), *Treponema pallidum* (Scully 1995; Ramirez-Amador *et al*. 1996; Siegel 1996; Rivera-Hidalgo & Stanford 1999). streptococci, *Mycobacterium chelonae* (Pedersen & Reibel 1989) or other organisms (Blake & Trott 1959; Littner *et al*. 1982). Although oral manifestations of syphilis and gonorrhea are most likely to be observed during secondary disease, all stages of the disease can give rise to oral lesions. The gingival lesions manifest as fiery red edematous painful ulcerations,

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as asymptomatic chancres or mucous patches, or as atypical non-ulcerated, highly inflamed gingivitis. Biopsy supplemented by microbiologic examination reveals the background of the lesions.

Gingival diseases of viral origin

Herpes virus infections

A number of viral infections are known to cause gingivitis (Scully *et al*. 1998b). The most important are the herpes viruses: herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) and varicella zoster virus. These viruses usually enter the human body in childhood and may give rise to oral mucosal disease followed by periods of latency and sometimes reactivation. HSV-1 usually causes oral manifestations, whereas herpes HSV-2 is mainly involved in anogenital infections and only occasionally is involved in oral infection (Scully 1989).

Primary herpetic gingivostomatitis

HSV infections are among the most common viral infections. HSV is a DNA virus with low infectiosity, which after entering the oral mucosal epithelium, penetrates a neural ending and by retrograde transport through the smooth endoplasmatic reticulum (200–300 mm/day) travels to the trigeminal ganglion where it can remain latent for years. The virus has also been isolated in extraneural locations such as the gingiva (Amit *et al*. 1992). Sometimes HSV may also be involved in recurring erythema multiforme. It is presently unknown whether the virus plays a role in other oral diseases, but HSV has been found in gingivitis (Ehrlich *et al*. 1983), acute necrotizing gingivitis (Contreras *et al*. 1997), and periodontitis (Parra & Slots 1996).

When a newborn is infected, sometimes from the parent's recurrent herpes labialis, he/she is often wrongly diagnosed as "teething". With increased hygiene in industrialized societies, more and more primary infections occur at older ages, that is during adolescence and adulthood. It has been estimated in the US that there are about half a million cases of primary infection per year (Overall 1982). The primary herpetic infection may run an asymptomatic course in early childhood, but may also give rise to severe gingivostomatitis, which occurs mostly before adolescence (Fig. 18-1). This manifestation includes painful severe gingivitis with redness, ulcerations with serofibrinous exudate, and edema accompanied by stomatitis (Figs. 18-2, 18-3). The incubation period is 1 week. A characteristic feature is the formation of vesicles, which rupture, coalesce, and leave fibrin-coated ulcers (Scully *et al*. 1991; Miller & Redding 1992). Fever and lymphadenopathy are other classic features. Healing occurs spontaneously without scarring in 10–14 days (Fig. 18-4). During this period pain can render eating difficult.

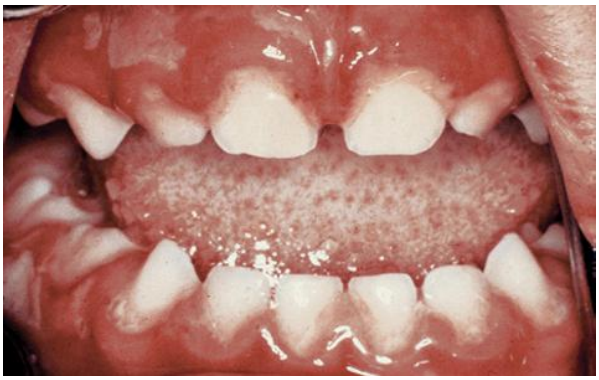

Fig. 18-1 Herpetic gingivostomatitis in a 3-year-old child. Erythematous swelling of attached gingiva with serofibrinous exudate along the gingival margin.

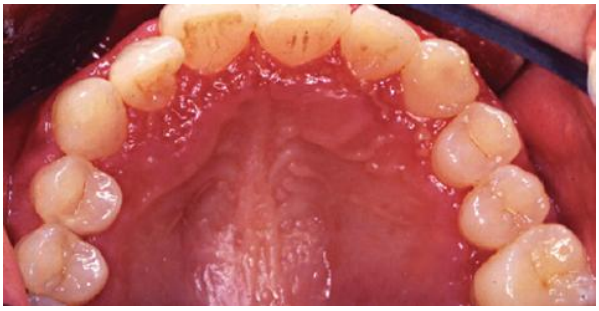

Fig. 18-2 Herpetic gingivostomatitis affecting palatal gingiva. Numerous vesicles and small ulcerations.

The virus remains latent in the ganglion cell, probably through integration of its DNA in that of the chromosomal DNA (Overall 1982). Reactivation of the virus occurs in 20–40% of primary infected individuals (Greenberg 1996) and usually presents as herpes labialis, but recurrent intraoral herpes infections are also seen. Herpes labialis occurs in general more than once per year, usually at the same location on the vermilion border and/or the skin adjacent to it, where neural endings are known to cluster. A large variety of factors trigger reactivation of latent virus: trauma, ultraviolet light exposure, fever, menstruation, and others (Scully *et al*. 1998b).

While recurrences at the vermilion border are well recognized, recurrent intraoral herpes lesions often remain undiagnosed because they are considered aphthous ulcerations (Lennette & Magoffin 1973; Sciubba 2003), irrespective of the fact that aphthous ulcers do not affect keratinized mucosa. Recurrent intraoral herpes typically presents a less dramatic course than does the primary infection. A characteristic manifestation is a cluster of small painful ulcers in the attached gingiva and hard palate (Yura *et al*. 1986) (Fig. 18-5). The diagnosis can be made on the basis of the patient history and clinical findings supported by isolation of HSV from lesions. The polymerase chain reaction (PCR) has largely superseded most other methods and is a rapid and reliable diagnostic tool that provides subtype diagnosis. Laboratory diagnosis may also involve examination of a blood sample

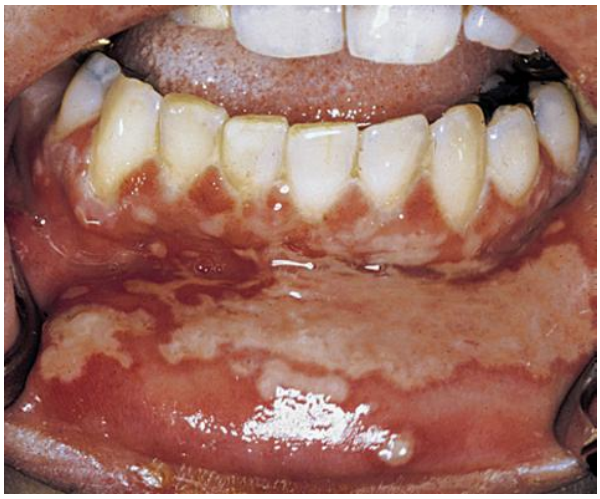

Fig. 18-3 Herpetic gingivostomatitis in a 38-year-old woman. Widespread ulceration of the lower lip mucosa and gingiva.

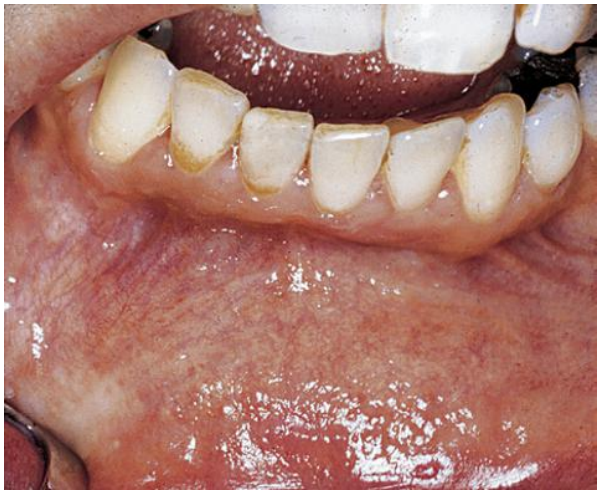

Fig. 18-4 Same patient as shown in Fig. 18-3, 4 weeks later. Healing without loss of tissue or scar formation.

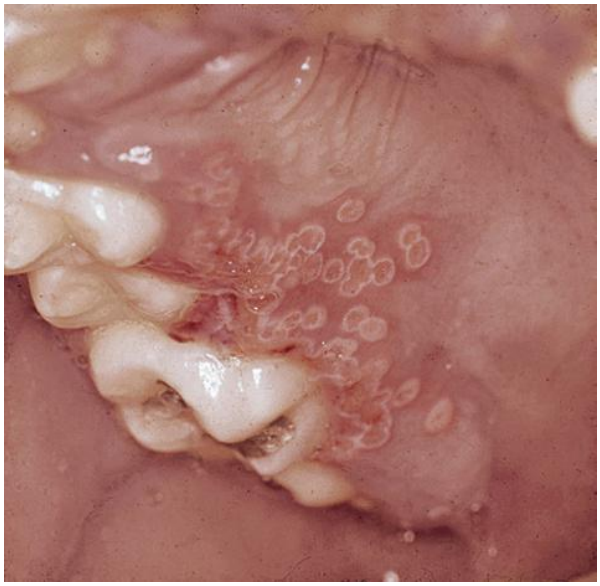

Fig. 18-5 Recurrent intraoral herpes infection. Ruptured vesicles of right palatal gingiva and mucosa.

for increased antibody titer against HSV. However, this is most relevant in cases of primary infection, because the antibody titer remains elevated for the rest of the individual's lifetime. The histopathologic features of cytologic smears from the gingival lesions are not specific, but the presence of giant cells and intranuclear inclusion bodies may indicate intracellular activity of the virus (Burns 1980).

Immunodeficient patients, such as human immunodeficiency virus (HIV)-infected individuals, are at increased risk of acquiring the infection (Holmstrup & Westergaard 1998). In the immunocompromised patient the recurrence of herpes infection, either gingival or elsewhere, may be severe and even life threatening.

The treatment of herpetic gingivostomatitis includes careful plaque removal to limit bacterial superinfection of the ulcerations, which delays their healing. In severe cases, including patients with immunodeficiency, the systemic use of antiviral drugs such as acyclovir, valacyclovir or famciclovir is recommended (O'Brien & Campoli-Richards 1989; Mindel 1991; Arduino & Porter 2006). Resistance to acyclovir, especially among immunodeficient patients on long-term therapy, is a growing concern (Westheim *et al*. 1987) and explains why other antiviral drugs may be relevant. Prophylactic antiviral treatment before dental treatment has been recommended for patients at risk of experiencing a recurrence, as well as to minimize transmission of the disease (Miller *et al*. 2004).

Herpes zoster

Varicella zoster virus causes varicella (chicken pox) as the primary self-limiting infection. It occurs mainly in children and later reactivation of the virus in adults causes herpes zoster (shingles). Both manifestations can involve the gingiva (Straus *et al*. 1988; Scully 1995). Chicken pox is associated with fever, malaise, and a skin rash. The intraoral lesions are small ulcers, usually on the tongue, palate, and gingiva (Miller 1996; Scully *et al*. 1998b). The virus remains latent in the dorsal root ganglion from where it can be reactivated years after the primary infection (Rentier *et al*. 1996). Later reactivation results in herpes zoster, with unilateral lesions following the infected nerve (Miller 1996). The reactivation normally affects the thoracic ganglia in elderly or immunocompromised patients. Reactivation of virus from the trigeminal ganglion occurs in 20% of reported cases (Hudson & Vickers 1971). If the second or third branch of the trigeminal nerve is involved, skin lesions may be associated with intraoral lesions, or intraoral lesions may occur alone (Eisenberg 1978), for instance affecting the palatal gingiva (Fig. 18-6). Initial symptoms are pain and paraesthesia, which may be present before lesions occur (Greenberg 1996). The associated pain is usually severe. The lesions, which often involve the gingiva, start as vesicles. They soon rupture to leave fibrin-coated ulcers, which often coalesce to irregular

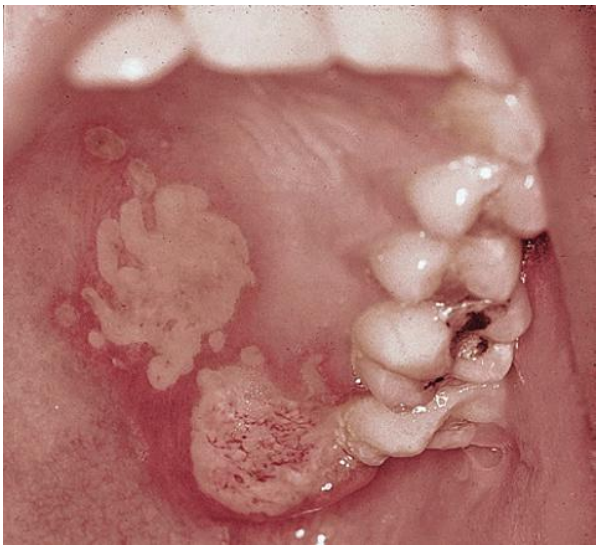

Fig. 18-6 Herpes zoster of left palatal gingiva and mucosa. Irregular fibrin-coated ulcerations with severe pain.

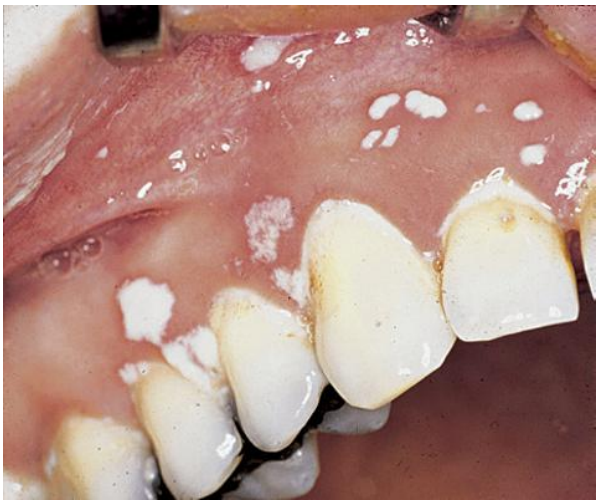

Fig. 18-7 Pseudomembranous candidosis of maxillary gingiva and mucosa in an HIV-seropositive patient. The lesions can be scraped off, leaving a slightly bleeding surface.

forms (Millar & Traulis 1994) (Fig. 18-6). In immunocompromised patients, including those infected with HIV, the infection can result in severe tissue destruction with tooth exfoliation and necrosis of alveolar bone and high morbidity (Melbye *et al*. 1987; Schwartz *et al*. 1989). The diagnosis is usually obvious due to the unilateral occurrence of lesions associated with severe pain. Healing of the lesions usually takes place in 1–2 weeks.

Treatment consists of a soft or liquid diet, rest, atraumatic removal of plaque, and diluted chlorhexidine rinses. This may be supplemented by antiviral drug therapy.

Gingival diseases of fungal origin

Fungal infection of the oral mucosa includes a range of diseases such as aspergillosis, blastomycosis, candidosis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, and paracoccidioidomycosis infections (Scully *et al*. 1998b), but some of the infections are very uncommon and not all of them manifest as gingivitis. This section focuses on candidosis and histoplasmosis, both of which may cause gingival infection.

Candidosis

Various *Candida* species are recovered from the mouth of humans, including *C. albicans, C. glabrata, C. krusei, C. tropicalis, C. parapsilosis,* and *C. guillermondii* (Cannon *et al*. 1995). The most common fungal infection of the oral mucosa is candidosis mainly caused by the organism *C. albicans* (Scully *et al*. 1998b). *C. albicans* is a normal commensal of the oral cavity but also an opportunistic pathogen. The prevalence of oral carriage of *C. albicans* in healthy adults ranges from 3% to 48% (Scully *et al*. 1995), the large variation being due to differences in examined populations and the procedures used. The proportion of *C. albicans* in the total oral yeast population can reach about 50–80% (Wright *et al*. 1985). The proteinase-positive strains of *C. albicans* are associated with disease (Negi *et al*. 1984; Odds 1985) and invasion of keratinized epithelia such as that of the gingiva. Invasion and increased desquamation is due to hyaluronidase production. Infection by *C. albicans* usually occurs as a consequence of reduced host defense (Holmstrup & Johnson 1997), including immunodeficiency (Holmstrup & Samaranayake 1990) (Figs. 18-7, 18-8, 18-9), reduced saliva secretion, smoking, and treatment with corticosteroids, but may be due to a wide range of predisposing factors. The occurrence of oral candidosis may act as a predictor of immune and virologic failure in HIV-infected patients treated with antiviral drugs (Miziara & Weber 2006). Disturbances in the oral microbial flora, such as after therapy with broad-spectrum antibiotics, may also lead to oral candidosis. The predisposing factors are, however, often difficult to identify. Based on their site, infections may be defined as superficial or systemic. Candidal infection of the oral mucosa is usually a superficial infection, but systemic infections are not uncommon in debilitated patients.

In otherwise healthy individuals, oral candidosis rarely manifests in the gingiva. This is surprising when considering the fact that *C. albicans* is frequently isolated from the subgingival flora of patients with severe periodontitis (Slots *et al*. 1988). The most common clinical characteristic of gingival candidal infections is redness of the attached gingiva, often associated with a granular surface (Fig. 18-10).

Various types of oral mucosal manifestations are pseudomembranous candidosis (also known as thrush in neonates), erythematous candidosis, plaque-type candidosis, and nodular candidosis (Holmstrup & Axéll 1990). Pseudomembranous candidosis shows whitish patches (Fig. 18-7), which can be wiped off the mucosa with an instrument

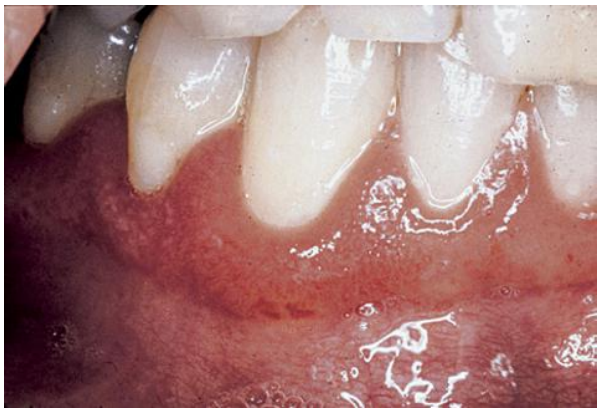

Fig. 18-8 Erythematous candidosis of attached mandibular gingiva in an HIV-seropositive patient. The mucogingival junction is not visible.

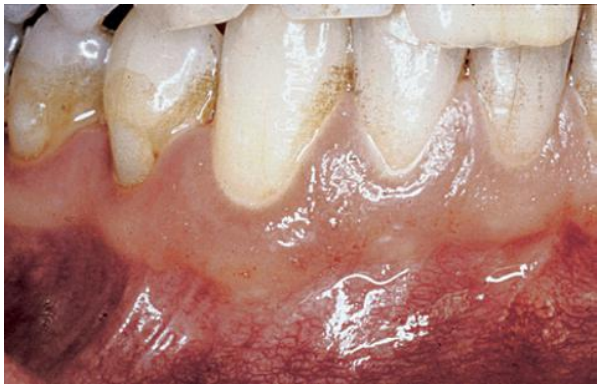

Fig. 18-9 Same patient as shown in Fig. 18-8 after topical antimycotic therapy. The mucogingival junction is visible.

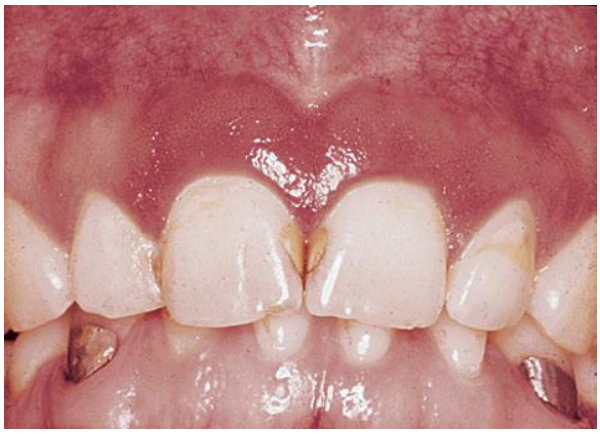

Fig. 18-10 Chronic erythematous candidosis of maxillary attached gingiva of the incisor region.

or gauze to leave a slightly bleeding surface. The pseudomembranous type usually has no major symptoms. Erythematous lesions can be found anywhere in the oral mucosa (Fig. 18-10). The intensely red lesions are usually associated with pain, which is sometimes severe. The plaque type of oral candidosis usually affects smokers and presents with a whitish plaque, which cannot be removed. There are usually no symptoms and the lesion is clinically indistinguishable from oral leukoplakia. Nodular candidal lesions are infrequent in the gingiva. Slightly elevated nodules of a white or reddish color characterize them (Holmstrup & Axéll 1990).

A diagnosis of candidal infection can be accomplished on the basis of culture, smear, and biopsy. A culture on Nickerson's medium at room temperature is easily handled in the dental premises. Microscopic examination of smears from suspected lesions is another easy diagnostic procedure, either performed as direct examination by phase-contrast microscopy or as light microscopic examination of periodic acid–Schiff-stained or Gram-stained smears. Mycelium-forming cells in the form of hyphae or pseudohyphae and blastospores are seen in great numbers among masses of desquamated cells. Since oral carriage of *C. albicans* is common among healthy individuals, positive culture and smear does not necessarily imply candidal infection (Rindum *et al*. 1994). Quantitative assessment of the mycologic findings and the presence of clinical changes compatible with the above types of lesions are necessary for a reliable diagnosis, which can also be obtained on the basis of identification of hyphae or pseudohyphae in biopsies from the lesions.

Topical treatment involves application of antifungals, such as nystatin, amphotericin B or miconazole. Nystatin may be used as an oral suspension. Since it is not resorbed, it can be used in pregnant or lactating women. Miconazole exists as an oral gel. It should not be given during pregnancy and it can interact with anticoagulants and phenytoin. The treatment of severe or generalized forms also involves systemic antifungals such as fluconazole.

Linear gingival erythema

Linear gingival erythema (LGE) is regarded as a gingival manifestation of immunosuppression characterized by a distinct linear erythematous band limited to the free gingiva (Holmstrup 1999) (Fig. 18-11). It is characterized by inflammation of disproportionate intensity for the amount of plaque present. There is no evidence of pocketing or attachment loss. A further characteristic of this type of lesion is that it does not respond well to improved oral hygiene or to scaling (EC Clearinghouse on Oral Problems 1993) and the diagnosis should be considered if the lesion persists after removal of plaque at the initial visit (Umadevi *et al*. 2006) . The extent of gingival banding measured at a number of affected sites has been shown to depend on tobacco usage (Swango *et al*. 1991). While 15% of affected sites were originally reported to bleed on probing and 11% exhibited spontaneous bleeding (Winkler *et al*. 1988), a key feature of LGE is now considered to be lack of bleeding on probing (Robinson *et al*. 1994).

Some studies of various groups of HIV-infected patients have revealed prevalences of gingivitis with band-shaped patterns of 0.5–49% (Klein *et al*. 1991;

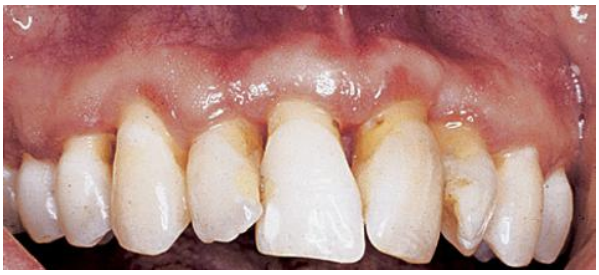

Fig. 18-11 Linear gingival erythema of maxillary gingiva. Red banding along the gingival margin, which does not respond to conventional therapy.

Swango *et al*. 1991; Barr *et al*. 1992; Laskaris *et al*. 1992; Masouredis *et al*. 1992; Riley *et al*. 1992; Ceballos-Salobrena *et al*. 1996; Robinson *et al*. 1996). These prevalence values reflect some of the problems with non-standardized diagnosis and selection of study groups. A few studies of unbiased groups of patients have indicated that gingivitis with band-shaped or punctate marginal erythema may be relatively rare in HIV-infected patients, and is probably a clinical finding which is no more frequent than in the general population (Drinkard *et al*. 1991; Friedman *et al*. 1991).

It is interesting to note that, whereas there was no HIV-related preponderance of red banding, diffuse and punctate erythema was significantly more prevalent in HIV-infected than in non–HIV-infected individuals in a British study (Robinson *et al*. 1996). Red gingival banding as a clinical feature alone was, therefore, not strongly associated with HIV infection.

There are indications that candidal infection is the background of some cases of gingival inflammation including LGE (Winkler *et al*. 1988; Robinson *et al*. 1994), but studies have revealed a microflora comprising both *C. albicans* and a number of periopathogenic bacteria consistent with those seen in conventional periodontitis, that is *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Campylobacter rectus* (Murray *et al*. 1988, 1989, 1991). By DNA probe detection, the percentage of positive sites in HIV-associated gingivitis as compared with matched gingivitis sites of HIV-seronegative patients for *A. actinomycetemcomitans* was 23% and 7% respectively, for *P. gingivalis* 52% and 17%, for *P. intermedia* 63% and 29%, and for *C. rectus* 50% and 14% (Murray *et al*. 1988, 1989, 1991). *C. albicans* has been isolated by culture from about 50% of HIV-associated gingivitis sites, 26% of unaffected sites in HIV-seropositive patients, and 3% of healthy sites of HIV-seronegative patients. The frequent isolation and the pathogenic role of *C. albicans* may be related to the high levels of the yeasts in the saliva and oral mucosa of HIV-infected patients (Tylenda *et al*. 1989).

An interesting histopathologic study of biopsy specimens from the banding zone has revealed no inflammatory infiltrate but an increased number of blood vessels, which explains the red color of the lesions (Glick *et al*. 1990). The incomplete inflammatory reaction of the host tissue may be the background to the lack of response to conventional treatment.

A number of diseases present clinical features resembling those of LGE and which, accordingly, do not resolve after improved oral hygiene and debridement. Oral lichen planus is frequently associated with an inflammatory red band of the attached gingiva (Holmstrup *et al*. 1990), as sometimes is mucous membrane pemphigoid (Pindborg 1992) or erythematous lesions associated with renal insufficiency because of the salivary ammonia production associated with the high levels of urea.

There is little information about treatment based on controlled studies. Conventional therapy plus rinsing with 0.12% chlorhexidine gluconate twice daily has been shown to give significant improvement after 3 months (Grassi *et al*. 1989). It was mentioned above that LGE in some cases might be related to the presence of *Candida* strains. In accordance with this finding, clinical observations suggest that improvement is frequently dependent on successful eradication of intraoral *Candida* strains, which results in disappearance of the characteristic features (Winkler *et al*. 1988). Consequently, attempts to identify the presence of fungal infection either by culture or smear is recommended, followed by antimycotic therapy in *Candida*-positive cases.

Histoplasmosis

Histoplasmosis is a granulomatous disease caused by *Histoplasma capsulatum*, a soil saprophyte found mainly in feces from birds and cats. The infection occurs in the North-Eastern, South-Eastern, mid Atlantic, and central states of the US. It is also found in Central and South America, India, East Asia, and Australia. Histoplasmosis is the most frequent systemic mycosis in the US. Airborne spores from the mycelial form of the organism mediate it (Rajah & Essa 1993). In the normal host, the course of the infection is subclinical (Anaissie *et al*. 1986). The clinical manifestations include acute and chronic pulmonary histoplasmosis and a disseminated form, mainly occurring in immunocompromised patients (Cobb *et al*. 1989). Oral lesions have been seen in 30% of patients with pulmonary histoplasmosis and in 66% of patients with the disseminated form (Weed & Parkhill 1948; Loh *et al*. 1989). The oral lesions may affect any area of the oral mucosa (Chinn *et al*. 1995), including the gingiva, which appears to be one of the most frequent sites affected (Hernandez *et al*. 2004). The lesions start as nodular or papillary, and later may become ulcerative with loss of gingival tissue and pain (Figs. 18-12, 18-13). They are sometimes granulomatous and the clinical appearance may resemble a malignant tumor (Boutros *et al*. 1995). The diagnosis is based on clinical appearance and histopathology and/or culture, and the treatment consists of systemic antifungal therapy.

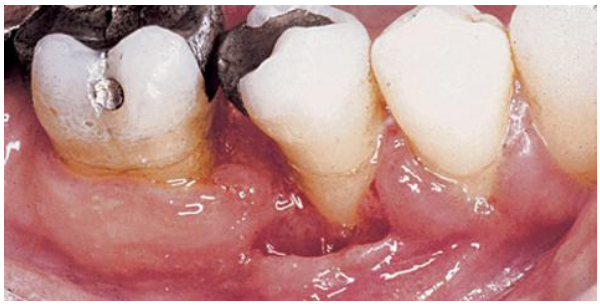

Fig. 18-12 Gingival histoplasmosis with loss of periodontal tissue around the second premolar.

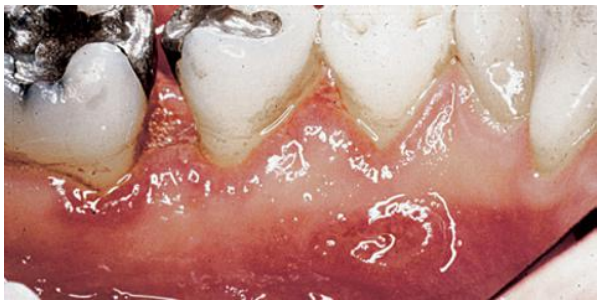

Fig. 18-13 Same patient as shown in Fig. 18-12. Lingual aspect with ulceration in the deeper part of the crater-like lesion.

Gingival lesions of genetic origin

Hereditary gingival fibromatosis

Gingival hyperplasia (synonymous with gingival overgrowth, gingival fibromatosis) may occur as a side effect to systemic medications, including phenytoin, cyclosporine, and nifedipine (Coletta & Graner 2006). These lesions are to some extent plaque dependent and they are reviewed in Chapter 19. Gingival hyperplasia may also be of genetic origin. Such lesions are known as hereditary gingival fibromatosis (HGF), which is an uncommon condition characterized by diffuse gingival enlargement, sometimes covering major parts of or the entire tooth surfaces. The lesions develop irrespective of effective plaque removal.

HGF may be an isolated disease entity or part of a syndrome (Gorlin *et al*. 1990), associated with other clinical manifestations, such as hypertrichosis (Horning *et al*. 1985; Cuestas-Carneiro & Bornancini 1988), mental retardation (Araiche & Brode 1959), epilepsy (Ramon *et al*. 1967), hearing loss (Hartsfield *et al*. 1985), growth retardation (Bhowmick *et al*. 2001), and abnormalities of the extremities (Nevin *et al*. 1971; Skrinjaric & Basic 1989). Most cases are related to an autosomal dominant mode of inheritance, but cases have been described with an autosomal recessive background (Emerson 1965; Jorgensen & Cocker 1974; Singer *et al*. 1993). The most common syndrome of HGF includes hypertrichosis, epilepsy, and mental retardation; the latter two features, however, are not present in all cases (Gorlin *et al*. 1990).

Typically, HGF presents as large masses of firm, dense, resilient, insensitive fibrous tissue that covers

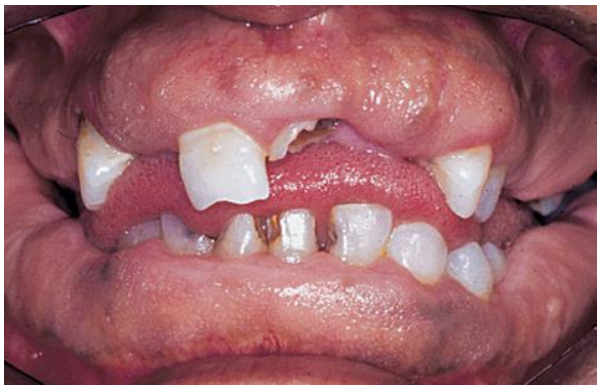

Fig. 18-14 Hereditary gingival fibromatosis. Facial aspect with partial coverage of teeth.

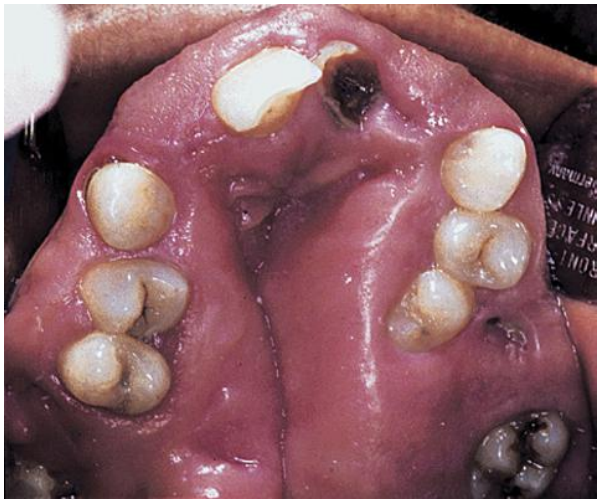

Fig. 18-15 Same patient as shown in Fig. 18-14. The maxillary gingival fibromatosis is severe and has resulted in total disfiguration of the dental arch.

the alveolar ridges and extends over the teeth, resulting in extensive pseudopockets. The color may be normal or erythematous if inflamed (Figs. 18-14, 18-15). Depending on the extent of the gingival enlargement, patients complain of functional and esthetic problems. The enlargement may result in protrusion of the lips and the patient may chew on a considerable hyperplasia of tissue covering the teeth. HGF is seldom present at birth but may be noted at an early age. If the enlargement is present before tooth eruption, the dense fibrous tissue may interfere with or prevent the eruption (Shafer *et al*. 1983).

Studies have suggested that an important pathogenic mechanism may be enhanced production of transforming growth factor-beta1 (TGF-β1) which reduces the proteolytic activities of HGF fibroblasts, which again favors the accumulation of extracellular matrix (Coletta *et al*. 1999). A locus for autosomal dominant HGF has been mapped to a region on chromosome 2 (Hart *et al*. 1998; Xiao *et al*. 2000), although at least two genetically distinct loci seem to be responsible for this type of HGF (Hart *et al*. 2000) and a novel locus for maternally inherited human gingival fibromatosis has been reported at human chromosome 11p15 (Zhu *et al*. 2006).

The histologic features of HGF include moderate hyperplasia of a slightly hyperkeratotic epithelium with extended rete pegs. The underlying stroma is almost entirely made up of dense collagen bundles with only a few fibroblasts. Local accumulation of inflammatory cells may be present (Shafer *et al*. 1983). Histologic examination may facilitate the differential diagnosis from other genetically determined gingival enlargements, such as Fabry's disease, characterized by telangiectasia.

The treatment is surgical removal, often in a series of gingivectomies, but relapses are not uncommon. If the volume of the overgrowth is extensive, a repositioned flap to avoid exposure of connective tissue by gingivectomy may better achieve elimination of pseudopockets.

Gingival diseases of systemic origin

Mucocutaneous disorders

A variety of mucocutaneous disorders present gingival manifestations, sometimes in the form of desquamative lesions or ulceration of the gingiva. The most important of these diseases are lichen planus, pemphigoid, pemphigus vulgaris, erythema multiforme, and lupus erythematosus.

Lichen planus

Lichen planus is the most common mucocutaneous disease manifesting on the gingiva. The disease may affect the skin and oral as well as other mucosal membranes in some patients, while others may present with either skin or oral mucosal involvement alone. Oral involvement alone is common and concomitant skin lesions in patients with oral lesions have been found in 5–44% of cases (Andreasen 1968; Axéll & Rundquist 1987). The disease may be associated with severe discomfort and since it has been shown to possess a premalignant potential (Holmstrup 1992), it is important to diagnose and treat the patients and to follow them at the regular oral examinations (Holmstrup *et al*. 1988; Mattson *et al*. 2002; Mignogna *et al*. 2007).

The prevalence of oral lichen planus (OLP) in various populations has been found to be 0.1–4% (Scully *et al*. 1998a). The disease may afflict patients at any age, although it is seldom observed in childhood (Scully *et al*. 1994).

Skin lesions are characterized by papules with white striae (Wickham striae) (Fig. 18-16). Itching is a common symptom, and the most frequent locations are the flexor aspects of the arms, thighs, and neck. In the vast majority of cases, the skin lesions disappear spontaneously after a few months, which is in sharp contrast to the oral lesions, which usually persist for many years (Thorn *et al*. 1988).

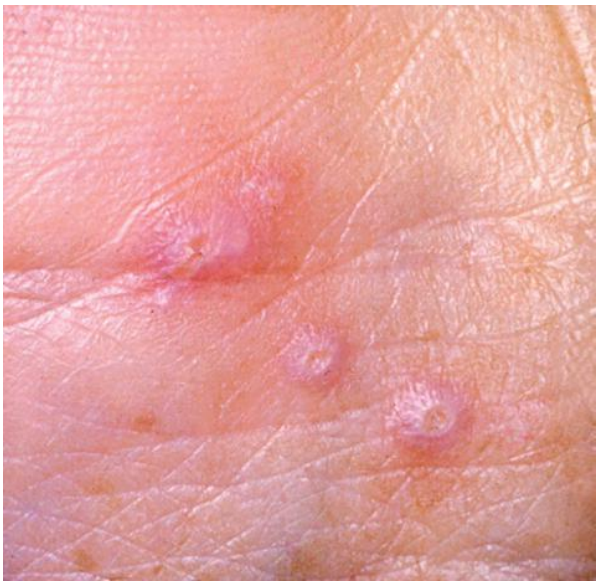

Fig. 18-16 Skin lesions of lichen planus. Papules with delicate white striations.

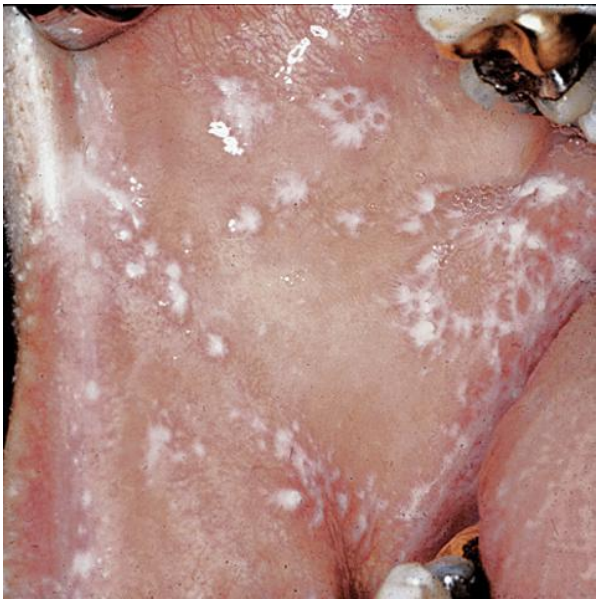

Fig. 18-17 Oral lichen planus. Papular lesion of right buccal mucosa.

A variety of clinical appearances is characteristic of OLP. These include:

- Papular (Fig. 18-17)
- Reticular (Figs. 18-18, 18-19)
- Plaque-like (Fig. 18-20)
- Erythematous (atrophic) (Figs. 18-21, 18-22, 18-23, 18-24, 18-25)
- Ulcerative (Figs. 18-22, 18-26)
- Bullous (Fig. 18-27).

The simultaneous presence of more than one type of lesion is common (Thorn *et al*. 1988). The most characteristic clinical manifestations of the disease and the basis of the clinical diagnosis are white papules (Fig. 18-17) and white striations (Figs. 18-18, 18-19,

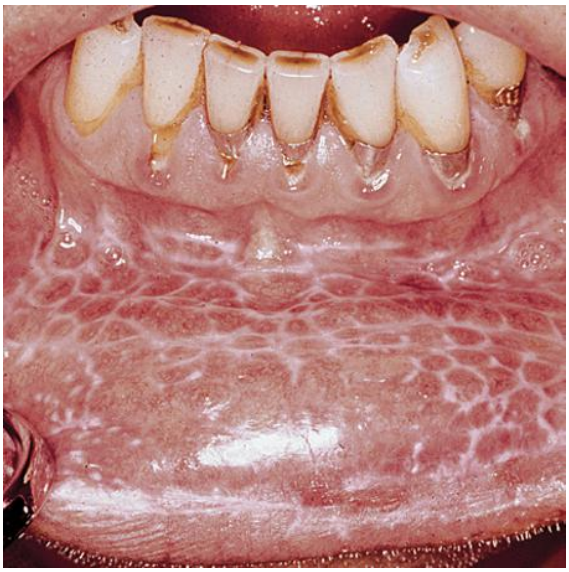

Fig. 18-18 Oral lichen planus. Reticular lesion of lower lip mucosa. The white striations are denoted Wickham's striae.

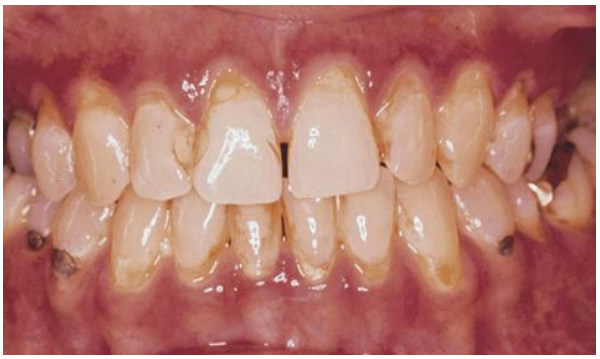

Fig. 18-21 Oral lichen planus. Erythematous lesions of facial maxillary and mandibular gingiva. Such lesions were previously termed desquamative gingivitis. Note that the margin of the gingiva has a normal color in the upper incisor region, which distinguishes the lesions from plaque-induced gingivitis.

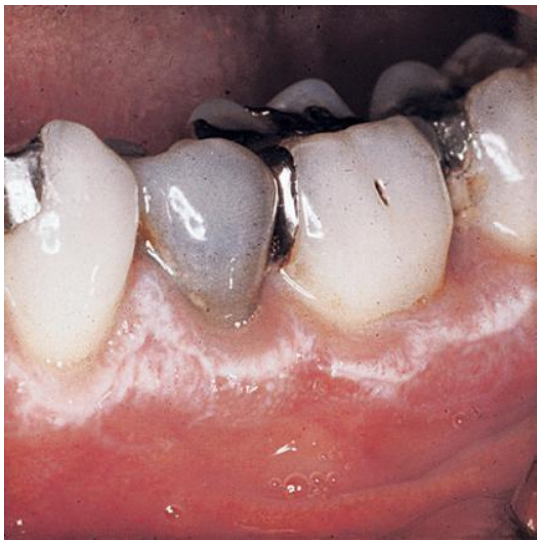

Fig. 18-19 Oral lichen planus. Reticular lesions of gingiva in the lower left premolar and molar region.

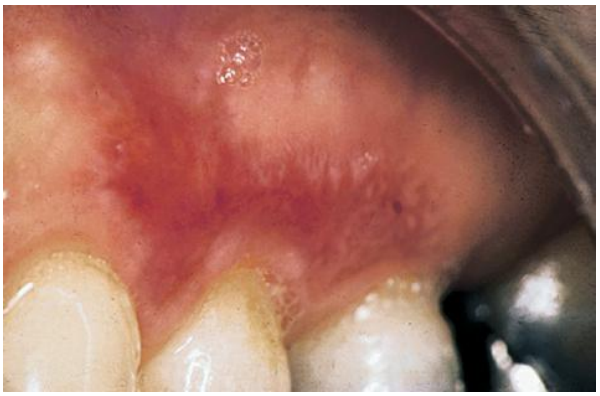

Fig. 18-22 Oral lichen planus. Erythematous and ulcerative lesion of the maxillary gingiva.

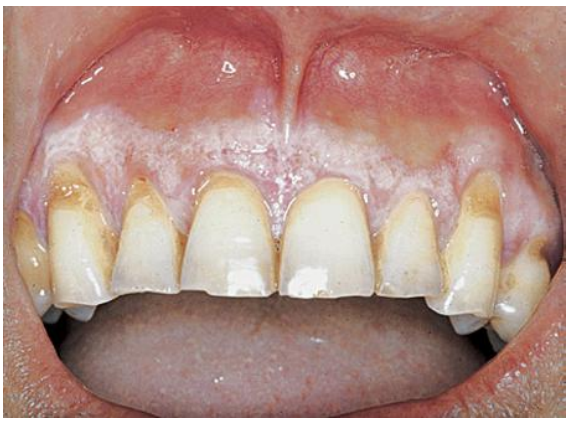

Fig. 18-20 Oral lichen planus. Plaque-type lesion of maxillary gingiva.

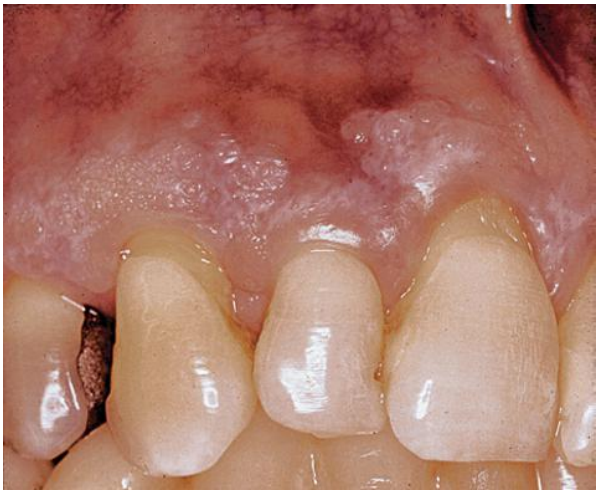

Fig. 18-23 Oral lichen planus. Erythematous and reticular lesion of maxillary gingiva. Several types of lesions are often present simultaneously.

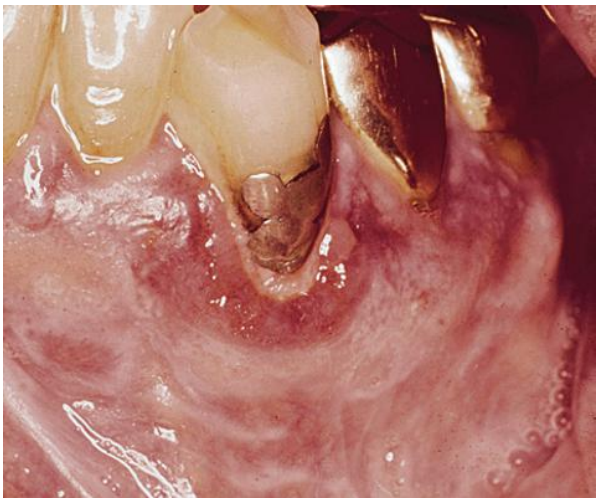

Fig. 18-24 Oral lichen planus. Erythematous and reticular lesion of the lower left canine region. Plaque accumulation results in exacerbation of oral lichen planus, and erythematous lesions compromise oral hygiene procedures. This may lead to a vicious circle that the dentist can help in breaking.

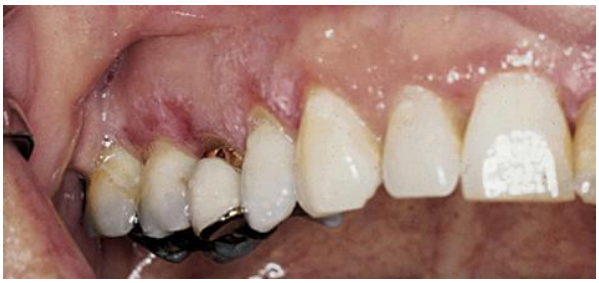

Fig. 18-25 Oral lichen planus. Erythematous and reticular lesion of right maxillary gingiva in a patient using an electric toothbrush, which is traumatic to the marginal gingiva. The physical trauma results in exacerbation of the lesion with erythematous characteristics and pain.

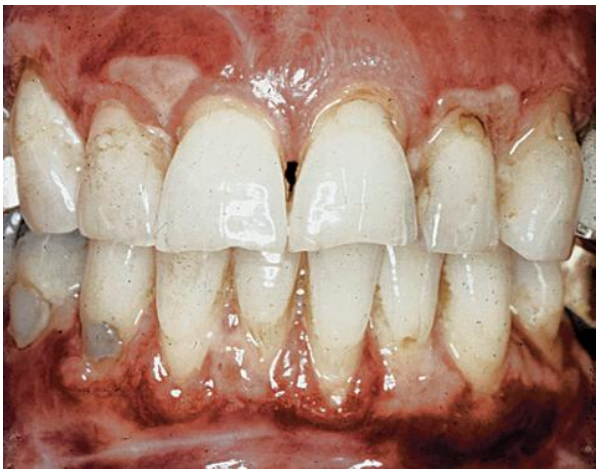

Fig. 18-26 Oral lichen planus. Erythematous and ulcerative/reticular lesions of the maxillary and mandibular incisor regions. This 48-year-old woman suffered from severe discomfort when eating, drinking, and toothbrushing.

18-26, 18-28), which often form reticular patterns (Thorn *et al*. 1988), usually bilaterally (Ingafou *et al*. 2006). Sometimes erythematous and ulcerative lesions are referred to as erosive (Rees 1989). Papular,

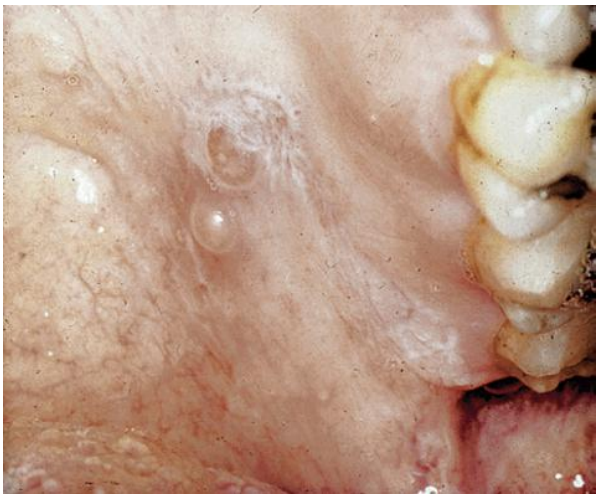

Fig. 18-27 Oral lichen planus. Bullous/reticular lesion of the left palatal mucosa.

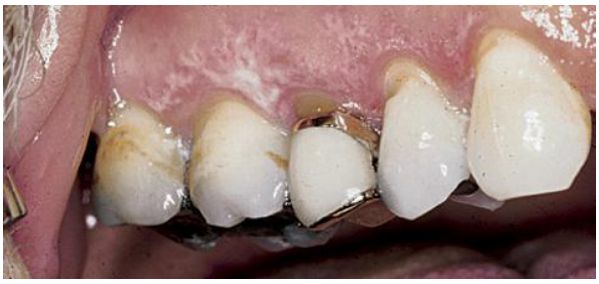

Fig. 18-28 Same patient as shown in Fig. 18-25 after modified toothbrushing procedure with no traumatic action on the marginal gingiva. There is no longer pain.

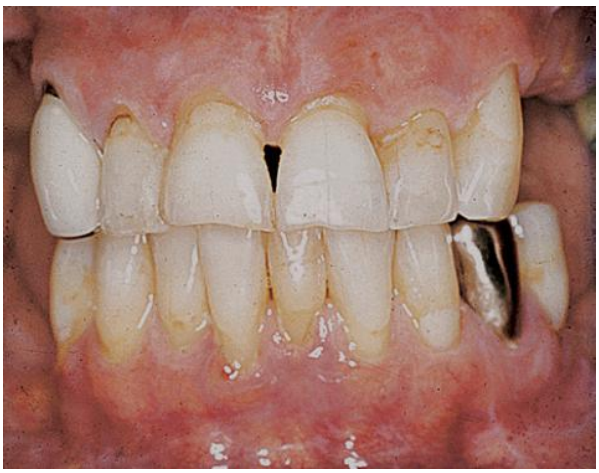

Fig. 18-29 Same patient as shown in Fig. 18-26 after periodontal treatment and extraction of teeth with deep pockets. An individual oral hygiene program, which ensured gentle, meticulous plaque removal, has been used by the patient for 3 months. The erythematous/ulcerative lesions are now healed and there are no more symptoms.

reticular, and plaque-type lesions usually do not give rise to significant symptoms, whereas erythematous and ulcerative lesions are associated with moderate-to-severe pain, especially in relation to oral hygiene procedures and eating. Any area of the oral mucosa may be affected by OLP, but the lesions often change in clinical type and extent over the years. Such changes

may imply the development of plaque-type lesions, which are clinically indistinguishable from oral leukoplakia. This may give rise to a diagnostic problem if other lesions more characteristic of OLP have disappeared (Thorn *et al*. 1988).

A characteristic histopathologic feature in OLP is a subepithelial, band-like accumulation of lymphocytes and macrophages characteristic of a type IV hypersensitivity reaction (Eversole *et al*. 1994). The epithelium shows hyperortho- or hyperparakeratinization and basal cell disruption with transmigration of lymphocytes into the basal and parabasal cell layers (Eversole 1995). The infiltrating lymphocytes have been identified as CD4- and CD8-positive cells (Buechner 1984; Walsh *et al*. 1990; Eversole *et al*. 1994). Other characteristic features are Civatte bodies, which are dyskeratotic basal cells. Common immunohistochemical findings of OLP lesions are fibrin in the basement membrane zone, and deposits of IgM, C3, C4, and C5 may also be found. None of these findings is specific for OLP (Schiødt *et al*. 1981; Kilpi *et al*. 1988; Eversole *et al*. 1994).

The subepithelial inflammatory reaction in OLP lesions is presumably due to an unidentified antigen in the junctional zone between the epithelium and connective tissue or to components of basal epithelial cells (Holmstrup & Dabelsteen 1979; Walsh *et al.* 1990; Sugerman *et al*. 1994). A lichen planus-specific antigen in the stratum spinosum of skin lesions has been described (Camisa *et al*. 1986), but does not appear to play a significant role in oral lesions since it is rarely identified there. It is still an open question whether OLP is a multivariate group of etiologically diverse diseases with common clinical and histopathologic features or a disease entity characterized by a type IV hypersensitivity reaction to an antigen in the basement membrane area. The clinical diagnosis is based on the presence of papular or reticular lesions. The diagnosis may be supported by histopathologic findings of hyperkeratosis, degenerative changes of basal cells, and subepithelial inflammation dominated by lymphocytes and macrophages (Holmstrup 1999).

The uncertain background of OLP results in several border zone cases of so-called oral lichenoid lesions (OLLs), a final diagnosis for which is difficult to establish (Thornhill *et al*. 2006). The most common OLLs are probably lesions in contact with dental restorations (Holmstrup 1991) (see later in this chapter). Other types of OLL are associated with various types of medications, including antimalarials, quinine, quinidine, non-steroidal anti-inflammatory drugs, thiazides, diuretics, gold salts, penicillamine, and beta-blockers (Scully *et al*. 1998a). Graft-versus-host reactions are also characterized by a lichenoid appearance (Fujii *et al*. 1988) and a group of OLLs is associated with systemic diseases including liver disease (Fortune & Buchanan 1993; Bagan *et al*. 1994; Carrozzo *et al*. 1996). This appears to be particularly evident in Southern Europe and Japan where hepatitis C has been found in 20–60% of OLL cases (Bagan *et al*. 1994; Gandolfo *et al*. 1994; Nagao *et al*. 1995).

Several follow-up studies have demonstrated that OLP is associated with increased development of oral cancer, the frequency of cancer development being in the range of 0.5–2% (Holmstrup *et al.* 1988; Mattson *et al*. 2002; Ingafou *et al*. 2006; Mignogna *et al*. 2007).

When gingiva is involved, the most important part of the therapeutic regimen is atraumatic meticulous plaque control, which results in significant improvement in many patients (Holmstrup *et al*. 1990) (Figs. 18-25, 18-26, 18-28, 18-29). Individual oral hygiene procedures with the purpose of effective plaque removal without traumatic influence on the gingival tissue should be established for all patients with symptoms. In cases of persistent pain, typically associated with atrophic and ulcerative lesions, antifungal treatment may be necessary if the lesions host yeast, which is the case in 37% of OLP cases (Krogh *et al*. 1987). In painful cases who have not responded to the treatment above, topical corticosteroids, preferably in a paste or an ointment, should be used three times daily for a number of weeks. However, in such cases, relapses are very common, which is why intermittent periods of treatment may be needed over an extended period of time.

Pemphigoid

Pemphigoid is a group of disorders in which autoanibodies towards components of the basement membrane result in detachment of the epithelium from the connective tissue. Bullous pemphigoid predominantly affects the skin, but oral mucosal involvement may occur (Brooke 1973; Hodge *et al*. 1981). If only mucous membranes are affected, the term benign mucous membrane pemphigoid (BMMP) is often used. The term cicatricial pemphigoid is also used to describe subepithelial bullous disease limited to the mouth or eyes and infrequently other mucosal areas. This term is problematic for the oral lesions, because usually oral lesions do not result in scarring, whereas this is an important concern for ocular lesions (Scully *et al*. 1998b). It is now evident that BMMP comprises a group of disease entities characterized by an immune reaction involving autoantibodies directed against various basement membrane zone antigens (Scully & Laskaris 1998). These antigens have been identified as hemidesmosome or lamina lucida components (Leonard *et al*. 1982, 1984; Manton & Scully 1988; Domloge-Hultsch *et al*. 1992, 1994), and sera from patients with oral lesions have been shown to recognize the alpha-6 integrin subunit (Rashid *et al*. 2006). In addition, complement-mediated cell destructive processes may be involved in the pathogenesis of the disease (Eversole 1994). The trigger mechanisms behind these reactions, however, have not yet been revealed.

The majority of affected patients are female with a mean age at onset of 50 years or over

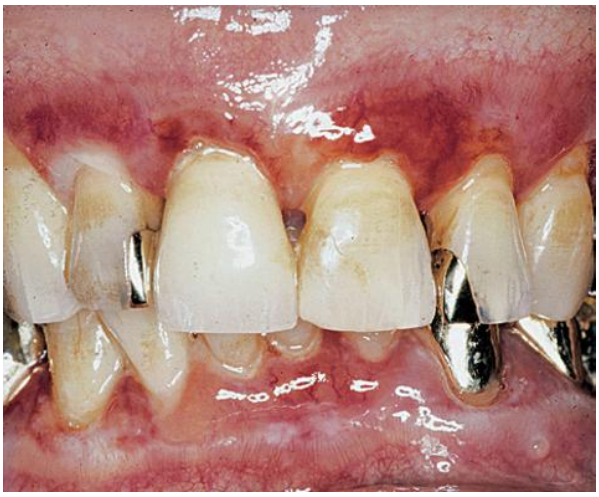

Fig. 18-30 Benign mucous membrane pemphigoid affecting the attached gingiva of both jaws. The lesions are erythematous and resemble erythematous lichen planus lesions. They result in pain associated with oral procedures, including eating and oral hygiene procedures.

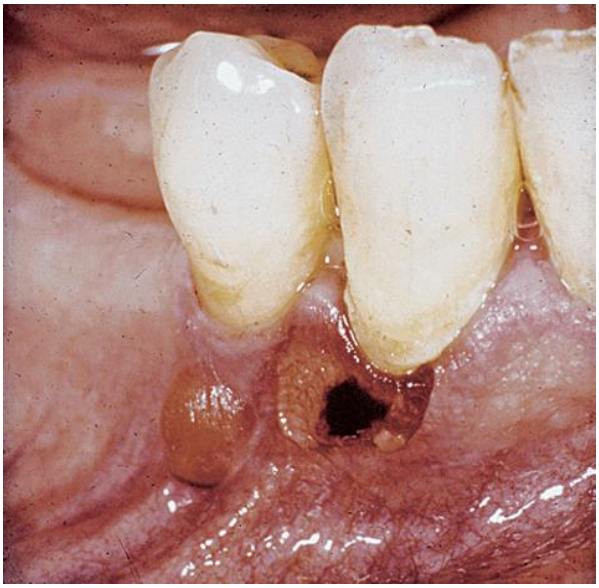

Fig. 18-31 Benign mucous membrane pemphigoid with intact and ruptured gingival bulla.

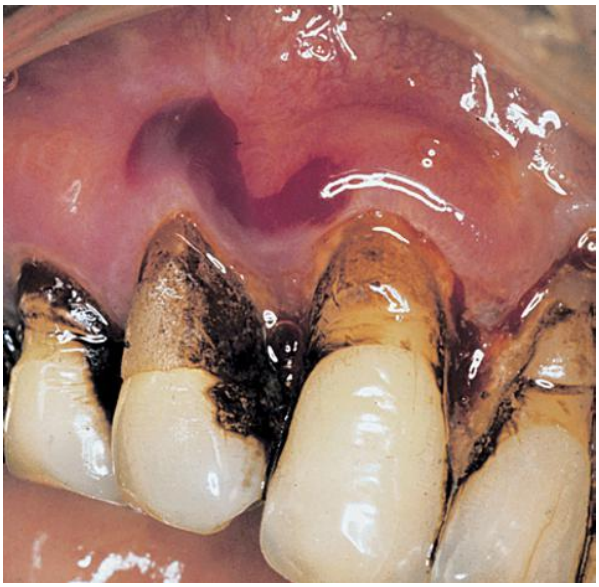

Fig. 18-32 Benign mucous membrane pemphigoid with hemorrhagic gingival bulla. The patient uses chlorhexidine for daily plaque reduction.

Fig. 18-33 Benign mucous membrane pemphigoid. Eye lesion with scar formation due to coalescence of palpebral and conjunctival mucosa.

(Shklar & McCarthy 1971). Oral involvement in BMMP is almost inevitable and usually the oral cavity is the first site of disease activity (Silverman *et al*. 1986; Gallagher & Shklar 1987). Any area of the oral mucosa may be involved in BMMP, but the main manifestation is desquamative lesions of the gingiva presenting as intensely erythematous attached gingiva (Laskaris *et al*. 1982; Silverman *et al*. 1986; Gallagher & Shklar 1987) (Fig. 18-30). The inflammatory changes, as always when not caused by plaque, may extend over the entire gingival width and even over the mucogingival junction. Rubbing the gingiva may precipitate bulla formation (Dahl & Cook 1979). This is denoted a positive Nicholsky sign and is caused by the destroyed adhesion of the epithelium to the connective tissue. The intact bullae are often clear to yellowish or they may be hemorrhagic (Figs. 18-31, 18-32). This, again, is due to the separation of epithelium from connective tissue at the junction, resulting in exposed vessels inside the bullae. Usually, the bullae rupture rapidly leaving fibrin-coated ulcers. Sometimes, tags of loose epithelium can be found due to rupture of bullae. Other mucosal surfaces may be involved in some patients. Ocular lesions are particularly important because scar formation can result in blindness (Williams *et al.* 1984) (Fig. 18-33).

The separation of epithelium from connective tissue at the basement membrane area is the main diagnostic feature of BMMP. A non-specific inflammatory reaction is a secondary histologic finding. In addition, immunohistochemical examination can help distinguish BMMP from other vesiculobullous diseases, in particular pemphigus, which is life threatening. Deposits of C3, IgG, and sometimes

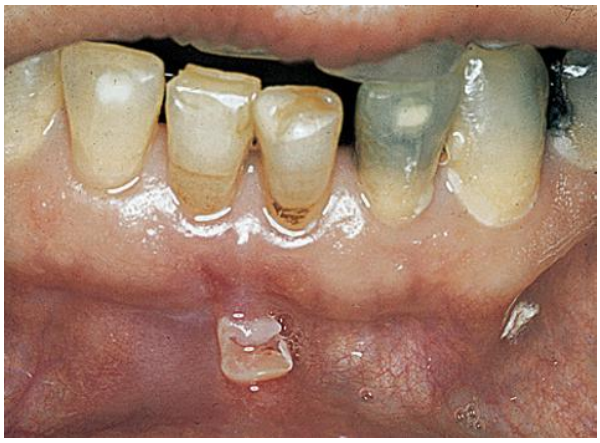

Fig. 18-34 Pemphigus vulgaris. Initial lesion resembling recurrent aphthous stomatitis.

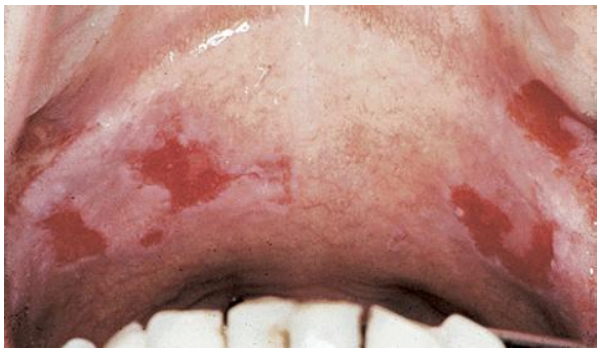

Fig. 18-35 Pemphigus vulgaris. Erosions of soft palatal mucosa. The erosive lesions are due to loss of the superficial part of the epithelium, leaving the connective tissue covered only by the basal cell layers.

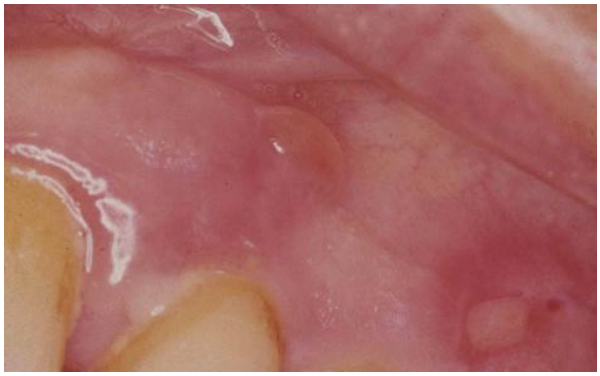

Fig. 18-36 Pemphigus vulgaris. Intact and ruptured gingival bullae.

other immunoglobulins as well as fibrin are found at the basement membrane zone in the vast majority of cases (Laskaris & Nicolis 1980; Daniels & Quadra-White 1981; Manton & Scully 1988). It is important to involve perilesional tissue in the biopsy because the characteristic features may have been lost within lesional tissue (Ullman 1988). Circulating immunoglobulins are not always found in BMMP by indirect immunofluorescence (Laskaris & Angelopoulos 1981). However, a study has shown that 75% of 20 patients with oral pemphigoid phenotype without scarring possessed circulating autoantibodies against the BP180 molecule, indicating a prominent role for this protein as a target antigen in this type of pemphigoid with only oral lesions (Calabresi *et al*. 2007).

Therapy consists of professional atraumatic plaque removal and individual instruction in gentle, but careful, daily plaque control, eventually supplemented with daily use of chlorhexidine and/or topical corticosteroid application if necessary. As for all the chronic inflammatory oral mucosal diseases, oral hygiene procedures are very important and controlling the infection from plaque bacteria may result in a considerable reduction of disease activity and symptoms. It is also important to prevent the development of attachment loss due to periodontitis in those patients with difficulties in maintaining oral hygiene (Tricamo *et al*. 2006). However, the disease is chronic in nature and formation of new bullae is inevitable in most patients. Topical corticosteroids, preferably applied as a paste at night, temper the inflammatory reaction.

Pemphigus vulgaris

Pemphigus is a group of autoimmune diseases characterized by formation of intraepithelial bullae in skin and mucous membranes. The group comprises several variants of which pemphigus vulgaris (PV) is the most common and most serious (Barth & Venning 1987).

Individuals of a Jewish or Mediterranean background are more often affected by PV than others. This is an indication of a strong genetic background to the disease (Pisanti *et al*. 1974). The disease may occur at any age, but is typically seen in the middle-aged or elderly. It presents with widespread bulla formation, often including large areas of skin, and if left untreated the disease is life threatening. Intraoral onset of the disease with bulla formation is very common and lesions of the oral mucosa, including the gingiva, are frequently seen. Early lesions may resemble aphthous ulcers (Fig. 18-34), but widespread erosions are common at later stages (Fig. 18-35). Gingival involvement may present as painful desquamative lesions or as erosions or ulcerations, which are the remains of ruptured bullae (Fig. 18-36). Such lesions may be indistinguishable from BMMP (Zegarelli & Zegarelli 1977; Sciubba 1996). Since the bulla formation is located in the spinous cell layer, the chance of seeing an intact bulla is even more reduced than in BMMP. Involvement of other mucous membranes is common (Laskaris *et al*. 1982). The ulcers heal slowly, usually without scar formation, and the disease runs a chronic course with recurring bulla formation (Zegarelli & Zegarelli 1977).

Diagnosis of PV is based on the characteristic histologic feature of intraepithelial bulla formation due to destruction of desmosomes resulting in acantholysis. The bullae contain non-adhering free epithelial cells, denoted Tzank cells, which have lost their intercellular bridges (Coscia-Porrazzi *et al*. 1985;

Nishikawa *et al*. 1996). Mononuclear cells and neutrophils dominate the associated inflammatory reaction. Immunohistochemistry reveals pericellular epithelial deposits of IgG and C3. Circulating autoantibodies against interepithelial adhesion molecules are detectable in serum samples of most patients, but at the initial stage of the intraoral disease, antiepithelial antibody may not be elevated (Melbye *et al*. 1987; Manton & Scully 1988; Lamey *et al*. 1992; Lever & Schaumburg-Lever 1997). The background to bulla formation in PV is damage to the intercellular adhesion caused by autoantibodies to cadherin-type epithelial cell adhesion molecules (desmoglein 1 and 3) (Nousari & Anhalt 1995; Nishikawa *et al*. 1996; Lanza *et al*. 2006). The mechanism by which these molecules trigger the formation of autoantibodies has not yet been established.

Immediate referral of patients with PV to a dermatologist or internal medicine specialist is important because when recognized late, the disease can be fatal, although systemic corticosteroid therapy can presently treat most cases. Supplementary local treatment consists of gentle plaque control and professional cleaning, as mentioned for the chronic inflammatory oral mucosal diseases earlier. Sometimes, additional topical corticosteroid application is needed to control the intraoral disease activity.

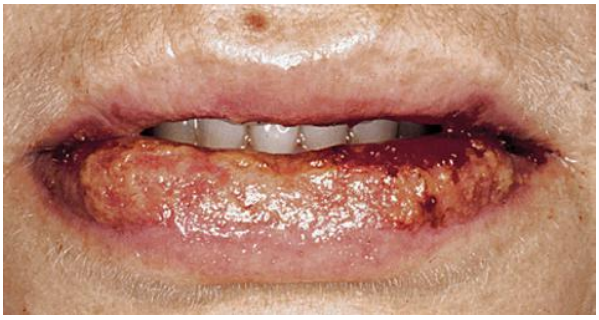

Fig. 18-37 Erythema multiforme with crust formation of the vermilion border of the lower lip.

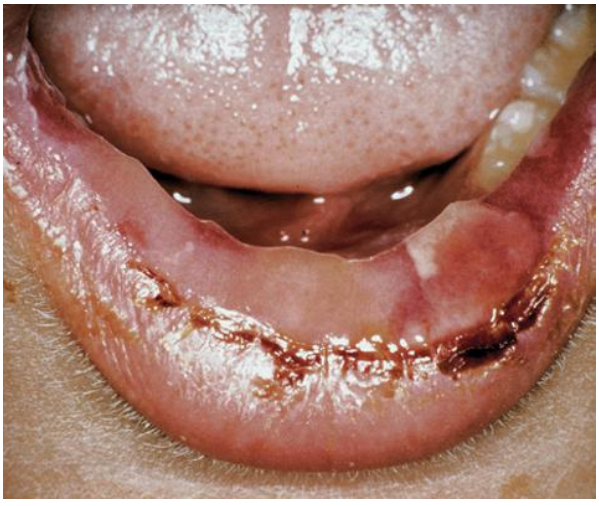

Fig. 18-38 Erythema multiforme with ulceration covered by heavy fibrin exudate.

Erythema multiforme

Erythema multiforme (EM) is a reactive acute, sometimes recurrent, vesiculobullous disease affecting mucous membranes and skin. A general malaise often precedes the lesions. The spectrum of the disease is from a self-limited, mild, exanthematic, cutaneous variant with minimal oral involvement to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis. The latter form of the disease has been described as Stevens–Johnson syndrome, with widespread mucous membrane lesions, that is oral, ocular, and genital, in addition to skin lesions (Lozada-Nur *et al*. 1989; Assier *et al*. 1995; Bystryn 1996; Ayangco & Rogers 2003). The multilocular entity has to be differentiated from other disorders such as Reiter's and Behçet's syndromes, which also affect the eyes, the oral mucosa, and often the genitalia. The pathogenesis of EM remains unknown, but the disease appears to be a cytotoxic immune reaction against keratinocytes (Ayangco & Rogers 2003) precipitated by a wide range of factors, including HSV (Lozada & Silverman 1978; Nesbit & Gobetti 1986; Ruokonen *et al*. 1988; Miura *et al*. 1992; Aurelian *et al*. 1998), *Mycoplasma pneumoniae* (McKellar & Reade 1986; Stutman 1987), and various drugs (Bottiger *et al*. 1975; Gebel & Hornstein 1984; Kauppinen & Stubb 1984).

EM may occur at any age but most frequently affects young individuals. It may or may not involve the oral mucosa, but oral involvement occurs in as many as 25–60% of cases (Huff *et al*. 1983); sometimes it is the only involved site. The characteristic oral lesions comprise swollen lips often with extensive crust formation of the vermilion border (Fig. 18-37). The basic lesions, however, are bullae that rupture and leave extensive ulcers, usually covered by heavy yellowish fibrinous exudates sometimes described as pseudomembranes (Figs. 18-38, 18-39). Such lesions

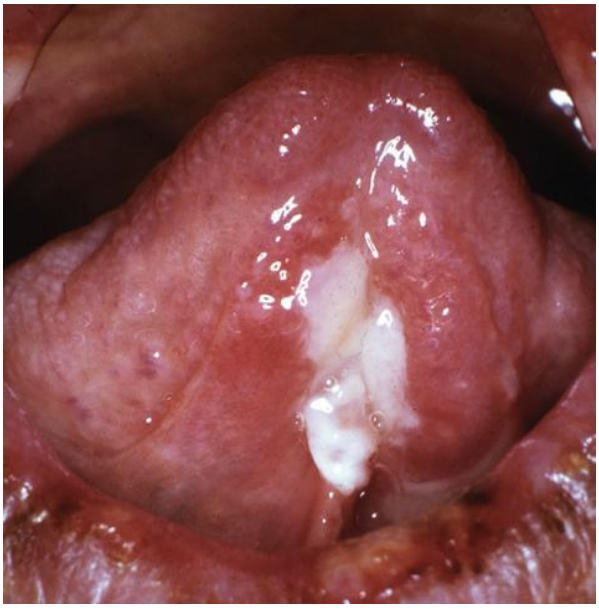

Fig. 18-39 Erythema multiforme. Fibrin-coated ulcerations of the ventral surface of the tongue and lower lip.

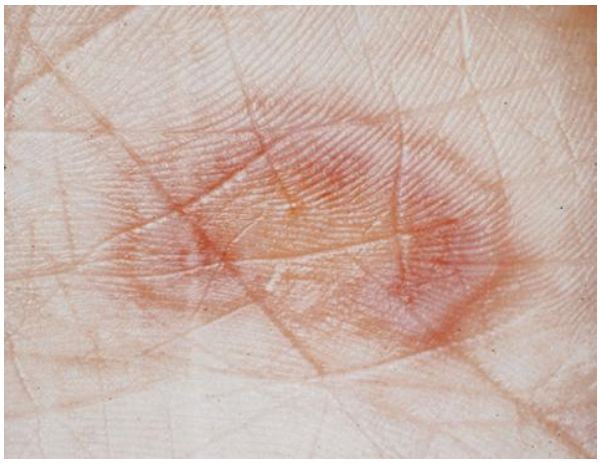

Fig. 18-40 Erythema multiforme. Skin lesion with characteristic iris appearance. A central bulla is surrounded by a blanched halo within an erythematous zone.

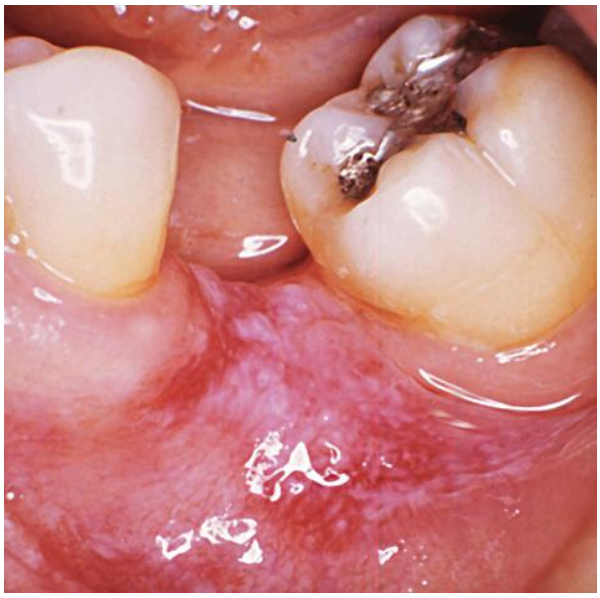

Fig. 18-41 Gingival discoid lupus erythematosus lesion. A central erythematous area with small white dots is surrounded by delicate white striae.

may also involve the buccal mucosa and gingiva (Huff *et al.* 1983; Lozada-Nur *et al*. 1989; Scully *et al*. 1991; Barrett *et al.* 1993). The skin lesions are characteristic due to the iris appearance with a central bulla surrounded by a blanched halo within an erythematous zone (Fig. 18-40). Similar intraoral lesions do occur but they are infrequent. The disease is usually self-limiting but recurrences are common. Healing of the lesions may take several weeks (Fabbri & Panconesi 1993).

The histopathology of EM shows intra- or subepithelial separation of the epithelium from connective tissue with perivascular inflammation (Reed 1985). Immunohistochemical findings are non-specific and in most instances the diagnosis relies on the clinical findings.

Although periodontal lesions are not the most frequent intraoral manifestation, they can sometimes pose a differential diagnostic problem. The typical crusty ulcerations of the vermilion border and the heavy fibrin exudates covering intraoral lesions are indicative of EM, and therefore are sometimes denoted erythema multiforme exudativum. The mucosal ulcerations may take weeks to heal and they are painful (Lozada-Nur *et al*. 1989).

As for any intraoral ulcerations, gentle plaque control and professional cleaning are mandatory. The treatment often involves systemic corticosteroids, but topical treatment may be effective in cases with minor lesions. Cases of recurrent EM caused by herpes infection may require prophylactic use of 400 mg acyclovir twice daily.

Lupus erythematosus

Lupus erythematosus (LE) is a group of autoimmune connective tissue disorders in which autoantibodies form to various cellular constituents, including nucleus and cytoplasmic membrane. All parts of the body may be affected, and the disease is much more prevalent among women than among men. The etiology of LE remains unknown, but deposits of antigen–antibody complexes appear to play a role in the tissue damage characteristic of the disease (Schrieber & Maini 1984). The prevalence of LE has been estimated at 0.05% (Condemi 1987).

There are two major traditional forms: discoid LE (DLE) and systemic LE (SLE), which may involve a range of organ systems, including the kidney, heart, central nervous system, vascular system, and bone marrow. Two new forms, acute and subacute cutaneous LE, have more recently been added to the classification, and represent different degrees of disease activity and increased risk of development of SLE (Wouters *et al*. 2004).

DLE is a mild chronic form, which involves skin and mucous membranes, sometimes including the gingiva as well as other parts of the oral mucosa (Schiødt 1984a, b). The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae with a periphery of telangiectasia (Fig. 18-41). The lesions can be ulcerated or clinically indistinguishable from leukoplakia or erythematous OLP (Fig. 18-42) (Schiødt 1984b). Sometimes patients present with brownish gingival lesions, which are a side effect of antimalarial drugs prescribed to these patients as part of their treatment (Fig. 18-43). Eight percent of patients with DLE develop SLE, and ulcerations may be a sign of SLE, which has a 25–40% prevalence of oral lesions (Schiødt 1984a; Pisetsky 1986; Jonsson *et al*. 1988). The characteristic Bordeaux-colored "butterfly" skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks (Standefer & Mattox 1986). The systemic type, which can still be fatal because of nephrologic and hematologic complications, also shows skin lesions on the face, but they tend to spread over the entire body.

Diagnosis is based on clinical and histopathologic findings. The epithelial changes, characteristic of oral LE lesions, are hyperkeratosis, keratin plugging,

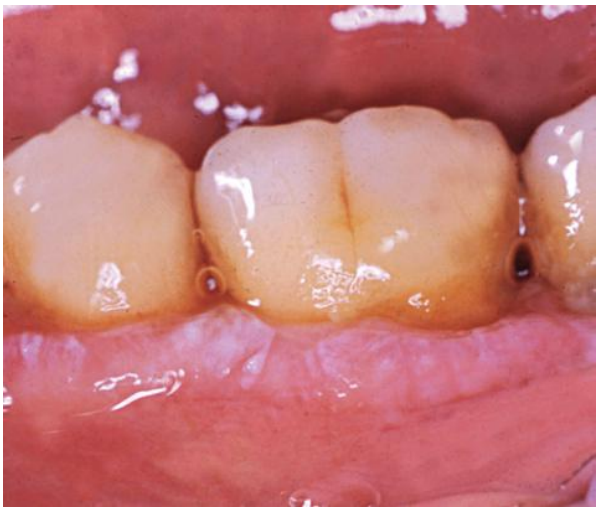

Fig. 18-42 Gingival plaque-type discoid lupus erythematosus lesion resembling frictional keratosis and leukoplakia.

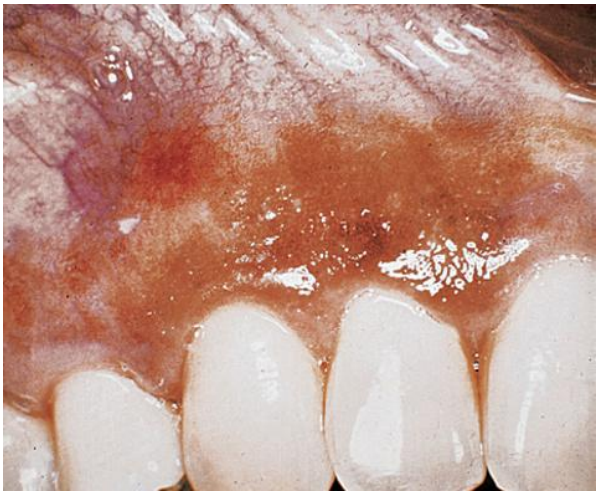

Fig. 18-43 Antimalarial drugs may result in brownish gingival discoloration. This is a patient with discoid lupus erythematosus receiving an antimalarial drug, chloroquine, as part of the treatment regimen.

and variation in epithelial thickness, as well as liquefaction degeneration of basal cells and increased width of the basement membrane. The subepithelial connective tissue harbors inflammation, sometimes resembling OLP, but often with a less distinct band-shaped pattern (Schiødt & Pindborg 1984). Immunohistochemical investigation reveals deposits of various immunoglobulins, C3, and fibrin along the basement membrane (Reibel & Schiødt 1986).

Systemic corticosteroid and other anti-inflammatory treatment regimens are required for SLE. Additional topical treatment is sometimes needed for the resolution of symptomatic intraoral lesions.

Drug-induced mucocutaneous disorders

A number of drugs cause reverse effects in the oral mucosa. Best known in the periodontal field is gingival hyperplasia related to intake of phenytoin, cyclosporine, and nifedipine. Because these lesions to some extent are plaque dependent, they are reviewed in Chapter 19. Other types of drugs may give rise to EM, as mentioned above.

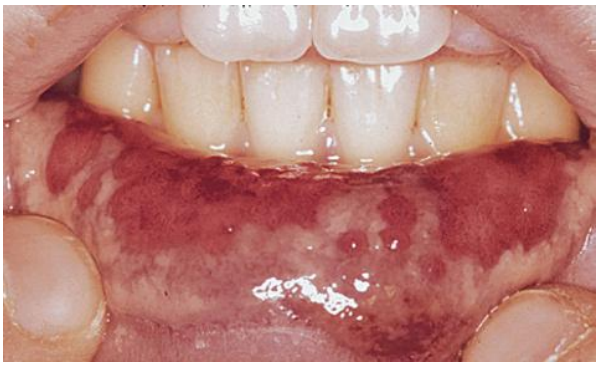

Fig. 18-44 Drug-induced stomatitis sometimes involves the gingiva. This is a mucosal lesion due to azathioprine, which is an antimetabolite used for immunosuppression.

Several other drugs may be associated with adverse effects that include lesions of the oral mucosa. An example is azathioprine, which is an antimetabolite used for immunosuppression in the treatment of autoimmune and other diseases, and to prevent rejection of transplants. Its mode of action is through inhibition of purine base synthesis, resulting in suppression of nucleic acid and protein synthesis, whereby the immune response is inhibited at various stages. Rapidly proliferating tissues such as the bone marrow, hair follicles, and gastrointestinal and oral mucosa may show side effects, for example oral ulceration, including of the gingiva. Other drugs frequently causing stomatitis are antineoplastic drugs used in cancer chemotherapy. Methotrexate is a cytostatic drug sometimes used in the treatment of leukemia and rheumatoid arthritis. Epithelial atrophy, superficial sloughing, intense erythema, and ulceration are characteristic findings in the oral mucosa of patients with adverse effects to chemotherapy (Pindborg 1992) (Fig. 18-44). The ulcerative lesions are frequent portals of entry for microorganisms from the mouth, and thereby are often sources of serious systemic infection in patients with suppression of the bone marrow and reduced defense systems against infection. Professional plaque removal, mouth rinsing with 0.1% chlorhexidine, and a prophylactic antibiotic regimen are important in such patients (Sonis 1998; Holmstrup & Glick 2002).

Allergic reactions

Allergic manifestations in the oral mucosa are uncommon. Several mechanisms may be involved in allergy, which is an exaggerated immune reaction. Oral mucosal reactions may be type I reactions (immediate type), which are mediated by IgE, or more often they are type IV reactions (delayed type) mediated by T cells. The rare intraoral occurrence may be due to the fact that much higher concentrations of allergen are required for an allergic reaction to occur in the oral mucosa than in skin and other surfaces (Amlot *et al*. 1985; Lüders 1987; Holmstrup 1999). This section

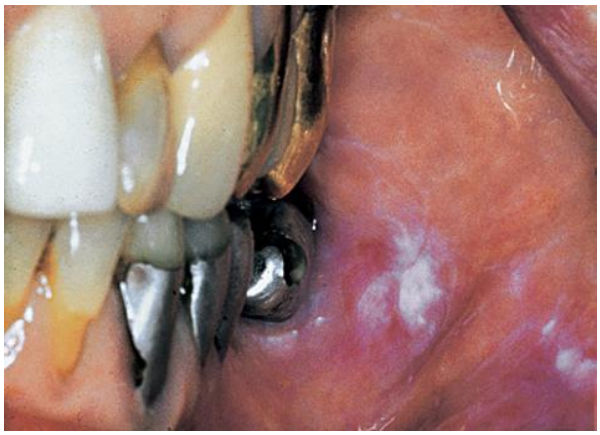

Fig. 18-45 Lichenoid contact lesion of the left buccal mucosa due to type IV hypersensitivity to mercury. The lesion is confined to the zone of contact with the amalgam fillings. These lesions usually recover after replacement of the mercury-containing fillings with composites or other materials devoid of allergy-provoking components.

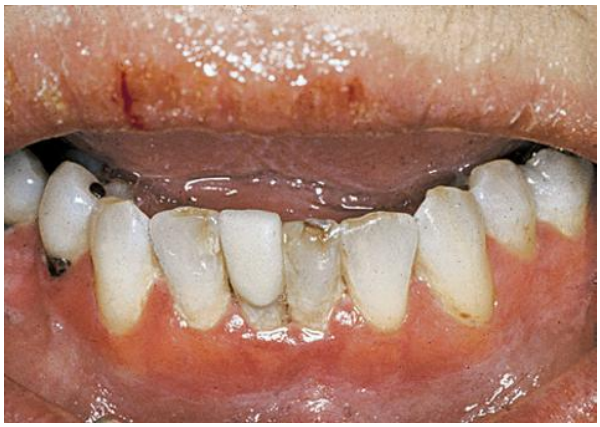

Fig. 18-46 Diffuse gingivitis and cheilitis due to contact allergy to a flavor additive in dentifrice.

covers allergies to dental restorative materials, toothpastes, mouthwashes, chewing gum, and food.

Reactions to dental restorative materials

The clinical manifestation of type IV allergy (contact allergy) occurs after a period of 12–48 hours following contact with the allergen. The effects on oral mucosa have been denoted contact lesions and prior contact with the allergen resulting in sensitization is a prerequisite for these reactions to occur (Holmstrup 1991). Oral mucosal reactions to restorative materials include reactions to mercury, nickel, gold, zinc, chromium, palladium, and acrylics (Ovrutsky & Ulyanow 1976; Zaun 1977; Bergman *et al*. 1980; Council on Dental Materials, Instruments and Equipment Workshop 1984; Fisher 1987). The lesions, which may infrequently affect the gingiva have clinical similarities with those for OLP, which is why they are denoted OLLs (see earlier in this chapter) or oral leukoplakia (Fig. 18-45). They are reddish or whitish, sometimes ulcerated lesions, but one of the crucial diagnostic observations is that the lesions resolve after removal of the offending material. Additional patch testing to identify the exact allergen gives supplementary information, but for dental amalgam it has been shown that there is no obvious correlation between the result of an epicutaneous patch test and the clinical result after removal of the fillings (Skoglund 1994). A clinical manifestation confined to the area of contact with the offending restorative material and the result after replacing this material indicate the diagnosis (Holmstrup 1999).

Reactions to oral hygiene products, chewing gum, and food

Toothpastes, mouth washes, and chewing gum

Contact allergy rarely occurs after the use of toothpastes (Sainio & Kanerva 1995; Skaare *et al*. 1997) and mouth washes (Sainio & Kanerva 1995). The constituents responsible for the allergic reactions may be flavor additives, for instance carvone and cinnamon (Drake & Maibach 1976) or preservatives (Duffin & Cowan 1985). These flavoring additives may be used also in chewing gum and result in similar forms of gingivostomatitis (Kerr *et al*. 1971). The clinical manifestations of allergy include a diffuse, fiery red edematous gingivitis, sometimes with ulcerations or whitening (Fig. 18-46). The labial, buccal, and tongue mucosa may be similarly affected, and cheilitis may also be seen. These characteristic clinical manifestations form the basis of the diagnosis, which may be supported by resolution of the lesions after stopping use of the allergen-containing agent (Holmstrup 1999).

Foods

The gastrointestinal tract is the largest immunologic organ in the body. It is constantly bombarded by a myriad of dietary proteins. Despite the extent of protein exposure, very few patients develop food allergies due to development of oral tolerance to these antigens (Chehade & Mayer 2005). Allergic reactions attributable to food may manifest both as type I and type IV reactions. Type I reaction with severe swelling has been described after intake of food components such as peanuts and pumpkin seed. Birch pollen allergy is associated with some types of oral mucosa allergy, and >20% of patients with oral allergy may be hypersensitive to kiwi, peach, apple, chestnut, and salami (Yamamoto *et al*. 1995; Antico 1996; Asero et al. 1996; Liccardi *et al*. 1996; Rossi *et al*. 1996; Helbling 1997; Wutrich 1997). Another food allergen that can result in gingivitis or gingivostomatitis is red pepper (Serio *et al*. 1991; Hedin *et al*. 1994). Unless it has been demonstrated that the lesions resolve after removal of the allergen, the diagnosis is difficult to establish.

Other gingival manifestations of systemic conditions

Gastrointestinal diseases: Crohn's disease

Crohn's disease is characterized by chronic granulomatous infiltrates of the wall of the last ileal loops, but any part of the gastrointestinal tract can be affected. As the oral cavity is part of the gastrointestinal tract,

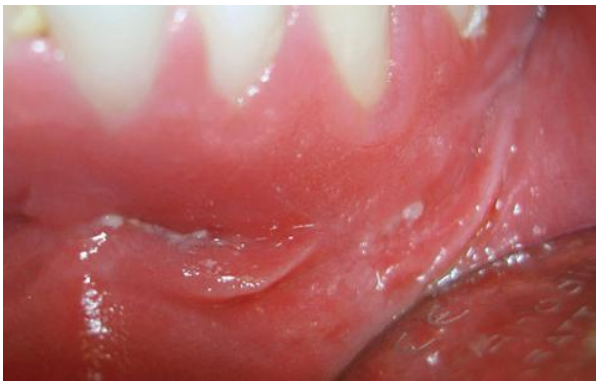

Fig. 18-47 A frequent oral finding in patients with Crohn´s disease is mucosal foldings, usually located in the buccal or labial sulcus. Such lesions may be the first clinical finding that leads to the diagnosis of the disease. Histopathologic examination of biopsies from these foldings reveals epitheloid cell granulomas. The foldings are characteristic for the other types of orofacial granulomatosis as well.

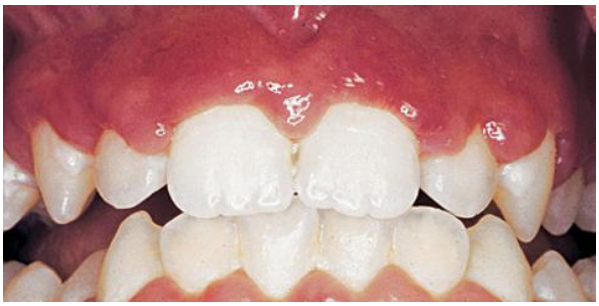

Fig. 18-48 Granulomatous gingival hyperplasia may be due to sarcoidosis, which is one of the orofacial granulomatoses; others are Crohn's disease and Melkersson–Rosenthal syndrome.

it is not surprising that Crohn's disease can occur from the rectum to the lips.

The number of reports of lesions involving the periodontium is limited (van Steenberghe *et al*. 1976), which is probably related to a tradition by many clinicians of using the term aphthous lesions for any ulcerative disease of the oral mucosa. The oral lesions have striking similarity to those of the intestinal tract, as revealed by rectoscopy, that is irregular long ulcerations with elevated borders with a cobblestone appearance. Usually, the periodontal lesions appear after the diagnosis has been established on the basis of the intestinal involvement, but sometimes the oral lesions are the first findings that lead to diagnosis. Characteristic clinical findings are mucosal foldings of the buccal or labial sulcus (Fig. 18-47). Exacerbations of the oral lesions appear in parallel with those of the intestine. An increased risk of periodontal destruction has been reported to be associated with a defective neutrophil function (Lamster *et al*. 1982).

The term orofacial granulomatosis has been used for a collective diagnosis of Crohn's disease, Melkersson–Rosenthal syndrome, and sarcoidosis, because these diseases show the same histopathologic features: non-caseating, epitheloid cell granulomas in the affected tissue. Rarely, all three diseases may present with gingival lesions, characterized by swellings (Pindborg 1992; Mignogna *et al*. 2001) and sarcoidosis, which is sometimes present as a fiery red granular gingival overgrowth (Fig. 18-48). Of 45 cases of oral sarcoidosis, 13% had gingival lesions (Blinder *et al*. 1997). A study of 35 patients with orofacial granulomatosis demonstrated ileal and colonic abnormalities in 54%, and granulomas were revealed in gut biopsies of 64% of the patients. Intestinal abnormality was significantly more likely if the age of onset was <30 years (Sanderson *et al*. 2005).

Local treatment consists of intralesional steroid injection (Mignogna *et al*. 2004; El-Hakim & Chauvin 2004) or paste application daily or twice daily during painful exacerbations, and meticulous oral hygiene to reduce additional inflammation of the oral cavity. Treatment of any inflammatory condition in the oral region, including periodontitis, periapical inflammation, and even mucosal lesions due to hypersensitivity to restorative dental materials, is important for resolution in some cases (Guttman-Yassky *et al*. 2003). An important differential diagnosis is a gingival lesion presumably associated with mouth breathing. This type of lesion, which may resemble those of orofacial granulomatosis, is confined to the area between the maxillary canine teeth. The erythematous surface has a dry and shiny appearance, and the lesion is primarily seen in patients with impaired lip closure. Deposition of bacteria on the facial side of the front teeth and the gingiva, facilitated by mouth breathing, may play a role in the development of this type of gingival lesion, which may also be seen in conjunction with lichenoid lesions of the mucosal side of the upper lip (Bäckman & Jontell 2007).

Hematologic disorders: Leukemia

Leukemia is a malignant hematologic disorder with abnormal proliferation and development of leukocytes and their precursors in blood and bone marrow. It can involve any of the subsets of leukocytes, polymorphonuclear leukocytes, lymphocytes or monocytes. Normal hematopoiesis is suppressed and, in most cases of leukemia, the white blood cells appear in the circulating blood in immature forms. The leukemic cell proliferation at the expense of normal hematopoietic cell lines causes bone marrow failure and a depressed blood cell count. As a consequence of the inability to produce sufficient functional white blood cells and platelets, death may result from infection or bleeding associated with neutropenia and thrombocytopenia, respectively.

The classification of leukemia is based on its course, acute or chronic, and origin of the cells involved. The basic forms are: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). Acute leukemias have an aggressive course, resulting in death within 6 months if untreated. They are rather rare and patients are usually either under 20 or over 60 years

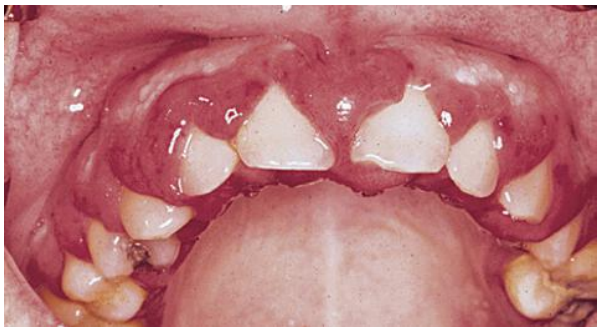

Fig. 18-49 Acute myelogenous leukemia with extensive swelling of the gingiva.

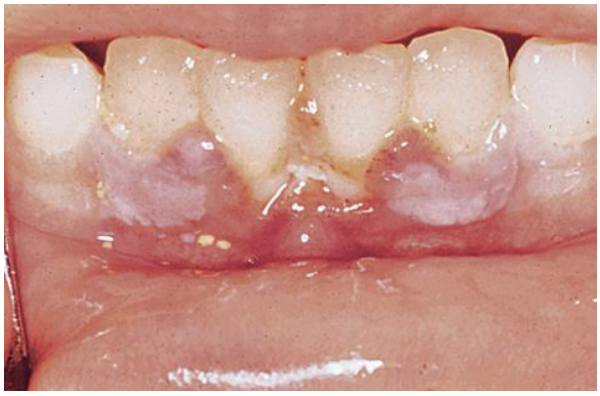

Fig. 18-50 Acute lymphocytic leukemia with gingival ulceration in a child.

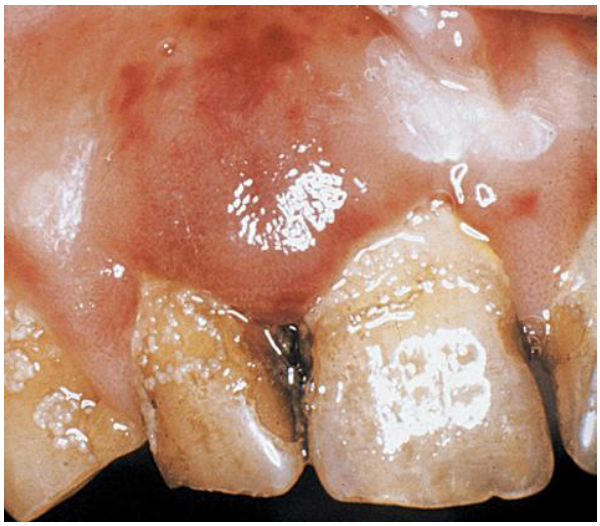

Fig. 18-51 Acute myelogenous leukemia with petechiae and swelling of the gingiva. This patient had several episodes of spontaneous bleeding from the gingiva, which prevented oral hygiene procedures from being undertaken.

of age. Chronic leukemias, of which the lymphocytic form is the most common, have less pronounced bone marrow failure and a more indolent course, usually lasting several years. They occur during adulthood and normally after the age of 40 years. Whereas the peripheral granulocyte count is markedly elevated in chronic leukemia, it may be elevated, decreased or normal in acute leukemia (McKenna 2000).

Gingival manifestations in leukemia, which include extensive swelling (Fig. 18-49), ulceration (Fig. 18-50), petecchia (Fig. 18-51), and erythema, are much more common in acute than in chronic forms. Sometimes, the manifestations lead to the diagnosis of leukemia; 69% of patients with acute leukemia had oral signs of leukemia on examination and 33% of the patients had gingival swelling (Pindborg 1992). In another study, gingival swelling was observed in 21% of AML patients, but in no patients with ALL (Meyer *et al*. 2000). In the latter group, on the other hand, 36% showed both gingival erythema and ulcers. In leukemic children, only 10–17% appear to have gingival swelling (Curtis 1971; Michaud *et al*. 1977). The pronounced gingival swelling seen in patients with leukemia is mostly due to plaque-induced inflammation, since stringent plaque control appears to resolve the swelling (Barrett 1984); it may also be due to the presence of leukemic infiltrates, although this has been reported to be an uncommon feature of patients with leukemia (Barrett 1984). Gingival bleeding due to secondary thrombocytopenia is a common sign in patients with leukemia. It has been reported as the initial sign in 17.7% of patients with acute leukemias and in 4.4% of patients with chronic forms (Lynch & Ship 1967).

In general, the periodontal treatment of patients with leukemia is important; it aims to reduce plaque as a source of bacteremia and damage to the periodontal tissues, both during the disease course and during periods of chemotherapy. In such periods, potentially pathogenic bacteria occur in plaque simultaneously with granulocytopenia (Peterson *et al*. 1990). The reduction of periodontal inflammation may also prevent episodes of gingival bleeding. As with many other patients, chemical plaque control in combination with mechanical debridement appears to be most effective and is the preferred method of periodontal therapy in patients with leukemia (Holmstrup & Glick 2002). However, the increased tendency to bleeding in many of these patients may necessitate the use of alternative methods to toothbrushing. A study of professional plaque removal preceding mouth rinsing with 0.1% chlorhexidine in patients with AML showed that the additional initial removal of plaque and calculus was more effective in reducing gingival inflammation than mouth rinsing with chlorhexidine alone (Bergman *et al*. 1992). A 1-day antibiotic prophylaxis regimen with a combination of piperacillin and netilmicin was given prior to and after the mechanical debridement. Periodontal treatment always involves a close cooperation with the medical department or specialist responsible for coordination of the patient's treatment.

Traumatic lesions

The background to traumatic lesions of the oral tissues may be self-inflicted, iatrogenic or accidental. Chemical as well as physical and thermal injuries may affect the periodontium (Armitage 1999).

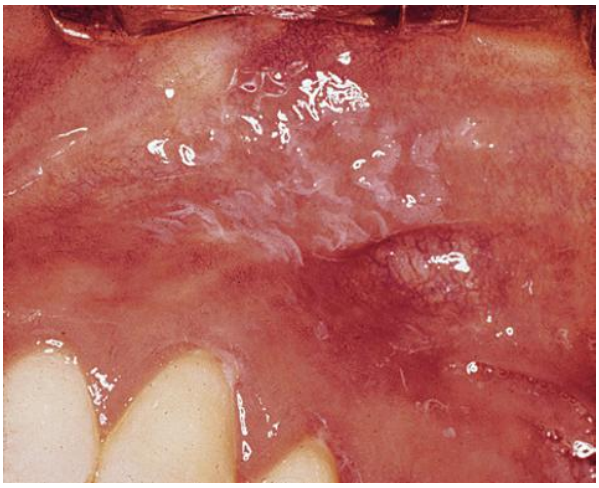

Fig. 18-52 Chlorhexidine-induced mucosal desquamation. This is a reversible type of lesion, which is completely normalized after stopping chlorhexidine use.

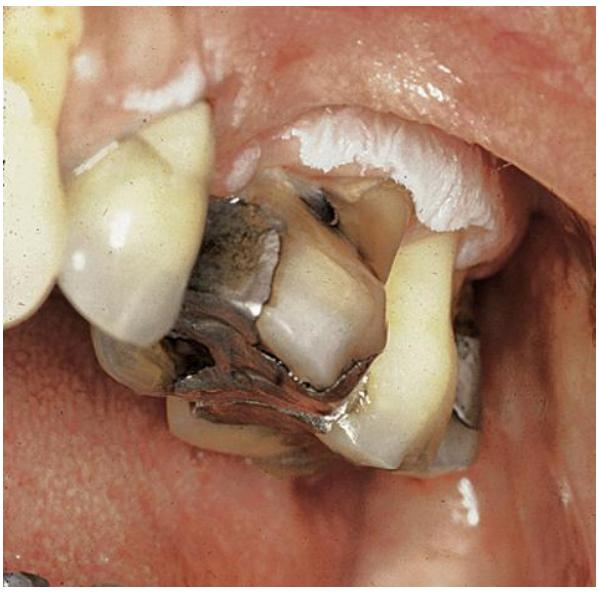

Fig. 18-53 Frictional keratosis due to violent toothbrushing. Note the cervical abrasion of adjacent teeth.

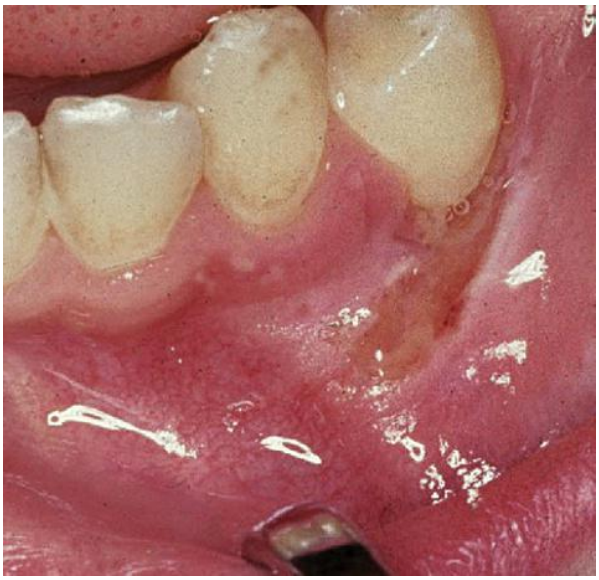

Fig. 18-54 Gingival wounding due to improper toothbrushing. Note the characteristic horizontal extension of the lesion, affecting the most prominent part of the tooth arch.

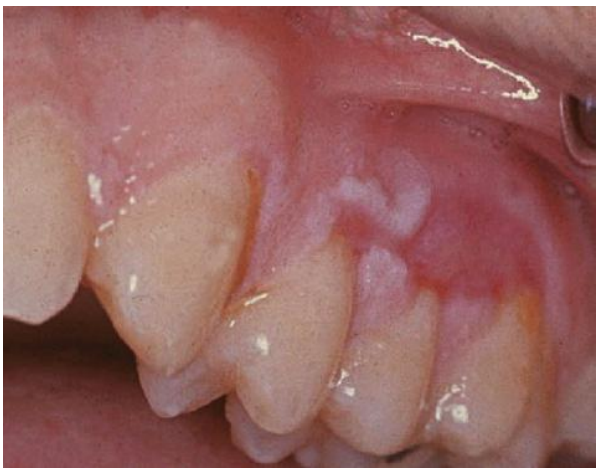

Fig. 18-55 Gingival wounding due to improper toothbrushing. Note the characteristic horizontal extension of the lesion and the uninflamed, unaffected interdental papillae.

Chemical injury

Surface etching by various chemical products with toxic properties may result in mucosal reactions, including reactions of the gingiva. Chlorhexidine-induced mucosal desquamation (Fløtra *et al*. 1971; Almquist & Luthman 1988) (Fig. 18-52), acetylsalicylic acid burn (Najjar 1977), cocaine burn (Dello Russo & Temple 1982), and slough due to dentifrice detergents are examples of such reactions (Muhler 1970). These lesions are reversible and resolve after quitting the toxic influence. Chemical injury to the gingival tissue may be caused by incorrect use of caustics by dentists. Paraformaldehyde used for pulp mummification may give rise to inflammation and necrosis of the gingival tissue if the cavity sealing is insufficient (Di Felice & Lombardi 1998). Usually, the diagnosis is obvious from the clinical findings and the patient history.

Physical injury

Oral hygiene agents and inexpedient procedures can be injurious to the gingival tissues. If physical trauma is limited, the gingival response is hyperkeratosis, resulting in a white leukoplakia-like, frictional keratosis (Fig. 18-53). In cases of more violent trauma, the damage varies from superficial gingival laceration to major loss of tissue resulting in gingival recession (Axéll & Koch 1982; Smukler & Landsberg 1984). Abrasiveness of dentifrice, strong brushing force, and horizontal movement of the toothbrush contribute to the gingival injury even in young patients. Characteristic findings in these patients are extremely good oral hygiene, cervical tooth abrasion, and unaffected tops of the interdental papillae at the site of injury (Figs. 18-54, 18-55, 18-56, 18-57). The condition has been termed traumatic ulcerative gingival lesion (Axéll & Koch 1982). Dental flossing may also cause gingival ulceration and inflammation

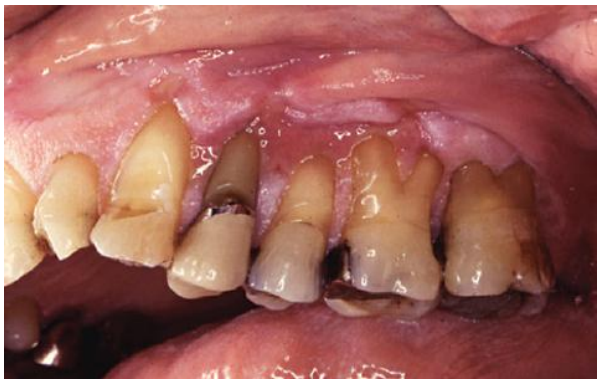

Fig. 18-56 Severe gingival recession and wounding due to improper toothbrushing. Note the unaffected interdental papillae.

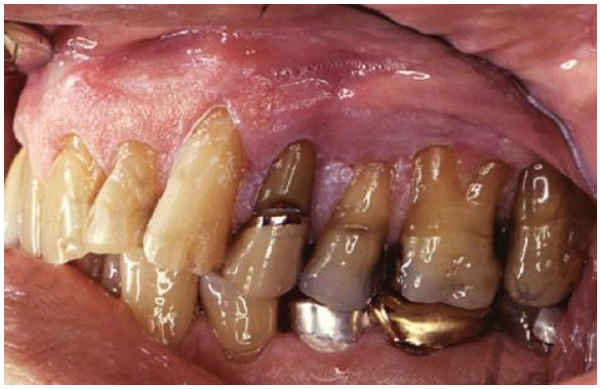

Fig. 18-57 Healing of the lesion shown in Fig. 18-56. The damage to the periodontal tissues is severe, leaving extended gingival recession.

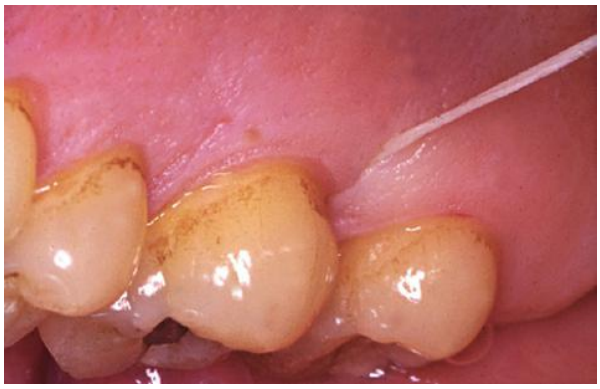

Fig. 18-58 Lesions after dental flossing are common and sometimes result in permanent fissuring of the gingival tissue.

primarily affecting the top of the interdental papillae (Fig. 18-58). The prevalence of such findings is unknown (Gillette & Van House 1980). Diagnosis of physical injuries is based on the clinical findings. An important differential diagnosis is necrotizing gingivitis (Blasberg *et al.* 1981) (see Chapter 22). The latter normally reveals itself as a necrotic gingival margin and interdental papillae, while brushing trauma leads to ulceration of a few millimeters of the gingival margin.

Self-inflicted physical injury to the gingival tissues can occur; sometimes these lesions are termed gingivitis artefacta. The lesions often show ulceration of

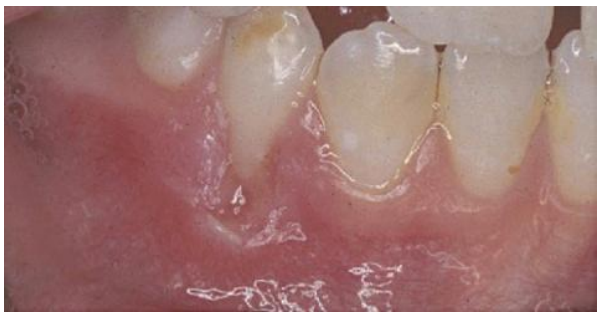

Fig. 18-59 Self-inflicted gingival recession with an ulcerated margin due to this 7-year-old boy's scratching with his fingernail.

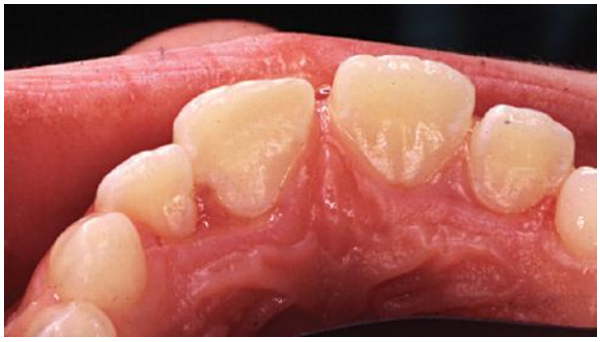

Fig. 18-60 Self-inflicted gingival ulceration of the palatal gingiva of the upper right incisor region in the same boy as shown in Fig. 18-59. This lesion was also caused by fingernail scratching.

the gingival margin and this is often associated with recession. Such lesions are most common in children and young adults and two-thirds appear to occur in female patients. The lesions, which may be hemorrhagic, are usually produced by picking at or scratching the gingiva with a finger or a fingernail (Fig. 18-59, 18-60). Sometimes the lesions are made by instruments (Pattison 1983). The correct diagnosis is often difficult to establish based on clinical findings, and identification of the cause may be impossible.

Thermal injury

Extensive thermal burns of the oral mucosa are very rare, but minor burns particularly from hot beverages, are seen occasionally. Their site of predilection is the palatal and labial mucosa, but any part of the oral mucosa can be involved, including the gingiva (Colby *et al*. 1961). The area involved is painful and erythematous, and may slough a coagulated surface. Vesicles may also occur (Laskaris 1994) and sometimes the lesions present as ulceration, petechia or erosion (Fig. 18-61). Obviously, the history is important for reaching the correct diagnosis. Common causes are hot coffee, pizza, and melted cheese, but dental treatments involving improper handling of hot hydrocolloid impression material, hot wax or cautery instruments are other causes (Colby *et al*. 1961).

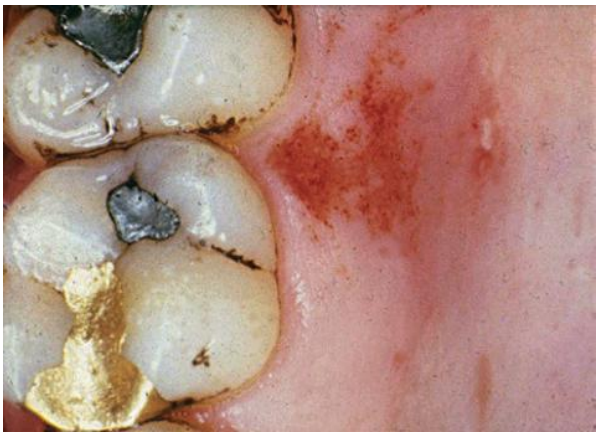

Fig. 18-61 Thermal burn with slight erosion and petechiae of palatal gingiva due to hot coffee intake.

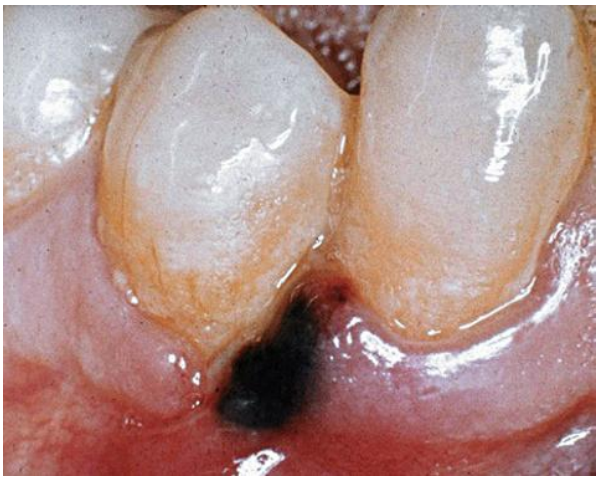

Fig. 18-62 Amalgam tattoo of attached gingiva.

Foreign body reactions

Another type of tissue reaction is established through epithelial ulceration that allows entry of foreign material into the gingival connective tissue. This can happen via abrasion or cutting (Gordon & Daley 1997b), a route of tissue injury, which is best exemplified by the amalgam tattoo (Buchner & Hansen 1980) (Fig. 18-62). Gingival inflammation associated with foreign bodies has been termed foreign body gingivitis. A clinical study of this condition has shown that it often presents as a red or combined red–white painful chronic lesion which is frequently misdiagnosed as lichen planus (Gordon & Daley 1997a). An X-ray microanalysis of foreign body gingivitis showed that most of the identified foreign bodies were of dental material origin, usually abrasives (Gordon & Daley 1997b). Another way in which foreign substances can enter the tissues is self-inflicted injury, for instance due to chewing on sticks or self-induced tattooing (Gazi 1986). It is uncertain whether the inflammatory reaction in such cases is due to a toxic or an allergic reaction.

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Chapter 19

Plaque-Induced Gingival Diseases

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For almost four millennia the clinical manifestations of gingival diseases have been noted by mankind. Throughout the centuries the notion of cause, effect, and management of these diseases was largely dormant, resulting in a dubious realm of remedies that were dominated by superstition, frequently were subjective, often palliative, sometimes painful, and rarely successful. It was not until the last half of the 20th century that our views about the nature of gingival diseases began to emerge, with pivotal human experiments showing the unmistakable role of dental biofilms in the initiation and progression of gingival inflammation (Löe *et al*. 1965). In the 21st century, we are living in a time of radical shifts of culture and science, one in which evidence-based dentistry increasingly plays a pervasive role in our knowledge regarding gingival diseases.

As more clinical evidence becomes available, the scope and nature of various forms of gingivitis become evident. More specifically, there has been growing acceptance that gingivitis does not represent a single disease but rather a spectrum of diseases that are the outcome of a variety of different processes. It is true that inflammation of the gingiva induced by bacteria is the most common form of gingivitis; however, this has created a bias toward naming all manifestations that affect the gingival tissues (e.g. atrophic, desquamative, neoplastic, etc.) as gingivitis. Although inflammation of the gingival tissues can be induced by a variety of methods (e.g. trauma, chemical agents, temperature extremes, ionizing radiation, viruses, fungi, immune defects, etc.), at this time gingival diseases are considered to be disease entities that are initiated by dental plaque and are restricted to gingival tissues. This chapter will focus on the commonly occurring and diverse family of complex and distinct pathologic entities found within the gingiva that are initiated by dental plaque and that can be influenced by systemic conditions, endogenous hormones, genetic factors, drugs, and malnutrition.

Classification criteria for gingival diseases

Categorization of diseases affecting the gingiva requires an evaluation of patient signs and symptoms, medical and dental histories, a clinical examination that includes the extent, distribution, duration, and physical description of lesions affecting the gingiva, clinical or relative attachment levels, and radiographs. The universal features of gingival diseases include clinical signs of inflammation, signs and symptoms

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

Table 19-1 Universal features of gingival diseases.

- Signs and symptoms that are confined to the gingiva
- Presence of dental plaque to initiate and/or exacerbate the severity of the lesion
- Clinical signs of inflammation (enlarged gingival contours due to edema or fibrosis, color transition to a red and/or bluish-red hue, elevated sulcular temperature, bleeding upon stimulation, increased gingival exudate)
- Clinical signs and symptoms associated with stable attachment levels on a periodontium with no loss of attachment or on a stable but reduced periodontium (see Fig.19-8)
- Reversibility of the disease by removing the etiology(ies)
- Possible role as a precursor to attachment loss around teeth

Source: Mariotti (1999). Reproduced from the American Academy of Periodontology.

Table 19-2 Common clinical changes from gingival health to gingivitis.

Parameter	Normal gingiva	Gingivitis
Color	Coral pink (correlated to mucocutaneous pigmentation)	Red/bluish-red hue
Contour	Scalloped outline that envelops teeth. Papillary gingiva fills interdental space while marginal gingival forms a knife-edged appearance with tooth surface	Edema blunts marginal tissues leading to loss of knife edge adaptation to tooth and produces bulbous papillary tissues resulting in minimization of tissue scalloping
Consistency	Firm and resilient	Tissue is soft and exhibits pitting edema
Bleeding on provocation	Negative	Positive
Gingival exudate	Minimal	Significantly increased
Sulcular temperature	~34 °C	Slight increase

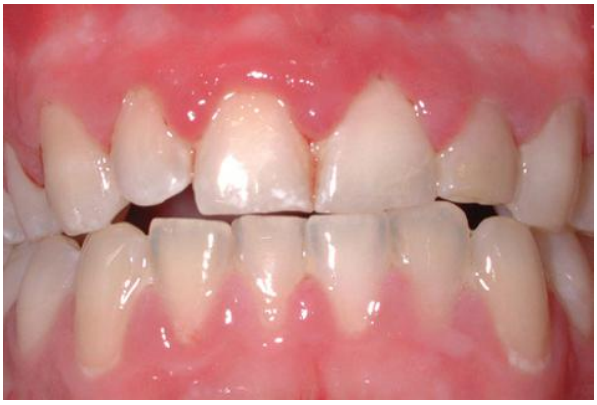


Fig. 19-1 Changes in gingival color and contour associated with plaque-induced gingivitis.

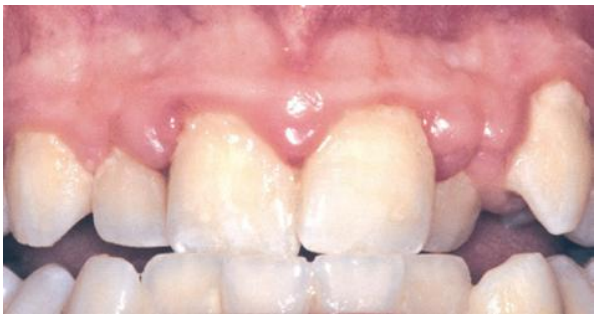


Fig. 19-2 Gingival inflammation as a result of tooth anatomic factors (malocclusion).

that are confined to the gingiva, reversibility of the diseases by removal of etiology(ies), the presence of bacteria-laden plaque to initiate and/or exacerbate the severity of the lesion, and a possible role as a precursor to attachment loss around teeth (Table 19-1).

Clinical signs of gingival inflammation involve enlarged gingival contours due to edema or fibrosis (Muhlemann & Son 1971; Polson & Goodson 1985), color transition to a red and/or bluish-red hue (Muhlemann & Son 1971; Polson & Goodson 1985), elevated sulcular temperature (Haffajee *et al*. 1992; Wolff *et al*. 1997), bleeding upon probing (Löe *et al*., 1965; Muhlemann & Son, 1971; Greenstein *et al*. 1981; Engelberger *et al*. 1983; Page & Eke, 2007), and increased gingival exudates (Löe & Holm-Pedersen 1965; Engelberg 1966; Oliver *et al*. 1969; Rudin *et al*. 1970; Goodson, 2003) (Table 19-2, Fig. 19-1). Clinical signs of gingival inflammation indicative of a gingival disease must be associated with stable (i.e. unchanging) attachment levels on a periodontium with no loss of attachment or alveolar bone or on a stable but reduced periodontium.

The classification of gingival diseases relies on the presence of dental plaque and factors that modify the inflammatory status of the gingiva. Local or systemic factors can modify plaque-induced gingivitis. Local factors include tooth anatomic factors (Fig. 19-2), dental restorations (Fig. 19-3) and appliances (Fig. 19-4), root fractures (Fig. 19-5), and cervical root resorption (Fig. 19-6) (Blieden 1999), whereas systemic factors involve the endocrine system, hematologic diseases, drugs, or malnutrition (Mariotti 1999). Table 19-3 presents a classification of plaque-induced gingival diseases (Mariotti 1999).

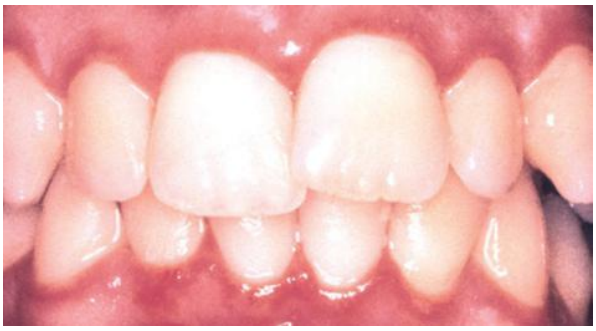


Fig. 19-3 Gingival inflammation associated with violation of the biologic width and overhanging restorations retaining plaque.

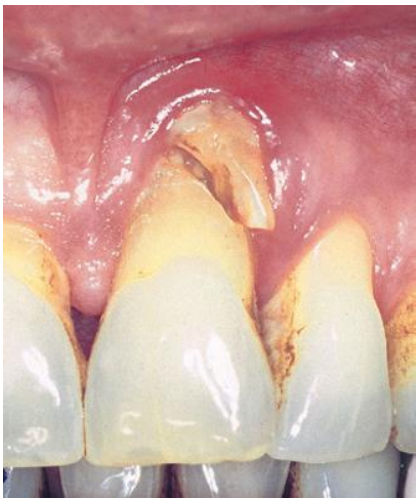


Fig. 19-5 Root fracture with associated periodontal destruction and gingival inflammation.

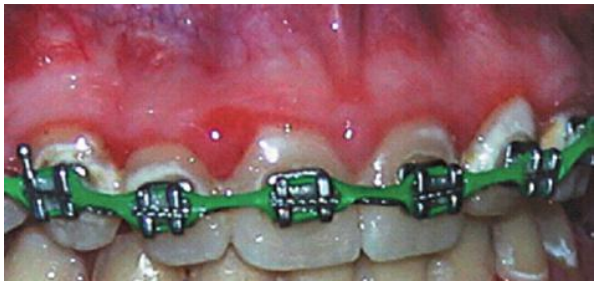


Fig. 19-4 Presence of appliances, such as braces, allows for the accumulation of plaque, resulting in gingival inflammation.

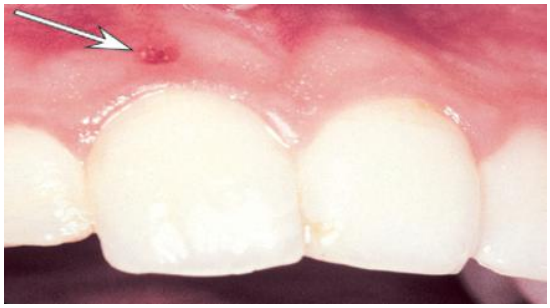


Fig. 19-6 Early cervical resorption and associated inflammation. The arrow indicates gingival inflammation resulting from cervical tooth resorption.

Table 19-3 Plaque-induced gingival diseases.

Associated with bacterial plaque only	Associated with a periodontium that exhibits no attachment loss Associated with a stable but reduced periodontium	Plaque-induced gingivitis
Associated with bacterial plaque and modified by systemic factors	Associated with endogenous sex steroid hormones	Puberty-associated gingivitis Menstrual cycle-associated gingivitis Pregnancy-associated gingivitis Pregnancy-associated pyogenic granuloma
	Associated with medications	Drug-influenced gingival enlargements Oral contraceptive-associated gingivitis
	Associated with systemic diseases	Diabetes mellitus-associated gingivitis Leukemia-associated gingivitis
	Associated with malnutrition	Ascorbic acid deficiency gingivitis

Adapted from Mariotti (1999). Reproduced from the American Academy of Periodontology.

Plaque-induced gingivitis

Plaque-induced gingivitis is inflammation of the gingiva resulting from bacteria located at the gingival margin. The relationship of plaque to gingival inflammation has often been postulated as the cause for gingivitis, but it was not until the elegant experimental human gingivitis studies that a plaque bacterial etiology was confirmed (Löe *et al*. 1965). Epidemiologic data have shown plaque-induced gingivitis to be prevalent at all ages of dentate populations (US Public Health Service 1965, 1972, 1987; Stamm 1986; Bhat 1991; Albandar 2002; Gjermo *et al*. 2002; Baelum & Schutz 2002; Corbet *et al*. 2002; Sheiham & Netuveli 2002; Hugoson & Norderyd, 2008) and this disease has been considered to be the most common form of periodontal disease (Page 1985; AAP 2000). In children, the prevalence of plaque-induced gingivitis continues to increase

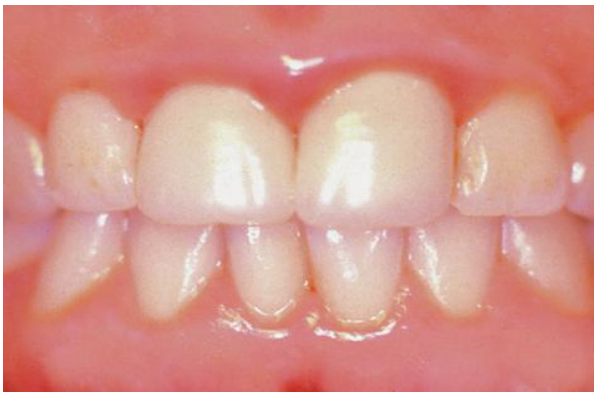


Fig. 19-7 Typical generalized marginal and papillary gingivitis.

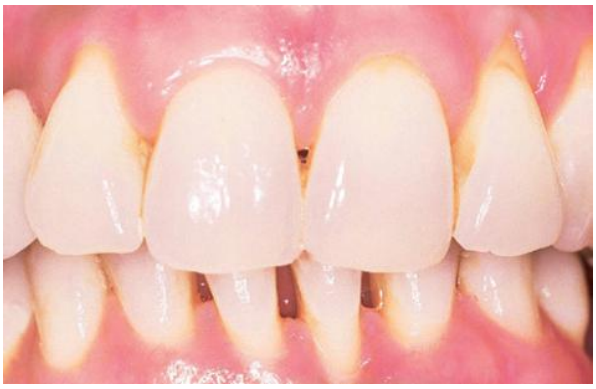


Fig. 19-8 Treated periodontitis case displaying gingival health on a reduced periodontium. If such a case developed inflammation and no further loss of attachment could be demonstrated, the diagnosis of plaque-induced gingivitis would be appropriate.

until it reaches a zenith at puberty (Parfitt 1957; Hugoson *et al*. 1981; Stamm 1986; Mombelli *et al*. 1989). The initial changes from health to plaque-induced gingivitis may not be detectable clinically (Page & Schroeder 1976), but as plaque-induced gingivitis progresses to more advanced forms of this disease, clinical signs and symptoms become more obvious.

Plaque-induced gingivitis begins at the gingival margin and can spread throughout the remaining gingival unit. Clinical signs of gingival inflammation involving changes to gingival contour, color, and consistency (Muhlemann & Son 1971; Polson & Goodson 1985) are associated with a stable periodontium which exhibits no loss of periodontal attachment or alveolar bone (Fig. 19-7). In children, gingivitis is not as intense as that found in young adults with similar amounts of dental plaque (Matsson 1978; Matsson & Goldberg 1985). This age-related difference in the development and severity of gingivitis may be associated with the quantity and/or quality of dental plaque, response of the immune system, and/or morphologic differences in the periodontium between children and adults (Bimstein & Matsson 1999). More specifically, dental plaque of children usually contains lower concentrations of putative periodontal pathogens and the thicker junctional epithelium is coupled with increased vascularity in the gingival connective tissues and a developing immune system (Bimstein & Matsson 1999). In contrast to children and young adults, gingival inflammation in senior adult populations is more pronounced even when similar amounts of dental plaque are present (Fransson *et al*. 1996). The reason for the difference in senior adults may be the result of age-related differences in cellular inflammatory response to plaque (Fransson *et al*. 1996, 1999).

The intensity of the clinical signs and symptoms of gingivitis will vary between individuals (Tatakis & Trombelli 2004; Trombelli *et al*. 2004), as well as between sites within a dentition. The common clinical findings of plaque-induced gingivitis include erythema, edema, bleeding, sensitivity, tenderness, and enlargement (Löe *et al*. 1965; Suzuki 1988). Radiographic analysis and/or probing attachment levels of individuals with plaque-induced gingivitis will not indicate loss of supporting structures. Histopathologic changes include proliferation of basal junctional epithelium leading to apical and lateral cell migration, vasculitis of blood vessels adjacent to the junctional epithelium, progressive destruction of the collagen fiber network with changes in collagen types, cytopathologic alteration of resident fibroblasts, and a progressive inflammatory/immune cellular infiltrate (Page & Schroeder 1976). Although the composition of bacterial flora associated with plaque-induced gingivitis differs from the flora associated with gingival health (Teles *et al*. 2007; Hojo *et al*. 2009), there are no specific bacterial flora that are pathognomonic for plaque-induced gingivitis (Ranney 1993; Socransky & Haffajee, 2005). Similar to the changes observed in the bacterial composition during plaque-induced gingivitis, the gingival transcriptome (i.e. the set of all RNA molecules) dramatically changes, with leukocyte transmigration, cell adhesion, and antigen processing/presentation being the leading differentially regulated pathways during the inflammatory process (Jönsson *et al*. 2011).

Plaque-induced gingivitis on a reduced periodontium

Destructive periodontal diseases result in the loss of attachment and a decrease in the height and volume of alveolar bone around teeth, leading to an overall reduction of the periodontium. It should be noted that not all inflammation present around teeth with attachment and bone loss denotes a periodontitis lesion. If there is resolution of periodontal inflammation subsequent to periodontal treatment that results in healthy periodontal tissues (but with a reduced connective tissue attachment and alveolar bone height), then recurrent inflammation must be considered to be plaque-induced gingivitis (Mariotti 1999). Therefore, plaque-induced gingivitis on a reduced periodontium is characterized by the return of bacteria-induced inflammation of the gingival margin on a reduced periodontium with no evidence of progressive attachment loss (i.e. no indication of active disease) (Fig. 19-8). The clinical findings for plaque-induced gingivitis on a reduced periodontium

are similar to those for plaque-induced gingivitis, except for the presence of pre-existing attachment and bone loss.

Gingival diseases associated with endogenous hormones

Since the 19th century, evidence has accumulated to support the concept that tissues of the periodontium are modulated by androgens, estrogens, and progestins. The majority of information concerning sex hormone-induced effects has been gender-specific observations in the gingiva. Much of the evidence that has been documented concerning the effects of sex steroid hormones on the periodontium has come from observing the changes in gingival tissues during distinct endocrinologic events (e.g. puberty, pregnancy, etc.). Although a significant amount of data has shown the gingiva to be a target for sex steroid hormones, the etiology for the changes has not been thoroughly elucidated (Mariotti 1994; Mariotti & Mawhinney 2013). The principal explanations for sex steroid hormone-induced changes in the gingiva have pointed to changes of microbiota in dental plaque, immune function, vascular properties, and cellular function in the gingiva (Mariotti 1994, 2005; Kumar 2013; Mariotti & Mawhinney, 2013). The actions of sex steroid hormones in the periodontium are multifactorial (Mariotti 1994; Mariotti & Mawhinney 2013). Theoretically, sex steroid hormones will affect the host by influencing cellular (i.e. in the blood vessels, epithelium, and connective tissue) and immune function and, together with hormone-selected bacterial populations that occupy the gingival sulcus, induce specific changes in gingival tissues that become clinically observable (Mariotti 1994; Mariotti & Mawhinney 2013).

Puberty-associated gingivitis

Puberty is not a single episode but a complex process of endocrinologic events that produce changes in the physical appearance and behavior of adolescents. The incidence and severity of gingivitis in adolescents are influenced by a variety of factors, including plaque levels, dental caries, mouth breathing, crowding of the teeth, and tooth eruption (Stamm 1986); however, the dramatic rise in steroid hormone levels during puberty in both sexes has a transient effect on the inflammatory status of the gingiva (Mariotti 1994; Mariotti & Mawhinney 2013). Several studies have demonstrated an increase in gingival inflammation in circumpubertal aged individuals of both genders without a concomitant increase in plaque levels (Parfitt 1957; Sutcliffe 1972; Hefti *et al*. 1981; Mombelli *et al*. 1989) (Fig. 19-9). Although puberty-associated gingivitis has many of the clinical features of plaque-induced gingivitis, this disease will develop frank signs of gingival inflammation in the presence of relatively small amounts of plaque during the circumpubertal period.

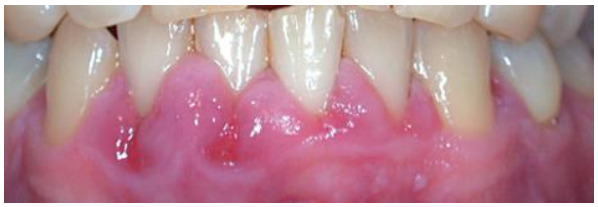


Fig. 19-9 Gingival inflammation can result from an increased secretion of sex steroid hormones during puberty.

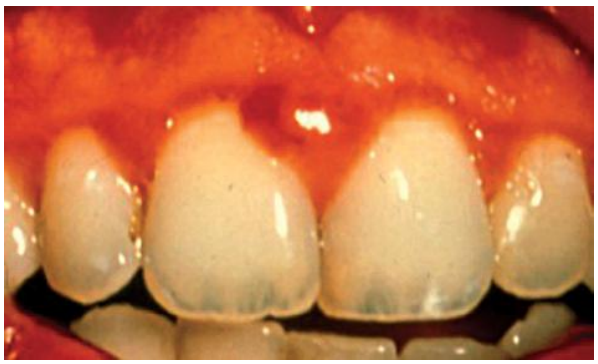


Fig. 19-10 Heightened gingival response to plaque during pregnancy results in pregnancy-associated gingivitis.

Menstrual cycle-associated gingivitis

Following menarche, there is a periodicity of sex steroid hormone secretion over a 25–30-day period: the menstrual cycle. A clinical case report of significant and observable inflammatory changes in the gingiva during the menstrual cycle has been described (Muhlemann 1948); however, women rarely exhibit overt gingival changes that fluctuate in conjunction with the menstrual cycle (Mariotti 1994; Mariotti & Mawhinney 2013). The more common gingival inflammatory changes involve less dramatic signs of inflammation in the gingiva during ovulation (Machtei *et al*. 2004). More specifically, gingival exudate increased approximately 20% during ovulation in roughly three-quarters of women tested (Hugoson 1971), while observable signs of gingival inflammation have been shown to be clinically insignificant (Machtei *et al*. 2004). Since these changes in crevicular fluid flow and gingival color are not readily observable, most young women with gingival inflammation induced by the menstrual cycle will present with a very mild, and not clinically observable, form of the condition.

Pregnancy-associated gingival diseases

Some of the most remarkable endocrine and oral alterations accompany pregnancy due to the prominent increase in plasma hormone levels over several months. During human gestation, pregnancy-associated gingivitis is characterized by an increase in the prevalence and severity of gingivitis during the second and third trimesters of pregnancy (Löe & Silness 1963; Löe 1965; Hugoson 1971; Arafat 1974b; Gürsoy *et al*. 2008) (Fig. 19-10). Both longitudinal and

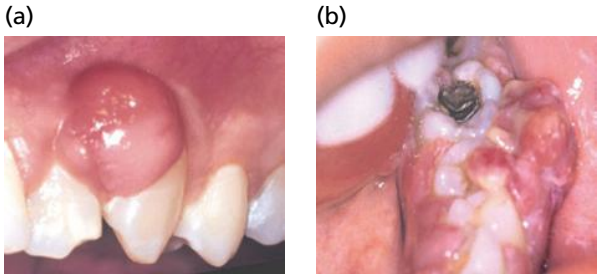


Fig. 19-11 (a) Pyogenic granuloma of pregnancy. (b) Large pyogenic granuloma of pregnancy interfering with occlusal function.

cross-sectional studies have found the prevalence and severity of gingival inflammation to be significantly higher in the pregnant versus the post-partum subject even though plaque scores remained the same between the two groups (Löe & Silness 1963; Hugoson 1971; Moss *et al*. 2005; Gürsoy *et al*. 2008). In addition, gingival probing depths are deeper (Löe & Silness 1963; Hugoson 1971; Miyazaki *et al*. 1991), bleeding on probing or toothbrushing is increased (Arafat 1974b; Miyazaki *et al*. 1991), and gingival crevicular fluid flow is elevated in pregnant women (Hugoson 1971). The features of pregnancy-associated gingivitis are similar to those of plaque-induced gingivitis, except for the propensity to develop frank signs of gingival inflammation in the presence of relatively little plaque during pregnancy.

Pregnancy-associated pyogenic granuloma or "pregnancy tumor" was described over a century ago (Coles 1874); this is not a tumor but an exaggerated inflammatory response during pregnancy to an irritation that results in a solitary polyploid capillary hemangioma which can easily bleed upon mild provocation (Sills *et al*. 1996) (Fig. 19-11). Pregnancy-associated pyogenic granuloma presents clinically as a painless, protuberant, mushroom-like, exophytic mass that is attached by a sessile or pedunculated base and arises from the gingival margin or more commonly from an interproximal space (Sills *et al*. 1996). Pregnancy-associated pyogenic granuloma has been reported to occur in 0.5–5.0% of pregnant women (Ziskin & Nesse 1946; Maier & Orban 1949; Arafat 1974a; Kristen 1976). It is more common in the maxilla (Sills *et al*. 1996) and may develop as early as the first trimester (Sills *et al*. 1996), ultimately regressing or completely disappearing following parturition (Ziskin & Nesse 1946).

Gingival diseases associated with medications

In the past century, an astonishing array of medications for the alleviation of human diseases has led to the creation of new side effects in the oral cavity. Drugs that specifically affect the gingival tissues have principally caused an increase in inflammation and/or size.

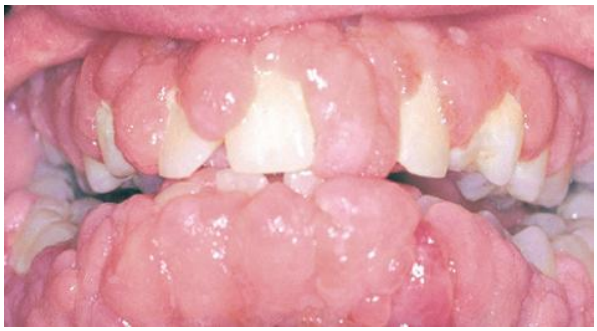


Fig. 19-12 Severe enlargement of the gingiva associated with cyclosporine medication in a kidney transplant patient.

Drug-influenced gingival enlargement

Esthetically disfiguring overgrowth of gingiva is a significant side effect which may be associated with (Hassell & Hefti 1991; Seymour *et al*. 1996; Seymour 2006):

- Anticonvulsants (e.g. phenytoin, sodium valproate, etc.)
- Immunosuppressant (e.g. cyclosporine A) (Fig. 19-12)
- Calcium channel blocking agents (e.g. nifedipine, verapamil, etc.).

The common clinical characteristics of drug-influenced gingival enlargements (Table 19-4) include patient variations in the pattern of enlargement (i.e. genetic predisposition) (Hassell & Hefti 1991; Seymour *et al*. 1996), a tendency to occur more often in the anterior gingiva (Hassell & Hefti 1991; Seymour *et al*. 1996), a higher prevalence in younger age groups (Esterberg & White 1945; Rateitschak-Pluss *et al*. 1983; Hefti *et al*. 1994), onset within 3 months of use (Hassell 1981; Hassell & Hefti 1991; Seymour 1991; Seymour & Jacobs 1992) that is usually first observed in the papilla (Hassell & Hefti 1991); although enlargement can be found in the periodontium with or without bone loss, it is not associated with attachment loss or tooth mortality (Hassell & Hefti 1991; Seymour *et al*. 1996). Furthermore, all of these drugs produce clinical lesions and histologic characteristics that are indistinguishable from one another (Hassell & Hefti 1991; Seymour *et al*. 1996).

The influence of plaque on the induction of gingival enlargements by drugs in humans has not been fully elucidated (Hassell & Hefti 1991); however, it does appear that the severity of the lesion is affected by the oral hygiene of the patient (Steinberg & Steinberg 1982; Addy *et al*. 1983; Hassell *et al*. 1984; Tyldesley & Rotter 1984; Daley *et al*. 1986; McGaw *et al*. 1987; Modeer & Dahllof 1987; Yahia *et al*. 1988; Barclay *et al*. 1992).

The first description of a drug causing an enlargement of the gingiva was reported in 1939 and the drug was phenytoin (Kimball 1939). Phenytoin, which is used on a chronic regimen for the control of epileptic seizures, induces gingival enlargements in

Table. 19-4 Characteristics of drug-influenced gingival enlargement.

- Variation in inter- and intra-patient pattern
- Predilection for anterior gingiva
- Higher prevalence in children
- Onset within 3 months
- Change in gingival contour leading to modification of gingival size
- Enlargement first observed at the interdental papilla
- Change in gingival color
- Increased gingival exudate
- Bleeding upon provocation
- Found in gingiva with or without bone loss but is not associated with attachment loss
- Pronounced inflammatory response of gingiva in relation to the plaque present
- Reductions in dental plaque can limit the severity of the lesion
- Must be using phenytoin, cyclosporine A or certain calcium channel blockers; the plasma concentrations to induce the lesion have not been clearly defined in humans

Source: Mariotti (1999). Reproduced from the American Academy of Periodontology.

approximately 50% of patients using this agent (Angelopoulous & Goaz 1972). One prominent theory of the etiology of phenytoin-associated gingival enlargements suggests that the growth is an increase in connective tissue that has resulted from a multifaceted interaction of fibroblast biology, connective tissue metabolism, inflammation, growth factors, and cytokines in an environment dependent on complex gene interactions (Hassell & Hefti, 1991; Gulati 2012).

Calcium channel blockers have also been identified as agents that affect enlargement of the gingiva. Calcium channel blockers are a class of drugs that exert effects, principally at voltage-gated Ca^{2+} channels located in the plasma membrane, and are commonly prescribed as antihypertensive, antiarrhythmic, and antianginal agents. In 1984, calcium channel blockers were first linked to gingival enlargements (Ramon *et al*. 1984) and the prevalence of gingival lesions associated with these drugs has been estimated to be approximately 20% (Barclay *et al*. 1992), with nifedipine being the primary calcium channel blocker associated with gingival enlargement (Ellis *et al*. 1999). Presently, the mechanism(s) of gingival enlargement by calcium channel blockers is still under investigation, but these drugs may directly influence gingival connective tissues by stimulating an increase in gingival fibroblasts as well as an increase in the production of the connective tissue matrix (Fu *et al*. 1998).

The final drug class that has been associated with increases in gingival mass is cyclosporine A (CsA), which is a powerful immunoregulating drug used primarily in the prevention of organ transplant rejection (Seymour & Jacobs 1992). The clinical features of cyclosporine-influenced gingival enlargement were first described in 1983 (Rateitschak-Pluss *et al*. 1983) and cyclosporine appears to affect between 25% and 30% of the patients taking this medication (Hassell & Hefti 1991; Seymour *et al*. 1987). Hypotheses explaining why CsA affects the gingiva are diverse, but a leading theory suggests that its principal metabolite, hydroxycyclosporine (M-17), in conjunction with the parent compound, stimulates fibroblast proliferation (Mariotti *et al*. 1998). This increase in cell number coupled with a reduction in the breakdown of gingival connective tissues (Hassell & Hefti 1991) has been speculated to be the cause of excessive extracellular matrix accumulation in CsA-associated gingival enlargements (Seymour 2006).

Oral contraceptive-associated gingivitis

Oral contraceptives are one of the most widely utilized classes of drugs in the world. Today, as a result of the early onset of menarche, changing social mores, and increased emphasis on family planning, the use of oral contraceptives in adolescents and young adults has increased to reduce unwanted pregnancies. Clinical case reports have described gingival enlargement induced by oral contraceptives in otherwise healthy females with no history of gingival overgrowth (Lynn 1967; Kaufman 1969; Sperber 1969). In all cases, the increased gingival mass was reversed when oral contraceptive use was discontinued or the dosage reduced. Early clinical studies demonstrated that women using hormonal contraceptive drugs had a higher incidence of gingival inflammation in comparison to women who did not use these agents (Lindhe & Bjorn 1967; El-Ashiry *et al*. 1970; Pankhurst *et al*. 1981) and that long-term use of oral contraceptives may affect periodontal attachment levels (Knight & Wade 1974). All studies of the effect of oral contraceptives prior to the 1980s were studying much higher contraceptive concentrations than are currently available today. A more recent clinical study evaluating the effects of low-dose oral contraceptives on gingival inflammation in young women found no effect of these hormonal agents on gingival tissues (Preshaw *et al*. 2001). Furthermore, cross-sectional data from National Health and Nutrition Examination Survey (NHANES) III have failed to show a relationship between low-dose oral contraceptive use and increased levels of gingivitis (Taichman & Eklund 2005). From these data it appears that current low-dose compositions of oral contraceptives are not harmful to the periodontium (Preshaw 2013).

Gingival diseases associated with systemic diseases

Diabetes mellitus-associated gingivitis

Diabetes mellitus (DM) is a chronic systemic disease characterized by disorders in insulin production, metabolism of carbohydrate, fat, and protein, and

the structure and function of blood vessels. DM most commonly appears as one of two recognized clinical entities: type 1 DM (insulin-dependent DM or juvenile onset) and type 2 DM (non–insulin-dependent DM or adult onset). DM-associated gingivitis is a consistent feature in children with poorly controlled type 1 DM (Cianciola *et al*. 1982; Gusberti *et al*. 1983; Ervasti *et al*. 1985). The features of gingivitis associated with DM are similar to those of plaque-induced gingivitis, except that the level of diabetic control is more important than plaque control in determining the severity of the gingival inflammation (Cianciola *et al*. 1982; Gusberti *et al*. 1983; Ervasti *et al*. 1985). In adults with DM, it is difficult to detect the effects of this endocrine disease on gingival diseases since most studies have evaluated gingival inflammation in association with attachment loss (AAP 1999); however, young adults with type 1 DM developed an earlier and more pronounced inflammatory response compared to non-diabetic controls in experimental gingivitis studies (Salvi *et al*. 2005). These data suggest that the gingival inflammatory response in adults with diabetes is an overt response to the dental biofilm. In addition to the effects of DM on the gingiva, reports in the literature have suggested that reductions in gingival inflammation of patients with diabetes will also reduce the amount of insulin they need to control blood glucose levels (Mealey & Oates 2006). This has been a controversial premise given the conflicting results of numerous studies. Moreover, despite several meta-analyses of periodontal intervention studies to evaluate glycemic levels, there is no clear consensus to support the assertion that control of gingival inflammation will substantially affect glycemic control in patients with diabetes (Janket *et al.* 2005; Jones *et al*. 2007; Sgolastra *et al.* 2012)

Leukemia-associated gingivitis

Leukemia is a progressive, malignant hematologic disorder characterized by an abnormal proliferation and development of leukocytes and precursors of leukocytes in the blood and bone marrow. Leukemia is classified according to the duration (acute or chronic), the type of cell involved (myeloid or lymphoid), and the number of cells in the blood (leukemic or aleukemic). There are noticeable correlations of leukemias with age. For example, acute lymphoblastic leukemia accounts for 80% of all childhood leukemias, while acute myelogenous leukemia usually affects adults. Oral manifestations have primarily been described in acute leukemias and include cervical adenopathy, petechiae, mucosal ulcers, as well as gingival inflammation and enlargement (Fig. 19-13) (Lynch & Ship 1967; Javed *et al*. 2012). Signs of inflammation in the gingiva include swollen, glazed, and spongy tissues which are red to deep purple in appearance (Dreizen *et al*. 1984). Gingival bleeding

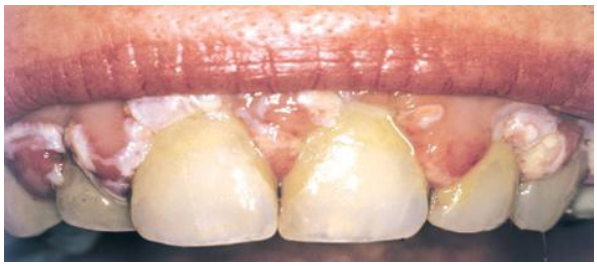


Fig. 19-13 Gingival changes associated with acute monocytic leukemia. Note the acute candidosis superimposed upon the infiltrative gingival changes.

is a common sign in patients with leukemia and is the initial oral sign and/or symptom in 17.7% and 4.4% of patients with acute and chronic leukemias, respectively (Lynch & Ship 1967). Gingival enlargement has also been reported, beginning at the interdental papilla, followed by at the marginal and attached gingiva (Dreizen *et al*. 1984). Although local irritants can predispose and exacerbate the gingival response in leukemia, they are not prerequisites for lesions to form in the oral cavity (Dreizen *et al*. 1984).

Linear gingival erythema

Infection with the human immunodeficiency virus (HIV) produces an irreversible and progressive immunosuppression that renders a person susceptible to a variety of oral diseases. In humans, HIV depletes CD4-positive lymphocytes (T helper cells), which leads to the development of a variety of fungal, viral, and bacterial oral infections (Connor & Ho 1992; Mataftsi *et al*. 2011).

Oral manifestations of HIV infection have been used to stage HIV disease (Justice *et al*. 1989; Royce *et al*. 1991; Prevention, 1992), identify prophylactic treatment of other serious infections (Force USPHST Force, 1993), and indicate disease prognosis (Dodd *et al*. 1991; Katz *et al*. 1992). In the gingiva, manifestations of HIV infection were formerly known as HIV-associated gingivitis, but currently are designated as linear gingival erythema (LGE). LGE is distinguished by a 2–3-mm marginal band of intense erythema in the free gingiva (Winkler *et al*. 1988). This band of gingival erythema may extend into the attached gingiva as a focal or diffuse erythema and/or extend beyond the mucogingival line into the alveolar mucosa (Winkler *et al*. 1988). LGE may be localized to one or two teeth but it is more commonly a generalized gingival condition.

With the advent of antiretroviral therapy for HIV-positive patients, the prevalence of HIV-specific lesions has been dramatically reduced (Mataftsi *et al*. 2011); even so, plaque accumulation with reduced CD4-positive counts, without antiretroviral therapy, will still account for a pronounced gingival inflammatory response (Kroidl *et al*. 2005).

Gingival diseases associated with malnutrition

Although some nutritional deficiencies can significantly exacerbate the response of the gingiva to plaque bacteria, the precise role of nutrition in the initiation or progression of periodontal diseases remains to be elucidated. Studies that have attempted to investigate the relationship of nutrition to periodontal disease examined the periodontal status of individuals in developed and in developing countries, but failed to show a relationship between periodontal disease and nutrition (Russell 1962; Waerhaug 1967; Wertheimer *et al*. 1967). While there is a paucity of information available regarding the effects of a specific, single nutritional deficiency on human periodontal tissues, severe ascorbic acid (vitamin C) deficiency or scurvy was one of the earliest nutritional deficiencies to be examined in the oral cavity (Lind 1953). Even though scurvy is unusual in areas with an adequate food supply, certain populations on restricted diets (e.g. infants from low socioeconomic families) are at risk of developing this condition (Oeffinger 1993). The classical clinical sign of scurvy is a bright red, swollen, ulcerated gingiva which is susceptible to hemorrhage (van Steenberghe 1997). Although there is no dispute about the necessity of dietary ascorbic acid for periodontal health, in the absence of frank scurvy, the effect of declining ascorbic acid levels on the gingiva can be difficult to detect clinically (Woolfe *et al*. 1980) and when it is detected, usually has characteristics that are similar to plaque-induced gingivitis (Fig. 19-14).

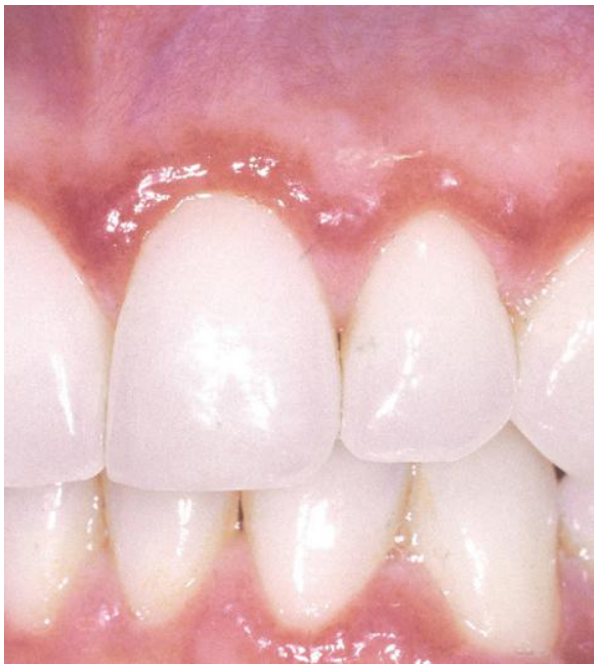


Fig. 19-14 Gingival changes associated with vitamin C deficiency. Note the absence of dental plaque and the distances of the color changes from marginal gingiva.

Gingival diseases associated with heredity

Benign, non-inflammatory fibrotic enlargement of the maxillary and/or mandibular gingiva associated with a familial aggregation has been designated by the terms gingivomatosis elephantiasis, familial elephantiasis, juvenile hyaline fibromatosis, congenital familial fibromatosis, idiopathic fibromatosis, idiopathic gingival fibromatosis, hereditary gingival hyperplasia, and hereditary gingival fibromatosis. Although there have been over 100 reports of gingival enlargements associated with heredity in the literature over the past century, knowledge concerning the natural history of this disease is extremely limited and the etiology of this rare condition has not been determined.

Hereditary gingival fibromatosis appears to be a slowly progressive gingival enlargement that develops upon eruption of the permanent dentition; however, gingival enlargement can also occur in the primary dentition (Emerson 1965; Jorgenson & Cocker 1974; Lai *et al*. 1995; Miyake *et al*. 1995). The disease can be localized or generalized and may ultimately cover the occlusal surfaces of teeth. The enlarged gingiva is non-hemorrhagic and firm, but there can be an overlay of gingival inflammation which can augment the enlargement (Fig. 19-15). The histologic features of hereditary gingival fibromatosis include dense fibrotic connective tissue as well as epithelial hyperplasia with elongated and increased rete pegs (Johnson *et al*. 1986; Clark 1987).

Hereditary gingival fibromatosis can be inherited as a simple Mendelian trait in some chromosomal disorders, and as a malformation syndrome (Witkop 1971; Jones *et al*. 1977; Skrinjaric & Bacic 1989; Takagi *et al*. 1991; Goldblatt & Singer 1992; Hallet *et al*. 1995). A mutation in the *son of sevenless-1* gene has been implicated as a genetic factor responsible for hereditary gingival fibromatosis (Hart *et al*. 2002). Research into the cellular responses of this disease suggests an accumulation of specific populations of gingival fibroblasts that result in an abnormal accumulation of connective tissues (Huang *et al*. 1997; Tipton *et al*. 1997; Lee *et al*. 2006).

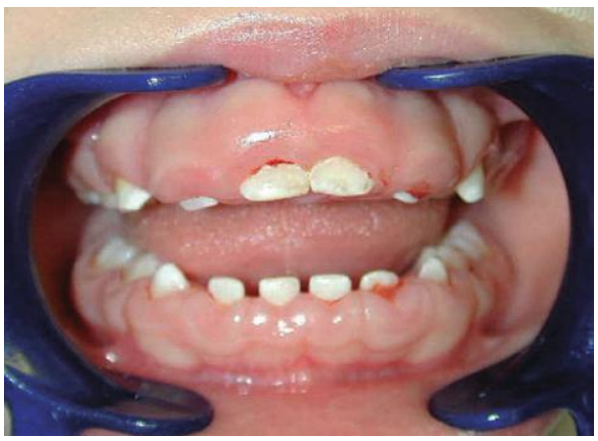


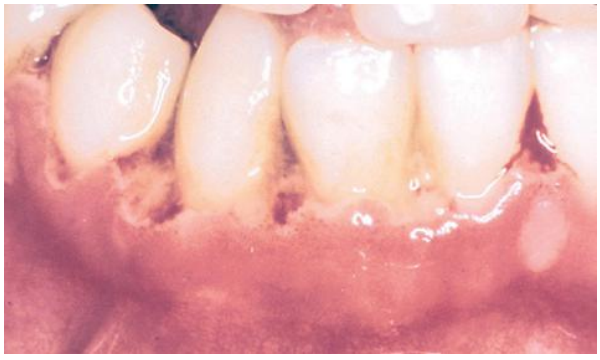
Fig. 19-15 Generalized, benign, non-inflammatory, fibrotic enlargement of gingival tissues.

Gingival diseases associated with ulcerative lesions

Necrotizing ulcerative gingivitis (NUG) has been observed for centuries and recognized by numerous names, including trench mouth and Vincent's infection. Acute necrotizing ulcerative gingivitis is a term now used to describe the clinical onset of the disease, but should not be used as a diagnostic classification since some forms of NUG may be recurrent or possibly chronic.

NUG is most often distinguished by a sudden onset. The clinical signs of NUG include intense gingival pain that usually is responsible for the patient seeking professional care; papillary necrosis, described as a "punched out" appearance of the gingival papilla; and gingival bleeding that requires little or no provocation (Fig. 19-16) (Grupe & Wilder 1956; Goldhaber & Giddon 1964; Johnson & Engel 1986). Although these three signs must be present to diagnose NUG, other signs and symptoms also may be present but do not necessarily occur in all individuals with this disease. These signs and symptoms include fever, malaise, lymphadenopathy, metallic taste, and malodor (Schluger 1943; Wilson 1952; Murayama *et al*. 1994). Systemic reactions of acute NUG are usually more severe in children. Significant destruction of the gingival connective tissue is possible with NUG, but when attachment loss occurs this condition should be considered as a necrotizing ulcerative periodontitis (NUP).

(a)



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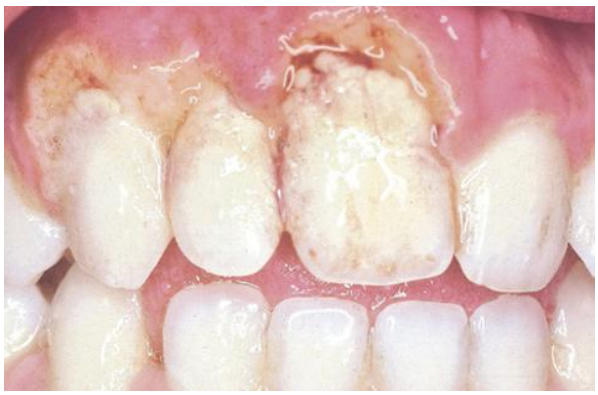

Fig. 19-16 Necrotizing ulcerative gingivitis. (a) Destruction of the interdental papilla, pseudomembrane, and spontaneous bleeding. (b) Although usually confined to the papilla, occasionally the marginal tissues are involved.

The etiology of NUG has been associated with a bacterial infection. The four zones of the NUG gingival lesion include the bacterial zone (the superficial area that consists of various bacteria and some spirochetes), neutrophil-rich zone (follows the bacterial zone and contains leukocytes and bacteria including spirochetes), necrotic zone (consists of disintegrated cells and connective tissue elements with many large and intermediate spirochetes), and spirochetal infiltration zone (the deepest zone that is infiltrated only with intermediate and large spirochetes) (Listgarten 1965). The cultivable flora of NUG that predominates includes *Provetella intermedia* and *Fusobacterium* spp., while microscopically *Treponema* and *Selenomonas* spp. are observed (Loesche *et al*. 1982; Rowland *et al*. 1993b). Additional factors such as smoking (AAP 1996), psychological stress (Moulton *et al*. 1952; Cohen-Cole *et al*. 1983), malnutrition (Grupe & Wilder 1956; Goldhaber & Giddon 1964; Johnson & Engel 1986), and immune suppression (Moulton *et al*. 1952; Rowland *et al*. 1993a) can predispose an individual to NUG.

NUG can affect any age group, but is considered to be a disease of young adults in industrialized countries (Melnick *et al*. 1988). In developing countries, NUG is a disease found in children from families with a low socioeconomic status (Melnick *et al*. 1988). The onset of NUG in children is associated with inappropriate nutritional intake, especially low protein consumption (Sheiham 1966; Taiwo 1995). In addition, viral infections such as measles can induce NUG in malnourished children (Enwonwu 1972; Osuji 1990). Even though NUG has occurred in epidemic patterns, this disease is not considered communicable (Rosebury 1942).

Treatment of plaque-induced gingival diseases

Personal and professional mechanical oral hygiene measures are critical aspects in the treatment of plaque-induced gingival diseases. Proper oral hygiene reduces the build-up of dental plaque on tooth surfaces and diminishes the incidence of various types of gingival diseases (Garmyn *et al*. 1998). For effective, self-care, mechanical plaque control, the appropriate use of manual (Jepsen 1998) or powered (van der Weijden *et al*. 1998) toothbrushes combined with interdental mechanical cleaning (Kinane 1998) is essential. Dentifrices also have important roles in the reduction of dental plaque: (1) to help in the removal of dental plaque by enhancing the mechanical scrubbing and cleaning power of the toothbrush (Mariotti 2014) and (2) as drug-delivery systems; agents (e.g. tricolsan) present in a toothpaste will provide a pharmacologic advantage by reducing the bacteria found in dental biofilms and/or inflammation in gingival tissues (DeVizio & Davies 2004). Additionally,

adjunctive, self-applied, locally delivered, pharmacologic agents (e.g. chlorhexidine) can also be an effective option for individuals with physical or medical limitations that constrain their ability to perform adequate home care.

Professional intervention is required as an adjunct to self-performed oral hygiene when plaque-retaining factors, such as dental calculus, defective restorations or anatomic factors, prevent an individual from effectively removing dental plaque. In instances where systemic factors modify the gingival response to dental biofilms, a combined treatment plan with the appropriate medical professional can be effective in addressing the root causes of the gingival inflammation.

Significance of gingivitis

Since gingival inflammation has been found to be a ubiquitous finding in children and adults, it has been suggested that this condition represents a normal response of the gingiva to an insult, and is not a disease. By analogy, a paper cut to a finger will induce an inflammatory response but would not be considered a "fingeritis" (i.e. a disease). On the other hand, inflammation in the gingiva that has been induced by a bacteria-laden biofilm changes the form and function of the tissue, creating a morbid condition in the gingiva that can be considered a disease.

Although the presence of gingival inflammation was once considered a normal variant of health, in the mid-20th century that concept changed dramatically when it was hypothesized that sites with untreated gingivitis were destined to progress to destructive periodontal disease. Although this concept was supported by some clinical studies showing an association between gingivitis and bone loss (Marshall-Day *et al*. 1955), longitudinal studies examining the natural history of periodontal disease failed to show complete conversion of chronic gingivitis to periodontitis (Löe *et al*. 1986). Gingival inflammation is probably a necessary precursor for periodontitis (Löe & Morrison 1986; Page & Kornman 1997; Schätzle *et al*. 2003, 2004; Lang *et al*. 2009), given that the risk of losing a tooth increases dramatically when surrounded by inflamed gingival tissue (Schätzle *et al*. 2003, 2004; Lang *et al*. 2009). Despite the increased risk for tooth loss associated with gingival inflammation, the presence of gingivitis does not mean that all sites that exhibit gingival inflammation progress to periodontitis (Schätzle *et al*. 2003, 2004).

If the majority of the adult population exhibits some form of plaque-induced gingivitis, how does one determine which inflamed sites within particular individuals are susceptible to conversion to destructive periodontal disease? There has been an awareness that differences in the inflammatory responsiveness to dental plaque cannot be fully accounted for by the quantity or quality of the plaque (Tatakis & Trombelli 2004). More specifically, there seems to be a differential gingival inflammatory response that is independent of the amount or rate of accumulation of dental plaque (Trombelli *et al*. 2004). Hence, the predilection of inflamed gingival sites to convert to destructive forms of periodontal disease may be dependent on the susceptibility and responsiveness of the individual to gingivitis (van der Velden *et al*. 1985a, b; Abbas *et al*. 1986; Winkel *et al*. 1987; Dietrich *et al*. 2006). In other words, these data suggest that specific types of inflammatory responses in the gingiva are necessary to initiate destruction of connective tissue attachment apical to the cementoenamel junction. As we learn more about different gingival inflammatory phenotypes, our notions about the initiation of periodontal destruction continue to emerge.

Exacerbations of the inflammatory response in the gingiva also occur during fluctuant periods of sex steroid hormone secretion. Although the periodontium has not been considered a classical target tissue for ovarian or testicular hormones, during puberty or pregnancy, the acute gingival inflammatory response is an expression of the protective nature of sex steroid hormones (Mariotti & Mawhinney 2013). More specifically, during times of possible vulnerability of the individual (e.g. pregnancy), the intensified inflammatory response in the periodontium is necessary to protect both the local (i.e. periodontal attachment) and systemic (i.e. toxic sepsis) environments by destroying, diluting or walling off the invading organisms (Mariotti & Mawhinney 2013).

As knowledge of gingival diseases evolves, their impact on the periodontium will become more transparent. Nonetheless, our current ability to clinically detect inflammation in gingival tissues, which subsequently leads to a diagnosis of a specific gingival disease, remains an important cornerstone for the periodontal management of the patient.

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Chapter 20

Chronic Periodontitis

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Chronic periodontitis is considered to start as *plaque-induced gingivitis* (see Chapter 19), a reversible condition that if left untreated may develop into *chronic periodontitis*. Chronic periodontitis lesions are distinguished by loss of attachment and bone, and are regarded as irreversible. In this chapter, various aspects of chronic periodontitis will be described, including its association with plaque-induced gingivitis.

Clinical features of chronic periodontitis

The clinical features of chronic periodontitis include signs and symptoms such as (1) color, texture, and volume alterations of the marginal gingiva; (2) bleeding on probing (BoP) from the gingival pocket area; (3) reduced resistance of the soft marginal tissues to probing (increased pocket depth or periodontal pocketing); (4) loss of probing attachment level; (5) recession of the gingival margin; (6) loss of alveolar bone (even or angular pattern); (7) root furcation exposure; (8) increased tooth mobility; and (9) drifting and eventually exfoliation of teeth.

Figure 20-1 shows the clinical status of a 30-year-old male with severe chronic periodontitis. The clinical examination revealed that (1) multiple sites, particularly the palatal aspects of the premolars, exhibited BoP; (2) many teeth showed signs of increased mobility; and (3) gingival recession had occurred at a large number of buccal, lingual, and interproximal sites. In addition, although the patient appears to be adequately cleaning several surfaces, multiple sites have levels of plaque and calculus that are clearly being ignored in the oral hygiene routine and are inconsistent with gingival and periodontal health.

Figure 20-2 shows the radiographic status of the same patient. In the radiographs it can be observed that a large number of teeth have lost substantial amounts of bone support. The lower first molar exhibits marked bone loss in the furcation area which is open for "through and through" probing. Subgingival and supragingival calculus is evident particularly in the lower anterior regions and is consistent with the clinical picture. Widened periodontal ligament spaces are evident in the molar regions, particularly in the upper posterior regions, and indicate that forces elicited during function may be working with the periodontal attachment loss to loosen the molars. Clear evidence of marked attachment loss affecting the stability of the teeth is seen in the lower anterior regions where a splint has been placed in

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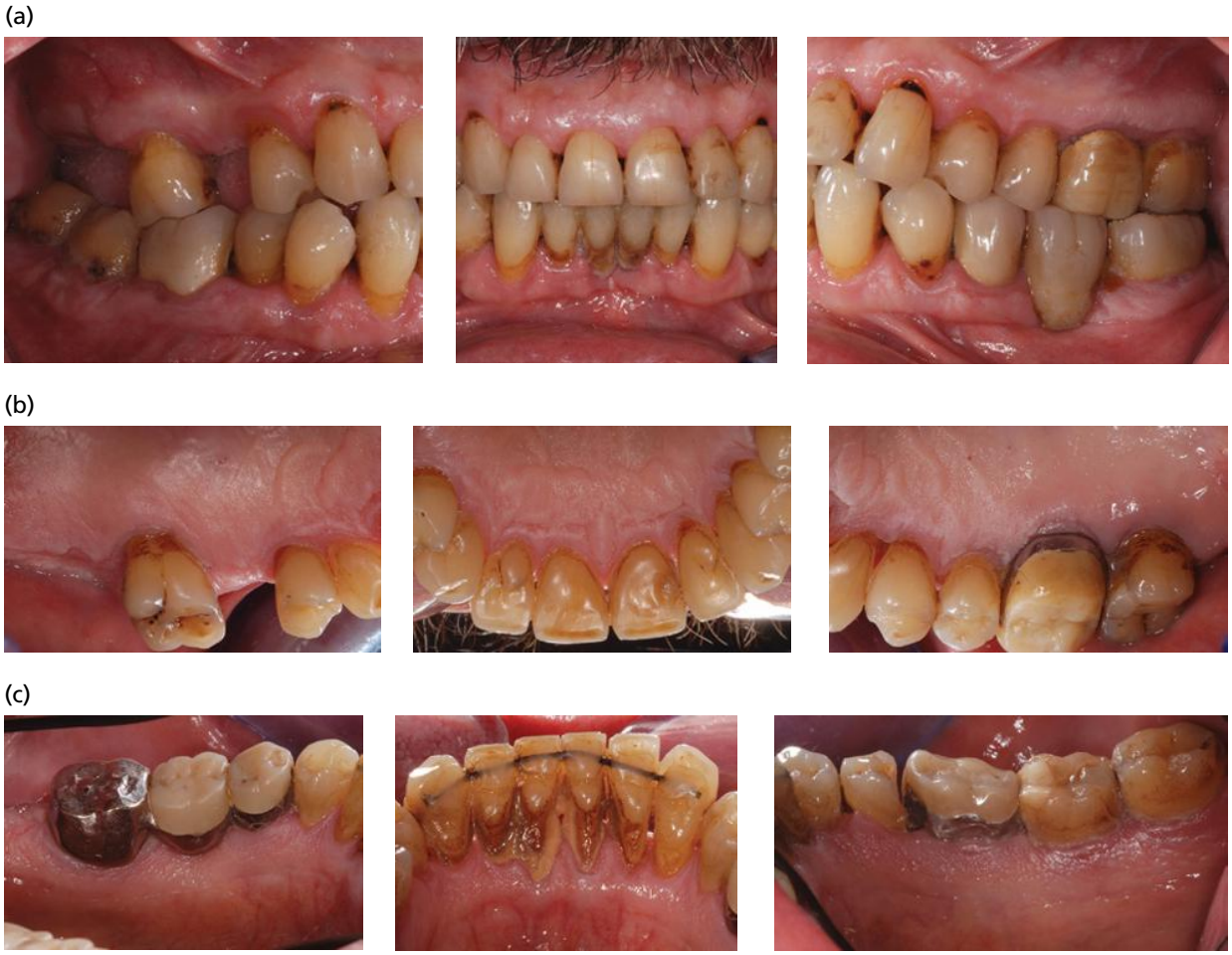

Fig. 20-1 (a–c) Severe chronic periodontitis in a 30-year-old male. Clinical status prior to treatment.

order to share the occlusal load and attempt to stabilize the teeth. As can be seen in the clinical views, this strategy may be hampered by poor patient oral hygiene which, by maintaining gingival inflammation, ensures poor quality of bone support in addition to poor quantity.

Gingivitis as a risk factor for chronic periodontitis

Findings from epidemiologic studies (cross-sectional as well as longitudinal) indicate that gingival inflammation is invariably a component of chronic periodontitis and that gingivitis precedes the onset of periodontitis (see Chapter 7). The interpretation of data from early cross-sectional studies led to the belief that untreated gingivitis always progresses to chronic periodontitis. More recent studies have demonstrated, however, that this is not the case. Gingivitis lesions may remain stable for many years, and may never progress to become periodontitis lesions with features such as attachment and bone loss. The two conditions have been considered, therefore, as separate disease entities, as the bacterial plaque challenge will induce overt gingivitis but the degree of response of the host (the susceptibility) will determine whether or not chronic periodontitis will develop.

In a review paper, Kinane and Attström (2005) evaluated epidemiologic and experimental data on gingivitis and chronic periodontitis. The independence of these two conditions was called into question. It was proposed that gingivitis and periodontitis most likely represent different aspects of the same disease, namely chronic periodontitis.

Gingivitis becomes manifest after only days or weeks of plaque accumulation (Löe *et al*. 1965), while destructive chronic periodontitis is a condition that in the majority of cases requires far longer periods (years or decades) of plaque and calculus exposure to develop (Lindhe *et al*. 1975; Löe *et al*. 1978). The proportion of untreated gingival lesions in a given subject or in a population that converts to destructive periodontitis lesions is at present unknown. Furthermore, the factors that cause the conversion are not well understood (Schätzle *et al*. 2003).

Findings from epidemiologic studies and prospective clinical trials have indicated that the presence of gingivitis may be regarded as a risk factor for chronic periodontitis. In a 2-year longitudinal study of 15–24-year-old Chinese adolescents from a rural district, it was observed that the percentage of sites that bled on probing at baseline examination was related to overall attachment loss after 2 years of

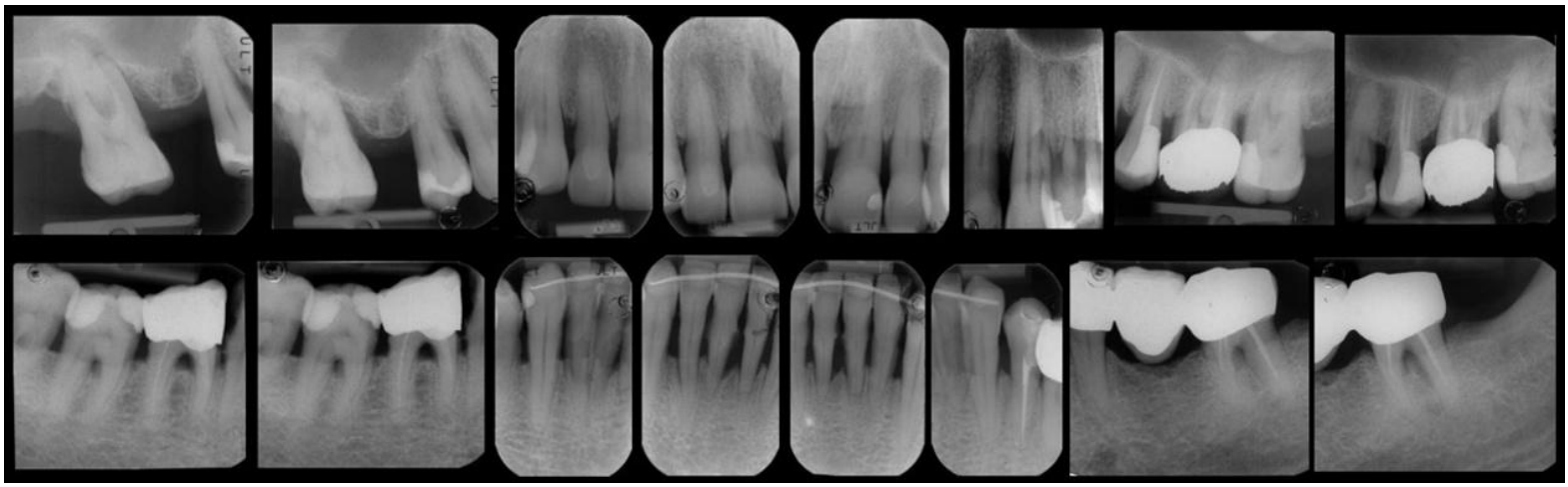

Fig. 20-2 Same patient as in Fig. 20-1. Radiographs from the initial examination.

monitoring (Suda *et al*. 2000). This suggests that gingival inflammation was a risk indicator for additional attachment loss in this cohort. The role of gingivitis in the pathogenesis of chronic periodontitis was further elucidated by Schätzle *et al*. (2004) in longitudinal studies on the initiation and progression of periodontal disease in a Norwegian population. The results demonstrated that gingival sites, which during a 20-year interval never showed signs of inflammation, experienced modest loss of attachment (1.86 mm). For sites which presented with mild inflammation at each examination, the corresponding attachment loss was 2.25 mm, while at sites with severe gingival inflammation, the mean loss of attachment was 3.23 mm. Moreover, while teeth surrounded by healthy gingival tissues were maintained during the study period, teeth with gingivitis lesions were 46 times more likely to be lost.

The above data indicate that gingival inflammation may represent a relevant risk factor not only for destructive chronic periodontitis but also for tooth loss. This conclusion is in agreement with results documenting the absence of gingivitis as a good indicator for long-term maintenance of periodontal health (subject-based stability) (Joss *et al*. 1994), as well as at a site level (Lang *et al*. 1990).

Susceptibility to chronic periodontitis

As stated above, plaque-induced gingivitis and chronic periodontitis represent different aspects of the same disease (Kinane & Attström 2005). The question is then whether or not both gingivitis and chronic periodontitis are affected by the subject response (the host response) to plaque. If this is the case, there are reasons to suggest that susceptibility to gingivitis may in fact also reflect susceptibility to chronic periodontitis.

Even in the very first reports from studies called "Experimental gingivitis in man" (Löe *et al*. 1965; Theilade *et al*. 1966) (see Chapter 13) evidence was presented that suggested that the onset and severity of the inflammatory response of the gingiva to plaque accumulation differed markedly among participants. The differences were, however, at that time attributed to differences in plaque accumulation rates (quantitative plaque differences) and/or differences in bacterial species present in plaque (qualitative plaque differences). More recent studies utilizing the "Experimental gingivitis in man" model have documented that significant differences in the inflammatory response occurred in different subjects, although quantitatively and/or qualitatively their plaque accumulation was similar (Trombelli *et al*. 2004, 2005). It was suggested that the intensity of the inflammatory response to the plaque challenge may represent an individual trait (Tatakis & Trombelli 2004). Thus, an individual's susceptibility to gingivitis may be dependent on host-related factors, possibly of genetic origin (Shapira *et al*. 2005; Scapoli *et al*. 2005, 2007; Trombelli *et al*. 2008, 2010).

With the use of the "Experimental gingivitis in man" model, it was also demonstrated that the susceptibility to gingivitis differed between two groups of patients with apparently different susceptibility to periodontitis (Abbas *et al*. 1986; Winkel *et al*. 1987). Thus, the group with greater periodontitis susceptibility had also a greater susceptibility to gingivitis. Furthermore, in more recent studies, it was documented that subjects with a history of aggressive periodontitis showed significantly more gingivitis in response to *de novo* plaque accumulation when compared to periodontally-healthy subjects matched for extent and rate of supragingival plaque accumulation (Trombelli *et al*. 2006). Thus, pre-existing gingivitis is indeed a risk indicator for chronic inflammatory periodontitis. The reader is referred to Chapter 12 for a comprehensive discussion of the risk factors for gingivitis.

Prevalence of chronic periodontitis

From epidemiologic studies (see Chapter 7) it was concluded that chronic periodontitis is the most commonly occurring form of periodontal disease. While most subjects above 50 years of age have suffered moderate amounts of periodontal tissue destruction, advanced forms of chronic periodontitis are seen in only a small (<10%) subset of the population. Both age of onset of chronic periodontitis and subsequently rate of progression of the disease vary between individuals, and are probably influenced by genetics (see Chapter 15) and environmental risk factors (see Chapters 7 and 12). Findings from examination of dizygotic and monozygotic twins indicated that (1) between 38% [regarding probing attachment loss (PAL)] and 82% (regarding gingivitis) of the population variance could be attributed to genetic factors (Michalowicz *et al*. 1991), and (2) that chronic periodontitis has heritability of about 50% (Michalowicz *et al*. 2000). More recent evidence is available evaluating whether or not genetic characteristics in general, and gene polymorphisms in particular, contribute to exacerbated gingival inflammation in response to plaque accumulation. Since the host immune response is a dominant gene expression pathway during gingivitis onset and resolution, with several genes being significantly up- or down-regulated (Offenbacher *et al*. 2009), studies have focused particularly on the potential association between cytokine gene polymorphism and gingivitis. In this context, data from observational, cohort studies suggested that gene polymorphisms related to specific cytokines which are also implicated in the pathogenesis of chronic periodontitis, such as interleukin-1 (IL-1), IL-10, and matrix metalloproteinase (MMP)-9, may affect the individual gingival inflammatory response to dental biofilm (Dashash *et al*. 2005; Scapoli *et al*. 2005; Dashash *et al*. 2007; Müller &

Table 20-1 Overall characteristics of chronic periodontitis.

- Prevalent in adults but may occur in children
- Amount of destruction of the periodontal tissues seen in a given patient is commensurate with oral hygiene and plaque levels, local predisposing factors, smoking, stress, and systemic risk factors
- Subgingival biofilm harbors a variety of bacterial species; the composition of the biofilm varies between subjects and sites
- Subgingival calculus is invariably present at diseased sites
- Chronic periodontitis is classified as localized when <30% of sites are affected and generalized when this level is exceeded
- Severity of chronic periodontitis at the site level may be classified based on the degree of attachment loss (PAL): *mild* = 1–2 mm, *moderate* = 3–4 mm and *severe* = ≥5 mm
- Although chronic periodontitis is initiated and sustained by microbial plaque, host factors determine the pathogenesis and (rate of) progression of the disease
- Rate of progression of chronic periodontitis is in most cases slow to moderate; periods of rapid tissue destruction may however occur
- Additional periodontal tissue breakdown is likely to occur in diseased sites that are left untreated

Barrieshi-Nusair 2007; Vokurka *et al*. 2009; Müller & Barieshi-Nusair 2010).

Chronic periodontitis on a population basis is often classified according to number (prevalence) of diseased sites (extent) and severity of tissue breakdown (PAL) at such sites: low, 1–10 diseased (gingivitis and PAL) sites; medium, 11–20 diseased sites; and high, >20 diseased sites. The amount of PAL at a given site may be used to describe the severity of chronic periodontitis: mild, 1–2 mm; moderate, 3–4 mm; and severe, (≥5 mm. It has been documented that the *extent* and *severity* of chronic periodontitis are useful predictors of future disease progression.

Clinical (probing) attachment loss of 1 or 2 mm at one or several sites can be found in nearly all members of an adult population. The prevalence of subjects with one or more sites with a PAL of ≥3 mm increases with age (Table 20.1). Furthermore, the number of diseased sites in any one individual increases with age. Also, the population prevalence (extent and severity) of chronic periodontitis increases with age.

Progression of chronic periodontitis

Chronic periodontitis is generally a slowly progressing form of periodontal disease that at any stage may exacerbate, leading to additional loss of attachment and bone.

Tissue destruction in chronic periodontitis does not affect all teeth evenly, but has a site predilection. In other words, in the same dentition, some teeth may be severely affected with periodontal tissue destruction, while other teeth are almost free of signs of attachment and bone loss. When considering changes in attachment level over time, it is also peculiar that only relatively few sites in a subject with chronic periodontitis undergo marked, additional tissue destruction during any given observation period. Based on data from a series of longitudinal studies, Socransky *et al.* (1984) proposed that chronic periodontitis progresses in episodes of exacerbation and remission. They termed this the "burst hypothesis" of disease progression. Findings from other similar studies, however, indicated that the progression of chronic periodontitis may be a continuous, slowly destructive process, rather than exhibiting a "burst" pattern. The current consensus is that the progression of chronic periodontitis in most subjects and at most sites is a continuous process, but that periods of exacerbation occasionally may occur. Clinically, the progressive nature of the disease can only be confirmed by repeated examinations over time, but it is a safe assumption that untreated lesions of chronic periodontitis will progress and cause additional attachment and bone loss. In an untreated population, there was a mean additional PAL of ≥3 mm in up to 27% of subjects over a 1-year period (Flemmig 1999). When progression was studied on a site basis, the overall annual incidence of progression ranged from 0.3% to 4.2% (Flemmig 1999). This indicates that the number of sites that actually exhibited progression within a given time varied considerably between subjects.

It is important to realize that factors associated with the initiation of chronic periodontitis may also influence disease progression. Furthermore, the extent and severity of disease within an individual, that is the number of sites with attachment loss, bone loss, and/or deep pockets, are good predictors of future disease occurrence. In fact, the best predictor of disease progression is previous disease experience.

Risk factors for chronic periodontitis

The term "risk factor" means an aspect of lifestyle, an environmental exposure, or an inborn or inherited characteristic, which on the basis of epidemiologic evidence is known to be associated with a given disease. Risk factors may be part of the causal chain of a disease and/or may predispose the host to develop a disease. An individual presenting with one or more risk factors has an increased probability of contracting the disease or of the disease being worse.

Bacterial factors

These factors are dealt with in Chapters 8 and 10, and from these the reader can ascertain that a cumulative risk for a given microbiota can be estimated. It is not clear, however, if the specific microbiota is the principal disease-causing factor or whether it reflects the disease process. Specific microorganisms have been considered as potential periodontal pathogens, but it is clear that although pathogens are necessary, their mere presence may not be enough for disease activity to occur. Microbial plaque (biofilm) is a crucial factor

in inflammation of the periodontal tissues, but the progression of gingivitis to periodontitis is largely governed by host-based risk factors (Michalowicz 1994; Shapira *et al*. 2005). Microbial biofilms of particular compositions will initiate chronic periodontitis (Marsh 2005) in certain individuals whose host response and cumulative risk factors predispose them to periodontal destruction rather than to gingivitis. The reader is referred to Chapter 8 for a more in-depth discussion of the biofilm and its role in disease induction and maintenance.

Age

Although the prevalence of periodontal disease increases with age, it is unlikely that becoming older in itself greatly increases susceptibility to periodontal disease. It is more likely that the cumulative effects of disease over a lifetime, that is deposits of plaque and calculus, and the increased number of sites capable of harboring such deposits, as well as attachment and bone loss experience, explain the increased prevalence of disease in older people.

Smoking

The association between periodontal disease and smoking is dealt with in detail in Chapter 12. Only a brief discussion of smoking as a risk factor for chronic periodontitis is thus given here. The literature consistently indicates a positive association between smoking and chronic periodontitis across the many cross-sectional and longitudinal studies performed over the years (Kinane & Chestnutt 2000): the risk attributable to tobacco for chronic periodontitis is between 2.5 and 7.0. It is not only the risk of developing the disease that is enhanced by smoking, but also the response to periodontal therapy is impaired in smokers. A further feature in smokers is that their signs and symptoms of both gingivitis and chronic periodontitis, mainly gingival redness and BoP, are masked by the dampening of inflammation seen for smokers as compared to non-smokers.

Systemic disease

It is difficult to determine the precise role any systemic disease may play in the pathogenesis of chronic periodontitis. There are several reasons for this. First, in epidemiologic studies attempting to evaluate the effect of systemic disease, control groups should be carefully matched in respect of age, gender, oral hygiene, and socioeconomic status. Many studies, particularly those conducted before the etiologic importance of dental plaque was recognized, failed to include such controls. Second, because of the chronicity of periodontal disease, longitudinal studies spanning several years are preferable in individuals both with and without systemic disease. Unfortunately, most of the available data are derived from cross-sectional studies (Kinane 1999).

A reduction in number or function of polymorphonuclear leukocytes (PMNs) generally results in an increased rate and severity of periodontal tissue destruction (Wilton *et al.* 1988). Many drugs, such as phenytoin, nifedipine, and cyclosporine, predispose to gingival overgrowth in response to plaque and thus may modify pre-existing chronic periodontitis (Ellis *et al*. 1999). Changes in circulating hormone levels may increase the severity of plaque-induced gingival inflammation, but typically do not result in any increased susceptibility to periodontitis. Hormonal changes following menopause have been associated with osteoporosis, but studies are lacking to link this disease or an estrogen-deficient state to a higher susceptibility to periodontal disease. Immunosuppressive drug therapy and any disease resulting in suppression of inflammatory and immune processes [such as human immunodeficiency virus (HIV) infection] may predispose the individual to exaggerated periodontal tissue destruction (Barr *et al*. 1992).

Nutritional deficiencies in animals have been shown to affect the periodontal tissues, but epidemiologic data do not support the suggestion that such deficiencies play an important role in chronic periodontal disease, although nutritional influences on inflammation are now accepted and are being actively researched (Ritchie & Kinane 2005). Gingival bleeding is the most consistent oral feature of vitamin C deficiency or scurvy, but there is also some evidence to suggest that avitaminosis C may aggravate established chronic periodontitis.

The periodontal features of histiocytosis X and other conditions in the rare histiocytoses disease group may present as necrotizing ulcerative periodontitis (Kinane 1999). Diabetes appears to be one of the most fascinating systemic diseases that interacts with periodontitis. Periodontitis severity and prevalence are increased in subjects with long-duration diabetes, particularly when poorly controlled, compared to in those without diabetes. On the other hand, periodontitis may also exacerbate diabetes as it may decrease glycemic control (Thorstensson 1995).

Despite the paucity of high quality data on individuals both with and without systemic disease, the following general conclusions can be drawn (Kinane 1999):

1. Blood cells have a vital role in supplying oxygen to, the hemostasis of, and the protection of the tissues of the periodontium. Systemic hematologic disorders can thus have profound effects on the periodontium by denying any of these functions necessary for the integrity of the periodontium.
2. The PMN cell is undoubtedly crucial to the defense of the periodontium. To exert this protective function, several activities of PMNs must be integrated, namely chemotaxis, phagocytosis, and killing or neutralization of the ingested organism or substance. Individuals with either quantitative (neutropenia) or qualitative (chemotactic or phagocytic)

PMN deficiencies exhibit severe destruction of the periodontal tissues, which is strong evidence that PMNs are an important component of the host's protective response to the subgingival biofilm. Quantitative deficiencies are generally accompanied by destruction of the periodontium of all teeth, whereas qualitative defects are often associated with localized destruction affecting only the periodontium of certain teeth (i.e. chronic periodontitis may be modified).

3. Leukemias which give rise to excessive numbers of leukocytes in the blood and tissues also cause a greatly depleted bone marrow function with concomitant anemia, thrombocytopenia, neutropenia, and reduced range of specific immune cells, leading to some characteristic periodontal features: anemic gingival pallor, gingival bleeding, and gingival ulceration. Leukemic features are further complicated by the potential for the proliferating leukocytes to infiltrate the gingiva and cause gingival enlargement.
4. In broad terms, leukemias result in gingival pathologies, whereas periodontal bone loss is the consequence of neutrophil functional defects or deficient numbers, and other severe functional defects such as deficiency of leukocyte adhesion receptors.
5. Numerous confounding variables must be considered in determining the true relationship between periodontitis and diabetes. The current consensus is that individuals with diabetes are at increased risk of periodontal disease, and whilst periodontitis can be successfully treated, both disease susceptibility and the outcome of therapy are influenced by poor metabolic control. Thus, it may be of benefit to the dentist to have knowledge of the control status of diabetes in an individual patient, as in the longer term metabolic control could indicate the probable outcome of periodontal therapy. In addition, it is now accepted that periodontal therapy can improve metabolic control in patients with diabetes, meaning that the relationship is two-way and periodontal therapy is beneficial to the control of both diseases.
6. Medications such as phenytoin, cyclosporine, and nifedipine may predispose to gingival overgrowth in patients with gingivitis.
7. Genetic traits, which result in diseases that modify the periodontal structures or change the immune or inflammatory responses, can result in gross periodontal destruction in the affected individual and although the destruction seen may imitate periodontitis, this is not etiopathologically chronic periodontitis.

Stress

Stressful life events and negative emotions have been shown to modulate several physiologic systems, including the endocrine and the immune system, leading to health changes (Kiecolt-Glaser *et al*. 2002; LeResche & Dworkin 2002). The association between stress and disease is particularly strong for infectious diseases, inflammatory conditions, and impaired wound healing (Kiecolt-Glaser *et al*. 2002; LeResche & Dworkin 2002; Broadbent *et al*. 2003). Specific periodontal conditions have been associated with psychosocial variables, including chronic periodontitis (Green *et al*. 1986; Linden *et al*. 1996; Genco *et al*. 1999; Wimmer *et al*. 2002; Pistorius *et al*. 2002), necrotizing ulcerative gingivitis (Shields 1977; Cohen-Cole *et al*. 1983; Horning & Cohen 1995), chronic and experimental gingivitis (Minneman *et al*. 1995; Deinzer *et al*. 1998; Waschul *et al*. 2003). In adults, the reported contribution of psychosocial factors to enhanced gingivitis expression (Deinzer *et al*. 1998) may relate to the stress-associated increase in plaque accumulation (Deinzer *et al*. 2001). However, the possible association of other psychosocial variables, such as personality traits and coping behavior which are associated with either susceptibility or resistance to stress, with changes in the inflammatory response of the gingiva to *de novo* plaque accumulation remains uncertain (Trombelli *et al*. 2005).

Most of the literature on stress and periodontal conditions is quite old, and reports of acute necrotizing ulcerative gingivitis (or trench mouth) were made on stressed soldiers on the front line during World War I. It is understood that stress may be immunosuppressive and that acute necrotizing ulcerative gingivitis may occur in the immunosuppressed patient (also in HIV patients), but there is insufficient data as yet to substantiate the assumption that psychosocial factors are indeed of etiologic importance in chronic periodontitis.

Genetics

There is convincing evidence from twin studies for a genetic predisposition to the periodontal diseases. Twin studies have indicated that risk of chronic periodontitis has a high inherited component (see Chapter 15). A great deal of research is underway attempting to identify the genes and polymorphisms associated with all forms of periodontitis. It is likely that chronic periodontitis involves many genes, the composition of which may vary across individuals and races. Much attention has focused on polymorphisms associated with the genes involved in cytokine production (Shapira *et al*. 2005). Such polymorphisms have been linked to an increased risk for chronic periodontitis, but these findings have yet to be corroborated (Kinane & Hart 2003; Kinane *et al.* 2005) (see Chapter 15).

Scientific basis for treatment of chronic periodontitis

Chronic periodontitis is initiated and sustained by microorganisms living in biofilm communities which are present in supra- and sub-gingival plaque in the

form of uncalcified and calcified (calculus) biofilms. Prevention of initiation or primary prevention of periodontitis is clearly related to preventing formation and/or eradication of the microbial plaque biofilm and it follows that prevention of gingivitis is a primary preventive measure for chronic periodontitis. Initial periodontal therapy or basic treatment of periodontitis involves the removal of both sub- and supra-gingival plaque. The clinical outcome is largely dependent on the skill of the operator in removing subgingival plaque and the skill and motivation of the patient in practicing adequate home care. A further variable is the innate susceptibility of the patient, which is related to the way in which his/her innate inflammatory and immune systems operate in response to the microbial challenge. In addition, local and systemic risk factors can influence the quantity and quality of both the microbial challenge and the host response to these pathogens. The relative contribution of these risk factors has yet to be fully determined, but their influence would be limited if the periodontium is kept free of microbial plaque. Thus, sub- and supra-gingival debridement and the quality of the patient's home care are of vital importance in preventing inflammation that manifests as both gingivitis and periodontitis.

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Chapter 21

Aggressive Periodontitis

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Periodontitis is an infection that can have many different clinical presentations. This has led to the recognition of different clinical syndromes. The question of whether or not these dissimilar clinical presentations represent different forms of disease has been open to discussion. Today, several lines of evidence support the existence of truly different forms of periodontitis. These include:

1. The growing evidence and clinical consensus of differential prognoses and need for specific treatment approaches for the various syndromes
2. Heterogeneity in etiology with possible therapeutic implications
3. Possible heterogeneity in genetic and environmental susceptibility.

At the 1999 International Classification Workshop (Lang *et al.* 1999), the different forms of periodontitis were reclassified into three major forms (chronic, aggressive, and necrotizing) and into periodontal manifestations of systemic diseases. This chapter deals with aggressive, type 1, periodontitis. Until recently, this group of diseases was defined primarily based on the age of onset/diagnosis and was thus named early-onset periodontitis (EOP). Features of this form of disease, however, can present themselves at any age and this form of periodontitis is not necessarily confined to individuals under the arbitrarily chosen age of 35 years.

Aggressive periodontitis (AgP) comprises a group of rare, often severe, rapidly progressive forms of periodontitis, often characterized by an early age of clinical manifestation and a distinctive tendency for cases to aggregate in families. At the above-mentioned classification workshop, AgP was characterized by the following major common features (Lang *et al*. 1999):

- Non-contributory medical history
- Rapid attachment loss and bone destruction
- Familial aggregation of cases.

Frequently, AgP presents early in the life of the individual; this implies that etiologic agents have been able to cause clinically detectable levels of disease over a relatively short time. This fact is central to the current understanding of these diseases, since it implies infection with a highly virulent microbial biofilm and/or a high level of subject susceptibility to periodontal disease. AgP, however, can occur at any age. Diagnosis of AgP requires exclusion of the presence of systemic diseases that may severely impair host defenses and lead to premature tooth loss (periodontal manifestations of systemic diseases).

The existence of specific forms of AgP has also been recognized based on specific clinical and laboratory features: localized aggressive periodontitis [LAP, formerly termed localized juvenile periodontitis (LJP)],

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and generalized aggressive periodontitis [GAP, formerly termed generalized juvenile periodontitis (GJP), generalized early-onset periodontitis (G-EOP) or rapidly progressive periodontitis (RPP)] (Tonetti & Mombelli 1999).

In spite of its rare occurrence, AgP has been the focus of many investigations aimed at understanding its etiology and pathogenesis. Difficulties in gathering sufficiently large populations, however, have resulted in few clinical studies addressing both diagnostic and therapeutic procedures for this disease. Utilization of both clinical and advanced diagnostic procedures as well as a variety of treatment approaches remains largely anecdotal and based on the specific experience of individual clinicians rather than on well-documented scientific evidence.

Classification and clinical syndromes

In the absence of an etiologic classification, aggressive forms of periodontal disease have been defined based on the following primary features (Lang *et al*. 1999):

- Non-contributory medical history
- Rapid attachment loss and bone destruction
- Familial aggregation of cases.

Secondary features that are considered to be generally, but not universally, present are:

- Amounts of microbial deposits inconsistent with the severity of periodontal tissue destruction
- Elevated proportions of *Aggregatibacter actinomycetemcomitans* (previously named *Actinobacillus actinomycetemcomitans*) and, in some Far East populations, *Porphyromonas gingivalis*
- Phagocyte abnormalities
- Hyper-responsive macrophage phenotype, including elevated production of prostaglandin E_2 (PGE_2) and interleukin-1β (IL-1β) in response to bacterial endotoxins
- Progression of attachment loss and bone loss may be self-arresting.

The International Classification Workshop identified clinical and laboratory features deemed specific enough to allow subclassification of AgP into localized and generalized forms (Lang *et al*. 1999; Tonetti & Mombelli 1999). The following features were identified:

- *Localized aggressive periodontitis* (LAP) (Fig. 21-1):
  - Circumpubertal onset
  - Localized first molar/incisor presentation with interproximal attachment loss on at least two permanent teeth, one of which is a first molar, and involving no more than two teeth other than first molars and incisors
  - Robust serum antibody response to infecting agents
- *Generalized aggressive periodontitis* (GAP) (Fig. 21-2):
  - Usually affecting persons under 30 years of age, but patients may be older
  - Generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors
  - Pronounced episodic nature of the destruction of attachment and alveolar bone
  - Poor serum antibody response to infecting agents.

Diagnosis of one of these AgP forms requires the absence of systemic diseases that may severely impair host defenses and lead to premature exfoliation of teeth. In such instances, the appropriate clinical diagnosis will be periodontal manifestation of systemic disease.

GAP represents the most heterogeneous group and includes the most severe forms of periodontitis. They comprise forms originally described as generalized juvenile periodontitis (emphasis on a possible relationship with LAP), severe periodontitis (emphasis on the advanced destruction in relation to the patient's age), or rapidly progressing periodontitis (emphasis on the fast rate of progression of lesions in these forms). Each of these GAP forms, however, remains highly heterogeneous in terms of clinical presentation and response to therapy. The European Workshop on Periodontology has therefore suggested that, while a better etiologic classification remains unavailable, these forms should be considered as a group to be further defined by the use of various clinical descriptors of the disease based on clinical, microbiologic, and immunologic parameters (Attström & Van der Velden 1993). A further rationale for an imprecise classification of these GAP forms comes from the fact that, given the severity of the disease and the heterogeneity of clinical presentation, each of these rare cases deserves individual consideration.

Subjects often present with attachment loss that does not fit the specific diagnostic criteria established for either AgP or chronic periodontitis; this occurrence has been termed *incidental attachment loss*. It includes: recession associated with trauma or tooth position; attachment loss associated with impacted third molars; attachment loss associated with removal of impacted third molars, etc. It may include initial clinical presentations of periodontitis. Patients with this clinical diagnosis should be considered as a high-risk group for AgP or chronic periodontitis.

Besides clinical presentation, a variety of radiographic, microbiologic, and immunologic parameters are currently being used, along with the assessment of environmental exposures such as cigarette smoking, to further describe the AgP affecting the individual subject. These descriptors are important in treatment selection and to establish long-term prognosis. They will be further discussed in the section on diagnosis later in this chapter.

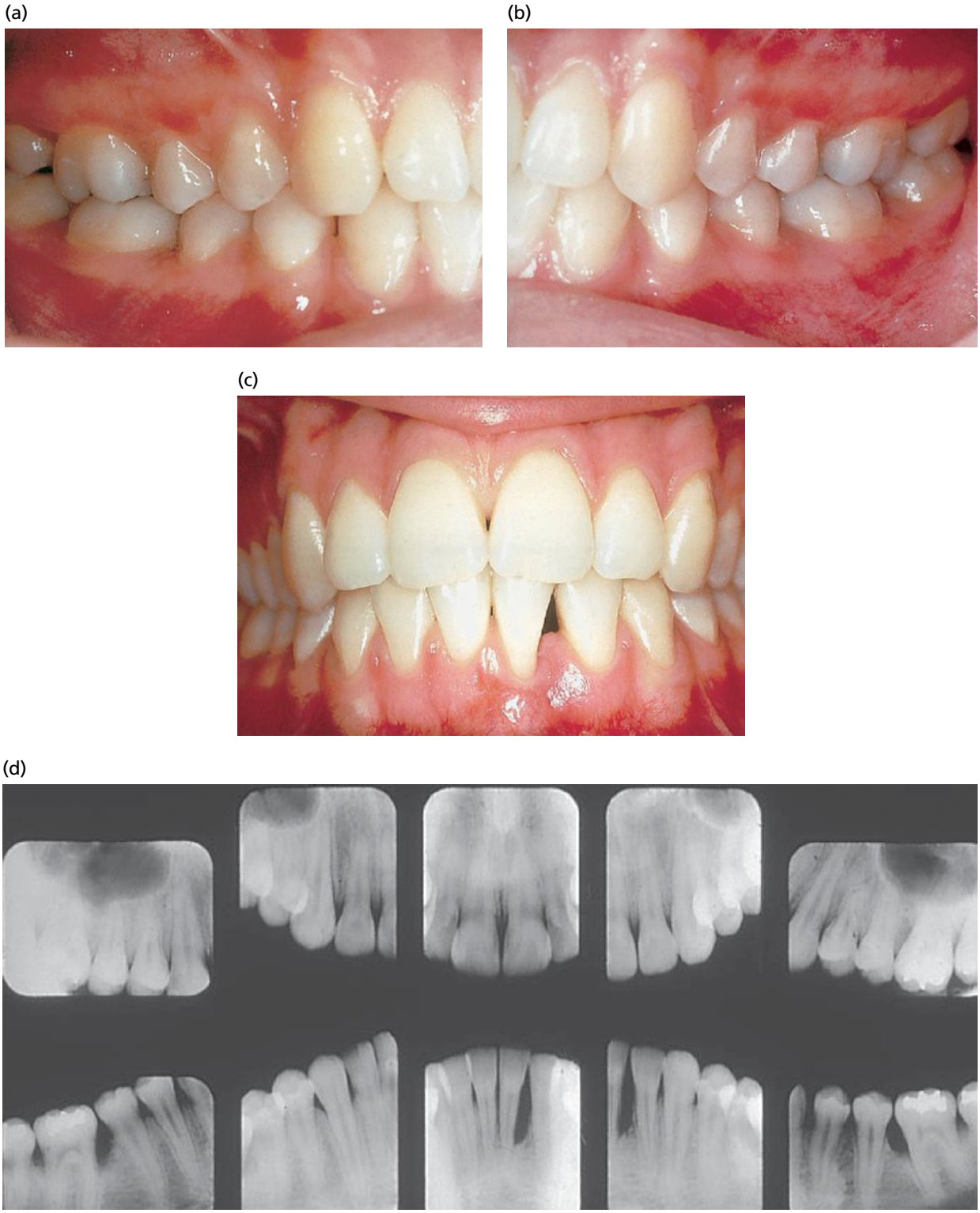
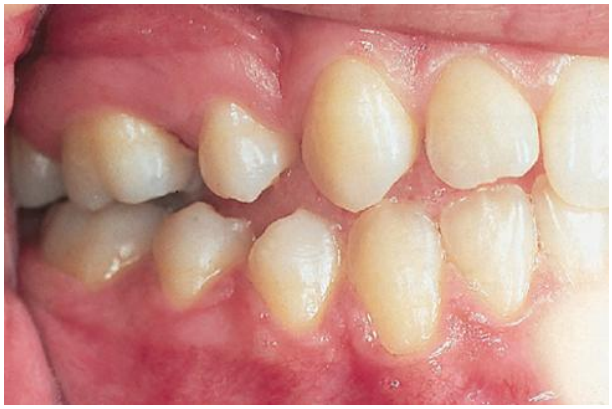


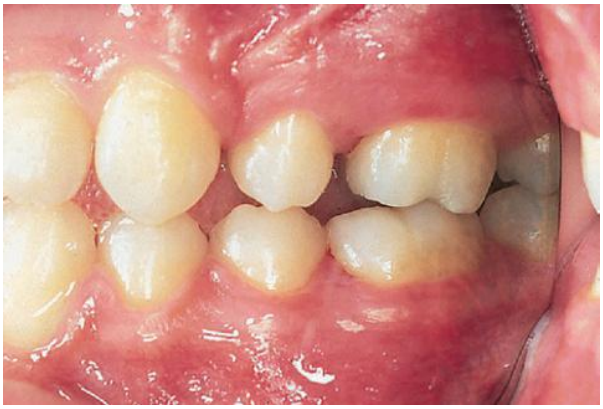
Fig. 21-1 (a–c) Clinical appearance of the periodontal tissues of a 15-year-old girl suffering from localized aggressive periodontitis (AgP). Note the proper oral hygiene conditions and the scalloped outline of the gingival margin. In the lower anterior region, the interdental papilla between teeth 31 and 32 has been lost. (d) Intraoral radiographs show the presence of localized angular bony defects, associated with clinical attachment level loss, at the mesial aspect of teeth 46 and 36, and at the distal aspect of tooth 31. No significant bone loss and/or attachment loss was detectable in other areas of the dentition. Diagnosis: localized aggressive periodontitis (LAP). (e–g) Clinical appearance of the 14-year-old sister of the proband depicted in (a–d). Note that in spite of the excellent oral hygiene status, bleeding on probing was provoked in the mesial of the molars, where deep pockets were present. (h) Angular bone loss is evident on the mesial aspect of teeth 16, 26, and 46.

It is also important to underline that, in the present state of uncertainty regarding both the causative agents and the genetic and environmental susceptibility to AgP, it is possible that, in spite of the lines of evidence presented above, LAP and GAP may simply represent phenotypic variations of a single disease entity. Conversely, it is possible that different AgP forms may manifest with a common clinical presentation. This aspect is of great diagnostic and therapeutic importance.

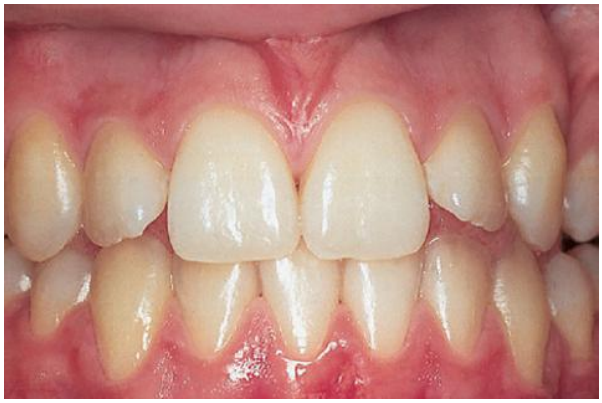
(e)



(f)



(g)



(h)

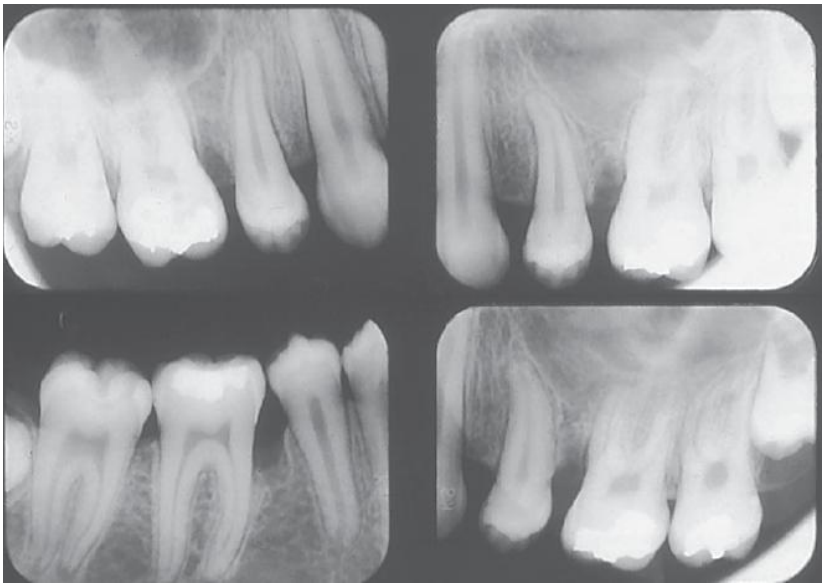


Fig. 21-1 *Continued.*

Some case reports have indicated that some subjects may experience periodontitis affecting the primary dentition, followed by LAP and later by GAP (Shapira *et al*. 1994a). One investigation indicated that 20–52% of LAP patients showed bone loss at primary molars, suggesting that LAP may initially affect the primary dentition in at least some cases (Sjødin *et al*. 1989, 1993). Furthermore, in LAP subjects an association between the number of lesions and the age of the subject has been described, suggesting an age-dependent shift from localized to generalized forms of AgP (Hormand & Frandsen 1979; Burmeister *et al*. 1984).

Epidemiology

Given the history of changes in disease definition of AgP and the fact that it does not represent just a new term for the previously defined EOP, available

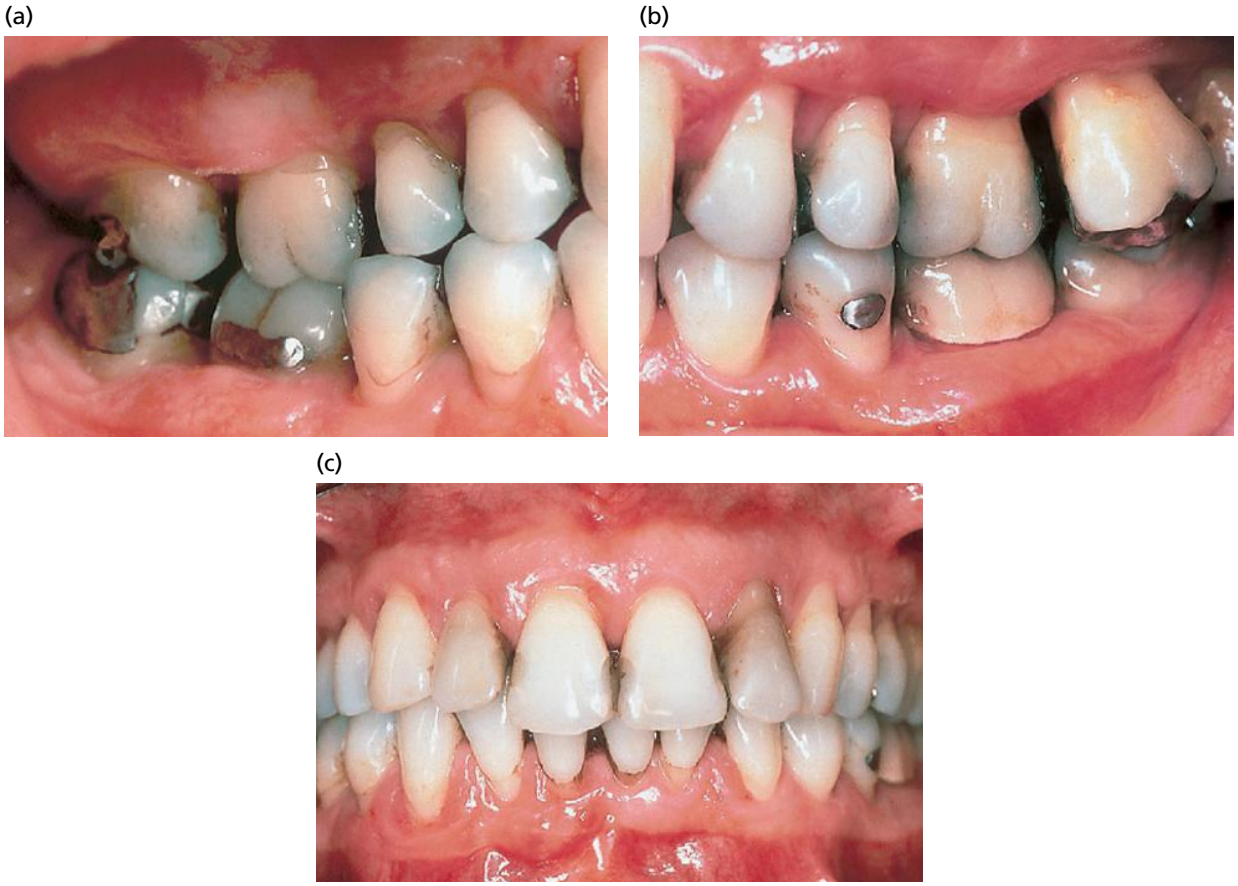


Fig. 21-2 (a–c) Clinical presentation in 1990 of a 32-year-old female with generalized severe bone loss and clinical attachment loss, recession of the gingival margin and presence of deep periodontal pockets. Presence of local factors, and intense inflammation and edema of the gingival margin are evident.

epidemiologic studies relate primarily to EOP. Relatively few investigations employing different epidemiologic techniques have estimated the prevalence and the progression of EOP in the primary and permanent dentition(s) of children and young adults. All available investigations, however, indicate that early-onset (aggressive) forms of periodontal diseases are detectable in all age and ethnic groups (Papapanou 1996). Wide variation in prevalence, however, has been reported, with some studies showing up to 51.5% of individuals affected. This variation is probably due to differences in the epidemiologic methodologies and definition of EOP employed.

Primary dentition

Little evidence is available concerning the prevalence of AgP affecting the primary dentition. In the few studies from industrialized countries, marginal alveolar bone loss has been found to affect the primary dentition of 5–11-year olds with frequencies ranging from 0.9% to 4.5% of subjects (Sweeney *et al*. 1987; Bimstein *et al*. 1994; Sjødin & Mattson 1994). In this respect, it should be emphasized that periodontitis affecting the primary dentition does not necessarily mean the presence of an aggressive form of periodontitis, but may indicate a chronic form of disease with relative abundance of local factors (plaque and calculus). A clinical case of localized periodontitis affecting the primary dentition is shown in Fig. 21-3. More severe cases affecting the primary dentition and leading to tooth exfoliation early in life are usually interpreted as periodontal manifestations of systemic (hematologic) diseases, such as leukocyte adhesion deficiency (Fig. 21-4) (see also Chapter 7).

Permanent dentition

In the permanent dentition of 13–20-year-old individuals, the majority of studies have reported a prevalence of periodontitis of <1% (usually 0.1–0.2% in Caucasian populations). The risk of developing periodontitis at such an early age, however, does not seem to be shared equally in the population: among US school children aged 5–17 years, the prevalence of periodontitis has been estimated to range from about 0.2% for Caucasian subjects to about 2.6% for Black subjects (Löe & Brown 1991). Furthermore, in these young age groups a higher prevalence of periodontitis has been reported in studies from some developing countries (see Chapter 7).

Longitudinal studies of disease progression in adolescents indicate that subjects with signs of destructive periodontitis at a young age are prone to further deterioration. Such deterioration appears to be more

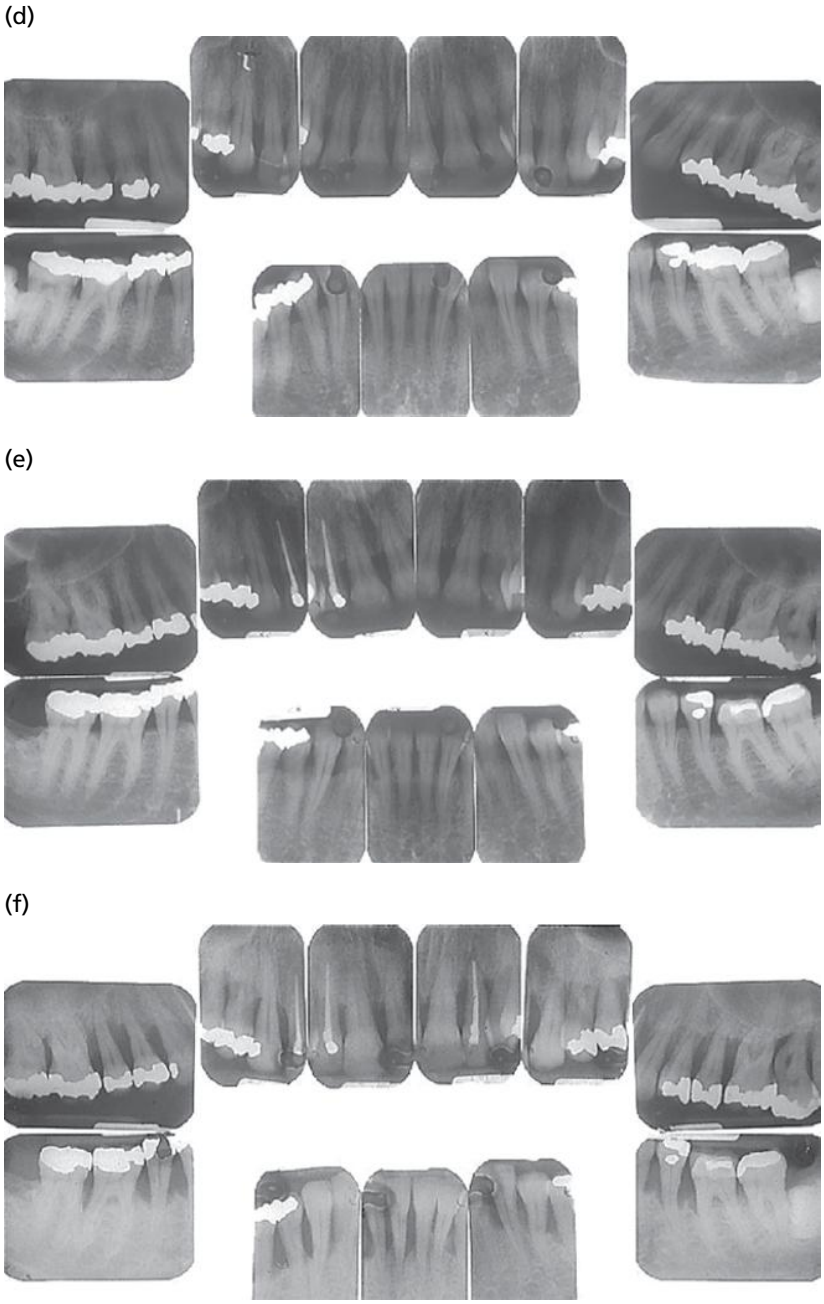


Fig. 21-2 *(Continued).* (d–f) Previous radiographic examinations were available from 1984 and 1987. Comparison of the radiographs obtained over the 6-year period from 1984 to 1990 indicates that most of the periodontal destruction occurred during the last 3 years. The patient had been smoking 20 cigarettes/day for >10 years. Diagnosis: generalized aggressive periodontitis (GAP) in a cigarette smoker.

pronounced at initially affected sites, and in patients diagnosed with LAP and from low socioeconomic groups. Deterioration of the periodontal status involves both an increase in extent (number of lesions within the dentition) and in severity of lesions (further alveolar bone loss at initially diseased sites) (Fig. 21-5) (Clerehugh *et al*. 1990; Lissau *et al*. 1990; Albandar *et al*. 1991a, b; Albandar 1993; Aass *et al*. 1994).

Some epidemiologic investigations have reported a high prevalence of attachment loss in adolescents and young adults who do not fit the characteristics of recognized periodontitis clinical syndromes. Such occurrences have been termed *incidental attachment loss*, and have been reported in 1.6–26% of subjects. This group is thought to comprise both initial forms of periodontitis (including AgP) and a variety of defects, such as recession due to traumatic toothbrushing, attachment loss associated with removal of impacted third molars, interdental caries/placement of restoration, etc.

Conclusion: A small but significant proportion of children and young adults is affected by some form of periodontitis. A substantial proportion of these subjects is thought to be affected by AgP. Given the severity of these forms of periodontal disease and their tendency to progress, early detection of periodontitis and AgP in particular, should be a primary concern

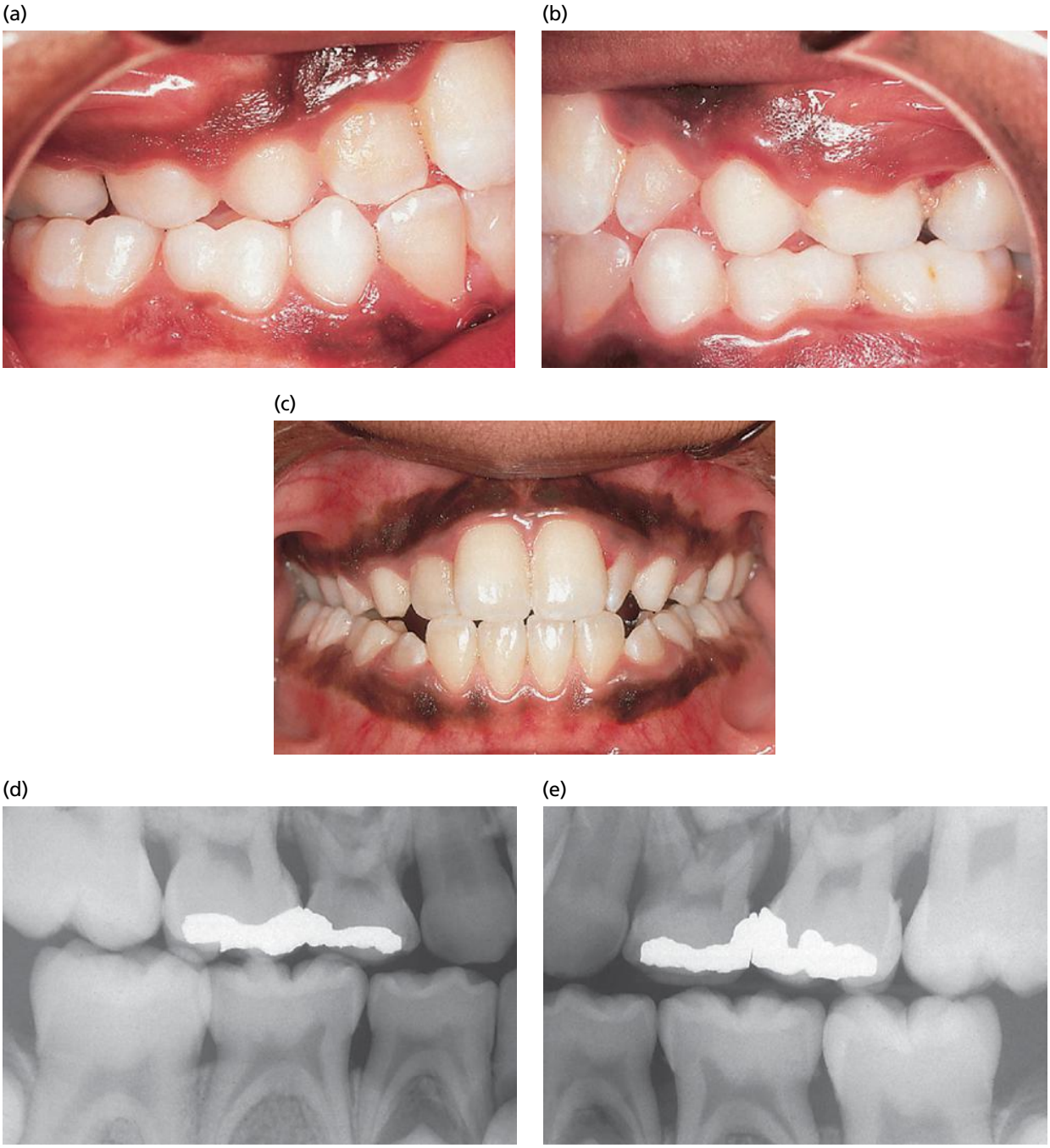


Fig. 21-3 Seven-year-old African–American female presenting with radiographic alveolar bone loss and probing attachment loss at the primary molars and permanent first molars and incisors. (a–c) Clinical photographs, buccal view. (d, e) Bitewing radiographs. Clinical presentation shows moderate plaque accumulation, localized gingival inflammation, with ulceration of the gingival margin and loss of the interdental papilla mesial aspect of tooth 65. In the primary molar regions there were 4–6-mm pockets with bleeding on probing. Bone loss and attachment loss were limited to the molar region. The mesial aspects of the first permanent molars were also initially involved. Radiographic subgingival calculus is evident. Note that the upper left posterior sextant seems to be more severely affected than the other posterior segments. Diagnosis: localized aggressive (type 1) periodontitis.

of both practitioners and public health officers. The whole population, including children and young adults, should receive a periodontal screening as part of their routine dental examination.

Screening

Given the low prevalence of AgP patients within the population, cost-effective detection of cases requires utilization of a sensitive screening approach, in other words the application of a diagnostic approach that can correctly identify most of the cases with disease. The objective of screening is the detection in a population of possibly diseased subjects who require a more comprehensive examination. In periodontology, the most sensitive diagnostic test for the detection of periodontitis is the measurement of attachment loss by probing. Application of this diagnostic procedure in the mixed dentition and in teeth that are not fully erupted, however, may be difficult.

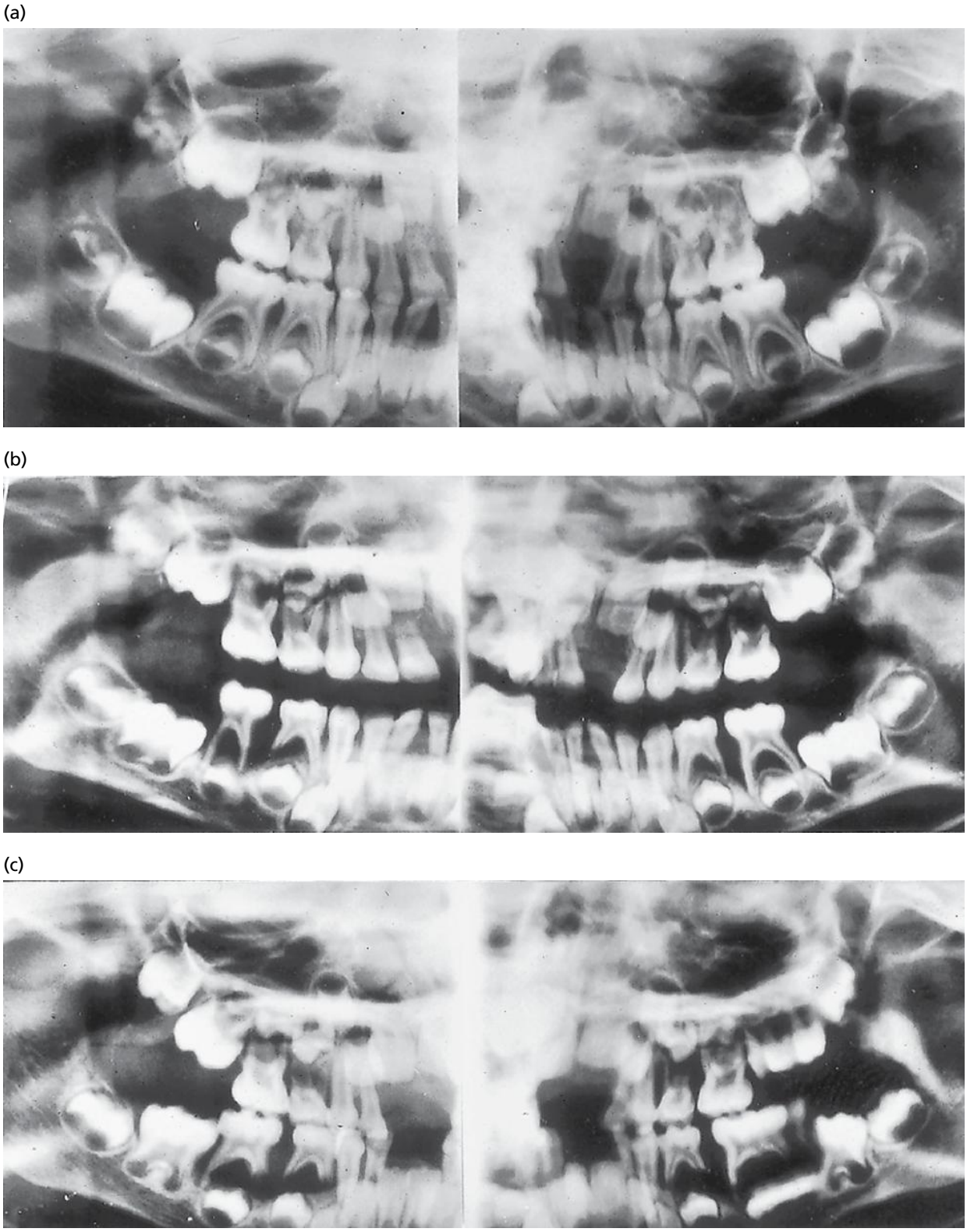


Fig. 21-4 Radiographs obtained from a Caucasian female with generalized prepubertal periodontitis. (a) Radiographic situation in April 1978 when she was 4–5 years old, (b) December 1978, and (c) August 1979. The radiographs illustrate the widespread alveolar bone loss that occurred over the 15-month period. During infancy, this patient had severe, recurrent skin and ear infections sustained by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively. Delayed healing was also observed following minor injuries. White cell counts revealed a persistent leukocytosis, with absolute neutrophil counts always >8000/mm^3. Gingival biopsy indicated that the inflammatory infiltrate consisted almost completely of plasma cells and lymphocytes. No neutrophils were present, in spite of the abundance of these cells in the circulation. This history and clinical manifestation appears to be consistent with the diagnosis of periodontal manifestations of systemic disease in a subject with leukocyte adhesion deficiency (LAD). (Source: Page *et al*. 1983. Reproduced from the American Academy of Periodontology.)

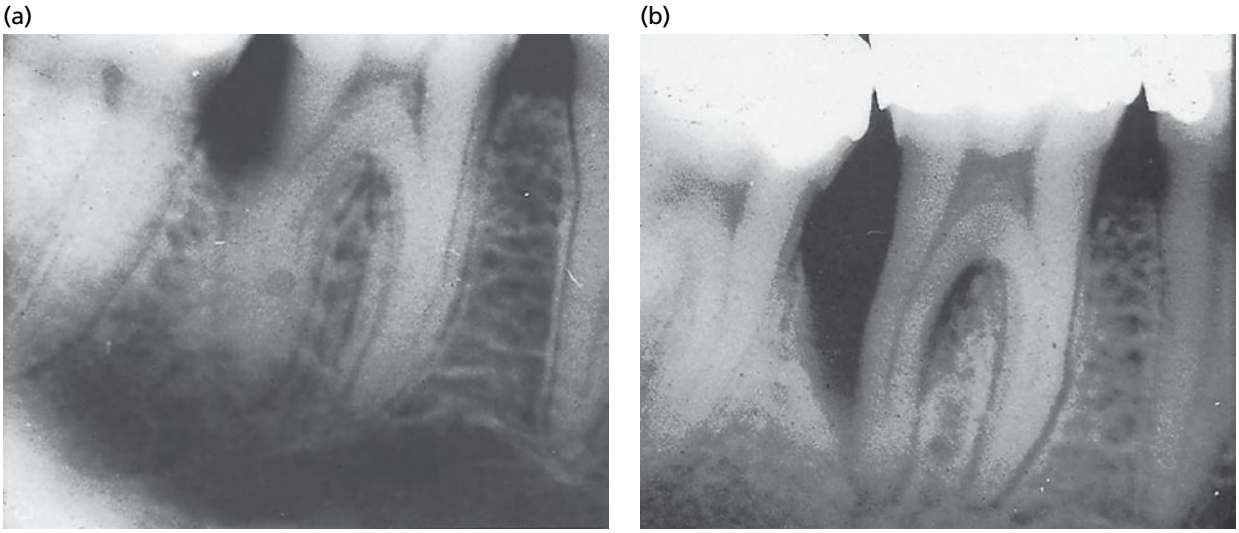


Fig. 21-5 Radiographs illustrating bone loss at the distal aspect of the mandibular first molar in a 15-year-old girl (a) and progression of disease 1 year later (b).

In younger subjects, therefore, a currently utilized screening approach is the measurement of the distance between the alveolar crest and the cementoenamel junction (CEJ) on bitewing radiographs. An advantage of this approach relates to the fact that in most industrialized countries, bitewing radiographs of children and young adolescents in mixed dentition are routinely taken for caries prevention programs; these radiographs should therefore be screened not only for carious lesions but also for the presence of marginal alveolar bone loss.

Previous investigations have attempted to determine the "normal" distance between the CEJ and the alveolar crest of primary and permanent molars in 7–9-year-old children (Sjødin & Mattson 1992; Needleman *et al*. 1997). Median distances at primary molars were 0.8–1.4 mm. These values were in agreement with those previously reported for primary molars of 3–11-year-old children (Bimstein & Soskolne 1988). The CEJ of permanent molars was 0–0.5 mm apical to the alveolar crest in 7–9-year olds. These values were age dependent, and related to the state of eruption of the tooth. In general, however, it should be noted that the majority of children present with distances significantly smaller than the 2–3 mm considered normal for the completely erupted dentitions of adults. In children, significantly greater distances have been detected at sites with caries, fillings or open contacts, indicating that these factors may contribute to bone loss in similar ways to those in adult patients. Furthermore, presence of one of these local factors may suggest a local cause of bone loss, other than periodontitis. A distance of 2 mm between the CEJ and the alveolar crest, in the absence of the above-mentioned local factors, argues therefore for a suspected diagnosis of periodontitis (Figs. 21-6, 21-7) (Sjødin & Mattson 1992). This tentative diagnosis will have to be confirmed by a complete periodontal examination. In utilizing bitewing radiographs for the screening of patients, clinicians should be aware that radiographic marginal bone loss (in the presence of probing attachment loss) is a highly specific diagnostic sign of periodontitis. Its sensitivity, however, is lower than that of periodontal probing because initial intrabony lesions may not appear on radiographs as a result of the masking effects of intact cortical plates (Suomi *et al*. 1968; Lang & Hill 1977). Some initial cases of periodontitis may therefore remain undetected.

In older adolescents and adults, periodontal probing is a more appropriate screening examination than the use of radiographs. It is important to differentiate between clinical use of periodontal probing to perform a complete periodontal examination, and its use as a screening tool. Using probing to detect attachment loss during a screening examination requires circumferential probing to evaluate all sites around the tooth. In a screening examination, however, attachment loss values for all sites are usually not recorded. Furthermore, the screening examination can be stopped once evidence of attachment loss has been detected, and therefore the need for a comprehensive examination has been established. The American Academy of Periodontology has endorsed a simplified screening examination for this purpose. This examination is based on a modification of the Community Periodontal Index of Treatment Needs (CPITN) (Ainamo *et al*. 1982; American Academy of Periodontology & American Dental Association 1992).

There is no evidence that orthopantomograms or cone-beam computed tomography (CT) are useful contributors to the screening process.

Once a case has been detected by a screening examination, a comprehensive periodontal examination will be necessary to establish a proper diagnosis. At this stage, once a case of periodontitis has been confirmed, a differential diagnosis between aggressive (type 1) periodontitis and chronic (type 2) periodontitis needs to be made in accordance with the criteria mentioned above and keeping in mind that

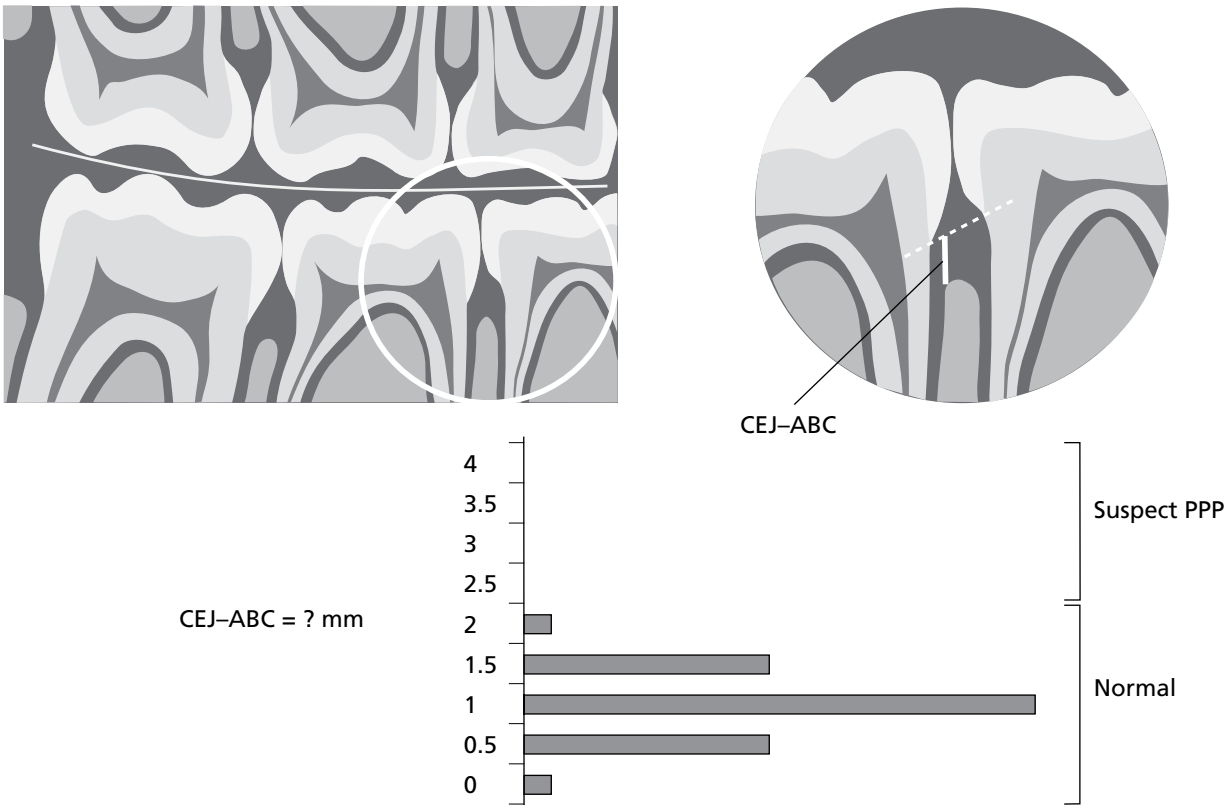


Fig. 21-6 Schematic representation of the use of bitewing radiographs to screen for prepubertal periodontitis in mixed dentition. The distance from the cementoenamel junction (CEJ) and the alveolar bone crest (ABC) is measured from a line connecting the CEJ of the two adjacent teeth. Measurements are taken for each mesial and distal surface. Normal CEJ–ABC distances for 7–9-year olds are <2.0 mm. If the measurement exceeds this value, prepubertal periodontitis (PPP) should be suspected, and a comprehensive periodontal examination should be performed.

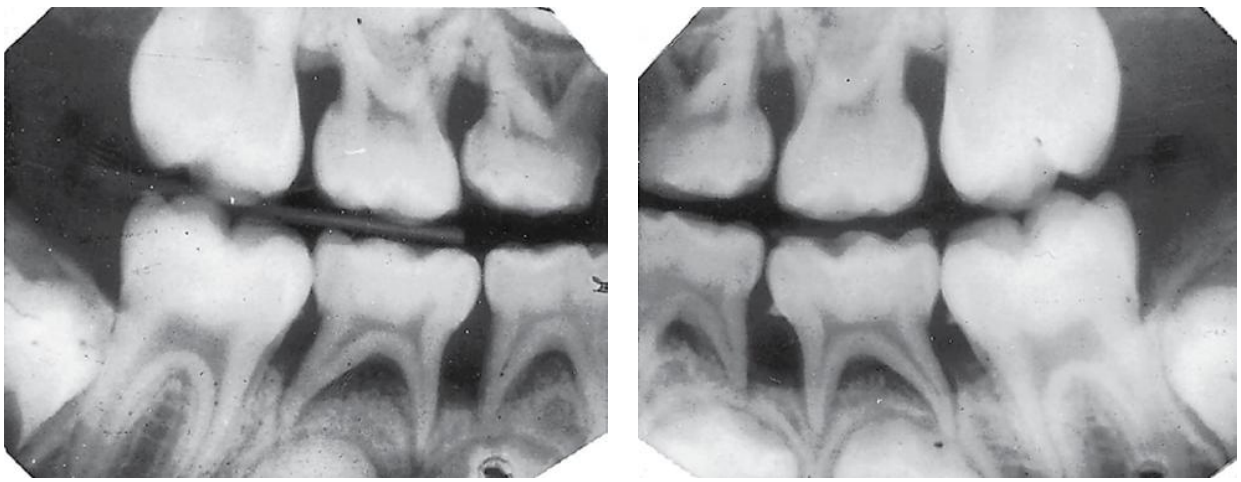


Fig. 21-7 Bitewing radiographs showing advanced bone loss at primary molars, and initial involvement of the mesial aspect of the first molar in a child with early-onset periodontitis. Note the marginal pattern of bone loss, which is significantly different from the pattern expected in association with the normal exfoliation of deciduous teeth. Subgingival calculus can also be observed.

cases who do not fit the AgP criteria should be diagnosed as chronic periodontitis.

Conclusion: Screening periodontal examinations should be performed as part of every dental visit. Marginal bone loss assessed on bitewing radiographs, though less sensitive than periodontal probing, may be used as a screening tool in subjects with primary and mixed dentitions. Attachment loss evaluated by periodontal probing is the most sensitive screening approach currently available; it should be used in older adolescents and adults. Differential diagnosis between AgP and chronic periodontitis is based on exclusion of AgP.

Etiology and pathogenesis

As a group, aggressive forms of periodontitis are characterized by severe destruction of the periodontal attachment apparatus at an early age. This early

manifestation of clinically detectable lesions is generally interpreted as being the expression of highly virulent causative agents or high levels of susceptibility of the individual patient, or a combination of the two.

Bacterial etiology

The evidence implicating bacteria in the etiology of periodontitis has been described in Chapter 10. The most abundant evidence regarding a bacterial etiology of AgP comes from studies of LAP. Evidence relating to other forms of AgP (GAP) will be discussed only when specifically different from LAP.

Acceptance of a bacterial etiology of aggressive forms of periodontitis has been particularly difficult since the clinical presentation of cases frequently shows little visible plaque accumulation, and proximal caries, another dental disease of bacterial origin affecting younger individuals, seems much less prevalent in LAP patients than in age-, gender-, and race-matched controls (Fine *et al*. 1984; Sioson *et al*. 2000). Of great importance, in this respect, were microscopic studies demonstrating the presence of a layer of bacterial deposits on the root surface of advanced AgP lesions (Listgarten 1976; Westergaard *et al*. 1978). Early studies attempted to identify the bacteria involved using culture techniques (Newman *et al*. 1976; Slots 1976; Newman & Socransky 1977). In these studies, Gram-negative organisms comprised approximately two-thirds of the isolates from deep periodontal pockets. In contrast, these organisms averaged only about one-third of the isolates in control sites with normal gingiva. A substantial part of the isolates was not identifiable at that time due to methodologic limitations and ambiguous classification schemes. Dominant microorganisms in LAP included *A. actinomycetemcomitans*, *Capnocytophaga* spp., *Eikenella corrodens*, saccharolytic *Bacteroides*-like organisms now classified as *Prevotella* spp., and motile anaerobic rods today labeled *Campylobacter rectus*. Gram-positive isolates were mostly streptococci, actinomycetes, and peptostreptococci. *A. actinomycetemcomitans*, *Capnocytophaga* spp., and *Prevotella* spp. were also shown to be the most prominent members of the subgingival microbiota of periodontitis lesions in the primary dentition. The microbial patterns observed in periodontal lesions of the primary dentition seemed, however, to be more complex than the ones found in LAP patients.

One of these organisms, *A. actinomycetemcomitans*, a short, facultatively anaerobic, non-motile, Gram-negative rod, received particular attention and was increasingly viewed as a key microorganism in LAP. This view was principally based on four lines of evidence (Socransky & Haffajee 1992):

1. Association studies, linking the organism to the disease: *A. actinomycetemcomitans* was isolated in periodontal lesions from >90% of LAP patients and was much less frequent in periodontally healthy individuals (Table 21.1) (see also Ashley *et al*. 1988; Van der Velden *et al*. 1989; Albandar *et al*. 1990; Gunsolley *et al*. 1990; Slots *et al*. 1990; Asikainen *et al*. 1991; Aass *et al*. 1992; Ebersole *et al*. 1994; Listgarten *et al*. 1995). In some studies it was possible to demonstrate elevated levels of *A. actinomycetemcomitans* in sites showing evidence of recent or ongoing periodontal tissue destruction (Haffajee *et al*. 1984; Mandell 1984; Mandell *et al*. 1987).
2. Demonstration of virulence factors: *A. actinomycetemcomitans* was shown to produce several

Table 21-1 Classical studies on the distribution of *Aggregatibacter actinomycetemcomitans* in localized acute periodontitis (LAP), gingivitis, adult periodontitis, and normal non-diseased subjects.

Study	Diagnosis	No. of subjects (sites)	Positive subjects (%)	Negative subjects (%)
Slots *et al*. (1980)	LAP	10 (34)	90	79
	Adult periodontitis	12 (49)	50	35
	Normal juveniles	10 (60)	20	3
	Normal adults	11 (66)	36	17
Mandell & Socransky (1981)	LAP	6 (18)	100	79
	Adult periodontitis	25 (50)	0	–
	Gingivitis	23 (46)	0	–
Zambon *et al*. (1983c)	LAP	29	97	–
	Adult periodontitis	134	21	–
	Normal juveniles/ adults	142	17	–
Eisenmann *et al*. (1983)	LAP	12 (12)	100	100
	Normal juveniles	10 (10)	60	60
Moore *et al*. (1985)	LAP	14 (31)	36	5
Asikainen (1986)	LAP	19 (38)	89	68

See text for a selection of more recent investigations.

potentially pathogenic substances, including a leukotoxin, that were capable of translocating across epithelial membranes, and could induce disease in experimental animals and non-oral sites (for review see Zambon *et al*. 1988; Slots & Schonfeld 1991).

3. Findings of immune responses towards this bacterium: investigators repeatedly reported significantly elevated levels of serum antibodies to *A. actinomycetemcomitans* in LAP patients (Listgarten *et al*. 1981; Tsai *et al*. 1981; Altman *et al*. 1982; Ebersole *et al*. 1982, 1983; Genco *et al*. 1985; Vincent *et al*. 1985; Mandell *et al*. 1987; Sandholm *et al*. 1987). Such patients were furthermore shown to produce antibodies locally against this organism at diseased sites (Schonfeld & Kagan 1982; Ebersole *et al*. 1985b; Tew *et al*. 1985).
4. Clinical studies showing a correlation between treatment outcomes and levels of *A. actinomycetemcomitans* after therapy: unsuccessful treatment outcomes were linked to a failure in reducing the subgingival load of *A. actinomycetemcomitans* (Slots & Rosling 1983; Haffajee *et al*. 1984; Christersson *et al*. 1985; Kornman & Robertson 1985; Mandell *et al*. 1986, 1987; Preus 1988).

In consideration of these findings, *A. actinomycetemcomitans* was one of the few oral microorganisms recognized by many to be a true infectious agent, and LAP as an infection essentially caused by *A. actinomycetemcomitans*. Accepting such a concept has far-reaching consequences with regards to strategies for prevention and therapy. For example, if *A. actinomycetemcomitans* is a real exogenous pathogen for LAP, or AgP in general, avoidance of exposure to the organism becomes a relevant issue in prevention (the mere presence of *A. actinomycetemcomitans* would be an indication for intervention), and the elimination of *A. actinomycetemcomitans* may be a valid treatment goal. Consequently, highly sensitive tests to detect the bacterium would be a useful diagnostic tools. Several studies have, in fact, provided evidence for transmission of *A. actinomycetemcomitans* between humans, for example from parent to child or between spouses (DiRienzo *et al*. 1990; Preus *et al*. 1992; Petit *et al*. 1993a, b; DiRienzo *et al*. 1994b; Poulsen *et al*. 1994; Von Troil-Lindén *et al*. 1995). Other studies have indicated that *A. actinomycetemcomitans* can be eliminated with appropriate mechanical treatment and adjunctive antibiotic therapy (Rams *et al*. 1992; Pavicic *et al*. 1994).

However, the view of LAP as an *A. actinomycetemcomitans* infection has not remained undisputed. It was contested by citing cross-sectional studies showing a high general *A. actinomycetemcomitans* prevalence in certain populations, particularly from developing countries (Eisenmann *et al*. 1983; Dahlén *et al*. 1989; McNabb *et al*. 1992; Al-Yahfoufi *et al*. 1994; Gmür & Guggenheim 1994). It was also argued that *A. actinomycetemcomitans* could be detected in subgingival plaque samples from sites with and without disease, and that there were patients with LAP who apparently neither showed the presence of *A. actinomycetemcomitans* in the oral flora nor had elevated antibody titers to the organism (Loesche *et al*. 1985; Moore 1987). A systematic review with the purpose of determining to what extent adjunctive microbiologic testing could distinguish between chronic and aggressive periodontitis concluded that the presence or absence of *A. actinomycetemcomitans* (as well as of four other suspected periodontal pathogens) could not discriminate subjects with AgP from those with chronic periodontitis (Mombelli *et al*. 2002). Although a diagnosis of AgP was more likely in a subject positive for *A. actinomycetemcomitans* than in an subject negative for this organism, any *A. actinomycetemcomitans*-positive subject with periodontitis was three times more likely to be suffering from chronic than from aggressive periodontitis.

If a putative pathogen can be detected frequently in subjects without a given clinical diagnosis, this suggests that not all humans are equally susceptible and/or that there is variation in virulence and pathogenic potential. Strong evidence has been produced in recent years demonstrating that the virulence of *A. actinomycetemcomitans* is in fact variable, and proving the existence of at least one particularly virulent subpopulation of *A. actinomycetemcomitans.*

Using monoclonal antibody technology, five serotypes (a, b, c, d, e) of *A. actinomycetemcomitans* can be distinguished. Each of these serotypes represents a separate evolutionary lineage. A serotype-dependent pattern of association with LAP was found in the US, where serotype b strains were more often isolated from patients with LJP than from other subjects (Zambon *et al*. 1983b, 1996). A higher frequency of serotype b strains was also reported in Finnish subjects with periodontitis (Asikainen *et al*. 1991, 1995). Differing results were, however, reported from other parts of the world, suggesting that there may be specific distribution patterns in ethnically distinct populations (Chung *et al*. 1989; Gmür & Baehni 1997; Hölttä *et al*. 1994). Using restriction fragment length polymorphism (RFLP) analysis, DiRienzo *et al*. (1994a, b) could discriminate 12 genotypes of *A. actinomycetemcomitans*. One of them (RFLP type II) was uniquely associated with periodontal disease. Others, however, were linked to healthy periodontal conditions.

Several properties of *A. actinomycetemcomitans* are regarded as important determinants of virulence and pathogenic potential (Table 21.2). All Gram-negative bacteria are enveloped by two membranes, of which the outer is rich in endotoxin. This identifying feature of Gram-negative bacteria has a lipid and a polysaccharide part and is therefore frequently termed lipopolysaccharide (LPS). LPS is set free when bacterial cells die or multiply. *A. actinomycetemcomitans* can also secrete membrane vesicles that can serve as transport vehicles to spread endotoxin as well as other pathogenic substances produced by the

Table 21-2 Determinants of virulence and pathogenic potential of *Aggregatibacter actinomycetemcomitans*.

Factor	Significance
Leukotoxin	Destroys human polymorphonuclear leukocytes and macrophages
Endotoxin	Activates host cells to secrete inflammatory mediators (prostaglandins, interleukin-1β, tumor necrosis factor-α)
Bacteriocin	May inhibit growth of beneficial species
Immunosuppressive factors	May inhibit IgG and IgM production
Collagenases	Cause degradation of collagen
Chemotactic inhibition factors	May inhibit neutrophil chemotaxis

bacterium. The LPS of *A. actinomycetemcomitans* can activate host cells, and macrophages in particular, to secrete inflammatory mediators such as prostaglandins, IL-1β, and tumor necrosis factor-alpha (TNF-α). It is also highly immunogenic, since high titers of antibodies against its antigenic determinant are frequently detected in infected individuals. Additional virulence factors interfering with fibroblast proliferation have been identified for certain strains of *A. actinomycetemcomitans*. Immunosuppressive properties of *A. actinomycetemcomitans*, as well as collagenolytic activity and inhibition of neutrophil chemotaxis, have been demonstrated (for review see Fives-Taylor *et al*. 1996). The key element of virulence and pathogenicity of *A. actinomycetemcomitans*, however, is considered to be the production of a leukotoxin, which plays an important role in the evasion of local host defenses. The leukotoxin produced by *A. actinomycetemcomitans* exhibits cytotoxic specificity and destroys human polymorphonuclear leukocytes (PMNs) and macrophages, but neither epithelial and endothelial cells nor fibroblasts. It belongs to the family of RTX (Repeats in ToXin) toxins, which are pore-forming lytic toxins (for details see Lally *et al*. 1996).

Leukotoxin production varies significantly among strains of *A. actinomycetemcomitans* (Zambon *et al*. 1983a; Kolodrubetz *et al*. 1989; Spitznagel *et al*. 1991; Brogan *et al*. 1994). The strain-specific difference in leukotoxin production seems to be regulated at the level of transcription (Spitznagel *et al*. 1991). Brogan *et al*. (1994) detected a 530-bp deletion in the promoter region of the leukotoxin operon and found that strains with this feature produced 10–20 times more leukotoxin. Subsequent analysis showed that the occurrence of such highly toxigenic strains coincided with the high frequency of serotype b in patients with LJP, and that these strains actually constituted a specific clone of serotype b, now referred to as the JP2 clone (the initial isolate of this clone is strain JP2, from an African–American child with prepubertal periodontitis) (Tsai *et al*. 1984). Extensive further research (Poulsen *et al*. 1994; Haubek *et al*. 1995, 1996, 1997; Tinoco *et al*. 1997; Bueno *et al*. 1998; He *et al*. 1999; Macheleidt *et al*. 1999; Mombelli *et al*. 1999; Contreras *et al*. 2000; Haraszthy *et al*. 2000; Haubek *et al*. 2001; Tan *et al*. 2001; Cortelli *et al*. 2005) has clearly identified the JP2 clone as a common isolate in patients of North and West African descent suffering from AgP, even if they lived in another geographic region (e.g. North and South America or Europe). The disease association with RFLP type II reflects the fact that the JP2 clone represents a subpopulation of strains showing the RFLP type II pattern.

Our current knowledge with regards to the genetic and phenotypic diversity of *A. actinomycetemcomitans*, and its distribution in various populations and cohorts, with or without a clinical diagnosis of LAP, suggests that *A. actinomycetemcomitans* may be considered an opportunistic pathogen, or even a commensal bacterial species as a whole. However, at least one distinct subpopulation, the JP2 clone, displays the properties of a true pathogen in at least one group of humans of North and West African descent (Kilian *et al*. 2006; Haubek *et al*. 2008). Prevention of vertical transmission of such virulent clones may be a feasible measure to prevent AgP (Van Winkelhoff & Boutaga 2005).

Generalized aggressive periodontitis (GAP), formerly named generalized early-onset periodontitis (G-EOP) and rapidly progressive periodontitis (RPP), has been frequently associated with the detection of *P. gingivalis*, *Tannerella forsythia*, and *A. actinomycetemcomitans*. In contrast to *A. actinomycetemcomitans*, which is facultatively anaerobic, *P. gingivalis* and *T. forsythia* are fastidious strict anaerobes. *P. gingivalis* produces several potent enzymes, in particular collagenases and proteases, endotoxin, fatty acids, and other possibly toxic agents (Shah 1993). A relationship between the clinical outcome of therapy and bacterial counts has also been documented for *P. gingivalis*, and non-responding lesions often contain this organism in elevated proportions. High local and systemic immune responses against this bacterium have been demonstrated in patients with GAP (Tolo & Schenck 1985; Vincent *et al*. 1985; Ebersole *et al*. 1986; Murray *et al*. 1989).

Bacterial damage to the periodontium

Disease-associated bacteria are thought to cause destruction of the marginal periodontium via two related mechanisms: (1) the direct action of the microorganisms or their products on the host tissues, and/or (2) as a result of their eliciting tissue-damaging inflammatory responses (see Chapter 13) (Tonetti 1993). The relative importance of these two mechanisms in AgP remains speculative. Investigations in humans have indicated that *A. actinomycetemcomitans* is able to translocate across the junctional epithelium and invade the underlying connective tissue (Saglie *et al*. 1988). These data support the hypothesis that

Table 21-3 Host defense mechanisms in the gingival sulcus.

- Intact epithelial barrier and epithelial attachment
- Salivary flushing action, agglutinins, antibodies
- Sulcular fluid flushing action, opsonins, antibodies, complement, and other plasma components
- Local antibody production
- High levels of tissue turnover
- Presence of normal flora or beneficial species
- Emigrating PMNs and other leukocytes

PMNs, polymorphonuclear leukocytes.
Adapted from Page (1990), from the University of North Carolina School of Dentistry.

direct bacterial invasion may be responsible for some of the observed tissue breakdown. Data from chronic periodontitis, however, seem to indicate that two-thirds of attachment loss and alveolar bone resorption is preventable through the action of non-steroidal anti-inflammatory drugs, and therefore tissue destruction seems to be driven by the inflammatory process (Williams *et al*. 1985, 1989). Apical spread of bacteria loosely adhering to the hard, non-shedding surface of the tooth is thought to be controlled through a first line of defense consisting of mechanisms such as the high turnover of junctional epithelium keratinocytes, the outward flow of crevicular fluid, and the directed migration of PMNs through the junctional epithelium; the efficiency of these innate immune mechanisms is highly enhanced by the presence of specific antibodies and complement fragments in the gingival crevicular fluid (Page 1990) (Table 21.3) (see Chapter 13).

Host response to bacterial pathogens

Both local and systemic host responses to AgP-associated microflora have been described. Local inflammatory responses have been characterized by an intense recruitment of PMNs both within the tissues and into the periodontal pocket. Such a preponderance of PMNs underlines the importance of these cells in the local defense against bacterial aggression and their potential role in host-mediated tissue destruction. B cells and antibody-producing plasma cells represent a significant component of the mononuclear cell-dominated connective tissue lesion (Liljenberg & Lindhe 1980). Plasma cells have been shown to be predominantly IgG-producing cells, with a lower proportion of IgA-producing cells (Mackler *et al*. 1977, 1978; Waldrop *et al*. 1981; Ogawa *et al*. 1989). Local IgG_4-producing cells, in particular, seem to be elevated. Another important component of the local inflammatory infiltrate is T cells. Subset analysis of local T cells has indicated a depressed T-helper-to-T-suppressor ratio as compared to both healthy gingiva and peripheral blood. These findings have been interpreted to suggest the possibility of altered local immune regulation (Taubman *et al*. 1988, 1991). Peripheral blood mononuclear cells from AgP patients have been reported to exhibit a reduced autologous mixed lymphocyte reaction, as well as a higher than normal response to B-cell mitogens (for review see Engel 1996). Local inflammatory responses are characterized by high levels of PGE_2, IL-1α, and IL-1β in both crevicular fluid and tissue (Masada *et al*. 1990; Offenbacher *et al*. 1993). PGE_2 production, in particular, has been shown to be highly elevated in AgP subjects when compared to periodontally healthy individuals and patients with chronic periodontitis.

Specific antibodies against AgP-associated microorganisms (Lally *et al*. 1980; Steubing *et al*. 1982; Ebersole *et al*. 1984, 1985a, b) and cleaved complement fragments (Schenkein & Genco 1977; Patters *et al*. 1989) have also been detected in crevicular fluid from AgP lesions. Of interest is the evidence indicating that crevicular fluid titers of antibodies against AgP-associated microorganisms are frequently higher than in the serum of the same patient (Ebersole *et al*. 1984, 1985a, b). This observation, together with substantial *in vitro* and *ex vivo* data, strongly suggests that substantial fractions of these antibodies are locally produced in the inflammatory infiltrate (Steubing *et al*. 1982; Hall *et al*. 1990, 1991, 1994). Substantial titers of antibodies against *A. actinomycetemcomitans* and *P. gingivalis* have also been detected in the serum of AgP patients. Furthermore, in some patients, titers of antibodies reactive to *A. actinomycetemcomitans* have been shown to be as high as those against *Treponema pallidum* present in tertiary syphilis (0.1–1 g/mL); this clearly indicates the extent of the host response that can be mounted against these periodontal pathogens (for a review see Ebersole 1990, 1996).

Investigations have identified the immunodominant *A. actinomycetemcomitans* antigen to be the serotype-specific carbohydrate; furthermore, it has been shown that the vast majority of antibodies reactive to this carbohydrate in AgP patients consist of IgG_2 (Califano *et al*. 1992). High titers and high avidity of *A. actinomycetemcomitans*-specific IgG_2 have been demonstrated in LAP patients, where high antibody titers are thought to be associated with the host's ability to localize attachment loss to a few teeth; conversely, GAP patients are frequently seronegative for *A. actinomycetemcomitans* or display low titers and avidity. Anti-*A. actinomycetemcomitans* serotype polysaccharide IgG_2, therefore, is considered to be protective against widespread AgP (Tew *et al*. 1996).

Of importance are findings reporting antibody response to *P. gingivalis* in GAP forms. Patients suffering from these forms of disease frequently show both low levels of serum antibodies against *P. gingivalis* and low levels of antibody avidity, indicating a specific inability of some GAP patients to cope effectively with these bacteria. Importantly, however, both titers and avidity of antibodies reacting with *P. gingivalis* can be improved as a result of therapy.

Another important aspect of the host response towards AgP microorganisms has been the recognition that the PMNs of some LAP and GAP patients show decreased migration and antibacterial functions (Genco *et al*. 1980, 1986; Van Dyke *et al*. 1982, 1986,

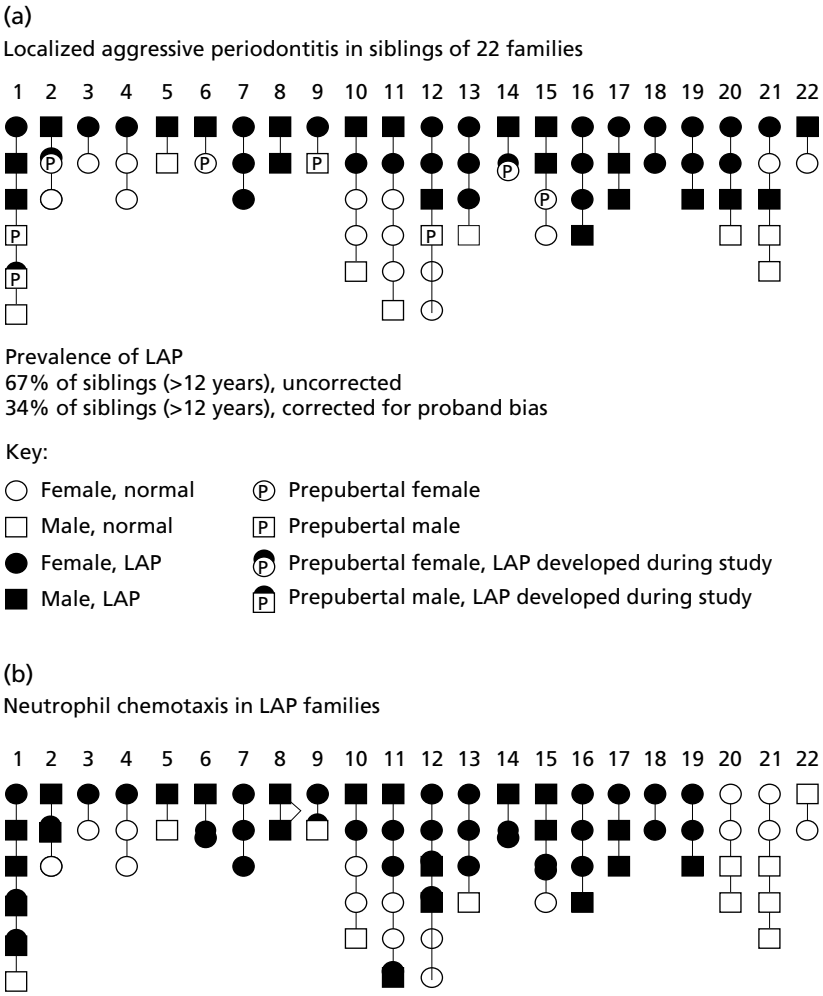


Fig. 21-8 (a) Patients suffering from localized aggressive periodontitis (LAP) in 22 families are represented by solid black shapes. In each family the proband is on the left. (b) Schematic representation of sibships involved in the study group. Numbers are the same as in (a). Solid black shapes represent patients exhibiting depressed neutrophil chemotaxis. In this group, after correcting for sampling bias, 40% of subjects presented with abnormal chemotaxis. Subjects in sibship 8 are identical twins. (Source: Van Dyke *et al*. 1985. Reproduced with permission from John Wiley & Sons.)

1988). These abnormalities are frequently minor in the sense that they are usually not associated with infections other than periodontitis. A key report has indicated that PMN abnormalities in LAP patients seem to cluster in families, much in the same way as AgP does (Fig. 21-8) (Van Dyke *et al*. 1985). This evidence has been interpreted as a suggestion that the LAP-associated PMN defect may be inherited. Other reports have indicated that PMN abnormalities in LAP patients may be, at least in part, the result of a hyperinflammatory state resulting in the presence of pro-inflammatory cytokines in the serum of some AgP patients (Shapira *et al*. 1994b; Agarwal *et al*. 1996).

Genetic aspects of host susceptibility

Several family studies have indicated that the prevalence of AgP is disproportionately high among certain families, where the percentage of affected siblings may reach 40–50% (Saxen & Nevanlinna 1984; Beaty *et al*. 1987; Long *et al*. 1987; Boughman *et al*. 1992; Marazita *et al*. 1994; Llorente & Griffiths 2006). Such a dramatic familial aggregation of cases indicates that genetic factors may be important in susceptibility to AgP. Genetic studies in these families suggest that the pattern of disease transmission is consistent with Mendelian inheritance of a gene of major effect (Saxen & Nevanlinna 1984; Beaty *et al*. 1987; Boughman *et al*. 1992; Hart *et al*. 1992; Marazita *et al*. 1994). This means that the observed familial pattern can be partly accounted for by one or more genes that could predispose individuals to develop AgP.

Segregation analyses have indicated that the likely mode of inheritance is autosomal dominant (Fig. 21-9a) (Saxen & Nevanlinna 1984; Beaty *et al*. 1987; Hart *et al*. 1992; Marazita *et al*. 1994). Most of these investigations were carried out in African–American populations; it is therefore possible that other modes of inheritance may exist in different populations. Segregation analysis can provide information about the mode of inheritance of a genetic trait, but does not provide information about the specific gene(s) involved. The chromosomal location of a gene of major effect for a trait such as AgP susceptibility can be determined by linkage analysis. An investigation utilizing this methodology reported linkage of LAP to the vitamin D-binding locus on region q of chromosome 4 in a large family of the Brandywine population (Boughman *et al*. 1986). These results, however, were not confirmed in a subsequent study utilizing a different population (Hart *et al*. 1993). Another study has linked localized AgP with the q25 region of chromosome 1 in an area close to the cyclooxygenase 2 (*COX-2*) gene (Li *et al*. 2004), and another has established evidence of linkage

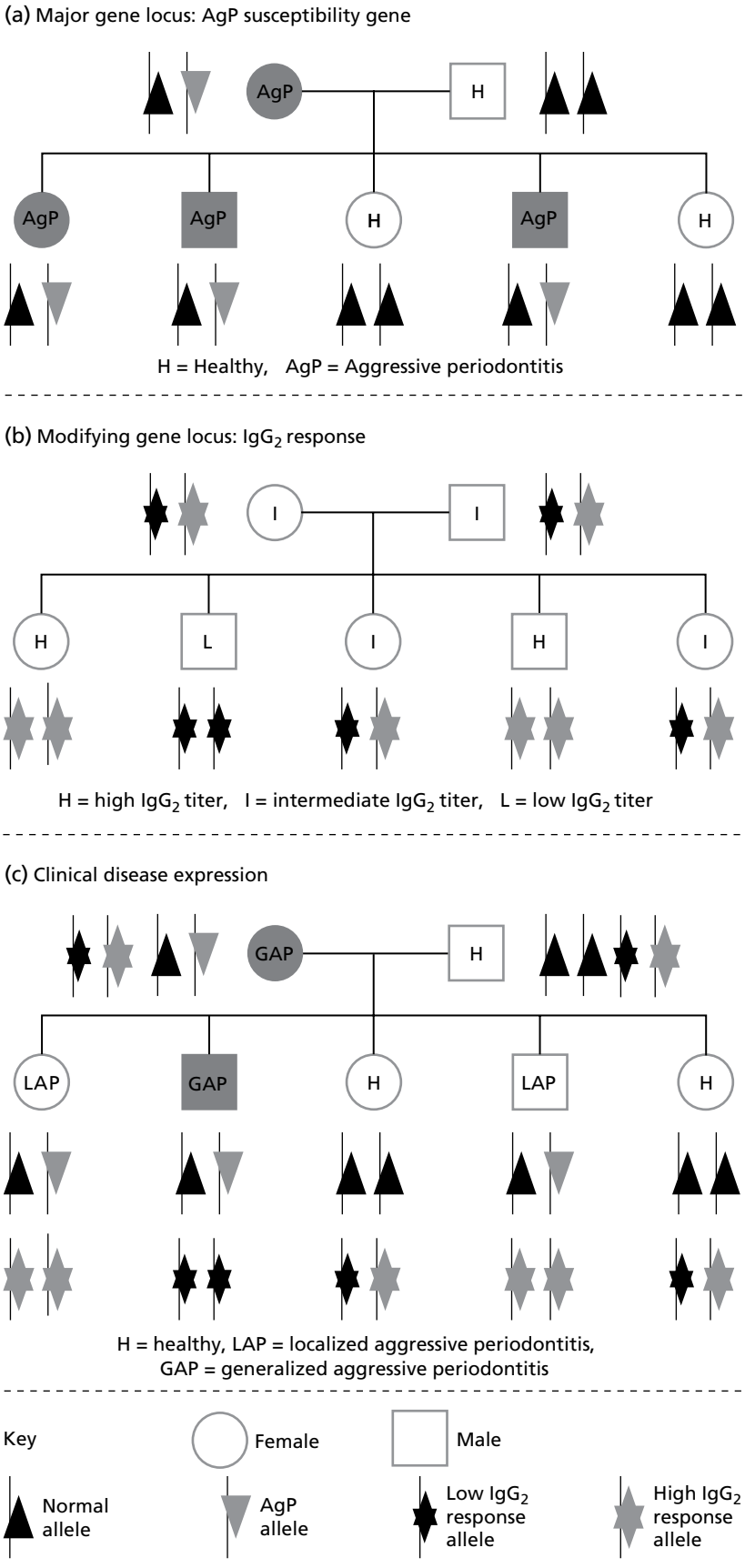


Fig. 21-9 (a) Genetic predisposition to aggressive periodontitis (AgP) is determined by a single gene of major effect, inherited as an autosomal dominant trait. (b) Modifying genes may control immune responses that determine the clinical extent and severity of periodontal destruction in AgP. Here an allele controlling IgG_2 levels is inherited as a co-dominant trait. (c) Independent inheritance of major locus and modifying locus illustrating how localized aggressive periodontitis (LAP) and generalized aggressive periodontitis (GAP) may segregate within the same family. The propensity to develop AgP is dependent upon the inheritance of a major susceptibility gene. The clinical phenotype is dependent upon the host's ability to produce IgG_2 in response to periodontopathic bacteria. High IgG_2 titers limit disease extension. Intermediate and low IgG_2 titers are less effective in limiting intermediate disease progression. (Adapted from Hart 1996, reproduced from the American Academy of Periodontology. Adapted from Schenkein & Van Dyke, 1994 from John Wiley & Sons.)

with the q13–14 region of chromosome 2 that contains the *IL-1* gene complex (Scapoli *et al*. 2005). Such data are currently considered to support the existence of genetic heterogeneity in LAP forms, and of distinct forms of AgP. Therefore, it is currently maintained that although formal genetic studies of AgP support the existence of a gene of major effect, it is unlikely that all forms of AgP are due to the same genetic variant (Hart 1996; Loos *et al*. 2005). This notion is consistent with the fact that numerous diseases and syndromes with

Table 21-4 Genes known to affect human polymorphonuclear leukocyte (PMN) function or host response to lipopolysaccharide (LPS) load and/or thought to be among the candidate genes of major effect in early-onset periodontitis (EOP) susceptibility.

Condition	OMIM[a]	Transmission	Chromosome location	Comments
Bactericidal permeability increasing protein (BPIP)	109195	AD	20q11–12	BPIP is associated with PMN granules and is bactericidal to Gram organisms. It binds to LPS with high affinity. BPIP is 45% homologous to LPS-binding protein
LPS binding protein (LBP)	151990	AD	20q11–12	Produced during acute phase of infection: binds to LPS and functions as a carrier for LPS; functions in monocyte response
Monocyte differentiation antigen (CD14)	158126	AD	5q31	Receptor for LBP–LPS complex
Prostaglandin synthase 2 (PTGS2)	600262	AR	1q25.2–3	Major role in regulation of prostaglandin synthesis. Dramatic induction of PTGS2 mRNA occurs in normal peripheral blood leukocytes in response to LPS
PMN actin dysfunction (NAD)	257150	AR	?	Carriers (heterozygotes) have a 50% decrease in actin filament assembly; affected individuals (homozygotes) have recurrent bacterial infections. PMN severely defective in migration and particle ingestion; basic defect due to failure of PMN actin polymerization
Myeloperoxidase deficiency (MPO)	254600	AR	17q12–21	Absence of MPO. MPO is a dimeric protein that catalyzes the production of oxidating agents with microbicidal activity against a wide range of microbes. Several variants have been described
IgE elevation with PMN chemotaxis defect	147060	AD	?	Impaired lymphocyte response to *Candida* antigen; recurrent bacterial infections
Fc receptor gamma IIA polymorphism (FCGR2A)	146790	AD	1q21–q23	Allelic variants of the Fc-gamma receptor 2A confer distinct phagocytic capacities providing a possible mechanism for hereditary susceptibility to infection. The H131 allele is the only FCGR2A that recognizes IgG_2 efficiently, and optimal IgG_2 handling occurs only in the homozygous state for H131. The allelic variant R131 has low binding of IgG_2
Immunoglobulin G_2m allotypes	N/A	?	N/A	Specific allotypes associated with IgG_2 response to specific bacterial antigens Subjects lacking specific allotypes may be selectively unable to mount efficient antibody response against specific antigens

[a] Online Mendelian Inheritance in Man (OMIM).
Adapted from Hart (1996), from the American Academy of Periodontology.

similar clinical appearance are known to result from different genetic polymorphisms.

Additional evidence for a genetic component to AgP was provided by a study demonstrating substantial levels of hereditability in quantitative parameters for periodontal disease severity of AgP patients (Diehl *et al*. 2005).

Based on current knowledge that AgP subjects have a high prevalence of PMN functional defects, that they produce high levels of inflammatory mediators in response to LPS stimulation, and that connective tissue homeostasis is relevant in periodontitis, several loci have been proposed as genes conferring increased susceptibility to AgP. Hart (1996) compiled a list of candidate genes (Table 21.4) associated with increased susceptibility to AgP.

A series of studies has been performed to assess whether or not specific polymorphisms in these candidate genes are associated with AgP (for a review see Shapira *et al*. 2005 and Loos *et al*. 2005). Significant associations have been observed for genes encoding proteins that are associated with neutrophil function (Fu *et al*. 2002; Loos *et al*. 2003; Kaneko *et al*. 2004; Jordan *et al*. 2005; Nibali *et al*. 2006; de Souza & Colombo 2006), with inflammation, and with the host's ability to effectively deal with exposure to

bacterial components such as endotoxin (Suzuki *et al.* 2004; Scapoli *et al.* 2005; Brett *et al.* 2005; Noack *et al.* 2006), and with connective tissue homeostasis (Suzuki *et al.* 2004; Park *et al.* 2006; Soedarsono *et al.* 2006). It should be emphasized, however, that the validity of the conclusions of the majority of these studies suffers from small sample sizes, study of a single or few specific polymorphisms in the gene, as well as failure to account for ethnic variations or to correct for environmental factors (e.g. cigarette smoking) (Tonetti & Claffey 2005). These three factors may be responsible for false-positive associations and larger studies need to be performed to establish consistent associations.

Besides genes of major effect that may determine susceptibility to AgP, other genes may act as modifying genes and influence clinical expression of the disease. In this respect, particular interest has focused on the impact of genetic control of antibody responses against specific AgP-associated bacteria and against *A. actinomycetemcomitans* in particular. These studies have indicated that the ability to mount high titers of specific antibodies is race dependent and probably protective (Gunsolley *et al*. 1987, 1988). This has been shown to be under genetic control as a co-dominant trait, independent of the risk for AgP. In individuals susceptible to AgP, therefore, the ability to mount high titers of antibodies (IgG_2 in particular) may be protective and prevent extension of disease to a generalized form (Schenkein 1994; Diehl *et al.* 2003) (Fig. 21-9b, c). Allelic variations in the Fc receptor for IgG_2 have also been suggested to play a role in suboptimal handling of *A. actinomycetemcomitans* infections. PMNs expressing the R131 allotype of FcγRIIa (i.e. with an Fc receptor containing an arginine instead of a histidine at amino acid 131) show decreased phagocytosis of *A. actinomycetemcomitans* (Wilson & Kalmar 1996).

Table 21-5 Effect of smoking on extent and severity of generalized acute periodontitis.

Smoking status	Mean percentage of sites with PAL >5 mm[a]	Mean PAL (mm)[a]
Smokers	49.0 ± 3.9	2.78 ± 0.2
Non-smokers	36.8 ± 3.8	2.14 ± 0.2

[a] Values adjusted for age and mean plaque index, subject as unit of analysis. Smokers showed significantly greater extent and severity of periodontal disease than non-smokers after correcting for age and oral hygiene level.
PAL, periodontal attachment loss.
Adapted from Schenkein *et al*. (1995), from the American Dental Association.

Environmental aspects of host susceptibility

Recent evidence has indicated that, besides genetic influences, environmental factors may affect the clinical expression of AgP. In a large study, cigarette smoking was shown to be a risk factor for patients with generalized forms of AgP (Schenkein *et al*. 1995). Smokers with GAP had more affected teeth and greater mean levels of attachment loss than patients with GAP who did not smoke (Table 21.5). Environmental exposure to cigarette smoking, therefore, seems to add significant risk of more severe and prevalent disease to this group of already highly susceptible subjects. The mechanism(s) for this observation are not completely understood, but findings from the same group indicate that IgG_2 serum levels as well as antibody levels against *A. actinomycetemcomitans* are significantly depressed in subjects with GAP who smoke. Since these antibodies are considered to represent a protective response against *A. actinomycetemcomitans*, it is possible that depression of IgG_2 in smokers may be associated with the observed increase in disease extent and severity in these subjects.

Current concepts

Aggressive forms of periodontitis are currently considered to be multifactorial diseases developing as a result of complex interactions between specific host genes and the environment. Inheritance of AgP

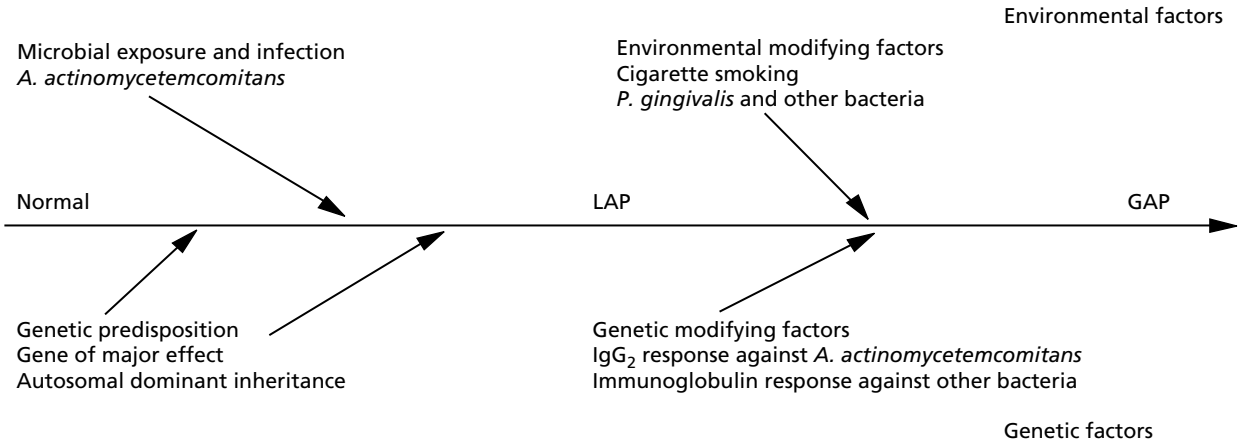


Fig. 21-10 Schematic representation of the current understanding of the ecogenetic interactions leading to the development of localized aggressive periodontitis (LAP) and generalized aggressive periodontitis (GAP) in African–American populations (see text for explanation).

susceptibility is probably insufficient for the development of disease: environmental exposure to potential pathogens endowed with specific virulence factors is also a necessary step. A host's inability to effectively deal with the bacterial aggression and to avoid inflammatory tissue damage results in the initiation of the disease process. Interactions between the disease process and environmental (e.g. cigarette smoking) and genetically controlled (e.g. IgG_2 response to *A. actinomycetemcomitans*) modifying factors are thought to contribute to determining the specific clinical manifestation of disease (Figs. 21-9a–c, 21-10).

Diagnosis

Clinical diagnosis

Clinical diagnosis is based on information derived from a specific medical and dental history, and from the clinical examination of the periodontium. Limitations that will be discussed in this section, however, frequently require supplementation of clinical and anamnestic parameters with other, more advanced, approaches to properly diagnose, plan treatment for, and monitor these diseases. The purpose of clinical diagnosis is the identification of patients suffering from AgP and of factors that have an impact on how the case should be treated and monitored.

In the diagnosis of AgP the initial question that the clinician should ask is:

- Is there periodontitis?

This may sound like a trivial question, but in fact many cases of AgP are currently not identified because of a failure to detect signs of periodontitis. Conversely, some clinicians attribute to periodontitis pathologic changes associated with other unrelated and sometimes self-limiting processes. Correctly answering this question requires systematic collection of clinical information regarding the following items:

- Is there loss of periodontal support (loss of clinical attachment and marginal resorption of alveolar bone)?
- Is the loss of attachment accompanied by pocket formation or mostly the result of recession?
- Is there a plausible cause for attachment loss other than periodontitis?
- Is there another process imitating periodontal disease by pseudopocket formation?

From a clinical standpoint, it is important to realize that clinically detectable loss of attachment may occur as a result of pathologic events other than periodontitis. Examples are traumatic injuries, removal or presence of impacted teeth (Kugelberg 1992), tooth position, orthodontic tooth movement, advanced decay, subgingival margins of restorations, etc. This means that the clinician must recognize different causes for attachment loss and must rule out other causes of attachment loss by a combination of careful clinical examination and assessment of the dental history. Orthodontic considerations are necessary to evaluate attachment loss without pocket formation (recession). In such instances, the appropriate clinical diagnosis may be *incidental attachment loss*.

After establishing the presence of periodontitis, the clinician should determine which clinical diagnosis best describes the disease in the individual patient: chronic, aggressive or necrotizing periodontitis. Since the current classification is based on the combination of clinical presentation, rate of disease progression, and pattern of familial aggregation of cases in the absence of a systemic cause for the clinical observations, the next question should address these parameters:

- Does the patient have a systemic condition that would in itself explain the presence of periodontitis?

As indicated, the diagnosis of chronic, aggressive or necrotizing periodontitis implies the presence of periodontal destruction in the absence of systemic diseases that may severely impair host defense. A well-constructed and well-taken medical history is fundamental to identifying the presence of systemic involvements accompanied by periodontitis (see Chapter 7). Careful questioning regarding recurrent infections, their familiarity, and the presence of severe diseases or their symptoms and signs should be part of the evaluation of all periodontal patients. Consultation with the attending physician and evaluation of laboratory parameters are frequently necessary. Understanding of the medical condition that may be associated with periodontitis is fundamental. Some conditions are relatively frequent disorders such as poorly controlled diabetes mellitus; others are rare inherited disorders such as palmoplantar keratosis (Papillon–Lefèvre and Heim–Munk syndromes) or hypophosphatasia. Some are inborn defects such as the leukocyte adhesion deficiencies (LADs); others are acquired following exposure to pharmacologic agents such as drug-induced granulocytopenia. A confirmed positive history of a significant systemic condition results in the diagnosis of *periodontal manifestation of systemic disease*.

In such instances, the periodontitis is likely to represent an oral manifestation of the systemic disease. Examples of significant conditions are acquired immune deficiency syndrome (AIDS), leukemia, neutropenia, diabetes or rare genetic diseases such as histiocytosis X, Papillon–Lefèvre syndrome or Chediak–Steinbrinck–Higashi syndrome (see Fig. 21-4).

In the absence of significant systemic components, the next question relates to the exclusion of the rare but clearly identified necrotizing/ulcerative forms:

- Does the patient have signs or symptoms of necrotizing periodontitis?

If the answer to both of the previous questions is negative, differential diagnosis between chronic

or aggressive periodontitis will be required. In this respect, it is important to observe that chronic periodontitis has been defined as the common form of periodontitis whose diagnosis is achieved by excluding the presence of AgP (Armitage 1999). Diagnosis of AgP is made by verification of the primary and secondary features described in the International Classification Workshop (see earlier discussion).

In this respect it must be recognized that the features include both clinical and laboratory aspects. In the diagnosis of a case, clinical and history parameters are initially utilized to raise the suspicion of the presence of AgP, while laboratory tests are frequently utilized to confirm the diagnosis. In this respect, it is important to realize that periodontal diagnosis based only on periodontal probing and dental radiography does not classify causes; rather, it describes destruction patterns.

A tentative clinical diagnosis of AgP is made based on the following criteria:

- Absence of significant systemic conditions
- Rapid attachment loss and bone destruction
- Familial aggregation of cases
- Lack of consistency between clinically visible bacterial deposits and severity of periodontal breakdown.

A rapid rate of destruction of the periodontium is a major criterion for the diagnosis of AgP. It is aimed at identifying cases characterized by high virulence of the microflora and/or high levels of susceptibility. Although correct application of this criterion requires the availability of clinical or radiographic data from more than one time point, the presence of severe destruction in relation to the age of the subject is frequently considered to be sufficient information to infer rapid progression.

Establishing the presence of familial aggregation of cases is based on a combination of history and clinical examination of family members of the affected individual. At this stage there is inadequate evidence to establish the best approach to obtain a significant estimation of familial aggregation. One study questioned the reliability of family history as a way to establish familial aggregation (Llorente & Griffiths 2006).

It is maintained that in the majority of cases of AgP, the amount of periodontal destruction seems to be higher than that expected from the mere accumulation of local factors. This observation, however, may not be true for all cases. In general, a discrepancy between local factors and the amount of periodontal tissue breakdown is considered to be an indication for either infection with particularly virulent microorganisms, or presence of a highly susceptible host. This information may be consequential in determining surgical goals of therapy, the impact of antibiotics, and the possible impact of suboptimal hygiene as a risk factor for disease recurrence.

The International Classification Workshop consensus indicated that not all listed primary and secondary features need to be present in order to assign a diagnosis of AgP and that the diagnosis may be based on clinical, radiographic, and historical data alone. It also indicated that laboratory testing, although helpful, may not be essential in making an AgP diagnosis.

Once an AgP diagnosis has been made based on the criteria above, differential diagnosis between LAP and GAP is necessary. In this respect, specific clinical features have been suggested. A diagnosis of LAP is made based on evidence of circumpubertal onset and localized first molar/incisor presentation with interproximal attachment loss on at least two permanent teeth, one of which is a first molar, and involving no more than two teeth other than first molars and incisors. A diagnosis of GAP takes into account the fact that this form of disease usually affects persons under 30 years of age (but patients may be older) and that it presents with generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors. Furthermore, this pathology is characterized by a pronounced episodic nature of the destruction of attachment and alveolar bone. The differential diagnosis may benefit from additional laboratory investigations of the individual host response to the infecting organisms.

In order to properly describe a specific AgP case, modifying factors should also be explored by addressing the question of the presence of modifying or contributory factors such as smoking or drug abuse. Such additional information is relevant since these factors may explain a specific presentation of disease in terms of extent and severity. Furthermore, these factors, unlike genetic factors, are amenable to modification through appropriate intervention. Therapy should therefore include an approach aimed at controlling the impact of these factors.

Even though differential diagnosis between AgP and chronic periodontitis, and between LAP and GAP, is mostly based on history and clinical presentation, it must be emphasized that clinical parameters alone cannot further discriminate forms of disease with similar clinical appearance. Inferences regarding a specific etiology are speculative under such circumstances and further laboratory testing is required for confirmation.

In the previous classification system, age at onset or age at diagnosis was considered helpful to further characterize specific clinical syndromes. LAP, in particular, is thought to occur in those aged from 13–14 to 25 years, while GAP is generally found in adolescents or young adults younger than 30–35 years. It should be realized, however, that (1) some cases may present with initial LAP at an earlier age; (2) LAP may start before puberty and affect the primary dentition; (3) patterns of periodontal destruction compatible with LAP may be initially detected at an age older than 25 years; and (4) there may be a tendency toward spreading from a localized to a generalized pattern of AgP in older subjects in these groups.

Another difficulty is related to the fact that periodontal destruction is often diagnosed when the attachment loss is already fairly advanced. In general, distinct alterations in the morphology of the periodontium and substantial tissue damage are necessary for establishing a clear diagnosis. Milder or initial stages of disease or sites at risk for future periodontal breakdown cannot be detected based on clinical parameters. This makes it difficult to intercept and treat initial forms of AgP. Furthermore, such difficulty makes it extremely important to examine the other members of the family of the proband as well: siblings may present with clinically undetectable disease in spite of the presence of the putative pathogens. A common strategy employed to overcome the insufficient ability of clinical parameters to detect early disease is to closely monitor high-risk patients such as the siblings of the probands. It is in this respect important to underline that "incidental attachment loss" may, in some cases, represent an initial manifestation of AgP. In such a case, an isolated periodontal lesion characterized by attachment loss with pocketing may represent the only clinically evident AgP lesion. Such subjects should, therefore, be considered at high risk for the development of AgP and require close monitoring and possibly further microbiologic diagnosis.

Microbiologic diagnosis

The presence of specific microorganisms is considered to be one of the secondary features of AgP. There is an ongoing debate on the utility of microbiologic tests to identify such organisms in order to optimize periodontal therapy. A systematic review has shown that the presence or absence of suspected periodontal pathogens such as *A. actinomycetemcomitans* at the species level cannot fully discriminate subjects with AgP from subjects with chronic periodontitis. Although it is more than ten times more likely that *A. actinomycetemcomitans*-negative patients suffer from chronic than from aggressive periodontitis, any *A. actinomycetemcomitans*-positive patient with periodontitis is three times more likely to be suffering from chronic than from aggressive periodontitis (Mombelli *et al*. 2002). The noted limitations in power of discrimination between AgP and chronic periodontitis should not be interpreted to mean that a test aimed at the detection of target microorganisms is completely useless in any clinical situation. Treatment studies suggest that *A. actinomycetemcomitans* is particularly difficult to suppress with conventional mechanical therapy (Mombelli *et al*. 1994a, 2000), longitudinal and retrospective studies have indicated an increased risk for periodontal breakdown in positive sites (Fine 1984; Slots *et al*. 1986; Bragd *et al*. 1987; Slots & Listgarten 1988; Rams *et al*. 1996), and results of treatment seemed to be better if *A. actinomycetemcomitans* could no longer be detected at follow-up (Bragd *et al*. 1987; Carlos *et al*. 1988; Haffajee *et al*. 1991; Grossi *et al*. 1994; Haffajee & Socransky 1994). Therefore, even if microbiologic testing alone cannot distinguish between chronic and aggressive periodontitis, access to microbiologic data may improve the outcome of periodontal therapy. This should be taken into account particularly with regards to the highly leukotoxic variant of *A. actinomycetemcomitans*, which shows a stronger association with AgP than does *A. actinomycetemcomitans* as a whole. In discussing the diagnostic potential of a test, one should also consider that the main difference between clinical groups may not be the prevalence but rather the amount of putative pathogens found in positive samples (Gunsolley *et al*. 1990).

In theory, microbiologic data may be useful to establish a differential diagnosis in patients clinically diagnosed with AgP, and may have an impact on the decision to supplement mechanical therapy with antimicrobials and on the choice of these agents. However, as outlined in more detail in Chapter 43, strictly based on evidence from well-performed randomized clinical trials, and except for patients with known medical contraindications (e.g. confirmed hypersensitivity), it is difficult to define clear-cut exclusion criteria for systemic antibiotic therapy in patients with AgP. In fact, no study has demonstrated better results for treatments without antibiotics in certain patients identified with microbiologic techniques. There is recent convincing data that supplementing mechanical treatment specifically with systemic amoxicillin and metronidazole substantially improves the clinical outcomes of therapy for AgP (Guerrero *et al*. 2005; Xajigeorgiou *et al*. 2006; Kaner *et al*. 2007; Akincibay *et al*. 2008; Johnson *et al*. 2008; Machtei & Younis 2008; Mestnik *et al*. 2010; Yek *et al*. 2010; Baltacioglu *et al*. 2011; Heller *et al*. 2011; Varela *et al*. 2011). Results of a few studies comparing different antimicrobial regimens are available (Akincibay *et al*. 2008; Machtei & Younis 2008; Baltacioglu *et al*. 2011). No study has demonstrated better results than achieved with a protocol of systemic amoxicillin plus metronidazole for any clinically or microbiologically defined variant of AgP.

Evaluation of host defenses

Several forms of AgP have been associated with impairment of host defenses. Classical studies have indicated that in some populations, both LAP and GAP are associated with high incidence of phagocyte functional disturbances, such as depressed neutrophil chemotaxis and other phagocyte antibacterial dysfunctions. In many of these patients, AgP was the only infection that was associated with reduced phagocyte function(s); this observation is important in two respects. First, AgP-associated phagocyte defects are frequently insignificant in terms of increasing susceptibility to infections other than periodontitis. Furthermore, it is likely that such "mild" leukocyte defects may go unnoticed until laboratory testing is

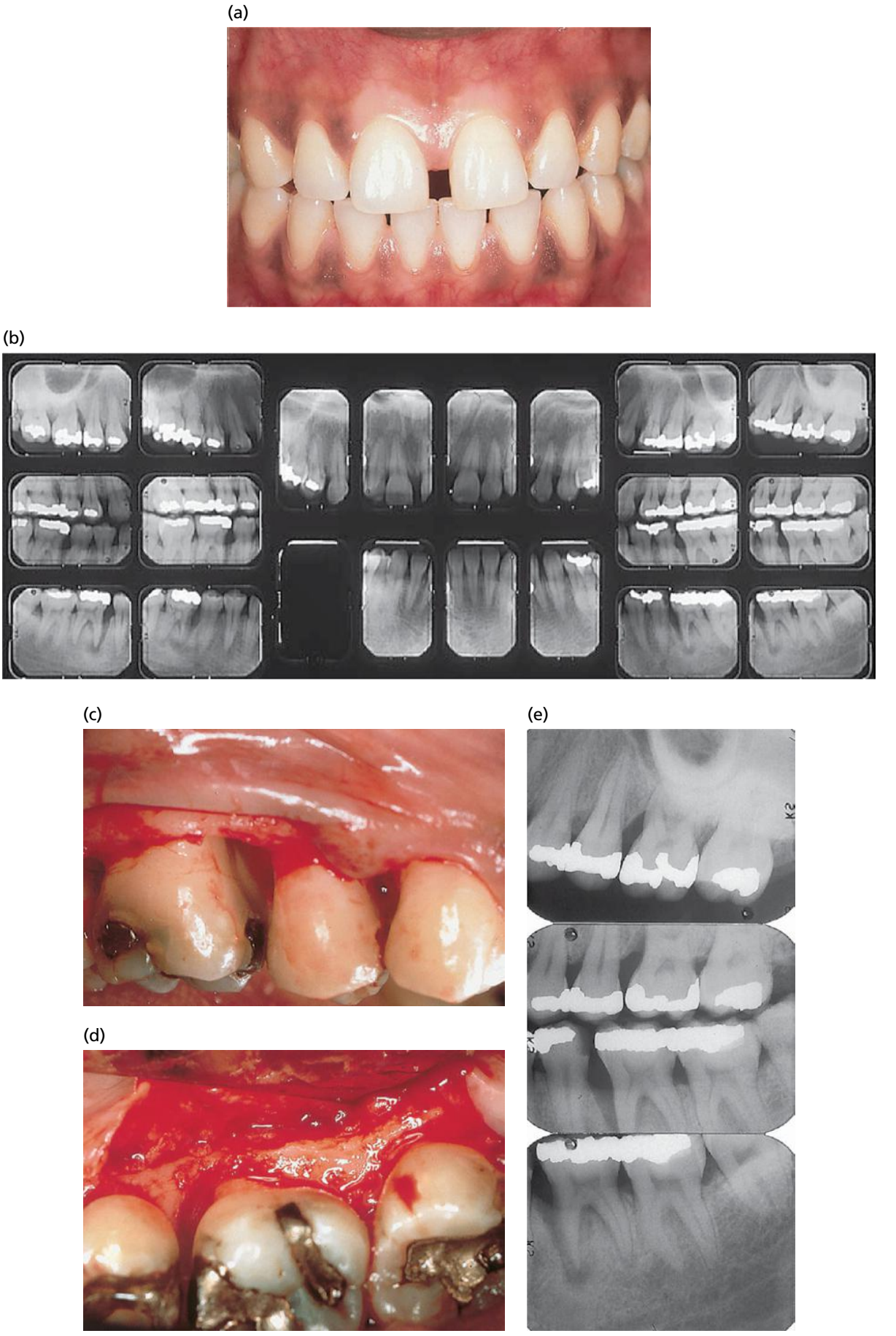


Fig. 21-11 (a, b) Clinical and radiographic presentation of a 22-year-old African–American female. Clinical attachment loss and alveolar bone loss are localized on the mesial aspect of the first molars, where deep, vertical defects are apparent. (c–e) Detailed views of the defect on the mesial aspect of tooth 26. No other tooth appears to be affected. Microbiology (DNA probe analysis of *A. actinomycetemcomitans*, *P. gingivalis*, and *P. intermedia*) confirmed the presence of high levels (>10^4 bacteria/sample) of *A. actinomycetemcomitans* in all four deep lesions. *P. intermedia* was also detectable in three of four sites, while *P. gingivalis* was undetectable. The patient did not display abnormal leukocyte functions; furthermore, she had a non-contributory medical history, and did not smoke. She had a younger brother (15 years old) and an older sister (27 years old); on clinical examination, the periodontium of both siblings appeared to be within normal limits. The following diagnosis was made: "localized aggressive periodontitis in a 22-year-old systemically healthy African–American female; associated with *A. actinomycetemcomitans* infection without clinically detectable levels of *P. gingivalis*; absence of demonstrable leukocyte defects; no known contributory factors; no cigarette smoking; no siblings displaying clinically detectable aggressive periodontitis".

performed in conjunction with periodontal diagnosis. Reports of such phagocyte defects relate mostly to AgP subjects from African–American groups; systematic evaluations of PMN and monocyte functions associated with clinical diagnosis of AgP in European Caucasians failed to confirm a high prevalence of abnormalities (Kinane *et al*. 1989a, b). It may be possible therefore to restrict the testing for these host defense parameters to specific populations. Another important aspect is that, so far, no specific study has attempted to associate treatment response or incidence of recurrent disease with the presence of the above-mentioned abnormalities.

More recent investigations have indicated that specific patterns of host response to bacterial pathogens are associated with different forms of AgP; this early evidence may be extremely helpful for the development of clinically useful tests to estimate the risk of developing AgP. In this respect, two findings deserve mention:

1. AgP patients show significantly higher levels of crevicular fluid PGE_2 than chronic periodontitis patients or healthy subjects. This finding may indicate that monocytes from these patients respond to bacterial and inflammatory stimuli with very high local release of inflammatory mediators. These may induce an exuberant inflammatory reaction associated with high levels of activation of tissue-degrading matrix metalloproteinases (MMPs).
2. GAP patients have a decreased ability to mount high titers of specific IgG_2 antibodies to *A. actinomycetemcomitans.* These subjects exhibit a tendency towards progressive periodontal destruction leading to tooth loss over a relatively short period of time. LAP patients, on the other hand, seem to have a better prognosis and do not express this trait. Since there are indications that at least some LAP cases may progress to generalized forms, early detection of patients infected with *A. actinomycetemcomitans* but producing low levels of specific antibodies, may allow early identification of a high-risk group for the development of GAP. Serum antibody titers (IgG_2 in particular) and/or avidity to *A. actinomycetemcomitans* may be particularly useful in the differential diagnosis of GAP and LAP syndromes and in the early detection of LAP cases with a high risk for progression to the more widespread forms of disease.

Genetic diagnosis

Given the disproportionately high incidence of AgP in the families of affected individuals, evaluation of siblings of the proband and other family members is a requirement. Clinical determination of different disease forms in the family should be followed by construction of a pedigree of the AgP trait. Such diagnosis may bring considerable information regarding the level of risk eventually shared within the family. Furthermore, it helps to establish the need for monitoring clinically unaffected individuals.

All the evidence gathered during the diagnostic process should contribute to the definition of a specific diagnosis. An example of such diagnosis is shown in Fig. 21-11: LAP in a 22-year-old systemically healthy African–American female patient, associated with *A. actinomycetemcomitans* infection without detectable levels of *P. gingivalis*, inconsistency between local factors and amount of clinically detectable breakdown, absence of demonstrable leukocyte defects, no known contributory factors, and no siblings displaying clinically detectable periodontitis.

Principles of therapeutic intervention

Treatment of AgP should only be initiated after completion of a careful diagnosis by a specifically trained periodontist. The severity of some of the AgP forms suggests that specialists, possibly working in association with highly specialized centers, could best perform both diagnosis and treatment of these rare forms of periodontitis. The roles of the general practitioner, the pedodontist or the orthodontist, however, are fundamental in the detection of possible cases to be referred for further evaluation and therapy.

Successful treatment of AgP is considered to be dependent on early diagnosis, directing therapy towards elimination or suppression of the infecting microorganisms and providing an environment conducive to long-term maintenance. The differential element of treatment of AgP, however, relates to specific efforts to affect the composition and not only the quantity of the subgingival microbiota.

Elimination or suppression of the pathogenic flora

A. actinomycetemcomitans elimination has been associated with successful therapy; conversely, recurrent lesions have been shown to still harbor this organism. Several investigators have reported that scaling and root planing of juvenile periodontitis lesions could not predictably suppress *A. actinomycetemcomitans* below detection levels (Slots & Rosling 1983; Christersson *et al*. 1985; Kornman & Robertson 1985). Soft tissue curettage and access flap therapy also had limited success in eliminating *A. actinomycetemcomitans* (Christersson *et al*. 1985).

A. actinomycetemcomitans is also difficult to eliminate by conventional mechanical therapy in adult periodontitis patients, and it is therefore not surprising to observe the presence of this microorganism in the subgingival microflora of many non-responding periodontitis patients (Bragd *et al*. 1985; van Winkelhoff *et al*. 1989; Renvert *et al*. 1990a, b; Rodenburg *et al*. 1990; Mombelli *et al*. 1994a). Similar but less systematic observations have also been reported for the ability to suppress the

microflora associated with some GAP forms, where high subgingival loads of *P. gingivalis*, *Bacteroides forsythus*, *A. actinomycetemcomitans*, and other highly virulent bacteria are frequently detected.

Use of antibiotics has been suggested as a rational complement to mechanical debridement in these cases. Regimens, including the adjunctive administration of tetracyclines or metronidazole, have been tested for the treatment of LAP and other forms of AgP (see Chapter 43).

The choice of antibiotic can either be empiric (based on published information on the efficacy of the regimen in similar populations) or guided by information about the nature of the involved pathogenic microorganism(s) and/or their antibiotic susceptibility profile. Both approaches have been suggested, but currently there is no direct evidence that microbiologic diagnosis and targeted selection of the antibiotic regimen provide an additional benefit compared to empiric use.

With regards to empiric use, effectiveness is based on outcomes of a series of trials that have assessed the clinical outcomes of therapy following administration of specific antibiotic regimens against placebo. Supported by a meta-analysis undertaken a decade ago (Haffajee *et al.* 2003) and numerous clinical trials conducted since then (Guerrero *et al*. 2005; Xajigeorgiou *et al*. 2006; Kaner *et al*. 2007; Akincibay *et al*. 2008; Johnson *et al*. 2008; Machtei & Younis 2008; Mestnik *et al*. 2010; Yek *et al*. 2010; Baltacioglu *et al*. 2011; Heller *et al*. 2011; Varela *et al*. 2011), significantly greater clinical improvements can be expected if thorough non-surgical periodontal treatment (i.e. scaling and root planing) is followed by systemic antibiotic therapy, specifically with amoxicillin and metronidazole. Subgingival *A. actinomycetemcomitans* especially can be eliminated or suppressed for a prolonged period by mechanical debridement supplemented with systemic amoxicillin plus metronidazole. Systemic antibiotics should only be administered as an adjunct to mechanical debridement because in undisturbed subgingival plaque, the target organisms are effectively protected from the antibiotic agent due to the biofilm effect (see Chapter 43).

Antibiotics have been used in essentially two ways for the treatment of AgP: (1) in combination with intensive instrumentation over a short period of time after achievement of adequate plaque control in a pretreatment motivation period; or (2) as a staged approach after completion of the initial therapy.

The following treatment approach (Guerrero *et al.* 2005) has been thoroughly validated in randomized controlled clinical trials (Guerrero *et al*. 2005; Mestnik *et al*. 2010; Aimetti et al 2012; Mestnik *et al.* 2012): (1) achievement of adequate supragingival plaque control (<25% of tooth sites with detectable plaque); (2) rigorous subgingival instrumentation with a combination of hand and ultrasonic instruments completed within 2 days; and (3) an adjunctive systemic antibiotic regimen consisting of metronidazole (500 mg, t.i.d. for 7 days) combined with amoxicillin (500 mg, t.i.d. for 7 days). The results of the placebo arm showed highly significant improvements in clinical parameters, including reductions of probing depth and improvement of clinical attachment levels throughout the dentition. The adjunctive antibiotic provided additional benefits in the deeper pockets for all parameters. Early results suggest that incomplete adherence to the antibiotic regimen results in suboptimal clinical outcomes (Guerrero *et al*. 2007). A follow-up analysis comparing the antibiotic retreatment of the placebo group of the Guerrero *et al.* (2005) trial (later antibiotic administration) with the mechanical retreatment of the antibiotic arm of the trial (early antibiotic administration) showed benefit from the earlier administration (Griffiths *et al*. 2011). These observations have been recently confirmed by a retrospective study (Beliveau *et al*. 2013).

The second approach implies starting therapy with an initial phase of mechanical instrumentation, including systematic scaling and planing of all accessible root surfaces and the introduction of meticulous oral hygiene. After a period of 3–6 months, the case is reassessed clinically. Based on persistence of periodontal lesions, a second phase of therapy is planned. Decisions are made as to how to gain access to deep lesions with appropriate surgical procedures and concerning the administration of antimicrobial agents. Microbial samples from the deepest pocket in each quadrant may provide additional information about the persistence of putative pathogens. Systemic antimicrobial therapy with an appropriate agent is initiated if judged necessary immediately upon completion of the surgical interventions or immediately after another round of mechanical instrumentation to ensure that subgingival plaque deposits have been reduced as much as possible and to disrupt the subgingival biofilm. This treatment option is preferred by some clinicians to minimize the potential overuse of antibiotics in periodontics. Currently, however, it needs to be pointed out that this approach is not backed by the same level of evidence as the first approach.

Microbiologic testing, if performed, may be repeated 1–3 months after completion of therapy to verify the elimination or marked suppression of the putative pathogen(s). After resolution of the periodontal infection, the patient should be placed on an individually tailored maintenance care program, including continuous evaluation of the occurrence and of the risk of disease progression. Optimal plaque control by the patient is of paramount importance for a favorable clinical and microbiologic response to therapy. Recurrence of disease is an indication for a repeat of the microbiologic tests, re-evaluation of the host immune response, and reassessment of the local and systemic modifying factors. Further therapy should be targeted against putative periodontal pathogens and should take into account the systemic immune responses of the subject.

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Chapter 22

Necrotizing Periodontal Disease

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Nomenclature

Necrotizing gingivitis (NG), necrotizing periodontitis (NP), and necrotizing stomatitis (NS) are the most severe inflammatory periodontal disorders caused by plaque bacteria. The necrotizing diseases usually run an acute course and therefore the term acute is often included in the diagnoses. They are rapidly destructive and debilitating, and they appear to represent various stages of the same disease process (Horning & Cohen 1995). A distinction between NG and NP has not always been made in the literature, but parallel to the use of the term gingivitis, NG should be limited to lesions involving gingival tissue only with no loss of periodontal attachment (Riley *et al*. 1992). Most often, however, the disease results in loss of attachment (MacCarthy & Claffey 1991), and a more correct term in cases with loss of attachment is NP, provided the lesions are confined to the periodontal tissues, including the gingiva, periodontal ligament, and alveolar bone. Further progression to include tissue beyond the mucogingival junction is characteristic of necrotizing stomatitis and distinguishes this disease from NP (Williams *et al*. 1990).

The necrotizing periodontal diseases have been mentioned under several names, including: "ulceromembranous gingivitis", "acute necrotizing ulcerative gingivitis" (ANUG), "Vincent's gingivitis" or "Vincent's gingivostomatitis", "necrotizing gingivostomatitis", and "trench mouth" (Pickard 1973; Johnson & Engel 1986; Horning & Cohen 1995). Vincent first described the mixed fusospirochetal microbiota of so-called "Vincent's angina", characterized by necrotic areas in the tonsils (Vincent 1898). A similar mixed microbiota has been isolated from NG lesions, but Vincent's angina and NG usually occur independently of each other, and should be regarded as separate disease entities.

NS has features in common with the far more serious *cancrum oris*, also denoted noma. This is a destructive and necrotizing, frequently mortal, stomatitis in which the same mixed fusospirochetal flora dominates. It occurs almost exclusively in certain developing countries, mostly in children suffering from systemic diseases including malnutrition (Enwonwu 1972, 1985). It has been suggested that cancrum oris always develops from pre-existing NG (Emslie 1963) and this connection

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has been supported by similarities between the microflora of NG and that of noma (Bolivar *et al*. 2012).

In the literature, a distinction between NG, NP, and NS is seldom made and the reader should be aware of the consequences of this lack of distinction. The uncertainty in the distinction is reflected in the present chapter by the use of the term necrotizing periodontal disease (NPD) as a common denominator for NG, NP, and necrotizing stomatitis.

Prevalence

During World War II, up to 14% of the Danish military personnel encountered NPD (Pindborg 1951a). Large numbers of civilians also suffered from the disease (King 1943; Stammers 1944). After World War II, the prevalence of NPD declined substantially and in industrialized countries NPD is now rare. It occurs most often in young adults. In the 1960s NPD was found in 2.5% of 326 US students during their first college year, but over the next year more students became affected, with a total of 6.7% demonstrating the disease during their first two college years (Giddon *et al*. 1964). Among 9203 students in Chile, 6.7% showed at least one necrotic ulcerated lesion on the papillae (Lopez *et al*. 2002), and the presence of necrotizing lesions was associated with the occurrence of clinical attachment loss (Lopez & Bælum 2004). Other studies in industrialized countries have reported prevalences of ≤0.5% (Barnes *et al*. 1973; Horning *et al*. 1990). In Scandinavia, the disease is now very rare among otherwise healthy individuals, with a prevalence of 0.001% among young Danish military trainees (Finn Prætorius, personal communication). NPD can be observed in all age groups but there are geographic differences in the age distribution. Among human immunodeficiency virus (HIV)-infected individuals, the disease seems to occur slightly more often. Studies among groups of HIV-infected individuals have revealed prevalences of NPD of between 0% and 27.7% (Holmstrup & Westergaard 1994; Reichart *et al*. 2003). However, most studies have included cohorts of individuals connected with hospitals or dental clinics. Studies conducted outside these environments have shown relatively low prevalences. NP was found in 1% of 200 HIV-seropositive individuals in Washington, DC (Riley *et al*. 1992), a prevalence that may not be so different from that in the general population (Drinkard *et al*. 1991; Friedman *et al*. 1991; Barr *et al*. 1992). A prevalence similar to that in the general population has been particularly true since the introduction of highly active antiretroviral therapy (HAART), which has resulted in a declining incidence and prevalence of oral conditions associated with HIV infection (Tappuni & Flemming 2001; Ryder *et al*. 2012). The route of HIV transmission may influence the occurrence of NPD among HIV-infected individuals. Thus, NPD was more prevalent among HIV-infected intravenous drug users than among HIV-infected non-intravenous drug users. Also, mean probing depth and clinical attachment level were significantly higher in the former group (Ranganathan *et al*. 2012).

In developing countries, the prevalence of NPD is higher than in industrialized countries, and the disease frequently occurs in children. NPD is practically never seen in Western countries. In Nigerian villages, between 1.7% and 26.9% of 2–6-year-old children were found to have NPD (Sheiham 1966), and in India, 54–68% of NPD cases occurred in children below 10 years of age (Migliani & Sharma 1965; Pindborg *et al*. 1966).

Clinical characteristics

Development of lesions

NG is an inflammatory, destructive gingival condition characterized by ulcerated and necrotic papillae and gingival margins, giving a punched-out appearance. The ulcers are covered by a yellowish–white or grayish slough, which has been termed a "pseudomembrane". However, the sloughed material has no coherence, and bears little resemblance to a membrane. It consists primarily of fibrin and necrotic tissue with leukocytes, erythrocytes, and masses of bacteria. Consequently, the term is misleading and should not be used.

The necrotizing lesions develop rapidly and are painful, but in the initial stages, when the necrotic areas are relatively few and small, pain is usually moderate. Severe pain is often the chief reason for patients seeking treatment. Bleeding is readily provoked on removal of the sloughed material and exposure of the ulcerated underlying connective tissue. Bleeding may also start spontaneously as well as in response to even gentle touch. In early phases of the disease, lesions are typically confined to the top of a few interdental papillae (Fig. 22-1). The first lesions are often seen interproximally in the mandibular anterior region, but they may occur in any interproximal space. In regions where lesions first appear, there are usually also signs of pre-existing chronic

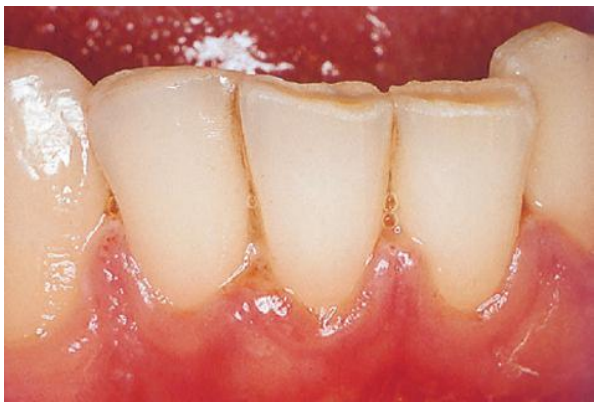


Fig. 22-1 Necrotizing gingivitis with initial punched out defects at the top of the interdental papillae of the mandibular incisor region. (Courtesy of F. Prætorius.)

gingivitis, but the papillae are not always edematous at this stage and gingival stippling may be maintained. Usually, however, the papillae rapidly swell and achieve a rounded contour, and this is particularly evident in the facial aspect. The zone between the marginal necrosis and the relatively unaffected gingiva usually exhibits a well-demarcated narrow erythematous zone, sometimes referred to as the linear erythema. This is an expression of hyperemia due to dilation of the vessels in the gingival connective tissue in the periphery of the necrotic lesions (see Fig. 22-17a).

A characteristic and pronounced *foetor ex ore* is often associated with NPD, but can vary in intensity and in some cases is not very noticeable. Strong *foetor ex ore* is not pathognomonic of NPD as it can also be found in other pathologic conditions of the oral cavity such as chronic destructive periodontal disease.

Interproximal craters

The lesions are seldom associated with deep pocket formation, because extensive gingival necrosis often coincides with loss of crestal alveolar bone. The gingival necrosis develops rapidly and within a few days the involved papillae are often separated into one facial and one lingual portion with an interposed necrotic depression, a negative papilla, between them. The central necrosis produces considerable tissue destruction and a regular crater is formed. At this stage of the disease, the disease process usually involves the periodontal ligament and the alveolar bone, and loss of attachment is now established. The diagnosis of the disease process is consequently NP. Along with the papilla destruction, the necrosis usually extends laterally along the gingival margin at the oral and/or facial surfaces of the teeth. Necrotic areas originating from neighboring interproximal spaces frequently merge to form a continuous necrotic area (Figs. 22-2, 22-3). Superficial necrotic lesions only rarely cover a substantial part of the attached gingiva, which becomes reduced in width as the result of the disease progression. The palatal and lingual marginal gingiva is less frequently involved than the corresponding facial area. Frequently, gingiva of semi-impacted teeth and in the posterior maxillary region are affected (Figs. 22-4, 22-5). Progression of

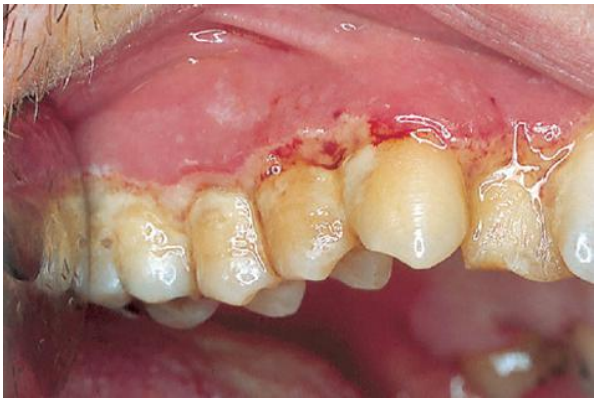


Fig. 22-2 Necrotizing gingivitis progressing along the gingival margin of the right maxilla. The interproximal necrotizing processes have merged.

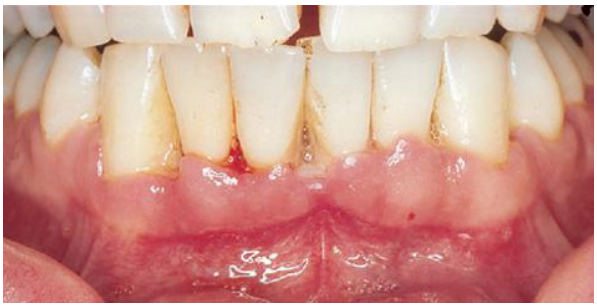


Fig. 22-3 Necrotizing periodontitis with more advanced lesions of the interdental papillae and gingival margin. Note the irregular morphology of the gingival margin as determined by the progressive loss of the interdental papillae.

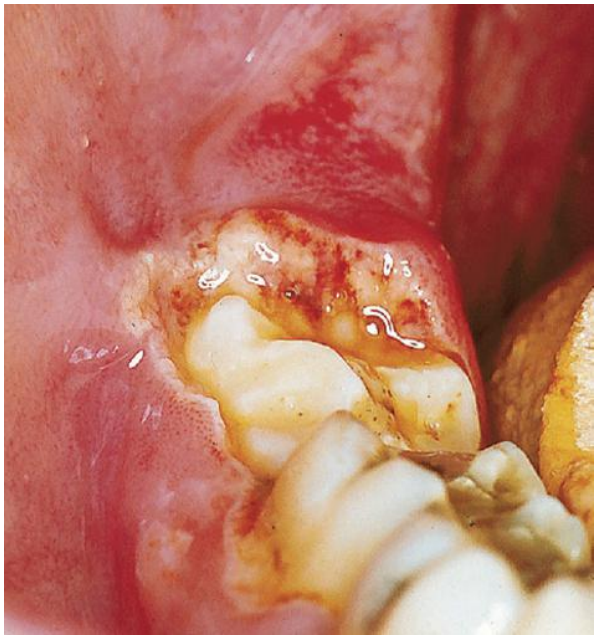


Fig. 22-4 Necrotizing gingivitis affecting the gingiva of the semi-impacted right mandibular third molar. (Courtesy of F. Prætorius.)

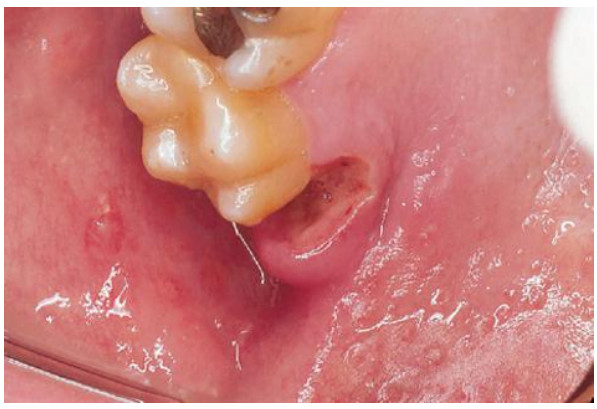
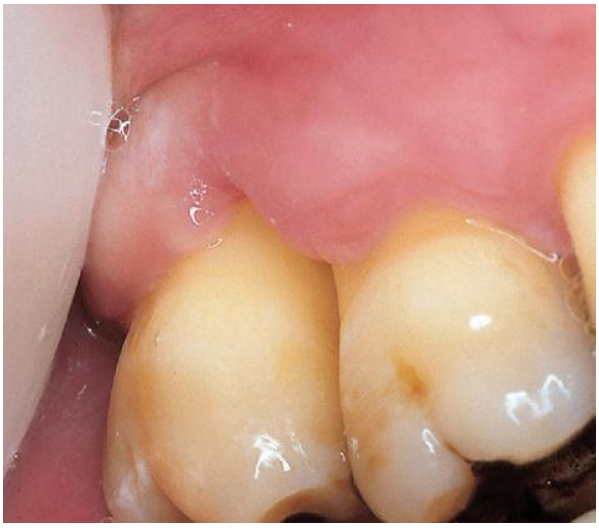


Fig. 22-5 Necrotizing periodontitis affecting the periodontium of the right maxillary second molar. Note the extensive punched-out lesion.

the interproximal process often results in destruction of most interdental alveolar bone (Fig. 22-6). In the more advanced cases, pain is often considerable and may be associated with a markedly increased salivary flow. As a result of pain, it is often difficult for the patients to eat, and a reduced food intake may be critical in HIV-infected patients because they may already have lost weight in association with their HIV infection.

(a)



(b)

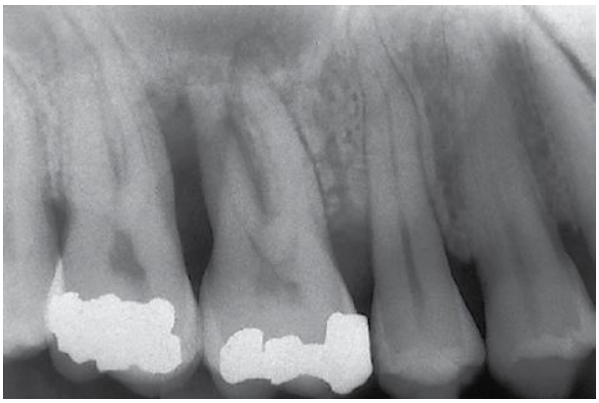


Fig. 22-6 (a) Necrotizing periodontitis often results in major loss of interdental tissue, including alveolar bone of the molar regions, as demonstrated in the radiograph (b).

Sequestrum formation

The disease progression may be rapid and result in necrosis of small or large parts of the alveolar bone. Such a development is particularly evident in severely immunocompromised patients, including HIV-seropositive individuals. The necrotic bone, denoted a sequestrum, initially is irremovable, but after some time becomes loose, whereafter it may be removed with forceps. Analgesia may not be required for this. A sequestrum may not only involve interproximal bone, but also adjacent facial and oral cortical bone (Fig. 22-7).

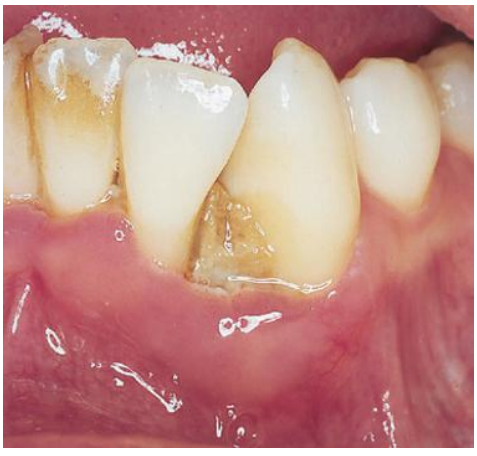
Involvement of alveolar mucosa

When the necrotic process progresses beyond the mucogingival junction, the condition is denoted NS (Williams *et al*. 1990) (Figs. 22-8, 22-9). The severe tissue destruction characteristic of this disease is related to the seriously compromised immune functions typically associated with HIV infection or malnutrition (Fig. 22-10). Importantly, it may be life threatening. NS may result in extensive denudation of bone, resulting in major sequestration with the development of an oroantral fistula and osteitis (SanGiacomo *et al.* 1990; Felix *et al.* 1991).

Swelling of lymph nodes

Swelling of the regional lymph nodes may occur in NPD, but is particularly evident in advanced cases. Such symptoms are usually confined to the submandibular lymph nodes, but the cervical lymph nodes may also be involved. In children with NPD, swelling of lymph nodes and increased bleeding tendency are often the most pronounced clinical findings (Jiménez & Baer 1975).

(a)



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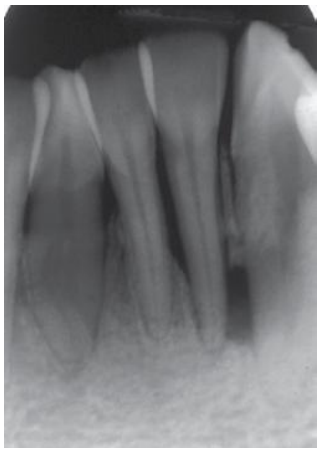
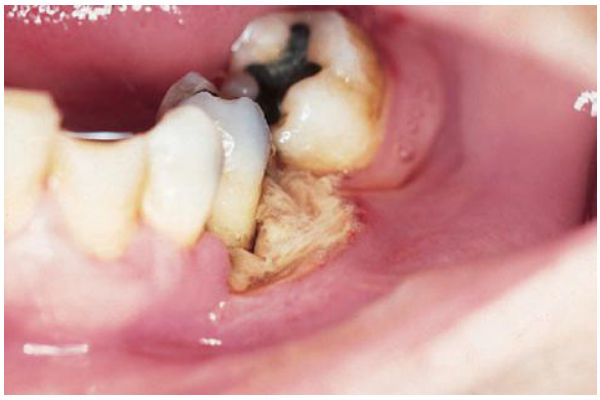


Fig. 22-7 (a) Necrotizing periodontitis with sequestration of alveolar bone between left mandibular lateral incisor and canine. (b) Extension of the sequestrum as seen in the radiograph covers the interdental septum almost to the roots.

(a)



(b)

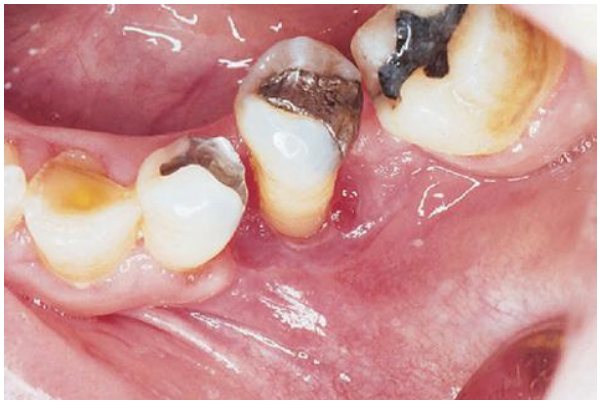


Fig. 22-8 (a) Necrotizing stomatitis affecting the periodontium of the left mandibular premolar region and adjacent alveolar mucosa. (b) After treatment and healing, no attached gingiva remains.

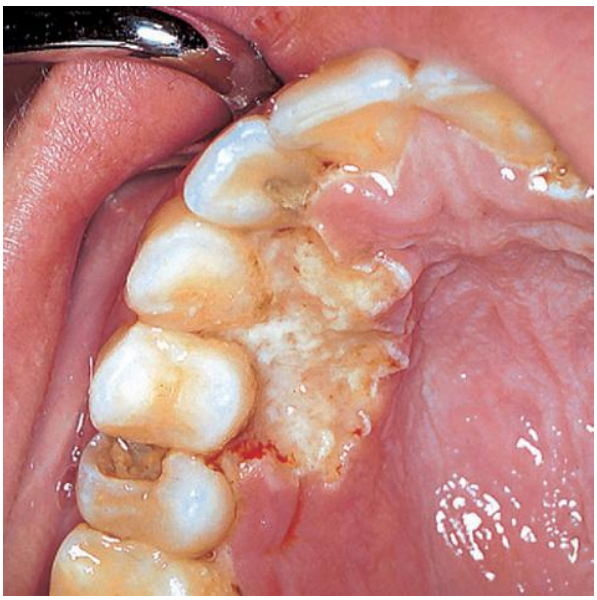
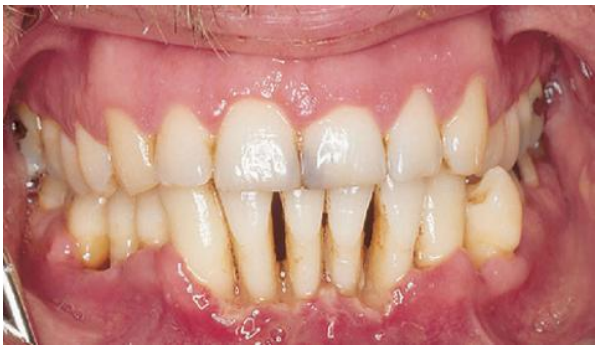


Fig. 22-9 Necrotizing stomatitis of the right maxilla with an extensive necrotic ulcer of palatal mucosa.

Fever and malaise

Fever and malaise is not a consistent characteristic of NPD. Some investigations indicate that elevated body temperature is not common in NG and that, when present, is usually moderate (Grupe & Wilder 1956; Goldhaber & Giddon 1964; Shields 1977; Stevens *et al*. 1984). A small decrease in body temperature in NG has even been described. The disagreement on this point may, in fact, be due to misdiagnosis of primary herpetic gingivostomatitis as NG (see below).

(a)



(b)

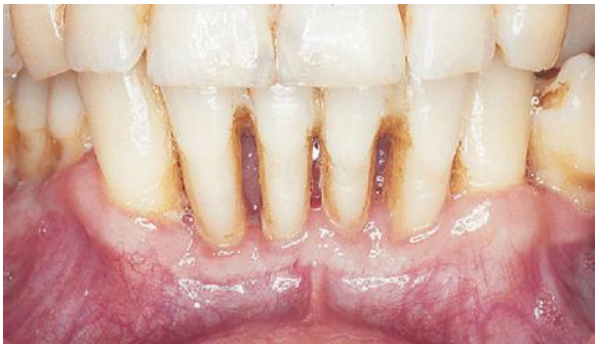


Fig. 22-10 (a) Necrotizing stomatitis affecting the mandible of an HIV-seropositive patient. (b) Two years after treatment the result is satisfactory, and there has been no recurrence.

Oral hygiene

The oral hygiene in patients with NPD is usually poor. Moreover, brushing of teeth and contact with the acutely inflamed gingiva is painful. Therefore, large amounts of plaque on the teeth are common, especially along the gingival margin. A thin, whitish film sometimes covers parts of the attached gingiva (Fig. 22-11). This film is a characteristic finding in patients who have neither eaten nor performed oral hygiene for days. It is composed of desquamated epithelial cells and bacteria in a meshwork of salivary proteins. It is easily removed.

In general, the clinical characteristics of NPD in HIV-seropositive patients do not essentially differ from those in HIV-seronegative patients. However, the lesions in HIV-seropositive patients may not be associated with large amounts of plaque and calculus. Thus, the disease activity in these patients sometimes shows limited correlation with etiologic factors as determined by the amount of bacterial plaque (Holmstrup & Westergaard 1994). Further, lesions of NPD in HIV-seropositive patients have sometimes been revealed in gingival tissue affected by Kaposi's sarcoma (Fig. 22-12).

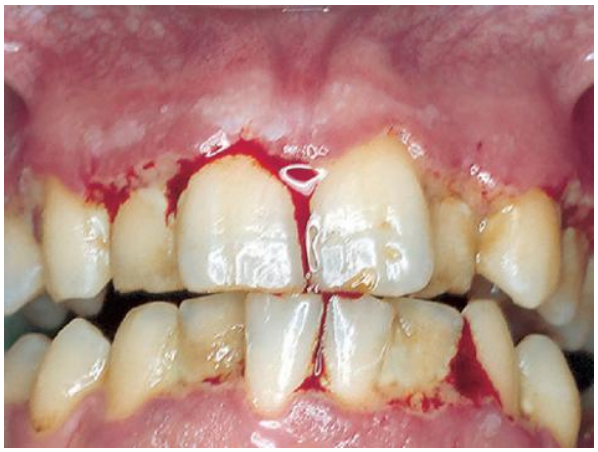


Fig. 22-11 A whitish film sometimes covers parts of the attached gingiva in patients with necrotizing periodontal disease, as demonstrated in the maxillary gingiva. The film is composed of desquamated epithelial cells which have accumulated because the patient has not eaten or performed oral hygiene for days.

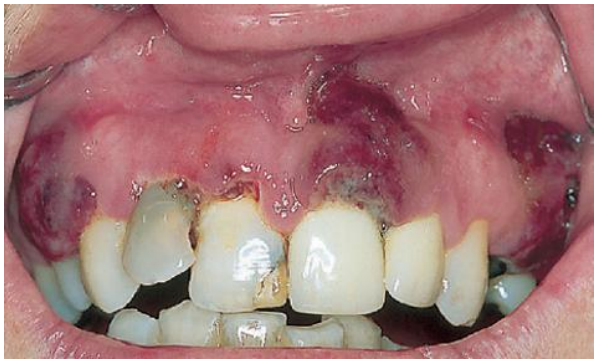


Fig. 22-12 Necrotizing periodontitis affecting Kaposi's sarcoma of the gingiva of the left maxillary central incisor in an HIV-infected patient. The sarcoma affected almost the entire maxillary gingiva after 9 months.

Acute and recurrent/chronic forms of necrotizing gingivitis and periodontitis

In most instances, the course of the diseases is acute, as characterized by the rapid destruction of the periodontal tissue. However, if inadequately treated or left untreated, the acute phase may gradually subside. The symptoms then become less unpleasant for the patient, but the destruction of the periodontal tissues continues, although at a slower rate, and the necrotic tissues do not heal completely. Such a condition has been termed chronic necrotizing gingivitis, or periodontitis in the case of attachment loss (Fig. 22-13). The necrotizing lesions persist as open craters, frequently with a content of subgingival calculus and bacterial plaque. Although the characteristic ulcerative, necrotic areas of the acute phase usually disappear, acute exacerbations with intervening periods of quiescence may also occur. In recurrent acute phases, subjective symptoms again become more prominent and necrotic ulcers reappear. Some authors prefer the term recurrent rather than chronic

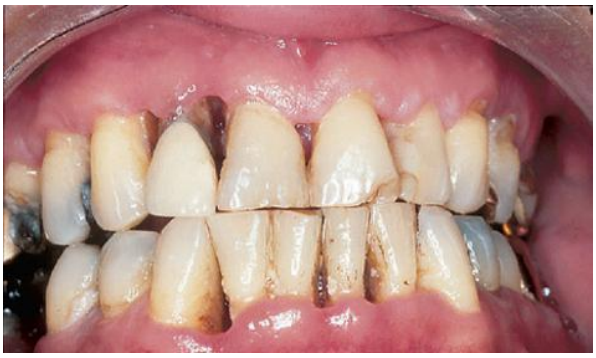


Fig. 22-13 Chronic necrotizing periodontitis with edematous gingiva particularly of the mandible. The slightly active necrotizing processes at the bottom of the negative papillae are not visible.

to describe this category of necrotizing disease (Johnson & Engel 1986). Plaque and necrotic debris in these phases are often less conspicuous than in the acute forms, because they are located in pre-existing interdental craters. Several adjoining interdental craters may fuse, resulting in total separation of facial and oral gingivae, which form two distinct flaps. Recurrent forms of NG and NP may produce considerable destruction of supporting tissues. The most pronounced tissue loss usually occurs in relation to the interproximal craters.

Diagnosis

The diagnosis of NG, NP, and NS is based on clinical findings as described above. The patient has usually noticed pain and bleeding from the gingiva, particularly upon touch. The histopathology of the necrotizing diseases is not pathognomonic for NG, and biopsy is certainly not indicated in the heavily infected area.

Differential diagnosis

NPD may be confused with other diseases of the oral mucosa. Primary herpetic gingivostomatitis (PHG) is not infrequently mistaken for NPD (Klotz 1973). The important differential diagnostic criteria for the two diseases are listed in Table 22-1. It should be noted that in the US and in Northern Europe, NPD occurs very rarely in children, whereas PHG is most commonly found in children. If the body temperature is markedly raised (≥38 °C), PHG should be suspected. NG and NP have a marked predilection for the interdental papillae, while PHG shows no such limitation and may occur anywhere on the free or the attached gingiva, or in the alveolar mucosa (Fig. 22-14). In PHG, the erythema is of a more diffuse character and may cover the entire gingiva and parts of the alveolar mucosa. The vesicular lesions in PHG, which disrupt and produce small ulcers surrounded by diffuse erythema, occur both on the lips and tongue, as well as on the buccal mucosa. PHG and NPD may occur

Table 22-1 Important characteristics for differential diagnosis between necrotizing periodontal disease (NPD) and primary herpetic gingivostomatitis (PHG)

	NPD	PHG
Etiology	Bacteria	Herpes simplex virus
Age	15–30 years	Frequently children
Site	Interdental papillae Rarely outside gingiva	Gingiva and the entire oral mucosa
Symptoms	Ulcerations, necrotic tissue and a yellowish–white plaque *Foetor ex ore* Moderate fever may occur	Multiple vesicles which disrupt, leaving small round fibrin-covered ulcerations *Foetor ex ore* Fever
Duration	1–2 days if treated	1–2 weeks
Contagious	No	Yes
Immunity	–	Partial
Healing	Destruction of periodontal tissue remains	No permanent destruction

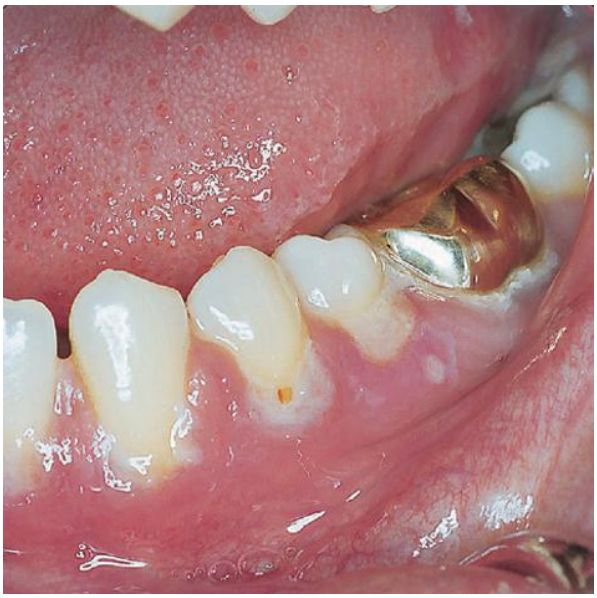


Fig. 22-14 Primary herpetic gingivostomatitis. Note that the ulcers affect the gingival margin but are not primarily interdental papillae. A circular ulcer of the gingiva of the second premolar is highly suggestive of the diagnosis.

simultaneously in the same patient, and in such cases there may be mucosal lesions outside the gingiva, and fever and general malaise tend to occur more frequently than in NPD alone.

Oral mucosal diseases that have been confused with NPD include desquamative gingivitis, benign mucous membrane pemphigoid, erythema multiforme exudativum, streptococcal gingivitis, and gonococcal gingivitis. All of these are clinically quite distinct from NPD.

In some forms of leukemia, especially acute leukemia, necrotizing ulcers may occur in the oral mucosa and are not infrequently seen in association with the gingival margin, apparently as an exacerbation of an existing chronic inflammatory condition. The clinical appearance can resemble NPD lesions, and the symptoms they produce may be the reason the patient seeks professional consultation. In acute leukemia the gingiva often appears bluish–red and edematous with varying degrees of ulceration and necrosis. Generally, the patient has more marked systemic symptoms than with ordinary NPD, but can for a while feel relatively healthy. The dentist should be aware of the possibility that leukemias show such oral manifestations, which require medical examination of the patient; biopsy is usually not indicated.

Histopathology

Histopathologically, NG lesions are characterized by ulceration with necrosis of the epithelium and superficial layers of the connective tissue and an acute, non-specific inflammatory reaction (Fig. 22-15). An important aspect is the role of the microorganisms in the lesions, because they have been demonstrated not only in the necrotic tissue components but also in vital epithelium and connective tissue.

Sometimes the histologic findings demonstrate the formation of regular layers with certain characteristics (Listgarten 1965), but there may be variations in regularity. The surface cover of yellowish–white or grayish slough, which can be observed clinically, under the light microscope appears to be a meshwork of fibrin with degenerated epithelial cells, leukocytes, and erythrocytes, and bacteria and cellular debris. At the ultrastructural level, bacteria of varying sizes and forms, including small, medium-sized and large spirochetes, have been revealed between the inflammatory cells, the majority of which are neutrophilic granulocytes. Moreover, in presumably vital parts of the surface epithelium, compact masses of spirochetes and short, fusiform rods have been found intercellularly.

The vital connective tissue at the bottom of the lesion is covered by necrotic tissue, characterized by disintegrated cells, many large and medium-sized spirochetes, and other bacteria which, judging from their size and shape, may be fusobacteria. In the superior part of the vital connective tissue characterized by intact tissue components, the tissue is infiltrated by large and medium-sized spirochetes, but no other microorganisms have been seen. In the vital connective tissue the vessels are dilated. They also proliferate to form granulation tissue, and the tissue is heavily infiltrated by leukocytes. As always in acute processes, the inflammatory infiltrate is dominated by neutrophils (Figs. 22-15b, 22-16). In the deeper tissue, the inflammatory process also comprises large numbers of monocytes and plasma cells (Listgarten 1965; Heylings 1967).

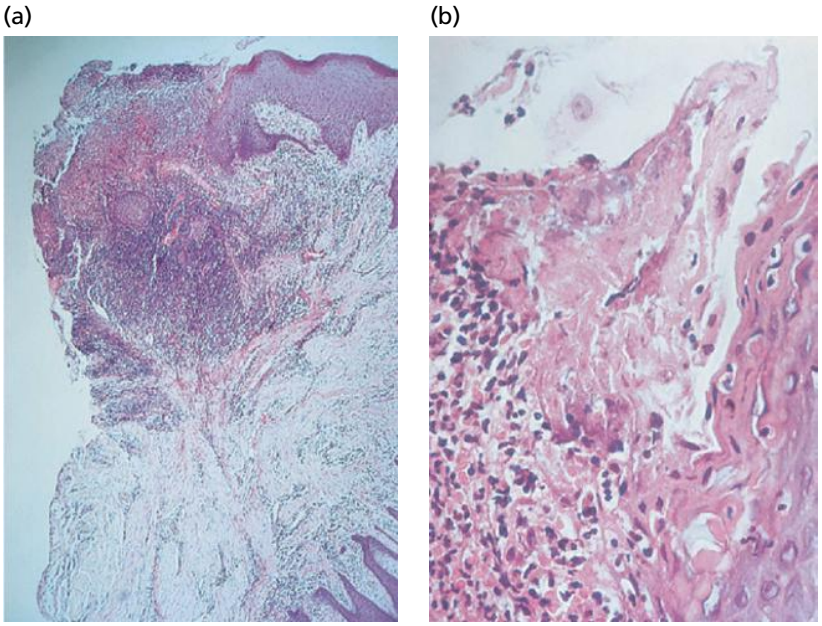


Fig. 22-15 Photomicrograph of the gingival tissue affected by necrotizing gingivitis. (a) Upper right part of the gingival biopsy shows gingival oral epithelium, whereas the upper left part has an ulcerated surface. Underneath the ulcer, the connective tissue is heavily infiltrated by inflammatory cells. (b) Higher magnification of the margin of the ulcer shows necrotic tissue infiltrated with neutrophils. The right border is covered by epithelium. (Courtesy of F. Prætorius.)

Microbiology

Microorganisms isolated from necrotizing lesions

Microbial samples from NPD lesions have demonstrated that there is a constant and a variable part of the flora. The "constant flora" primarily contained *Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Bacteroides melaninogenicus* subsp. *intermedius (Prevotella intermedia)*, and the "variable flora" consisted of a heterogeneous array of bacterial types (Loesche *et al*. 1982; Ramos *et al*. 2012). Although the characteristic bacterial flora of spirochetes and fusobacteria has been isolated in large numbers from the necrotic lesions in several studies, their presence is not evidence of their primary etiologic importance. Their presence could equally well result from secondary overgrowth. Moreover, the microorganisms associated with NG are also harbored by healthy mouths and mouths with gingivitis or periodontitis (Johnson & Engel 1986). An important role for *Treponema* spp. and *B. intermedius (P. intermedia)* has been suggested from studies of antibodies to such bacteria in NPD patients, compared to levels in age- and gender-matched controls with healthy gingiva or simple gingivitis (Chung *et al*. 1983). A recent study has demonstrated that Synergistetes cluster B bacteria were more strongly associated with NG than with common gingivitis (Baumgartner *et al*. 2012), but the significance of this finding is uncertain.

There is little available information about the microbiology of HIV-associated NPD. *Borrelia*, Gram-positive cocci, beta-hemolytic streptococci, and *Candida albicans* have been isolated from the lesions (Reichart & Schiødt 1989). It has also been proposed that human cytomegalovirus (HCMV) may play a role in the pathogenesis of NPD (Sabiston 1986). This virus has been found in the digestive tract of HIV patients (Kanas *et al*. 1987; Langford *et al*. 1990), and a case of oral HCMV infection with similarities to NP has been reported (Dodd *et al*. 1993). The increased frequency of HCMV and other herpes viruses found in necrotizing lesions among Nigerian children supports a contributory role for these viruses (Contreras *et al*. 1997), although it remains to be demonstrated in future studies whether cytomegalovirus does play a causal role.

Pathogenic potential of microorganisms

Our knowledge of the pathogenic mechanisms by which the bacterial flora produces the tissue changes characteristic of NPD is limited. One reason is that it has been difficult to establish an acceptable animal experimental model. However, several of the pathogenic mechanisms which have been associated with chronic gingivitis and periodontitis may also be of etiologic importance in the necrotizing forms of the diseases.

An important aspect in the pathogenesis of periodontitis is the capacity of the microorganisms to invade the host tissues. Among the bacteria isolated from necrotizing lesions, spirochetes and fusiform bacteria can invade the epithelium (Heylings 1967). The spirochetes can also invade the vital connective tissue (Listgarten 1965). The pathogenic potential is further substantiated by the fact that both fusobacteria and spirochetes can liberate endotoxins (Mergenhagen *et al*. 1961; Kristoffersen & Hofstad 1970).

A number of observations indicate that the effects of endotoxins are more prominent in NPD than in chronic gingivitis and periodontitis. The large masses of Gram-negative bacteria liberate endotoxins in close contact with connective tissue. Endotoxins may destroy tissue by direct toxic effects and indirectly by activating and modifying the tissue responses of the host (Wilton & Lehner 1980). Through a direct

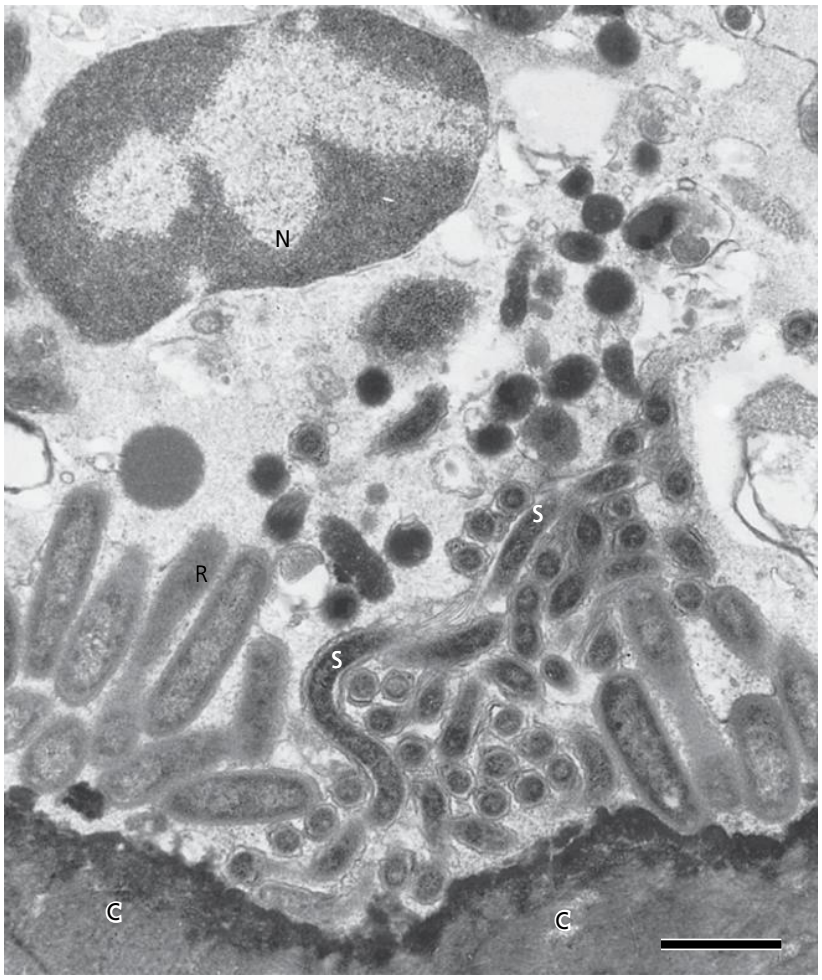


Fig. 22-16 Electron micrograph showing a phagocytosing neutrophil (N) close to the surface of a sequestrum (C), covered by numerous microorganisms including spirochetes (S) and rods (R). Bar = 1 µm.

toxic effect, endotoxins may lead to the damage of cells and vessels. Necrosis is a prominent feature in the so-called "Shwartzman reaction", which is caused by endotoxins. Indirectly, endotoxins can contribute to tissue damage in several ways: they can function as antigens and elicit immune reactions; they can activate complement directly through the alternative pathway and thereby liberate chemotoxins; and they can also activate macrophages, B and T lymphocytes and influence the host's immune reactions by interfering with cytokines produced by these cells. Studies have shown that endotoxins can stimulate catabolic processes with degradation of both connective tissue and bone induced by the released cytokines. The extent to which such reactions contribute to host defense or to tissue damage is not yet known.

An aspect which has been of major concern, especially in wartime, is the communicability of the disease. Several reports have considered this aspect, but it has been concluded that the necrotizing diseases are not transmissible by ordinary means of contact (Johnson & Engel 1986). Attempts to transmit the disease from one animal to another, or to produce necrotic lesions in experimental animals, have failed to yield conclusive results (MacDonald *et al*. 1963). Several suspect microorganisms and several combinations of microorganisms can produce similar lesions in experimental animals. A combination of four different bacteria, none of which is a fusobacterium or spirochete, has been found to possess such properties and there are indications that among the four bacterial species, *B. melaninogenicus* was the true pathogen (MacDonald *et al*. 1956, 1963). *B. melaninogenicus* may, under certain conditions, produce an enzyme which degrades native collagen (Gibbons & MacDonald 1961). It is still not clear, however, whether this microorganism is of particular importance in the pathogenesis of NPD. NG lesions have also been induced in dogs pretreated with steroids and inoculated with a fusiform–spirochete culture from dogs with gingival lesions similar to the NG lesions seen in humans (Mikx & van Campen 1982). However, the lesions produced in experimental animals may not be identical to those which occur in humans. It is also important to note that even if necrotic lesions can be transmitted by infectious material or bacterial cultures, this does not necessarily mean that the disease is truly contagious.

It is obvious from the above observations and assumptions that a fundamental question remains to be answered, and at this point it may be stated that the NPDs belong to those diseases to which Pasteur referred when he stated: "there are some bacteria that cause a disease, but there are some diseases that bring about a condition that is ideal for the growth of some bacteria" (Wilson 1952). If the microorganisms

mentioned above play a role in the etiology of the disease, then, presumably, the disease is caused by an opportunistic infection. Consequently, the pathogenic characteristics of the microorganisms are normally overcome by the host defense, and disease occurs when the host defense is impaired. The isolated microorganisms do possess biologic activities which may contribute to the pathogenesis, but the exact role of the various microorganisms has not yet been clarified (Johnson & Engel 1986).

Host response and predisposing factors

It is particularly evident for HIV-infected patients that the disease is associated with diminished host resistance, but among other predisposing factors, the basic mechanism may include altered host immunity. Changes in leukocyte function and immune system have been observed in some studies, although the biologic reason for and significance of these findings are unclear (Johnson & Engel 1986).

Significantly increased IgG and IgM antibody titers to intermediate-sized spirochetes and higher IgG titers to *B. melaninogenicus* subsp. *intermedius* have been found in NG patients as compared to age- and gender-matched healthy and gingivitis control groups (Chung *et al*. 1983). These results, however, are in disagreement with other data showing no differences in serum antibody levels to bacterial antigens (Wilton *et al*. 1971).

Total leukocyte counts have been found to be similar for patients and controls. NG patients, however, displayed marked depression in polymorphonuclear leukocyte chemotaxis and phagocytosis as compared with control individuals. Reduced mitogen-induced proliferation of peripheral blood lymphocytes has also been found in NG patients. It was suggested that elevated blood steroids may account for the reduced chemotactic and phagocytic responses (Cogen *et al*. 1983).

For many years it has been known that a number of predisposing factors may interact with the host defense systems and render the patient susceptible to NPD. Usually, a single one of these factors is not sufficient to establish disease. The factors which have been the focus of study include systemic diseases, including HIV infection and malnutrition, poor oral hygiene, pre-existing gingivitis and history of previous NPD, psychological stress and inadequate sleep, smoking and alcohol use, Caucasian ethnicity, and young age.

An analysis of suspected predisposing factors among American patients with NPD has shown that HIV seropositivity when present overwhelmed all other factors in terms of importance (Horning & Cohen 1995). Among the HIV-seronegative patients, the ranked importance of the predisposing factors was: history of previous NPD, poor oral hygiene, inadequate sleep, unusual psychological stress, poor diet, recent illness, social or greater alcohol use, smoking, Caucasian ethnicity, and age under 21 years. The various predisposing factors mentioned below are obviously not equally important in industrialized and developing countries, but many of these factors are known to relate to impaired immunity.

Systemic diseases

Systemic diseases which impair immunity predispose an individual to NPD. This is why NPD occurs more frequently in HIV-infected individuals and in patients with other leukocyte diseases, including leukemia (Melnick *et al*. 1988). Examples of other predisposing diseases are measles, chicken pox, tuberculosis, herpetic gingivostomatitis, and malaria, but malnutrition is also important. Whereas these examples of predisposing factors are rare in Western patients, they are evident in developing countries, where they often predispose to NPD and noma in children (Emslie 1963; Pindborg *et al.* 1966; Sheiham 1966; Pindborg *et al.* 1967; Enwonwu 1972, 1985). It is important to note that NPD is sometimes an early signal of impending serious illness (Enwonwu 1972), including agranulocytosis (Tewari *et al*. 2009). Also, chemotherapy in patients with acute leukemia may result in NPD (Santos *et al*. 2009).

HIV infection

In Africa, the general population shows a high HIV-seropositive prevalence rate, ranging up to 33% in some populations. In Europe, prevalences have been established for areas in Great Britain. The prevalence in patients attending London hospitals was below 0.7% in 1994 (Unlinked Anonymous HIV Surveys Steering Group 1996). In South Africa, NPD in otherwise systemically healthy individuals correlated with HIV infection, with a predictive value of 69.6% (Shangase *et al.* 2004). In industrialized countries, a significant proportion of patients with NPD are HIV infected, and no characteristics have been identified that distinguish NPD in HIV-seropositive from that in HIV-seronegative patients. A history of frequent relapses and poor response to traditional or drug therapy may be suggestive (Greenspan *et al*. 1986; Horning & Cohen 1995). Suspicion of HIV infection is also supported by the simultaneous presence of oral candidosis, "hairy leukoplakia", or Kaposi's tumor, but these lesions are far from always present in HIV-infected patients.

HIV infection attacks T-helper cells, causing a drastic change in the T-helper (CD4 positive)/T-suppressor (CD8 positive) ratio with severe impairment of the host's resistance to infection. Depleted peripheral helper T-lymphocyte counts correlate closely with the occurrence of NG, as demonstrated in a study of 390 US HIV-seropositive soldiers (Thompson *et al*. 1992), and an inverse correlation

between NPD and CD4-positive T-cell counts was recently found among patients who had not started HAART (Ranganathan *et al*. 2012). On the other hand, no correlation was found between CD4-positive T-cell count or neutrophil count and extent and severity of NPD in studies of South African patients (Phiri *et al*. 2010; Wood *et al*. 2011). Furthermore, a complete absence of T cells in gingival tissue of HIV-infected patients with periodontitis has been reported (Steidley *et al*. 1992). The lack of local immune effector and regulatory cells in HIV-seropositive patients could in fact explain the characteristic and rapidly progressive nature of periodontitis in these patients. Moreover, a protective effect against NPD has been encountered with HAART of the HIV infection (Tappuni *et al*. 2001), as well as against HIV-associated gingivitis and periodontitis (Masouredis *et al*. 1992). NP has been revealed as a marker for immune deterioration, with a 95% predictive value that CD4-positive cell counts were below 200 cells/mm^3, and, if untreated, a cumulative probability of death within 24 months (Glick *et al*. 1994). As a consequence of this finding, a test for HIV infection, if possible, may be recommended for all NPD patients.

Malnutrition

In developing countries, malnutrition has often been mentioned as a predisposing factor for NPD (Enwonwu 1972; Osuji 1990). Malnutrition results in lowered resistance to infection and protein malnutrition has been emphasized as the most common public health problem affecting underprivileged Nigerian children who are most often affected by NPD (Enwonwu 1985, 1994). In response to periodontal pathogens, phagocytes elaborate destructive oxidants, proteinases, and other factors. Periodontal damage may occur as the result of the interaction between these factors, the antioxidants, and the host-derived antiproteinases. Malnutrition is characterized by marked tissue depletion of the key antioxidant nutrients and impaired acute-phase protein response to infections. This is due to impairment in the production and cellular action of the cytokines. Other features of malnutrition include an inverted helper-to-suppressor T-lymphocyte ratio, histaminemia, hormonal imbalance with increased blood and saliva levels of free cortisol, and defective mucosal integrity. Malnutrition usually involves concomitant deficiencies of several essential macro- and micro-nutrients, and therefore has the potential to adversely influence the prognosis of periodontal infections (Enwonwu 1994).

Poor oral hygiene, pre-existing gingivitis, and history of previous necrotizing periodontal diseases

Many of the early studies of NPD showed that a low standard of oral hygiene contributed to the establishment of the disease (Johnson & Engel 1986). This has been supported by later studies in the US and Nigeria (Taiwo 1993; Horning & Cohen 1995). Consequently, NPD is usually established on the basis of pre-existing chronic gingivitis (Pindborg 1951b). It should be emphasized, however, that plaque accumulation as seen in NPD patients may also be enhanced by the discomfort experienced with oral hygiene practices due to the disease.

Based on questionnaires and personal interviews, 28% of NPD patients have been found to have a history of previous painful gingival infection and 21% had gingival scars suggestive of previous NPD (Horning & Cohen 1995).

Psychological stress and inadequate sleep

Just as other ulcerative gastrointestinal conditions have been shown to have psychogenic origins, psychological stress has often and for many years been mentioned as a predisposing factor for NPD (Johnson & Engel 1986). Epidemiologic investigations seem to indicate a more frequent occurrence of necrotizing diseases in periods when individuals are exposed to psychological stress (Pindborg 1951a, b; Giddon *et al.* 1963; Goldhaber & Giddon 1964). New recruits and deployed military personnel, college students during examination periods, patients with depression or other emotional disorders, and patients feeling inadequate to handle life situations are more susceptible to NPD (Pindborg 1951a, b; Moulton *et al*. 1952; Giddon *et al*. 1963; Cohen-Cole *et al*. 1983). Urine levels of corticosteroids have been used as a physiological measure of stress, and increased free cortisol levels in the urine of NPD patients as compared with controls have been encountered. The NPD patients showed significantly higher levels of trait anxiety, depression, and emotional disturbance than did control individuals (Co-hen-Cole *et al.* 1983). The role of anxiety and psychological stress in the pathogenesis of NG has been borne out by both psychiatric and biochemical investigations (Moulton *et al.* 1952; Shannon *et al*. 1969; Maupin & Bell 1975). There are several ways in which psychological stress factors may interfere with host susceptibility. Host tissue resistance may be changed by mechanisms acting through the autonomic nervous system and endocrine glands, resulting in elevation of corticosteroid and catecholamine levels. This may reduce gingival microcirculation and salivary flow and enhance nutrition of *P. intermedia*, but also depress neutrophil and lymphocyte functions, which facilitates bacterial invasion and damage (Johnson & Engel 1986; Horning & Cohen 1995).

Inadequate sleep, often as the result of lifestyle choices or job requirements, has been mentioned by many patients with NPD (Horning & Cohen 1995).

Smoking and alcohol use

Smoking has been listed as a predisposing factor for NPD for many years and presumably predisposes to other types of periodontitis as well (American Academy of Periodontology 1996).

Two studies from the 1950s found that 98% of patients with NPD were smokers (Pindborg 1951a; Goldhaber 1957). Later data have confirmed this by finding that among patients with NPD only 6% were non-smokers, in contrast to 63% in a matched control group (Stevens *et al*. 1984). The amount smoked also appears important since 41% of subjects with NG smoked >20 cigarettes daily, whereas only 5% of controls smoked that much (Goldhaber & Giddon 1964).

The relationship between tobacco usage and NPD appears to be complex. It has often been stated that smokers in general have poorer oral hygiene than non-smokers, but studies have shown that there is little difference in the level of plaque accumulation in smokers versus non-smokers. Also, there have been no conclusive studies to show that smoking adversely affects periodontal tissues by altering the microbial composition of plaque (American Academy of Periodontology 1996). Smoking could lead to increased disease activity by influencing host response and tissue reactions. As examples, smokers have depressed numbers of T-helper lymphocytes, and tobacco smoke can also impair chemotaxis and phagocytosis of oral and peripheral phagocytes (Eichel & Shahrik 1969; Kenney *et al*. 1977; Ginns *et al*. 1982; Costabel *et al*. 1986; Lannan *et al*. 1992; Selby *et al*. 1992). Among further effects of tobacco, nicotine-induced secretion of epinephrine resulting in gingival vasoconstriction has been proposed as one possible mechanism by which smoking may influence tissue susceptibility (Schwartz & Baumhammers 1972; Kardachi & Clarke 1974; Bergström & Preber 1986). The exact mechanism by which tobacco smoking predisposes to NPD, however, remains to be determined.

Social or heavy drinking has been admitted by NPD patients and its role as a predisposing factor can be explained by its numerous physiologic effects which add to other factors as general sources of debilitation (Horning & Cohen 1995).

Caucasian ethnicity

A number of American studies have demonstrated a 95% preponderence of Caucasian patients with NPD, including a study in which the referring population was 41% African–American (Barnes *et al*. 1973; Stevens *et al*. 1984; Horning & Cohen 1995), but a proportion of 49% of African–Americans in another study casts doubt on race as a predisposing factor alone, and the mechanism for this factor is unknown.

Young age

In industrialized countries, young adults appear to be the most predisposed to NPD. While the disease can occur at any age, the reported mean age for NPD is between 22 and 24 years. This may reflect a number of factors such as military population age and wartime stress, and probably is related to the involvement of other factors such as smoking (Horning & Cohen 1995).

Treatment

The treatment of the NPD is divided into two phases: acute and maintenance phase treatment.

Acute phase treatment

The aim of acute phase treatment is to eliminate disease activity as manifest by ongoing tissue necrosis laterally and apically. A further aim is to avoid pain and general discomfort which may severely compromise food intake. Among patients suffering from systemic diseases resulting in loss of weight, further weight loss due to reduced food intake should be avoided by rapid therapeutic intervention.

At the first consultation, scaling should be attempted as thoroughly as the condition allows. Ultrasonic scaling may be preferable to the use of hand instruments. With minimal pressure against the soft tissues, ultrasonic cleaning may accomplish the removal of soft and mineralized deposits. The continuous water spray combined with adequate suction usually allows good visibility. How far it is possible to proceed with debridement at the first visit usually depends on the patient's tolerance of pain during instrumentation. Obviously, toothbrushing in areas with open wounds does not promote wound healing. Therefore, patients should be instructed in substituting toothbrushing with chemical plaque control in such areas until healing is accomplished.

Hydrogen peroxide and other oxygen-releasing agents also have a long-standing tradition in the initial treatment of NPD. Hydrogen peroxide (3%) is still used for debridement in necrotic areas and as a mouth rinse (equal portions of 3% H_2O_2 and warm water). It has been thought that the apparently favorable effects of hydrogen peroxide may be due to mechanical cleaning and the influence on anaerobic bacterial flora of the liberated oxygen (Wennström & Lindhe 1979; MacPhee & Cowley 1981). Further adjunctive local oxygen therapy of NPD showed a more rapid clinical restitution with less periodontal destruction than in a group without oxygen therapy (Gaggl *et al*. 2006).

Twice-daily rinsing with a 0.2% chlorhexidine solution is a very effective adjunct to reduce plaque formation, particularly when toothbrushing is not performed. It also assists self-performed oral hygiene

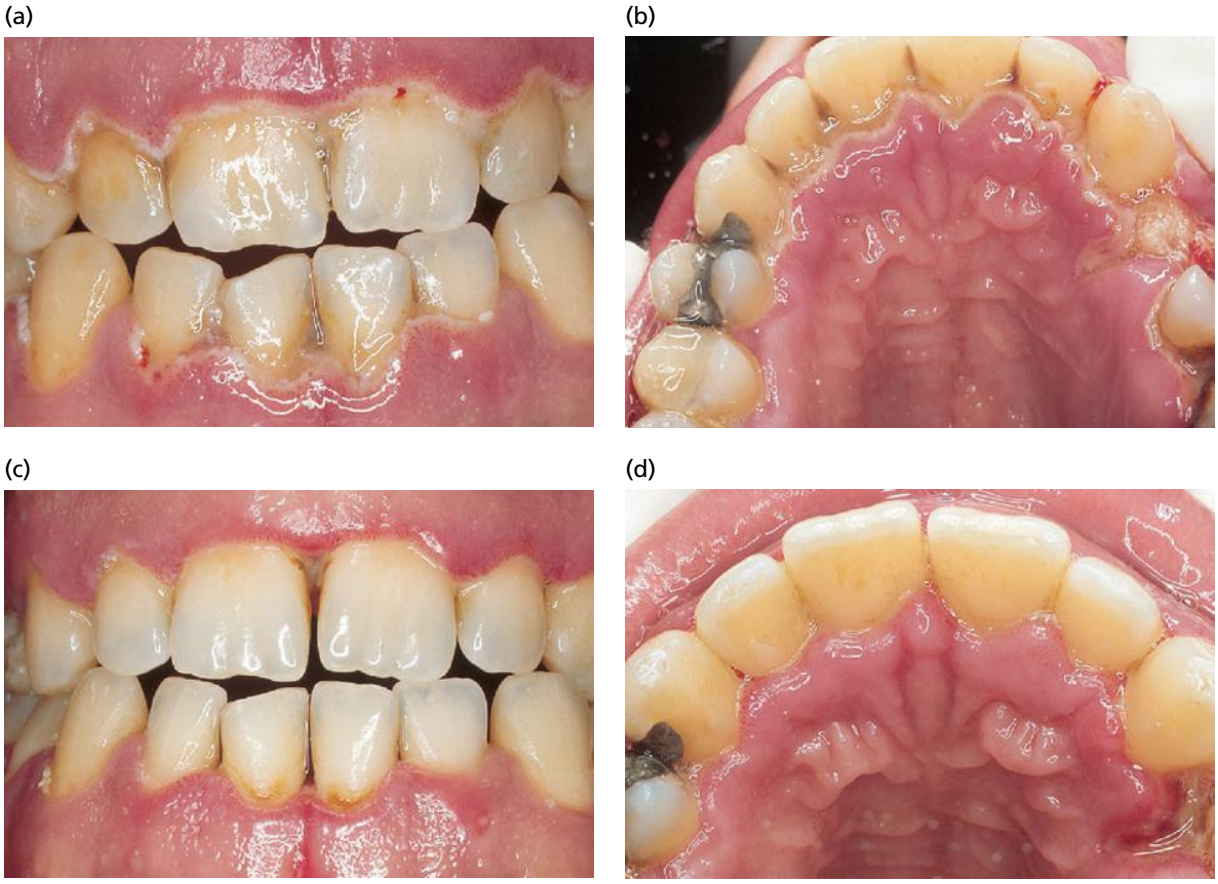


Fig. 22-17 Necrotizing periodontitis with severe pain. The entire gingival margin is the seat of a necrotic ulcer. (a) Facial aspect; (b) palatal aspect. (c, d) The patient was treated with scaling supplemented with metronidazole and the next day was free of symptoms and the clinical features were significantly improved.

during the first weeks of treatment. Its effect is discussed in Chapter 37. For an optimal effect of this medicament, it should be used only in conjunction with and in addition to systematic scaling and root planing. The chlorhexidine solution does not penetrate subgingivally and the preparation is readily inactivated by exudates, necrotic tissues, and masses of bacteria (Gjermo 1974). The effectiveness of chlorhexidine mouth rinses therefore is dependent upon simultaneous, thorough mechanical debridement.

In some cases of NPD, the patient's response to debridement is minimal or his/her general health is affected to such an extent that the supplementary use of systemic antibiotics or chemotherapeutics is indicated. This also applies to patients with malaise, fever, and lassitude. The choice of drug aims at a direct action on bacteria which are the cause of the inflammatory process in NPD.

Supplementary treatment with metronidazole 250 mg t.i.d. has been found to be effective against spirochetes and appears to be the first choice in the treatment of NPD (Proctor & Baker 1971; Shinn 1976; Loesche *et al*. 1982). The adjunctive use of metronidazole in HIV-associated NPD is reported to be extremely effective in reducing acute pain and promoting rapid healing (Scully *et al*. 1991). Acute pain usually disappears after a few hours (Fig. 22-17).

Antibiotics such as penicillins and tetracyclines are also effective. Penicillin 1 mIU t.i.d should be used as an adjunct to scaling, as for metronidazole, until the ulcers are healed. Topical application of antibiotics is not indicated in the treatment of NPD, because intralesional bacteria are frequent, and topical application does not result in a sufficient intralesional concentration of antibiotics.

It is important to emphasize that many HIV-seropositive patients with NPD at their initial visit are not aware of their serostatus. If HIV infection is a suspected predisposing factor, the patient can be referred to his/her physician for further examination. Some patients may prefer referral to a hospital department. Information on HIV serostatus is frequently not available at initiation of therapy, but the lack of information has no serious implications for the choice of treatment or for the handling of the patient. As a consequence of a lack of information on HIV-serostatus of patients seeking dental treatment in general, all procedures in the dental office must always include precautions to protect against transmission of the virus to the dentist, to the dental auxiliaries, and to other patients.

If the dentist asks the patient about his/her possible chance of having contracted HIV infection, this should be done with great care, because HIV infection

has serious implications for the patient. Consequently, a successful outcome depends on a confidential relationship between patient and dentist. In the case of a new patient, such a relationship is only established after at least a couple of appointments in the clinic.

Usually, in HIV-infected patients antibiotic prophylaxis as an adjunct to scaling does not appear to be necessary. Bacteria recovered from venipuncture 15 minutes after scaling were not detectable in samples obtained at 30 minutes (Lucartoto *et al*. 1992). Neither does removal of sequestra always appear to require antibiotic cover (Robinson 1991). HIV-infected patients are susceptible to candidal infections (Holmstrup & Samaranayake 1990) and if oral candidosis is present or occurs throughout the period of antibiotic treatment, treatment with appropriate antimycotic drugs such as miconazole may be necessary.

Patients with NPD should be seen almost daily as long as the acute symptoms persist. Appropriate treatment alleviates symptoms within a few days. Thereafter the patient should return in approximately 5 days. Systematic subgingival scaling should be continued with increasing intensity as the symptoms subside. Correction of restoration margins and polishing of restorations and root surfaces should be completed after healing of the ulcers. When the ulcerated areas are healed, the local treatment is supplemented with oral hygiene instruction and patient motivation. Instruction in gentle but effective toothbrushing and approximal cleaning is mandatory. In many cases the extensive tissue destruction results in residual soft tissue defects that are difficult for the patient to keep clean. Oral hygiene in these areas often requires the use of interproximal devices and soft, smaller brushes. Sometimes healing is delayed in HIV-infected patients and intensive professional control may be necessary for prolonged periods of time.

Patients with NPD are not always easily motivated to carry out a proper program of oral hygiene. They frequently have poor oral hygiene habits and possibly a negative attitude to dental treatment in general. As a result, some patients discontinue treatment as soon as pain and other acute symptoms are alleviated. Motivation and instruction should be planned to prevent this from happening, and should be reinforced during later visits. Patients with severely impaired immune functions, for instance due to HIV infection, may suffer from other infections or diseases during the period of treatment. This may complicate the treatment, because patients may be hospitalized.

Maintenance phase treatment

When the acute phase treatment has been completed, necrosis and acute symptoms in NPD will have disappeared. The formerly necrotic areas are healed and the gingival craters are reduced in size, although some defects usually persist. In such areas, bacterial plaque readily accumulates and the craters, therefore, predispose to recurrence of NPD or to further destruction because of a persisting chronic inflammatory process, or both. These sites, therefore, may require surgical correction. Shallow craters can be removed by simple gingivectomy, while the elimination of deep defects may require flap surgery. Treatment of NPD has not been completed until all gingival defects have been eliminated and optimal conditions for future plaque control have been established. If possible, elimination of predisposing factors is also very important to prevent recurrence. Due to delayed healing in HIV-infected patients, periodontal surgery is not recommended in these patients. Instead, intensive approximal cleaning is necessary to prevent recurrence of disease.

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Chapter 23

Effect of Periodontal Diseases on General Health

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Introduction

The concept that oral and general health are interrelated is far from new. Writings from ancient civilizations including the Assyrians, Hebrews, Greeks, and Romans corroborate the notion that "strong teeth" reflect good health, but also that various systemic ailments can be attributed to poor oral health (O'Reilly & Claffey 2000). In more modern times, a 1891 publication titled "The human mouth as a focus of infection" by the American dentist W.D. Miller (1891), followed by influential articles by the London physician William Hunter (1900, 1910) in the *British Medical Journal* and the *Lancet* at the turn of the 20th century, established the belief that "oral sepsis" (the term used to describe oral infections) played an etiologic role in the development of a number of diverse pathologic conditions, including "chronic dyspepsias, intestinal disorders, ill health, anemias and nervous complaints". The concept of "oral sepsis" evolved to that of "focal infection" (Billings 1912), according to which a circumscribed area of tissue infected with pathogenic organisms could lead to hematogenous dissemination resulting in infection of contiguous or non-contiguous organs. These beliefs translated into drastic treatment decisions, and scores of patients were edentulated in order to cure (or even prevent) multiple diseases. As is usually the case, empirical evidence gradually revealed that these radical practices were unsound (Cecil & Angevine 1938), the purported associations were increasingly refuted, and more conservative approaches to the treatment of oral pathologic conditions finally prevailed.

Interestingly, during the past two decades, and with the increased understanding that inflammation is at the heart of several pathologic conditions that were traditionally viewed as non-inflammatory, the potential effects of oral infection/inflammation on general health outcomes has regained attention and has been the focus of intense investigation. A new field of periodontal research has emerged, commonly referred to as "periodontal medicine", which explores the epidemiologic evidence related to these associations, as well as the potential pathobiologic mechanisms that may account for such links. This chapter will primarily review the biologic plausibility and epidemiologic evidence related to the association between periodontitis and (1) atherosclerotic vascular disease; (2) adverse pregnancy outcomes, and (3) diabetes mellitus, as these are the three most studied conditions thus far. Emerging data on associations with chronic renal disease and pulmonary infections will be discussed briefly as well.

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Atherosclerotic vascular disease

Biologic plausibility

A wealth of data originating from diverse areas of investigation have implicated chronic, low-level inflammation as an important factor in atherosclerotic vascular disease (AVD) (Ross 1999). Supporting studies stemming from a variety of disciplines such as cell biology, epidemiology, clinical trials, and experimental animal research have consistently revealed that atherosclerotic lesions involve an inflammatory component. Cellular interactions involved in atherogenesis are fundamentally similar to those in chronic inflammatory–fibroproliferative diseases, and atherosclerotic lesions represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease (Ross 1993, 1999).

As discussed in other chapters of this textbook, periodontal diseases represent mixed infections of the periodontal tissues in which several, primarily anaerobic, Gram-negative bacteria have a prominent role (Haffajee & Socransky 1994). Likewise, as reviewed in Chapter 7, the prevalence of these infections, especially those of mild or moderate severity, is substantial in most populations. The deepening of the periodontal sulcus occurring during the course of these infections is concurrent with a marked bacterial proliferation, resulting in levels reaching 10^9 or 10^{10} bacterial cells within a single pathologic periodontal pocket. The ulcerated epithelial lining of the periodontal pocket may constitute a substantial surface area in cases of generalized periodontitis (Hujoel *et al*. 2001) and is in constant contact with the biofilm of the subgingival dental plaque. Thus, the ulcerated pocket epithelium provides a gate through which lipopolysaccharide (LPS), bacterial outer membrane vesicles, fimbriae, and other antigenic structures of bacterial origin may challenge the immune system and elicit a local and systemic inflammatory host response (Ebersole & Taubman 1994). Importantly, a number of pathogenic species involved in periodontal infections display tissue invasion properties (Meyer *et al*. 1991; Sandros *et al*. 1994; Lamont *et al*. 1995). Further, frequent transient bacteremias occurring as a result of daily activities such as toothbrushing or chewing (Silver *et al*. 1977; Kinane *et al*. 2005; Forner *et al*. 2006; Crasta *et al*. 2009), as well as during invasive oral therapeutic procedures (Heimdahl *et al*. 1990; Lockhart *et al*. 2008) may confer a significant systemic bacterial challenge. Similarly, a number of pro-inflammatory mediators, including several interleukins, are produced locally in the inflamed gingival tissues (Salvi *et al*. 1998) and can also be disseminated systemically through the blood stream. Circulating levels of the same mediators also have been found to be higher during the course of several non-oral infections (Otto *et al*. 1999; Humar *et al*. 1999; Endo *et al*. 1992), and have been identified as important biomarkers of cardiovascular disease (CVD) (Hackam & Anand, 2003; Hansson 2005).

Central to the role of periodontal infection/inflammation as a risk factor for atherosclerosis is the concept of *vascular endothelial activation*. Figures 23-1, 23-2, and 23-3 summarize a number of potential biologic mechanisms through which periodontal bacteria or periodontitis-associated inflammatory mediators may initiate and perpetuate different well-described steps in atherogenesis. As shown in Fig. 23-1, circulating bacterial products such as LPS, outer membrane vesicles, and fimbriae, or inflammatory cytokines and chemokines result in an up-regulation of cell-surface receptors and in expression of adhesion molecules on the endothelial lining of the vasculature. As a result, peripheral blood monocytes are recruited and adhere to the activated endothelium. In addition, in a process collectively referred to as "molecular mimicry", antibodies targeted against specific bacterial proteins (such as the so-called "heat-shock" proteins that are evolutionarily well-conserved and highly homologous to host proteins), partly act as autoantibodies and induce apoptotic damage in the vascular endothelium. In a next step, outlined in Fig. 23-2, monocytes migrate into the subendothelial space, transform into tissue macrophages, take up oxidized low density lipoprotein cholesterol (LDL), and become foam cells. Apoptosis of LDL-laden macrophages results in the accumulation of lipids in the subendothelial space, that is in the formation of *atheromatic plaques*. Furthermore, invasive periodontal pathogens induce smooth muscle cell proliferation in the intima and neointima formation. Extracellular matrix build-up and extravasation of T cells result in the formation of a fibrous cap covering the atheroma. Finally, Fig. 23-3 outlines the maturation of atheromatic plaques that may ultimately lead to plaque rupture. The fibrous cap and its prothrombotic components are exposed after endothelial cell apoptosis. Enzymatic degradation of the extracellular matrix results in plaque rupture, exposure of prothrombotic plaque components, and subsequent thrombus formation that leads to the occlusion of the vessel. This manifests as a clinical event, for example as a myocardial infarction (MI) in the case of an occluded coronary artery, or as stroke in the case of an occluded cerebral vessel.

A number of studies have examined the presence of oral bacteria in atheromatic plaque lesions. Chiu (1999) investigated the relationship between the presence of multiple infectious agents in human carotid endarterectomy specimens and pathoanatomic features of the corresponding carotid plaques, and reported positive immunostainings for *Porphyromonas gingivalis* and *Streptococcus sanguis* in several carotid plaque specimens. The bacteria were immunolocalized in plaque shoulders and within a lymphohistiocytic infiltrate, associated with ulcer and thrombus formation, and adjacent to areas of strong labeling for apoptotic bodies. A similar study, using the polymerase chain reaction (PCR) to detect the presence of bacterial DNA in carotid endarderectomy specimens

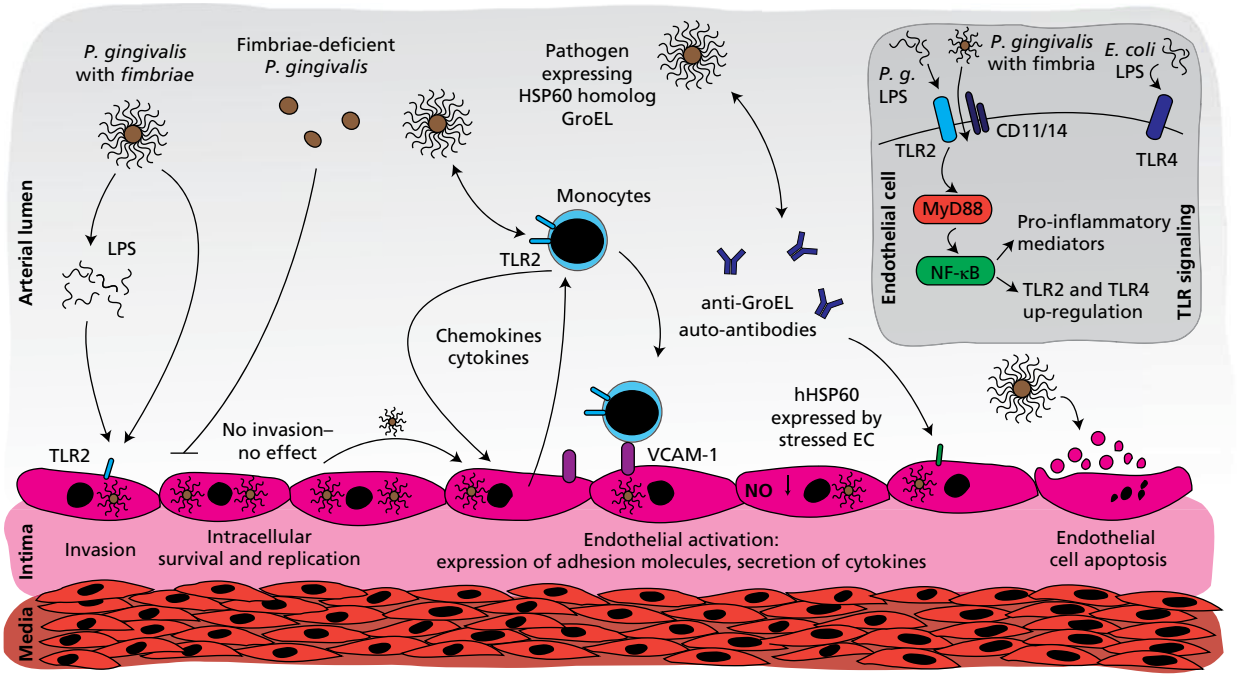

Fig. 23-1 Schematic overview of potential mechanisms linking periodontal infections and endothelial dysfunction/incipient atherosclerosis. Vascular endothelial cells are invaded by fimbriated pathogens, for example *P. gingivalis*. These pathogens can persist and multiply intracellularly. Activation of Toll-like receptor 2 (TLR2) by fimbriated bacteria or lipopolysaccharide (LPS) results in release of pro-inflammatory mediators and up-regulation of cell adhesion molecules. Monocytes are recruited by a gradient of chemotactic cytokines, such as monocyte chemoattractant protein 1 (MCP-1). Antibodies against bacterial heat-shock proteins, such as HSP60-related GroEL, autoreact with human HSP60 (hHSP60) expressed by activated endothelium, resulting in cell destruction. Further, *P. gingivalis* induces apoptosis of endothelial cells. (NO, nitrogen oxide; NF-κB, nuclear factor κB; VCAM-1, vascular cell adhesion protein 1; MyD88, myeloid differentiation primary response protein 88; TLR4, Toll-like receptor 4) (Source: Kebschull *et al.* 2010. Reproduced with permission from Sage.)

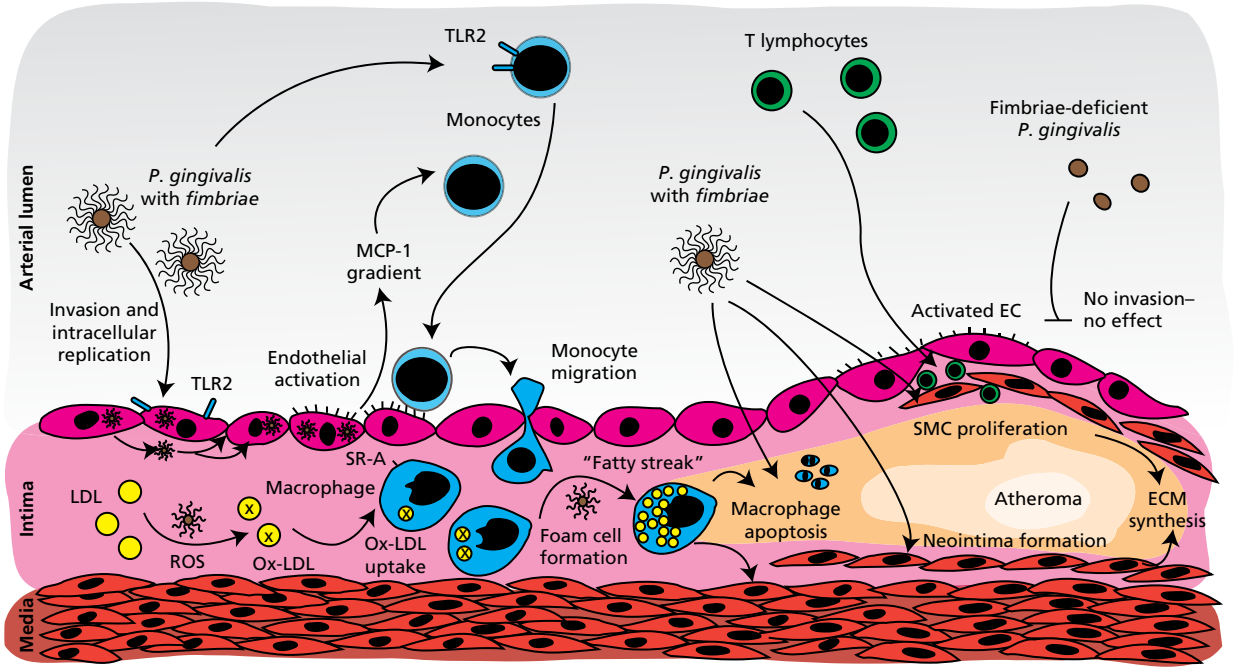

Fig. 23-2 Potential mechanisms linking periodontal infections and fatty-streak formation/plaque maturation. Monocytes activated by periodontal pathogens chemotactically migrate into the subendothelial space, transform into macrophages, and subsequently into foam cells after uptake of oxidized low density lipoprotein (oxLDL). Apoptosis of LDL-laden macrophages results in accumulation of lipids in the subendothelial space. Furthermore, periodontal pathogens induce smooth muscle cell proliferation in the intima and neointima formation. Extracellular matrix (ECM) build-up and extravasation of T cells consummate the formation of a fibrous cap covering the plaque. (MCP-1, monocyte chemoattractant protein 1; TLR2, Toll-like receptor 2; SR-A, macrophage scavenger receptor; ROS, reactive oxygen species; SMC, smooth muscle cell; EC, endothelial cell.) (Source: Kebschull *et al.* 2010. Reproduced with permission from Sage.)

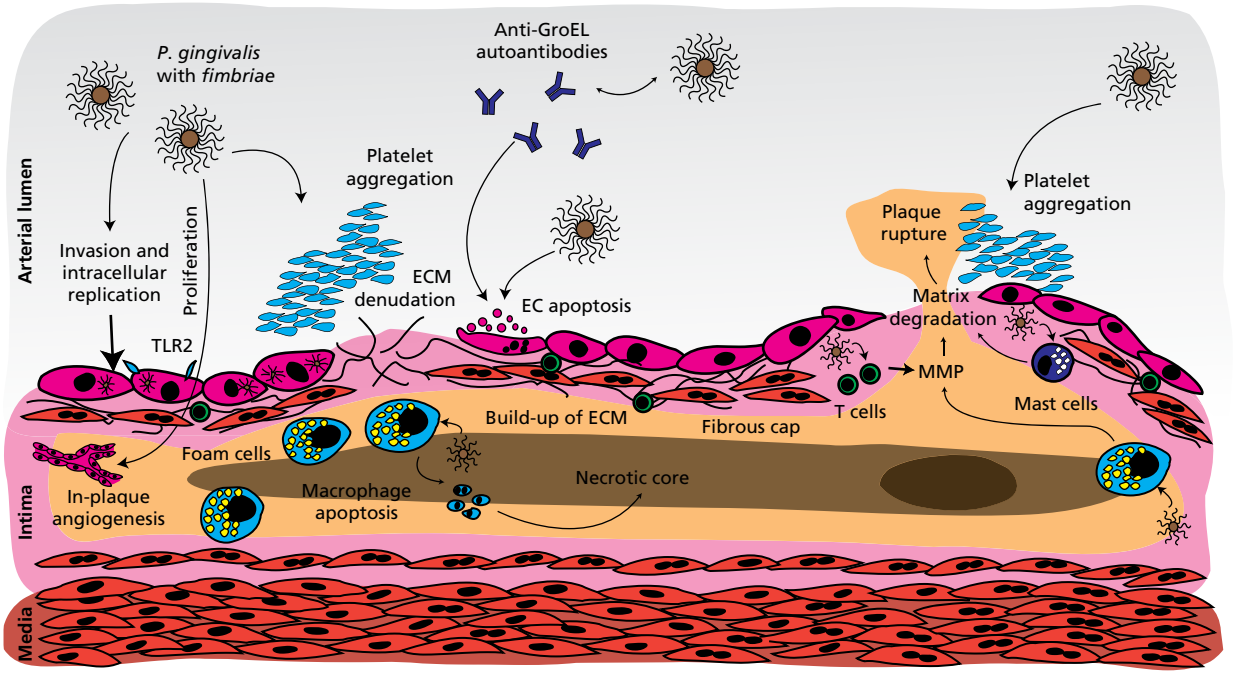

Fig. 23-3 Potential mechanisms linking periodontal infections to mature atherosclerotic plaques and plaque rupture. Pathogen-mediated in-plaque angiogenesis is a hallmark of plaque organization. Denudation of the fibrous cap and its prothrombotic components occurs after endothelial cell (EC) apoptosis mediated by whole periodontal pathogens, or antiendothelial autoantibodies. Plaque rupture is induced by pathogen-mediated extracellular matrix (ECM) degradation by EC, plaque macrophages, T cells, and plasma cells, leading to exposure of prothrombotic plaque components, and subsequent vessel occlusion. (MMP, matrix metalloproteinases; TLR2, Toll-like receptor 2.) (Source: Kebschull *et al.* 2010. Reproduced with permission from Sage.)

(Haraszthy *et al*. 2000), reported that 30% of the specimens examined were positive for *Treponema forsythia*, 26% for *P. gingivalis*, 18% for *Aggregatibacter actinomycetemcomitans*, and 14% for *Prevotella intermedia*. The validity of these data were confirmed by other investigators (Stelzel *et al*. 2002; Fiehn *et al*. 2005) and extended by Kozarov *et al*. (2005) who demonstrated that viable and invasive *A. actinomycetemcomitans* and *P. gingivalis* could be recovered from human atheromatic plaques. These observations were further corroborated by experimental animal studies that demonstrated that oral infection of atherosclerosis-prone (apolipoprotein-E deficient) mice with *P. gingivalis* resulted in accelerated atherosclerosis and in the concomitant presence of *P. gingivalis* DNA in their aortic tissue (Lalla *et al*. 2003). For a comprehensive review of the literature on the potential biologic mechanisms of periodontitis-induced atherogenesis, the reader is referred to the review by Kebschull *et al*. (2010).

Epidemiologic evidence

Epidemiologic evidence on the association between periodontitis and AVD has been generated by three different types of studies: (1) *association studies* (cross-sectional, case–control or longitudinal cohort studies) focusing on *surrogate markers* of AVD; (2) *association studies* focusing on *clinical AVD-related events* [i.e. coronary heart disease (CHD), MI, cerebrovascular disease, peripheral artery disease]; and (3) *intervention studies*, examining the effects of *periodontal therapy on AVD-related outcomes (surrogate markers or events)*. In the following text, we will summarize the data accordingly. We want to draw the attention of the reader to two fundamental issues that are important for the correct interpretation of the data: First, it must be realized that the *exposure variable*, in this case periodontitis as a potential risk factor for AVD, has been defined in these studies using a variety of measures that reflect poor periodontal status. Thus, studies have used traditional clinical or radiographic parameters, such as probing pocket depth, attachment level, and presence of gingival inflammation, but also surrogate markers of poor oral health such as tooth loss or edentulism. The latter two, although related to poor periodontal status, are clearly not synonymous with periodontitis. Furthermore, as discussed in detail in the Chapter 7, the definition of a "periodontitis case" using clinical variables or radiographic assessments of alveolar bone loss is dependent on threshold values of extent and severity, and these have varied greatly across studies. To further complicate the matter, a number of epidemiologic studies have used subgingival microbial profiles or levels of serum antibodies to periodontal bacteria, which reflect the infectious nature of periodontitis rather than its clinical phenotype, as the exposure variable. As discussed in Chapter 7, there is no universally acceptable appropriate definition of periodontitis, and there is a need for additional methodologic research in order to define the optimal exposure

variable to be used in the study of the association between periodontitis and systemic health outcomes such as AVD. The last point that needs to be emphasized, and which is a key determinant of the quality of an epidemiologic study, is whether the association between the exposure under investigation (i.e. periodontitis) and the outcome (i.e. AVD) has been adjusted for *additional exposures* that are known to affect AVD status (e.g. hyperlipidemia, hypertension, or physical activity), as well as for potential *confounders*, in other words, factors that are associated with both periodontitis and AVD (e.g. diabetes mellitus or smoking). Thus, it must be recognized that both the diverse exposure definitions across studies and the variable degree of adjustment for additional risk factors may underlie some of the non-concordant findings in the literature.

Associations with surrogate markers of AVD

Periodontitis patients have been shown to display higher white blood cell counts (Kweider *et al*. 1993; Loos *et al*. 2000) and C-reactive protein (CRP) levels (Ebersole *et al*. 1997; Slade *et al*. 2000; Loos *et al*. 2000) than periodontally healthy controls. Wu *et al*. (2000b) examined the relation between periodontal health status and serum total and high density lipoprotein (HDL) cholesterol, CRP, and plasma fibrinogen in the third National Health and Nutrition Examination Survey (NHANES III). Based on an analysis of a total of 10 146 subjects with available cholesterol and CRP levels and 4461 subjects with available fibrinogen levels, poor periodontal status was significantly associated with increased CRP and fibrinogen levels. Slade *et al*. (2000) explored the same database and reported that people with extensive periodontal disease had an approximately one-third increase in mean CRP and a doubling of the prevalence of elevated CRP compared with periodontally healthy people. Similarly, raised CRP levels were observed in edentulous subjects. Based on data obtained from 2973 participants in the second phase of NHANES III, aged ≥40 years, Dye *et al*. (2005) showed that a high serum IgG antibody level to *P. gingivalis* was significantly related to elevated serum CRP. In a sample comprising 5552 subjects aged 52–75 years from the Atherosclerosis Risk in Communities (ARIC) study (Slade *et al*. 2003), participants with extensive periodontal disease (≥30% of sites with a pocket depth of ≥4 mm) had 30% higher CRP levels than participants with an extent of periodontal disease between 0% and 30%. In a multivariate analysis stratified for body mass index (BMI), extensive periodontal pocketing remained associated with CRP levels when adjusted for age, sex, diabetes mellitus, cigarette use, and use of non-steroidal anti-inflammatory medications. In a meta-analysis of ten cross-sectional studies reporting levels of high sensitivity CRP (hsCRP) in periodontitis, Paraskevas *et al*. (2008) reported a statistically significant weighted mean difference for hsCRP between periodontitis patients and periodontally healthy controls of 1.56 mg/L. Given that an hsCRP level between 1 and 2 mg/L is currently considered to be associated with intermediate risk for CVD, and a level exceeding 3 mg/L with high risk (Ridker 2003), the above difference appears to be highly significant from a clinical point of view. Finally, Schwahn *et al*. (2004) reported on associations between periodontitis, edentulism, and high plasma fibrinogen levels (>3.25 g/L) in 2738 participants in the Study of Health in Pomerania (SHIP), aged 20–59 years. After adjustments for multiple co-variates (age, sex, BMI, education, use of alcohol, aspirin, and other medications, LDL levels, smoking, and other pathologic conditions including gastritis, bronchitis, and diabetes), presence of ≥15 pockets with a probing depth of ≥4 mm was significantly associated with high plasma fibrinogen levels with an odds ratio (OR) of 1.9 (95% CI 1.2–2.8). Less extensive pocketing or edentulism was not associated with high plasma fibrinogen levels.

Another group of studies has investigated the association between periodontitis and subclinical atherosclerosis, commonly measured by means of carotid artery intima–media thickness (IMT) assessments. Increased IMT has been documented to be directly associated with increased risk of MI and stroke (O'Leary *et al*. 1999). Beck *et al*. (2001) provided the first evidence that periodontitis may be linked to subclinical atherosclerosis. These authors analyzed cross-sectional data from 6017 participants in the ARIC study, and demonstrated that severe periodontitis conferred increased odds for higher carotid artery intima–media wall thickness (OR 2.09; 95% CI 1.73–2.53 for IMT of ≥1 mm). A couple of years later, the Oral Infection and Vascular Disease Epidemiology Study (INVEST), a prospective population-based cohort study of randomly selected subjects in a triethnic population comprising a total of 1056 subjects aged ≥55 years with no baseline history of stroke, MI, or chronic inflammatory conditions, investigated the relationship between carotid artery plaque and IMT with tooth loss and measures of periodontitis. In a first report based on data from 711 subjects (Desvarieux *et al*. 2003), loss of 10–19 teeth was associated with increase in prevalence of atherosclerotic plaques in a model adjusted for age, sex, smoking, diabetes, systolic blood pressure, LDL, HDL, ethnicity, education, toothbrushing, social isolation, physical activity, and years of residence in the US (OR 1.9; CI 1.2–3.0). Since in this cohort a higher number of lost teeth paralleled an increased severity of periodontal disease at the remaining teeth, it was assumed that tooth loss reflected, in part, current or cumulative periodontal disease. In a subsequent publication, Engebretson *et al*. (2005) reported on a subsample of 203 subjects from the INVEST cohort with available panoramic radiographs. In a logistic regression model, severe bone loss was defined as a whole-mouth average bone loss of ≥50% of the root length and was associated with the presence of carotid

atherosclerotic plaque after adjustment for age, sex, hypertension, coronary artery disease (CAD), diabetes, smoking, HDL, and LDL. In addition, log-transformed mean carotid plaque thickness increased over tertiles of periodontal bone loss, suggesting a dose-dependent association. A third INVEST report (Desvarieux *et al*. 2005) included 657 patients with available dental and medical variables as described above, as well as data on the prevalence and level of ten bacterial species, assessed by checkerboard DNA–DNA hybridization (Socransky *et al*. 1994) in up to eight subgingival plaque samples per subject. In this study, "etiologic bacterial burden" was defined as the aggregate colonization per subject by *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, and *Treponema denticola*. The data revealed that IMT and white blood cell counts increased significantly over tertiles of "etiologic" periodontal bacterial burden in a fully adjusted model including age, BMI, sex, race/ethnicity, smoking, systolic blood pressure, education, diabetes, HDL, and LDL. Importantly, the association was exclusively observed for "etiologic bacteria", as increased colonization by putative pathogens of the "orange complex" or a number of health-associated bacteria was not associated with increased IMT. A similar association was observed between "etiologic" bacterial burden and both diastolic and systolic blood pressure as well as prevalent hypertension (Desvarieux *et al*. 2010).

Interestingly, serum IgG antibody levels to specific periodontal pathogens were associated with carotid IMT of ≥1 mm in an ARIC-based subject sample of 4585 participants (Beck *et al*. 2005b). The strongest association emerged when the combined titer against *Campylobacter rectus* and *Micromonas micros* was used. Similarly, a research group from Finland reported on the association between serum titers to periodontal pathogens and IMT in a sub-sample of 1023 men aged 46–64 years from the Kuopio Ischemic Heart Disease Risk Factor study (Pussinen *et al*. 2005). Incident IMT thickening, assessed 10 years post baseline in participants with no prior CHD, increased significantly across tertiles of IgA titer levels to *A. actinomycetemcomitans* and *P. gingivalis*. Lastly, a report from the INVEST study based on 430 participants followed up over a median of 3 years demonstrated that progression of carotid IMT varied inversely across quartiles of longitudinal improvement in clinical and microbial periodontal status (Desvarieux *et al*. 2013).

Associations with clinical events

Tables 23-1, 23-2, and 23-3 summarize data from selected epidemiologic studies with a sample size of at least 1000 participants that have used periodontal status as an exposure and have reported OR, hazard ratios (HR) or relative risk (RR) for clinical AVD outcomes. Table 23-1 summarizes studies focusing on CHD, CAD or CVD, Table 23-2 studies on MI or acute coronary syndrome (ACS), and Table 23-3 studies on stroke. In these studies, periodontal disease has been broadly defined using a variety of measures that include self-reported assessments of tooth loss or periodontal status; clinically and/or radiographically assessed gingival inflammation, and extent and severity of pathologic periodontal pockets or clinical attachment loss; bacterial colonization by specific periodontal species; and serum IgG and IgA antibody titers to periodontal pathogens or specific bacterial antigens. The tables largely reflect the variability of the findings across studies, with many – but clearly not all – publications reporting statistically significant associations after adjustments for co-variates and potential confounders. At least three meta-analyses have been published summarizing the association between periodontal disease and clinical cardiovascular outcomes (Janket *et al*. 2003; Mustapha *et al*. 2007; Humphrey *et al*. 2008), consistently concluding that the available evidence suggests a moderate, positive association between periodontal diseases and AVD. This conclusion was corroborated by two recent narrative reviews (Kebschull *et al*. 2010; Lockhart *et al*. 2012). Interestingly, the effect of periodontitis on AVD events appears to differ with age. As shown in two publications from the Normative Aging Study (NAS) cohort, periodontitis was more strongly associated with incident CHD (Dietrich *et al*. 2008) and stroke (Jimenez *et al*. 2009) in younger versus older (>60 years) men. Another issue that has been vigorously debated in the literature is whether the association between periodontitis and AVD events can be attributed to the confounding effect of smoking (Hujoel *et al*. 2002; Spiekerman *et al*. 2003) or may be entirely spurious (Hujoel *et al*. 2003, 2006). However, recent studies have consistently reported positive associations between periodontal infections and AVD in never smokers. For example, a Korean case–control study reported an OR of 3.3 (95% CI 1.7–6.7) for non-fatal stroke among never smokers (Sim *et al*. 2008). Finnish data from a nested case–control study observed an OR for incident stroke among male never smokers of 3.31 (95% CI 1.31–8.40), while the OR among female never smokers was 2.36 (95% CI 1.44–3.88) (Pussinen *et al*. 2007). US data obtained from the Behavioral Risk Factor Surveillance Survey including 41 891 participants from 22 states showed that, among never smokers, the respective OR for CHD among participants missing 1–5 or 6–31 teeth were 1.39 (95% CI 1.05–1.85) and 1.76 (95% CI 1.26–2.45), respectively (Okoro *et al*. 2005). Thus, although adjustment for smoking is critically important when studying the role of periodontitis on AVD outcomes, the available evidence suggests that it is wrong to conclude that smoking alone, particularly residual confounding by smoking or environmental tobacco smoke, can completely explain the reported associations in observational epidemiologic studies.

Table 23-1 Selected epidemiologic studies with sample size >1000, associating periodontal status with coronary heart disease (CHD), coronary artery disease (CAD) or cardiovascular disease (CVD).

Study	n	Country	Age range (years)[a]	Design	Exposure[b]	Outcome	Adjustments[c]	Measure of association
Beck *et al*. (2005a)	5002	USA (subset of the ARIC study)	45–64	Cross-sectional	Periodontitis (clinical) Serum IgG to 17 periodontal species	CHD	1–9	No association with clinical periodontal status OR for high vs low IgG in ever smokers: *Td* 1.7 (1.2–2.3) *Pi* 1.5 (1.1–2.0) *Co* 1.5 (1.1–2.1) *Vp* 1.7 (1.2–2.3); OR for high vs low IgG in never smokers: *Pn* 1.7 (1.1 –2.6) *Aa* 1.7 (1.2–2.7) *Co* 2.0 (1.3–3.0)
Elter *et al*. (2004)	8363	USA (ARIC)	52–75	Cross-sectional	Periodontitis (clinical) Tooth loss	CHD	5– 9, 12	OR for combined high attachment loss and tooth loss: 1.5 (1.1–2.0); OR for edentulism: 1.8 (1.4–2.4)
Holmlund *et al*. (2010)	7674	Sweden	20–89	Cohort	Tooth loss Periodontitis (clinical)	CHD and CVD mortality	1, 3, 5	*CVD mortality* HR *for* <10 teeth vs >25 teeth: 4.41 (2.47–7.85); HR for severe periodontal disease vs no disease: 1.62 (0.59–4.46); *CHD mortality* HR for <10 teeth vs >25 teeth: 7.33 (4.11–13.07) HR for severe periodontal disease vs no disease: 0.78 (0.27–2.21)
Dietrich *et al.* (2008)	1203	USA (Normative Aging Study)	21–84	Cohort	Periodontitis (clinical/radiographic)	CHD	1–10	HR for ages <60 years: Clinical: 1.94 (1.23–3.05) Radiographic: 2.12 (1.26–3.60) HR for ages ≥60 years: Clinical: 0.73 (0.45–1.19) Radiographic: 1.81 (NR)
Heitmann & Gamborg (2008)	2932	Denmark (MONICA)	30–60	Cohort	Tooth loss	Fatal/non-fatal CVD, CHD	1, 2, 4, 5, 6, 8–10	HR (5th vs 1st quintile) for CVD: 1.50 (1.02–2.19); HR for CHD: 1.31 (0.74–2.31)
Tu *et al*. (2007)	12 223	Scotland	≤39	Cohort	Tooth loss	CVD mortality	1, 3–5, 8, 9	HR for those having >9 missing teeth: 1.35 (1.03–1.77

(*continued*)

Table 23-1 (*Continued*).

Study	n	Country	Age range (years)[a]	Design	Exposure[b]	Outcome	Adjustments[c]	Measure of association
Pussinen *et al*. (2005)	1023 men	Finland (Kuopio Ischemic Heart Disease Study)	46–64	Cohort	Serum IgA and IgG to *Aa*, *Pg*	CHD	1, 4–8, 13	RR for high *Aa* IgA: 2.0 (1.2–3.3) RR for high *Pg* IgA: 2.1 (1.3–3.4)
Tuominen *et al*. (2003)	6527	Finland	30–69	Cohort	Periodontitis (clinical) Tooth loss	CVD mortality	1, 4–8	RR for tooth loss: In men: 0.9 (0.5–1.6) In women: 0.3 (0.1–1.0) RR for periodontitis: In men: 1.0 (0.6–1.6) In women: 1.5 (0.6–3.8)
Abnet *et al*. (2001)	29584	China	40–69	Cohort	Tooth loss	CVD mortality	1, 3, 5	RR: 1.28 (1.17–1.40)
Howell *et al*. (2001)	22071	USA (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	CVD mortality	1, 5, 6, 8, 9, 10, 11, 14	RR: 1.00 (0.79–1.26)
Hujoel *et al*. (2000)	8032	USA (NHANES I follow-up study)	25–74	Cohort	Periodontitis (clinical)	CHD events (mortality, hospitalization, revascularization procedure)	1–12	HR for gingivitis: 1.05 (0.88–1.26) HR for periodontitis: 1.14 (0.96–1.36)
Morrison *et al*. (1999)	10368	Canada	35–84	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 5-8	RR for severe gingivitis: 2.15 (1.25–3.2) RR for periodontitis: 1.37 (0.80–2.35) RR for edentulism: 1.90 (1.17–3.10)
Beck *et al*. (1996)	1147 men	USA	21–80	Cohort	Periodontitis (clinical/ radiographic)	Incident CHD	1, 7–9	Incidence OR for those with "high" bone loss: 1.5 (1.04–2.14) Incidence OR for those with pockets of >3 mm at all their teeth: 3.1 (1.30–7.30)
DeStefano *et al*. (1993)	9760	USA (NHANES I follow-up study)	25–74	Cohort	Periodontitis (clinical)	Incident fatal and non-fatal CHD	1–11	RR for gingivitis: 1.05 (0.88–1.26) RR for periodontitis: 1.25 (1.06–1.48); RR for edentulism: 1.23 (1.05–1.44)

[a]For cohort studies, the reported age range applies to the baseline examination.
[b]Describes how periodontitis/oral health status was assessed (clinically, radiographically, by self-reported information, by serologic assessment of titers to specific periodontal bacteria, or by assessment of oral microbial colonization).
[c]Adjustments: Numbers describe the following variables: 1, age; 2, race or ethnicity; 3, gender; 4, socioeconomic status (income and/or education); 5, smoking habits; 6, diabetes (presence or duration/HbA1c); 7, hyperlipidemia (or LDL cholesterol and/or HD-cholesterol and/or triglycerides); 8, hypertension (or systolic and/or diastolic blood pressure); body mass index or waist-to-hip ratio or obesity; 10, alcohol consumption; 11, physical activity; 12, current access to dentist; 13, fibrinogen; 14, history of CVD; 15, C-reactive protein; 16, vitamin E intake.
OR, odds ratio; RR, relative risk; HR, hazard ratio; ARIC, Atherosclerosis Risk in Communities; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; NHANES I, National Health and Nutrition Examination Survey I; *Td*, *Treponema denticola*; *Pi*, *Prevotella intermedia*; *Co*, *Capnocytophaga ochracea; Vp*, *Veillonella parvula*; *Pn*, *Prevotella nigrescens*; *Aa*, *Aggregatibacter actinomycetemcomitans*.
Adapted from Lockhart *et al*. (2012), from LWW.

Table 23-2 Selected epidemiologic studies with sample size >1000, associating periodontal status with myocardial infarction (MI) or acute coronary syndrome (ACS).

Study	n	Country	Age range (years)	Design	Exposure	Outcome	Adjustments[a]	Measure of association
Holmlund *et al.* (2006)	4254	Sweden	20–70	Cross-sectional	Periodontitis (clinical/radiographic)	Self-reported, hospital-treated MI	1, 3, 5	OR for bone loss in ages 40–60 only: 2.69 (1.12–6.46)
Buhlin *et al.* (2002)	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Self-reported MI	Unadjusted	OR for bleeding gums: 0.55 (0.22–1.36) OR for loose teeth: 0.98 (0.32–3.04) OR for deep pockets: 1.32 (0.51–3.38); OR for dentures: 1.04 (0.47–2.30)
Arbes *et al.* (1999)	5564	USA (NHANES III)	40–90	Cross-sectional	Periodontitis (clinical)	Self-reported heart attack	1–9	OR for highest versus lowest extent of attachment loss: 3.77 (1.46–9.74)
Andriankaja *et al.* (2011)	1060	USA	35–69	Case–control	Presence of six periodontal pathogens (*Pg, Tf, Pi, Cr, Fn, Es*)	MI	1, 3–8	OR for *Tf*: 1.62 (1.18–1.22) *Pi*: 1.4 (1.02–1.92)
Lund Håheim *et al.* (2008)	1173 men	Norway	48–77	Case–control	Serum IgG to *Pg, Aa, Td,* and *Tf*	Self-reported MI	5–9, 15	OR for seropositivity for any of the four titers: 1.30 (1.01–1.68)
Andriankaja *et al.* (2007)	1461	USA	35–69	Case–control	Periodontitis (clinical)	Non-fatal MI	1, 3, 5–8	OR for mean attachment loss: 1.46 (1.26–1.69)
Howell *et al.* (2001)	22 071	USA (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	Non-fatal MI	1, 5, 6, 8, 9, 10, 11, 14	RR: 1.01 (0.82-1.24)

[a] Numbers describe the variables as listed in Table 23-1.
OR, odds ratio; RR, relative risk; NHANES III, National Health and Nutrition Examination Survey III; *Pg*, *Porphyromonas gingivalis*; *Tf*, *Tannerella forsythia*; *Pi*, *Prevotella intermedia*; *Cr*, *Campylobacter rectus*; *Fn*, *Fusobacterium nucleatum*; *Es*, *Eubacterium saburreum*; *Aa*, *Aggregatibacter actinomycetemcomitans*; *Td, Treponema denticola.*
Adapted from Lockhart *et al.* (2012), from LWW.

Table 23-3 Selected epidemiologic studies with sample size >1000, associating periodontal status with stroke.

Study	n	Country	Age range (years)	Design	Exposure	Outcome	Adjustments[a]	Measure of association
Lee *et al.* (2006a)	5123	USA	60–76+	Cross-sectional	Periodontal Health Status (PHS: a composite index of periodontitis and tooth loss)	Self-reported history of stroke	1, 5, 6, 8, 10, 15	OR for PHS class 5 vs. class 1: 1.56 (0.95–2.57)
Elter *et al.* (2003)	10 906	USA	Not reported	Cross-sectional	Periodontitis (clinical) Edentulism	Ischemic stroke or transient ischemic attack	1–9, 12	OR for highest quartile of attachment loss: 1.3 (1.02–1.7) OR for edentulism: 1.4 (1.5–2.0)
Buhlin *et al.* (2002)	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Ischemic and hemorrhagic stroke	Unadjusted	OR for bleeding gums: 1.83 (0.78–4.31); OR for loose teeth: 1.83 (0.66–5.12) OR for deep pockets: 0.68 (0.22–2.05) OR for dentures: 1.81 (0.74–4.42)
Holmlund *et al.* (2010)	7674	Sweden	20–89	Cohort	Tooth loss Periodontitis (clinical)	Stroke mortality	1, 3, 5	HR for <10 teeth vs >25 teeth: 0.91 (0.24–3.49); HR for severe periodontal disease vs no disease: 1.39 (0.18–10.45)
Choe *et al.* (2009)	867 256	Korea	30–95	Cohort	Tooth loss	Ischemic and hemorrhagic stroke	1, 5–11	HR for men having ≥7 missing teeth: 1.3 (1.2, 1.4) HR for women having ≥7 missing teeth: 1.2 (1.0, 1.3)
You *et al.* (2009)	2862	USA	45–85+	Cohort	Self-reported tooth loss	Self-reported stroke	1–8, 14–15	OR for participants having ≥17 missing teeth: 1.27 (1.09, 1.49)
Tu *et al.* (2007)	12 223	Scotland	≤39	Cohort	Tooth loss	Ischemic and hemorrhagic stroke	1, 3–5, 8, 9	HR for those having >9 missing teeth:1.64 (0.96–2.80)
Abnet *et al.* (2005)	29 584	China	40–69	Cohort	Tooth loss	Fatal stroke	1, 3, 5, 8, 9	RR for those with less than the median age-specific number of teeth: 1.11 (1.01–1.23)
Joshipura *et al.* (2003)	41 380 men	USA	40–75	Cohort	Self-reported periodontitis/ tooth loss	Ischemic stroke	1, 4–11, 16	HR for men with ≤24 teeth: 1.57 (1.24–1.98) HR for men with periodontitis: 1.33 (1.03–1.70)
Wu et al. (2000a)	9962	USA (NHANES I follow-up study)	25–74	Cohort	Gingivitis Periodontitis (clinical) Edentulism	Ischemic stroke	1–10	RR for gingivitis: 1.24 (0.74–2.08) RR for periodontitis: 2.11 (1.30–3.42) RR for edentulism: 1.41 (0.96–2.06)
Howell *et al.* (2001)	22 071	USA (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	Non-fatal stroke	1, 5, 6, 8–11, 14	RR 1.10 (0.88–1.37)
Morrison *et al.* (1999)	10 368	Canada	35–84	Cohort	Gingivitis Periodontitis (clinical)	Stroke mortality	1, 3, 5–8	RR for severe gingivitis: 1.81 (0.77–4.25) RR for periodontitis: 1.63 (0.72–3.67) RR for edentulism: 1.63 (0.77–3.42)

[a]Numbers describe the variables as listed in Table 23-1.
OR, odds ratio; RR, relative risk; HR, hazard ratio; NHANES I: National Health and Nutrition Examination Survey I.
Adapted from Lockhart *et al.* (2012), from LWW.

Intervention studies

Intervention studies, in other words studies that examine the effects of periodontal therapy on AVD-related outcomes, can provide critical information on the role of periodontal infection/inflammation as a risk factor for AVD and its sequelae. Data from intervention studies are of particular importance from a public health standpoint, as they reveal whether targeting a particular exposure by means of prevention or therapy translates into tangible benefits in terms of incidence reduction of the disease in question. Ideally, the value of the interventions should be assessed using randomized, placebo-controlled clinical trials that provide the highest level of evidence and minimize bias. In the case of the periodontitis–AVD association, the design and conduct of such studies is unfortunately particularly challenging, primarily due to the extended time course of evolution of AVD, the relatively low incidence of AVD-related clinical events, which necessitates the inclusion of large subject samples in order to obtain adequate power, as well as ethical considerations related to the follow-up of untreated periodontal disease over prolonged time periods. Therefore, intervention trials conducted to date have been largely limited to the study of the effects of periodontal therapy on surrogate markers of risk for AVD or on pathways related to the pathobiology of the disease. For example, D'Aiuto *et al*. (2004b) reported on 94 systemically healthy patients with generalized severe periodontitis who received non-surgical therapy and extractions. In logistic regression analysis, the reduction of CRP levels 6 months after periodontal therapy was significantly associated with the number of extracted teeth (OR 1.4; CI 1.1–1.8) and median probing depth reduction in pockets initially of ≥5 mm (OR 4.7; CI 1.4–15.8). In subsequent publications (D'Aiuto *et al*. 2005; D'Aiuto & Tonetti, 2005), non-surgical periodontal therapy with and without adjunctive local antibiotics resulted in a reduction of median CRP levels at 2 months, with a more pronounced effect in non-smokers than smokers. Circulating interleukin-6 (IL-6) levels were significantly reduced only in the group that received adjunctive local antibiotics (intensive treatment), but no significant changes were observed in LDL and HDL cholesterol and triglyceride levels. The same group (D'Aiuto *et al*. 2006) reported 6-month data on the effect of standard versus intensive therapy. In comparison to baseline levels, a significant reduction in white blood cell counts, CRP levels, IL-6 levels, total cholesterol, LDL, and systolic blood pressure were observed in the intensive treatment group, whereas an increase in HDL levels was observed in the standard treatment group. Similarly, Taylor *et al*. (2006) reported that patients undergoing full-mouth extractions who had at least two teeth with probing depths of ≥6 mm, attachment loss and bleeding on probing, showed a significant reduction in CRP levels from 2.5 mg/L to 1.8 mg/L, and this effect was more pronounced in non-smokers. The most recent meta-analysis of intervention studies that examined the effect of periodontal therapy on hsCRP levels (Paraskevas *et al*. 2008) concluded that there is modest evidence that treatment results in a statistically significant weighted reduction of 0.50 mg/L (95% CI 0.08–0.93; $P = 0.02$). Exploring further the apparent heterogeneity in the short-term post-treatment responses in the level of serologic inflammatory markers, Behle *et al*. (2009) used a composite score ("Summary Inflammatory Score") to represent the aggregate post-treatment response to a panel of 19 individual biomarkers. These investigators demonstrated that approximately one-third and one-fourth, respectively, of the treated patients showed a marked reduction or a pronounced increase in systemic inflammation, while the remainder remained seemingly unchanged. Interestingly, periodontal therapy resulted in significant differential regulation of multiple genes expressed in peripheral blood monocytes, especially in genes related to innate immunity, apoptosis, and cell signaling, in a manner compatible with the promotion of an antiatherogenic phenotype (Papapanou *et al*. 2007). Thus, although it appears that the above studies indicate a general trend towards a periodontal treatment-induced suppression of systemic inflammation, the effects of such treatment on specific markers are not entirely consistent across studies and their sustainability over time is not convincingly established.

Another set of studies has focused on the effects of periodontal therapy on endothelial dysfunction, a marker of vascular disease (Verma *et al*. 2003). Endothelial dysfunction is defined as the reduced vasodilator capability of peripheral blood vessels and is assessed by measuring the difference in the diameter of a peripheral artery prior to and after reactive hyperemia induced through occlusion of blood flow (Celermajer *et al*. 1992). Two earlier studies established that endothelial dysfunction is more pronounced in patients with periodontitis than periodontally-healthy controls (Amar *et al*. 2003; Mercanoglu *et al*. 2004). Three small-sized, single arm intervention studies (i.e. studies that assessed the same individuals before and after periodontal therapy) have reported positive effects of periodontal therapy on endothelial dysfunction: one study involved non-surgical periodontal therapy (Mercanoglu *et al*. 2004), the second study employed adjunctive systemic antibiotics (Seinost *et al*. 2005), and the third study (Elter *et al*. 2006) provided periodontal therapy according to the principle of "full-mouth disinfection" (a treatment modality that includes full-mouth scaling and root planing in two visits within 24 hours in combination with adjunctive oral rinsing/pocket irrigation with an antiseptic solution). Likewise, a single-arm study conducted on 35 patients with mild-to-moderate periodontitis showed that non-surgical periodontal therapy resulted in diminished IMT thickness at 6 and 12 months after

treatment completion (Piconi *et al*. 2009). A larger randomized controlled trial involving a total of 120 patients with severe periodontitis, 61 of whom received full-mouth subgingival debridement completed within a single session and accompanied by extensive application of local antibiotics in all deep periodontal pockets (Tonetti *et al*. 2007), demonstrated a significant improvement in endothelium-dependent dilatation (EDD) in the treatment group at a 6-month follow-up examination. Notably, this intense intervention resulted in a transient deterioration of EDD and a significant increase in multiple inflammatory mediators in the plasma immediately after the intervention.

To date, only a single, multicenter pilot study has examined the effects of periodontal therapy on cardiac events. The Periodontitis and Vascular Events (PAVE) study (Beck *et al*. 2008; Offenbacher *et al*. 2009b) randomized patients with periodontitis and a history of severe CVD to either community care or a study protocol that consisted of oral hygiene instruction and mechanical periodontal therapy. Over a 25-month follow-up period, cardiovascular adverse events occurred with similar frequency in the community control and the periodontal treatment groups. However, the administered periodontal therapy resulted in a rather limited improvement of periodontal status at 6 months after the intervention, and these positive effects were not sustainable at the 1-year follow-up. The interpretation of the findings of this study is further complicated by the fact that a substantial proportion of the individuals randomized in the community care group did receive some form of preventive or periodontal care outside the study. Lastly, obesity appeared to nullify the ability of periodontal treatment to reduce CRP levels. Important lessons were thus learned from this pilot trial that will inform the design of future randomized controlled trials with respect to (1) the required intensity of the protocol-provided periodontal intervention in order to result in clinically and biologically meaningful and sustainable positive effects on the periodontal status; (2) the role of coexisting risk factors for AVD that may negate the treatment-induced positive modulation of systemic inflammation; and (3) the overall feasibility of the study design.

Adverse pregnancy outcomes

Definitions and biologic plausibility

Preterm infants are born prior to the completion of 37 weeks of gestation. An estimated 11–12.5% of pregnancies end in preterm birth (PTB), and this rate appears to be on the rise in several developed countries, despite significant advances in obstetric medicine and improvements in prenatal care utilization (Goldenberg & Rouse 1998; Shapiro-Mendoza & Lackritz 2012). Of particular interest are the *very preterm infants*, born prior to 32 gestational weeks, the majority of whom require neonatal intensive care due to their increased perinatal mortality, primarily due to impaired lung development and function. The overall contribution of PTB to infant mortality and morbidity is substantial and includes a number of acute and chronic disorders, including respiratory distress syndrome, cerebral palsy, pathologic heart conditions, epilepsy, blindness, and severe learning disabilities (McCormick 1985; Veen *et al*. 1991).

Preterm infants often weigh less at birth and *low birth weight* (LBW) (i.e. <2500 g) has been used as a surrogate for prematurity in cases where the exact gestational age at birth is difficult to assess. Birth weight is further classified as *very low* (<1500 g) or *moderately low* (1500–2500 g). An additional term used is "*small for gestational age*", defined as birth weight within the 10th percentile of normal weight at a particular gestational age, and may, thus, affect even full-term infants as a result of intrauterine growth retardation (Ashworth 1998).

A number of risk factors for PTB have been identified (Goldenberg *et al*. 2000). These include young maternal age (Wessel *et al*. 1996; Lao & Ho 1997; Scholl *et al*. 1988), multiple gestation (Lee *et al*. 2006b), small weight gain during pregnancy (Honest *et al*. 2005), cervical incompetence (Althuisius & Dekker 2005), smoking, alcohol, and drug abuse (Myles *et al*. 1998), black race (Kleinman & Kessel, 1987; David & Collins 1997), and a number of maternal infections (uterine track infections, bacterial vaginosis, chorioamnionitis) (Romero *et al*. 2001). Obstetric history of PTB is a robust marker of future PTB (Mutale *et al*. 1991). Importantly, approximately 50% of the variance in the incidence of PTB remains unexplained (Holbrook *et al*. 1989).

Despite the established role of genitourinary tract infections in the pathobiology of PTB, women with preterm labor do not invariably present with positive amniotic fluid cultures (Romero *et al*. 1988), leading to the hypothesis that PTB may be indirectly mediated through *distant* infections resulting in translocation of bacteria, bacterial vesicles or LPS in the systemic circulation. The possibility that periodontal infections may constitute such maternal infections that adversely influence birth outcomes was raised for the first time in the late 1980s (McGregor *et al*. 1988). Transient bacteremias occur commonly in subjects with inflamed gingiva (Ness & Perkins 1980; Kinane *et al*. 2005; Forner *et al*. 2006) and may conceivably reach the placental tissues, providing the inflammatory impetus for labor induction (Offenbacher *et al*. 1998). An interesting publication in this context by Hill (1998) reported that amniotic fluid cultures from women with vaginosis rarely contained bacteria common to the vaginal tract, but frequently harbored Fusobacteria of oral origin, which are common constituents of the periodontal microbiota. Thus, these authors proposed that oral bacteria may reach amniotic fluids and influence maternal fetal tissues via a hematogenous spread resulting in a

chorioamniotic challenge. In line with these observations, experimental evidence on the role of oral infections on pregnancy outcomes was first provided in a series of studies by Collins *et al*. (1994a, b) who demonstrated that injection of the pregnant hamster with *P. gingivalis* resulted in intrauterine growth retardation, smaller fetuses, and an increase in pro-inflammatory mediators such as IL-1β and prostaglandin E_2 (PGE_2) in the amniotic fluid. Subsequent studies in pregnant mice and rabbits (Boggess *et al*. 2005) confirmed and expanded these observations to include experimental infections by *C. rectus*.

Epidemiologic evidence

Association studies

The first study that reported an association between adverse pregnancy outcomes and poor periodontal conditions was a case–control study (Offenbacher *et al*. 1996) that included 124 mothers, of whom 93 ("cases") gave birth to children with a birth weight of <2500 g or prior to 37 weeks of gestation. Forty-six mothers who delivered infants of normal birth weight at term served as controls. Assessments included a broad range of known obstetric risk factors, such as tobacco use, drug use, alcohol consumption, level of prenatal care, parity, genitourinary infections, and nutrition. The data showed a small, albeit statistically significant, difference in attachment loss between cases and controls (3.1 versus 2.8 mm). Multivariate logistic regression models, controlling for other risk factors and co-variates, demonstrated that periodontitis, defined as ≥60% of all sites with attachment loss of ≥3 mm, conferred adjusted OR of 7.9 for preterm, LBW babies. Several case–control studies have since been published, most of which reported a positive association between periodontitis and adverse pregnancy outcomes (Offenbacher *et al*. 1996; Dasanayake *et al*. 2001; Canakci *et al*. 2004; Goepfert *et al*. 2004; Mokeem *et al*. 2004; Radnai *et al*. 2004; Jarjoura *et al*. 2005), although a number of studies failed to document an association (Davenport *et al*. 2002; Buduneli *et al*. 2005; Moore *et al*. 2005). A systematic review and meta-analysis of case–control studies (Corbella *et al*. 2012) included 17 studies and a total of 10 148 women, and reported statistically significant OR for periodontitis and both PTB (OR 1.78; 95% CI 1.58–2.01) and LBW (OR 1.82; 95% CI 1.51–2.20), although the authors cautioned that uncontrolled or inadequately reported confounders may have affected the association demonstrated by the pooled data.

Non-uniform data were also generated by cohort studies – studies that evaluated the periodontal status of pregnant women prior to the completion of the second trimester and compared prospectively the incidence of adverse pregnancy outcomes in women with and without periodontitis. In the first prospective cohort study reporting a positive relationship between periodontitis and prematurity, Jeffcoat *et al*. (2001) assessed the periodontal condition of 1313 primarily African–American pregnant women at 21–24 weeks of gestation and reported that in women with generalized periodontitis, defined as ≥90% of all sites with attachment loss of ≥3 mm, adjusted OR were 4.45, 5.28, and 7.07 for delivery prior to 37, 35, and 32 weeks of gestation. Corroborating data were reported in additional cohorts in the US (Offenbacher *et al*. 2001), Chile (Lopez *et al*. 2002a), and Switzerland (Dortbudak *et al*. 2005). Similar positive associations were reported for very preterm deliveries (Offenbacher *et al*. 2006), small-for-gestational-age infants (Boggess *et al*. 2006a), pre-eclampsia (Boggess *et al*. 2003; Contreras *et al*. 2006; Herrera *et al*. 2007; Nabet *et al*. 2010), and antepartum vaginal bleeding and risk for premature delivery prior to 35 gestational weeks (Boggess *et al*. 2006b). In contrast, four cohort studies (Romero *et al*. 2002; Holbrook *et al*., 2004; Moore *et al*. 2004; Rajapakse *et al*. 2005) failed to document such associations. Of particular interest is the study by Moore *et al*. (2004) who reported data on 3738 women recruited when presenting for an ultrasound scan at approximately 12 weeks of pregnancy. Regression analysis indicated no significant relationships between the severity of periodontal disease and either PTB or LBW, although a positive correlation was reported between poorer periodontal health and late miscarriage.

Nevertheless, a recent systematic review of all available association studies (cross-sectional, case–control, and prospective cohort studies) by Ide and Papapanou (2013) concluded that maternal periodontitis is modestly, but significantly, associated with PTB, LBW, and pre-eclampsia.

Intervention studies

Contrary to the logistical difficulties associated with the conduct of intervention studies of periodontal therapy and atherosclerosis-related outcomes described above, testing whether treatment of periodontal disease in pregnant women results in a reduction of adverse pregnancy outcomes is feasible. The first published intervention study (Mitchell-Lewis *et al*. 2001) examined a cohort of 213 young, predominantly African–American women with respect to clinical periodontal status, and analyzed the available birth outcome data for 164 women, 74 of whom received oral prophylaxis during pregnancy and 90 who received no prenatal periodontal treatment. In this cohort with a particularly high incidence of PTB/LBW of 16.5%, no differences in clinical periodontal status were observed between women with normal and adverse birth outcomes ("cases"). However, cases harbored statistically significantly higher levels of *T. forsythia* and *C. rectus* in their subgingival plaque and had consistently elevated counts for a number of species examined. Interestingly, PTB/LBW occurred in 18.9% of the women who did

Table 23-4 Intervention studies with sample size >200, examining the effect of periodontal therapy during pregnancy on adverse pregnancy outcomes.

Study	N	Country	Sample characteristics	Periodontal disease definition	Interventions	Outcomes
Lopez *et al*. (2002b)	Tx group: 200 Ctr group: 200	Chile	Low SES	≥4 teeth with PD ≥4 mm and with CAL ≥3 mm	Tx group: SRP during gestation Ctr group: SRP after delivery	RR for PLBW: 0.18 (0.05-0.6) RR for PTB: 0.19 (0.04-0.85) RR for LBW: 0.16 (0.02-1.33)
Jeffcoat *et al.* (2003)	Tx group 1: 123 Tx group 2: 120 Ctr group: 123	USA	85% African–American	>3 sites with CAL ≥ 3 mm	Tx group 1: SRP + placebo capsule Tx group 2: SRP +250 mg metronidazole for 1 week Ctr group: supragingival prophylaxis + placebo capsule	RR for PTB <37 weeks: 0.5 (0.2–1.3) RR for PTB <37 weeks: 0.2 (0.02–1.4) Adjunctive metronidazole did not improve outcomes
Michalowicz *et al.* (2006)	Tx group: 413 Ctr group: 410	USA	White: 28.6% Black: 45.2% Hispanic: 42.5%	BoP ≥35% and ≥4 teeth with PD ≥4 mm and CAL ≥2 mm	Tx group: SRP during gestation Ctr group: SRP after delivery	RR for PTB: 0.93 (0.63–1.37) RR for LBW: 0.92 (0.61–1.39) RR for SGA: 1.04 (0.68–1.58)
Gazolla *et al.* (2007)	Tx group: 266 Ctr group: 62	Brazil	White: 48.4% Black: 34.9%	Three-level classification according to PD/CAL: 1. ≥4 teeth with PD 4–5 mm and CAL 3–5–mm at the same site 2. ≥4 teeth with PD and CAL 5–7 mm at the same site 3. ≥4 teeth with PD and CAL ≥7 mm at the same site	Tx group: SRP + chlorhexidine 0.12% oral rinse twice a day during gestation Ctr group: "dropped out"	Incidence of PTB/LBW: 7.5% in Tx group 79.0% in Ctr group RR for PTB/LBW: 0.10 (0.06–0.15)
Offenbacher *et al.* (2009a)	Tx group: 903 Ctr group: 903	USA	White: 61.0% Black: 37.6%	≥3 sites with CAL ≥3 mm	Tx group: SRP during gestation Ctr group: SRP after delivery	Incidence of PTB: 13.1% in Tx group 11.5% in Ctr group RR for PTB: 1.2 (0.09–1.66) RR for IUGR: 0.80 (0.60–1.06) RR for LBW: 1.01 (0.72–1.42)
Newnham *et al*. (2009)	Tx group: 538 Ctr group: 540	Australia	White: 73.6% Asian: 16.2% Aboriginal: 4.2% African: 3.7% Hispanic: 1.1%	PD ≥4 mm at ≥12 sites	Tx group: SRP during gestation Ctr group: SRP after delivery	Incidence of PTB: 9.7% in Tx group 9.3% in Ctr group RR for PTB: 1.02 (0.91–1.15)
Macones *et al.* (2010)	Tx group: 376 Ctr group: 380	USA	Black: 87.3% Hispanic: 8.7% White: 2.5%	≥3 teeth with CAL ≥3 mm	Tx group: SRP during gestation Ctr group: supragingival prophylaxis	Incidence of PTB: 16.2% in Tx group 13.0% in Ctr group RR for PTB <37 weeks: 1.24 (0.87–1.77) RR for PTB <35 weeks: 1.56 (0.91–2.68) RR for LBW <2500 g: 1.38 (0.92–2.08)

PD, probing depth; CAL, clinical attachment loss; BoP, bleeding on probing; RR, relative risk; PTB, preterm birth; LBW, low birth weight; Tx, treatment; Ctr, control; SRP, scaling and root planing; SES, socioeconomic status.
Adapted from Xiong *et al*. (2011), from Elsevier.

not receive periodontal intervention, and in 13.5% of those who received such therapy, reflecting a substantial, although statistically non-significant, incidence reduction of approximately 30%. The small sample size in combination with the fact that the participants were not randomly assigned to the two treatment groups were important shortcomings of the study design.

Several additional intervention studies have been published since, and the key features and main findings from studies involving a sample size of >200 women are summarized in Table 23-4. Six of the seven studies assigned randomly the enrolled pregnant women with periodontitis to treatment and control groups, while the control group in the study by Gazolla *et al*. (2007) consisted of women who "dropped out" of treatment. Of note, the study by Jeffcoat *et al*. (2003) involved two "active" treatment groups, one that received scaling and root planning and a placebo pill, and a second that received adjunctive systemic metronidazole as well. Five of the seven studies, and actually the ones of higher methodological quality (Jeffcoat *et al*. 2003; Michalowicz *et al*. 2006; Offenbacher *et al*. 2009a; Newnham *et al*. 2009; Macones *et al*., 2010), failed to detect any positive effect of periodontal therapy on pregnancy outcomes, including PTB at <37 or <35 gestational weeks, or LBW of <2500 g or <1500 g. Interestingly, adjunctive use of systemic metronidazole did not enhance the effect of periodontal therapy on gestational outcomes, a finding which is in line with an earlier multicenter trial that suggested that systemic metronidazole used in the treatment of asymptomatic bacterial vaginosis does not reduce the occurrence of PTB (Carey *et al*. 2000).

Thus, despite the biologic plausibility of the link between maternal periodontal infections and adverse pregnancy outcomes, and the promising data of the early association studies, the findings summarized in Table 23-4, as well as meta-analyses presented in recent systematic reviews (Polyzos *et al*. 2010; Baccaglini 2011; Chambrone *et al*. 2011; Michalowicz *et al*. 2013), indicate that periodontal therapy during gestation does not result in improved obstetric outcomes. It must be emphasized, however, that the failure of the trials to demonstrate an effect of therapy on PTB or LBW should not be interpreted as evidence indicating that periodontal infection/inflammation is unrelated to adverse pregnancy outcomes. There are several reasons why interventions targeting a true risk factor may still fail: these may include inappropriate timing of the intervention, failure of the intervention to adequately change the level of exposure to the presumed causative/contributory factor, as well as the possibility that the risk factor may have resulted in irreversible damage that is no longer modifiable through intervention. In the case of treatment of maternal periodontitis during pregnancy, we must note that the periodontal status of the pregnant women did not improve dramatically after therapy in most studies. In addition, the transient bacteremias that are induced during therapy may counteract the potential beneficial effects of treatment. Thus, although treatment of periodontitis during gestation was shown to be safe for the mother and the fetus (Michalowicz *et al*. 2008), the second trimester of pregnancy may not be the most appropriate time for the delivery of periodontal treatment. The potential effects on obstetric outcomes of therapy delivered before conception are unknown and may be entirely different (Xiong *et al*. 2011). Likewise, the potential beneficial effects of periodontal therapy on subgroups with excessive risk for prematurity have not yet been assessed and warrant further investigation in future studies (Kim *et al*. 2012).

Diabetes mellitus

Biologic plausibility

The role of diabetes mellitus as a risk factor for periodontitis is reviewed in detail in Chapters 7 and 14. However, accumulating evidence suggests the presence of an inverse association as well, in other words, that periodontitis may affect the diabetic state. As reviewed above, periodontal infections result in an elevation of serum pro-inflammatory cytokines and prothrombotic mediators (Loos 2005; Kebschull *et al*. 2010) which, in turn, may result in insulin resistance, may adversely impact metabolic control, and, long-term, may lead or contribute to the development of diabetic complications. In an experimental animal study, ligature-induced periodontitis in Zucker fatty rats was associated with deterioration of glucose metabolism (Pontes Andersen *et al*. 2007). A study in adults with type 2 diabetes demonstrated a dose–response relationship between severity of periodontitis and plasma levels of tumor necrosis factor-alpha (TNF-α) (Engebretson *et al*. 2007), a cytokine known to promote insulin resistance (Hotamisligil *et al*. 1993; Gupta *et al*. 2005; Shoelson *et al*. 2006). Further support for a potential effect of periodontitis on the diabetic state comes from evidence that periodontal treatment in non-diabetic individuals results in a reduction of systemic inflammation (D'Aiuto *et al*. 2004a; 2006; Paraskevas *et al*. 2008). Interestingly, periodontal therapy in patients with type 2 diabetes suppressed serum TNF-α (Iwamoto *et al*. 2001), whereas treatment of periodontitis in individuals with type 1 diabetes resulted in lower TNF-α secretion by peripheral blood-derived macrophages and reduction in serum CRP and E-selectin (Lalla *et al*. 2007). A number of studies have further demonstrated that periodontal therapy can reduce circulating inflammatory mediators, such as CRP, TNF-α, IL-6, and fibrinogen, and increase the levels of adiponectin in individuals with diabetes (O'Connell *et al*. 2008; Katagiri *et al*. 2009; Matsumoto *et al*. 2009; Correa *et al*. 2010; Sun *et al*. 2010). These effects may result in improved insulin sensitivity, and eventually lead to improved glycemic control and overall diabetes outcomes.

Epidemiologic evidence

Association studies

Table 23-5 provides a summary of longitudinal studies that examined the association between baseline periodontal status and development of diabetes complications or incident diabetes. In one of the first studies that demonstrated that periodontitis entails higher risk for diabetic complications, Thorstensson *et al*. (1996) followed 39 pairs of patients with type 1 diabetes, each consisting of a person with severe periodontitis, matched with respect to age, sex, and diabetes duration with a person with no or only mild periodontal disease. After a median follow-up of 6 years, a significantly higher incidence of proteinuria and cardiovascular complications, including angina, intermittent claudication, transient ischemic attack, MI, and stroke was found in the patients with severe periodontitis. Three prospective studies of Pima Indians in the Gila River community in Arizona, a population with a high prevalence of type 2 diabetes, extended these findings. Taylor *et al*. (1996) were the first to demonstrate that severe periodontitis at baseline entailed increased risk for poor glycemic control [glycated hemoglobin A1c (HbA1c) >9%] at follow-up. Saremi *et al*. (2005) demonstrated a significantly increased adjusted relative risk for cardiorenal mortality (3.2; 95% CI 1.1–9.3) over a median follow-up of 11 years in patients with type 2 diabetes and severe periodontitis, when compared to a group comprising patients with diabetes but with no, mild or moderate periodontitis. Lastly, periodontitis and edentulism were found to predict incident microalbuminuria and end-stage renal disease in patients with type 2 diabetes (Shultis *et al*. 2007).

More recently, two cohort studies explored the association between periodontitis in diabetes-free individuals and the development of type 2 diabetes over time. The first (Demmer *et al*. 2008) used data from 9296 non-diabetic participants in NHANES I and its Epidemiologic Follow-Up study. Periodontal disease was recorded at baseline by means of a no longer utilized clinical index system (Periodontal Index), or by using tooth loss as its surrogate. In adjusted analyses, participants with severe tooth loss at baseline had an OR of 1.7 (P <0.05) for incident diabetes when compared to those least affected, and those in the upper three quintiles of the Periodontal Index had elevated OR ranging from 1.50 to 2.08, although no dose–response association could be established. Limitations of this study include the rather imprecise method of assessment of periodontitis and the lack of laboratory data to exclude undiagnosed diabetes at baseline. In contrast, no association between baseline periodontitis and incident diabetes could be demonstrated after adjustments in a 7-year prospective study of 5848 non-diabetic individuals in Japan (Ide *et al*. 2011), despite significant positive associations in the unadjusted analyses. Of note, periodontal conditions were not assessed with adequate precision in this study either.

Intervention studies

As discussed earlier, systemic inflammation promotes insulin resistance and dysregulates glycemia (Hu *et al*. 1990; Pradhan *et al*. 2001; Shoelson *et al*. 2006). Since periodontitis contributes to systemic inflammation (Kebschull *et al*. 2010), it is conceivable that treatment of periodontal infections may result in improved glycemic control. Table 23-6 summarizes the design and findings of a selection of recent intervention studies that examined the effect of periodontal therapy on the level of HbA1c, one of the key indicators of metabolic control in diabetes. As shown in Table 23-6, most of these studies have a modest sample size, have not included patients with type 1 diabetes, and have a follow-up time that ranged between 3 and 18 months. Three studies (Stewart *et al*. 2001; Kiran *et al*. 2005; Koromantzos *et al*. 2011) provided only mechanical, non-surgical periodontal therapy in the treatment arm, three studies (Promsudthi *et al*. 2005; Yun *et al*. 2007; Jones *et al*. 2007) used adjunctive systemic antibiotics, and one study (Katagiri *et al*. 2009) also included topical application of an antibiotic ointment to all deep pockets. On the other hand, a recent 6-month multicenter randomized controlled trial that included 514 participants with type 2 diabetes and periodontitis (Engebretson *et al*. 2013) showed no positive effect of scaling and root planing on HbA1c levels. Limitations of the above study include the suboptimal control of periodontal inflammation in the treatment arm, the high levels of obesity in the patient sample that may have counteracted the systemic anti-inflammatory effects of periodontal therapy, and the relatively good metabolic control of diabetes before the initiation of the intervention, with a mean HbA1c at baseline of 7.8%.

Obviously, no unanimous conclusion can be drawn from the listed studies on the ability of periodontal therapy to significantly improve metabolic control in diabetes. However, two systematic reviews (Simpson *et al*. 2010; Teeuw *et al.* 2010) that combined evidence from intervention trials concluded that there is a statistically significant effect of periodontal therapy on HbA1c levels, amounting to a reduction of 0.40% (P = 0.03 and P = 0.04, respectively). This estimate is fairly similar to the one produced by an earlier meta-analyses (0.46%) (Darré *et al*. 2008). Importantly, the magnitude of the effect appears to be significant from a clinical standpoint: Data generated by the United Kingdom Prospective Diabetes Study (Stratton *et al*. 2000) indicate a 35% reduction in the risk of microvascular complications for every percentage point decrease in HbA1c. In addition, an average 0.20% reduction in HbA1c was associated with a 10% reduction in mortality in the general population (Khaw *et al*. 2001). Additional larger clinical trials are obviously needed to confirm the validity of the findings available so far, as well as to clarify issues such as (1) the effect of periodontal therapy on metabolic

Table 23-5 Longitudinal studies examining the association between periodontal status and diabetes complications or incident diabetes.

Study	n	Country	Diabetes type	Follow-up time	Findings
Thorstensson *et al.* (1996)	39 case–control pairs matched for age, gender, and diabetes duration	Sweden	1	Median of 6 years	Significantly higher incidence of proteinuria (P <0.05), stroke (P <0.01), TIA (P <0.05), angina (P <0.001), MI (P <0.01), heart failure (P <0.01), and intermittent claudication in cases vs controls
Taylor *et al.* (1996)	88 individuals with radiographic assessments of bone loss (80 with clinical periodontal data)	USA	2	Median of 2 years	Severe periodontitis at baseline was significantly associated with increased risk for HbA1c ≥9% at follow-up, after adjustments for age, baseline level of glycemic control and complications, diabetes duration, and smoking
Saremi *et al.* (2005)	628 individuals	USA	2	Median of 11 years	Severe periodontitis at baseline had a significant effect on death from cardiorenal disease: death rate ratio 4.5 (95% CI 2.0–10.2), adjusted for age, gender, and diabetes duration; death rate ratio was 3.5 (95% CI 1.2–10.0), adjusted for age, gender, and BMI
Shultis *et al*. (2007)	529 individuals with no MAU and GFR ≥60 mL/min/1.73 m^2 at baseline	USA	2	Median of 9.4 years for MAU; 14.9 years for ESRD	Severe periodontitis at baseline was associated with a 2.1 increase in incidence of MAU (P=0.01) and a 3.5 increase in incidence of ESRD (P=0.02) when compared to no/mild periodontitis, after adjustments for age, gender, diabetes duration, BMI, and smoking
Demmer *et al.* (2008)	9269 individuals with available periodontal data at baseline	USA (NHANES I and its follow-up study)	Diabetes-free	Mean of 17 years	Among the three highest quintiles of baseline periodontitis severity, adjusted OR for incident diabetes were 2.08 (95% CI 1.51–2.87), 1.71 (1.19–2.45), and 1.50 (0.99–2.27) when compared to individuals without periodontitis
Ide *et al*. (2011)	5848 civil service officers with available periodontal data at baseline	Japan	Diabetes-free	Mean of 7.5 years	Incident diabetes was significantly associated with severe periodontitis after adjustment for age and sex (hazard ratio 1.49; 95% CI 1.03-2.14), but not after adjustment for additional variables including smoking, BMI, hypertension and triglyceride levels (hazard ratio 1.28: 95% CI 0.89-1.86)

BMI, body mass index; HbA1c, hemoglobin A1c; MAU, microalbuminuria; ESRD, end-stage renal disease; GFR, glomerular filtration rate; MI, myocardial infarction; NHANES I, First National Health and Nutrition Examination Survey; TIA, transient ischemic attack, OR, odds ratio.
Adapted from Lalla & Papapanou (2011), from Macmillan Publishers.

Table 23-6 Intervention studies examining the effect of periodontal therapy on glycemic control in diabetes.

Study	n	Country	Study type/diabetes type	Interventions	Outcomes
Stewart *et al.* (2001)	36 patients in each group (intervention and control)	USA	Controlled clinical trial Type 2 diabetes	Intervention group: SRP + extractions, whenever needed Control group: no treatment	HbA1c at 18 months: Intervention group: –1.9% Control group: –0.8 Significant difference between groups (p = 0.02)
Promsudthi *et al.* (2005)	27 patients in intervention group; 25 in control group	Thailand	Controlled clinical trial Type 2 diabetes	Intervention group: SRP + systemic doxycycline Control group: no treatment	HbA1c at 3 months: Intervention group: –0.19% in intervention group Control group: +0.12% Non-significant difference between groups ($P > 0.05$)
Kiran *et al.* (2005)	22 patients in each group (intervention and control)	Turkey	Randomized controlled trial Type 2 diabetes	Intervention group: SRP Control group: no treatment	HbA1c at 3 months: Intervention group: –0.86% Control group: +0.31% Significant difference between groups ($P = 0.033$)
Yun *et al.* (2007)	23 patients in each group (intervention and control)	China	Randomized controlled trial Type 2 diabetes	Intervention group: SRP + systemic doxycycline Control group: systemic doxycycline	HbA1c at 16 weeks: Intervention group: –0.77% Control group: –0.58% Non-significant difference between groups ($P > 0.05$)
Jones *et al.* (2007)	82 patients in intervention group; 83 in control group	USA	Randomized controlled trial Type 2 diabetes	Intervention group: SRP + systemic doxycycline Control group: "usual care"	Adjusted HbA1c at 4 months: Intervention group: –0.65% Control group: –0.51% Non-significant difference between groups ($P > 0.05$)
Katagiri *et al.* (2009)	32 patients in intervention group; 17 in control group	Japan	Randomized controlled trial Type 2 diabetes	Intervention group: SRP + topical minocycline ointment in all periodontal pockets Control group: oral hygiene instruction	HbA1c at 6 months: Intervention group: –0.14% Control group: –0.09% Non-significant difference between groups ($P > 0.05$)
Koromantzos *et al.* (2011)	30 patients in each group (intervention and control)	Greece	Randomized controlled trial Type 2 diabetes	Intervention group: SRP; Control group: supragingival debridement	HbA1c at 6 months: Intervention group: –0.72% Control group: –0.13% Significant difference between groups ($P < 0.01$)
Engebretson *et al.* (2013)	257 patients in each group (intervention and control)	USA	Randomized controlled trial Type 2 diabetes	Intervention group: SRP + chlorhexidine oral rinse for 2 weeks; supportive periodontal therapy at 3 and 6 months Control group: oral hygiene instructions at baseline, 3 and 6 months	HbA1c at 6 months: Intervention group: +0.17% Control group: +0.11% Non-significant difference between groups ($P = 0.55$)

SRP, scaling and root planing; HbA1c, hemoglobin A1c.
Adapted from Lalla & Papapanou (2011), from Macmillan Publishers.

control in type 1 diabetes patients; (2) whether the effect differs according to pretreatment levels of metabolic control and/or pretreatment severity of periodontitis and other co-morbidities; and (3) the extent to which adjunctive antibiotics account for the observed improvement in glycemic control.

Other associations

Chronic renal disease

Renal function is commonly measured by means of the glomerular filtration rate (GFR), which is estimated on the basis of an equation that incorporates the patient's serum creatinine concentration, age, sex, and race (Levey *et al*. 2006). In a healthy adult, GFR ranges between 100 and 120 mL/min/1.73 m^2 body surface area. Functional loss of renal glomeruli caused by renal interstitial disease results in the retention of toxic compounds that are normally excreted by the kidney, disturbances in blood electrolytes and acid–base balance, anemia, renal osteodystrophy secondary to hypocalcemia, hyperphosphatemia and resulting hyperparathyroidism, hypertension, and growth retardation in younger patients. Chronic kidney disease (CKD) is classified on the basis of GFR into five stages, ranging from stage 1 that signifies incipient CKD to stage 5 that represents end-stage renal disease (ESRD), a fatal condition in the absence of renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation).

Common causes of CKD include diabetes mellitus, glomerulonephritis, and chronic hypertension. As discussed earlier, the increased incidence of diabetes complications in individuals with severe periodontal disease (Thorstensson *et al*. 1996; Saremi *et al*. 2005), the evidence demonstrating an adverse effect of periodontitis on endothelial function (Amar *et al*. 2003; Tonetti *et al*. 2007), and the recently reported contributory effects of periodontitis to hypertension (Desvarieux *et al*. 2010), all support the biologic plausibility of an association between periodontitis and CKD that can be mediated by means of periodontitis-induced systemic inflammation.

The first publication suggesting an association between periodontitis and CDK was a cross-sectional analysis of data from 5537 participants in the ARIC study that showed a statistically significantly elevated OR for GFR of <60 mL/min/1.73 m^2 in individuals with either moderate or severe periodontal disease when compared to those with no periodontal disease or only gingivitis (Kshirsagar *et al*. 2005). In a more recent cross-sectional analysis of 6199 participants in the 2001–2004 NHANES study, Grubbs *et al*. (2011) defined CKD as a GFR of <60 mL/min/1.73 m^2 or a urinary albumin-to-creatinine ratio of ≥30 mg/g and reported that periodontitis was associated with a greater than two-fold higher risk of CKD. This association was only moderately attenuated after adjustments for age, sex, race/ethnicity, tobacco use, hypertension, diabetes, educational attainment, poverty index ratio, and dental care use. A dose–response relationship between periodontitis severity, incident macroalbuminuria, and ESRD was demonstrated in patients with type 2 diabetes (Shultis *et al*. 2007). Additional publications reported an association between serum IgG antibody levels to specific periodontal pathogens and impaired renal function in the ARIC (Kshirsagar *et al*. 2007b) and NHANES III datasets (Fisher *et al*. 2008). Nevertheless, several reports have failed to document an association between periodontitis and CKD, although they generally originate from limited-sized studies that specifically focus on dialysis patients (Gavalda *et al*. 1999; Castillo *et al*. 2007; Garcez *et al*. 2009; Vesterinen *et al*. 2011). Furthermore, studies carried out in patients with ESRD undergoing hemodialysis demonstrated that periodontitis was associated with hypoalbuminemia (Kshirsagar *et al*. 2007a), which is a strong predictor of death in these patients (Lowrie & Lew 1990), as well as with increased cardiovascular disease-associated mortality (Kshirsagar *et al*. 2009; Chen *et al*. 2011). Finally, a small exploratory single cohort trial suggested that non-surgical periodontal treatment in subjects with generalized chronic periodontitis may positively affect renal function as indicated by surrogate measures of GFR (Graziani *et al*. 2010).

Pulmonary infections

Emerging evidence suggests that poor oral status may influence lung function and contribute to the development of bacterial pulmonary infection (pneumonia). High-risk groups for acquisition of pneumonia of oral bacterial origin are residents of nursing homes, hospitalized individuals, as well as patients requiring mechanical ventilation due to respiratory failure. A comprehensive review of the role of periodontal infections in pneumonia in these groups was provided by Raghavendran *et al*. (2007).

In general, the pathogenesis of pneumonia involves aspiration of bacteria-containing secretions of oropharyngeal origin and inadequate clearance of the bacteria by host defense mechanisms. Frail, elderly individuals or subjects with compromised immunity are particularly susceptible, as are individuals with endotracheal tubes that may facilitate the seeding of oropharyngeal microbiota into the lower airway. Given the complexity of the microbiota associated with periodontitis (Paster *et al*. 2006), and the enhanced pathogenicity of polymicrobial inocula when compared to mono-infections in experimental pneumonia models (Kimizuka *et al*. 2003; Okuda *et al*. 2005), an association between periodontitis and pulmonary infections is plausible. Interestingly, in a prospective study of 697 80-year-old subjects in Japan (Awano *et al*., 2008), the adjusted mortality due to pneumonia over a 5-year period was approximately four times higher in individuals with ≥10 teeth with probing depth of >4 mm, than in those with fewer teeth and shallower pockets.

Finally, a number of trials have examined whether oral antimicrobial interventions may contribute to a reduction in incident pulmonary infections. These have included studies focusing on the prevention of ventilator-associated pneumonia (Pugin *et al*. 1991; Bergmans *et al*. 2001), nosocomial pneumonia (DeRiso *et al*., 1996; Fourrier *et al*. 2000; Houston *et al*. 2002; Fourrier *et al*. 2005), or pneumonia in elderly residents of nursing homes (Yoneyama *et al*. 1996, 2002). Although the studies were not uniformly successful in reducing the incidence of the respective outcomes, the data are generally supportive of the notion that oral antibacterial interventions are valuable in the control of pulmonary infections.

Concluding remarks

Somewhat provocatively, it has been stated that modern science has a tendency to recycle original discoveries made a long time ago. The notion certainly applies to some extent to the association between periodontitis and systemic diseases. Our views have certainly evolved since the times when the "focal infection" theory prevailed, and our reaction to the potential threat that oral infections may pose to general health are more measured and are geared towards prevention and anti-infective/anti-inflammatory approaches rather than indiscriminate extraction therapy. As discussed in this chapter, the proposed associations are biologically plausible, and the magnitude of the biologic effects of periodontal diseases on general health outcomes is gradually being defined. In addition, it is increasingly evident that periodontal treatment results in lower levels of systemic inflammation. Nevertheless, we cannot yet draw any conclusions on whether periodontal diseases constitute causative exposures for any of the discussed conditions, neither are there sufficient data available that demonstrate that treatment of periodontitis may prevent the incidence of specific *clinical* adverse events. Ongoing research will hopefully clarify these issues in the near future. Importantly, the studies reviewed underscore that the oral cavity is an integral part of the human body, and that "health" must encompass oral – and periodontal – health as well. Last, but certainly not least, these studies have provided a unique opportunity for oral health researchers to expand their investigative sphere, interact fruitfully with colleagues in medicine, and acquire more knowledge. Irrespective of the definitive conclusions of these research efforts, their byproducts may prove to be just as important as the elucidation of the research task *per se*.

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Chapter 24

Abscesses in the Periodontium

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Introduction

Abscesses in the periodontium are one of the main reasons patients seek emergency care in the dental clinic. They are characterized as a localized purulent inflammation present in the periodontal tissues that causes pain and swelling, and, depending on the origin of the infection, they can be associated with different symptoms. These abscesses are caused by a broad group of acute infections that may originate from the tooth and/or the periodontium.

Classification and etiology

Although defined by the general term periodontal abscesses, this group of acute periodontal conditions has been classified depending on the evolution as chronic or acute, and depending on the location as single or multiple, gingival or periodontal if occurring in the supporting periodontal tissues. A classification was proposed by Meng (1999) that included: *gingival abscesses* (in previously healthy sites, caused by impaction of foreign bodies), *periodontal abscesses* (either acute or chronic, in relation to a periodontal pocket), and *pericoronal abscesses* (in relation to a partially erupted tooth). This classification was included in the revised classification system for periodontal diseases developed by the American Academy of Periodontology International Workshop for a Classification of Periodontal Diseases in 1999, which for the first time included periodontal abscesses as an independent entity.

The most appropriate classification of periodontal abscesses, however, is the one based on etiology. Depending on the origin of the acute infectious process, two types of abscesses may occur:

1. *Periodontitis-related abscess*: the acute infection originates from bacteria present at the subgingival biofilm in a deepened periodontal pocket
2. *Non-periodontitis-related abscess*: the acute infection originates from bacteria coming from another local source, such as a foreign body impaction, or from alterations of the integrity of the root leading to bacterial colonization.

In a periodontitis patient, a periodontal abscess represents a period of active tissue breakdown and is the result of an acute exacerbation of a chronic infection residing in the periodontal tissues. The abscess formation is usually due to the marginal closure of a deep periodontal pocket that prevents proper drainage. The existence of deep, tortuous pockets and deep concavities associated with furcation lesions, therefore, favors the development of these acute conditions. This acute inflammatory process is characterized by the local accumulation of neutrophils, remnants of tissue breakdown, and pus formation. If this pus retention is not drained from the pocket, the destructive process may progress rapidly.

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

Different pathogenic mechanisms can lead to abscess formation in the *periodontium*:

- *Exacerbation of a chronic lesion*. Such abscesses may develop in a deepened periodontal pocket without any obvious external influence, and may occur in (1) an untreated periodontitis patient or (2) as a recurrent infection during supportive periodontal therapy (Silva *et al.* 2008).
- *Post-therapy periodontal abscesses*. There are various causes of abscess formation during the course of active therapy:
  - *Post-scaling periodontal abscess* (Dello Russo 1985). When these lesions occur immediately after scaling or after routine professional prophylaxis, they are usually related to the presence of small fragments of remaining calculus that obstruct the pocket entrance once the edema in the gingival tissues has receded (Dello Russo 1985; Carranza 1990). This type of abscess formation can also occur when small fragments of calculus have been forced into the deep, previously non-inflamed periodontal tissues (Dello Russo 1985).
  - *Post-surgery periodontal abscess*. When an abscess occurs immediately following periodontal surgery, it is often the result of incomplete removal of subgingival calculus or the presence of foreign bodies in the periodontal tissues, such as sutures, regenerative devices, or pieces of periodontal pack (Garrett *et al.* 1997).
  - *Post-antibiotic periodontal abscess*. Treatment with systemic antibiotics without appropriate subgingival debridement in patients with advanced periodontitis may also cause abscess formation (Helovuo & Paunio 1989; Topoll *et al.* 1990; Helovuo *et al.* 1993). In these situations, the subgingival biofilm may be partially protected from the action of the antibiotic, resulting in an acute infection that leads to inflammation and tissue destruction. Helovuo *et al.* (1993) followed up patients with untreated periodontitis who were given broad-spectrum antibiotics (penicillin, erythromycin) for non-oral reasons and reported that 42% of them developed marginal abscesses within 4 weeks of the antibiotic therapy.

Non–periodontitis-related abscess formation may also occur in relation to a periodontal pocket, but in such cases, there is always an external local factor that explains the acute inflammatory process. These include:

- A foreign body impacted in the gingival sulcus or periodontal pocket (Gillette & Van House 1980; Abrams & Kopczyk 1983), such as oral hygiene devices (toothbrush, tooth picks, etc.) (Gillette & Van House, 1980; Abrams & Kopczyk 1983), orthodontic appliances, food particles, or even pieces of nail in subjects with nail-biting habits (Sousa *et al.* 2010).
- Anatomic factors affecting the root morphology, such as invaginated roots (Chen *et al.* 1990), presence of fissures (Goose 1981), external root resorption, root tears (Haney *et al.* 1992; Ishikawa *et al.* 1996;) or iatrogenic endodontic perforations (Abrams *et al.* 1992).

Prevalence

The prevalence of periodontal abscesses was studied in emergency dental clinics (Ahl *et al.* 1986; Galego-Feal *et al.* 1996), in general dental clinics (Lewis *et al.* 1990), in periodontitis patients before treatment (Gray *et al.* 1994), and in periodontitis patients during supportive periodontal therapy (SPT) (Kaldahl *et al.* 1996; McLeod *et al.* 1997).

Among all dental conditions in need of emergency treatment, periodontal abscesses represent between 8% and 14% (Ahl *et al.* 1986; Galego-Feal *et al.* 1996). Gray *et al.* (1994) monitored periodontal patients in a military clinic and found that periodontal abscesses had a prevalence of 27.5%. In this population, 13.5% of the patients undergoing active periodontal treatment had experienced abscess formation, while untreated patients showed a higher percentage of 59.7%. McLeod *et al.* (1997) followed 114 patients in SPT and identified 42 patients (27.5%) who had suffered from acute periodontal abscesses.

Kaldahl *et al.* (1996) studied the occurrence of periodontal abscesses in a prospective longitudinal treatment study over 7 years of periodontal maintenance. In the 51 patients included, 27 abscesses were detected and of these, 23 occurred in teeth treated only by coronal scaling, while only three occurred in teeth treated by root planing and one in teeth treated with surgical therapy. Of the 27 abscesses, 16 had an initial probing pocket depth of >6 mm, while at eight sites the probing depth was 5–6 mm.

Abscesses occur more often in molar sites, which represent >50% of all sites affected by abscess formation (Smith & Davies 1986; McLeod *et al.* 1997; Herrera *et al.* 2000a). This may be due to the presence of pockets involving the furcation and the complex anatomy and root morphology of multirooted teeth. In a clinical report in Colombian patients, however, the lower anterior incisors were the most frequently affected teeth (Jaramillo *et al.* 2005).

The occurrence of a periodontal abscess is important not only because it causes acute symptoms in the patient, but also because these acute infections may influence the prognosis of the affected teeth. When abscesses develop during SPT in teeth with residual deep periodontal pockets and reduced periodontal support, this additional periodontal destruction is frequently the main indication for tooth extraction (Chace & Low 1993; McLeod *et al.* 1997).

Pathogenesis and histopathology

The periodontal abscess lesion contains bacteria, bacterial products, inflammatory cells, tissue breakdown products, and serum. The precise pathogenesis of this

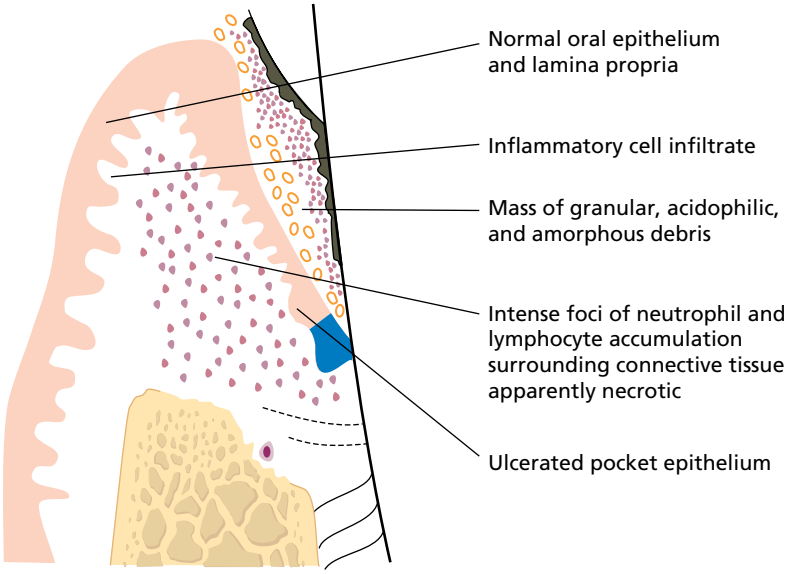

Fig. 24-1 Schematic diagram showing the pathology of a periodontal abscess.

lesion is still obscure. It is hypothesized that the occlusion of the periodontal pocket lumen, due to trauma or tissue tightening, will prevent proper drainage, resulting in the extension of the infection from the pocket into the soft tissues of the pocket wall, and the formation of the abscess. Although the invasion of bacteria into the soft tissue pocket wall could be the initiating event, it is the accumulation of leukocytes and the formation of an acute inflammatory infiltrate that causes the connective tissue destruction, encapsulation of the bacterial mass, and formation of pus. The accumulation of inflammatory cells and the resulting secretion of extracellular enzymes and inflammatory mediators, such as catabolic cytokines, is the main cause of connective tissue destruction. The bacterial load and virulence, together with the tissue resistance, will determine the course of this acute inflammatory process.

The histopathology of the abscess shows a central area filled with neutrophils, bacteria, and debris of soft tissue destruction. At a later stage, a pyogenic membrane, composed of macrophages and neutrophils, is organized to enucleate this central core. The rate of tissue destruction within the lesion will depend on the growth of bacteria inside the foci and their virulence, as well as on the local pH. An acidic environment will favor the release of lysosomal enzymes from the granulocytes and promote tissue destruction (DeWitt *et al.* 1985).

De Witt *et al.* (1985) studied biopsies sampled from 12 abscesses. These biopsies extended apically to the center of the abscess and were processed histologically. This revealed a normal oral epithelium and lamina propria, but the presence of an inflammatory cell infiltrate located laterally to the pocket epithelium. Within this infiltrate, there were accumulations of neutrophils and lymphocytes, together with tissue destruction and a mass of granular, acidophilic, debris (Fig. 24-1). Some of these biopsies were evaluated by electron microscopy, which demonstrated the presence of Gram-negative bacteria invading the pocket epithelium and the infiltrated connective tissue.

Microbiology

In review articles and textbooks it is usually cited that that purulent oral infections are polymicrobial and mainly caused by endogenous bacteria (Tabaqhali 1988). There are very few studies, however, that have investigated the specific microbiota of periodontal abscesses. Newman and Sims (1979) studied nine abscesses and found that 63.1% of the microbiota was comprised of strict anaerobes. Topoll *et al.* (1990) analyzed 20 abscesses in ten patients who had taken antibiotics prior to the study. They reported that 59.5% of the microbiota was made up of strict anaerobes. Herrera *et al.* (2000a) reported that 45.1% of the bacteria in the abscess material were anaerobes.

These studies have shown that the microbiota of periodontal abscesses does not differ from the microbiota of chronic periodontitis lesions. This microflora is polymicrobial and dominated by non-motile, Gram-negative, strict anaerobic, rod-shaped species. Among these bacteria, *Porphyromonas gingivalis* is probably the most virulent and relevant microorganism. The reported occurrence of *P. gingivalis* in periodontal abscesses ranged from 50% to 100% in bacterial culture studies (Newman & Sims 1979; van Winkelhoff *et al.* 1985; Topoll *et al.* 1990; Hafström *et al.* 1994; Herrera *et al.* 2000a; Jaramillo *et al.* 2005). Using molecular techniques, such as the polymerase chain reaction (PCR), Ashimoto *et al.* (1998) found *P. gingivalis* in all of the seven abscesses they studied. Eguchi *et al.* (2008), using a commercial molecular test (IAI-PadoTest 4.5; IAI Inc., IAI Institute, Zuchwil, Switzerland), also reported high prevalences of *P. gingivalis, Tannerella forsythia*, and *Treponema denticola*, and low prevalences of *Aggregatibacter actinomycetemcomitans*. Other anaerobic species that are usually found

include *Prevotella intermedia*, *Prevotella melaninogenica*, and *Fusobacterium nucleatum*. Spirochetes (*Treponema* spp.) are found in most cases (Ashimoto *et al.* 1998). The majority of the Gram-negative anaerobic species are non-fermentative and display moderate-to-strong proteolytic activity. Strict anaerobic, Gram-positive species frequently present in periodontal abscesses include *Parvimonas micra*, *Actinomyces* spp., and *Bifidobacterium* spp. Facultative anaerobic Gram-negative bacteria that can be isolated from periodontal abscesses include *Campylobacter* spp., *Capnocytophaga* spp., and *A. actinomycetemcomitans* (Hafström *et al.* 1994). The presence of Gram-negative enteric rods has also been reported (Jaramillo *et al.* 2005).

Diagnosis

The diagnosis of a periodontal abscess should be based on the overall evaluation and interpretation of the patient's symptomatology, together with the clinical and radiologic signs found during the oral examination (Corbet 2004).

The most frequent sign of a periodontal abscess is the presence of an ovoid elevation in the periodontal tissues along the lateral side of the root (Fig. 24-2). Abscesses located deep in the periodontium may be more difficult to identify as they may manifest as a diffuse swelling or simply a red area (Fig. 24-3), rather than a prominent swelling of the soft tissues. Another common finding is suppuration either through a fistula or, most commonly, through the pocket opening (Fig. 24-4). This suppuration may be spontaneous or occur when pressure is applied to the outer surface of the lesion.

The clinical symptomatology usually includes pain (from light discomfort to severe pain), tenderness of the gingiva, swelling, and sensitivity to percussion of the affected tooth. Other related symptoms are tooth elevation and increased tooth mobility (Fig. 24-5).

During the periodontal examination, the abscess is usually found at a site with a deep periodontal pocket. Signs associated with periodontitis such as bleeding on probing, suppuration, and sometimes increased tooth mobility are also frequently present (Smith & Davies 1986; Hafström *et al.* 1994; Herrera *et al.* 2000a). The radiographic examination may either reveal a normal appearance of the interdental bone or evident bone loss, ranging from just a widening of the periodontal ligament space to pronounced bone loss involving most of the affected root (Fig. 24-6).

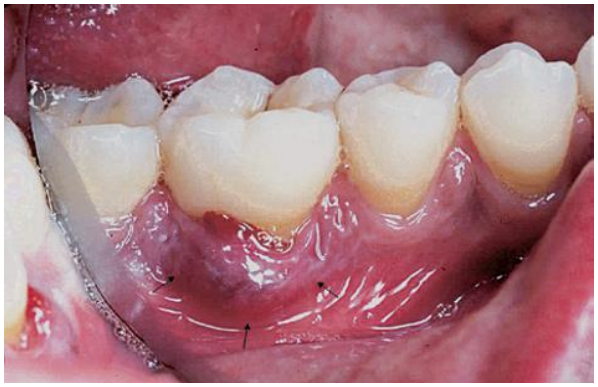

Fig. 24-2 Periodontal abscess associated with a lower right first molar. Note the association between the abscess formation and the furcation lesion in this molar. The arrows indicate the apical limits of the abscess.

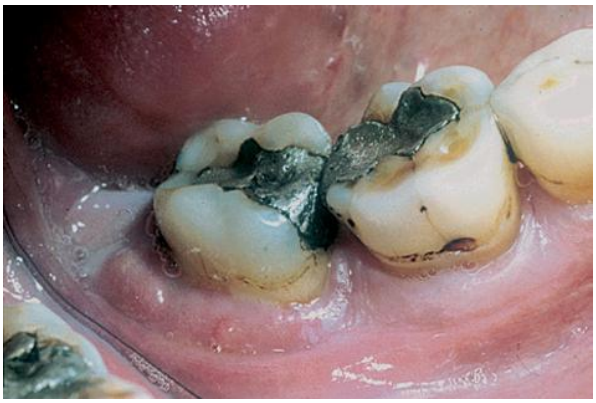

Fig. 24-3 Periodontal abscess associated with a mandibular second molar. Note the diffuse swelling affecting the entire buccal surface of the molar.

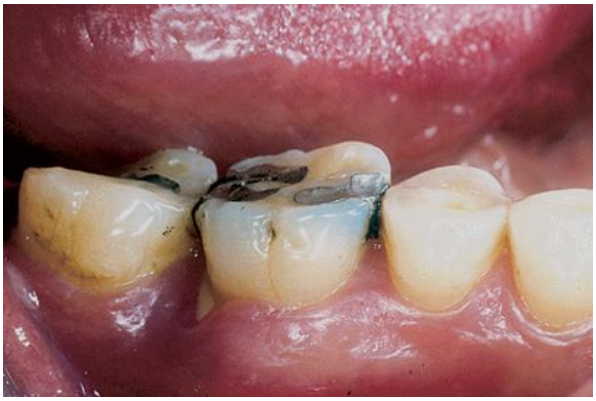

Fig. 24-4 Periodontal abscess associated with a lower right first molar. Note the spontaneous suppuration expressed through the gingival margin.

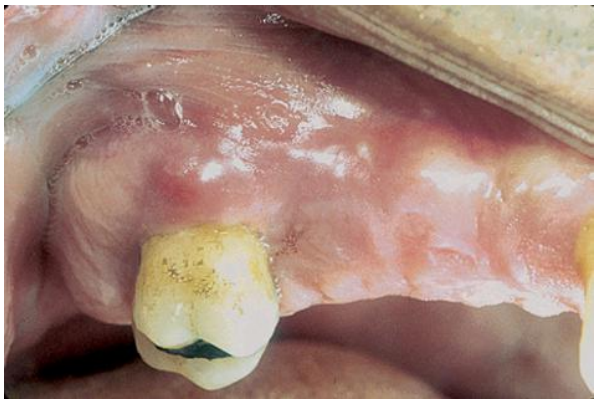

Fig. 24-5 Periodontal abscess associated with an upper right third molar. Note how this lesion is associated with tooth extrusion and mobility.

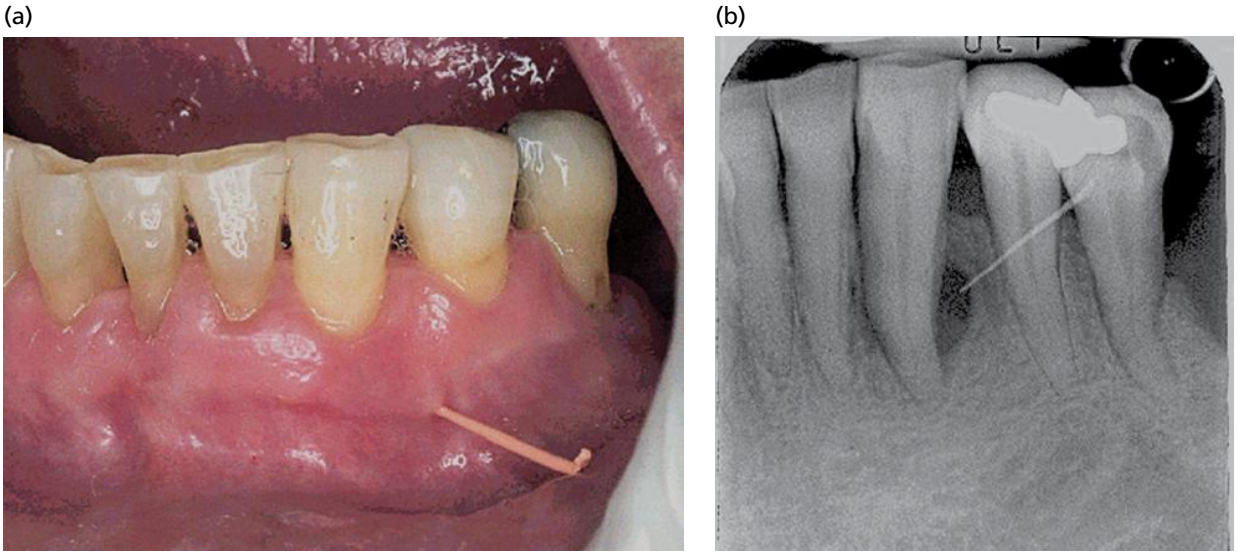

Fig. 24-6 (a) Periodontal abscess associated with a lower left canine. Note the fistulous tract opening demonstrated with a gutta-percha point. (b) Radiographic image of the lower canine shown in (a). Diagnosis of a periodontal abscess was made from the positive tooth vitality and absence of caries or restoration in the canine, and the presence of a deep periodontal pocket in the lingual aspect of this tooth.

In some patients, the occurrence of a periodontal abscess may be associated with elevated body temperature, malaise, and regional lymphadenopathy (Smith & Davies 1986; Carranza 1990; Ibbott *et al.* 1993; Herrera *et al.* 2000a). Herrera *et al.* (2000a) studied the laboratory data from patient's blood and urine taken immediately after the diagnosis of a periodontal abscess and reported that in 30% of the patients the number of blood leukocytes was elevated. The absolute number of blood neutrophils and monocytes was also elevated in 20–40% of the patients.

Differential diagnosis

The differential diagnosis of periodontal abscesses should always consider other abscesses that may occur in the oral cavity. Acute infections, such as periapical abscesses, lateral periapical cysts, vertical root fractures, and endoperiodontal lesions may have a similar appearance and symptomatology, although their etiology is different and therefore, their appropriate therapy will depend on an accurate differential diagnosis. Signs and symptoms indicating a periodontal origin include: a history of periodontal disease or previous periodontal therapy, presence of deep periodontal pockets with suppuration when probed, and, usually, tooth vitality. Radiographically, these affected teeth show crestal bone loss and frequently angular bony defects and furcation lesions. A likely periapical (endodontal) origin will include the following signs and symptoms: a history of caries or presence of advanced caries lesions, presence of restorations or root canal therapy, questionable or non-responsive to pulpal vitality tests, and presence of a sinus fistulous tract. Radiologically, there is usually evidence of a periapical radiolucency associated with a carious, restored or endodontically treated tooth. From the radiograph, the quality of the root canal therapy and the existence of endodontic files or perforations can be appreciated.

Although rare, other lesions in the oral cavity that have a similar appearance to a periodontal abscess must be considered. Parrish *et al.* (1989) described three cases of osteomyelitis in periodontitis patients, initially diagnosed as periodontal abscesses. The first sign of a tumor may be a periodontal abscess in the gingiva, such as squamous cell carcinomas (Torabinejad & Rick 1980; Kirkham *et al.* 1985; Kim *et al.* 2012), metastatic carcinomas from pancreatic origin (Selden *et al.* 1998), metastatic head and neck cancers (Elkhoury *et al.* 2004), eosinophilic granulomas diagnosed from rapid bone destruction after periodontal therapy (Girdler 1991), or a pyogenic granuloma (Panseriya & Hungund 2011). In cases where the abscess does not respond to conventional therapy, a biopsy and histopathologic diagnosis is always recommended (see also Chapter 18).

Treatment

The treatment of the periodontal abscess usually includes two stages: (1) the management of the acute lesion and (2) the appropriate treatment of the original and/or residual lesion, once the emergency situation has been controlled.

For the treatment of the acute lesion, different alternatives have been proposed: incision and drainage, scaling and root planing, periodontal surgery, and the use of different locally or systemically administered antibiotics.

Some authors have recommended a purely mechanical treatment with either surgical drainage through the pocket, or scaling and planing of the root

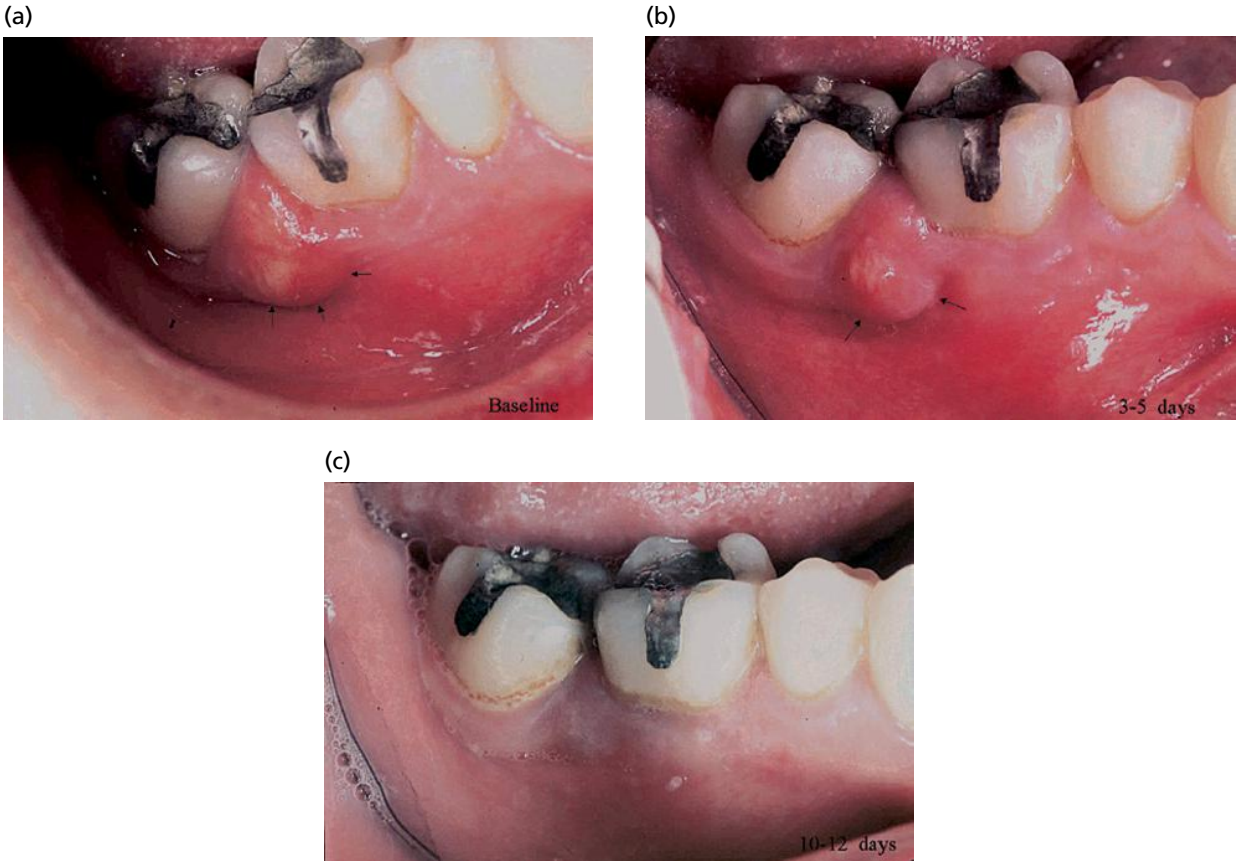

Fig. 24-7 Treatment of a periodontal abscess with systemic antibiotics (azithromycin, 500 mg for 3 days), without any mechanical therapy. (a) Baseline situation (arrows indicate apical limits of the abscess); (b) 5 days after antibiotic therapy (arrows indicate apical limits of the abscess); (c) 12 days after antibiotic therapy, just before the final periodontal instrumentation.

surface, together with compression and debridement of the soft tissue wall (Ahl *et al.* 1986; Ammons 1996). However, this mechanical therapy may cause irreversible damage to healthy periodontal tissues adjacent to the lesion, particularly when the swelling is diffuse or is associated with marked tissue tension. In order to avoid this damage to healthy periodontal tissues, other authors have recommended systemically administered antibiotics alone as the initial treatment for abscesses with marked swelling, tension, and pain. In such instances, once the acute condition has receded, mechanical debridement, including root planing, should be performed.

The clinical evidence on the efficacy of these different therapeutic approaches in the treatment of periodontal abscesses is scarce, since only a few prospective clinical studies are available. Smith and Davies (1986) studied 62 abscesses in 55 patients. Their proposed treatment included incision, drainage, and systemic metronidazole (200 mg t.i.d. for 5 days), and after the acute phase, regular periodontal treatment. Hafström *et al.* (1994) recommended supragingival debridement, together with systemic tetracycline therapy for 2 weeks, and reported good clinical outcomes when drainage and irrigation were added to the protocol. Similar good results were obtained in a controlled parallel study in which two systemic antibiotic regimens (amoxicillin/clavulanate, 500 + 125 mg t.i.d. for 8 days, and azithromycin, 500 mg once per day for 3 days) were used as the only treatment during the initial phase of therapy. This was followed by regular periodontal treatment once the acute phase had resolved (Herrera *et al.* 2000b). The study showed that the short-term clinical outcome with the use of both antibiotic regimens was successful, and the infectious process and abscess symptomatology were controlled without the use of concomitant or prior mechanical debridement (Fig. 24-7). There was a rapid reduction of pain, significant resolution of edema, redness and swelling, and the suppuration almost entirely disappeared. Periodontal outcome measurements, such as bleeding and periodontal probing depth, were also significantly reduced. Short-term microbiologic results demonstrated a reduction of the microbiota in the abscess, as well as the number of selected periodontal pathogens (Herrera *et al.* 2000b). None of these antibiotic therapies was able, however, to entirely resolve the infection, which implies that mechanical debridement, sometimes including the elevation of a surgical flap, is essential for the definitive treatment of this condition. Moreover, two different studies have provided information on the antibiotic susceptibility profiles of periodontal pathogens isolated from periodontal

Table 24-1 Antimicrobial agents that may be used in the treatment of periodontal abscesses.

Antimicrobial agent	Effective against	Properties
Penicillin V	Streptococci, some strict anaerobes	Poorly absorbed, affected by beta-lactamases, bactericidal
Amoxicillin	Most Gram-positive oral species, many Gram-negative species	Well absorbed, affected by beta-lactamases, but can be protected by clavulanic acid, bactericidal
Cephalexin	Anaerobes, streptococci, strict anaerobes, facultative	Well absorbed, affected by beta-lactamases, not effective against methicillin-resistant staphylococci, bactericidal
Ceftibuten	Gram-negative rods, broad-spectrum against Gram-negative and positive bacteria	Resistant to most β-lactamases, bactericidal, not effective against staphylococci, pseudomonads
Clindamycin	Gram-positive cocci including staphylococci	Bacteriostatic or bactericidal depending on local concentration and susceptibility of the pathogen, drug of choice in case of rapid local spread
Metronidazole	Gram-positive and Gram-negative anaerobes	Well absorbed, not effective against facultative bacteria, bactericidal
Azithromycin	Most anaerobes, Gram-positive and negative bacteria, many strict anaerobes	Good tissue concentration, bacteriostatic for most pathogens

abscesses and have reported the presence of resistant strains (Herrera *et al.* 2000b; Jaramillo *et al.* 2005). Antibiotics were locally administered in a study of 91 patients (Eguchi *et al.* 2008). These authors reported the use of irrigation with sterilized physiologic saline and 2% minocycline hydrochloride ointment (Periocline; Sunstar Inc., Osaka, Japan), compared with irrigation with sterilized physiologic saline without the local antibiotic. At 7 days, the microbiologic outcomes (frequency of detection) in the test group were better, as well as the periodontal pocket depth reduction (0.56 mm versus 0.18 mm).

Table 24-1 shows a number of different antibiotics that may be used in the treatment of a periodontal abscess. Recommended doses and regimens may differ between different countries. In principle, a high dose of the antibiotic delivered over a short period of time is recommended. If the patient is recovering appropriately, the antibiotic regimen should not be extended beyond 5 days. However, incision, drainage and debridement should always be considered as the first treatment option.

Complications

Tooth loss

Periodontal abscesses have been suggested as the main cause for tooth extraction during the phase of SPT (Chace & Low 1993). A tooth with a history of repeated abscess formation is considered to be a tooth with a questionable prognosis (Becker *et al.* 1984). In a retrospective study, 45% of teeth with periodontal abscesses during SPT were extracted (McLeod *et al.* 1997). Another retrospective study including 455 teeth with a questionable prognosis showed that 55 teeth (12%) were lost after a mean of 8.8 years, and that the main reason for tooth extraction was periodontal abscess formation (Chace & Low 1993). Smith and Davies (1986) evaluated 62 teeth with abscesses; 14 (22.6%) teeth were extracted as initial therapy, and nine (14.5%) after the acute phase. Of the 22 teeth treated and subsequently monitored, 14 had to be extracted over the following 3 years. A recent literature review suggested that an early diagnosis and an adequate therapy might be important in the management of a periodontal abscess in patients SPT, since under these conditions the prognosis of the affected tooth may not be affected (Silva *et al.* 2008).

Dissemination of the infection

A number of publications, mainly case reports, have described the spread of infection from a periodontal abscess to the systemic circulation and to different parts of the body. Two possible sources of dissemination of bacteria have been described:

- *Inside the tissues during therapy.* A case of pulmonary actinomycosis was related to the treatment of a periodontal abscess affecting a tooth that had been ultrasonically scaled 1 month earlier (Suzuki & Delisle 1984). A case of brain abscess was reported in a healthy patient with a periodontal abscess who had been treated 2 weeks earlier with drainage and curettage without systemic antibiotics. The microbiologic study of the brain lesions demonstrated, among other bacteria, *P. melaninogenica* and *Bacteroides* spp. (Gallaguer *et al.* 1981). A retrospective study on total knee arthroplasty infections (Waldman *et al.* 1997) discovered that nine of 74 infections had been previously treated for an oral infection, including the drainage of a periodontal abscess.

- *Due to bacteremia from an untreated abscess*. Cellulitis in breast cancer patients has been reported following gingivitis or the formation of a periodontal abscess (Manian 1997), due to transient bacteremia and reduced host defenses (radiation therapy and axillary dissection). A periodontal abscess was associated with the development of a cervical necrotizing fasciitis (Chan & McGurk 1997). A necrotizing cavernositis was also related to a severe periodontal infection, including three periodontal abscesses (Pearle & Wendel 1993).

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Chapter 25

Lesions of Endodontic Origin

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Introduction

In the study of the pathogenesis and causality of periodontal disease processes, lesions of endodontic origin are significant as they frequently extend to and manifest themselves in the attachment apparatus. Not only do these lesions produce signs and symptoms of inflammation in apical areas of teeth, they may also induce tissue destruction along the lateral aspects of roots and in furcations of two- and multi-rooted teeth. In either instance, the lesions are maintained by noxious elements that derive from the pulpal space along openings to the periodontal tissues. Pathways connecting the two tissue compartments include foramina at the apex and lateral ramifications termed accessory canals.

Microorganisms residing in necrotic areas of a more or less broken down pulp usually maintain these lesions. Lesions of endodontic origin may also appear or persist following endodontic treatment (hereafter referred to as post-treatment endodontic lesions). In these cases, treatment measures aimed at either preventing the establishment of a root canal infection or resolving an already manifest infection have been unsuccessful. As root canal infections have been assumed to impact both the progression of periodontitis and the potential to achieve optimal results from periodontal therapy, the first part of this chapter describes the specific features and dynamic events that are associated with lesions of the pulp and the manner by which they may interfere with the periodontium.

The fact that the periodontium and the dental pulp are anatomically interconnected implies that exchange of noxious agents also may occur in the opposite direction, that is from the external environment to the pulp. A prerequisite for this is that those communication pathways that are normally secured by healthy periodontal tissue have been uncovered. This will occur as periodontal disease advances. The lesion of the pulp that may follow may cause both pain and tissue destruction. Resorptive processes and treatment measures aimed at managing periodontal disease enhance this potential as the accompanying exposure of dentinal tubules, by loss of cementum, establishes yet another passage across the body of the tooth structure. In fact, a common complication of periodontitis and periodontal therapy is commonly termed root dentin hypersensitivity, a condition associated with the direct exposure of dentin to the oral environment (Holland *et al*. 1997; for review see Gillam & Orchardson 2006).

The second part of this chapter is concerned with the consequences for the vital pulp of root surface exposure by periodontal disease and periodontal therapy. It also covers aspects of the mechanisms and clinical management of root dentin hypersensitivity.

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Disease processes of the dental pulp

Causes

The dental pulp is normally well protected from injurious influences by an intact hard tissue encasement and by a healthy periodontium. The healthy condition of the pulp, however, is regularly challenged under clinical conditions. While some adverse influences are of minor significance and cause only negligible tissue injury and minimal discomfort to the patient, others threaten the pulp's vital functions and can result in infectious complications, with effects both locally and systemically. Lesions of the pulp may have either a direct infectious background or may be induced by non-infectious injury. Both causes will be covered here in some detail.

Of the non-infectious impairments, accidental trauma causing rupture of the neurovascular supply at the apex and major internal bleeding represents a distinct threat to the vitality of the pulp. Hence, concussions, subluxations, and various forms of tooth displacements may result in widespread ischemia leading to complete necrosis of the tissue. As the potential for tissue regeneration is slim in the fully developed tooth (Kristerson & Andreasen 1984), such pulp tissue necrosis, although not primarily infected, acts as a target for microbial invasion. The infecting microorganisms usually originate from the oral cavity. Following their penetration of cracks in the enamel and the dentinal tubules (Love 1996), multiplication in the necrotic pulp results in the development of inflammatory lesions of the periodontal tissues (Bergenholtz 1974; Sundqvist 1976).

Most pulpal conditions are initiated and maintained by infectious elements that access the pulp following loss of hard tissue integrity. Tooth destruction by caries is by far the most common source of bacterial exposure and is especially threatening when the lesion has reached the vicinity of the pulp tissue proper (see later). Also, fractures of teeth and dental restorative work bring an inherent risk for detrimental bacterial effects, should a restoration fail to seal completely the defect in the tooth substance (Bergenholtz 2000). Most risky are extensive restorations like full coverage crowns, which often require substantial sacrifice of healthy tooth tissue. Clearly in the short term, before the permanent restoration is cemented, the exposed tissue is subject to leakage of bacterial elements along the margins of the temporary restoration, especially if it adapts poorly to the remaining tooth substance. Yet, even though the pulp may have survived the initial stress of the cutting trauma and bacterial leakage, the injury induced usually results in considerable repair phenomena (scars). Such tissue changes involve hard tissue depositions and soft tissue fibrosis, which occur at the expense of vascularity and nerve tissue support (Bender & Seltzer 1972). Tissue alterations of this nature logically result in impaired immune defense function and, thus, reduce the potential for the pulp to resist future bacterial challenges.

Clinical follow-ups of teeth supplied with single crowns or included as abutments in bridge works have indeed demonstrated that pulp tissue necrosis is not a rare complication and may affect 10–20% of the treated teeth over a 10–15-year period (Bergenholtz & Nyman 1984; Karlsson 1986; Saunders & Saunders 1998; Cheung *et al*. 2005). In fact, the incidence of infected pulp necrosis has been reported to increase over the course of time (Bergenholtz & Nyman 1984; Cheung *et al*. 2005). A similar increased rate of pulpal infections has also been reported for young permanent teeth suffering traumatic ischemic injuries where pulps have been partly or completely replaced by hard tissue repair (Jacobsen & Kerekes 1977; Robertson *et al*. 1998).

Conclusion: Injurious elements that may put the vital functions of the pulp at risk include deep caries, accidental trauma, and dental restorative procedures. A single insult, such as a traumatic injury, may cause an immediate breakdown of the tissue by severing the neurovascular supply. In other instances, tissue breakdown is preceded by a direct bacterial exposure or follows tissue repair to non-infectious and infectious insults.

Progression and dynamic events

Although any injury may have serious implications for the vitality of the pulp, its ability to withstand insults, especially of a microbial nature, is far better if an intervening layer of dentin remains than if the tissue is directly exposed through the hard tissue barrier. In the former case, even a thin dentin wall, although permeable, usually allows the pulp to mount an appropriate inflammatory response to offset bacterial threats. The common observation that the pulp rarely suffers breakdown beneath a caries lesion confined to dentin is strong evidence of the pulp's defense potential (Reeves & Stanley 1966; Massler 1967; Kamal *et al*. 1997; see also review by Björndal & Mjör 2001). The mechanisms involved relate both to innate and adaptive immune responses (for reviews see Jontell *et al*. 1997; Hahn & Liewehr 2007; Farges *et al*. 2009), as well as to changes in dentin that constrict its permeability (for reviews see Pashley 1996; Bergenholtz 2000).

Experimental evidence to this effect derives from observations in both humans (Lundy & Stanley 1969; Warfvinge & Bergenholtz 1986) and experimental animals (Lervik & Mjör 1977; Warfvinge & Bergenholtz 1986; Taylor *et al*. 1988). In some of these studies, test cavities were prepared deep into dentin and were left unrestored and open to the oral environment (Lundy & Stanley 1969; Taylor *et al*. 1988). In other experimental series, similar cavities were challenged with soft carious dentin (Mjör & Tronstad 1972; Lervik & Mjör 1977) or components of dental plaque bacteria (Bergenholtz & Lindhe 1975; Warfvinge & Bergenholtz 1986). Reflecting the permeability of dentin to microbial elements, inflammatory sequelae consisting of

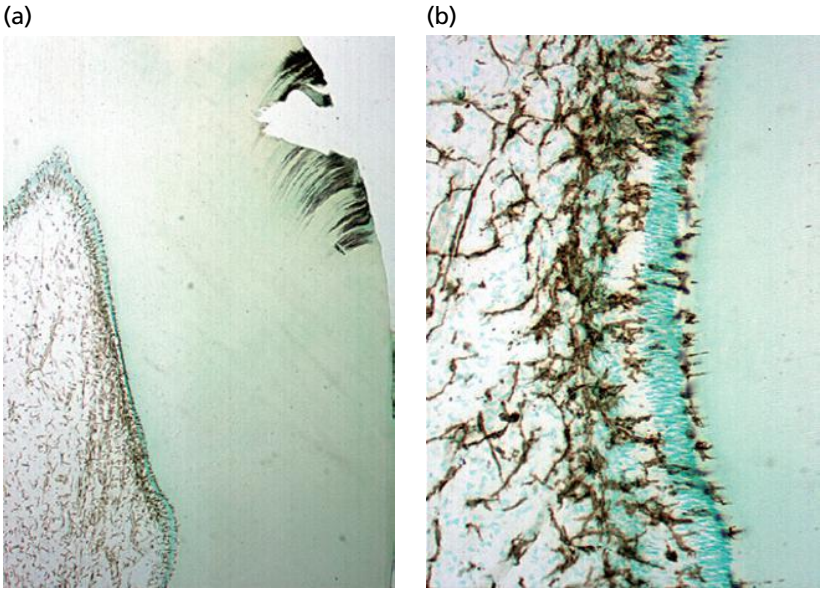


Fig. 25-1 (a) Defense response of a human dental pulp to superficial caries in dentin (defect and dark stain at upper right-hand corner) as represented by increased accumulation of Class II molecule-expressing dendritic cells. (b) Extensions of cytoplasmatic processes into the dentinal tubules are numerous. (Courtesy of T. Okiji.)

increased vascular permeability, migration of polymorphonuclear leukocytes (PMNs) (Bergenholtz & Lindhe 1975; Warfvinge & Bergenholtz 1986), and nerve fiber sproutings (Taylor *et al*. 1988) rapidly emerged in the pulp adjacent to the exposed dentinal tubules. The adaptive immune defense is also activated at very early stages as indicated by an increased presence of antigen-presenting cells, including dendritic cells, which soon appear in areas of the pulp next to both cavity preparations (Ohshima *et al*. 1995) and superficial caries (Kamal *et al*. 1997; Yoshiba *et al*. 1996) (Fig. 25-1). Yet, over the course of time, these responses subside and reparative dentin and soft tissue repair emerge, along with a reduction of immunocompetent cells and neural elements, at the site of the previous inflammatory event (Lundy & Stanley 1969; Lervik & Mjör 1977; Warfvinge & Bergenholtz 1986; Taylor *et al*. 1988; Kamal *et al*. 1997; Yoshiba *et al*. 2003). In the experiments involving unrestored human teeth (Lundy & Stanley 1969), patients experienced pain and increased sensitivity of the exposed dentin along with the initial inflammatory episode. As repair and healing progressed, the pain symptoms disappeared.

An important point is that although inflammatory responses develop rapidly and early to bacterial challenges, microorganisms *per se* are rarely able to penetrate the dentinal barrier and enter the pulp tissue, so long as it retains vital functions. Staining for bacteria in the histologic analysis of Lundy and Stanley (1969), for example, revealed that in no case, observed after 2–240 days, were organisms identified in the pulp tissue proper, while the exposed dentinal tubules were invaded to a varying extent. This finding once again demonstrates that dentin and pulp in concert are able to oppose bacterial threats.

By contrast, direct exposure of the pulp to the oral environment puts its vital functions at a clear risk as bacteria in the oral cavity now may gain direct access to the tissue. Even a minuscule exposure is critical, unless properly treated. There is little self-healing capacity that can bridge the defect as the pulp lacks epithelium and defense mechanisms may only prevent bacterial invasion of the pulpal space for a limited period of time.

Three clinical cases, displayed in Figs. 25-2, 25-3, and 25-4, demonstrate how pulpal inflammatory processes may typically develop and eventually progress to the adjoining periodontal tissues. In these cases, caries had advanced to expose the tissue at an earlier point in time.

In the first example (Fig. 25-2), an inflammatory lesion is present at the site where caries has exposed the pulpal tissue. A rather thick layer of reparative dentin has formed at the roof of the pulp chamber next to the exposure, indicating a repair response to previous irritation (Fig. 25-2a). Note that, except for the lesion area, the pulp displays normal tissue morphology with intact odontoblast layers lining the periphery of the tissue. Bacteria have accumulated (shown by blue stain in dentin) near the exposure site (Fig. 25-2c). The high magnification in Fig. 23-2d reveals numerous bacterial profiles in the pulp tissue proper as well, where they are opposed by infiltrating PMNs in the lesion area. In this particular case, the inflammatory process was clearly localized and both radiographic (Fig. 25-2a) and histologic examination gave no indication of interference with the periodontium.

A more advanced pulpal lesion is demonstrated in Fig. 25-3, where the inflammatory response to the distally located caries process in the lower molar has extended to the furcation area along a wide accessory canal (Fig. 25-3b). The alveolar bone in the furcation is resorbed and has been replaced by inflammatory tissue displaying proliferating epithelium (Fig. 25-3c). There is also an apical radiolucency at the distal root, while the apical region of the mesial root seems to be unaffected (Fig. 25-3a).

The third case (Fig. 25-4) shows necrosis of the coronal pulp following what has obviously been a

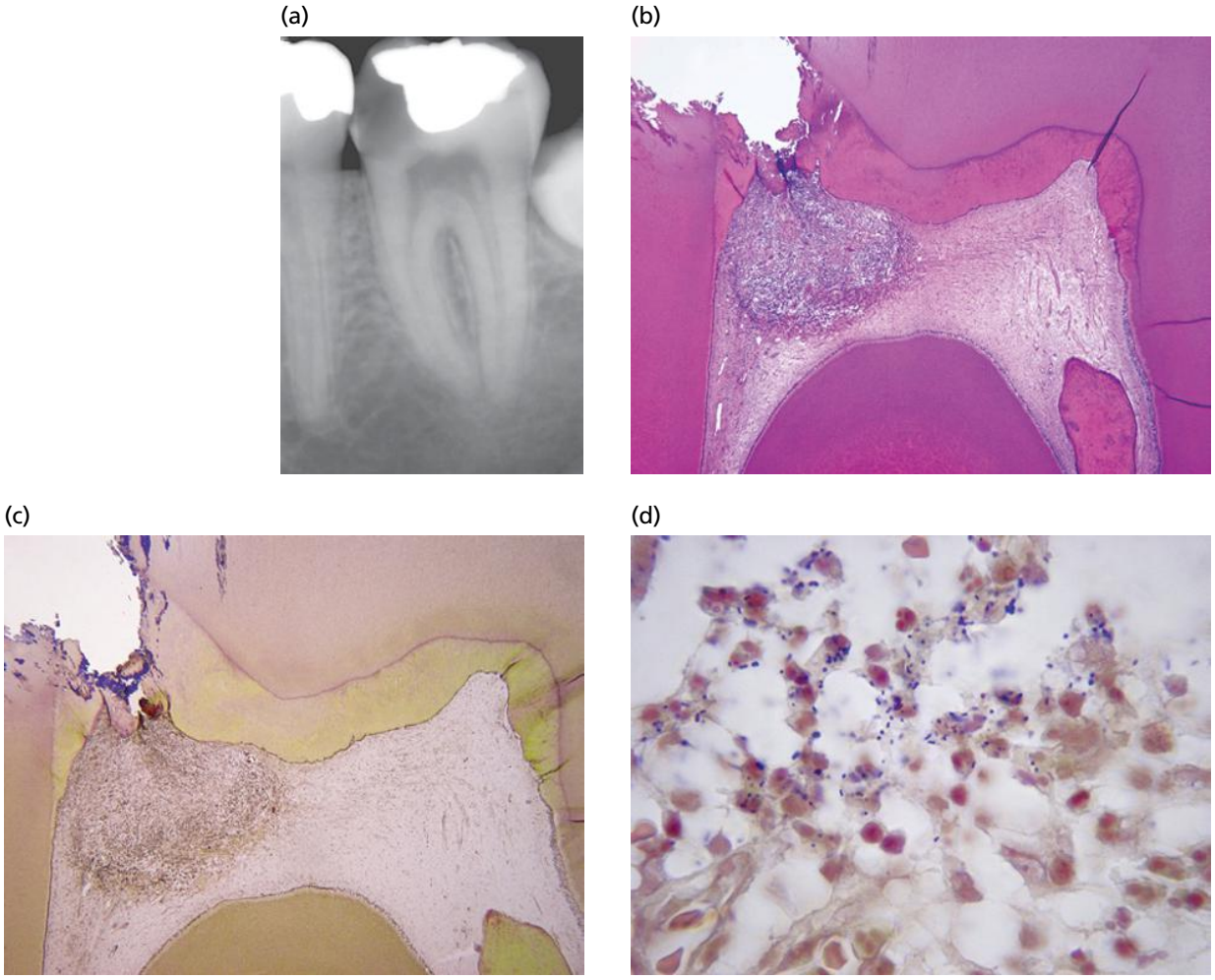


Fig. 25-2 (a) Radiograph of a second lower molar in a 30-year-old man with deep caries at the mesial aspect of the tooth. Patient suffered from typical signs of pulpitis including radiating pain and percussion sensitivity. (b) Localized inflammatory response in the pulp adjacent to the site of caries exposure. Except for hard tissue repair at the roof of the pulp chamber, the remainder of the pulp shows normal tissue structures. (c) Bacterial elements stained blue are prevalent at the exposure site as well as in the tissue lesion *per se* (d) (see also text).

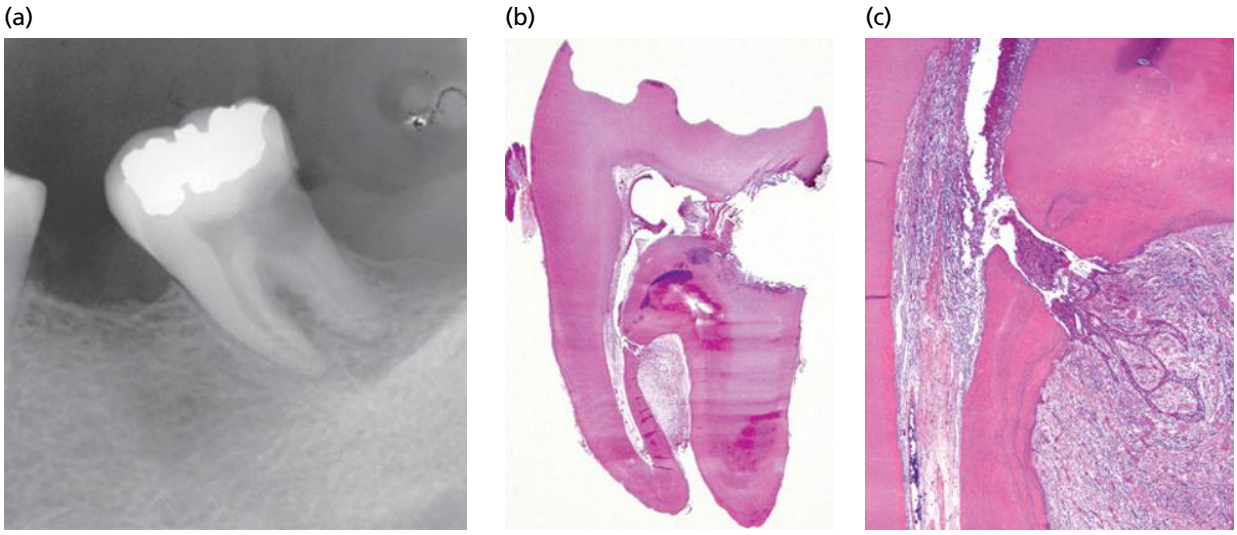


Fig. 25-3 (a) Tooth specimen of a 48-year-old man who presented with spontaneous pain, pain on mastication, percussion, and tooth mobility. (a) Deep caries lesion at the distal aspect. (b) Extensive inflammatory tissue destruction of the coronal pulp extends into the furcation along an accessory canal. (c) Higher magnification of the pulp–accessory canal–furcal area shows the expansion of the inflammatory process. Some epithelial proliferation can be seen at the exit of the accessory canal. More apically, the pulp has retained normal tissue structures. There was no clinical swelling or remarkable pocket probing depth in this case, indicating periodontal involvement (see also text).

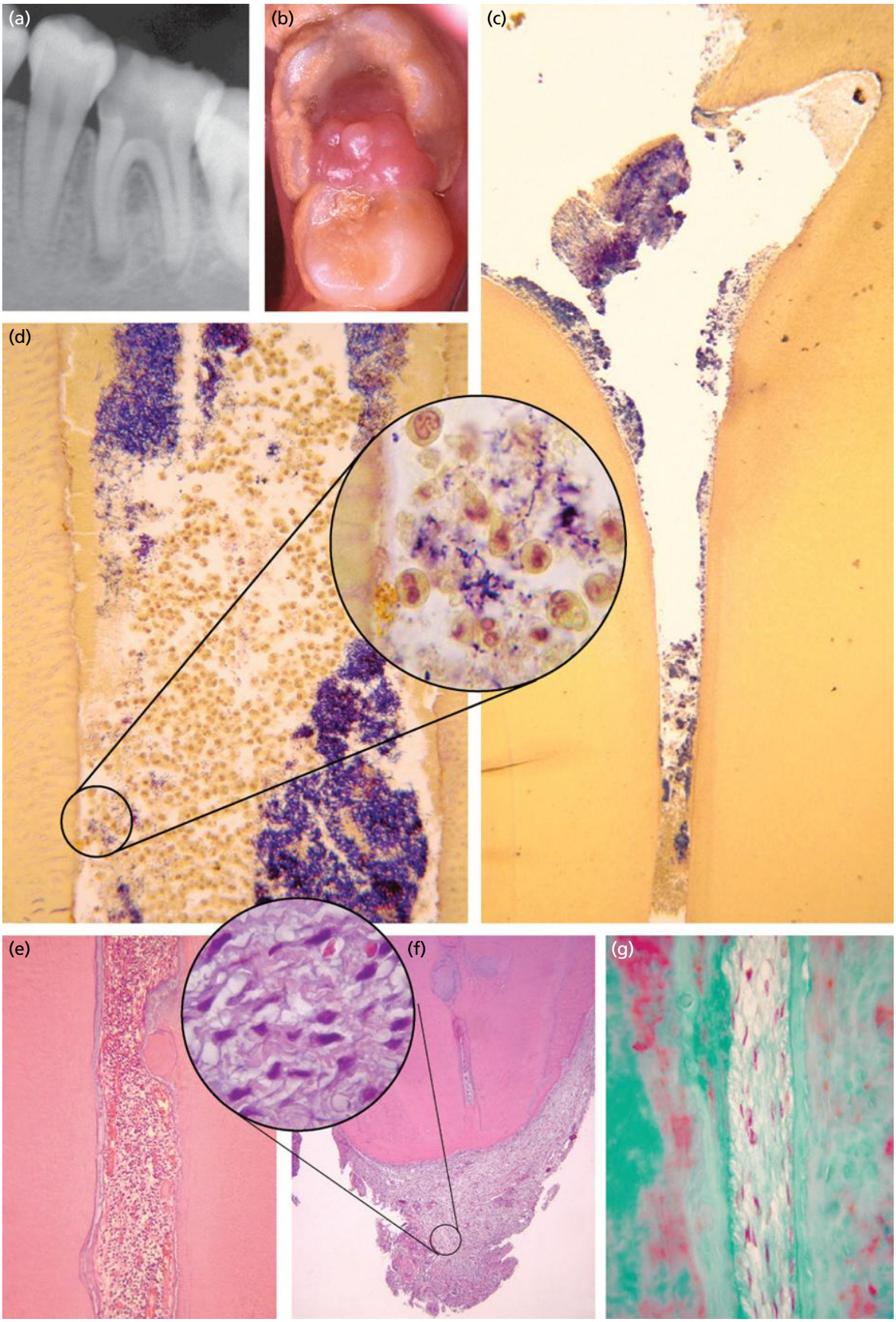


Fig. 25-4 (a–g) Tooth specimen of a 19-year-old female with extensive caries in a first lower molar that has led to partial pulp tissue breakdown, bacterial invasion, and establishment of an inflammatory defense line inside the pulpal space (see also text). (Source: Ricucci & Bergenholtz 2004. Reproduced with permission from John Wiley & Sons.)

rather long-standing caries process in a lower first molar. There are radiographic signs of apical periodontitis on both the distal and the mesial roots, and a widened periodontal ligament space in the furcation (Fig. 25-4a). At the mesial aspect of the tooth, gingival tissue has proliferated into the pulp chamber (Fig. 25-4b). Figure 25-4c displays an area of the pulpal space at the entrance to the distal root canal, where the pulp is necrotic and where bacterial cells have aggregated on the canal walls in a biofilm structure. Further down in the middle portion of the root, numerous PMNs meet the bacterial front and are engaged in phagocytosis (Fig. 25-4d and inset). In more apical portions of the canal, numerous widened blood vessels are seen along with an infiltrated pulp connective tissue (Fig. 25-4e). The most apical portion of the pulp shows normal tissue structure (Fig. 25-4g). The soft tissue attached to the root tip (Fig. 25-4f and inset), representing the apical radiolucency at the distal root in Fig. 25-4a, shows no inflammatory infiltrates.

Conclusion: The cases selected demonstrate an important function of the inflammatory defense in general that also applies to the dental pulp, which is to confine infectious elements and limit spread to other body compartments. The cases also demonstrate that a pulpal lesion has its prime focus directed at the source of the bacterial exposure. Hence, it is only following extension due to breakdown of the pulp and advancement of the bacterial front that periodontal tissue involvement is imminent. In some cases, this may occur at a rather early stage of the pulp tissue lesion, if an accessory canal becomes involved and connects with the marginal periodontium, such as in the case displayed in Fig. 25-3. In the absence of patent accessory canals, extensive breakdown of the pulp is first required before periodontal tissue lesions may become evident.

Accessory canals

Accessory canals are lateral ramifications off the root canal system that connect the neurovascular system of the pulp with that of the periodontal ligament. Such anastomoses are formed during the early phases of tooth development, but may become blocked or reduced in width during the completion of root formation. Patent communications of varying sizes, numbers, and locations, however, may remain in the fully developed tooth and serve as additional pathways for the neurovascular supply of the pulp beyond that of the main apical foramen.

Accessory canals can be observed in all groups of teeth. In fact, careful examinations of large numbers of extracted teeth, rendered transparent and injected with contrasting medium in the pulp chamber to allow three-dimensional visualization, have revealed accessory canals in cervical and middle root areas as well as in the apical root portions (de Deus 1975; Vertucci 1984). Clearly, the majority is found apically, whereas the prevalence tapers off in the middle and cervical root segments (de Deus 1975; Vertucci 1984). In a study of 1140 extracted human teeth from adult subjects, de Deus (1975) reported accessory canals in 27% of the examined teeth. These canals were distributed at various levels of the root (Fig. 25-5). Yet, in a study where teeth were examined in serial sections by histology, the frequency of accessory canals was found to be considerably higher. Investigating a sample of 493 teeth, Ricucci & Siqueira (2010b) observed accessory canals and/or apical ramifications at a rate of 75%. The high prevalence in this study can be explained by the ability of histology to detect even the finest ramifications, which may escape detection in teeth cleared and injected with disclosing solutions.

Molars harbor accessory canals more frequently than premolars and anterior teeth (Ricucci & Siqueira 2010b). Patent canals are especially common in the furcation areas, where they have been found in between 20% and 80% of examined teeth (Lowman *et al*. 1973; Vertucci & Williams 1974; Gutmann 1978; Vertucci 1984; Ricucci & Siqueira 2010b). Vertucci (2005) has distinguished different directions of entry by which accessory canals enter the furcation of mandibular molars. In some cases they run more or less vertically from the pulpal chamber. They may also extend off either root canal in a horizontal direction; 80% derive from the distal root canal (Vertucci 2005) (Fig. 25-6).

When accessory canals do occur, the potential for dissemination of inflammatogenic elements from a diseased pulp to the periodontium is obvious. There is no documentation yet available to indicate how often such lesions develop. Although clinical observations demonstrate occurrence (Figs. 25-3, 25-7, 25-8, 25-9), the rate at which endodontic lesions appear in the marginal periodontium from accessory and furcation canals seems to be low, as indicated by the lack of reports of this being a significant clinical problem. It is to be expected that the wider the accessory canals, the greater is the likelihood for overt lesions to develop. Diameters of furcation canals in mandibular molars, for example, have been reported to vary from just a few micrometers to 720 μm (Vertucci 2005). Consequently, thin accessory canals, with the potential to mediate only release of some infectious elements, may cause no more than a minor periodontal reaction that goes clinically undetected.

In the discussion of the extent to which accessory canals contribute to endodontic lesions in the periodontium, it is important to recognize the events that may occur in these spaces. Histologic observations of teeth with diseased pulps have demonstrated that the tissue therein will reflect the condition of the pulp in the main canal (Langeland 1987; Ricucci & Siqueira 2010b). Thus, it will remain

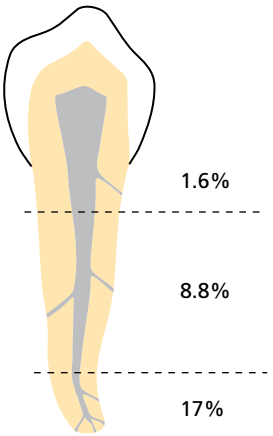


Fig. 25-5 Frequency of accessory canals at different levels of the root. Observations were made after teeth had been rendered transparent and the root canal system revealed with India ink. The percentages given for the coronal portion include those of bi- and tri-furcations of two- and multi-rooted teeth. (Data are average values from de Deus 1975.)

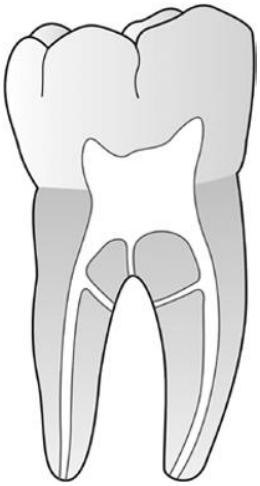


Fig. 25-6 Furcal canals of two- and multi-rooted teeth, when present, may extend into the periodontium from the pulpal space either in a horizontal or vertical direction or both. (Adapted from Vertucci 2005, with permission from John Wiley & Sons.)

vital and functional if this is also the case for the pulp in the main canal. Similarly, it may be inflamed if the adjacent area of the pulp is inflamed, and partially or totally necrotic if the pulp in the main canal is necrotic. In the latter case, inflammatory tissue may partly fill the ramification with bacterial organisms colonizing the pulpal portion of it (Fig. 25-9). Also, the entire ramification lumen may be clogged with bacteria

Subsequent to breakdown of the attachment apparatus in periodontitis, the neurovascular supply of the pulp along the accessory canals will certainly be severed as well. The extent to which the pulp will become critically inflamed concomitantly has been the subject of some controversy. While pulpal lesions of limited extension have been observed in teeth with periodontitis (Rubach & Mitchell 1965), possibly accompanied by symptoms of pulpitis, the pulp appears unlikely to succumb unless the subgingival biofilm has reached the vicinity of the main apical foramen (see later).

Conclusion: Although accessory canals do occur, most teeth seem to lack wide enough accessory canals to sustain periodontal tissue lesions in the cervical and middle root regions. This fact may explain why pulpal inflammatory lesions extending to the marginal periodontium are rarely seen. Most often they become centered on the root apices only. When present with a diameter similar to that of the apical foramen, accessory canals can certainly mediate lesions of endodontic origin in the marginal periodontium. In endodontically treated teeth, iatrogenic root perforations, carried out in conjunction with root canal instrumentation or post preparations, may serve as yet another pathway for dissemination of noxious elements to the periodontium (see Chapter 41).

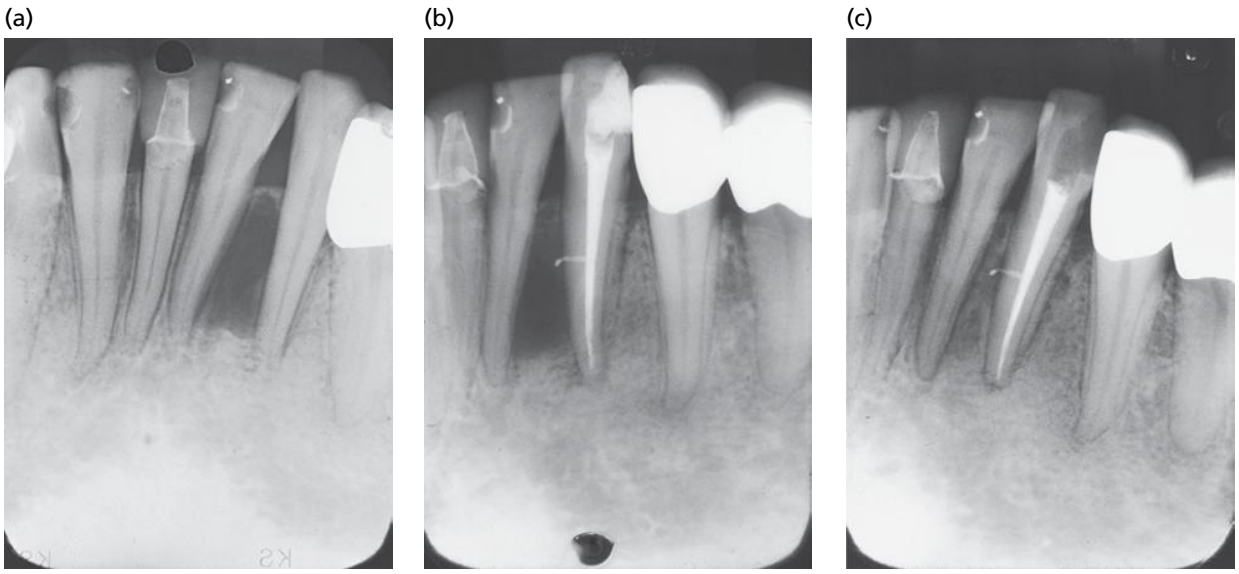


Fig. 25-7 (a) Lateral, alveolar bone destruction is observed between the roots of teeth 31 and 32. (b) Lesion in this case turned out to be associated with an accessory canal (filled in conjunction with the root filling procedure) emanating from an infected necrotic pulp in tooth 32. (c) Two-year recall of the endodontic treatment shows near complete resolution of the bone lesion. (Courtesy of C. Jacobsson.)

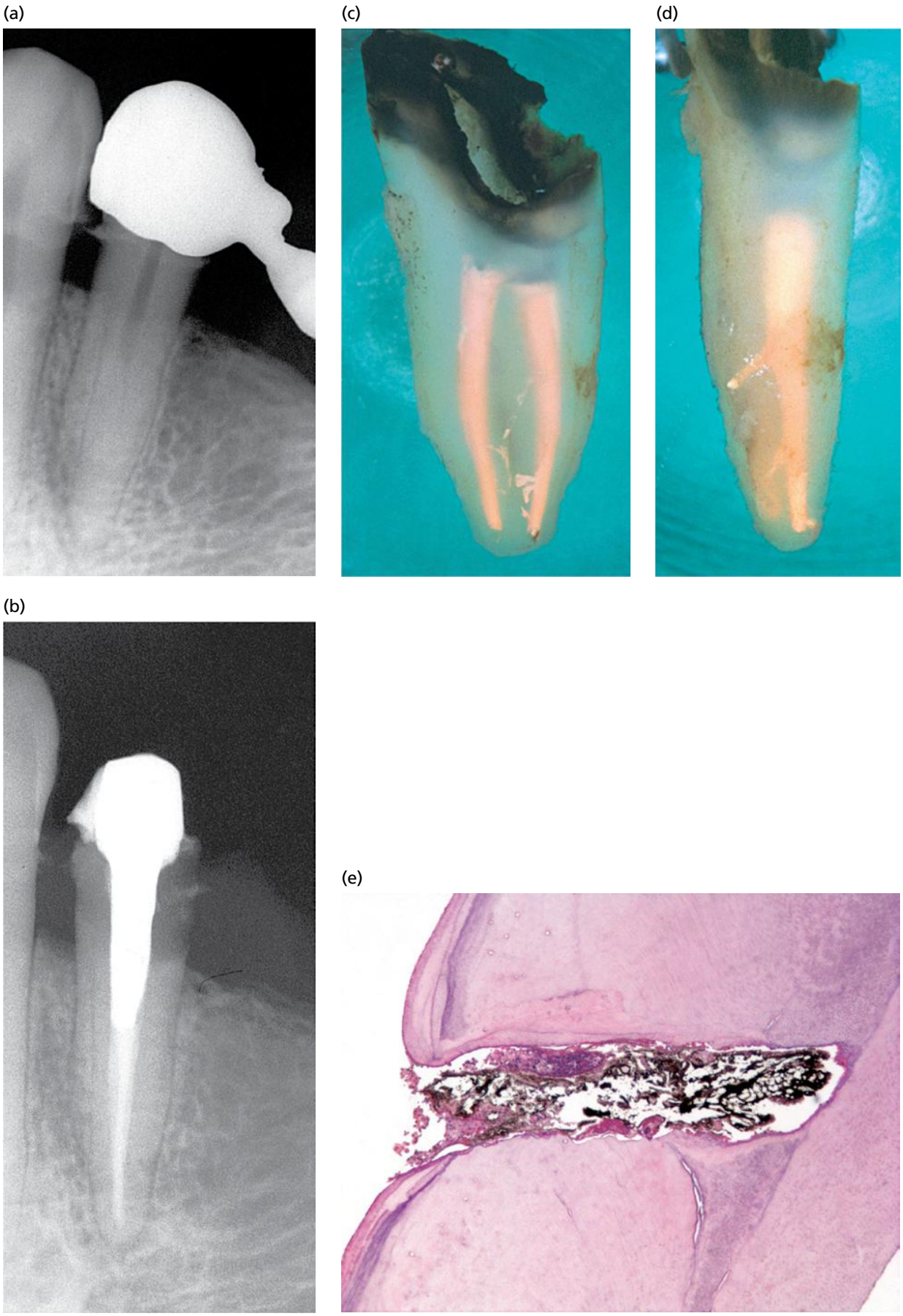


Fig. 25-8 Radiographs of a lower premolar molar (a) prior to endodontic treatment, (b) prior to extraction due to extensive caries 11 years after endodontic treatment. Note that there is no bone lesion in the periodontium. (c, d) Cleared specimens show numerous accessory canals filled with root filling material. (e) Histologic section of an accessory canal only partially filled with root filling material (stained black). Inflammatory tissue elements are interspersed.

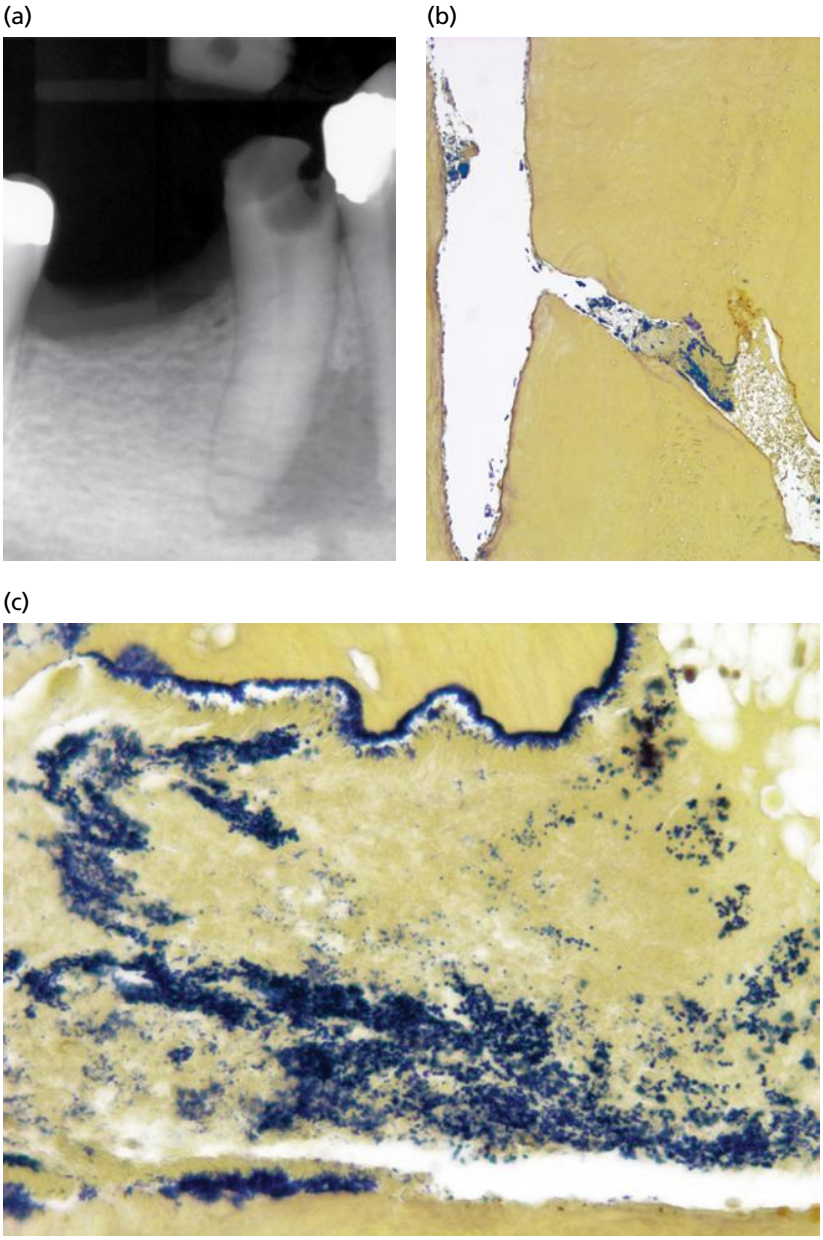


Fig. 25-9 (a) Non-restorable mandibular second premolar with a necrotic pulp and a large radiolucency located on the mesial aspect of the root. Patient had a history of several pain episodes and severe swellings. (b) Longitudinal section passing through the main canal, encompassing a lateral canal at the transition between the apical and the middle third of the root. A bacterial biofilm fills the pulpal half of the accessory canal. (c) High power view of the accessory canal content featuring amorphous necrotic debris heavily colonized with stainable bacteria. Note the adherence of the biofilm to the dentinal walls. (Source: Siqueira & Ricucci 2010. Reproduced with permission from John Wiley & Sons.)

Periodontal tissue lesions to primary root canal infection

The ultimate outcome of an inflammatory breakdown of the pulp is microbial takeover of the pulpal space (primary root canal infection) (Fig. 25-10). As host defense mechanisms are unable to reach far into root canals of necrotic pulps in order to combat the infection and pave the way for regeneration of pulpal tissue, an inflammatory defense zone is established in the periodontal tissues at the exits of accessory canals and apical foramina. Hence, lesions of this nature remain as chronic processes unless treated. Because the inflammatory process most frequently becomes positioned near root apices, the term apical periodontitis is commonly employed. As lesions may also develop along the lateral aspects of roots, the expression endodontic lesion will be used throughout this chapter to denote a periodontal lesion in any position that is sustained by noxious elements of endodontic origin.

Features of the microbiota

The bacterial species that are able to initiate and maintain primary endodontic lesions have been studied in great detail over the years, primarily by sampling infected root canals followed by laboratory processing and phenotypic identification. The

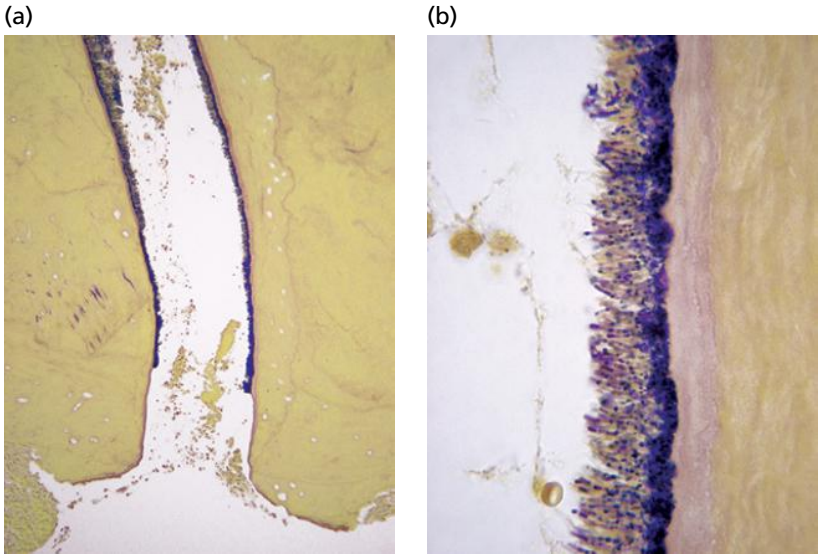


Fig. 25-10 (a) Tooth specimen with complete absence of pulp tissue. (b) Filaments and coccoid organisms are attached in a biofilm to the root canal walls. (Source: D. Ricucci, published in Svensäter & Bergenholtz 2004, reproduced with permission from John Wiley & Sons.)

purpose of such studies has been to identify organisms that are prevalent and which can be linked to more or less aggressive forms of apical periodontitis. Culture studies, especially those using techniques for isolation, cultivation, and identification of anaerobic bacteria, were of paramount importance to establish the infectious etiology of endodontic lesions. They revealed anaerobic oral bacteria as the main candidate pathogens associated with these lesions (Möller 1966; Bergenholtz 1974; Sundqvist 1976). In recent years, molecular identification methods, including polymerase chain reaction (PCR)-based and DNA hybridization methods, have greatly impacted the knowledge of the bacterial diversity in primary endodontic infections (Siqueira & Rôças 2014). In fact, the microbiota shows features similar to those of deep periodontal pockets as disclosed by culture and molecular studies (Kerekes & Olsen 1990; Siqueira & Rôças 2009b). The primary endodontic infections are characterized by a mixed community dominated by anaerobic bacteria, with a mean of 10–20 species/phylotypes per individual canal (Munson *et al.* 2002; Siqueira *et al.* 2004; Siqueira & Rôças 2005; Rôças & Siqueira 2008). A single infected canal may be colonized by 10^3–10^8 bacterial cells (Sundqvist 1976; Vianna *et al.* 2006b; Siqueira *et al.* 2007; Blome *et al.* 2008). The radiographic size of the endodontic lesion is directly proportional to the bacterial density and diversity in the root canal, that is the larger the lesion the more complex the microbiota (Sundqvist 1976; Rôças & Siqueira 2008).

Bacterial species/phylotypes frequently detected in primary infections by culture or molecular methods or both belong to diverse genera of Gram-negative (*Fusobacterium*, *Dialister*, *Porphyromonas*, *Prevotella*, *Tannerella*, and *Treponema*) and Gram-positive (*Parvimonas*, *Filifactor*, *Pseudoramibacter*, *Olsenella, Actinomyces*, *Peptostreptococcus, Streptococcus*, *Propionibacterium*, and *Eubacterium*) bacteria (Sundqvist 1976, 1992; Gomes *et al.* 1996; Siqueira *et al.* 2000; Fouad *et al.* 2002; Khemaleelakul *et al.* 2002; Munson *et al.* 2002; Foschi *et al.* 2005; Saito *et al.* 2006; Sakamoto *et al.* 2006; Rôças & Siqueira 2008; Siqueira & Rôças 2009a; Ribeiro *et al.* 2011). The pathogens implicated in periodontitis, such as *Tannerella forsythia, Porphyromonas gingivalis*, and *Treponema denticola,* have also been proposed as candidate pathogens in primary root canal infections (Gomes *et al.* 2007; Rôças *et al.* 2001). However, their association in trio, forming the so-called red complex, does not seem to be as important as it is in the pathogenesis of periodontitis (Fig. 25-11). *Aggregatibacter actinomycetemcomitans*, another important periodontal pathogen, has not been consistently detected in endodontic infections (Siqueira & Rôças 2009b), which suggests that the milieu of the necrotic root canal is not conducive to the establishment of this species.

Molecular studies have shown that about one-half of the bacterial species represent as yet uncultivated and uncharacterized bacteria (Ribeiro *et al.* 2011; Sakamoto *et al.* 2006). It is therefore reasonable to assume that several of these unrecognized bacteria participate in the pathogenesis of different forms of endodontic lesions. Yet, bacterial community profiling analyses have demonstrated a great interindividual variability in terms of species composition regardless of clinical disease condition (Siqueira *et al.* 2004; Machado de Oliveira *et al.* 2007; Li *et al.* 2010; Santos *et al.* 2011; Hong *et al.* 2013), indicating a heterogeneous etiology for endodontic lesions. A geography-related pattern in community profiles also seems to exist (Machado de Oliveira *et al.* 2007; Siqueira *et al.* 2008).

Endodontic lesions may present as symptomatic infections. One example is the acute apical abscess, which typically is characterized by intense pain and intraoral as well as facial swellings (see Chapter 41). While the infection often is confined to the root canal space, it may also reach the periapical tissues and, in abscessed cases, even spread to anatomical compartments of the head, neck, and throat. The microbiota involved with these abscesses is mixed

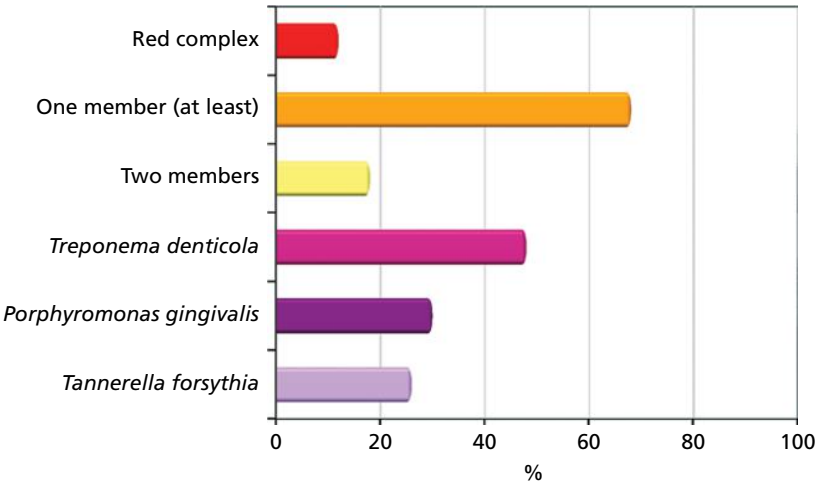


Fig. 25-11 Distribution of red complex bacteria in 50 cases of necrotic pulps with periradicular pathosis. (Data from Rôças *et al*. 2001.)

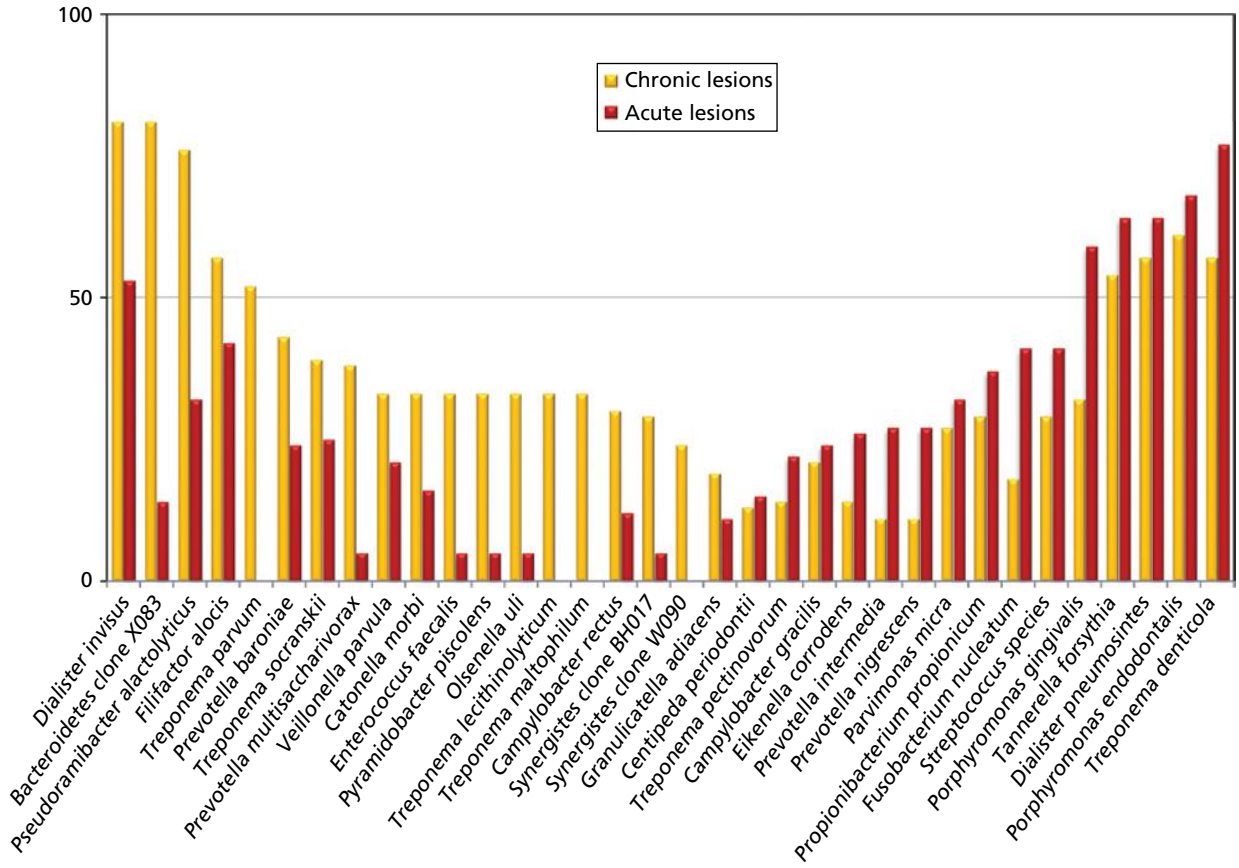


Fig. 25-12 Bacterial species/phylotypes detected in endodontic infections associated with chronic and acute endodontic lesions by species-specific nested polymerase chain reaction. (Data from Siqueira & Rôças 2005.)

but dominated by anaerobic bacteria (Williams *et al.* 1983; Kuriyama *et al.* 2000; Khemaleelakul *et al.* 2002; de Sousa *et al.* 2003; Siqueira *et al.* 2004; Sakamoto *et al.* 2006; Flynn *et al*. 2012). The bacterial load may range from 10^4 to 10^9 colony forming units (Williams *et al.* 1983; Lewis *et al.* 1986; Khemaleelakul *et al.* 2002), which means that the number of species is comparatively higher in canals of abscessed teeth than in canals of teeth with non-symptomatic and established lesions of apical periodontitis (Siqueira *et al*. 2004; Sakamoto *et al*. 2006).

There is no firm evidence in support of a single species being specifically involved with any particular sign or symptom of endodontic lesions. While some Gram-negative anaerobic bacteria have been found in association with symptomatic lesions (Sundqvist 1976; Griffee *et al.* 1980; van Winkelhoff *et al.* 1985; Yoshida *et al.* 1987; Gomes *et al.* 1996; Sakamoto *et al.* 2006), similar or even higher frequencies of the same organisms have been observed in asymptomatic teeth (Haapasalo *et al.* 1986; Baumgartner *et al*. 1999; Jung *et al.* 2000; Fouad *et al.* 2002; Siqueira *et al.* 2000; Rôças & Siqueira 2008) (Fig. 25-12). Hence, mechanisms other than the presence of a single pathogen seem to be the cause of symptomatic endodontic infections (Siqueira & Rôças 2013). These may include differences in virulence

among clonal types of the same species; bacterial interactions in multispecies communities resulting in additive or synergistic effects; bacterial population density; environment-regulated expression of virulence factors; and host resistance, which in turn may be modulated by systemic diseases, concomitant virus infection, environmental factors (stress, smoking), and genetic patterns (Siqueira & Barnett 2004).

In addition to bacteria, other microorganisms have been found in endodontic infections. Fungi, especially *Candida* species, although rarely recovered in primary infections, are more commonly detected in teeth with post-treatment disease (Waltimo *et al.* 1997; Cheung & Ho 2001; Peciuliene *et al.* 2001; Siqueira & Rôças 2004). Archaea and viruses may also be found, although their role in endodontic lesions has yet to be clarified. Archaea are prokaryotes distinct from bacteria that have been traditionally recognized as extremophiles, but recently detected in the human microbiota; in a few primary infected root canals, *Methanobrevibacter* spp. were recovered (Vianna *et al.* 2006a; Vickerman *et al.* 2007).

Although viruses cannot thrive in the necrotic root canal, there is a report of the presence of human immunodeficiency virus (HIV) in non-inflamed vital pulps of patients infected with this virus (Glick *et al.* 1991). Also, different herpesviruses have been detected in samples from periapical inflammatory lesions (Sabeti *et al.* 2003; Sabeti & Slots 2004; Chen *et al.* 2009; Saboia-Dantas *et al.* 2007; Ferreira *et al.* 2011). Their role in the disease process remains to be elucidated.

Evidence is mounting that endodontic lesions are biofilm-induced disease processes (Svensäter & Bergenholtz 2004). Morphologic studies demonstrate bacteria colonizing the root canal system in primary or persistent/secondary infections as sessile biofilm-like structures, usually covering the dentinal root canal walls (Nair 1987; Molven *et al.* 1991; Siqueira *et al.* 2002; Carr *et al.* 2009; Ricucci *et al.* 2009; Schaudinn *et al.* 2009) (see Fig. 25-10). Apical ramifications, lateral canals, and isthmuses connecting main root canals have all been shown to harbor bacterial cells frequently organized into biofilms (Nair *et al.* 2005; Ricucci & Siqueira 2010b) (Figs. 25-13, 25-14). Moreover, biofilms adhered to the apical root surface (extraradicular biofilms) have been reported in some

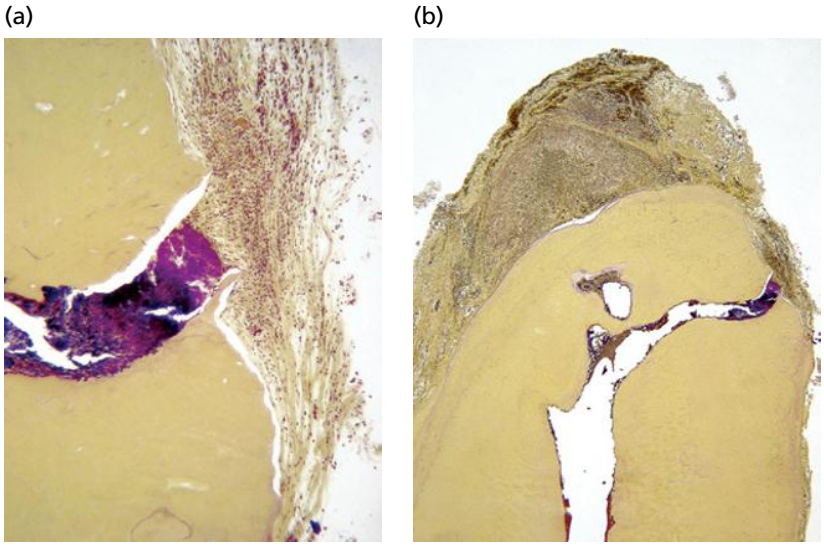


Fig. 25-13 (a) Demonstration of bacterial front (blue stain) near the root canal exit of a root with attached periapical tissue lesion. (b) Low magnification. (Source: Ricucci & Bergenholtz 2004. Reproduced with permission from John Wiley & Sons.)

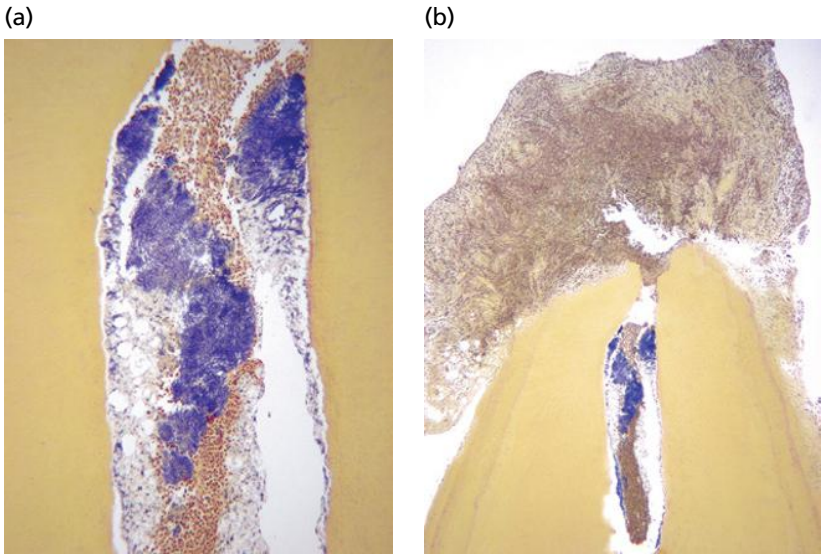


Fig. 25-14 (a) Display of bacterial masses (blue stain) attached to the walls of a root canal well inside the apical foramen. A band of inflammatory cells appear to be in combat with the infection. (b) Low magnification overview of the root with attached periapical tissue lesion. (Source: Ricucci & Bergenholtz 2004. Reproduced with permission from John Wiley & Sons.)

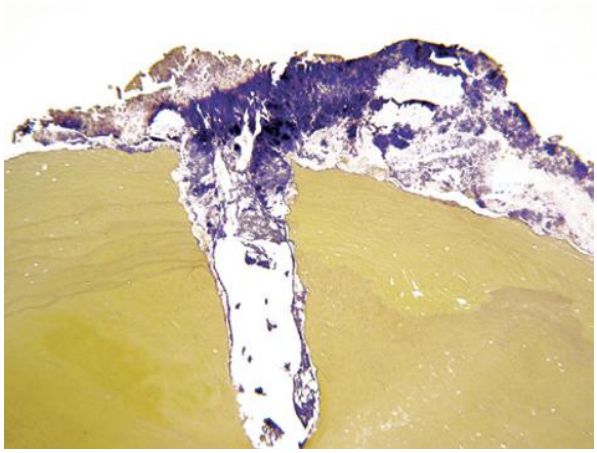


Fig. 25-15 Accumulation of bacterial mass (blue stain) at the external root surface of a tooth with an infected necrotic pulp. (Source: Ricucci & Bergenholtz 2004. Reproduced with permission from John Wiley & Sons.)

cases and regarded as a possible cause of post-treatment endodontic lesions (Fig. 25-15) (Tronstad *et al.* 1990; Ricucci *et al.* 2005).

Evaluating the prevalence of biofilms in 106 roots of untreated (primary root canal infections) and treated (persistent/secondary infections) teeth with endodontic lesions, Ricucci & Siqueira (2010a) reported the following main findings: (1) intraradicular biofilms were observed in the apical segment of 77% of the root canals of teeth with endodontic lesions (80% in untreated canals and 74% in treated canals); (2) intraradicular biofilms were usually thick and multilayered (composed of several layers of bacterial cells); (3) dentinal tubules underneath biofilms were often invaded by bacteria from the bottom of the biofilm structure; (4) biofilms were also seen covering the walls of apical ramifications, lateral canals, and isthmuses; (5) biofilm structures were much more common in root canals of teeth with large lesions; (6) extraradicular biofilms were infrequent, and when present were associated with intraradicular biofilms and clinical symptoms.

Periodontal tissue responses

The shape and character of the periodontal tissue response to a root canal infection may vary. Often lesions assume a limited and stable extension around the root apices and at orifices of accessory canals. The inflammatory process may then remain unchanged in size for years, although cyst transformation can result in substantial destruction of alveolar bone (Fig. 25-16). The initial expansion of an emerging lesion or exacerbation of an asymptomatic lesion can result in rapid and extensive destruction of the attachment apparatus. In certain cases, the periodontal tissue support can be lost to an extent that the gingival sulcus is involved, from where drainage of pus occurs to the oral environment (Fig. 25-17). Such an apical marginal communication along the root surface may later become a permanent pathway for pus that will be released periodically along what is simply a fistulous tract.

The character of the infecting microbiota, its overall metabolic activity, the infectious load, interactions among the community members, and the virulence factors they produce, together with the capacity of the host defense to confine and neutralize the bacterial elements, are important parameters that determine the course of the inflammatory process. Hence, growing and multiplying bacteria with capacities to invade the periodontal tissues and evade host defense mechanisms can induce acute manifestations of endodontic lesions. Monoinfections (caused by a single species) are normally unable to cause these lesions, which rather are maintained by groups of different species forming virulent partnerships, as inferred by culture studies (Dahlén 2002) and studies utilizing molecular methodology (Sakamoto *et al.* 2006; Siqueira *et al.* 2004). Hence, the disease outcome is dependent upon the varied bacterial interactions that occur among the members of the multispecies community in root canals and the pathogenicity that these interactions collectively result in (Siqueira & Rôças 2009a).

The endodontic microbiota associated with asymptomatic lesions is apparently less aggressive. This is likely to be linked to the poor nutritional supply that usually prevails in root canals and which puts the bacteria in a low state of metabolic activity. Nutrients are available primarily from tissue components of the necrotic pulp. In the absence of inflammatory exudate entering the root canal along apical foramina and accessory canals, bacteria will consequently have little drive to grow, multiply, and invade the periodontal tissue compartment. When this condition of relative starvation is broken by an increase of the nutritional supply, suppressed virulent strains can be revived and become the dominant organisms at the expense of the less virulent members of the microbial community. Consequently, acute exacerbations of asymptomatic endodontic lesions may occur, for example, when saliva and gingival exudates gain access to the root canal space following its direct exposure to the oral environment. Similarly, during endodontic treatment, inadvertent enlargement of the apical foramen increases the passageway for protein-rich inflammatory exudate into the root canal space.

While expanding bone resorption, exudation and influx of phagocytic cells characterize the acute manifestations of endodontic lesions, a balanced host–parasite relationship will be established sooner or later (Stashenko 1990; Nair 1997; Stashenko *et al.* 1998). Microscopically, the established lesion is characterized by a richly vascularized granulation tissue, which is infiltrated, to a varying degree, by inflammatory cells (Fig. 25-18). PMNs play a most important role in confining the infection to the pulpal space (Stashenko *et al.* 1995) and constitute an important cellular front line of host defense (see Fig. 25-14). The remainder

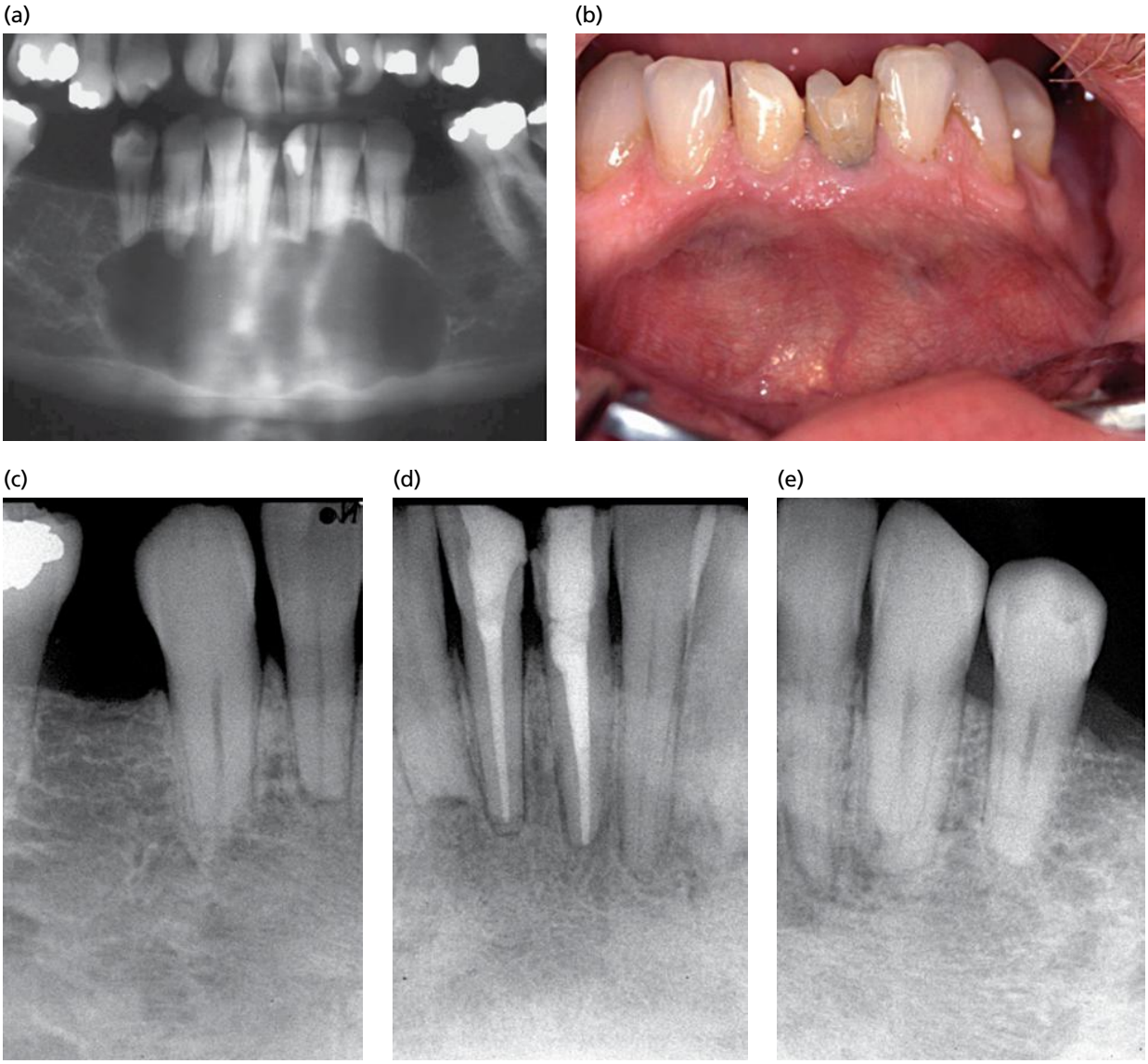


Fig. 25-16 (a) Extensive destruction of alveolar bone as a result of cyst transformation of a periapical lesion emanating from tooth 31. Note the root resorption of neighboring teeth. (b) Buccal protrusion of the process was non-painful to palpation. All teeth responded vital to pulp testing except for the root-filled tooth 31 and tooth 41. The latter tooth, however, had a vital pulp as revealed on entering the root canal. Treatment, carried out in collaboration with Dr Ulf Lekholm, included placement of an obturator for drainage, decompression, and saline irrigation of the cyst cavity over 6 months. Following its reduction, teeth 31 and 41 received completion of endodontic treatment and a residue of the process was excised surgically. (c–e) Complete resolution of the process 10 months post surgery.

of the lesion will be composed of a mixed cellular response (Fig. 23-18c) typical of a longstanding infectious process where various immunocompetent cells (*viz.* dendritic cells, macrophages, plasma cells, T and B cells) are prevalent (Torabinejad & Kettering 1985; Babal *et al*. 1987; Okiji *et al*. 1994; for reviews see Stashenko *et al*. 1998; Marton & Kiss 2000; Nair 2004; Marton & Kiss 2014). PMNs may nevertheless be dominant in areas of the main lesion and even form abscess cavities. With increasing distances from the root canal apertures, the established lesion harbors a decreasing number of inflammatory cells and an increasing amount of fibrovascular elements representing attempts at repair. More peripherally, there is a much stronger expression of fibroblastic activity and formation of new vessels. In the most peripheral portions of the lesion, a collagen-rich connective tissue normally separates it from the surrounding bone tissue (Bergenholtz *et al*. 1983) (Fig. 25-18a, d).

In the established lesion, the relative distribution of cellular and tissue elements may show great variation and some, but far from every lesion, may also contain proliferating epithelial cells (Nair 1997). The origin of epithelial strands is thought to be the epithelial rests of Malassez (Ten Cate 1972) that are stimulated to divide and proliferate by the release of pro-inflammatory cytokines and growth factors during the process of inflammation (Thesleff 1987; Lin *et al*. 1996; Suzuki *et al*. 2002). In the lesion, they appear to take a random course, but sometimes they may also attach to the root surface (Fig. 25-19) and eventually block the root canal exit

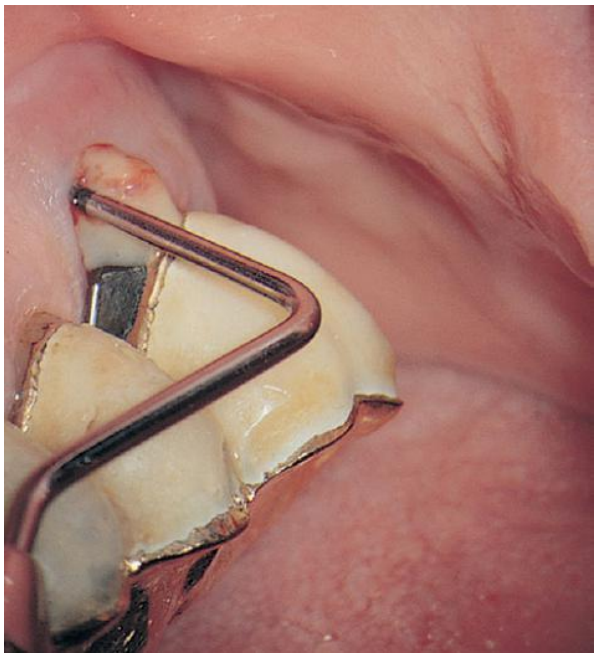


Fig. 25-17 Drainage of pus upon periodontal probing from a lesion of endodontic origin associated with an upper molar.

for bacterial advancement into the periapical tissue compartment (Nair & Schroeder 1985). Their contribution to periodontal pocket formation upon an endodontic lesion, developing in close proximity to the epithelial sulcus of the marginal periodontium, remains obscure.

Conclusion: Inflammatory processes of the periodontium associated with necrotic dental pulps have an infectious etiology similar to periodontal disease. An essential difference between the two disease entities is their different source of infection. While periodontal disease is maintained by bacterial biofilms in the dentogingival region, endodontic lesions are directed towards infectious elements released from the pulpal space. Bacteria involved in endodontic infections are predominantly anaerobic species usually organized in biofilms adhering to the inner walls of the root canal. Thus, the infection is commonly confined to the root canal space. Bacteria may be occasionally found in the periapical soft tissue lesion *per se* either in clusters or as bacterial biofilms on the external root surface.

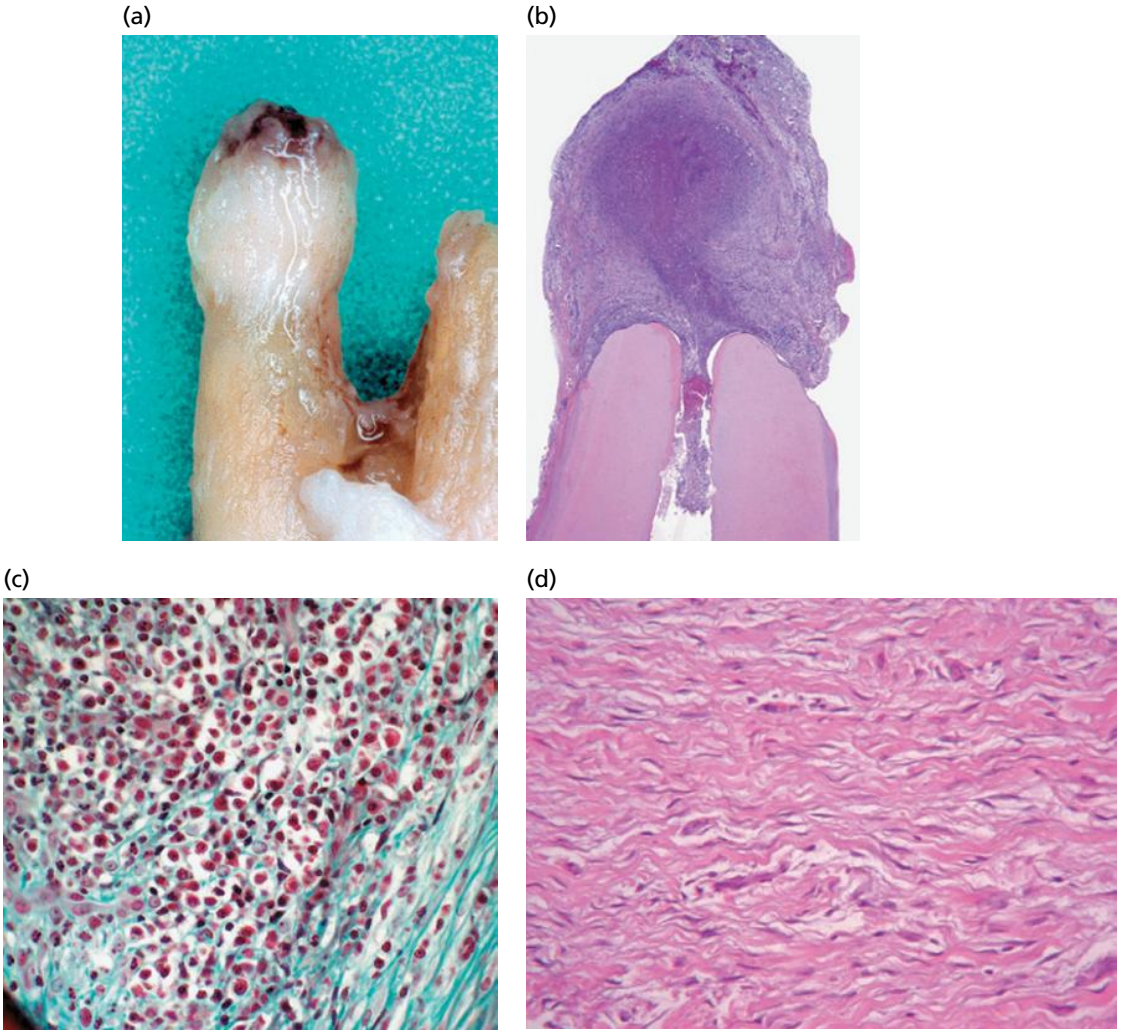


Fig. 25-18 Series of images demonstrating features of apical inflammatory lesions caused by root canal infection. (a) Soft lesion attached to the tip of the palatal root of an extracted upper molar. (b) Longitudinally cut tissue section through the root tip shows an overview of the lesion. The outer collagen-rich connective tissue confines the soft tissue lesion and attaches it to the root surface. (c) Typical mixed inflammatory cell infiltrate at the center of a lesion (from an apical lesion in a monkey). (d) In the most peripheral portion the connective of an established lesion is rich in collagen and devoid of inflammatory cells.

Endodontic lesions rarely involve the marginal periodontium, unless abscessed. Cyst transformation may occur but even then marginal involvement is not common. In its balanced form, the endodontic lesion is clearly localized and constitutes an immunologically active protection zone, which serves to prevent the dissemination of endodontic pathogens to surrounding tissues and distant body compartments.

Post-treatment endodontic lesions

Endodontic treatment seeks to curb symptomatic and non-symptomatic presentations of endodontic infections with the ultimate goal of maintaining or restoring the health of the periodontal tissues apically and laterally to the roots of teeth. Similar to the treatment of marginal periodontitis, the success of endodontic treatment depends largely on how effectively the cleaning procedure can be carried out. The complicated nature of the root canal system of many teeth, however, may limit the potential to completely get rid of diseased or infected and dead pulp tissue. The use of chemicals for disinfection purposes is therefore important in endodontics, especially in cases of infected pulp necrosis. Filling the instrumented root canal properly by leaving no unfilled spaces then determines the long-term outcome. Fluids and exudate from either the oral environment or the periapical tissue lesion may otherwise seep into the root canal and nourish residual bacteria that may have survived the treatment procedure, thus causing an emergent (developed after treatment), persistent (persisted despite treatment), or recurrent (redeveloped after having healed) post-treatment endodontic lesion. A root canal filling that occupies the entire instrumented canal space from its coronal entrance to its apical terminus is therefore a key goal of a well-executed endodontic treatment (for an overview of endodontic treatment principles, see appropriate texts).

As indicated by numerous cross-sectional population studies, post-treatment lesions are commonly observed in teeth in which the endodontic treatment has not met key standards for prevention and control of endodontic infection (for review see Eriksen *et al.* 2002). Post-treatment disease may nevertheless occur in 10–15% of treated teeth, even if state-of-the art treatment procedures are applied (Kerekes & Tronstad 1979; Sjögren *et al.* 1990; Ricucci *et al*. 2011). Hence, regardless of the technical quality of the root canal treatment, the causes of failure are to be found in either a persistent/secondary intraradicular infection, or sometimes in an associated extraradicular infection (see below).

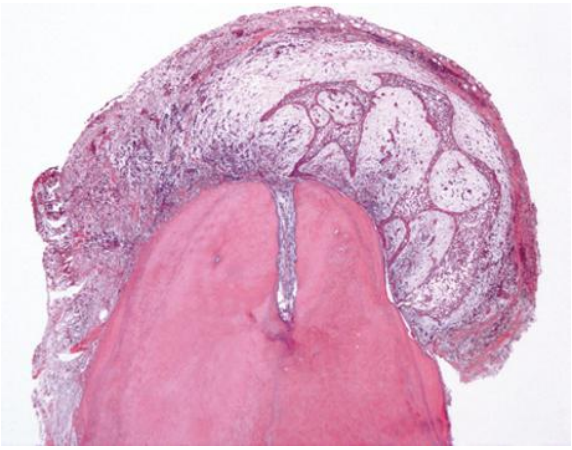
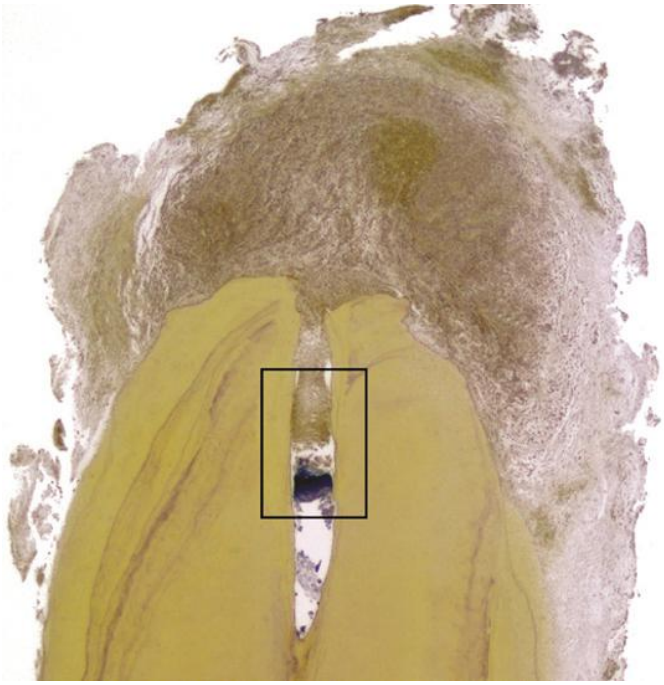


Fig. 25-19 Periapical inflammatory process with proliferating epithelium partially attached to the root surface.

(a)



(b)

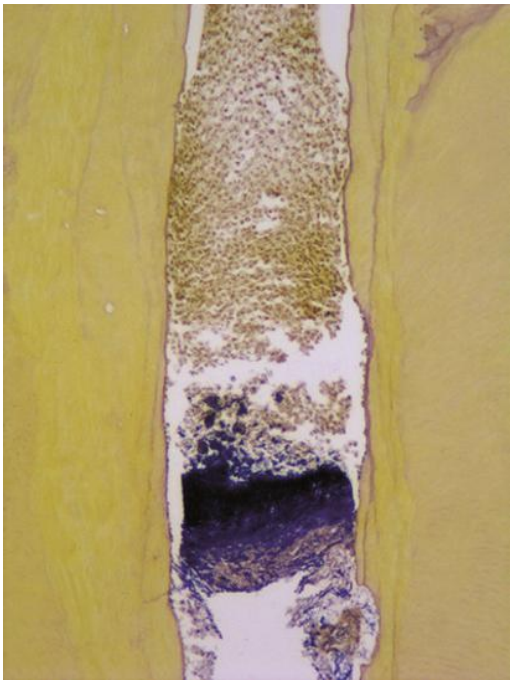
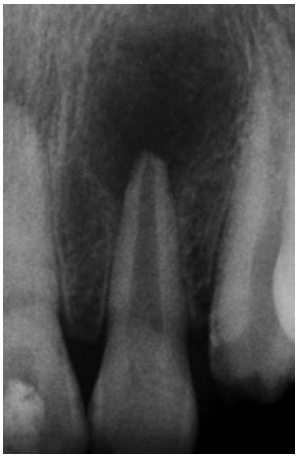
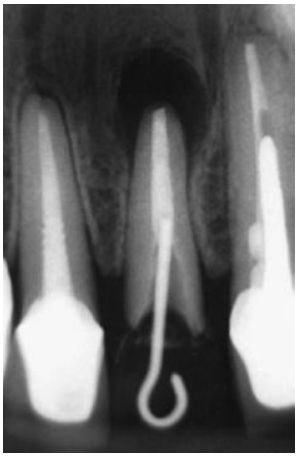


Fig. 25-20 (a) Root tip of an extracted tooth with attached periapical inflammatory lesion. (b) High magnification of insert in (a) shows the bacterial front line well inside the apical foramen, where it is opposed by polymorphonuclear leukocytes.

The microbiota in root canal-treated teeth with a post-treatment endodontic lesion exhibits a decreased diversity and density in comparison with primary root canal infections. Well-treated canals may harbor one to five species, while the number of species in canals with inadequate endodontic treatment, similar to untreated canals, can reach up to 10–30 (Pinheiro *et al.* 2003; Siqueira & Rôças 2004; Sakamoto *et al.* 2008). A single treated canal with post-treatment disease can harbor from 10^3 to 10^7 bacterial cells (Peciuliene *et al.* 2001; Sedgley *et al.* 2006; Blome *et al.* 2008).

Culture and molecular studies have revealed that *Enterococcus faecalis* is the most frequently detected species in association with post-treatment disease (Engström 1964; Molander *et al.* 1998; Sundqvist *et al.* 1998; Pinheiro *et al.* 2003; Siqueira & Rôças 2004; Sedgley *et al.* 2006; Gomes *et al.* 2008; Schirrmeister *et al.* 2009), although its pathogenetic potential is not well confirmed (Chávez de Paz 2007). While the Gram-negative anaerobic segment is less frequently represented, other Gram-positive bacterial species, especially streptococci, may also be prevalent (Molander *et al.* 1998; Sundqvist *et al.* 1998; Pinheiro *et al.* 2003; Siqueira & Rôças 2004; Gomes *et al.* 2008; Sakamoto *et al.* 2008). Like primary endodontic infections, about one-half of the

Table 25-1 Characteristics of the root canal infection in primary and post-treatment endodontic lesions.

	Primary lesions	**Post-treatment lesion**
	Untreated teeth	Root canal-treated teeth
		
Type of infection	Primary intraradicular Extraradicular (abscess)	Persistent secondary intraradicular Extraradicular
Community	Multispecies	Multispecies, sometimes single
No. of species/canal	10–20	• Adequate treatment: 1–5 • Inadequate treatment: 10–30
No. of cells/canal	10^3–10^8	10^3–10^7
Most prevalent bacterial groups	Gram-negative/Gram-positive anaerobes	Gram-positive facultatives
Most prevalent species/genera	*Fusobacterium nucleatum* *Dialister* spp. *Porphyromonas* spp. *Prevotella* spp. *Treponema* spp. *Tannerella forsythia* *Filifactor alocis* *Pseudoramibacter alactolyticus* *Pyramidobacter piscolens* *Synergistes* spp. *Eikenella corrodens* *Olsenella* spp. *Parvimonas micra* *Campylobacter* spp.	*Enterococcus faecalis* *Candida albicans* (fungus) *Streptococcus* spp. *Pseudoramibacter alactolyticus* *Propionibacterium propionicum* *Filifactor alocis* *Dialister* spp. *Actinomyces* spp. *Pseudomonas aeruginosa* Enteric rods
Treatment	Root canal treatment Extraction	Root canal retreatment Apical surgery Extraction

species detected in persistent/secondary infections still remain to be cultivated and phenotypically characterized (Sakamoto *et al.* 2008).

Even though in most cases of post-treatment disease, bacteria are likely to be confined to the root canal space (Siqueira & Lopes 2001; Ricucci *et al.* 2009), case reports have indicated that post-treatment disease may also be related to extraradicular infection with *Actinomyces* spp. or *Propionibacterium propionicum*, a condition referred to as periapical actinomycosis (Sundqvist & Reuterving 1980; Happonen *et al.* 1986; Sjögren *et al.* 1988; Siqueira 2001; for review Haapasalo *et al.* 2008). Even though the front line of the infection in some cases may be established at the apical foramen or even beyond it, the host tissue–bacterial interface zone usually localizes somewhat short of the apical foramen (Fig. 25-20). In what may be a rare condition (Siqueira & Lopes 2001), bacteria in primary endodontic infections may overcome the host defenses and aggregate as a biofilm on the outer root surface (Lomçali *et al.* 1996) (see Fig. 23-15). Such structures have also been observed on root ends of teeth, which have not responded favorably to endodontic treatment (Tronstad *et al.* 1990; Ricucci *et al.* 2005).

Conclusion: Post-treatment endodontic lesions are usually caused by a persistent or secondary infection of the root canal space. The microbiota differs from the primary infection in terms of diversity and types of species involved (Table 25-1). While in some cases the cause of a persistent endodontic lesion may be an extraradicular bacterial infection, failure to attain the treatment objectives of endodontics often relates to inadequate infection control caused by insufficiently cleaned, shaped, disinfected as well as filled root canals.

Effects of periodontal disease and periodontal therapy on the condition of the pulp

Influences of periodontal disease

The formation of bacterial plaque on detached root surfaces following periodontal disease has the potential to induce inflammation in the pulp along the very same pathways as an endodontic infection can affect the periodontium in the opposite direction. Thus, bacterial products and substances released by the inflammatory process in the periodontium may gain access to the pulp via exposed accessory canals and apical foramina, as well as dentinal tubules.

A clear association between progressive periodontal disease and pulpal involvement, however, does not exist. While inflammatory alterations as well as localized inflammatory cell infiltrates and necrosis of pulp tissue have been observed adjacent to accessory canals in teeth exposed by periodontal disease (Seltzer *et al.* 1963; Rubach & Mitchell 1965), a number of clinical studies has failed to confirm a direct relationship between progression of periodontitis and pulp tissue changes (Mazur & Massler 1964; Czarnecki & Schilder 1979; Torabinejad & Kiger 1985). In the cases observed in these studies, the pulp remained fully functional without overt inflammatory changes even though the periodontal tissue breakdown was severe. As already pointed out, an important reason for the lack of pulp tissue involvement is that patent accessory canals are not invariably present and especially not in the cervical root portions. Another reason is that cementum obviously gives protection. It is only when the cementum layer has been damaged by, for example, instrumentation in periodontal therapy, wear from tooth cleaning, external root resorption, and root surface caries, that dentinal tubules can serve as pathways for microbial elements to the pulp (Figs. 25-21, 25-22, 25-23, 25-24).

The fact that tissue changes develop infrequently and even then only locally in the pulp of teeth subjected to periodontitis was underscored by an experimental study in monkeys (Bergenholtz & Lindhe 1978). Following a ligature-induced breakdown of the attachment apparatus, it was found that the majority of the root specimens examined (70%) exhibited no inflammatory changes, despite the fact that approximately 30–40% of the periodontal attachment was lost. The remaining roots (30%) displayed only small inflammatory cell infiltrates and/or formations of reparative dentin in the pulp subjacent to root areas exposed by the periodontal tissue destruction. These tissue changes were associated with root surface resorption (Fig. 25-21), supporting the view that dentinal tubules have to be uncovered before external irritants can be transmitted to the pulp. Consequently, the lack of correlation found in clinical observations between periodontal disease and pulp tissue alterations, may simply depend on the fact that few open pathways exist to the pulp in many periodontally involved teeth. Furthermore, as described

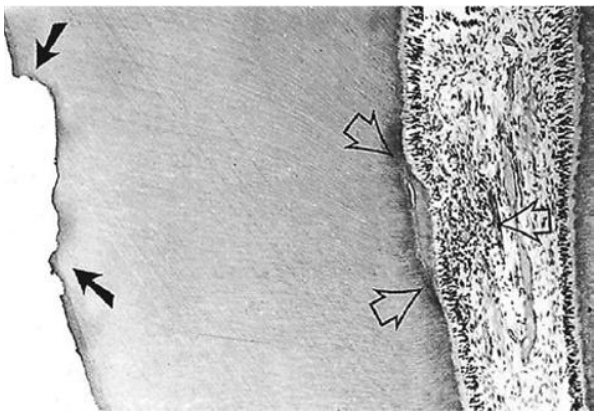


Fig. 25-21 Histologic section of a monkey tooth exposed to experimental periodontal tissue breakdown. Beneath the resorptive defects in the external root surface (black arrows), a minor inflammatory cell infiltrate and a small rim of reparative dentin have formed in the pulp (open arrows). (Source: Bergenholtz & Lindhe, 1978. Reproduced with permission from John Wiley & Sons.)

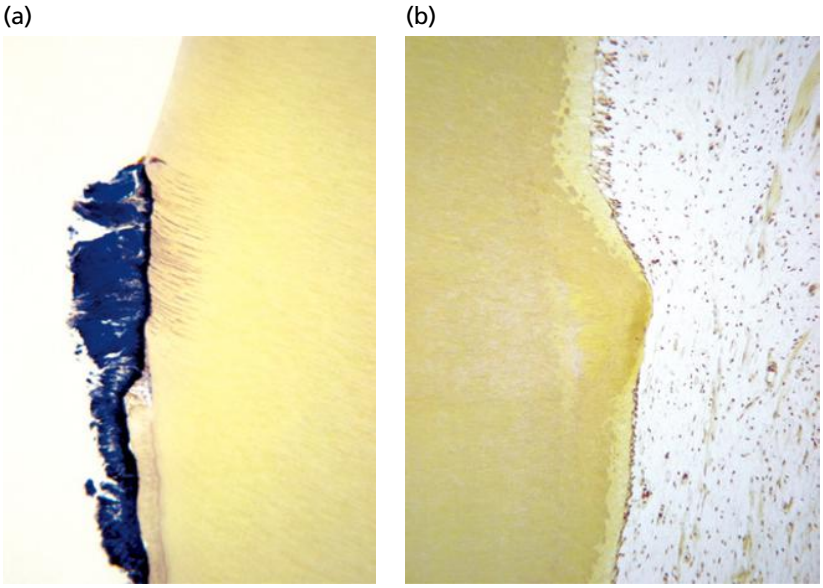


Fig. 25-22 (a) Histologic section of a human tooth specimen with bacterial accumulations on the external root surface. Where the cementum layer is missing bacterial organisms have entered the dentinal tubules. (b) Adjacent pulp tissue is minimally affected with slight disruption of the predentin zone and the odontoblast layer.

above, once the dentin–pulp complex has been exposed to bacterial elements, repair and healing will often be instituted soon after the initial inflammatory events, leaving the remaining tissue unaffected as a result of an effective host defense

In the study by Bergenholtz and Lindhe (1978), destructive periodontal disease was produced experimentally over a comparatively short period (5–7 months), while in humans a similar degree of destruction of periodontal tissue normally requires several years. It has been reported that the pulp of teeth with longstanding periodontal disease develops fibrosis and various forms of intrapulpal mineralizations (Bender & Seltzer 1972; Lantelme *et al*. 1976) (Fig. 25-23). If there is an association, it seems reasonable to assume that tissue changes of this nature represent the accumulated response of the pulp to the relatively weak, but repeatedly occurring, insults to the tissue over time, for example by microbial elements reaching the pulp over root surface exposures. Nonetheless the pulp can obviously remain healthy for as long as periodontal disease has not arrived at a terminal stage, when plaque accumulation and associated inflammatory lesions interfere with the neurovascular supply of the tissue through the main apical foramen (Langeland *et al*. 1974; Ricucci & Siqueira 2013) (Fig. 25-25).

Conclusion: Available documentation suggests that the vital functions of the pulp are rarely threatened by periodontal disease influences. In teeth with moderate breakdown of the attachment apparatus, the pulp usually remains functional and healthy. Breakdown of the pulp presumably does not occur until the periodontal disease process has reached a terminal stage, that is when plaque and the periodontal inflammatory process have progressed to the main apical foramina, whereby a retrograde destructive inflammatory pulpal lesion is initiated (see Fig. 25-25). Consequently, as long as the neurovascular supply through the main apical foramina remains intact, the pulp is usually capable of withstanding injurious elements released by the lesion in the periodontium.

Influence of periodontal treatment measures

Pocket/root debridement in periodontal therapy by hand instrumentation [scaling and root planing (SRP)] or ultrasonics is indispensable in the treatment of periodontal disease. However, this treatment is associated with a number of undesired side effects. Except for recession of gingival tissues resulting in exposure of root surfaces, the instrumentation *per se* may also inadvertently remove root cementum and the superficial parts of dentin. Thereby a large number of dentinal tubules will become exposed to the oral environment as treated root surfaces are normally left unprotected. Subsequent contact with microbial elements in the oral cavity is potentially harmful to the pulp and bacterial invasion of the exposed dentinal tubules may occur (Adriaens *et al*. 1988; Love 1996) (see Fig. 25-22). While localized inflammatory lesions may be initiated in the pulp, the experimental study by Bergenholtz and Lindhe (1978) did not record an increased incidence of pulpal lesions in teeth subjected to SRP in comparison to non-treated teeth subjected to periodontal tissue breakdown alone. In this study, root surfaces denuded of root cementum were exposed to the oral environment for up to 30 days. The finding that plaque accumulation on root dentin exposed by one session of SRP does not seriously threaten the vitality of the pulp has been confirmed in similarly designed experimental studies (Nilvéus & Selvig 1983; Hattler & Listgarten 1984). Yet, root dentin hypersensitivity may follow such treatment measures, causing an uncomfortable problem that is difficult to manage (see later).

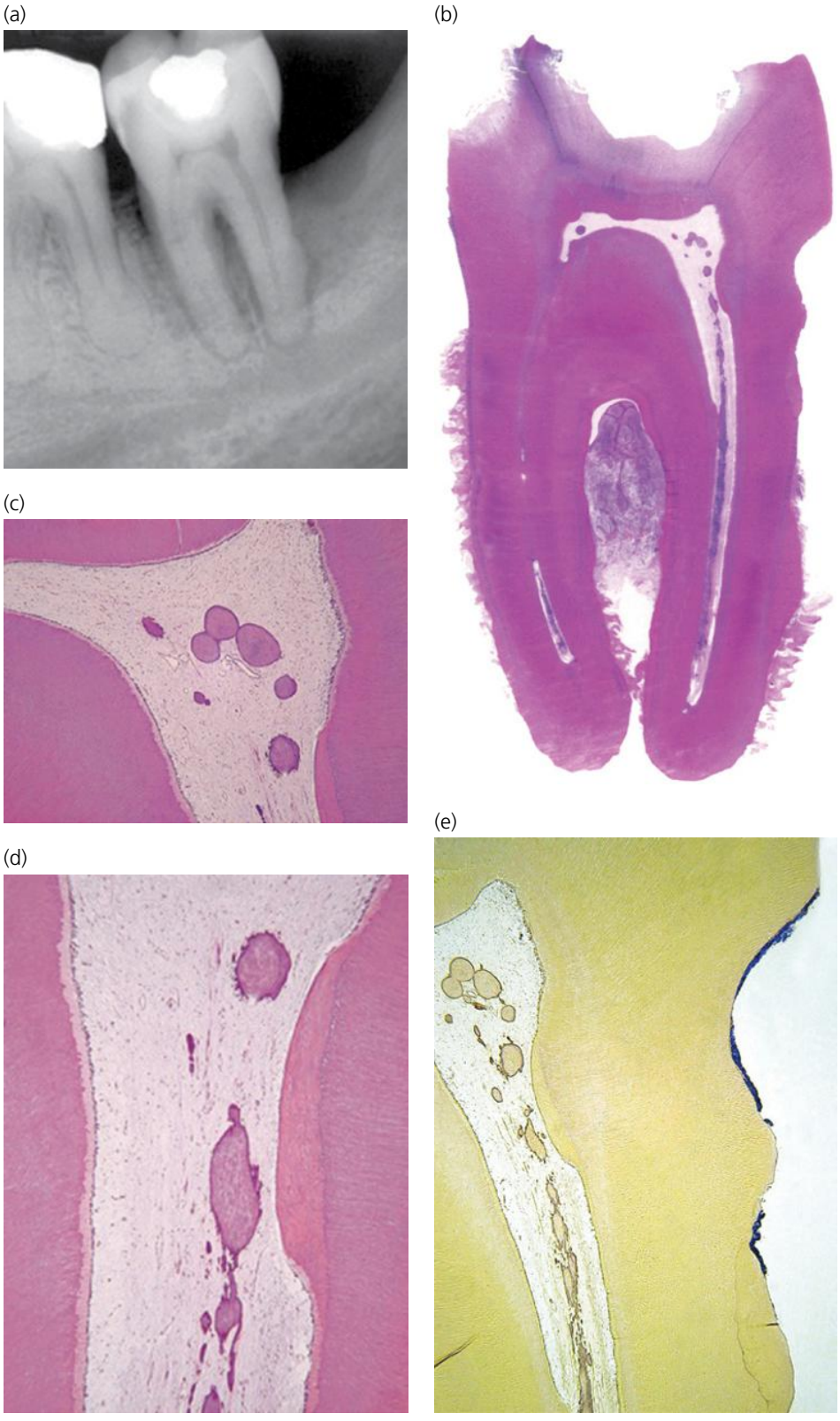


Fig. 25-23 (a) Lower molar with advanced periodontal tissue destruction. (b) Low power microphotograph demonstrates numerous mineralizations in the pulp tissue, which otherwise is in a healthy condition as demonstrated in (c) and (d). (e) Bacterial plaque accumulations on the external surface of the distal root.

During the maintenance phase of periodontal therapy, there are reasons to restrict repeated instrumentations, as instrumentation always removes some dentin. Such therapy can result in weakening of the tooth structure and also in extensive reparative dentin formation in the pulp (Fig. 25-26).

Conclusion: Results of clinical observations and animal experiments support the view that pocket/root debridement procedures normally do not threaten the vitality of the pulp. Localized inflammatory alterations may occur adjacent to instrumented root surfaces, followed by tissue repair in the form of hard tissue depositions on the root canal walls.

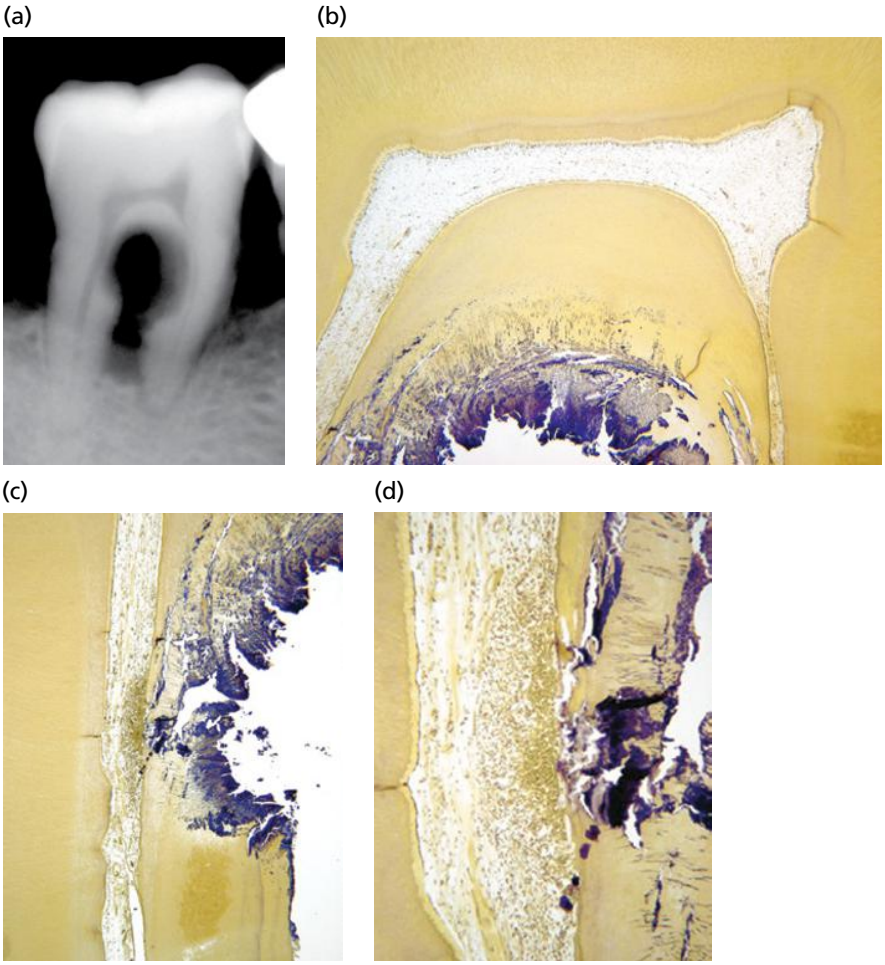


Fig. 25-24 (a) Tooth with extensive caries in the furcation region of a lower molar. (b) Note the overall normal tissue morphology of the pulp except for an area at the mid-root portion of the distal root, where the caries process has reached the pulp (c, d).

Root dentin hypersensitivity

Symptoms

Patients who have received pocket/root debridement in periodontal therapy may frequently experience sensitivity of the treated teeth to evaporative, tactile, thermal, and osmotic stimuli (Fischer *et al*. 1991; Kontturi-Närhi 1993; Chabanski *et al*. 1996; Tammaro *et al*. 2000; for review see Gillam & Orchardson 2006). Usually, the symptoms, when they occur, develop and peak during the first week, and then subside or disappear within the subsequent weeks; they are, although uncomfortable, most often a temporary and sustainable problem (Schuurs *et al*. 1995; Chabanski *et al* 1996; Gillam *et al*. 1999; Fardal *et al*. 2002). Occasionally, the condition may become a chronic pain problem and may persist for months or years. Although the number of well-controlled studies on the incidence after periodontal therapy is few (von Troll *et al*. 2002), patients appear to be especially at risk after periodontal surgery. In a comprehensive questionnaire survey, severe painful symptoms were reported to prevail in 26% of the subjects 6 months to 5 years after the completion of treatment, while 16%, treated non-surgically, reported pain symptoms (Kontturi-Närhi 1993). In a prospective, clinical trial comprising 35 patients in need of periodontal therapy for moderate-to-advanced periodontitis, the number of sensitive teeth increased following non-surgical periodontal instrumentation in comparison to non-instrumented teeth after initiating a self-performed oral hygiene program (Tammaro *et al*. 2000). While affecting a majority of the patients, pain was generally reported to be minor. Only a few teeth in a small number of the patients developed highly sensitive root surfaces.

The main initial symptom is sharp pain of rapid onset that disappears once the stimulus is removed. In more severe, long-standing cases, shorter or longer periods of lingering, dull or aching pain may be provoked, especially by cold drinks but also by hot and sweet food items. These symptoms of a pulpitis character may not only be localized to the tooth (teeth) in question, but also to both quadrants of the jaw. Even minimal contact with a toothbrush may elicit intense pain – a condition which is not only uncomfortable but also one that is likely to hinder proper oral hygiene measures.

Mechanisms

The painful condition has been given many names, including dentin sensitivity, cervical dentin hypersensitivity, root dentin sensitivity, and root dentin

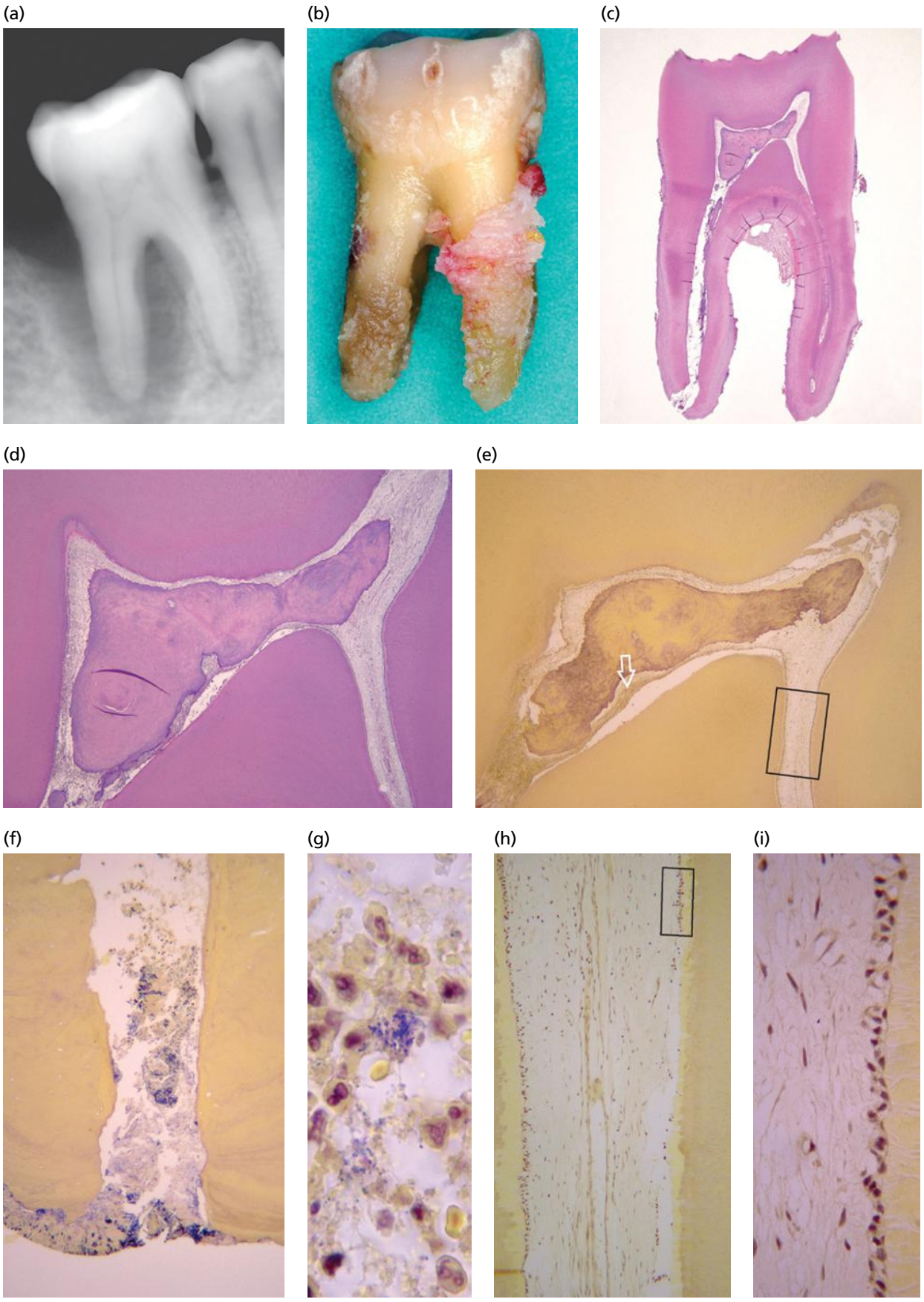


Fig. 25-25 (a) Extensive periodontal tissue breakdown circumscribing the distal root of a lower molar. (b, f) Plaque and calculus cover the root surface to the apical foramen. (c–g) Pulp is necrotic and infected all the way to the extensive hard tissue deposition in the coronal pulp (arrow in e). (f, g, i) Microphotographs enlarging marked area in (e) and (h) indicate that the pulp tissue of the mesial root is completely unaffected and displays normal tissue morphology. Tooth was sensitive in pulp vitality testing.

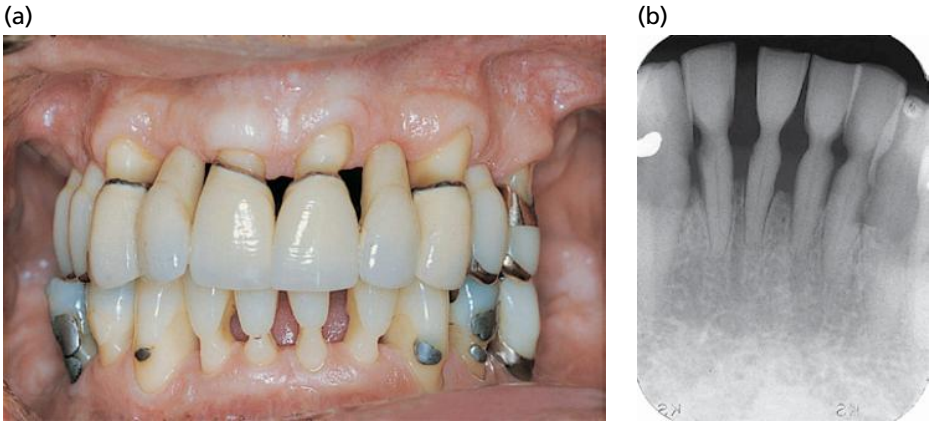


Fig. 25-26 (a) Clinical photograph of a patient in the maintenance phase for periodontal disease. While the gingival condition is excellent and there are no pocket probing depths, there is substantial loss of cervical root dentin. (b) Coronal portions of the pulp are obliterated by reparative dentin. One of the lower incisors later had a horizontal fracture, but without exposure of the pulp. (Courtesy of S. Nyman.)

hypersensitivity, reflecting some of the confusion that exists regarding its etiology (Gillam & Orchardson 2006). The fact that root surfaces become sensitive to a variety of externally derived stimuli after periodontal instrumentation is not surprising as dentinal tubules become exposed to the oral environment and subject to hydrodynamic forces. Hence, a variety of pain-evoking stimuli, including evaporative, tactile, thermal, and osmotic stimuli, may elicit sudden fluid shifts in the exposed tubules, thereby inducing a painful sensation according to the hydrodynamic theory of dentin sensitivity (Brännström 1966; Pashley 1996). This mechanism alone can certainly explain the sensitivity patients experience immediately after the instrumentation procedure and during a short period afterwards, but it does not explain why the symptoms affect only certain teeth and increase over the course of time, as well as prevail as a serious pain condition in certain patients.

The increase in pain intensity may have several explanations. To begin with, the smear layer formed on the root surface by the SRP procedure will be dissolved within a few days (Kerns *et al*. 1991). This in turn will increase the hydraulic conductance of the involved dentinal tubules (Pashley 1996) and thus decrease the peripheral resistance to fluid flow across dentin. Thereby, pain sensations will be more readily evoked. Open dentinal tubules will furthermore serve as pathways for diffusive transport of bacterial elements in the oral cavity to the pulp, which may initiate a localized inflammatory pulpal lesion (Bergenholtz & Lindhe 1975, 1978). Indeed, experiments in dogs have shown that dentin exposures left unprotected greatly enhance the sensitivity of the responding nerve fibers (Närhi *et al*. 1994). A large number of intradental A-delta fibers, normally inactive, then are able to respond (Närhi *et al*. 1996). Their receptive field will also widen (Närhi *et al*. 1996). In addition, sprouting of new terminal branches from pulpal axons may occur in the area subjacent to the root surface defect (Taylor *et al*. 1988). As already stated, sprouting of nerves is a temporary event and will subside if inflammation disappears; a feature which is consistent with their involvement in root dentin hypersensitivity (Byers & Närhi 1999). The increased sensitivity to cold that patients frequently experience has in recent years been linked to specific cold receptors existing in the pulp (Chidchuangchai *et al.* 2007; Ajcharanukul *et al.* 2011). In other words, an essential component of the increasing root sensitivity patients experience after an instrumentation procedure is likely to be related to a peripheral sensitization of pulpal nociceptors leading to what is termed primary hyperalgesia.

The fact that root dentin hypersensitivity often disappears a few weeks after the instrumentation procedure is best explained by the development of a natural occlusion of the exposed dentinal tubules. The deposition of mineral crystals in the tubular lumen may play an important role (Yoshiyama *et al*. 1989, 1990) (Fig. 25-27), first by inactivating the hydrodynamic mechanism for dentinal pain and second, by restricting the potential for an inward diffusion of bacterial elements to the pulp. The observation of few open tubules in non-sensitive root dentin (Hiatt & Johansen 1972; Absi *et al*. 1987; Yoshiyama *et al*. 1989; Cuenin *et al*. 1991; Oyama & Matsumoto 1991; Kontturi-Närhi 1993), while hypersensitive root areas show large numbers of wide, tubular apertures on their surfaces (Absi *et al*. 1987; Yoshiyama *et al*. 1989; Cuenin *et al*. 1991; Oyama & Matsumoto 1991; Kontturi-Närhi 1993), supports this view.

The fact that only certain individuals become seriously affected may be related to local factors in the oral cavity, as well as to the level of the subjects' pain perception. Certain dietary factors, in particular fruit juices, yoghurt, and wines, have been implicated in the causation of root dentin hypersensitivity (Addy *et al*. 1987). By their acidity and ability to etch dentin, these substances may dissolve occlusions of the dentinal tubules or prevent them from forming.

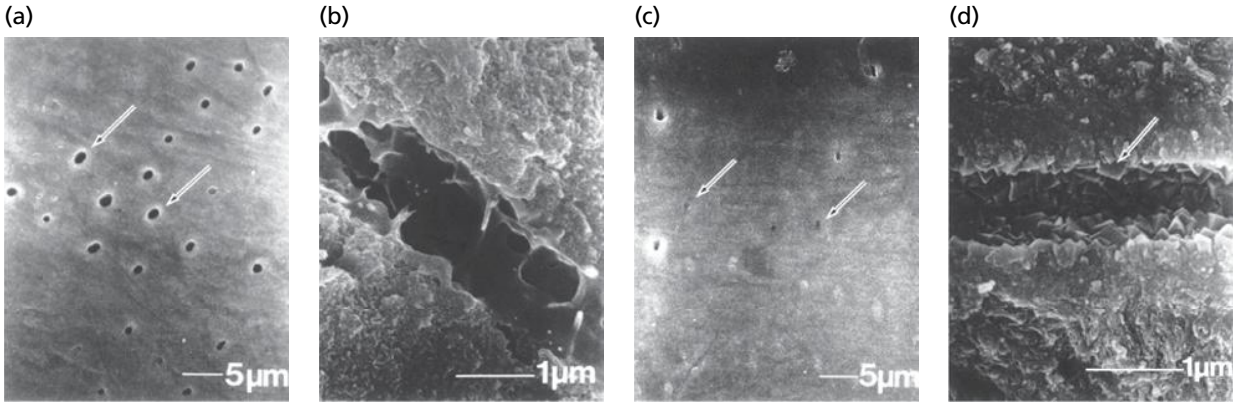


Fig. 25-27 Scanning electron microscopic images of root surface biopsies of hypersensitive (a, b) and of non-sensitive root dentin areas of human teeth (c, d). Numerous wide tubular apertures are seen in (a) (arrows). These tubules show no evidence of hard tissue deposition after being opened longitudinally (b). By contrast, most tubules are occluded in (c) (arrows) and below the surface rhombohedral crystals of 0.1–0.3 µm are present (d) (arrow). (Courtesy of M. Yoshiyama.)

It needs be recognized that pain is not only an expression of injury and noxious stimuli, but also a psychobiologic phenomenon with both a physiologic and psychological basis for its perception and reaction to it. Indeed, a variety of emotional elements may influence the subjective interpretation of pain. Anxiety, fear, and depression are factors that are known to affect pain perception, as well as the subject's ability to identify coping methods (Eli & Svensson 2010).

An important consideration in the deliberation of the mechanisms behind enhanced and lingering pain symptoms of root dentin hypersensitivity is the potential for central nervous system sensitization (Sessle 2011). It is now well documented that frequent and repeated pain stimulations result in structural and functional changes that allow the brain to respond more rapidly and more effectively to the same stimuli. Such an increase of the excitability of central neurons has a downside in that pain may continue as a memory function even if the peripheral cause has been eliminated. Thus, it is possible that central sensitization phenomena explain failure of treatment attempts in some patients.

Aspects of clinical management

Any treatment approach to root dentin hypersensitivity should be preceded by a careful consideration of conditions that may be the cause of, or contributory to, the symptoms. Cracked teeth including cusp fractures, fractured or leaky restorations, caries, erosions by acidic foods and regurgitations, as well as a variety of other exposures of dentin to the oral environment may cause pulpal pain sensations to the very same stimuli that elicit root dentin hypersensitivity. An area of exposed dentin may furthermore be more sensitive if there is irritation of the pulp from other areas of the tooth, for example from the margin of a restoration that is not well sealed from the oral environment (Närhi *et al*. 1994). Particular care should be taken to check and alleviate traumatic occlusion to reduce the excitability of pulpal nociceptors. Furthermore, dietary counseling should be given to patients who admit excessive consumption of citrus fruits, apples, or any other food or beverages that are acidic in nature, and caution given to avoid toothbrushing immediately afterwards.

Self-performed plaque control is important for the prevention and treatment of root dentin hypersensitivity. It has been observed clinically that, with time, teeth in patients with excellent oral hygiene habits develop hard, smooth, and insensitive root surfaces. Electron microscopic examination of dentin of such root surfaces has revealed that mineral deposits obliterate the tubular openings (Hiatt & Johansen 1972). However, when severe symptoms of root dentin hypersensitivity have emerged, it is often not possible to motivate the patient to maintain the degree of plaque control that is necessary to allow for a natural occlusion of the dentinal tubules. In such situations, an agent with the capacity to block the tubular openings may be beneficial, at least temporarily, so that proper oral hygiene measures can be reinforced.

In-office treatment or recommendation to use sensitivity-relieving toothpastes or both may then be attempted. However, the products and compounds presently available provide unpredictable remedy and at best only temporary relief (Gillam & Orchardson 2006; Cunha-Cruz *et al*. 2011). Since tubular patency of the exposed dentin seems to play a crucial role in the pathogenesis of hypersensitivity, most procedures are logically aimed at inducing occlusion of the peripheral openings. Some agents commonly employed, primarily for dentist-applied treatment, act by causing an astringent or coagulating effect on the tubular content. Over the years a variety of compounds have been used, including strontium chloride, sodium monofluorophosphate, sodium fluoride, calcium hypophosphate, calcium hydroxide, mineral trioxide aggregate (MTA), potassium nitrate, potassium oxalates, glutaraldehyde, ferric oxalate, stannous fluoride, bioactive glasses, and lasers (reviewed by Miglani *et al*. 2010) Among these, fluorides, glutaraldehyde/2-hydroxyethylmethacrylate (HEMA), potassium nitrates, and bonding

agents currently seem to be popular agents among practitioners (Cunha-Cruz *et al.* 2010). Recently, a desensitizing paste containing 8% arginine and calcium carbonate was developed for in-office use and in toothpastes (Cummins 2009). Also, a milk protein based on casein phosphopeptide and amorphous calcium phosphate, so-called Tooth Mousse, has, by virtue of its capacity to remineralize white spot caries lesions (Reynolds 2009), received interest as a means to prevent and treat root dentin hypersensitivity.

There may be several explanations why in-office treatments sometimes fail to remedy the problem. One is likely to be technical in nature in that it is often difficult to attain a completely dry dentin surface during the application of, for example, an astringent solution. Hence, the release of gingival fluid from the sulcus is not easily restrained by compressed air or other methods. Consequently, upon application of the agent, protein from the gingival exudate might primarily be coagulated rather than the tubular content. The precipitate is then easily removed upon subsequent tooth cleaning measures, leaving the tubules non-occluded. Furthermore, most agents may only cause a superficial block that will be dissolved over the course of time. Also, topical applications do not address the pain mechanisms associated with either peripheral or central sensitization of nociceptors. Agents able to decrease the excitability of intradental nerves have, therefore, been proposed based on the assumption that potassium ions released from formulations containing potassium salts (e.g. chlorides, nitrates, citrate, and oxalates) penetrate dentinal tubules and temper intradental nerve activity (Markowitz & Kim 1992; Orchardson & Peacock 1994). However, toothpastes with potassium-containing preparations as active ingredients showed promise in some clinical trials, but their ability to provide lasting effects was not confirmed in a meta-analysis comprising six studies (Poulsen *et al.* 2006). Similarly, a systematic review of clinical trials on potassium oxalates did not find evidence of clinical efficacy beyond the placebo effect, with the possible exception of 3% monohydrogen–monopotassium oxalate (Cunha-Cruz *et al.* 2011).

It needs be recognized that demonstrating a significant treatment effect of a given compound in clinical trials is fraught with several difficulties. One is to assemble a sample of patients of sufficient number that is well defined in terms of duration and level of the pain condition. Another is that dentin hypersensitivity may go into natural remission at any time. A large placebo effect operates in controlled trials of this nature and will narrow the gap within which treatment differences between test and control substances can be revealed (Yates *et al*. 1998, 2004). Furthermore, studies in this field have shown great heterogeneity in terms of study protocol regarding pain stimuli and scales, randomization, and allocation concealment, making comparisons of data between studies precarious (Cunha-Cruz *et al.* 2011). As of yet, there does not seem to be a universally accepted protocol to guide clinical studies evaluating desensitizing agents.

Any pain treatment should take into consideration the potential to prevent the condition from emerging in the first place. However, no well-proven protocol has yet been confirmed to effectively prevent root dentin hypersensitivity. Attempts to block the exposed dentinal tubules immediately following SRP should be an obvious approach and a couple of placebo-controlled studies have shown promise in that significantly fewer sensitive teeth were attained subsequent to instrumentation when 6% ferric oxalate (Wang *et al*. 1993), 3% potassium oxalate (Pillon *et al*. 2004) or 8% arginine and calcium carbonate (Hamlin *et al.* 2009) were applied topically. The long-term outcome of such procedures awaits confirmation.

Conclusion: Root dentin hypersensitivity frequently develops as an uncomfortable and sometimes difficult to treat ailment subsequent to SRP procedures in periodontal therapy. Although the exact mechanism for this condition is not well established, it is clearly related to open dentinal tubules that allow hydrodynamic mechanisms to elicit painful sensations upon external stimulation. Both peripheral and central sensitizations are likely to contribute to the more intense and lingering pain symptoms some patients develop after root dentin exposure.

Diagnosis and treatment planning should consider contributory etiologic factors, including overconsumption of acidic food items. Root dentin hypersensitivity should also be checked against other conditions causing similar pain symptoms and rule out cracked teeth, leaky restoration margins, caries in the tooth or in neighboring teeth, as well as trauma from occlusion. A large number of treatment methods are available for both in-office and over-the-counter applications. Some aim to block tubular patency of the exposed root dentin and others to decrease excitability of intradental nerves for reduced pain transmission. Unpredictable treatment results are to be expected and only temporary relief may be attained. In severe cases of root dentin hypersensitivity, where no remedy is achieved with any advice or treatment approach, pulpectomy and subsequent root filling are a last resort.

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Part 7: Peri-implant Pathology

Chapter 26

Peri-implant Mucositis and Peri-implantitis

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Definitions

Peri-implant disease is a collective term used to describe inflammatory processes in tissues that surround implant(s), that is peri-implant mucositis and peri-implantitis (Albrektsson & Isidor 1994). Peri-implant mucositis is defined as an inflammatory lesion that resides in the mucosa, while peri-implantitis also affects the supporting bone (Lindhe & Meyle 2008) (Fig. 26-1).

Peri-implant mucosa

Following implant installation, a transmucosal passage is formed around the abutment portion of the device. The ridge mucosa at such sites adapts to the new functional demands and a peri-implant mucosa becomes established. The mucosa surrounding implants and the gingiva surrounding teeth have many features in common (Berglundh *et al*. 1991). Both types of tissues are lined with a keratinized oral epithelium; at clinically healthy sites, this is continuous with a thin non-keratinized barrier or junctional epithelium that faces the implant or the tooth surface. In the connective tissue immediately lateral to these thin epithelial linings, small infiltrates of inflammatory cells (neutrophils, macrophages, T cells, B cells) are frequently seen (Liljenberg *et al*. 1997). The inflammatory cells represent the host's defense against bacterial products and hence they may be considered as an important component of the biologic seal that separates the peri-implant and periodontal attachment tissues from the oral cavity (see also Chapters 3 and 13).

Peri-implant mucositis

Clinical features and diagnosis

The clinical features of peri-implant mucositis are in many respects similar to those of gingivitis at teeth and include classical symptoms of inflammation, such as swelling and redness (see Chapter 19). Differences in the morphology of the peri-implant mucosa and the lack of light transmission through the metal of the device or the crown restoration, however, may mask visible signs of inflammation. Assessment of peri-implant mucositis must therefore always include assessment of bleeding following probing (Fig. 26-2).

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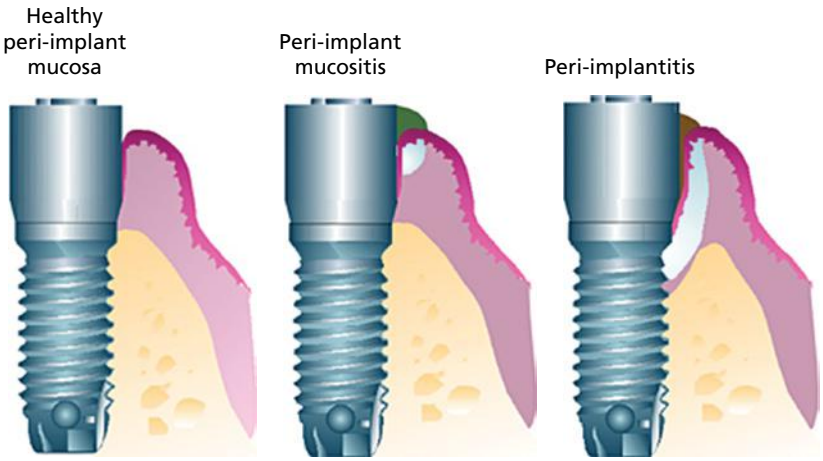

Fig. 26-1 Schematic drawing illustrating healthy peri-implant mucosa, peri-implant mucositis, and peri-implantitis.

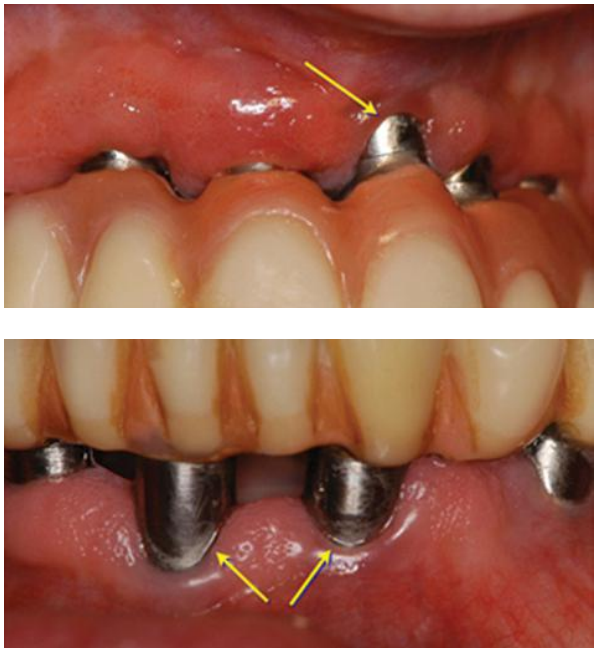

Fig. 26-2 Clinical symptoms of peri-implant mucositis, including varying signs of redness and swelling. Probing resulted in bleeding from the margin of the mucosa (arrows).

Clinical models

The response of the gingiva and the peri-implant mucosa to early and more longstanding periods of plaque formation was analyzed both in studies in humans and in experiments in animals. Pontoriero *et al*. (1994) engaged 20 partially edentulous human subjects in a clinical "Experimental gingivitis in man" (Löe *et al*. 1965) study. All subjects had been treated for advanced periodontal disease and thereafter had been restored with implants in one or several segments of the dentition. During a 6-month period following the prosthetic rehabilitation, the subjects were enrolled in a meticulous maintenance program that included regularly repeated supportive measures. A baseline examination was subsequently performed including assessment of plaque, soft tissue inflammation, probing pocket depth (PPD), soft tissue recession, and composition of oral biofilms. The participants refrained from all oral hygiene measures for 3 weeks. It was observed that during this interval, plaque build-up (amount and composition) and the soft tissue response to the microbial challenge, for example inflammation and PPD change, developed in a similar manner in the tooth and implant segments of the dentition.

Zitzmann *et al*. (2001) studied the response to plaque formation in the soft tissues at implant and tooth sites in humans. Twelve subjects with healthy periodontal and peri-implant conditions were asked to refrain from tooth/implant cleaning for a period of 3 weeks (Fig. 26-3). Clinical examinations were performed and soft tissue biopsies were harvested prior to and at the end of the plaque accumulation period. It was demonstrated that plaque build-up was associated with clinical signs of soft tissue inflammation and also an increase in the scale of soft tissue infiltrate by inflammatory cells.

Salvi *et al*. (2012) reported on the reversibility of experimentally-induced gingivitis/peri-implant mucositis in a study including 15 partially dentate subjects. Following an initial period of plaque formation to induce mucosal inflammation, oral hygiene procedures were re-instituted. The inflammation gradually resolved in the gingiva as well as in the peri-implant mucosa.

Preclinical models

In a carefully supervised experiment in the dog, Berglundh *et al*. (1992) compared the reaction of the gingiva and the peri-implant mucosa to 3 weeks of *de novo* plaque formation. The mandibular premolars in one side of the mandible were extracted, leaving the premolars on the contralateral side as controls. After 3 months of socket healing, implants were inserted in the edentulous ridge. The animals were placed in a plaque-control program to allow for ideal healing of the mucosa at the implants and to prevent gingivitis from occurring in the tooth segments of the dentition. After this healing period, the dogs were examined and samples from the minute biofilms that

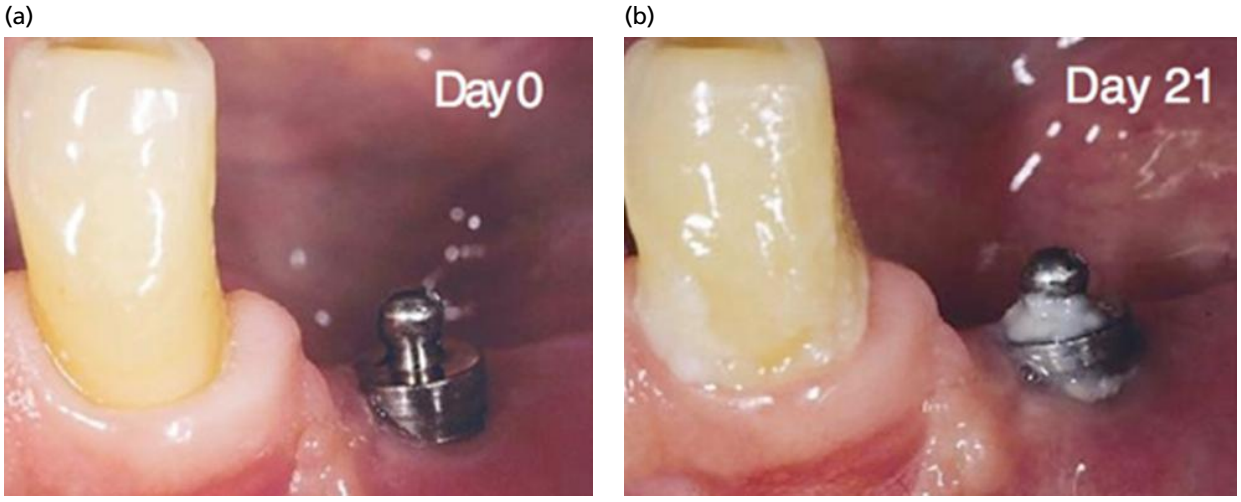

Fig. 26-3 (a) Clinical photograph of a site with healthy gingiva and peri-implant mucosa. (b) Same site following 3 weeks of plaque formation.

were present on the implant and the tooth surfaces were harvested. The plaque-control program was terminated and the animals given a soft diet that allowed gross plaque formation. Re-examinations, including clinical assessment, sampling of plaque from teeth and implants, as well as biopsy, were performed after 3 weeks. During the course of the study, it was observed that similar amounts of plaque formed on the teeth and implant segments of the dentition. The compositions of the developing plaques on the teeth and implants were also similar. It was therefore concluded that early microbial colonization on titanium implants followed the same pattern as that on teeth (Leonhardt *et al*. 1992). Both the gingiva and the peri-implant mucosa responded to this microbial colonization with the establishment of overt inflammatory lesions, that is infiltrates of leukocytes in the connective tissue. The lesions in the gingiva and in the peri-implant mucosa were similar both with respect to size and location. Hence, both lesions were consistently found in the marginal portion of the soft tissues and between the keratinized oral epithelium and the junctional or barrier epithelium.

With increasing duration of plaque build-up (3 months) in the dog model described above, the lesions in the peri-implant mucosa seemed to expand and progress further "apically", while the gingival lesions remained unchanged (Ericsson *et al*. 1992). Furthermore, the lesions in the peri-implant mucosa contained a much smaller number of fibroblasts than the corresponding infiltrates in the gingiva. In any inflammatory lesion of longstanding, periods of breakdown and periods of repair interchange. It was suggested, therefore, that in the gingival lesion, the amount of tissue breakdown that occurred during the 3-month interval was more or less fully compensated for by tissue build-up during a subsequent phase of repair. In the lesions in the peri-implant mucosa, the tissue breakdown was not fully recovered by reparative events. This reduced build-up may have been the reason for the resulting additional propagation and spread of the lesion in the peri-implant mucosa.

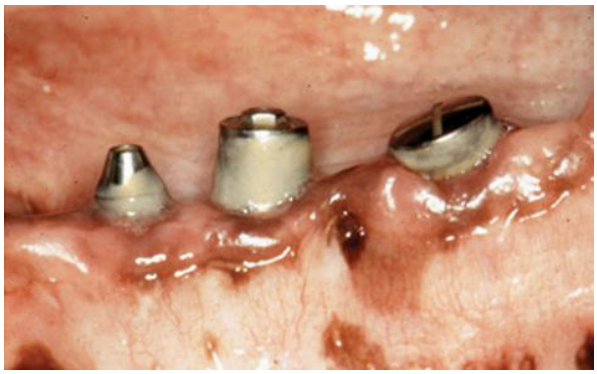

Fig. 26-4 Clinical photograph showing 5 months of undisturbed plaque formation on three different types of implants in a Beagle dog.

In a similar dog experiment, Abrahamsson *et al.* (1998) studied soft tissue lesions after 5 months of plaque formation at three different implant systems (Fig. 26-4). They observed that the response of the peri-implant mucosa to longstanding plaque formation appeared to be independent of the implant system that harbored the biofilm and that the apical extension of the inflammatory lesion was consistently within the dimensions of the barrier epithelium for all three implant systems (Fig. 26-5).

Conclusion: Peri-implant mucositis and gingivitis have many features in common. The host response to bacterial challenge at teeth and implants includes the development of clinical signs of inflammation and the establishment of inflammatory lesions in the mucosal/gingival connective tissues. Since peri-implant mucositis represents the obvious precursor of peri-implantitis, as does gingivitis for periodontitis, treatment of mucositis appears to be an important prerequisite for the prevention of peri-implantitis (Lang *et al*. 2011).

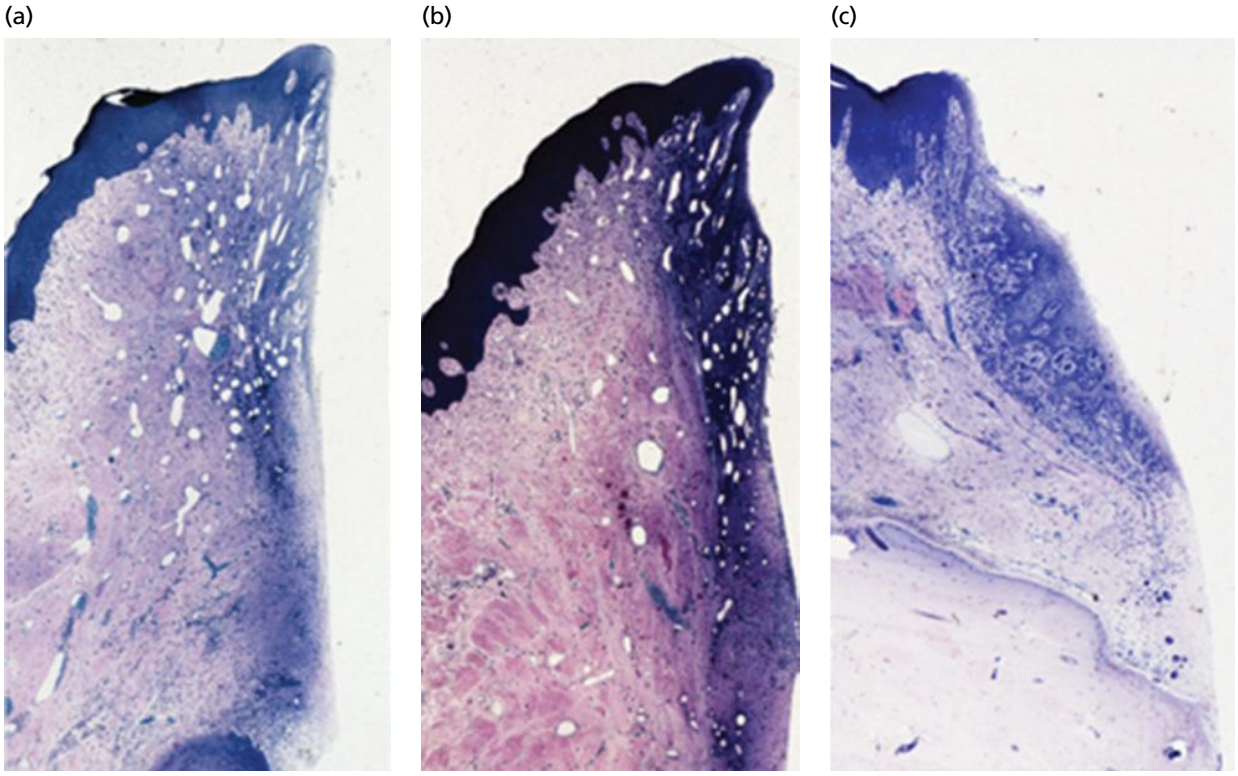

Fig. 26-5 (a–c) Microphotographs illustrating inflammatory cell infiltrates (ICT) established in the peri-implant mucosa around the three implant types shown in Fig. 26-4. The apical extension of the ICT is consistently within the dimension of the barrier epithelium for all three implant types.

Peri-implantitis

Clinical features and diagnosis

Peri-implantitis represents a clinical condition that includes the presence of an inflammatory lesion in the peri-implant mucosa and loss of peri-implant bone. Therefore, diagnosis of peri-implantitis requires detection of both bleeding on probing (BoP) and bone loss on radiographs. Peri-implantitis initially affects the marginal part of the peri-implant tissues and the implant may remain stable and in function for varying periods of time. Implant mobility is therefore not an essential symptom for peri-implantitis, but may occur in the final stage of disease progression and indicates complete loss of integration.

As pointed out for the clinical characteristics of peri-implant mucositis, various factors such as the morphology of the peri-implant mucosa and position of the implant may also influence the clinical appearance of inflammation in peri-implantitis. Probing is therefore a prerequisite in the examination of peri-implant tissues and should include assessment of both BoP and PPD. Pus is a common finding in peri-implantitis sites (Fransson *et al*. 2008).

Hence, the clinical appearance of peri-implantitis may vary and may not always be associated with overt signs of pathology. Two different cases are shown in Figs. 26-6 and 26-7. While plaque and calculus together with clinical signs of inflammation are present in the case shown in Fig. 26-6, the case shown in Fig. 26-7 does not reveal such symptoms. Probing the site shown in Fig. 26-7, however, revealed a PPD of about 10 mm, BoP, and suppuration.

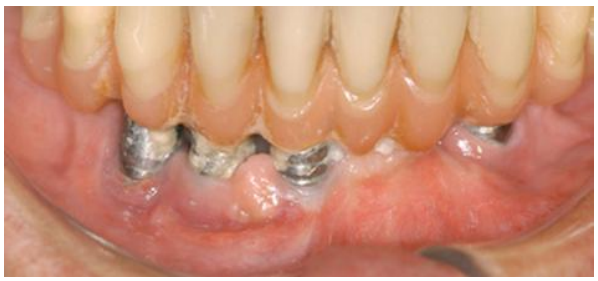

Fig. 26-6 Clinical symptoms of peri-implantitis. Note the large amounts of plaque and calculus and visible signs of inflammation in the peri-implant mucosa.

Bone loss around implants observed in radiographs obtained from sites with peri-implantitis (Fig. 26-8) appears also to be symmetric, that is there is a similar amount of bone loss at mesial, distal, buccal, and lingual aspects of the implants. The morphology of the osseous defect, however, may vary depending on the buccal–lingual (palatal) dimension of the alveolar ridge. Thus, in sites where the width of the ridge exceeds that of the peri-implantitis lesion, a buccal and lingual bone wall may remain and a crater form. Conversely, in sites with a narrow ridge, the buccal and lingual bone will be resorbed and lost during progression of peri-implantitis.

Conclusion: Symptoms of peri-implantitis relate to the infectious/inflammatory nature of the lesion.

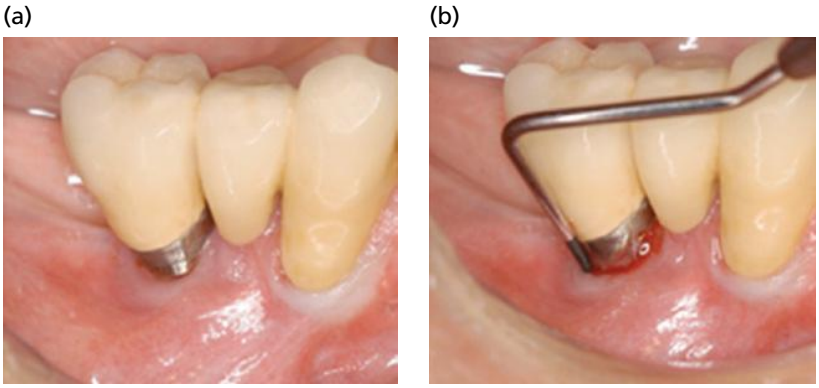

Fig. 26-7 Clinical photographs from an implant-supported crown in the premolar position in the left side of the mandible. (a) No or minor signs of inflammation in the surrounding mucosa. (b) Probing resulted in bleeding and suppuration from the implant site in the lateral incisor position.

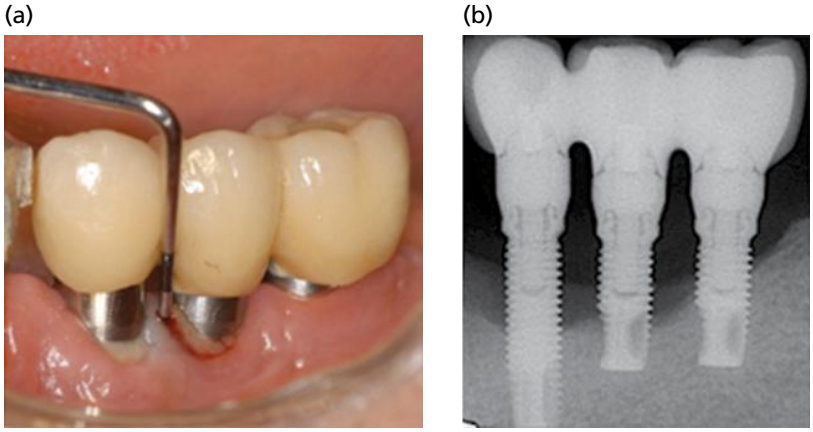

Fig. 26-8 Clinical (a) and radiographic (b) characteristics of three implant sites with peri-implantitis in the left side of the mandible. Note the presence of swelling and suppuration in the peri-implant mucosa (a) and the pronounced bone loss around the implants in the radiograph (b).

Thus, in addition to radiographic evidence of bone loss, consistently there are clinical signs of mucosal inflammation, including swelling and redness of the mucosa as well as bleeding on gentle probing. Suppuration from the "pocket" is also a frequent finding. The implant may remain stable until only minute amounts of "osseointegration" remain.

Human biopsy material

While precise information exists on the histopathology of human periodontitis, so far only few studies have evaluated peri-implantitis lesions in humans (Berglundh *et al*. 2011). Studies providing information on tissues harvested from peri-implantitis sites disclosed that the mucosa contained large inflammatory cell infiltrates. Sanz *et al*. (1991) analyzed soft tissue biopsies from six patients with peri-implantitis and reported that 65% of the connective tissue portion was occupied by inflammatory cells. Piattelli *et al*. (1998) described some pathologic features of tissues harvested from 230 retrieved implants: at sites where the implants had been removed due to peri-implantitis, "an inflammatory infiltrate, composed of macrophages, lymphocytes and plasma cells, was found in the connective tissue around the implants". In a study including 12 human peri-implantitis lesions, Berglundh *et al*. (2004) found that the mucosa contained very large lesions in which numerous plasma cells, lymphocytes, and macrophages were present (Fig. 26-9). It was furthermore observed that the inflammatory cell infiltrate consistently extended to an area apical to the pocket epithelium and that the apical part of the soft tissue lesion frequently reached the bone tissue. Berglundh *et al*. (2004) also reported that numerous neutrophil granulocytes (polymorphonuclear leukocytes) were present in the lesions. Such cells occurred not only in the pocket epithelium and associated areas of the lesions, but also in perivascular compartments in the center of the infiltrate, that is distant from the implant surface. In the apical part of the lesion, the inflamed connective tissue appeared to be in direct contact with the biofilm on the implant surface. Gualini and Berglundh (2003) used immunohistochemical techniques to analyze the composition of peri-implantitis in a study of six subjects. Neutrophils were found in large numbers in the central portions of the infiltrate. This finding was in agreement with that made by Hultin *et al*. (2002) who analyzed the exudate that could be harvested from implant sites in 17 patients with peri-implantitis and reported the presence of large numbers of neutrophils. Immunohistochemical techniques have also been used to evaluate differences between peri-implantitis and periodontitis lesions. Bullon *et al*. (2004) observed that both types of lesions contained T and B lymphocytes, plasma cells, and macrophages, while

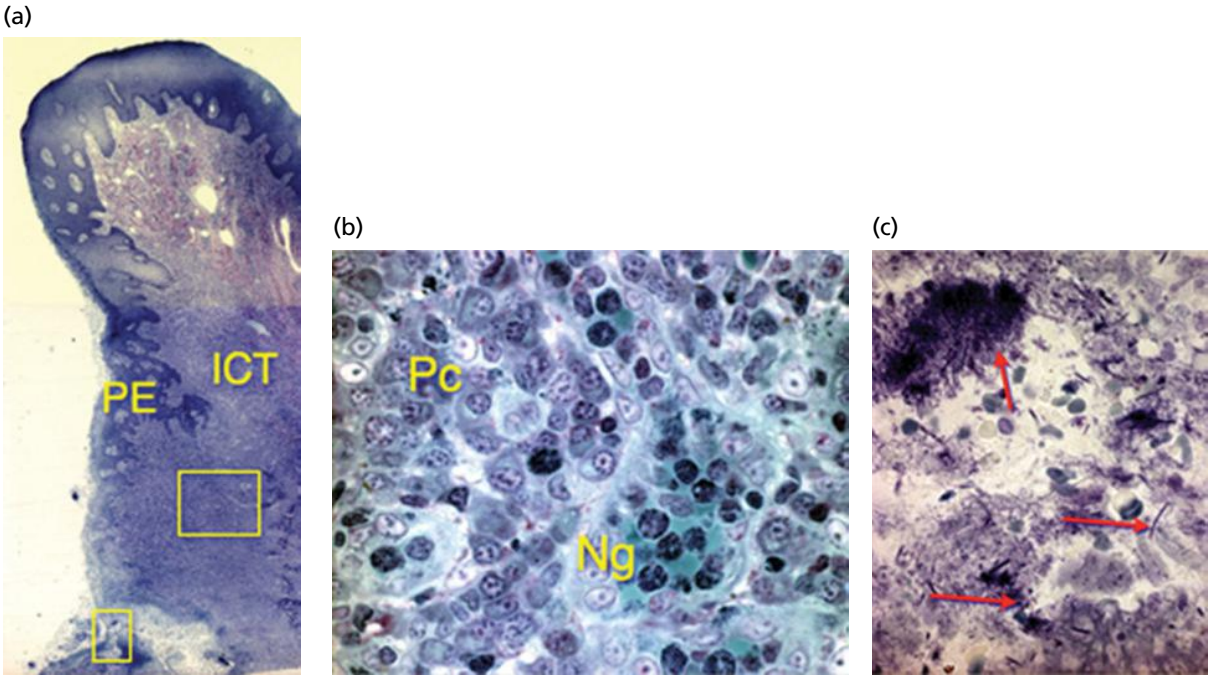

Fig. 26-9 (a) Microphotograph showing a human peri-implantitis lesion. Note the large inflammatory cell infiltrate (ICT) lateral to the pocket epithelium (PE). The implant was positioned to the left. (b) Outlined area in (a) in the profound portion of the ICT including large numbers of plasma cells (Pc) and neutrophil granulocytes (Ng). (c) Outlined area in (a) in the apical part of the ICT facing the pocket. Arrows indicate clusters of microorganisms.

Konttinen *et al*. (2006) reported that the number of cells positive for interleukin-1 alpha (IL-1α) and IL-6 was larger and the number of tumor necrosis factor-alpha (TNF-α)–positive cells smaller in peri-implantitis than in periodontitis lesions.

Preclinical models

In order to study the ability of the peri-implant mucosa to respond to long-standing plaque exposure and to manage the associated inflammatory lesions, an experimental periodontitis/peri-implantitis model was developed in the dog (Lindhe *et al*. 1992) and in the monkey (Lang *et al*. 1993; Schou *et al*. 1993). Although the experiments had somewhat varying design, their outcomes were almost identical and, hence, only the result from the dog model will be reported.

In the dog model (Lindhe *et al*. 1992), the premolars were extracted on one side of the mandible, implants were inserted, and abutment connection performed 3 months later. During the healing phase, a strict plaque control regimen was maintained and healthy tissue conditions were thereby established in all tooth and implant sites to be monitored. On a given day, the periodontitis and peri-implantitis lesions were induced. This was accomplished by terminating the plaque control regimen and placing cotton ligatures around the neck of both the premolar teeth and the implants. The ligatures were forced into a position apical to the soft tissue margins. A "pocket" between the tooth/gingiva and implant/mucosa was thereby created, a submarginal biofilm rapidly formed, and inflammatory lesions developed in the neighboring tissues. Radiographs obtained after 6 weeks of the experiment revealed that a substantial amount of bone tissue had been lost at both teeth and implant sites. The ligatures were removed. After a further 4 weeks, the animals were re-examined, radiographs obtained, bacteria sampled, and biopsies of tooth and implant sites harvested. It was observed that the plaque that had formed in the deep "pockets" was similar at tooth and implant sites, and was dominated by Gram-negative and anaerobic species (Leonhardt *et al*. 1992). This observation is consistent with findings in humans indicating that the microbiota at teeth and implants shares many features, but also that the microbiota at healthy and diseased sites – tooth sites as well as implant sites – is very different. Thus, implants and teeth that are surrounded by healthy soft tissues are associated with biofilms with small numbers of Gram-positive coccoid cells and rods. Sites with extensive periodontal and peri-implant inflammation harbor biofilms with large numbers of Gram-negative anaerobic bacteria (see Chapters 10 and 11).

Histopathologic examination of the biopsy samples from the dog study (Lindhe *et al*. 1992) revealed that there were marked differences in the size and location of the inflammatory lesions at periodontal and peri-implant sites. Thus, while the lesions in the plaque-associated periodontal sites were consistently separated from the alveolar bone by a 1-mm wide zone of non-inflamed connective tissue, the lesion in the peri-implant tissue in most situations extended to

the alveolar bone. It was concluded that the pattern of spread of inflammation was different in periodontal and peri-implant tissues. It was suggested that the peri-implant tissues, in variance with the periodontal tissues, are poorly organized to resolve progressive, plaque-associated lesions. The validity of this conclusion was substantiated in subsequent studies (Marinello *et al*. 1995; Ericsson *et al*. 1996; Persson *et al*. 1996; Gotfredsen *et al*. 2002), using similar models but allowing for different periods of tissue breakdown.

In the preclinical studies reported above, the experimental models used ligatures to induce peri-implantitis by disrupting the soft tissue seal around the implant and thereby allowing a biofilm to form in a submarginal location. The ensuing host response included an inflammatory lesion in the mucosa that over time became progressively larger. Cells in the lesion activated systems of reactions that promoted degradation of connective tissue and bone. The placement of a new ligature in a more "apical" position allowed the destructive process to continue. The size and type of ligature (e.g. cotton, silk), their corono apical position in the pocket, as well as the number of replacements determined the rate and magnitude of tissue breakdown in this so-called experimental peri-implantitis model (Berglundh *et al*. 2011).

Zitzmann *et al.* (2004) used 21 sites in dogs to study experimental peri-implantitis. After the lesions had become established, the ligatures were removed and the sites were monitored for an additional 12-months. It was observed that in 16 sites the destructive conditions persisted and caused progressive bone loss. In the remaining five sites, however, the lesions became encapsulated and no further breakdown of peri-implant bone took place.

This so-called "spontaneous progression model" (Zitzmann *et al*. 2004) was subsequently used by Berglundh *et al*. (2007). They examined the tissue reaction around custom-made implants with either a smooth, polished surface or a roughened SLA (sandblasted, large grit, acid etched) surface. During the pre-experimental period of ligature-induced breakdown, similar amounts of bone loss occurred around the two types of implants. Evaluation 5 months after the removal of ligatures, however, revealed that bone loss had progressed and that the size of the inflammatory lesion in the connective tissue was larger at the implants with the rough than with the smooth surface. The area of plaque was also larger at implants with the rough surface. It was concluded that the progression of peri-implantitis, if left untreated, is more pronounced at implants with a moderately rough surface than at implants with a polished surface.

While the study by Berglundh *et al*. (2007) used implants with custom-made surfaces, Albouy *et al*. (2008, 2009) analyzed differences in spontaneous progression of experimental peri-implantitis between commercially available implants with SLA, TiOblast, TiUnite, and turned surfaces. Spontaneous progression occurred with all implant types during the 6-month period after ligature removal. The histologic examination revealed that all specimens presented with large inflammatory lesions that extended apical of the pocket epithelium. The pocket compartment was occupied by pus, biofilm, and calculus, and the uncovered apical part of the inflammatory cell infiltrate faced the biofilm. Osteoclasts in large numbers were detected on the surface of the crestal bone and other giant-like cells occurred in the soft tissue lesion, distant from the crestal bone.

Albouy *et al*. (2012) in a subsequent experiment in dogs repeated the spontaneous progression model using implants with a similar geometry and with two different surfaces (turned and TiUnite). During the 6 months after ligature removal, a significantly larger amount of bone loss occurred around the implants with the modified surface than around the implants with the turned surface. In addition, the dimensions of inflammatory lesions, pocket epithelium, and biofilm were larger at the implants with a modified surface.

The spontaneous progression model was also used in an experiment aimed at evaluating differences between peri-implantitis and periodontitis. Thus, Carcuac *et al*. (2013) used the dog model and two kinds of implants. Experimental peri-implantitis and periodontitis were induced by ligature placement plaque formation. The ligatures were removed after 10 weeks and bone level changes were evaluated in radiographs during the following 6 months. It was reported that the amount of bone loss that occurred following ligature removal was significantly larger at implants with a modified surface than at implants with a turned surface and at teeth (Fig. 26-10). The results from the histologic examination confirmed previous findings (Lindhe *et al*. 1992) and revealed that peri-implantitis sites exhibited inflammatory lesions that were larger and extended closer to the bone crest than those in periodontitis (Figs. 26-11 and 26-12). Carcuac *et al.* (2013) also reported that the lesions in peri-implantitis contained larger proportions of neutrophil granulocytes and osteoclasts than lesions in periodontitis.

Conclusion: Peri-implantitis lesions are poorly encapsulated, extend to the marginal bone tissue, and may, if allowed to progress, lead to the loss of the implant. The large numbers of neutrophils in the peri-implantitis lesion and the absence of an epithelial lining between the lesion and the biofilm, indicate that the peri-implantitis lesions have features that are different from those of periodontitis lesions. Progression of peri-implantitis is more pronounced at implants with rough than at those with smooth surfaces.

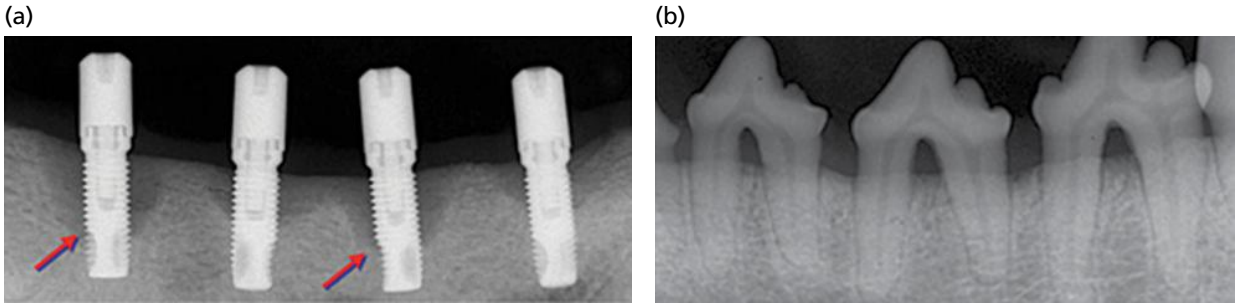

Fig. 26-10 Radiographs showing (a) experimental peri-implantitis and (b) periodontitis in the Labrador dog. Compare the greater bone loss around the implant with a modified and a turned surface (arrows).

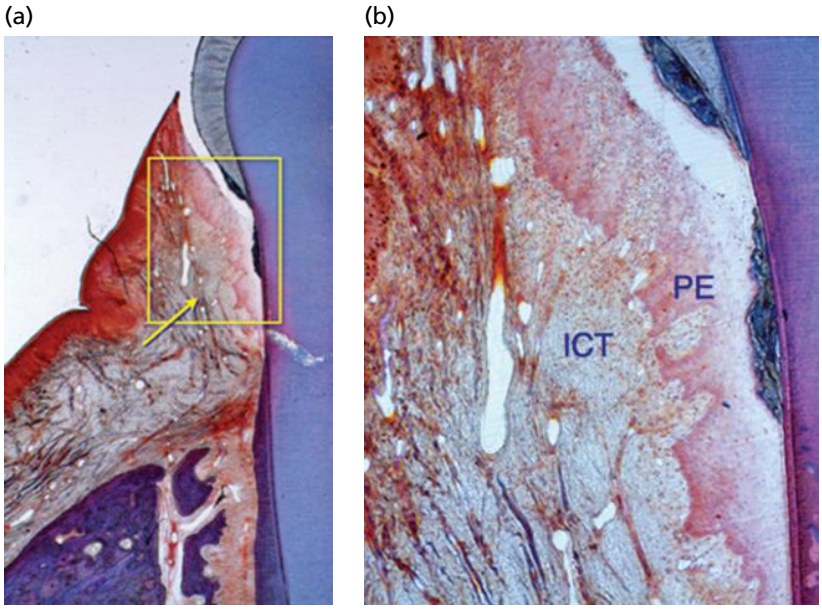

Fig. 26-11 (a) Microphotograph of a buccolingual ground section showing a periodontitis lesion. Note the apical extension of the infiltrate (arrow), but also the presence of a zone of normal connective tissue between the infiltrate and the bone crest. (b) Larger magnification of outlined area in (a). Note the calculus on the tooth surface, the pocket epithelium (PE), and the infiltrate (ICT).

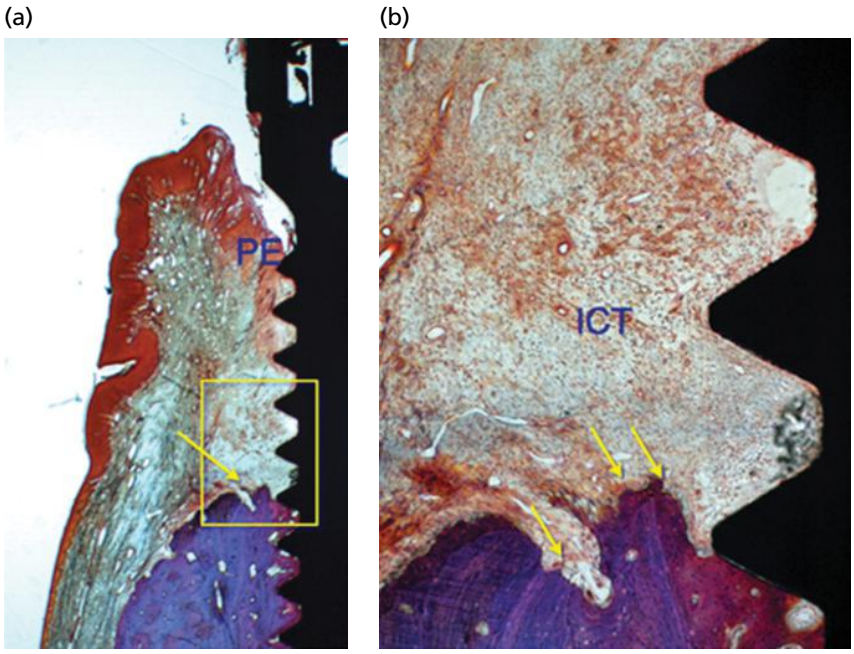

Fig. 26-12 (a) Microphotograph of a buccolingual ground section showing a peri-implantitis lesion. The apical portions of the infiltrate (arrow) extend into contact with the bone. (b) Close-up of outlined area in (a) showing the large infiltrate (ICT) apical of the pocket epithelium and in direct contact with the biofilm on the implant surface. Osteoclasts (arrows) are present on the bone surface. (PE, pocket epithelium.)

Prevalence of peri-implant diseases

Peri-implant mucositis

It is well known that assessments of the prevalence of periodontal diseases are influenced by the selection of case definitions. A higher threshold for disease criteria results in a lower prevalence. Similarly, case definitions also influence the assessment of prevalence of peri-implant diseases. Tomasi and Derks (2012) in a review identified seven different case definitions for peri-implant mucositis and another seven case definitions for peri-implantitis. BoP is a critical marker for the detection of inflammation in the peri-implant mucosa and, hence, is useful in the assessment of peri-implant mucositis. Thus, implant sites that are BoP positive but exhibit no bone loss should be diagnosed as peri-implant mucositis.

Reports on the prevalence of mucositis have, in addition to BoP, included varying levels of PPD for the diagnosis of peri-implant mucositis. Thus, Roos-Jansåker *et al*. (2006a) in a cross-sectional study on 206 patients with 987 implants applied a case definition that combined BoP and PPD of ≥4 mm, and reported that 48% of the patients and 16% of the implants had mucositis. Roos-Jansåker *et al*. (2006a) also reported that BoP at implant sites occurred in about 50% of the implants with no history of bone loss. Koldsland *et al*. (2010) in a cross-sectional study on 109 implant patients reported that about 40% of the patients and 27% of the implant sites presented with BoP and no detectable bone loss. Based on the above findings, it is reasonable to conclude that peri-implant mucositis is common in patients with dental implants.

Peri-implantitis

BoP is a marker also for peri-implantitis, that is implant sites that exhibit peri-implant mucositis together with *detectable bone loss* (in radiographs). In a consensus report from the VIII European Workshop on Periodontology (Sanz & Chapple 2012) it was recommended that a threshold of detectable bone loss around implants should be two to three times the measurement error, that is inter- and intra-examiner variability (about 0.4 mm). As for most diseases, data on the prevalence of peri-implantitis should be presented on a subject basis, whereas information regarding the number or proportion of affected implants may serve as a description of the extent of the disease.

While the finding of BoP and/or pus is an accepted clinical parameter, the amount of bone loss (assessed in radiographs) that will allow the diagnosis peri-implantitis is controversial. Table 26-1 describes studies on the prevalence of peri-implantits using different

Table 26-1 Studies on the prevalence of peri-implantitis that included >100 patients with a mean follow-up of >5 years. Different case definitions with regards to threshold levels on bone loss were used.

Study	Number of patients/implants	Function time range (years) (mean)	Case definitions Thresholds of bone loss	Prevalence (%) in patients/implants
Fransson *et al*. (2005)	662/3413	5–20 (9.1)	Bone level ≥3 threads (1.8 mm apical of reference point) and detectable bone loss (0.6 mm) from year 1	27.8/12.4
Roos-Jansåker *et al*. (2006a)	216/987	9–14 (10.8)	Bone loss from year 1 of: 0.6–1.2 mm 1.8–2.4 mm >3 mm	55.6/18.2 14.4/4.6 7.4/2.0
Koldsland *et al*. (2010)	109/351	1–16 (8.4)	Bone loss from connection of prosthesis of: >0.4 mm >2 mm >3 mm	47.1/36.6 20.4/11.4 11.7/6.0
Roccuzzo *et al*. (2010)	101/246	10	Bone loss of ≥3 mm	22.8/NR
Zetterqvist *et al*. (2010)	112/304	5	Bone loss of >5 mm	<1/<1
Marrone *et al*. (2013)	103/266	>5 (8.5)	Bone loss of >2 mm	37/23
Mir-Mari *et al*. (2012)	245/964	1–18 (6.3)	Bone level ≥2 threads (1.2 mm apical of reference point)	16.3/9.1
Cecchinato *et al*. (2013)	133/407	3–11 (5.8)	Bone loss from year 1 of: >0.5 mm >1 mm >1.5 mm >2 mm	 30/17 19/11 14/6 8/4

NR, not reported.

case definitions regarding threshold levels of bone loss. Fransson *et al*. (2005) evaluated the prevalence of progressive bone loss at implants (Brånemark System) with a function time of 5–20 years in 662 subjects. Implants that presented with bone levels at three or more threads of an implant (i.e. 1.8 mm apical to the implant neck) were identified. In addition, progressive bone loss at such implants was defined as bone loss (one thread; 0.6 mm) occurring between the 1-year examination and the 5–20 years of follow-up examination. It was reported that 27.8% (184) of the 662 included subjects had one or more implants with "progressive" bone loss. In a subsequent clinical study, Fransson *et al*. (2008) reported that about 94% of the implant sites with "progressive" bone loss exhibited BoP. The extent of peri-implantitis and the pattern of bone loss were also analyzed. About 40% of the implant sites in the peri-implantitis–affected subjects exhibited progressive bone loss. Peri-implantitis occurred in all jaw locations but was most frequent in the mandibular front region (Fransson *et al*. 2009). Further analysis using multilevel modeling revealed that bone loss in peri-implantitis had a non-linear pattern and increased over time (Fransson *et al*. 2010).

Roos-Jansåker *et al*. (2006a) examined 216 implant-treated patients after 9–14 years of function and reported that 16% of the subjects and 6.6% of the implants had peri-implantitis. However, they used a different definition of peri-implantitis from that used by Fransson *et al*. (2005) and suggested that a certain amount of bone loss (1.8 mm compared with the 1-year data) together with BoP should be required for the diagnosis of peri-implantitis. Data presented in the study by Roos-Jansåker *et al*. (2006a) indicated that different thresholds of bone loss influenced the reported prevalence of peri-implantitis. Thus, bone loss of 0.6–1.2 mm from year 1 was detected in 56.6% of the patients (see Table 26-1). Similar findings were reported by Koldsland *et al*. (2010) from a study of the prevalence of peri-implantitis in a group of 109 patients: using threshold bone losses of 0.4 mm, 2 mm, and 3 mm, 47.1%, 20.7%, and 11.7% of the patients displayed peri-implantitis, respectively. High thresholds for bone loss were also applied by Roccuzzo *et al*. (2010) and Zetterqvist *et al*. (2010). In the 10-year prospective study on 101 implant patients by Roccuzzo *et al*. (2010), 22.8% of the patients presented with bone loss of ≥3 mm, while in the 5-year study by Zetterqvist *et al*. (2010), only one of 112 patients exhibited bone loss of >5 mm. Cecchinato *et al*. (2013) presented data on peri-implantitis using four different thresholds of bone

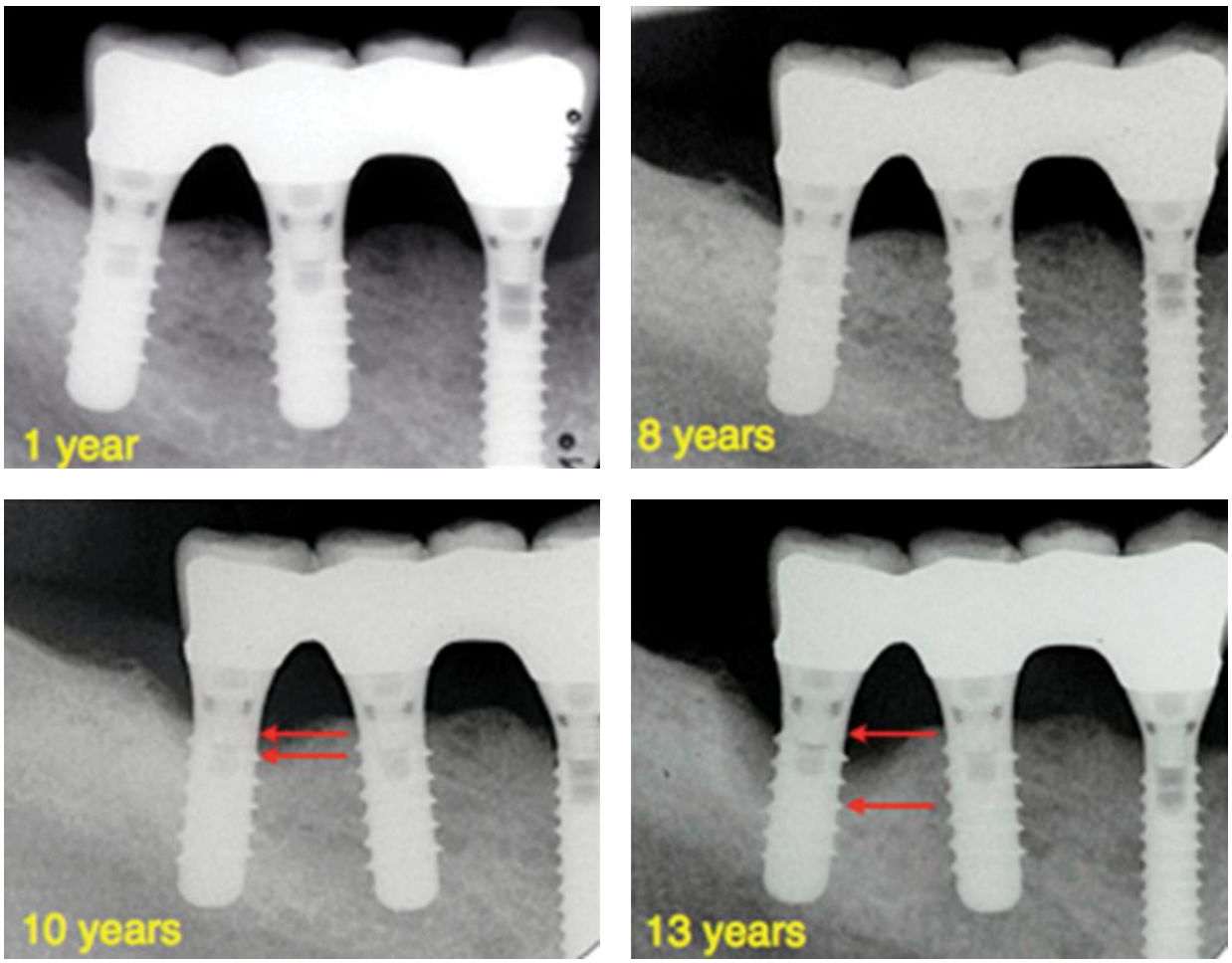

Fig. 26-13 Radiographic characteristics of three implant sites in the right side of the mandible at 1, 8, 10, and 13 years of follow-up. While no bone loss occurred between the 1-year and the 8-year examinations, the 10-year and 13-year examinations revealed that about 1 mm and 4 mm, respectively, of bone loss occurred around the posterior implant.

loss ranging from 0.5 to 2 mm. Over this range, the prevalence of the condition declined from 30% to 8% of the examined patients.

Taken together, the threshold level of bone loss used in a case definition strongly influences the results from the assessment of prevalence of peri-implantitis. This problem is illustrated in Fig. 26-13. The radiographic bone loss that occurred around the posterior implant between the 8-year and the 10-year examination was about 1 mm, while the bone loss that was assessed at 13 years of follow-up amounted to 4 mm. Thus, the use of a threshold level of bone loss of ≥1 mm would not account for the bone level change that occurred between 8 and 10 years.

Consensus statements from the 8th EFP Workshop identified shortcomings in assessments of the prevalence of peri-implantitis (Tomasi & Derks 2012; Sanz & Chapple 2012). The cross-sectional studies referred to in the reviews mainly used convenience samples of limited size. Such samples may not represent the target population (i.e. the true prevalence). Current data, however, indicate that both peri-implant mucositis and peri-implantitis are common in patients with dental implants. The proportion of patients exhibiting one or more implants with peri-implantitis, identified with case definitions that included bone loss of >0.5 mm after year 1, varies between 30% and 55%.

Risk factors for peri-implantitis

Risk factors for peri-implantitis can be categorized according to the patient, clinician/treatment procedures, and implant characteristics.

Patients at risk

There is evidence that patients with a high susceptibility to periodontitis exhibit a higher risk for peri-implantitis. A number of systematic reviews have been published in this field and outcomes of implant therapy in periodontally compromised patients are discussed in detail in Chapter 33. Although few clinical studies were included in the systematic reviews, they consistently showed higher frequencies of implant loss, marginal bone loss, and clinical signs of inflammation in peri-implant soft tissues in patients with a history of periodontitis (Hardt *et al*. 2002; Karoussis *et al*. 2003; Roos-Jansåker *et al*. 2006b). In line with the association between history of periodontitis and peri-implantitis, it is logical to assume that known modifying factors for periodontitis, such as smoking and diabetes, may also be valid for peri-implantitis. Heitz-Mayfield (2008) in a review concluded that poor oral hygiene, history of periodontitis, and cigarette smoking are risk indicators for peri-implant diseases. Roccuzzo *et al*. (2010) in a 10-year prospective study reported that patients with a history of severe periodontitis and, in particular, a subgroup of these patients who did not attain a supportive periodontal therapy program, presented with a larger number of lost implants and a higher number of sites with marginal bone loss than periodontally healthy patients. This underlines the importance of supportive therapy in general, but in particular in patients with a history of severe periodontitis.

Design of suprastructure

Treatment procedures and the design of prosthesis may also be regarded as a potential risk for peri-implantitis. The neglect of access for self-performed and professional infection control procedures when designing the supraconstruction to be connected to implants entails an increased risk for peri-implant disease. In the attempt to accomplish appropriate prosthetic rehabilitation in terms of function, as well as to address phonetic and esthetic demands, clinicians may overlook the need for self-performed oral hygiene (Fig. 26-12). It is imperative that the implant-supported prosthesis allows appropriate access for infection control.

Implant surface characteristics

Risk factors for peri-implant disease also relate to specific features of the implants, such as design and surface characteristics. While clinical evidence in this field is weak, data from preclinical studies indicate that implant surface characteristics influence progression of peri-implantitis. Baelum and Ellegaard (2004) presented data on 128 patients whose dentition was restored with implant-supported prosthesis using either implants with a rough surface [titanium plasma sprayed (TPS)] or implants with a moderately rough surface (TiOblast). Patients with the rough surface implants presented with higher frequencies of implant loss after 5 (5.7% versus 2.6%) and 10 years (22.3% versus 2.6%) of follow-up. While the proportions of implants demonstrating pronounced bone loss (≥3.5 mm) after 5 years were 5.6% and 5.0% for the two types of implants, the data obtained from the 10-year examination indicated a higher frequency of such sites for the rough surface implants than the moderately rough surface implants (13.6% versus 5.0%). It should be realized, however, that the patients examined at the 5-year and 10-year follow-up in this study represented only about 30–50% of the total sample. Åstrand *et al*. (2004) in a 3-year study on 28 patients with implants with a turned or rough (TPS) surface reported that peri-implantitis was found in seven of the rough surface implants but in none of the turned surface implants. Mir-Mari *et al*. (2012) presented data from a cross-sectional study on the frequency of peri-implantitis in a group of 245 patients who had received implants with a turned surface, TiUnite surface, and Osseotite surface. While the overall proportion of implants exhibiting peri-implantitis was 9.1%, the frequencies for the different surface categories were 9.3% (turned), 10.1% (TiUnite), and 6.0% (Osseotite). The authors also presented the results on frequencies on peri-implantitis

with regards to the function time of the different types of implants and concluded that turned implants had the longest mean follow-up (11.3 years), while TiUnite and Osseotite surface implants were followed up for 3.5 and 5.9 years, respectively. The results thus indicate that implant surface characteristics may influence the onset of peri-implantitis.

In the series of preclinical studies described above (Berglundh *et al*. 2007; Albouy *et al*. 2008, 2009, 2012) it was demonstrated that the implant surface characteristics influenced the degree of spontaneous progression of experimentally induced peri-implantitis. It should be kept in mind, however, that in these studies, a limited number of implant types were evaluated. It is thus not possible to determine if any particular type of implant system or implant surface is associated with a greater risk for peri-implantitis. On the other hand, the experimental studies do demonstrate that continuous plaque formation at sites where a peri-implantitis lesion has become established and ligatures removed, may result in additional destruction of soft and hard tissue components of peri-implant tissues and that this progression of disease is influenced by implant surface characteristics.

Conclusion

Studies in man and experiments in animals have documented that *de novo* formation of a biofilm on the implant surface initiates a host response that involves the establishment of an inflammatory lesion in the peri-implant mucosa (peri-implant mucositis). This lesion is initially located in the connective tissue immediately lateral to the barrier epithelium and is, in many respects, similar to that which develops in the gingiva when plaque forms on adjacent tooth surfaces. In the continued presence of a submarginal biofilm, the lesion in the marginal mucosa around implants may occasionally spread in an "apical" direction to involve the hard tissue, compromise osseointegration, cause varying degrees of marginal bone loss (peri-implantitis), and eventually cause the loss of the implant.

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Part 8: Tissue Regeneration

Chapter 27

Periodontal Wound Healing

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Introduction

The structure and function of the periodontium is determined by the integration of four main tissues: periodontal ligament (PDL), tooth root cementum, alveolar bone, and gingiva. Collectively, they provide a biologic and physical barrier to multiple challenges that the teeth sustain as a result of the occlusal function and the challenging microbial environment of the oral cavity. This integrity is most commonly compromised due to chronic inflammation triggered by complex bacterial communities. Nonetheless, the periodontium represents a resilient organ that could be described as a dynamic structure that is sensitive to a variety of factors and with an inherent capacity to translate mechanical stimuli into biochemical signals that govern its homeostasis (Burger *et al*. 1995; Duncan & Turner 1995; Marotti 2000; Marotti & Palumbo 2007; Bonewald & Johnson 2008). Its structure and function during remodeling and healing is determined by the orchestration of important bioactive proteins [platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), insulin-like growth factor-1 (IGF-1), transforming growth factor beta 1 (TGF-β1), etc.] (Long *et al*. 2002; Sato *et al*. 2002; Tsuji *et al*. 2004; Yang *et al*. 2006), resulting in an increased adaptive potential that protects and maintains the integrity of its four fundamental components (Fig. 27-1).

In humans, the detrimental changes that the tooth-supporting tissues undergo are primarily the result of inflammatory periodontal diseases that undermine and disrupt the functional and structural integrity of the alveolar bone, the PDL, and the cementum. The restoration of the original structure, properties, and function of these tissues is the ideal and desired outcome of periodontal therapy. Unfortunately, altered healing often disrupts the normal restoration of the periodontium and as a result different clinically compromised outcomes can be identified.

Wound healing: Outcomes and definitions

Before exploring the cascade of cellular and molecular events of wound healing, it is essential that the particular healing patterns that have been recognized in the periodontal complex are appreciated (Table 27-1). From a basic histologic point of view, the types of healing outcomes that can be met in the periodontium are described in Table 27-2.

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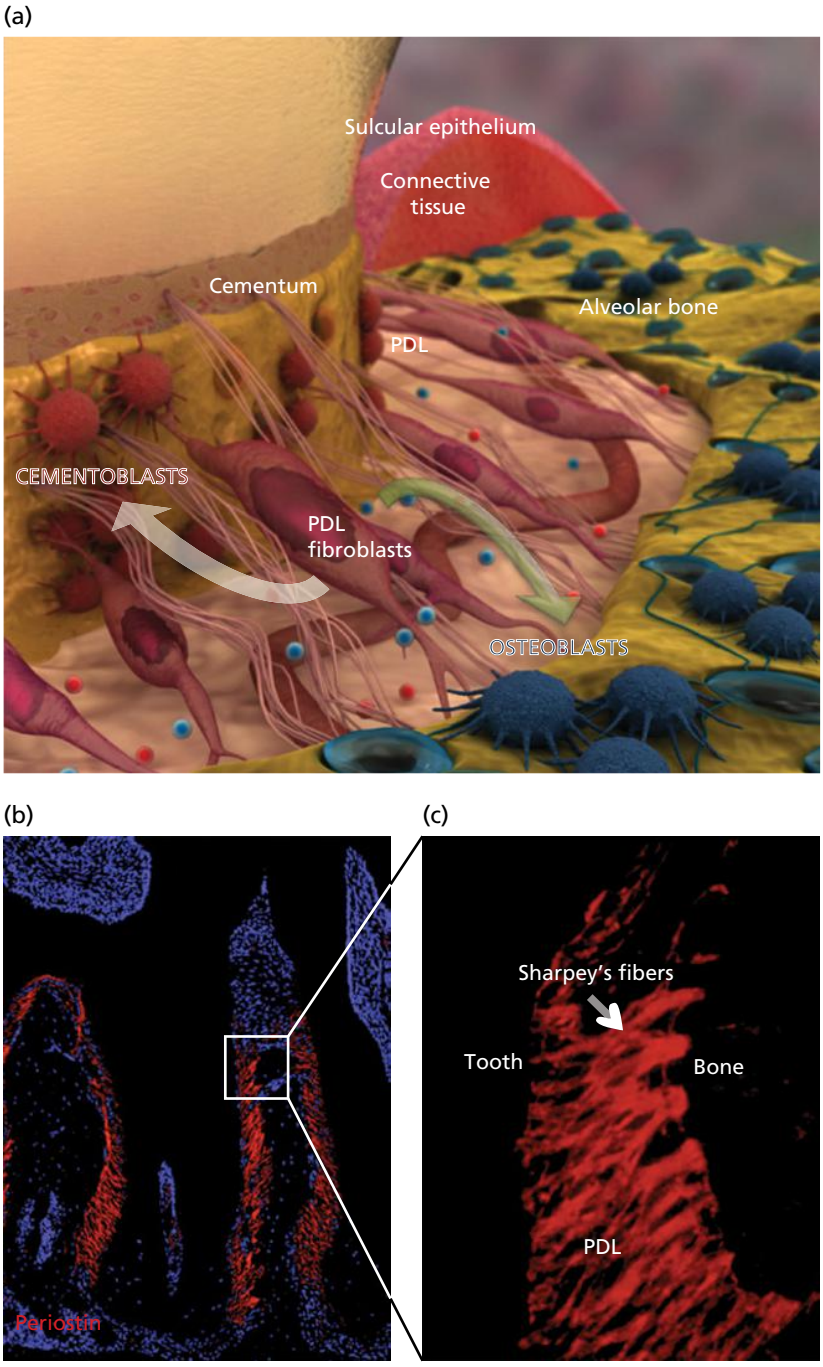

Fig. 27-1 (a) The tooth-supporting apparatus (i.e. periodontium) includes the alveolar bone, the periodontal ligament (PDL), the cementum, and the gingiva. Collectively, they represent a dynamic tissue complex with mechanical and biologic functions that synergistically determine the tissue adaptive potential and its ability to sustain microbiologic and mechanical challenges. (b) The functional periodontal system is characterized by distinct fibrilar structures known as Sharpey's fibers that connect the alveolar bone to the tooth surface cementum (red fluorescent immunostaining for periostin).

Table 27-1 Healing patterns in the periodontal tissues.

Healing by first intention	Involves the wound edges being brought together using sutures. Primary intention wounds are associated with minimal tissue loss and regeneration predominates over fibrosis
Healing by second intention	Occurs in surgical wounds that are left to heal without approximating the edges. The wound then fills with granulation tissue from the bottom up. The epithelium then fills in over the top of the granulation tissue. Scarring is evident as there is significant fibrosis
Healing by third intention	Where there is great loss of tissue, the wound must heal by contraction of the wound edges and the formation of granulation tissue. In some cases, the presence of a foreign body or infection may be suspected, and these wounds are left open deliberately for several days until the potential complication has resolved. When resolution has occurred, the wound edges can be brought together (approximated) and the wound proceeds to heal
Partial-thickness healing	Occurs when a partial-thickness wound is closed primarily by epithelialization. This wound healing involves the superficial portion of the dermis (lamina propria). There is minimal collagen deposition and an absence of wound contraction

Table 27-2 Outcomes of periodontal wound healing.

Repair	Healing of a wound by tissue that does not fully restore the architecture or the function of the part. Within the periodontal wound, it refers to restoration of a normal gingival sulcus at the same level as the base of the previous pathologic periodontal pocket. Often repair is typified by the presence of a long junctional epithelium
Reattachment	Refers to the reattachment of the gingiva to areas from which it was mechanically removed
New attachment	Occurs when newly generated fibers are embedded in new cementum on a portion of the root that was uncovered by disease
Regeneration	Reproduction or reconstruction of a lost or injured part in such a way that the architecture and function of the lost or injured tissues are completely restored. This takes place by growing precursor cells replacing lost tissue
Resorption	Loss or blunting of some portion of a root, sometimes idiopathic, but also associated with orthodontic tooth movement, inflammation, trauma, endocrine disorders, and neoplasia
Ankylosis	Fusion of the tooth and the alveolar bone

Table 27-3 Applications of cell therapies for periodontal tissue engineering.

Cell type	Graft type	Defect type	Studies
Bone marrow stromal cells	Auto	Class III defects	Kawaguchi *et al*. (2004), Hasegawa *et al*. (2006)
	Auto	Periodontal fenestration	Li *et al*. (2009)
	Auto	Osteotomy	Yamada *et al*. (2004a–c)
Adipose stromal cells		Periodontal palatal defects	Tobita *et al*. (2008)
Periodontal ligament cells	Auto	Class II defects	Dogan *et al*. (2003)
	Auto	Periodontal fenestration	Akizuki *et al*. (2005)
	Allo/xeno	Periodontal fenestration	Lekic *et al*. (2001)
Periodontal ligament stem cells	Allo	Ectopic	Seo *et al*. 2004)
	Allo	Periodontal fenestration	Dogan *et al*. (2003), Chang *et al*. (2007)
	Auto	Periodontal defects	Liu *et al*. (2008)
Cementoblasts	Allo	Ectopic	Jin *et al*. (2003)
	Allo	Periodontal fenestration	Zhao *et al*. (2004)
Dental follicle cells	Allo	Ectopic	Jin *et al*. (2003), Zhao *et al*. (2004)
	Allo	Periodontal fenestration	Zhao *et al*. (2004)

Source: Rios *et al*. (2011). Reproduced with permission from the American Academy of Periodontology.

Wound healing biology

The process of wound healing is the body's primary mechanism to restore tissue integrity upon injury. If wound healing does not occur properly, chronic disruption of the protective barrier may lead to severe physiologic, immunologic, and metabolic abnormalities. Wound healing basically represents a dynamic process that involves several cell types and biologic mediators. Within the active system of the periodontal wound, cell populations migrate, differentiate, and proliferate; epithelial and connective tissues interact; and a vast array of cytokines and extracellular matrix (ECM) molecules orchestrates the whole process that takes place in overlapping phases.

Phases of wound healing

The general principles of healing, and the cellular and molecular events observed in extraoral sites, also apply to the healing processes that take place following periodontal surgery. Traumatic injury causes capillary damage and hemorrhage, and, as a result, a blood clot is formed. The formation of a clot is the immediate response to any trauma. The clot has two functions: it temporarily protects the denuded tissues and it serves as a provisional matrix for cell migration. The blood clot consists of all cellular components of blood (including red and white blood cells and platelets) in a matrix of fibrin, plasma fibronectin, vitronectin, and thrombosporin. Beyond this, the process has been divided into three stages:

1. Inflammation phase
2. Granulation phase
3. Matrix formation and remodeling (maturation) phase (Wikesjo *et al*. 1992).

Each of the steps of wound healing is essential to success, but the initial healing process often determines the outcome.

Inflammatory phase

The growth factors present in the clot recruit inflammatory cells, and then serve to regulate the granulation process. Within hours of injury, inflammatory cells (predominantly neutrophils and monocytes) populate the clot. These cells cleanse the wound of bacteria and necrotic tissue through phagocytosis and release of enzymes and toxic oxygen products. Within 3 days, the inflammatory reaction moves into its late phase. Macrophages migrate into the wound area and these macrophages contribute to the cleansing process by phagocytosis of used polymorphonuclear leukocytes and erythrocytes. Additionally, macrophages release a number of biologically active molecules such as inflammatory cytokines and tissue growth factors, which recruit further inflammatory cells as well as fibroblastic and endothelial cells, thus playing an essential role in the transition of the wound from the inflammatory into the granulation tissue formation phase.

Granulation phase

The neutrophil population is overtaken by macrophages within a few days. Macrophages also serve the purpose of wound decontamination. They play an important role in the formation of granulation tissue. Granulation tissue formation begins on approximately day 4. Macrophages constitutively release growth factors that promote the healing process. Growth factors and cytokines secreted by macrophages are involved in the proliferation and migration of fibroblasts, endothelial cells, and smooth muscle cells into the wound area. The cells in the wound proliferate around the radius of the wound site developing cell-to-cell and cell-to-matrix connections. Macrophages and fibroblasts continue to express growth factors that regulate the healing process, both in an exocrine and autocrine manner. Studies have shown that wound sites supplemented with growth factors have an accelerated rate of granulation tissue formation (Sporn *et al*. 1983). At 7 days after initiation of wound healing, granulation dominates the wound site and the initial collagen fibers are being formed. Eventually, cells and matrix form cell-to-cell and cell-to-matrix links that generate a concerted tension resulting in tissue contraction. The phase of granulation tissue formation gradually develops into the final phase of healing in which the reformed, more cell-rich tissue undergoes maturation and sequenced remodeling to meet functional needs

Maturation phase

Fibroblasts responsible for the replacement of the provisional ECM produce a new collagen-rich matrix. Approximately 1 week following wounding, and once the collagen matrix has been synthesized, some fibroblasts undergo transformation into myofibroblasts and express α-smooth muscle actin. This transformation and synthesis is responsible for wound contraction. Endothelial cells, responsible for angiogenesis, migrate into the provisional wound matrix to form vascular tubes and loops, and as the provisional matrix matures, the endothelial cells undergo programmed cell death (apoptosis) and the number of vascular units is reduced. Maturation of the granulation tissue will lead to the regeneration or repair (scar formation) of the injured tissues. Whether the damaged tissues heal by regeneration or repair depends upon two crucial factors: the availability of the necessary cell type(s) and the presence or absence of cues and signals necessary to recruit and stimulate these cells.

Factors that affect healing

It is important to remember that in the periodontium as well as in other areas of the body the healing potential is affected by local and systemic factors.

Local factors

Healing after gingival and periodontal surgery can be delayed and altered by numerous local factors. Some of these factors include:

- Plaque microorganisms
- Excessive tissue manipulation during treatment
- Trauma to the tissues
- Presence of foreign bodies
- Repetitive treatment procedures that disrupt the orderly cellular activity during the healing process
- Inappropriate vascular perfusion to the surrounding area.

Healing is therefore improved by debridement (removal of degenerated and necrotic tissue), immobilization of the healing area, and pressure on the wound. The cellular activity in healing entails an increase in oxygen consumption. However, healing of the gingival tissue is not accelerated by artificially increasing the oxygen supply beyond the normal requirements (Glickman *et al*. 1950).

Systemic factors

It is clearly reported that healing capacity diminishes with age (Holm-Pedersen & Löe 1971). Healing is also impaired by insufficient food intake; systemic disorders that interfere with the use of nutrients; and deficiencies in vitamin C (Barr 1965), proteins (Stahl 1962), and other nutrients.

Hormones also have an impact on healing. Systemically administered glucocorticoids such as cortisone hinder repair by depressing the inflammatory reaction or by inhibiting the growth of fibroblasts, the production of collagen, and the formation of endothelial cells. Systemic stress, thyroidectomy, testosterone, adrenocorticotropic hormone, and large doses of estrogen suppress the formation of granulation tissue and impair healing (Butcher & Klingsberg 1963).

Progesterone increases and accelerates the vascularization of immature granulation tissue (Lindhe & Brånemark 1968) and appears to increase the susceptibility of the gingival tissue to mechanical injury by causing dilation of the marginal vessels (Hugoson 1970).

Periodontal wound healing

For functional periodontal regeneration to occur, temporal and spatial progress in a similar sequence to that involved in the natural formation and development of the periodontium is needed (Chen *et al*. 2011). Although the exact cellular and molecular events are still not clear, cells must first migrate and attach to the denuded root surface. By using the rat fenestration defect model, a microenvironment that favors the proliferation, migration, and maturation of mesenchymal progenitors to the defective area of the PDL or the host bone has been observed (Lekic *et al*. 1996a, b). This process is mediated and coordinated by soluble factors, other cells, and ECM. The early healing process follows the conserved sequence of wound healing that is initiated by blood coagulation and migration of neutrophils and monocytes for wound debridement and bone resorption. Bone formation typically initiates from the bony margins of the lesions (Rajshankar *et al*. 1998). Within days after surgery, a thin cementum layer with a connective tissue attachment can be observed, particularly on the apical side of the teeth where the cementum is thicker compared with the narrow coronal region (King *et al*. 1997). Once mineralized tissues are established, PDL fiber orientation, directionality, and integration into both cementum and alveolar bone are mediated by appropriate mechanical loading (Mine *et al*. 2005; Rios *et al*. 2011). It is therefore crucial that investigators, according to the timeline these processes follow, select the appropriate time point(s) to determine the therapeutic efficacy "window" of a candidate periodontal-engineered device or bioactive molecule (Fig. 27-2).

Periodontal wound healing certainly is considered a more complex process compared to epidermal wound healing. The native periodontium includes cementum, a functionally oriented PDL, alveolar bone, and gingiva. The interfaces between these tissues as well as the transgingival position of the tooth represent a constant challenge during the restoration of the integrity of the native structures as they seek to create a new connection to the non-vascular and non-vital hard tissue of the root surface within the context of an open system that is permanently contaminated and under a significant "bacterial load". It is therefore not surprising that the healing that results following all types of gingival and periodontal therapy can be quite variable.

The most basic requirement for successful periodontal treatment is a clean, biofilm-free, decontaminated root surface. Therapy includes both surgical and non-surgical modalities, which result in instrumentation of the affected tissue. This creates a wound in

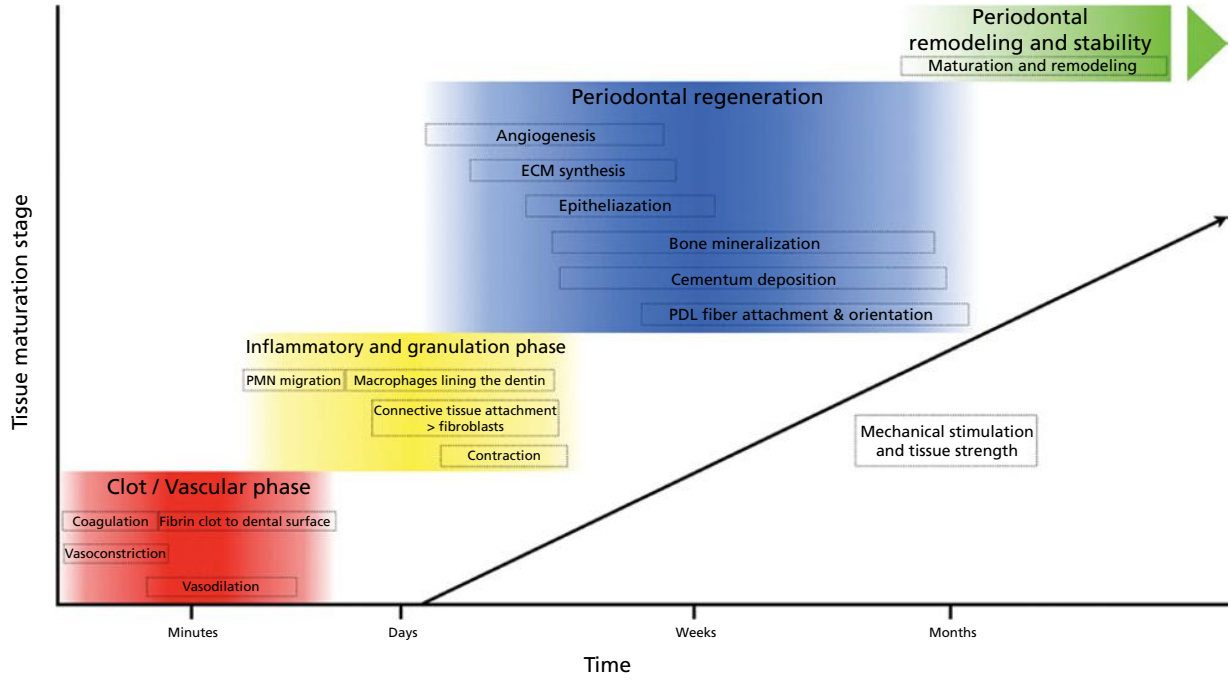

Fig. 27-2 Stages of periodontal wound healing. Optimal periodontal healing requires different processes in a sequential manner. After the initial coagulation phase, inflammatory reaction, and granulation tissue formation events, progenitor cells involved in multitissue regeneration are locally recruited and mediate the bioavailability of important growth factors. As the healing progresses, mechanical stimuli increase and promote an organized extracellular matrix (ECM) synthesis as well as cementum and bone formation and maturation. Once those structures are established, periodontal ligament (PDL) fibers are organized and oriented. Progressively, the tissues mature and ultimately increase in mechanical strength. Remodeling processes continue in the regenerated periodontium as an essential mechanism that monitors the adaptation potential to the challenging local and systemic environment.

periodontal tissues that are stressed by inflammation. The results of therapy are dependent on the ability of the body to heal afterwards and the mechanisms that dictate these processes. It is important to understand that the order of events during wound healing after therapy depend on a complex set of biologic communications in the area of interest.

Research on periodontal wound healing in the past provided the basic understanding of the mechanisms favoring periodontal tissue regeneration. A number of valuable findings at both the cellular and molecular levels was revealed and subsequently used in the engineering of the regenerative biomaterials that are available in periodontal medicine today.

The morphology of a periodontal wound comprises the gingival epithelium, gingival connective tissue, PDL, and hard tissue components such as alveolar bone and cementum or dentin on the dental root surface. This particular composition affects both the healing events in each tissue component as well as in the entire periodontal site. While the healing of gingival epithelia and their underlying connective tissues concludes in a number of weeks, the regeneration of PDL, root cementum, and alveolar bone generally occurs over a number of weeks or months. With the aim of wound closure, the final outcome of wound healing in the epithelium is the formation of the junctional epithelium surrounding the dentition (Caton *et al*. 1980). The healing of gingival connective tissue, on the other hand, results in a significant reduction of its volume, thus clinically causing both gingival recession and reduction of the periodontal pocket depth. PDL is shown to regenerate on newly formed cementum created by cementoblasts originating from the PDL granulation tissue (Karring *et al*. 1985). Furthermore, alveolar bone modeling occurs following the stimulation of mesenchymal cells from the gingival connective tissue, which are transformed into osteoprogenitor cells by locally expressed BMPs (Krebsbach *et al*. 2000; Sykaras & Opperman 2003).

A series of classical animal studies demonstrated that the tissue derived from alveolar bone or gingival connective tissue lacks cells with the potential to produce a new attachment between the PDL and newly formed cementum (Karring *et al*. 1980; Nyman *et al*. 1980). Moreover, granulation tissue derived from the gingival connective tissue or alveolar bone results in root resorption or ankylosis when placed in contact with the dental root surface. It should be expected, therefore, that these complications would occur more frequently following regenerative periodontal surgery, particularly following those procedures which include the placement of grafting materials to stimulate bone formation. The reason for root resorption is rarely identified; however, it may be that following the surgical intervention, the dentogingival epithelium migrates apically along the root surface, forming a protective barrier against the root surface (Bjorn *et al*. 1965; Karring *et al*. 1984). The findings from these animal experiments revealed that ultimately the PDL tissue contains cells with the potential to form a new connective tissue attachment (Karring *et al*. 1985).

Typically, the down-growth of the epithelium along the tooth root surface reaches the level of the PDL before the latter has regenerated with new layers of cementum and newly inserted connective tissue fibers. Therefore, in order to enable and promote the healing towards the rebuilding of cementum and PDL, the gingival epithelium must be hindered in its creation of a long junctional epithelium along the root surface down to the former level of the PDL.

These principles of periodontal wound healing provide the basic understanding of the events that follow wounding in surgical interventions. In order to achieve new connective tissue attachment, the granulation tissue derived from PDL cells has to be given both space and time to format and mature to new cementum and PDL.

Healing after periodontal surgery

Healing after gingival and periodontal surgery represents a more complex situation, particularly in cases where the periodontal tissue is apposed to an instrumented root surface deprived of its periodontal attachment. In this case, the wound margins are not two opposing vascular gingival margins but comprise the rigid non-vascular mineralized tooth surface on one side, and the connective tissue and epithelium of the gingival flap on the other (Fig. 27-3). Early healing events at the dentogingival interface have been examined using dentin blocks implanted in edentulous alveolar ridges, submerged under gingival flaps, in dogs (Wikesjo *et al*. 1991).

Clot formation at the interface between the tooth and a gingival flap is initiated as blood elements are imposed onto the root surface during surgery and at wound closure in a seemingly random manner.

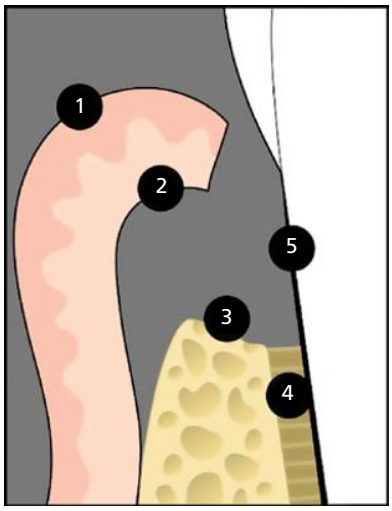

Fig. 27-3 Periodontal wound following flap surgery: (1) gingival epithelium; (2) gingival connective tissue; (3) alveolar bone; (4) periodontal ligament; and (5) cementum or dentin on the dental root surface.

This represents the very first healing event at the tooth–gingival flap interface (i.e. the absorption and adhesion of plasma proteins onto the root surface) (Wikesjo *et al*. 1991). Within minutes, a fibrin clot attached to the root surface is developed. Within hours, the early phase of inflammation may be observed as inflammatory cells, predominantly neutrophils and monocytes, accumulate on the root surface, and within 3 days the late phase of inflammation dominates the healing picture as macrophages migrate into the wound followed by the formation of granulation tissue. At 7 days, a connective tissue attachment may be forming at the root surface as collagenous elements appear to be orientated in close proximity to the dentin surface. Resorptive remodeling of the dentin surface may be evident at this observation interval.

Within 14 days, the newly formed collagen fibers may show an arrangement indicative of physical attachment to the dentin (Selvig *et al*. 1988). Ramfjord *et al.* (1966) reported that collagen maturation of collagenous tissues and functional orientation of the connective tissue takes 3–5 weeks. In addition, new bone deposition starts to occur from days 10–21 (Wilderman 1964). Eventually, cementum formation may be initiated, but not until at least 3 weeks after wound closure (Hiatt *et al*. 1968).

Only a few experimental studies have evaluated the functional integrity of a maturing periodontal wound. Hiatt *et al.* (1968) examined the tensile strength of the tooth–gingival flap interface following reconstructive surgery of relatively small surgical dehiscence defects over the maxillary canine teeth in the dog. They found that the tensile strength increased from approximately 200 g at 3 days post surgery to 340 g at 5–7 days post surgery, and to >1700 g at 2 weeks post surgery. In other words, they found that a relatively limited periodontal wound might not reach functional integrity until 2 weeks post surgery. These data suggest that wound integrity during the early healing phase depends primarily on the stabilization of the gingival flaps offered by suturing.

Histologic studies have shown that various surgical periodontal procedures can lead to different patterns of healing. Empirically, periodontal healing has generally been characterized by maturation of the gingival connective tissue, some regeneration of alveolar bone and cementum, and, most importantly, epithelialization of the root surface (Listgarten & Rosenberg 1979). Long junctional epithelium is commonly found on the root surface after traditional periodontal surgery and provides protection against bacterial invasion and ankylosis. However, downgrowth of epithelium from the gingival margin prevents the coronal migration of PDL cells, which are responsible for the formation of connective tissue attachment (Fig. 27-4).

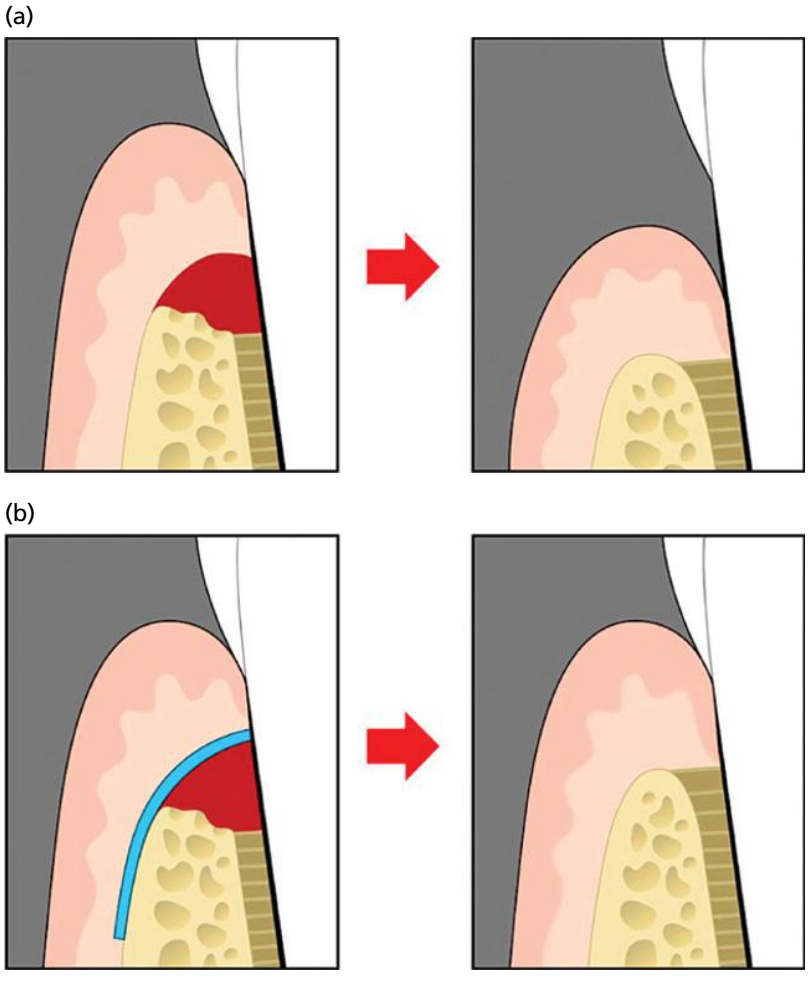

Fig. 27-4 (a) Regular healing process following the periodontal flap adaptation with significant reduction of the attachment apparatus. (b) In order to enable and promote the healing towards the rebuilding of the cementum and periodontal ligament, the gingival epithelium must be hindered from creating a long junctional epithelium along the root surface down to the former level of the periodontal ligament (e.g. by placement of a bioresorbable membrane).

Soft tissue management in early regenerative attempts adhering to the principle of epithelial exclusion has included repeated subgingival curettage during healing to control epithelialization of the root surface. More recent approaches have included the prevention of the gingival epithelium from contacting the root surface during the early healing phase by utilization of a cell-occluding membrane. Human as well as animal studies have reported the success with a membrane in facilitating the migration and proliferation of cells from the PDL and alveolar bone in the wound space (Nyman *et al*. 1982; Gottlow *et al*. 1984).

The general concepts of healing have been applied in the environment of periodontal tissues. Several investigations have been conducted in attempts to elucidate the exact mechanisms that guide the process and determine the final healing pattern.

Advanced regenerative approaches to periodontal tissue reconstruction

Periodontal regeneration is assessed by probing measures, radiographic analysis, direct measurements of new bone, and histology (Reddy & Jeffcoat 1999). Many cases that are considered clinically successful, including cases with significant regrowth of alveolar bone, may histologically still show an epithelial lining along the treated root surface instead of newly formed PDL and cementum (Listgarten & Rosenberg 1979). In general, however, the clinical outcome of periodontal regenerative techniques has been shown to depend on (1) patient-associated factors such as plaque control, smoking habits, residual periodontal infection, or membrane exposure in guided tissue regeneration (GTR) procedures; (2) effects of occlusal forces that deliver intermittent loads in axial and transverse dimensions; as well as (3) factors associated with the clinical skills of the operator, such as the failure of primary closure of the surgical wound (McCulloch 1993). Even though modified flap designs and microsurgical approaches have been shown to positively affect the outcome of both soft and hard tissue regeneration, the clinical success for periodontal regeneration remains limited in many cases. Moreover, the surgical protocols for regenerative procedures are skill demanding and may therefore may not be achievable for a number of clinicians. Consequently, both clinical and preclinical research continues to evaluate advanced regenerative approaches (Ramseier *et al*. 2012) using new barrier

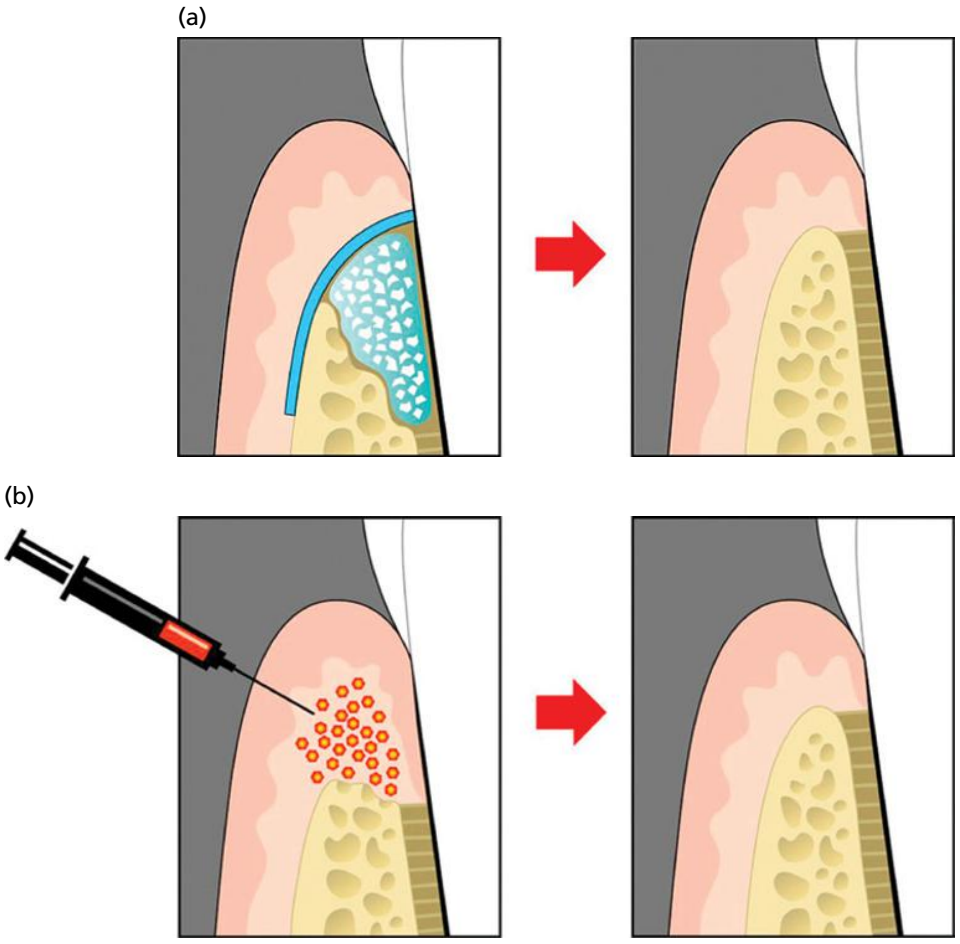

Fig. 27-5 Advanced approaches for regenerating tooth-supporting structures. (a) Application of a graft material (e.g. bone ceramic) and growth factor into an infrabony defect covered by a bioresorbable membrane. (b) Application of gene vectors for the transduction of growth factors producing target cells.

membrane techniques (Jung *et al*. 2006), cell-growth stimulating proteins (Giannobile 1996; Dereka *et al*. 2006; Kaigler *et al*. 2006) or gene delivery applications (Ramseier *et al*. 2006), respectively, in order to simplify and enhance the rebuilding of missing periodontal support (Fig. 27-5).

Regenerative surgery

Regenerative periodontal therapy comprises techniques that are particularly designed to restore lost parts of the tooth-supporting structures, including cementum, PDL, and bone. The most common periodontal indications for these procedures include deep infrabony defects, furcation defects of upper premolar and molar teeth, and localized gingival recession defects. The clinical success for periodontal regeneration still remains limited in many cases. Consequently, both clinical and preclinical research continues to advance the field of periodontal regenerative therapy by evaluating innovative tissue engineering approaches that include optimized scaffold fabrication technology, new barrier membrane techniques (Jung *et al*. 2006), cell-growth stimulating proteins (Giannobile 1996; Dereka *et al*. 2006; Kaigler *et al*. 2006) as well as cell and gene delivery applications (Ramseier *et al*. 2006) (Fig. 27-6).

Guided tissue regeneration

Histologic findings from periodontal regeneration studies and Melcher's concepts of "compartmentalization" revealed that a new connective tissue attachment could be predicted if the cells from the PDL settle on the root surface during healing (Melcher 1976). Hence, the clinical applications of GTR in periodontics involve the placement of a physical barrier membrane to enable the previously periodontitis-affected tooth root surface to be repopulated with cells from the PDL, cells from the lamina propria of the gingival corium, cementum cells, and alveolar bone. GTR techniques utilize barrier membranes to facilitate the migration of bone cells and PDL cells to the defects by refraining soft tissue cells from penetrating it. This knowledge has been the key to developing standard clinical procedures for the placement of a fabricated membrane in GTR. GTR has recently been combined with the delivery of different factors that are incorporated to augment the regenerative response.

Clinical applications of growth factors for use in periodontal regeneration

A number of studies have focused on the modification of the periodontitis-involved root surface in order to advance the formation of a new connective tissue attachment. However, despite histologic evidence of regeneration following root surface biomodification with citric acid, the outcomes of controlled clinical trials have failed to show any improvements in clinical conditions compared to non–acid-treated controls (Fuentes *et al*. 1993; Mariotti 2003). In recent years, biomodification of the root surface with enamel matrix proteins during periodontal surgery and following demineralization with ethylenediaminetetra-acetic acid (EDTA) has been introduced to promote periodontal regeneration. The application of enamel matrix proteins (amelogenins) has also been evaluated as a promoter of periodontal regeneration since it initiates events that occur during the growth of periodontal tissues (Gestrelius *et al*. 2000). The commercially available product, Emdogain®, a purified acid extract of porcine origin contains *enamel matrix derivate* (EMD), which has demonstrated the ability to advance periodontal regeneration (Sculean *et al*. 2007). Thus far, EMD alone or in combination with grafts has demonstrated its potential to effectively treat intraosseous defects and the clinical results appear to be stable long term (Trombelli & Farina 2008).

Platelet-derived growth factor (PDGF) is a member of a multifunctional polypeptide family and exerts its biologic effects on cell proliferation, migration, ECM synthesis, and antiapoptosis (Heldin *et al*. 1989; Rosenkranz & Kazlauskas 1999). The clinical application of PDGF has been shown to successfully advance alveolar bone repair and clinical attachment level gain. Initial clinical trials reported the successful repair of class II furcations using demineralized freeze-dried bone allograft (DFDBA) saturated with rhPDGF-BB (Nevins *et al*. 2003). Subsequently, rhPDGF-BB mixed with a synthetic beta-tricalcium phosphate (β-TCP) matrix was shown to advance the repair of deep infrabony pockets as measured by radiographic bone fill in a large multicenter randomized controlled trial (Nevins *et al*. 2005, 2013). Both studies also demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal osseous defects.

Bone morphogenetic proteins (BMPs) are multifunctional polypeptides which have potent bone regenerative capacity. Fiorellini *et al*. (2005) reported that in a human buccal wall defect model, bone formation following tooth extraction was significant when the defect was treated with recombinant human BMP-2 (rhBMP-2) delivered by a bioabsorbable collagen sponge, compared to treatment with the collagen sponge alone. Furthermore, BMP-7, also known as osteogenic protein 1 (OP-1), stimulates bone regeneration around teeth, endosseous dental implants, and in maxillary sinus floor augmentation procedures (Giannobile *et al*. 1998; van den Bergh *et al*. 2000).

In general, topical delivery of growth factors to periodontal wounds has shown promise, but as yet the impact is insufficient for the promotion of predictable periodontal tissue engineering (Kaigler *et al*. 2006). Growth factor proteins, once delivered to the target site, tend to suffer from instability and quick dilution, presumably due to proteolytic breakdown, receptor-mediated endocytosis, and solubility of the

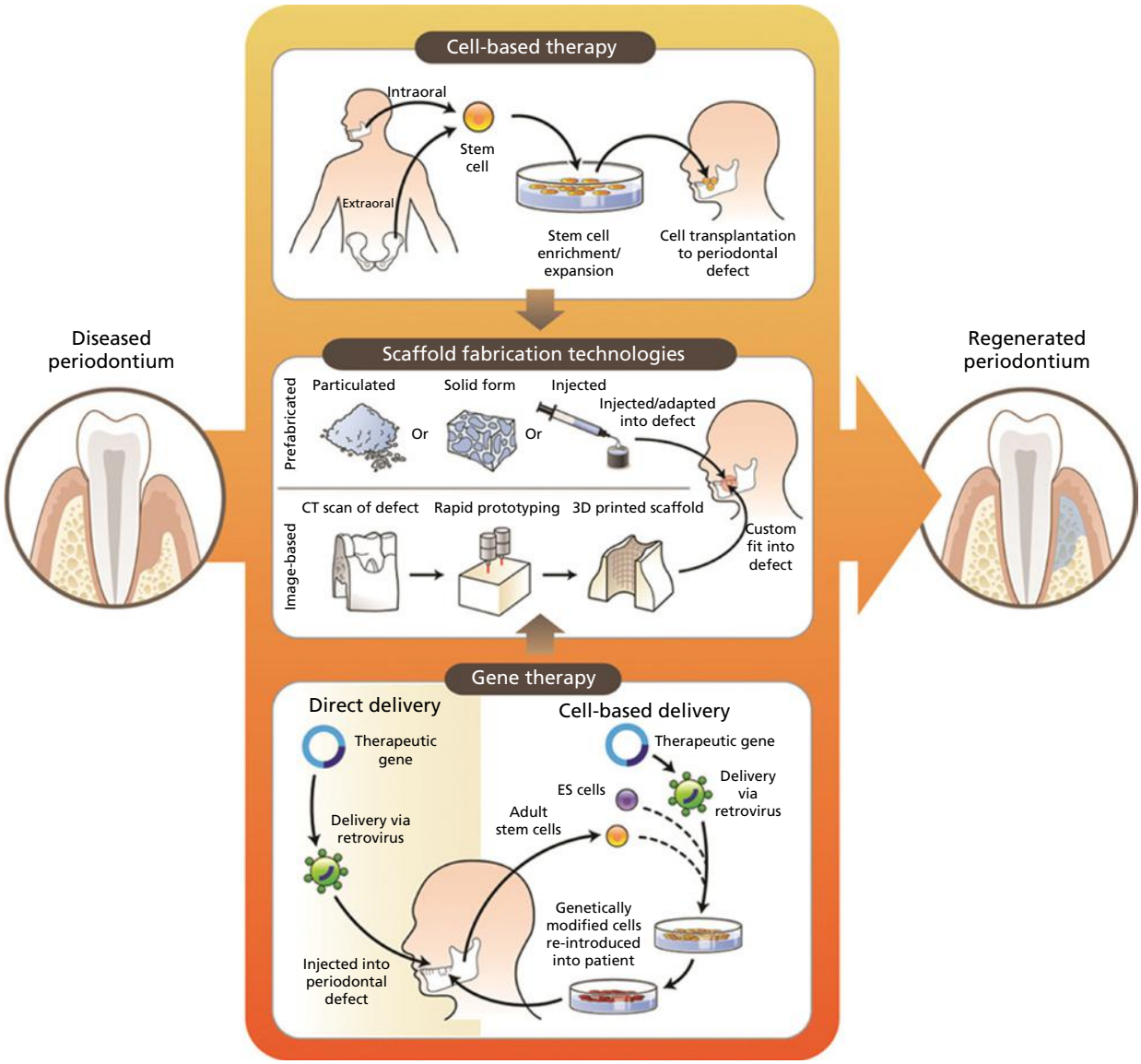

Fig. 27-6 Cell- and gene-based technologies using scaffolding matrices for periodontal tissue engineering. Extraoral and intraoral stem cells represent a viable and accessible alternative source to harvest and expand multipotent colonies. Adequate cell density could be reached *in vitro* in a controlled environment and made readily available for reimplantation into a periodontal defect site. The available direct and cell-based delivery of a therapeutic gene has being shown to increase the regenerative potential and enhance the availability of important factors. The gene of interest is either injected directly into the periodontal defect via a retrovirus or alternatively is incorporated into a stem cell that is subsequently expanded and delivered to the area of interest. Prefabricated and image-based scaffolds are becoming an essential component of regenerative medicine. A defined supporting structure allows the localization and guidance of the appropriate cells and proteins, and the establishment of a mechanically competent environment. Currently, scaffolds for periodontal regeneration are available in particulated, solid, and injectable forms. New developing technology has allowed the customization of scaffolds that would fit into the periodontal defect and include an external and an internal architecture that enhances tissue orientation and regeneration. This schematic diagram highlights the potential of integrating the available tissue engineering strategies to enhance the outcome of periodontal regenerative therapy. (ES cells, embryonic stem cells.)

delivery vehicle. Because their half-lives are significantly reduced, the period of exposure may not be sufficient to act on osteoblasts, cementoblasts or PDL cells. A recent clinical trial evaluated the regenerative effects of systemic delivery of teriparatide, a recombinant form of parathyroid hormone (PTH). The study demonstrated a periodontal anabolic effect favoring a regenerative outcome. Following periodontal surgery, teriparatide was systemically delivered for 6 weeks and results compared with a placebo control. Delivery of this recombinant molecule in this fashion was associated with improved clinical outcomes, including greater resolution of alveolar bone defects and accelerated osseous wound healing (Bashutski *et al*. 2010).

Cell therapy for periodontal regeneration

Another emerging regenerative approach in the management of soft and hard tissue defects involves cell therapy (Table 27-1). For regeneration of interdental papillae, early investigations of cell therapy

using cultivated fibroblasts have shown success in the treatment of interdental papillary insufficiency (McGuire & Scheyer 2007). For larger soft tissue defects, a human oral mucosa equivalent, made of autogenous keratinocytes (EVPOME) placed on a cadaveric dermal carrier (Alloderm®), has shown efficacy in wound healing when compared to the dermal carrier alone (Izumi *et al.* 2003). EVPOME has also been successfully used to treat patients affected by squamous cell carcinoma of the tongue, leukoplakia of the tongue, gingiva, and buccal mucosa, or hypoplasia of the alveolar ridge (Hotta *et al*. 2007). In other soft tissue applications, allogenic foreskin fibroblasts have been utilized to promote keratinized tissue formation at mucogingival defects (McGuire & Nunn 2005). A tissue-engineered living cellular construct comprised of viable neonatal keratinocytes and fibroblasts has been evaluated for its ability to increase keratinized gingiva around teeth, and rendered similar clinical outcomes to conventional gingival autografts (McGuire *et al.* 2011). This cell construct also has a strong potential to stimulate the expression of angiogenic factors as compared with autogenous free gingival grafts

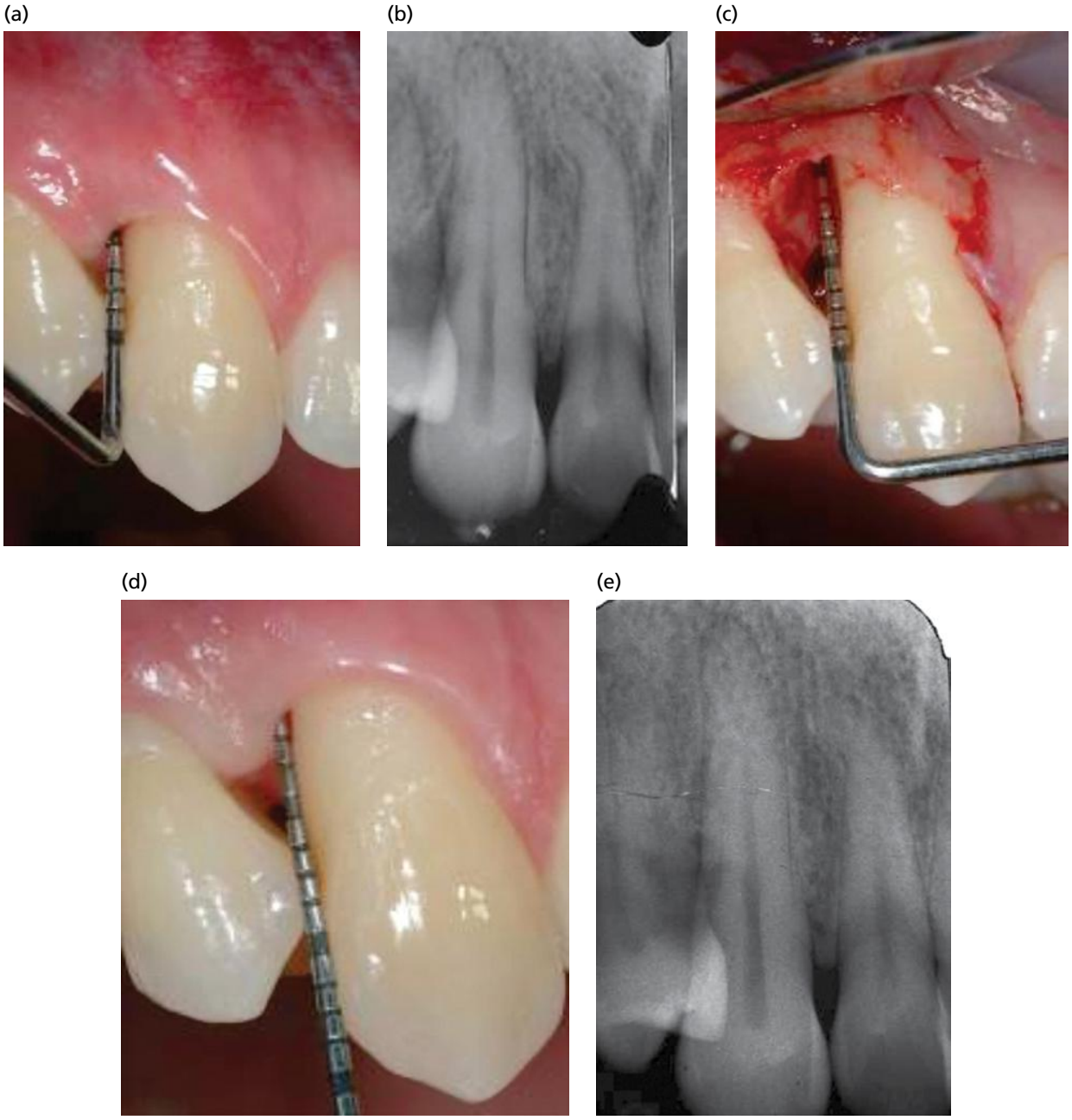

Fig. 27-7 (a) A 32-year-old male patient with severe periodontitis. Tooth 13 shows a probing pocket depth (PPD) of 10 mm distobuccal and a clinical attachment level (CAL) of 14 mm. (b) Periapical radiograph shows the infrabony defect distal to tooth 13. (c) After the buccal incision of the papilla, the interdental tissue is preserved attached to the palatal flap. After debridement of the granulation tissue and root planing, the infrabony defect is classified and measured: the predominant component is a 7-mm deep three-wall defect. One year after surgical intervention, the distal site of tooth 13 shows a PPD of 2 mm (gain of 8 mm from initial measurement) and a CAL of 7 mm (gain of 7 mm) (d) and the radiograph shows defect filling (e).

during early wound-healing stages and, therefore, constitutes a promising material for gingival grafting (Morelli *et al.* 2011).

The benefits of using somatic cells for the regeneration of soft and hard tissues in the craniofacial area have been illustrated in several preclinical and clinical studies. However, their lack of self-renewal capability and their commitment toward a single cellular phenotype limit their use in the treatment of more challenging craniofacial defects. Stem cells might have a greater potential in this arena as they can reproduce themselves (*self-renewal*) and differentiate into a variety of specialized cell types (*potency*). *Bone marrow stromal cells* (BMSCs) are characterized by elevated renewal potency and by the ability to differentiate into osteoblasts, chondroblasts, adipocytes, myocytes, and fibroblasts when transplanted *in vivo* (Prockop 1997). MSCs can be obtained from a variety of sources, but autologous MSCs isolated from bone marrow of the iliac crest offer a predictable and a cost-effective therapy for the treatment of severely atrophic maxillary and mandibular ridges when compared to harvested autogenous bone (Soltan *et al*. 2007). Bone repair cells (ixmyelocel-T®; Aastrom Biosciences) consisting of autologous bone marrow-derived cells expanded in an *ex vivo*, closed, and automated single-pass perfusion (SPP) have recently demonstrated the ability to accelerate bone regeneration in localized alveolar defects (Kaigler *et al* 2013). Because these cells include MSCs, they may not only serve to provide a source of stem and progenitor cells to a wound healing site, but may also be actively involved in the establishment of a vasculature which can support and sustain tissue regeneration.

Gene therapeutics for periodontal tissue repair

Although encouraging results for periodontal regeneration have been reported from various clinical investigations using recombinant tissue growth factors, topical protein delivery from existing vehicles

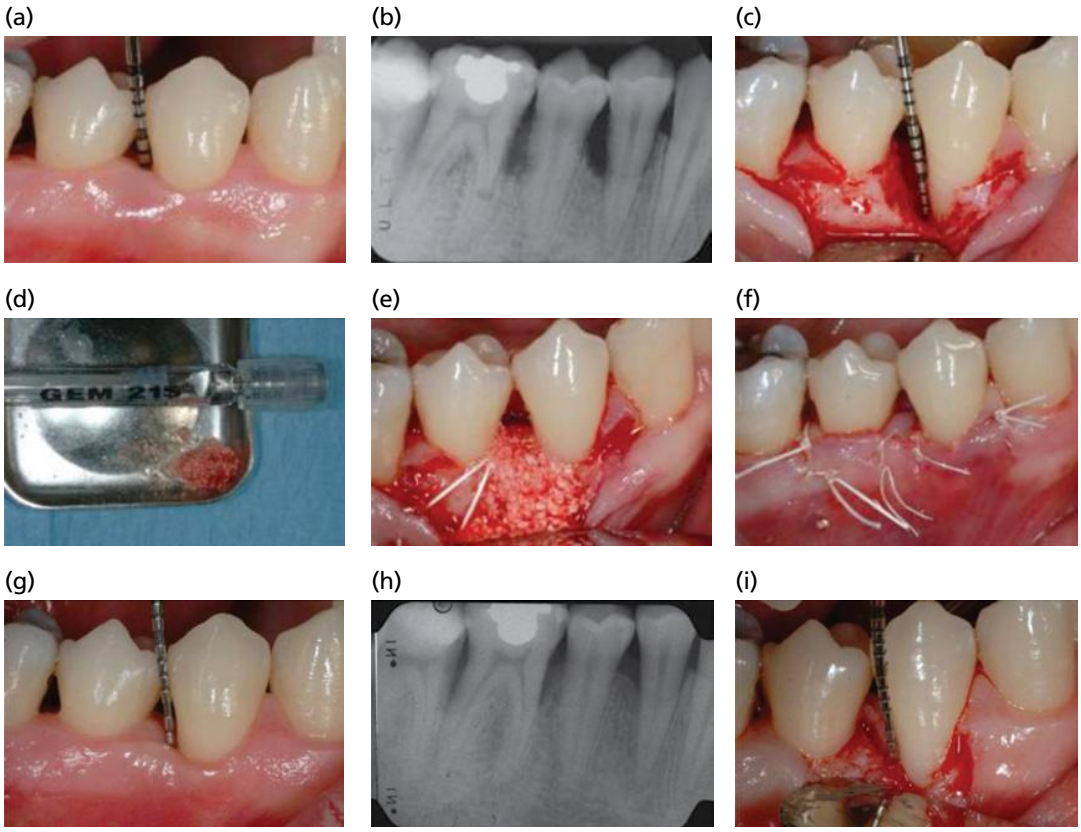

Fig. 27-8 (a) A 27-year-old patient at the re-evaluation visit after the initial phase showed three sites with a pocket probing depth (PPD) of <6 mm; the one distal to tooth 44 had a PPD of 7 mm and no gingival recession. (b) Periapical radiograph shows a one-wall defect distal to tooth 44 and a lesion between teeth 45 and 46. (c) Measurement of the pure one-wall defect shows an infrabony component of 6 mm. (d) Grafting material of the GEM 21S® is mixed with a few particles of autogenous bone chips, collected from the surgical area with a Rhodes instrument, and with the liquid component of the GEM 21S® [platelet-derived growth factor (PDGF)]. (e) Liquid PDGF is placed in the defect together with the graft to rebuild the lost bone. (f) An off-set internal mattress suture is performed to keep and stabilize the flap coronal. A second internal mattress suture is performed with 7-0 Gor Tex® to allow optimal adaptation of the flap margins without interference from the epithelium. The two internal mattress sutures are tied but not knotted until there is a perfect tension-free closure of the wound. Two additional interrupted 7-0 sutures are placed to assure stable contact between the connective tissues of the edges of the flaps. The mesial and distal papilla are stabilized with additional interrupted sutures. Nine months after surgery the PPD is 2 mm (g), the periapical radiograph shows a good bone fill of the one-wall bony defect (h), and surgical re-entry shows formation of new bone (i).

has limitations such as transient biologic activity, protease inactivation, and poor bioavailability. Therefore, newer approaches seek to develop methodologies that optimize growth factor targeting to maximize the therapeutic outcome of periodontal regenerative procedures. Genetic approaches in periodontal tissue engineering show early progress in achieving delivery of growth factor genes such as *PDGF* or *BMP* to periodontal lesions (Kaigler *et al*. 2006). Gene transfer methods may circumvent many of the limitations with protein delivery to soft tissue wounds (Giannobile 2002; Baum *et al*. 2003). It has been shown that growth factors (Franceschi *et al*. 2000; Krebsbach *et al*. 2000; Jin *et al*. 2004) or soluble forms of cytokine receptors (Taba *et al*. 2005) applied by gene transfer are more sustainable than proteins applied in a single application. Thus, gene therapy may achieve greater bioavailability of growth factors within periodontal wounds and thus provide greater regenerative potential.

Conclusion

The periodontal healing process is governed by a complex multifactorial mechanism in which a number of local and systemic, micro- and macro-environmental variables interplay to define the final result. Only a profound understanding of biologic and clinical variables affecting the outcome of gingival and periodontal surgical procedures will allow clinicians to manipulate critical factors effectively in order to optimize the outcome and increase the predictability of periodontal regenerative (Figs. 27-7, 27-8). This chapter has given a brief presentation of the healing mechanisms which are initiated in periodontal tissues following basic periodontal surgical procedures. The complexity of the cellular and molecular events that are activated during and after a periodontal intervention lead to some important conclusions:

- As clinicians, we must minimize any deviations from the strict surgical protocols in order to ensure the risk of any unfavorable healing events is minimized.
- As scientists, we should be able to translate the clinical signs and symptoms into the language of physiology and histology, and understand their nature so that interventions can be modified accordingly.

Acknowledgments

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Chapter 28

Concepts in Periodontal Tissue Regeneration

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Introduction

In risk assessment in periodontal patients, the presence of sites with a residual pocket depth of ≥6 mm after active treatment plays a significant role in predicting future periodontal destruction (Haffajee *et al*. 1991; Grbic & Lamster 1992; Claffey & Egelberg 1995). Thus, an important goal of periodontal therapy is to reduce pocket depth in order to prevent further disease progression. Usually, this goal can be accomplished by non-surgical therapy in patients with moderate periodontitis, whereas in severe cases, particularly in the presence of intrabony defects and furcations, the treatment must be supplemented with periodontal surgery. A fundamental objective of periodontal surgery is to provide access for proper instrumentation and cleaning of the root surface; in addition, most surgical procedures result in the elimination or the reduction of the soft tissue component of the periodontal pocket. Generally, the elimination of deep pockets is achieved by gingivectomy or apical displacement of raised tissue flaps, sometimes associated with bone contouring. In recent years, however, the use of regenerative procedures aimed at restoring the lost periodontal support has become more common.

Periodontal treatment, both surgical and non-surgical, results in recession of the gingival margin after healing (Isidor *et al*. 1984). In severe cases of periodontitis, this recession may lead to poor esthetic outcomes, especially visible in the front tooth region of the maxilla and at sites at which bone contouring procedures have been used. Treatment of such cases without bone contouring, on the other hand, may make residual pockets inaccessible to proper self-performed tooth cleaning during post-treatment maintenance. These problems can be avoided or reduced by applying regenerative procedures to restore the lost periodontal attachment in the bone defects. Thus, the indication for regenerative periodontal therapy is often based on esthetic considerations, as well as the fact that this treatment may improve the function or long-term prognosis of the treated teeth.

Gingival recession and root exposure may represent an esthetic problem to the patient, and are often associated with root sensitivity. In such situations

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there is an obvious indication to apply regenerative periodontal therapy to obtain root coverage that may not only improve esthetics but also reduce root sensitivity. Successful root coverage implies regeneration of the attachment apparatus, including cementum with inserting collagen fibers, on the exposed root surface, as well as restoration of the anatomy of the mucogingival complex.

Another indication for regenerative periodontal therapy is an open furcation in multirooted teeth. The furcation area is often inaccessible to adequate instrumentation and frequently the roots show concavities and furrows which make proper cleaning of the area difficult/impossible after resective surgery. Considering the long-term results and complications reported following treatment of furcations by traditional resective therapy (Hamp *et al*. 1975; Bühler 1988), it is reasonable to anticipate that the long-term prognosis of furcation-involved teeth can be improved considerably by successful regenerative periodontal therapy.

Case reports also exist demonstrating that "hopeless" teeth with deep vertical defects, increased tooth mobility or through-and-through furcations can be successfully treated with regenerative periodontal therapy (Gottlow *et al*. 1986). However, controlled clinical trials or serial case reports presenting a reasonable predictability of treating such advanced cases are not available.

Regenerative periodontal surgery

Regenerative periodontal therapy comprises procedures which are specially designed to restore those parts of the tooth-supporting apparatus which have been lost due to periodontitis. Regeneration is defined as a reproduction or reconstruction of a lost or injured part in such a way that the architecture and function of the lost or injured tissues are completely restored (American Academy of Periodontology 1992). This means that the attachment of the tooth has been regenerated when new cementum with inserting collagen fibers has formed on the detached root surface, while regeneration of the periodontal supporting apparatus (periodontium) also includes regrowth of the alveolar bone.

Procedures aimed at restoring lost periodontal support have also been described as "reattachment" or "new attachment" procedures. The term "reattachment" was used to describe the regeneration of a fibrous attachment to a root surface surgically or mechanically deprived of its periodontal ligament tissue, whereas the term "new attachment" was preferred in the situation where the fibrous attachment was restored on a root surface deprived of its connective tissue attachment due to the progression of periodontitis. Research findings, however, indicate that there is no difference regarding the possibility of restoring a connective tissue attachment, whether this has been lost because of periodontal disease or mechanically removed (Nyman *et al*. 1982; Isidor *et al*. 1985). Therefore, it was suggested that the term "new attachment" should be used to describe the formation of new cementum with inserting collagen fibers on a root surface deprived of its periodontal ligament tissue, whether or not this has occurred because of periodontal disease or by mechanical means, and that the term "reattachment" should be confined to describing the reunion of surrounding soft tissue and a root surface with preserved periodontal ligament tissue (Isidor *et al*. 1985).

Periodontal regeneration has been reported to occur following a variety of surgical approaches involving root surface biomodification, often combined with coronally advanced flap procedures, the placement of bone grafts or bone substitutes in periodontal defects, or the use of organic or synthetic barrier membranes [guided tissue regeneration (GTR)]. However, many cases that clinically are considered successful, including cases with significant regrowth of alveolar bone, may histologically show an epithelial lining along the treated root surface instead of deposition of new cementum (Caton & Zander 1976; Listgarten & Rosenberg 1979).

Successful regeneration is assessed by periodontal probing, radiographic analysis, bone sounding, and histologic examination of biopsy specimens. Although histology remains the gold standard in assessing true periodontal regeneration, periodontal probing, direct bone measurements, and radiographic measurements of osseous changes are used in the majority of studies of regenerative therapy (Reddy & Jeffcoat 1999).

At the American Academy of Periodontology World Workshop in Periodontics in 1996, the fulfillment of the following criteria was required in order for a periodontal regenerative procedure to be considered as a therapy which can encourage regeneration:

1. Human histologic specimens demonstrating formation of new cementum, periodontal ligament, and bone coronal to a notch indicating the apical extension of the periodontitis-affected root surface
2. Controlled human clinical trials demonstrating improved clinical probing attachment and bone
3. Controlled animal histologic studies demonstrating formation of new cementum, periodontal ligament, and bone.

In addition, however, it seems reasonable to require that a regenerative procedure is based on a biologic concept which, based on current knowledge about periodontal wound healing, can explain why the treatment results in periodontal regeneration.

Periodontal wound healing

Regeneration of the periodontium must include the formation of new cementum with inserting collagen fibers on the previously periodontitis-involved root surfaces and the regrowth of the alveolar bone. However, whether regrowth of alveolar bone should always be considered a requirement for success

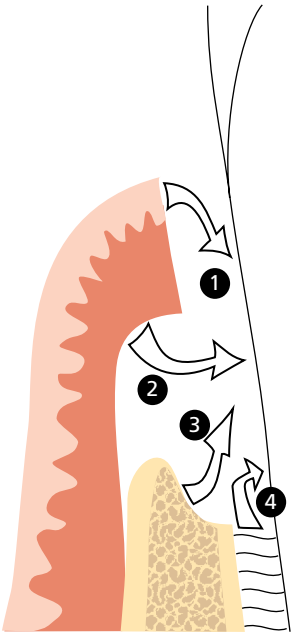

Fig. 28-1 Following flap surgery, the curetted root surface may be repopulated by (1) epithelial cells, (2) gingival connective tissue cells, (3) bone cells, or (4) periodontal ligament cells.

following regenerative periodontal surgery is a matter of discussion. The basis for this discussion is that a fibrous attachment may exist without opposing bone in a normal dentition, not affected by periodontitis, in the presence of bone dehiscenses and fenestrations (see Fig. 1-74).

In 1976, Melcher suggested in a review paper that the type of cell which repopulates the root surface after periodontal surgery determines the nature of the attachment that will form. After flap surgery, the curetted root surface may be repopulated by four different types of cell (Fig. 28-1):

1. Epithelial cells
2. Cells derived from the gingival connective tissue
3. Cells derived from the bone
4. Cells derived from the periodontal ligament.

Previously, in most attempts to restore lost tooth support, particular attention was directed towards the regeneration of the alveolar bone. An investigation was carried out in dogs in order to examine the relationship between the re-establishment of a connective tissue attachment to the root surface and the regrowth of alveolar bone (Nyman & Karring 1979). After elevation of mucoperiostal flaps, the marginal 5–7 mm of the buccal alveolar bone of each experimental tooth was removed (Fig. 28-2). During this procedure, care was taken to minimize mechanical injury to the connective tissue attachment on the root surface. Prior to flap closure, a notch, serving as a landmark for the histologic measurements, was prepared in the root surface at the level of the surgically reduced bone crest. After 8 months of healing, the animals were sacrificed. Histologic analysis demonstrated that although a connective tissue attachment

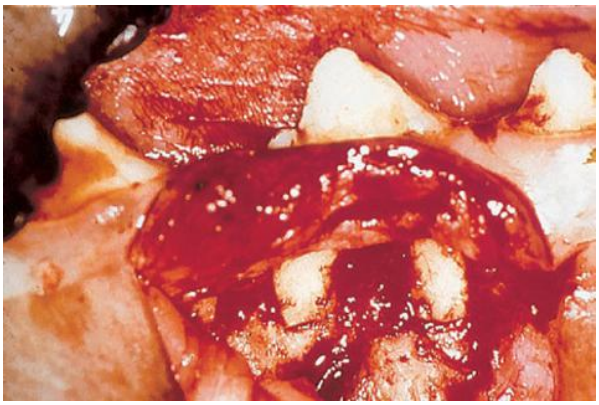

Fig. 28-2 Following flap elevation, the buccal bone, including a part of the inter-radicular and interproximal alveolar bone, is removed without injuring the connective tissue attachment on the root surface.

was consistently re-established on the roots, the amount of bone regeneration varied widely. In some roots, bone regrowth was negligible (Fig. 28-3), whereas in others the bone had regenerated to its normal level. These results demonstrated that the amount of bone regrowth is unrelated to the re-establishment of a connective tissue attachment.

Another experiment in monkeys (Lindhe *et al*. 1984) examined whether the presence of bone may stimulate the formation of a new connective tissue attachment. Mandibular and maxillary incisors were extracted and re-implanted in their own sockets under the following four experimental conditions (Fig. 28-4):

1. Non–root-planed teeth were re-implanted into sockets with normal bone height
2. Teeth, root planed in their coronal portion, were re-implanted into sockets with normal bone height
3. Non–root-planed teeth were re-implanted into sockets with a reduced bone height
4. Teeth, root planed in their coronal portion, were re-implanted into sockets with reduced bone height.

Histologic examination after 6 months of healing revealed that a fibrous reunion was established in areas where the periodontal connective tissue attachment was retained at the time of re-implantation. However, in areas where the periodontal ligament tissue had been removed, the epithelium had consistently migrated to the apical extension of root instrumentation (Fig. 28-5). This healing occurred irrespective of the presence or absence of bone, indicating that the establishment of a connective tissue attachment is unrelated to the presence of alveolar bone.

Using orthodontic appliances, Karring *et al*. (1982) tilted maxillary second and third incisors in the labial direction in dogs. Subsequently, these teeth were moved back to their original position. During the same period the contralateral incisors were moved to a labially deviated position. The orthodontic appliances were then used to retain the teeth in these positions for a period of 5 months before sacrifice of the

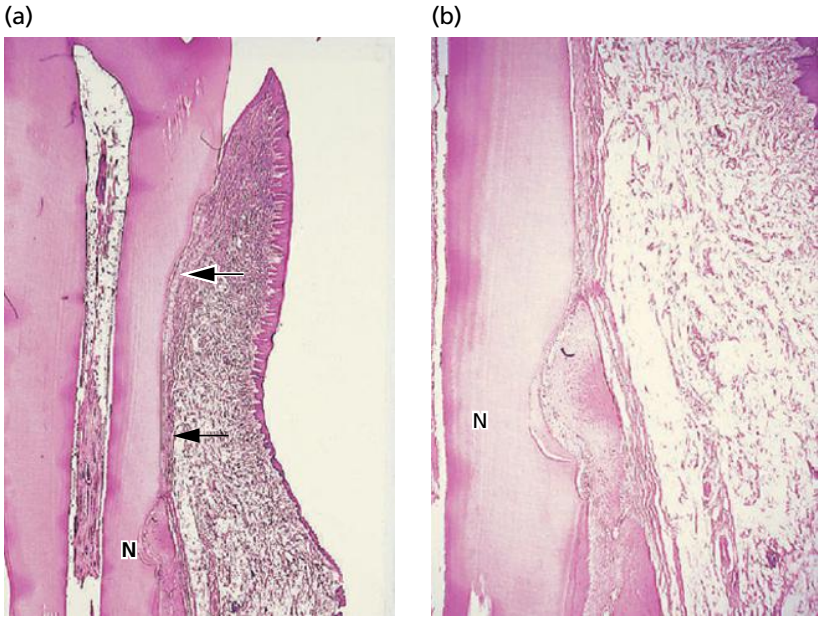

Fig. 28-3 (a) Microphotograph of a specimen 8 months following bone removal. A connective tissue attachment is re-established (arrows). Bone regeneration is negligible and is confined to the notch (N) in the root surface. (b) Higher magnification of the newly formed bone in the notch area (N).

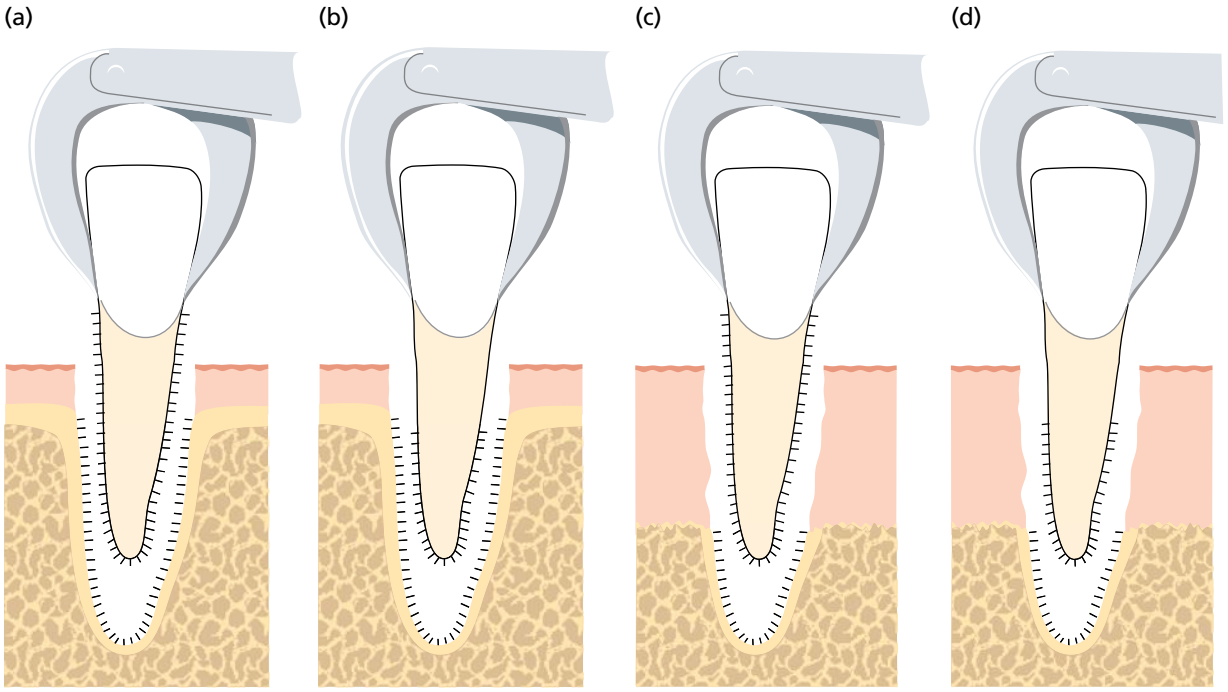

Fig. 28-4 Schematic drawing showing the four experimental conditions (a–d) under which experimental teeth were extracted and re-implanted in their own sockets.

animals. Histologic analysis demonstrated that in all experimental teeth, the apical termination of the junctional epithelium was at the cementoenamel junction. In the teeth which were retained in their labially displaced position, the level of the alveolar bone was reduced to a position about 4.5 mm apical of the cementoenamel junction (Fig. 28-6a), while in the teeth which were moved back to their original position, the alveolar bone crest was located at a normal level relative to the cementoenamel junction (Fig. 28-6b). This experiment demonstrated that bone resorption or bone regeneration may be induced by orthodontic forces on teeth with a pristine connective tissue attachment. The experiments described above indicate that the re-establishment of a connective tissue attachment to the root surface and the regeneration of the alveolar bone are not related to each other.

The use of bone grafts in regenerative periodontal therapy is based on the assumption that the promotion of bone regrowth may also induce cells in the bone to produce a new cementum layer with inserting collagen fibers on previously periodontitis-involved root surfaces. However, histologic studies in both humans and animals have demonstrated that grafting procedures often result in healing with a long junctional epithelium rather than a new connective tissue attachment (Caton & Zander 1976; Listgarten & Rosenberg 1979; Moscow *et al*. 1979).

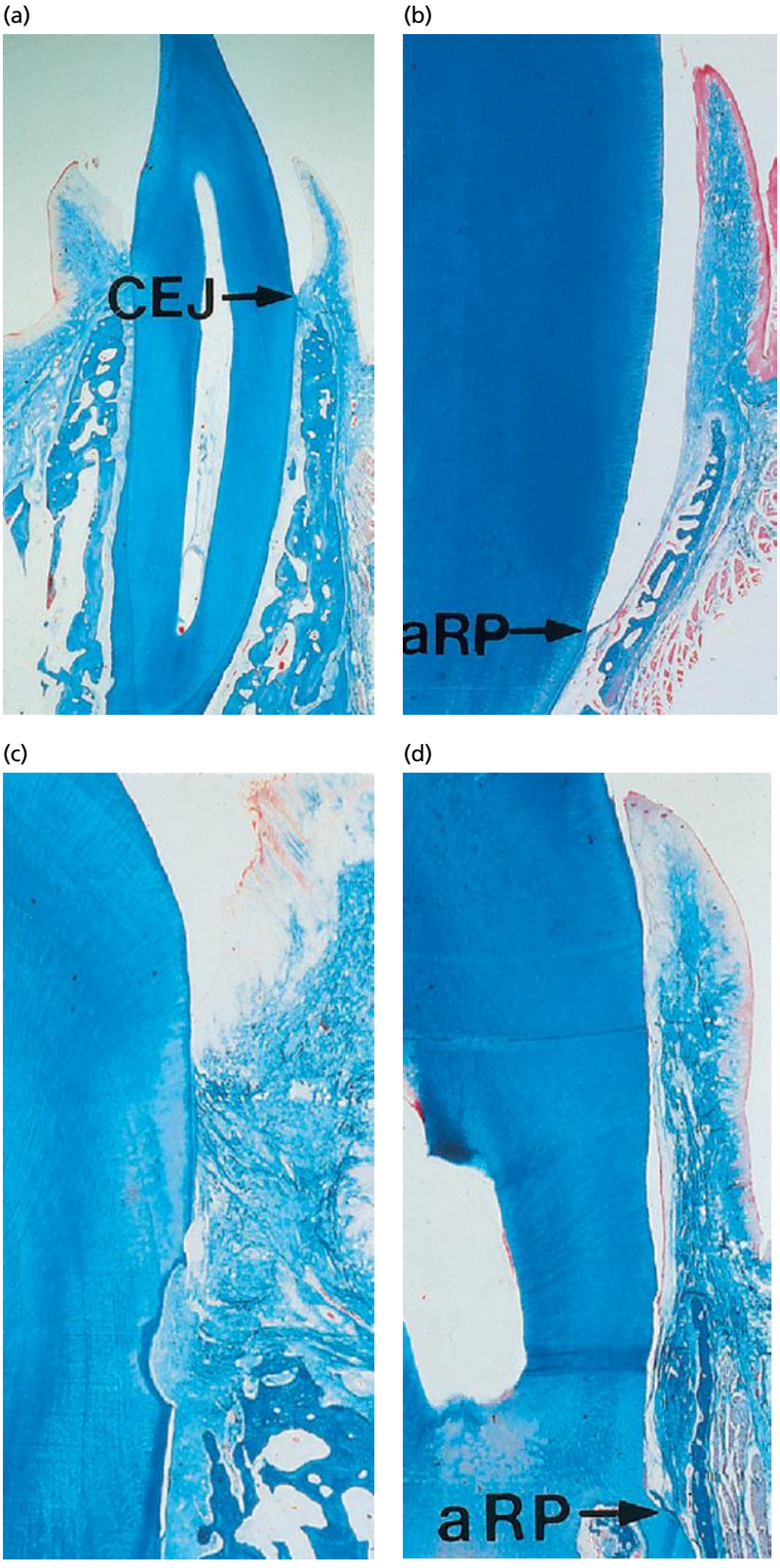

Fig. 28-5 Microphotographs showing the histologic features after 6 months of healing, under the four experimental conditions illustrated in Fig. 25-4a–d. The teeth in (b) and (d) are those that are root planed in their coronal portion, and the teeth in (a) and (b) are those re-implanted in sockets with normal bone height. A fibrous reunion was established in areas where the connective tissue attachment was retained (a and c), while the epithelium has migrated to the apical extension of root instrumentation (aRP) where the attachment was removed (b and d). (CEJ, cementoenamel junction.)

Ellegaard *et al*. (1973, 1974, 1975, 1976) and Nielsen *et al*. (1980, 1981) reported that grafting materials in periodontal bony defects may be:

1. *Osteoproliferative (osteogenetic)*: new bone is formed by bone-forming cells contained in the grafted material
2. *Osteoconductive*: the grafted material does not contribute to new bone formation *per se* but serves as a scaffold for bone formation originating from adjacent host bone
3. *Osteoinductive*: bone formation is induced in the surrounding soft tissue immediately adjacent to the grafted material.

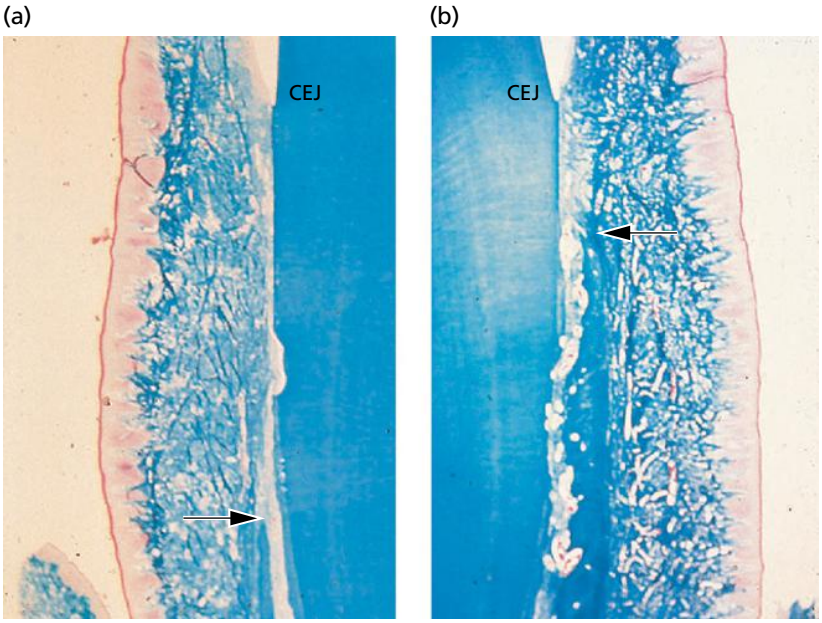

Fig. 28-6 Microphotographs of (a) a tooth retained in its labially displaced position and (b) a tooth moved back to its original position. The level of alveolar bone (arrow) is reduced in (a), while it has regenerated to its normal level (arrow) in (b). The apical termination of the junctional epithelium is at the cementoenamel junction (CEJ) in both situations.

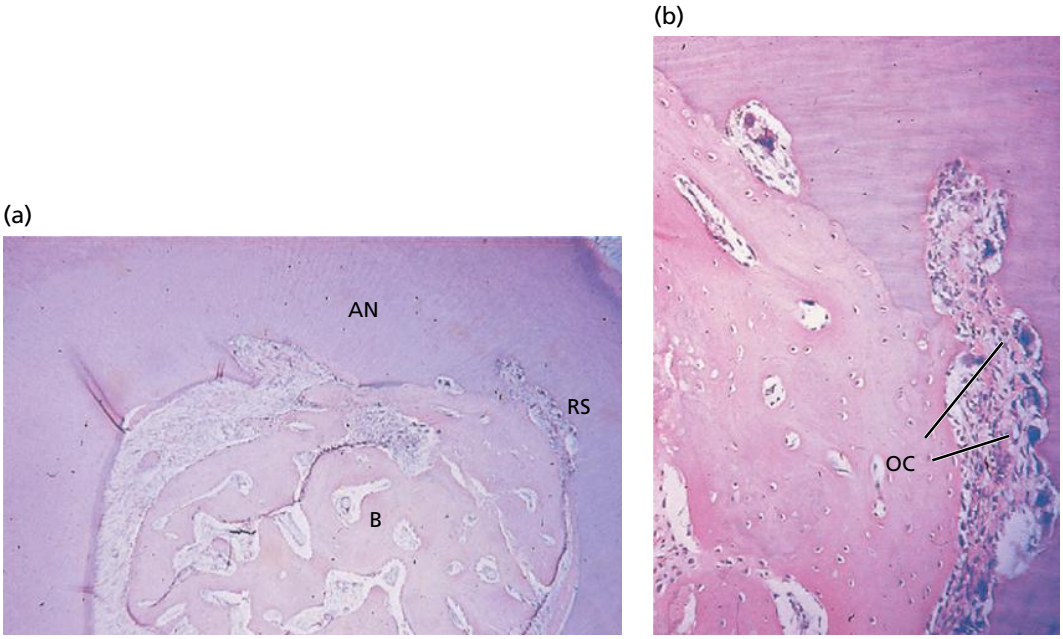

Fig. 28-7 (a) Microphotograph of furcation 6 weeks after grafting with iliac crest marrow. The furcation is completely filled with bone (B), but ankylosis (AN) and root resorption (RS) can be seen. (b) Higher magnification of the area in (a) showing ankylosis and resorption. (OC, osteoclasts.)

These studies, where various types of bone graft were placed in intrabony defects or inter-radicular lesions, revealed that cells survived transplantation only in iliac bone marrow grafts. Transplantation of iliac bone marrow grafts almost consistently resulted in bone fill in the experimental defects, but healing was frequently accompanied by ankylosis and root resorption (Fig. 28-7). The iliac bone marrow grafts exerted an osteogeneic effect, and it was suggested that this was responsible for the induction of root resorption (Ellegaard *et al*. 1973, 1974). Bone grafts harvested from jaw bone and xenografts did not actively contribute to bone formation, but served as a scaffold for new bone formation (i.e. an osteoconductive effect). Often, however, these bone grafts were not reached by the new bone growing out from the host bone, but existed as isolated particles surrounded by a bone-like or cementum-like substance (Fig. 28-8). It was found that the treated bifurcation defects became filled mainly with granulation tissue derived from the periodontal ligament (Fig. 28-9). Nielsen *et al*. (1980) suggested that this invasion of ligament tissue inhibited bone formation and that the new cementum on the root surface in the bifurcation defects, including the cementum-like substance observed around the implanted bone particles, was formed by periodontal ligament cells (Fig. 28-8). Thus, it appeared from these studies that the key cells in periodontal regeneration are periodontal ligament cells rather than bone cells.

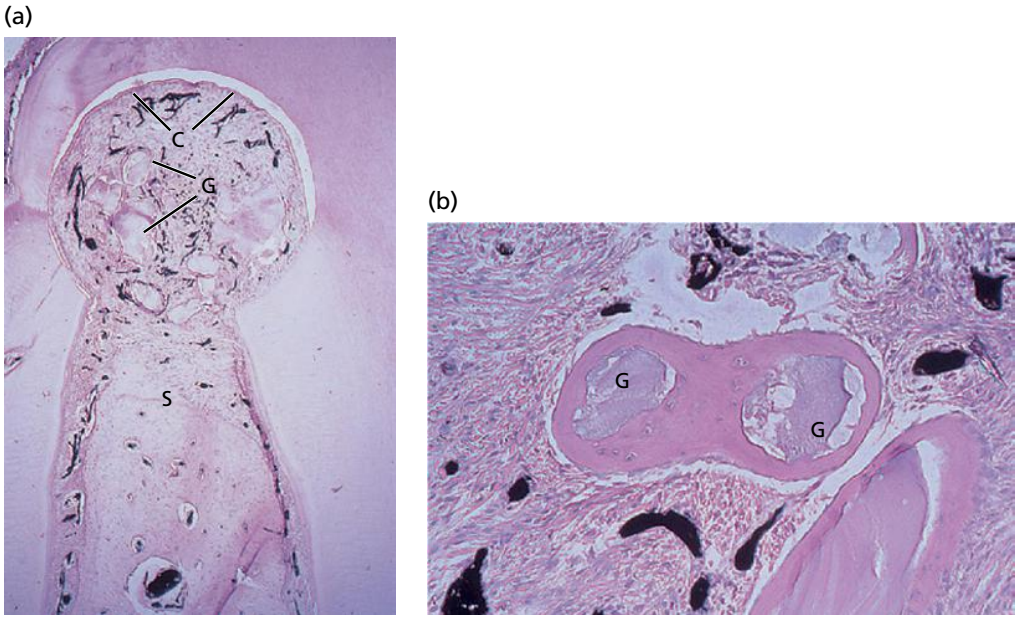

Fig. 28-8 (a) Microphotograph of a healed bifurcation defect following transplantation of non-vital bone grafts. The grafts (G) have not been reached by bone formation from the inter-radicular septum (S), but occur as isolated particles surrounded by "cementum". Cementum (C) and new connective tissue attachment formation have taken place along the entire circumference of the bifurcation. (b) High magnification of isolated bone grafts (G) with newly-formed "cementum" on the surface.

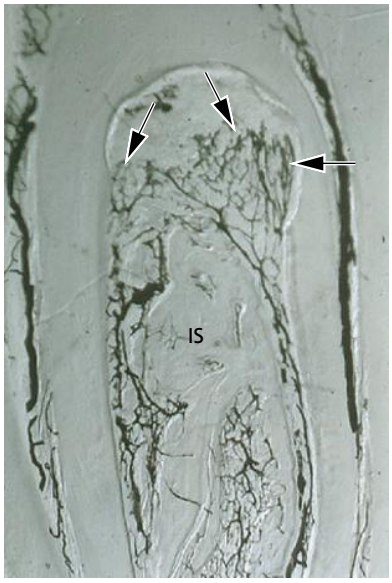

Fig. 28-9 Cleared specimen from a 1-week-old bifurcation defect treated with bone grafts. Judging from the course of the blood vessels, the granulation tissue in the defect has developed mainly from the periodontal ligament (arrows) and only to a minor extent from the inter-radicular septum (IS).

Regenerative capacity of bone cells

The ability of newly formed tissue originating from bone to produce a new connective tissue attachment was examined in a study by Karring *et al*. (1980). Roots of periodontitis-affected teeth were extracted and placed in surgically created sockets in edentulous areas of dogs. The implanted roots were covered with tissue flaps (submerged) and the results of healing were examined histologically after 3 months. A periodontal ligament was re-established in the apical portion of the re-implanted roots where, at the time of implantation, remnants of periodontal ligament tissue were preserved. In the coronal portion of the roots which were previously exposed to periodontitis and then scaled and planed, healing had consistently resulted in ankylosis and root resorption (Fig. 28-10). On the basis of this finding, it was concluded that tissue derived from bone lacks cells with the potential to produce a new connective tissue attachment.

Regenerative capacity of gingival connective tissue cells

Another experiment (Nyman *et al*. 1980) examined the potential of gingival connective tissue to produce a new connective tissue attachment. Teeth were treated as described in the experiment above but were not transplanted into sockets. Instead they were placed in bone concavities prepared on the buccal aspect of the jaw and subsequently covered by tissue flaps. Thus, half the circumference of the roots was in contact with bone while the remaining half faced the gingival connective tissue at the subsurface of the flaps. Histologic examination after 3 months of healing showed areas with periodontal ligament in the apical portion of the roots where, at the time of implantation, periodontal ligament tissue was preserved. In the coronal, previously exposed part of the roots, no signs of new connective tissue attachment were present. The root portion located in contact with gingival connective tissue demonstrated connective tissue with fibers oriented parallel to the root surface and without attachment to the root. However, root resorption occurred at the majority of the surfaces (Fig. 28-11). On the basis of this result it was concluded that gingival connective tissue also lacks

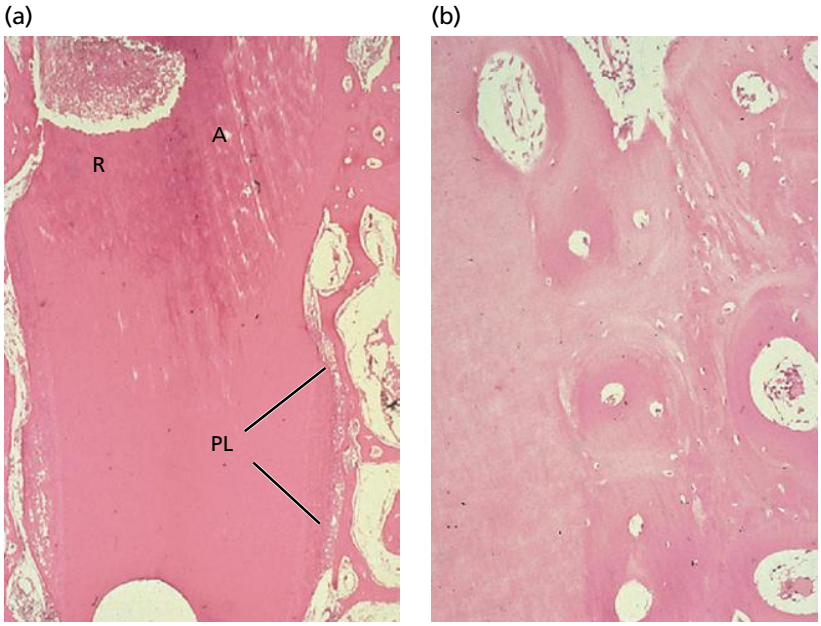

Fig. 28-10 (a) Microphotograph of a re-implanted root after 3 months of healing. A periodontal ligament (PL) has become re-established in the apical portion of the root, whereas ankylosis (A) and root resorption (R) are the predominant features in the coronal portion. (b) High magnification of the ankylosis seen in (a).

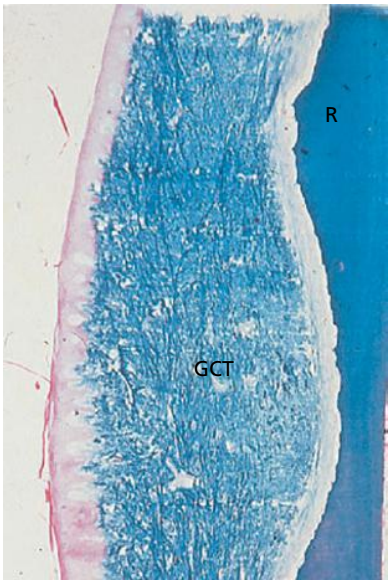

Fig. 28-11 Microphotograph of root (R) which has been re-implanted with its surface facing the gingival connective tissue (GCT). The surface exhibits extensive resorption.

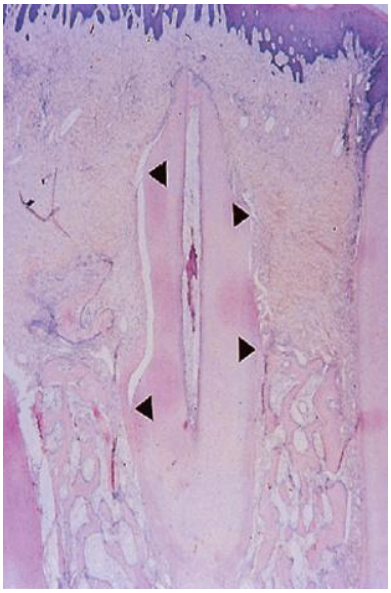

Fig. 28-12 Microphotograph showing new attachment formation (between the arrowheads) on a submerged root with a non-impaired periodontal ligament. Coronal to the cementum, root resorption is the predominant feature.

cells with the potential to produce a new connective tissue attachment.

Regenerative capacity of periodontal ligament cells

In the experiments described above, root resorption was also observed occasionally in the apical portion of the extracted and re-implanted roots (Karring *et al*. 1980; Nyman *et al*. 1980). It was suggested that this occurred because the periodontal ligament tissue retained on this part of the root had been injured during extraction, thereby allowing bone or gingival connective tissue to contact the root surface during healing and induce resorption. It was assumed that this damage to the retained periodontal ligament tissue had also restricted its potential to proliferate in the coronal direction along the root surface. Indeed, in a later study (Karring *et al*. 1985), where periodontitis-involved roots were retained in their sockets and subsequently submerged, significant amounts of new connective tissue attachment formed on the coronal portion of the roots (Fig. 28-12). The finding of new attachment only on the roots with a non-impaired periodontal ligament, and never on the extracted and re-implanted roots with an impaired ligament, indicates that periodontal ligament tissue contains cells with the potential to form a new connective tissue attachment on a detached root surface.

Active root resorption occurred consistently at the root surfaces above the coronal extension of the new

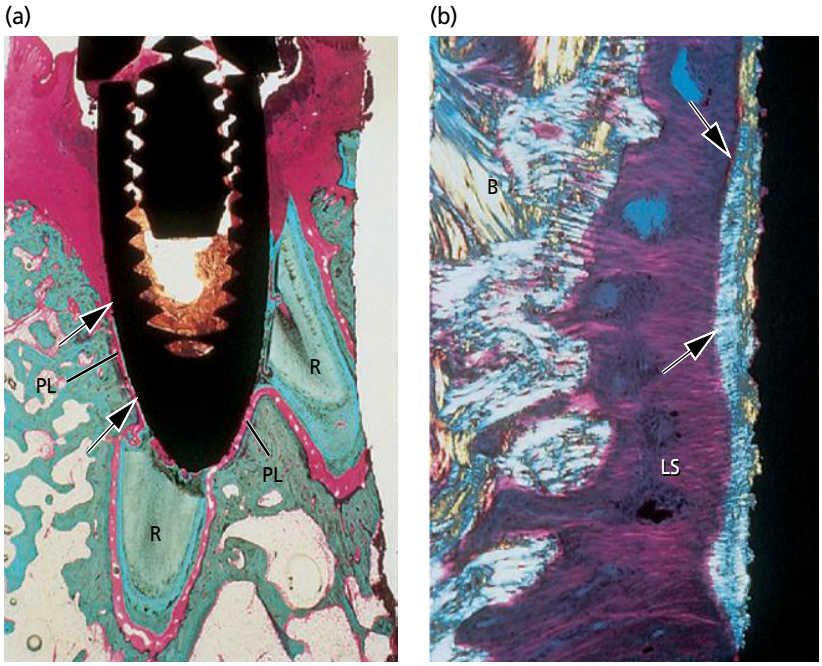

Fig. 28-13 (a) Microphotograph of a titanium implant placed in contact with retained root tips. A distinct cementum layer (arrows) and periodontal ligament (PL) in continuity with that on the roots (R) is visible on the implant surface. (b) High magnification in polarized light of the periodontal ligament formed around the implant seen in (a). A cementum layer (arrows) with Sharpey's fibers is present at the implant surface. Principal fibers, oriented perpendicular to the surface, are running across the ligament space (LS) and are inserting in the opposing bone (B) as in natural teeth (see Fig. 1-71).

attachment (Fig. 28-12). It was suggested that this resorption was induced by gingival connective tissue which had proliferated apically from the covering tissue flap. Thus, only cells in the periodontal ligament seem capable of regenerating lost periodontal attachment.

The final evidence that the progenitor cells for new attachment formation reside in the periodontal ligament was provided by studies in which titanium dental implants were placed in contact with retained root tips whose periodontal ligament served as a source of cells which could populate the implant surface during healing (Buser *et al*. 1990a, b; Warrer *et al*. 1993). Microscopic analysis revealed that a distinct layer of cementum with inserting collagen fibers had formed on the surfaces of the implants (Fig. 28-13a), and that these fibers, often oriented perpendicular to the surface, were embedded in the opposite bone (Fig. 28-13b). Control implants (Fig. 28-14) placed without contact with retained roots healed with the characteristic features of osseointegration (i.e. direct contact between bone and implant surface).

Further proof of the ability of periodontal ligament cells to produce a new connective tissue attachment was provided by Parlar *et al*. (2005) using a novel and unique experimental model in dogs. After resection of the crowns of the canine teeth in the dogs, the roots were hollowed to a depth of 5 mm, leaving a thin dentinal wall. Slits were then prepared in the cavity wall to create passages from this chamber to the surrounding periodontal ligament. A titanium implant was placed into the center of each

Fig. 28-14 Microphotograph of a titanium implant placed without contact with retained roots (control). This implant has healed with a direct contact between the bone and the implant surface (osseointegration).

chamber, and finally a collagen barrier was placed over the chamber before the roots were submerged. Histologic analysis after 4 months of healing revealed that a periodontal ligament, bone, and root cementum had formed between the implant and the dentinal wall of the chamber. Due to the invasion of

periodontal ligament tissue through the slits into the chamber, cementum had formed on the implant as well as on the dentinal wall, and a periodontal ligament was consistently interposed between the implant and the bone and between the bone and the dentinal wall.

Thus, there is strong evidence that the progenitor cells for periodontal attachment formation reside in the periodontal ligament and not in the alveolar bone as previously assumed (Melcher *et al*. 1987).

Role of epithelium in periodontal wound healing

Some of the roots in the experiment described above (Karring *et al*. 1985) penetrated the covering mucosa at early stages of healing, thereby allowing the epithelium to grow apically along the root surface. The amount of new connective tissue attachment on these roots was considerably smaller than that formed on the roots which remained submerged throughout the study. This finding and those of other investigators (Moscow 1964; Kon *et al*. 1969; Proye & Polson 1982) indicate that the apical migration of epithelium reduces the coronal gain of attachment, evidently by preventing periodontal ligament cells from repopulating the root surface (Fig. 28-15).

Down-growth of epithelium into the periodontal lesion most likely occurs to a varying extent during healing following most flap and grafting procedures applied in regenerative periodontal therapy, which may explain the varying results reported. This view is supported by the results of the monkey study by Caton *et al*. (1980). These investigators examined healing in ligature-induced periodontal lesions following treatment with four different regenerative surgical procedures:

1. Root planing and soft tissue curettage
2. Widman flap surgery without bone grafting
3. Widman flap surgery with the placement of frozen autogeneous red bone marrow and cancellous bone
4. Beta-tricalcium phosphate in intrabony defects.

Healing following all of these treatment modalities resulted in the formation of a long junctional epithelium extending to, or close to, the same level as before treatment.

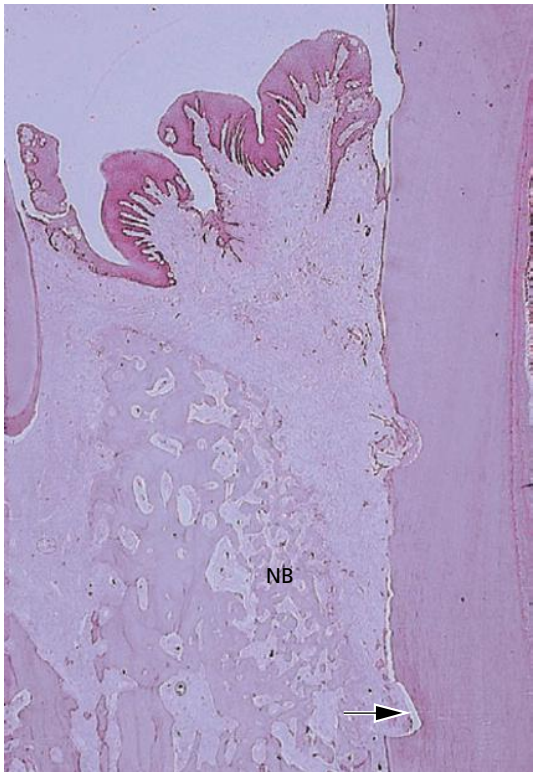

Fig. 28-15 Microphotograph illustrating an intrabony defect after regenerative treatment. New bone (NB) has formed in the defect, but epithelium has migrated apically along the root surface to the notch (arrow) in the root surface indicating the bottom of the defect before treatment.

Root resorption

In the experimental studies described previously, granulation tissue, derived from gingival connective tissue or bone, caused root resorption when contacting the curetted root surface during healing following surgery (Karring *et al*. 1980, 1985; Nyman *et al*. 1980). It should be expected, therefore, that this phenomenon would occur as a frequent complication of periodontal surgery, particularly following those procedures which include the placement of grafting materials to stimulate bone formation. The reason why root resorption is rarely seen is most likely that, postoperatively, the dentogingival epithelium migrates apically to form a protective barrier against the root surface (Fig. 28-15). This view is supported by the results of an experimental study in monkeys (Karring *et al*. 1984) in which roots, which previously had been subjected to ligature-induced periodontitis, were extracted and re-implanted in contact with bone and connective tissue, and covered with a tissue flap (submerged). After varying time intervals, the submerged roots were exposed to the oral cavity by a second incision (wounding) through the covering mucosa, thereby permitting the epithelium to migrate into the wound. In specimens where the wounding occurred within 2 weeks (Fig. 28-16), the previously diseased part of the roots was covered by epithelium and showed no signs of resorption. With increasing intervals between implantation of the roots and the wounding, a steadily diminishing part of the diseased root surface was covered by epithelium, and root resorption and ankylosis became progressively more pronounced (Fig. 28-17). This observation concurs with results presented by Björn *et al*. (1965) who treated 11 periodontally diseased teeth in seven human volunteers, using the submerging technique which prevented apical migration of the dentogingival epithelium. The authors reported that root resorption was indeed a common complication following this kind of therapy.

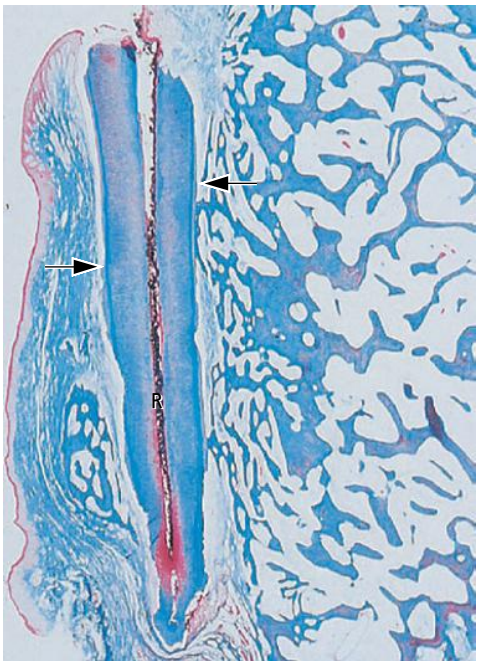

Fig. 28-16 Microphotograph of an implanted root (R) where epithelium was allowed to migrate into the wound after 2 weeks. The epithelium has migrated along the coronal, previously periodontitis-involved, root surfaces down to the level indicated by the arrows. In the areas covered by epithelium, there are no signs of resorption. Apical to this level, the root surfaces demonstrate root resorption.

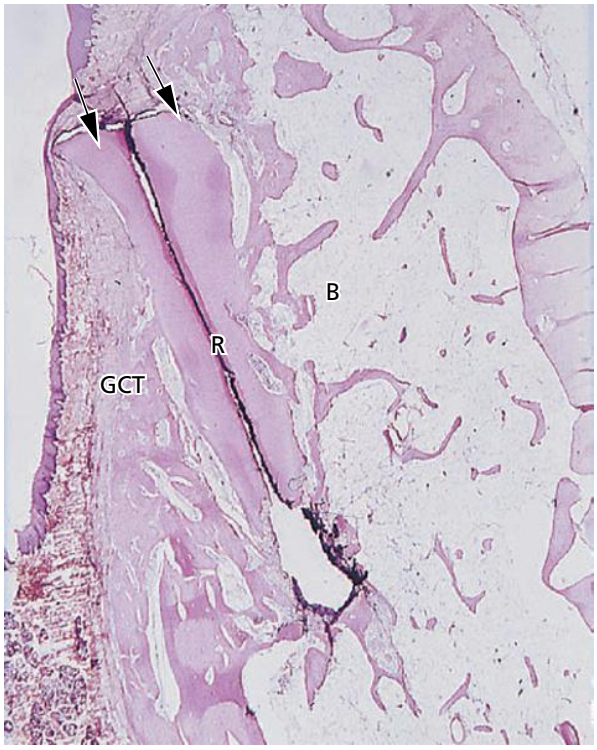

Fig. 28-17 Microphotograph of an implanted root (R) where epithelium was allowed to migrate into the wound after 4 weeks. The epithelium (arrows) covers only the coronal cut root surface. Extensive resorption is seen on the surface facing the gingival connective tissue (GCT) and resorption and ankylosis are seen on the surface facing the bone tissue (B).

Regenerative concepts

One of the first methods used in attempts to obtain new attachment was scaling and root planing combined with soft tissue curettage (i.e. mechanical removal of the diseased root cementum and the pocket epithelium). Studies in humans (e.g. McCall 1926; Orban 1948; Beube 1952; Waerhaug 1952; Schaffer & Zander 1953; Carranza 1954, 1960) and in animals (e.g. Beube 1947; Ramfjord 1951; Kon *et al.* 1969) showed that this type of periodontal therapy resulted not only in the establishment of gingival health, but also in a reduction of the initially recorded pocket depth. This decrease in the depth of the periodontal pocket was assumed to be partly the result of shrinkage of the initially inflamed gingiva, but partly also the effect of the formation of a new connective tissue attachment in the apical part of the pocket.

The possibility of obtaining new attachment became widely accepted with the work of Prichard (1957a, b), in which new attachment formation in intrabony periodontal lesions was reported as a predictable outcome of treatment. Seventeen cases were presented of whom four were subjected to a re-entry surgical procedure, revealing that these defects were filled with bone. The technique of Prichard (1957b, 1960) was only used for the treatment of three-wall intrabony defects, and the results obtained suggested that the morphology of the periodontal bony defect was essential for the establishment of a predictable prognosis. Goldman and Cohen (1958) introduced a classification of periodontal intrabony defects which was based on the number of osseous walls surrounding the defect, being either three-wall, two-wall or one-wall defects or a combination of such situations (Fig. 28-18).

The technique of Prichard (1957a, b, 1960) included the elevation of tissue flaps in order to get access to the defect. All granulation tissue in the defect was removed and the root surface was scaled and planed. In order to enhance regeneration of bone, small perforations were made with a bur at several sites on the bone walls. The flaps were sutured to accomplish complete coverage of the defect. Many clinical investigators have claimed that new attachment resulted following this type of treatment, but there is little quantitative or qualitative documentation (Patur & Glickmann 1962; Wade 1962, 1966; Ellegaard & Löe 1971). Patur and Glickmann (1962) reported a clinical study including 24 intrabony defects treated according to the Prichard technique (Prichard, 1957a, b). The outcome was evaluated by comparing preoperative and postoperative radiographs, measurements of the alveolar bone level adjacent to the root, and study casts taken during operation and postoperatively after reflecting buccal and lingual flaps. The authors reported that new attachment had occurred in two-wall and three-wall intrabony defects but not in one-wall defects. Results from a study by Ellegaard

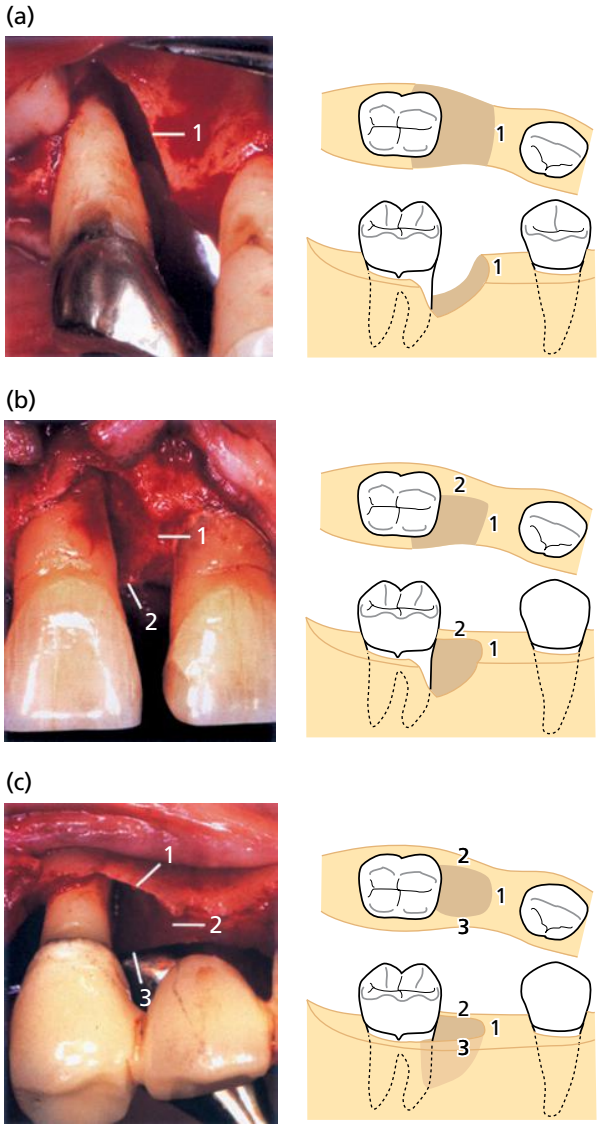

Fig. 28-18 Progression of periodontitis at a different rate on neighboring tooth surfaces results in the development of intrabony defects. Based on the number of surrounding bone walls, such defects are classified as one-wall (a), two-wall (b) or three-wall (c) defects.

and Löe (1971) comprising 191 defects in 24 patients with periodontal disease indicated that complete regeneration, determined radiographically and by periodontal probing, had occurred in around 70% of the three-wall defects, in 40% of the combined two-wall and three-wall defects, and in 45% of the two-wall defects.

In a later study by Rosling *et al*. (1976), 124 intrabony defects in 12 patients were treated by means of the modified Widman flap procedure (Ramfjord & Nissle 1974). Following treatment the patients were recalled twice per month for professional tooth cleaning. Re-examination performed clinically and on radiographs 2 years after therapy demonstrated bone fill-in of two-wall as well as three-wall defects. The authors suggested that this regrowth of bone was also associated with the formation of new connective tissue attachment and ascribed the successful healing mainly to the optimal standard of oral hygiene which was maintained in all patients during healing. A clinical study with almost identical results was presented by Polson and Heijl (1978). The results of several histologic studies in animals and humans, on the other hand, indicate that formation of new periodontal attachment is by no means predictable following subgingival curettage or flap surgery (Listgarten & Rosenberg 1979; Caton & Nyman 1980; Caton *et al*. 1980; Steiner *et al*. 1981; Stahl *et al*. 1983; Bowers *et al*. 1989a).

Grafting procedures

In a number of clinical trials and animal experiments, the flap approach was combined with the placement of bone grafts or implant materials into the curetted bony defects with the aim of stimulating periodontal regeneration. The various graft and implant materials used so far can be placed into four categories:

1. *Autogenous grafts*: grafts transferred from one position to another within the same individual. This type of graft comprises cortical bone or cancellous bone and marrow, and is harvested either from intraoral or extraoral donor sites.
2. *Allogeneic grafts*: grafts transferred between genetically dissimilar members of the same species. Frozen cancellous bone and marrow and freeze-dried bone have been used.
3. *Xenogeneic grafts*: grafts taken from a donor of another species.
4. *Alloplastic materials*: synthetic or inorganic implant materials which are used as substitutes for bone grafts.

The rationale behind the use of bone grafts or alloplastic materials is the assumption that both the regrowth of alveolar bone and the formation of new attachment would be stimulated because these materials may either (1) contain bone-forming cells (osteogenesis) or (2) serve as a scaffold for bone formation (osteoconduction), or because (3) the matrix of the bone grafts contains bone-inducing substances (osteoinduction) (Urist 1980; Brunsvold & Mellonig 1993). Such complete regeneration of the periodontal attachment apparatus following grafting procedures would imply, however, that cells derived from bone possess the ability to form new cementum with inserting collagen fibers on a previously periodontitis-involved root surface (Melcher *et al*. 1987). This assumption is in conflict with current knowledge about the biology of periodontal wound healing, that repopulation of the detached root surface with cells from the periodontal ligament is the prerequisite for new attachment formation. This means that all therapeutic procedures involving the placement of bone grafts or bone substitute implants are based on a biologic concept which cannot explain how such treatment results in regeneration of the periodontium.

The effect of using bone grafts or alloplastic materials for periodontal regeneration has mainly

been examined in case reports, while histologic evidence of new attachment and controlled clinical studies is limited. The results from such reports vary and the documentation presented usually consists of preoperative and postoperative probing attachment levels (PALs), radiographic interpretations or re-entry procedures.

Root surface biomodification

Much research has been directed to altering the periodontitis-involved root surface in a manner that will promote the formation of a new connective tissue attachment. Removal of bacterial deposits, calculus, and endotoxins from the cementum is generally considered essential for the formation of a new connective attachment (Garrett 1977). However, it was suggested by Stahl *et al*. (1972) that demineralization of the root surface, exposing the collagen of the dentin, would facilitate the deposition of cementum by inducing mesenchymal cells in the adjacent tissue to differentiate into cementoblasts. The biologic concept is that exposure of collagen fibers of the dentin matrix may facilitate adhesion of the blood clot to the root surface and thereby favor migration of the fibroblasts. However, it is doubtful whether this concept is in accordance with current knowledge about periodontal wound healing since there is no evidence that the exposure of collagen fibers of the dentin matrix facilitates repopulation of the root surface with cells derived from the periodontal ligament. As mentioned previously, periodontal ligament cells are required for the accomplishment of a new connective tissue attachment.

Several studies using various animal models have demonstrated an improved healing response histologically following citric acid and tetracycline root surface demineralization (Register & Burdick 1976; Crigger *et al*. 1978; Polson & Proye 1982; Claffey *et al*. 1987). However, in a study in dogs where naturally occurring furcations were treated with citric acid, several specimens demonstrated ankylosis and root resorption (Bogle *et al*. 1981). This finding corroborates that of Magnusson *et al*. (1985) in monkeys, where citric acid conditioning in combination with coronally displaced tissue flaps was evaluated after 6 months. These investigators found root resorption on 28 of 40 surfaces examined and 21 of these also showed ankylosis.

New connective tissue attachment following citric acid demineralization of root surfaces has been demonstrated histologically in humans (Cole *et al*. 1980; Frank *et al*. 1983; Stahl *et al*. 1983; Stahl & Froum 1991). Cole *et al*. (1980) showed histologic evidence of a new connective tissue attachment and bone formation coronal to reference notches placed in the apical extent of calculus identified on the root surface at the time of surgery. However, despite histologic evidence of regeneration following root surface biomodification with citric acid, results of controlled clinical trials failed to show any improvements in clinical conditions compared to controls not treated with acid (Moore *et al*. 1987; Fuentes *et al*. 1993).

Modification of the root surface with the use of topically applied enamel matrix proteins (Emdogain®) during surgery and following demineralization with ethylenediaminetetra-acetic acid (EDTA) has been introduced to enhance periodontal regeneration. The biologic concept is that the application of enamel matrix proteins (including amelogenins) may promote periodontal regeneration because it mimics events that take place during the development of the periodontal tissues (Hammarström 1997; Gestrelius *et al*. 2000). This view is based on the finding that the cells of Hertwig's epithelial root sheath deposit enamel matrix proteins on the root surface prior to cementum formation and that these proteins are the initiating factor for the formation of cementum. The commercially available product Emdogain®, a purified acid extract of porcine origin, contains enamel matrix derivatives (EMDs), which are supposed to be able to promote periodontal regeneration. However, it is not completely clear how this concept is in accordance with current knowledge about periodontal wound healing, since no evidence has been provided that it is cells derived from the periodontal ligament that are encouraged to repopulate the root surface after treatment. In fact, a study in dogs (Araùjo *et al*. 2003) where re-implanted roots that had been extracted and deprived of vital cementoblasts and subsequently treated with EMD failed to prevent ankylosis and root resorption, indicating that the root surfaces did not become repopulated with cells with the capacity to form cementum. A subsequent study *in vitro* also failed to confirm that EMDs have any significant effect on periodontal ligament cell proliferation (Chong *et al*. 2006).

In case series reports, a 4–4.5 mm gain of clinical attachment and about a 70% bone fill in intrabony defects were reported following treatment with EMD (Heden *et al*. 1999; Heden 2000). In a multicenter clinical study involving 33 subjects with 34 paired intrabony defects, application of EMD resulted in larger amounts of PAL gain (2.2 mm) and statistically significantly more bone gain (2.6 mm) than open-flap debridement after 36 months, evaluated clinically and radiographically (Heijl *et al*. 1997). Similar results were reported in another split-mouth clinical trial (23 patients) (Froum *et al*. 2001). In that study a probing pocket depth (PPD) reduction of 4.9 mm, a PAL gain of 4.3 mm, and a bone gain of 3.8 mm (evaluated by re-entry surgery) were observed after EMD application in 53 intrabony defects. These values were statistically significantly larger than those obtained by flap surgery (2.2 mm, 2.7 mm, and 1.5 mm, respectively, in 31 defects).

In a prospective multicenter randomized controlled clinical trial, the clinical outcomes of papilla preservation flap surgery [simplified papilla preservation flap (SPPF)] with or without the application of

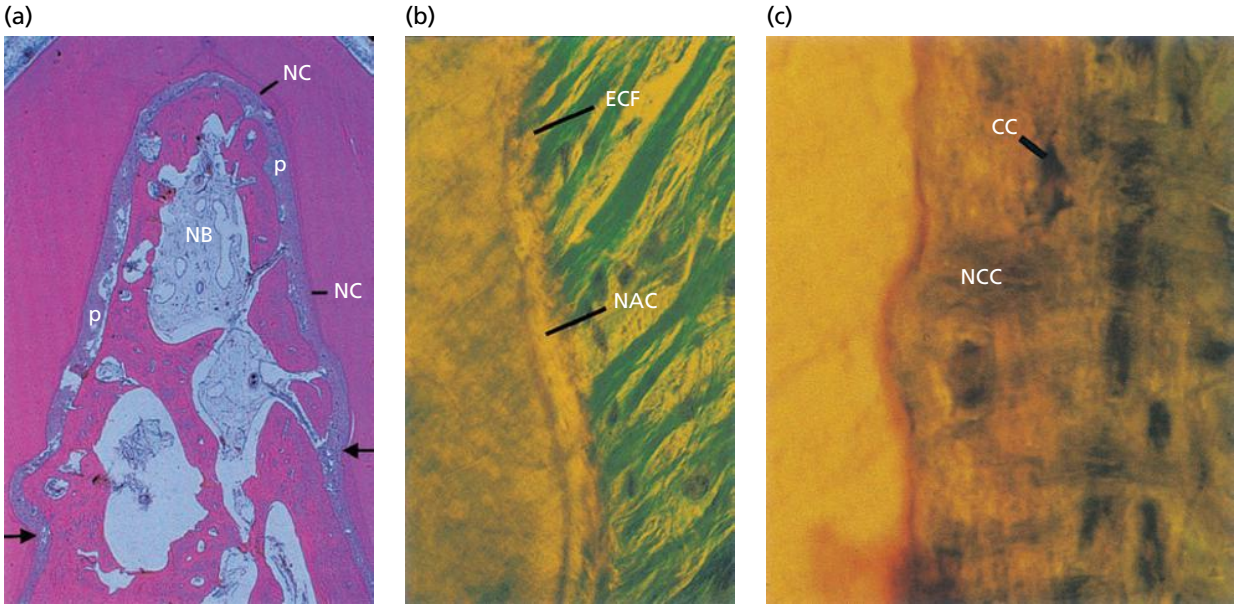

Fig. 28-19 (a) Photomicrograph of a grade III furcation defect in a dog following root surface biomodification with enamel matrix proteins and subsequently covered with a resorbable membrane. The defect has healed completely with bone (NB), a periodontal ligament (p), and new cementum (NC). The arrows indicate the apical extension of the lesion. (b) Cementum (NAC) formed on the root surface in the apical portion of the defect was acellular with inserting extrinsic collagen fibers (ECF), while (c) new cellular cementum (NCC) had formed in the coronal portion. (cc, cells.)

enamel matrix proteins were compared (Tonetti *et al*. 2002). A total of 83 test and 83 control patients with similar baseline periodontal conditions and defect characteristics were treated with either SPPF and Emdogain® or with SPPF alone. The test defects exhibited significantly more clinical attachment level (CAL) gain than the controls (3.1 ± 1.5 mm and 2.5 ± 1.5 mm, respectively).

When application of EMD was compared with GTR treatment, similar clinical improvements were obtained. In a randomized controlled clinical study, Pontoriero *et al*. (1999) compared EMD application with GTR with resorbable (two kinds: Guidor and Resolut) and non-resorbable (e-PTFE) membranes in intrabony defects. After 12 months, there were no significant differences among the groups, and EMD application resulted in a PPD reduction of 4.4 mm and a PAL gain of 2.9 mm, while the corresponding values from the membrane-treated sites (both GTR groups combined) were 4.5 mm and 3.1 mm, respectively. Silvestri *et al*. (2000) reported a PPD reduction of 4.8 mm and a PAL gain of 4.5 mm after EMD application in intrabony defects versus 5.9 mm and 4.8 mm, respectively, after GTR with non-resorbable membranes. Similar results were reported by other investigators (Sculean *et al*. 1999a, b; Silvestri *et al*. 2000, 2003; Sanz *et al*. 2004). There are studies indicating that following the application EMD in intrabony defects, clinical improvements can be achieved by the additional use of some bone graft materials (Zucchelli *et al*. 2003; Gurinsky *et al*. 2004; Trombelli *et al*. 2006), although others have failed to demonstrate a beneficial effect of this combined treatment (Sculean *et al*. 2005).

Histologic evidence of new cementum formation with inserting collagen fibers on a previously periodontitis-affected root surface and the formation of new alveolar bone in human specimens have been demonstrated following EMD treatment (Mellonig 1999; Sculean *et al*. 1999b). However, while in the study of Mellonig (1999) healing had occurred with acellular cementum on the root surface, the newly formed cementum in the study of Sculean *et al*. (1999b) displayed a predominantly cellular character. The ability of EMD to produce regeneration has been confirmed in controlled animal experiments (Fig. 28-19), following the treatment of intrabony, furcation, and dehiscence defects (Hammarström *et al*. 1997; Araùjo & Lindhe 1998; Sculean *et al*. 2000). In a later study, it was shown in monkeys that the combined application of EMD and autogenous bone grafts may improve periodontal regeneration in periodontal defects, compared to flap surgery alone (Cochran *et al*. 2003).

Guided tissue regeneration

The experimental studies (Karring *et al*. 1980; Nyman *et al*. 1980; Buser *et al*. 1990a, b; Warrer *et al*. 1993) described previously have documented that the progenitor cells for the formation of a new connective tissue attachment reside in the periodontal ligament. Consequently, it should be expected that a new connective tissue attachment would be predictably achieved if such cells populate the root surface during healing. This view was confirmed in a study in monkeys in which both gingival connective tissue and gingival epithelium were prevented from contacting the root surface during healing by the use of

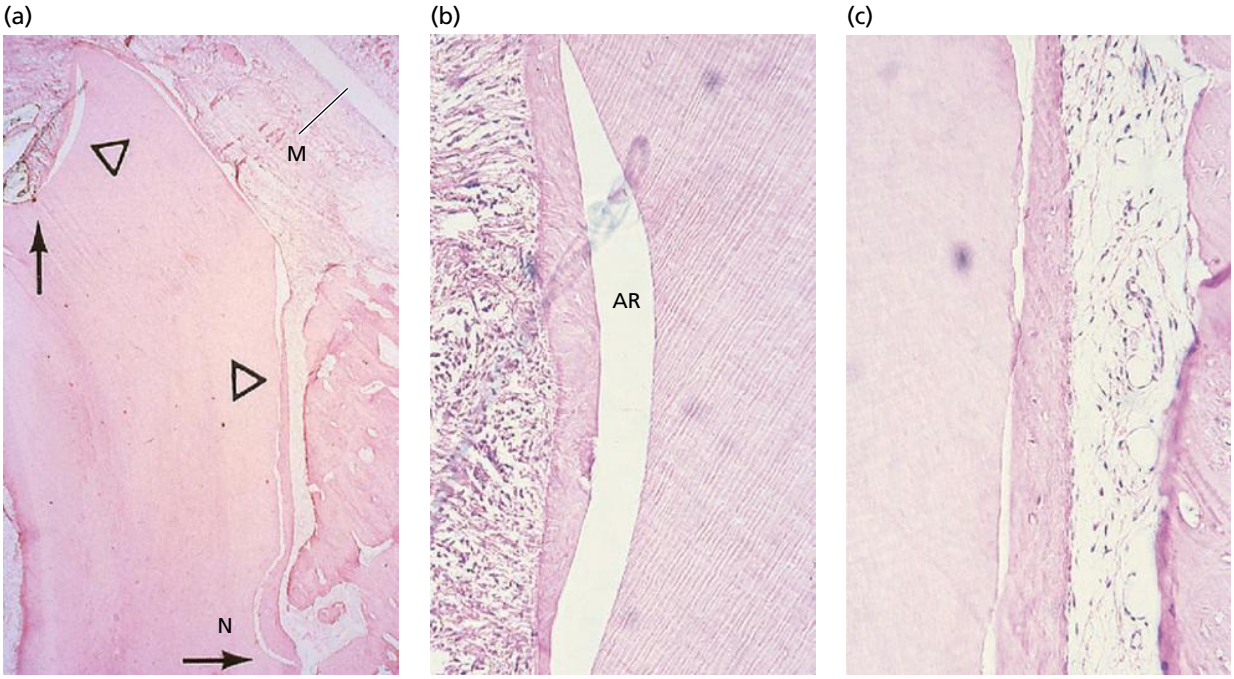

Fig. 28-20 (a) Microphotograph of membrane (M)-covered root. Newly formed cementum is visible along the entire length of the buccal root surface coronal to the notch (N) and also on part of the coronal cut surface (arrow). (b, c) Higher magnifications of the areas at the upper and lower triangles in (a), showing that collagen fibers are inserted into the newly formed cementum. (AR, artifact.)

a barrier membrane (Gottlow *et al*. 1984). After reduction of the supporting tissues around selected experimental teeth, the root surfaces were exposed to plaque accumulation for 6 months. Soft tissue flaps were then raised and the exposed root surfaces were curetted. The crowns of the teeth were resected and the roots were submerged. However, prior to complete closure of the wound, a membrane was placed over the curetted root surfaces on one side of the jaws in order (1) to prevent gingival connective tissue from contacting the root surface during healing, and (2) to provide a space for in-growth of periodontal ligament tissue. No membranes were placed over the contralateral roots. The histologic analysis after 3 months of healing demonstrated that the roots covered with membranes exhibited considerably more new attachment than the non-covered roots (Fig. 28-20). In four of the nine test roots, new cementum covered the entire length of the root. In all control specimens, the surface coronal to the newly formed cementum presented multinucleated cells and resorption cavities. In one control specimen, virtually half the root was resorbed. Coronal regrowth of alveolar bone had occurred to a varying extent in test and control roots, and no relationship was found between the amount of new cementum formation and the degree of bone regrowth. The results of this study strongly suggested that the exclusion of epithelial and gingival connective tissue cells from the healing area by the use of a physical barrier may allow (guide) periodontal ligament cells to repopulate the detached root surface. This observation provided the basis for the clinical application of the treatment principle termed "guided tissue regeneration" (GTR).

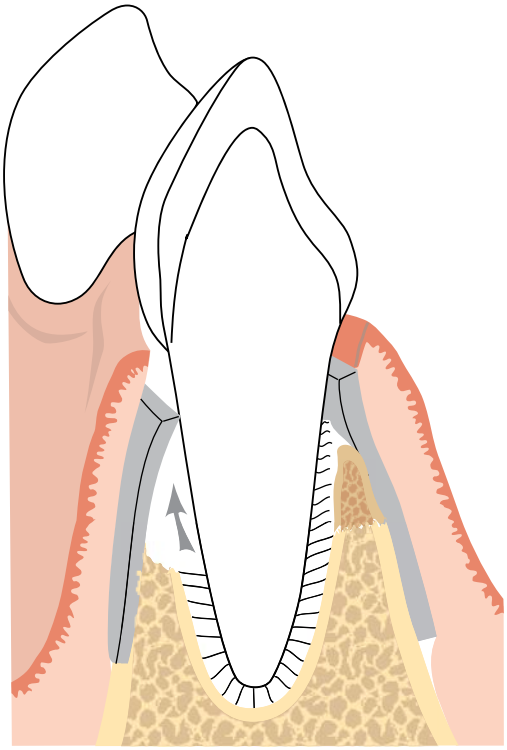

Fig. 28-21 Schematic diagram showing the placement of the physical barrier which prevents the epithelium and gingival connective tissue from contacting the root surface during healing. At the same time, the membrane allows cells from the periodontal ligament (arrow) to repopulate the previously periodontitis-involved root surface.

Thus, GTR treatment involves the placement of a physical barrier to ensure that the previous periodontitis-affected root surface becomes repopulated with cells from the periodontal ligament (Fig. 28-21).

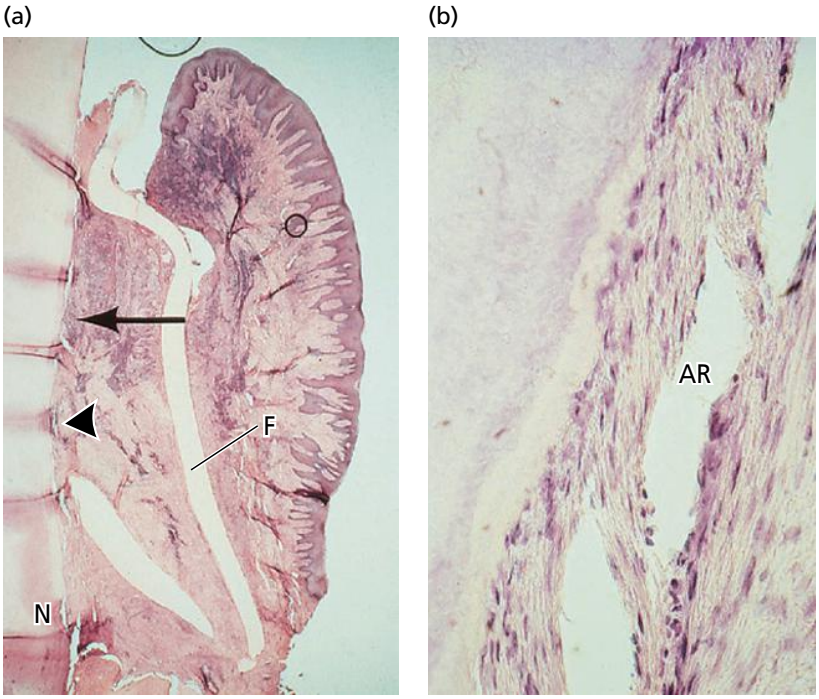

Fig. 28-22 (a) Microphotograph of a human tooth 3 months following guided tissue regeneration treatment using a Millipore filter (F). New cementum with inserting collagen fibers (about 5 mm) has formed from the notch (N) to the level of the arrow. Bone formation beneath the filter is lacking, probably due to the inflammatory infiltrate seen in the tissues adjacent to the filter. (b) Higher magnification of the area indicated by the arrowhead in (a) showing newly formed cementum with inserting collagen fibers. (AR, artifact.)

Treatment of the first human tooth with GTR was reported by Nyman *et al*. (1982). Due to extensive periodontal destruction, the tooth was scheduled for extraction. This offered the possibility of obtaining histologic documentation of the result of the treatment. Following elevation of full thickness flaps, scaling of the root surface, and removal of all granulation tissue, an 11-mm deep periodontal lesion was ascertained. Prior to flap closure, a membrane was adjusted to cover parts of the detached root surfaces, the osseous defect, and parts of the surrounding bone. Histologic analysis after 3 months of healing revealed that new cementum with inserting collagen fibers had formed on the previously exposed root surface (Fig. 28-22). In a later study (Gottlow *et al*. 1986), 12 cases treated with GTR were evaluated clinically, and for five of these cases histologic documentation was also presented. The results showed that considerable, but varying, amounts of new connective tissue attachment had formed on the treated teeth. Frequently, however, bone formation was incomplete. The varying results were ascribed to factors such as the amount of remaining periodontal ligament, the morphology of the treated defect, technical difficulties regarding membrane placement, gingival recession, and bacterial contamination of the membrane and the wound during healing.

GTR has been studied in a number of clinical trials (e.g. Tonetti *et al*. 2004) for the treatment of various periodontal defects such as intrabony defects (for review see Cortellini & Bowers 1995), furcation involvements (for review see Machtei & Schallhorn 1995; Karring & Cortellini 1999), and localized gingival recession defects (Pini-Prato *et al*. 1996). The efficiency of GTR in producing periodontal regeneration in these defects has been documented in animal studies (Gottlow *et al*. 1990; Araùjo *et al*. 1998; Laurell *et al*. 2006) and in several controlled clinical trials.

The clinical outcomes of GTR are most frequently evaluated by changes in CAL, bone levels, PPD, and the position of the gingival margin. In some of the studies on grade II and III furcations, horizontal changes in clinical attachment, bone level, and pocket depth were also measured. However, evidence of true regeneration of periodontal attachment can only be provided by histologic means.

Assessment of periodontal regeneration

In most studies on the effect of regenerative periodontal surgery, the outcomes are evaluated by probing attachment level measurements, radiographic analysis or re-entry operations. However, such methods do not provide proof of a true gain of attachment (i.e. formation of cementum with inserting collagen fibers coronal to the attachment level before treatment).

Periodontal probing

The inability of periodontal probing to determine accurately the coronal level of the connective tissue attachment has been demonstrated by several investigators (Listgarten *et al*. 1976; Armitage *et al*. 1977; Van der Velden & de Vries 1978). It is known from these studies that, in the inflamed periodontium, the probe does not stop precisely at the coronal level of the connective tissue attachment. Usually, it penetrates 0.5 mm or more into the connective tissue, surpassing the transition between the apical extension of the dentogingival epithelium and the coronal level of

connective tissue attachment. After therapy, when the inflammatory lesion is resolved, the probe tip tends to stop coronal to the apical termination of the epithelium. Following treatment of intrabony defects, new bone may form so close to the tooth surface that the probe cannot penetrate (Caton & Zander 1976). Thus, a gain of PAL following therapy does not necessarily mean that a true gain of connective tissue attachment has been accomplished. More likely, it is a reflection of improved health of the surrounding soft tissues which offer increased resistance to probe penetration.

Radiographic analysis and re-entry operations

Healing of intrabony defects following regenerative surgery is often documented by measurements made on radiographs obtained in a standardized and reproducible manner and/or assessed in conjunction with a re-entry operation. Analysis of radiographs before and after therapy, and inspection of the treated area during a re-entry operation, can certainly provide evidence of new bone formation. However, such "bone fill" does not prove formation of new root cementum with inserting collagen fibers (i.e. a new periodontal ligament). In fact, it was demonstrated by Caton and Zander (1976) and Moscow *et al*. (1979) that despite the fact that bone regeneration has occurred adjacent to the root in intrabony defects, a junctional epithelium is interposed between the newly formed bone and the curetted root surface. This means that radiographic analysis and assessments of bone formation by re-entry operations are unreliable methods for the documentation of new attachment formation.

Histologic methods

In several studies healing has been analyzed in histologic sections of block biopsies obtained after various forms of regenerative periodontal therapy. Histologic analysis is the only valid method to assess the formation of a true new attachment, but it requires that the location of the attachment level prior to therapy can be assessed with reasonable accuracy. In a few studies, histologic reference notches were placed in the apical extent of calculus deposits, identified on the root surface at the time of surgery (Cole *et al*. 1980; Bowers *et al*. 1989b, c). Usually, however, a reference is obtained by producing a notch in the root surface at the level of the reduced bone height. Although such a notch may not reflect the exact extent of the periodontitis-involved root surface prior to treatment, it is considered an adequate landmark for the assessment of new attachment (Isidor *et al*. 1985). It was also suggested that clinical signs of probing attachment gain and bone fill can be accepted as evidence of periodontal regeneration in the evaluation of GTR procedures (Lindhe & Echeverria 1994). This suggestion was based on evidence of a new attachment apparatus in histologic specimens from human biopsies harvested following GTR treatment (Nyman *et al*. 1982; Gottlow *et al*. 1986; Becker *et al*. 1987; Stahl *et al*. 1990; Cortellini *et al*. 1993) and on the biologic concept of GTR (Karring *et al*. 1980, 1985, 1993; Nyman *et al*. 1980; Gottlow *et al*. 1984).

Conclusion

There is evidence that the progenitor cells for regeneration of a lost periodontal attachment are present in the periodontal ligament. Consequently, a periodontal regenerative procedure needs to encourage repopulation of the previous periodontitis-affected root surface with cells from the periodontal ligament.

GTR and conditioning of the root surface with enamel matrix proteins represent the best documented regenerative procedures for obtaining periodontal regeneration in periodontal lesions, although there is some uncertainty whether enamel matrix proteins in fact stimulate the proliferation of periodontal ligament cells.

Placement of bone grafts or bone substitute implants is based on a biologic concept which cannot explain how such treatment results in regeneration of the periodontium.

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Part 9: Examination Protocols

Chapter 29

Examination of Patients

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Patient's history

As a basis for comprehensive treatment planning and understanding of the patient's needs, social and economic situations, as well as general medical conditions, the history of the patient is a revealing documentation. In order to expedite history taking, a health questionnaire may be filled out by the patient prior to the initial examination. This questionnaire should be constructed in such a way that the professional can immediately identify compromising or risk factors that may modify the treatment plan and hence, may have to be discussed in detail with the patient during the initial visit. The assessment of the patient's history requires an evaluation of the following six aspects: (1) chief complaint, (2) social and family history, (3) dental history, (4) oral hygiene habits, (5) smoking history, and (6) medical history and medications.

Chief complaint and expectations

It is essential to realize the patient's needs and desires for treatment. If a patient has been referred for specific treatment, the extent of the desired treatment has to be defined and the referring dentist should be informed of the intentions for treatment. Self-referring patients usually have specific desires and expectations regarding treatment outcomes. These may not be congruent with the true assessment of a professional with respect to the clinical situation. Optimal treatment results for an individual patient may only be achieved if the patient's demands can be balanced with the objective evaluation of the disease and the projected treatment outcomes. Therefore, the patient's expectations have to be taken seriously and must be considered in the evaluation to achieve harmony with the clinical situation.

Social and family history

Before assessing the clinical condition in detail, it is advantageous to elucidate the patient's social environment and to get a feel for his/her priorities in life, including attitude towards periodontal therapy and rehabilitation with dental implants. Likewise, a family history may be important, especially with respect to aggressive forms of periodontitis.

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Dental history

These aspects include an assessment of previous dental care and maintenance visits, if not documented by a referring dentist. In this context, information regarding signs and symptoms of periodontitis noted by the patient, such as migration and increasing mobility of teeth, bleeding gums, food impaction, and difficulties in chewing, have to be explored. Chewing comfort and the possible need for tooth replacement with dental implants is determined.

Oral hygiene habits

In addition to the exploration of the patient's routine dental care, including frequency and duration of daily toothbrushing, his/her knowledge about interdental cleansing devices and additional chemical supportive agents and regular use of fluorides should be assessed.

Smoking history

Since cigarette smoking has been documented to be the second most important risk factor after inadequate plaque control (Kinane *et al*. 2006) in the etiology and pathogenesis of periodontal diseases, the importance of smoking counseling cannot be overestimated. Moreover, based on the fact that cigarette smokers display an increased risk for biologic implant complications and implant loss compared with nonsmokers (Strietzel *et al*. 2007; Heitz-Mayfield & Huynh-Ba 2009), the assessment of the smoking history represents an important step in the consideration of candidates for implant therapy. Determination of the smoking status should include detailed information about exposure time and quantity. Further aspects of smoking cessation programs are presented in Chapter 35.

Medical history and medications

General medical aspects may be extracted from the health questionnaire constructed to highlight any medical risk factors for routine periodontal and/or implant therapy. The four major complexes of complications encountered in patients may be prevented by checking the medical history with respect to: (1) cardiovascular and circulatory risks, (2) bleeding disorders, (3) infective risks, and (4) allergic reactions. Further aspects are presented in Chapter 31.

In light of the increasing consumption of medications in the aging population, an accurate assessment of the patient's prescribed medications and their potential interactions and effects on therapeutic procedures has to be made. With respect to treatment planning with dental implants, it may be appropriate to contact the patient's physician for detailed information relevant to systemic risks (Bornstein *et al*. 2009).

Genetic testing before periodontal and implant therapy

Cytokine gene polymorphisms may modulate the host response to bacterial challenge and influence susceptibility to periodontitis and peri-implantitis. Based on current evidence, however, it may be considered premature to recommend systematic genetic screening of patients with periodontal diseases and candidates for implant therapy (Huynh-Ba *et al*. 2007, 2008).

Signs and symptoms of periodontal diseases and their assessment

Periodontal diseases are characterized by gingival color and texture alterations, for example redness and swelling, as well as an increased tendency to bleeding on probing (BoP) the gingival sulcus/pocket area (Fig. 29-1). In addition, the periodontal tissues may exhibit a reduced resistance to probing that is perceived as increased probing depth and/or tissue recession. Advanced stages of periodontitis may also be associated with increased tooth mobility as well as drifting or flaring of teeth (Fig. 29-2).

On radiographs, periodontitis may be recognized by moderate-to-advanced loss of alveolar bone (Fig. 29-3). Bone loss is defined either as "horizontal" or "angular". If bone loss has progressed at similar rates in the dentition, the crestal contour of the remaining bone will be even and bone loss is defined as "horizontal". In contrast, angular bony defects are the result of bone loss that has occurred at different rates around teeth/tooth surfaces and, hence, is defined as "vertical" or "angular" bone loss.

In a histologic section, periodontitisis is characterized by the presence of an inflammatory cell infiltrate within a 1–2-mm wide zone of gingival connective tissue adjacent to the subgingival biofilm on the tooth (Fig. 29-4). Within the infiltrated area there is a pronounced loss of collagen. In more advanced forms of periodontitis, marked loss of connective tissue attachment to the root and apical down-growth of the dentogingival epithelium along the root are important characteristics.

Outcomes from experimental and clinical research have demonstrated that chronic and aggressive forms of periodontal disease:

- Affect individuals with various susceptibility at different rates (Löe *et al*. 1986)
- Affect different parts of the dentition to a varying degree (Papapanou *et al*. 1988)
- Are site specific in nature for a given area (Socransky *et al*. 1984)
- Are sometimes progressive in character and, if left untreated, may result in tooth loss (Löe *et al*. 1986)
- Can be successfully treated and maintained long term (Hirschfeld & Wasserman 1978; Rosling *et al*. 2001; Axelsson *et al*. 2004).

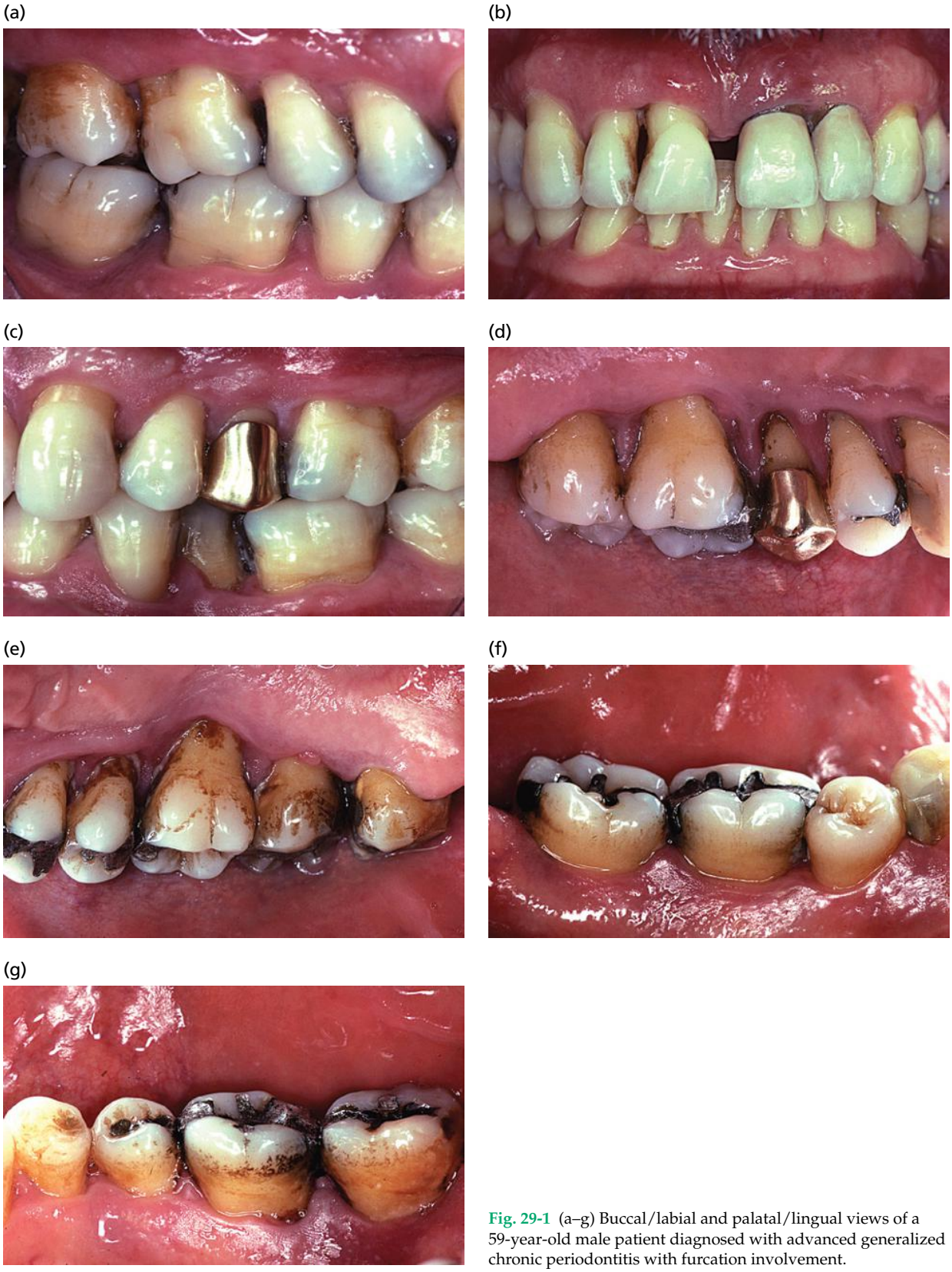

Fig. 29-1 (a–g) Buccal/labial and palatal/lingual views of a 59-year-old male patient diagnosed with advanced generalized chronic periodontitis with furcation involvement.

For effective treatment planning, the location, topography, and extent of periodontal lesions must be recognized in all parts of the dentition. It is, therefore, mandatory to examine all sites of all teeth for the presence or absence of periodontal lesions. This in turn means that single-rooted teeth have to be examined at four sites at least (e.g. mesial, buccal, distal, and oral) and multirooted teeth at six sites at least (e.g. mesiobuccal, buccal, distobuccal, disto-oral, oral, and mesio-oral) with special attention to the furcation areas.

Since periodontitis includes inflammatory alterations to the gingiva and a progressive loss of periodontal attachment and alveolar bone, comprehensive examination must include assessments of such pathologic alterations.

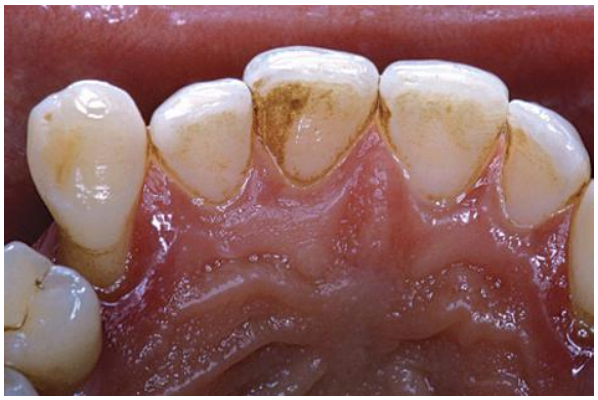

Fig. 29-2 Buccal migration of tooth 13 as a sign of advanced periodontitis.

Figure 29-1 shows the clinical status of a 59-year-old patient diagnosed with advanced generalized chronic periodontitis. The examination procedures used to assess the location and extent of periodontal disease will be demonstrated by using this case as an example.

Gingiva

Clinical signs of gingivitis include changes in color and texture of the soft marginal gingival tissue and BoP.

Various index systems have been developed to describe gingivitis in epidemiologic and clinical research (see Chapter 7). Even though the composition of the inflammatory infiltrate can only be identified on histologic sections, inflamed gingival tissue can be correctly diagnosed on the basis of the tendency to BoP. The symptom "bleeding on probing" to the bottom of the gingival sulcus/pocket is associated with the presence of an inflammatory cell infiltrate.

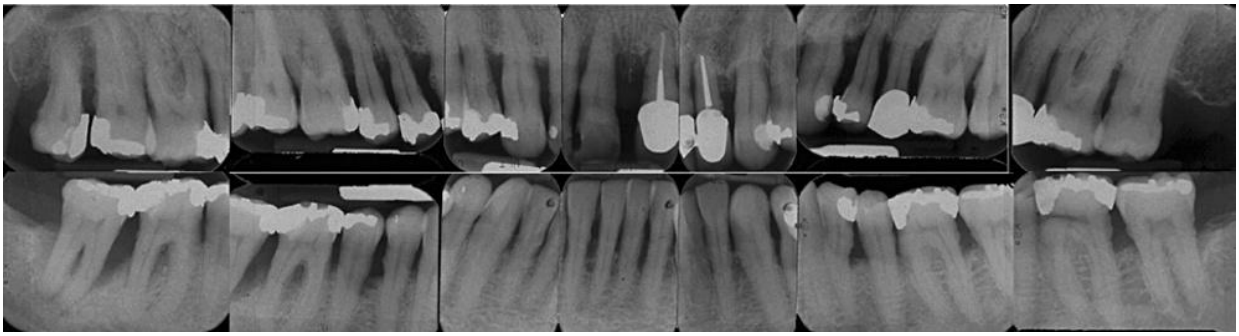

Fig. 29-3 Periapical radiographs of the patient presented in Fig. 29-1.

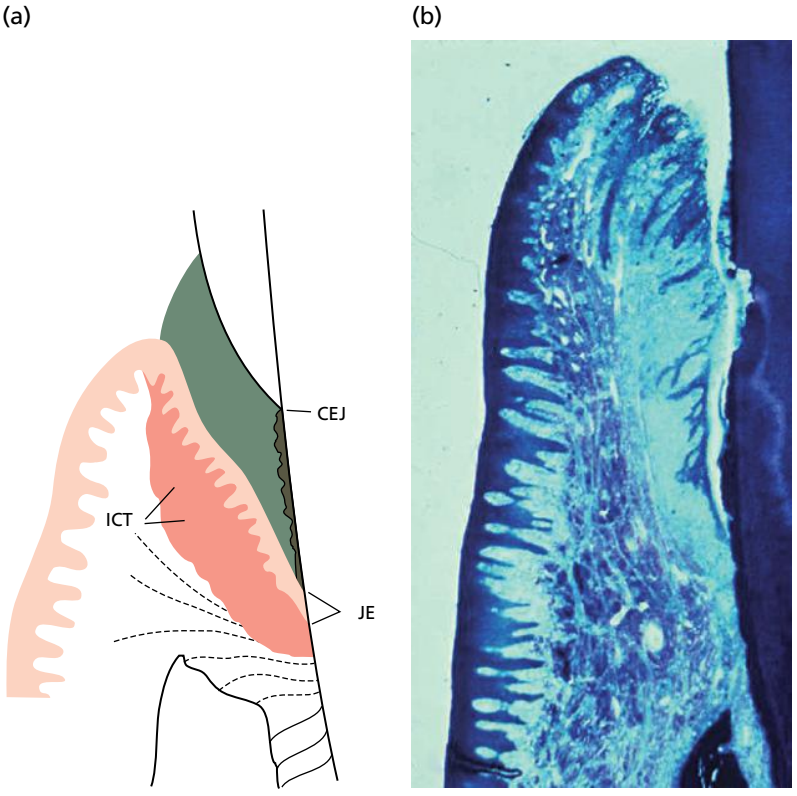

Fig. 29-4 (a) Schematic diagram and (b) histologic section showing the characteristics of periodontal disease. Note the zone of infiltrated connective tissue (ICT) lateral to the junctional epithelium (JE). (CEJ, cementoenamel junction.)

The occurrence of such bleeding, especially in repeated examinations, is indicative of disease progression (Lang *et al*. 1986), although the predictive value of this single parameter remains rather low (i.e. 30%). On the other hand, the absence of BoP yields a high negative predictive value (i.e. 98.5%) and, hence, is an important indicator of periodontal stability (Lang *et al*. 1990; Joss *et al*. 1994). Since trauma to the tissues provoked by probing should be avoided if the true vascular permeability changes associated with inflammation are to be assessed, a probing pressure of 0.25 N should be applied when assessing "bleeding on probing" (Lang *et al*. 1991; Karayiannis *et al*. 1992). The identification of the apical extent of the gingival lesion is made in conjunction with *pocket probing depth* (PPD) measurements. In sites where "shallow" pockets are present, inflammatory lesions residing in the overt portion of the gingiva are distinguished by probing in the superficial marginal tissue. When the infiltrate resides in sites with attachment loss, the inflammatory lesion in the apical part of the pocket must be identified by probing to the bottom of the deepened pocket.

Bleeding on probing

A periodontal probe is inserted to the "bottom" of the gingival/periodontal pocket by applying light force and is moved gently along the tooth (root) surface (Fig. 29-5). If bleeding is provoked upon retrieval of the probe, the site examined is considered "BoP"-positive and, hence, is inflamed.

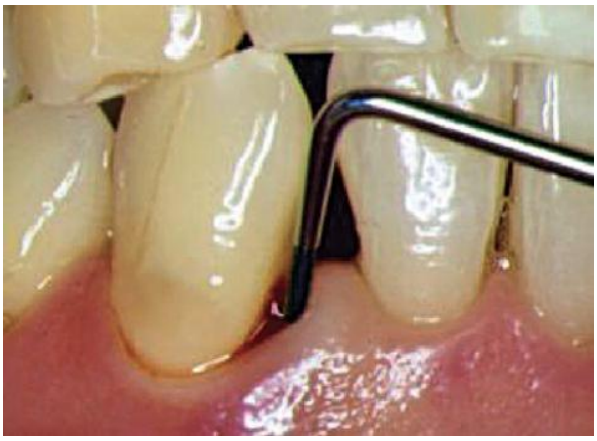

Fig. 29-5 Pocket probing depth in conjunction with bleeding on probing.

Figure 29-6 shows the chart used to identify BoP-positive sites in a dichotomous way at the initial examination. Each tooth in the chart is represented and each tooth surface is indicated by a triangle. The inner segments represent the palatal/lingual gingival units, the outer segments the buccal/labial units, and the remaining fields the two approximal gingival units. The fields of the chart corresponding to the inflamed gingival units are marked in red. The mean BoP score (i.e. gingivitis) is given as a percentage. In the example shown in Fig. 29-1, 104 of a total of 116 gingival units bled on probing, amounting to a BoP percentage of 89%. This method of charting not only serves as a means of documenting areas of health and disease in the dentition, but charting during the course of therapy or maintenance will disclose sites which become healthy or remain inflamed. The topographical pattern will also identify sites with consistent or repeated BoP at various observation periods.

Keratinized mucosa at implant recipient sites

In order to maintain health and tissue stability around dental implants, the presence of a minimum width of keratinized mucosa has been postulated. A width of keratinized mucosa of <2 mm has been debated in the literature as a contributing factor for impaired plaque control with consequent increase in inflammation around dental implants (Bouri *et al*. 2008; Schrott *et al*. 2009; Crespi *et al*. 2010). The findings of a systematic review, however, showed that the evidence in support of the need for keratinized mucosa around dental implants in order to maintain health and stability is limited (Wennström & Derks 2012). Nevertheless, the dimensions of the keratinized mucosa in edentulous areas should be evaluated in candidates for implant therapy.

Periodontal ligament and root cementum

In order to evaluate the amount of tissue lost in periodontitis and also to identify the apical extension of the inflammatory lesion, the following parameters should be recorded:

- Pocket probing depth (PPD)
- Probing attachment level (PAL)
- Furcation involvement (FI).
- Tooth mobility (TM).

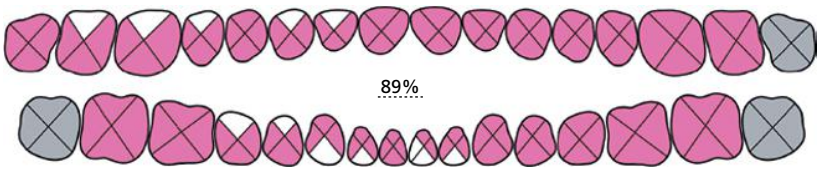

Fig. 29-6 Chart used to identify bleeding on probing-positive sites in a dichotomous way at the initial examination and during maintenance care.

Assessment of probing pocket depth

The probing depth, that is the distance from the gingival margin to the bottom of the gingival sulcus/pocket, is measured to the nearest millimeter by means of a graduated periodontal probe with a standardized tip diameter of approximately 0.4–0.5 mm (Fig. 29-7).

Fig. 29-7 Examples of graduated periodontal probes with a standardized tip diameter of approximately 0.4–0.5 mm.

The pocket depth should be assessed at each surface of all teeth in the dentition. In the periodontal chart (Fig. 29-8), PPDs of <4 mm are indicated in black numbers, while deeper PPDs (i.e. ≥4 mm) are marked in red. This allows an immediate evaluation of diseased sites (i.e. red numbers) both from an extent and a severity point of view. The chart may be used for case presentation and discussion with the patient.

Results from PPD measurements will only in rare situations [when the gingival margin co-incides with the cementoenamel junction (CEJ)] give proper information regarding the extent of loss of probing attachment. For example, an inflammatory edema may cause swelling of the free gingiva resulting in coronal displacement of the gingival margin without a concomitant migration of the dentogingival epithelium to a level apical to the CEJ. In such a situation,

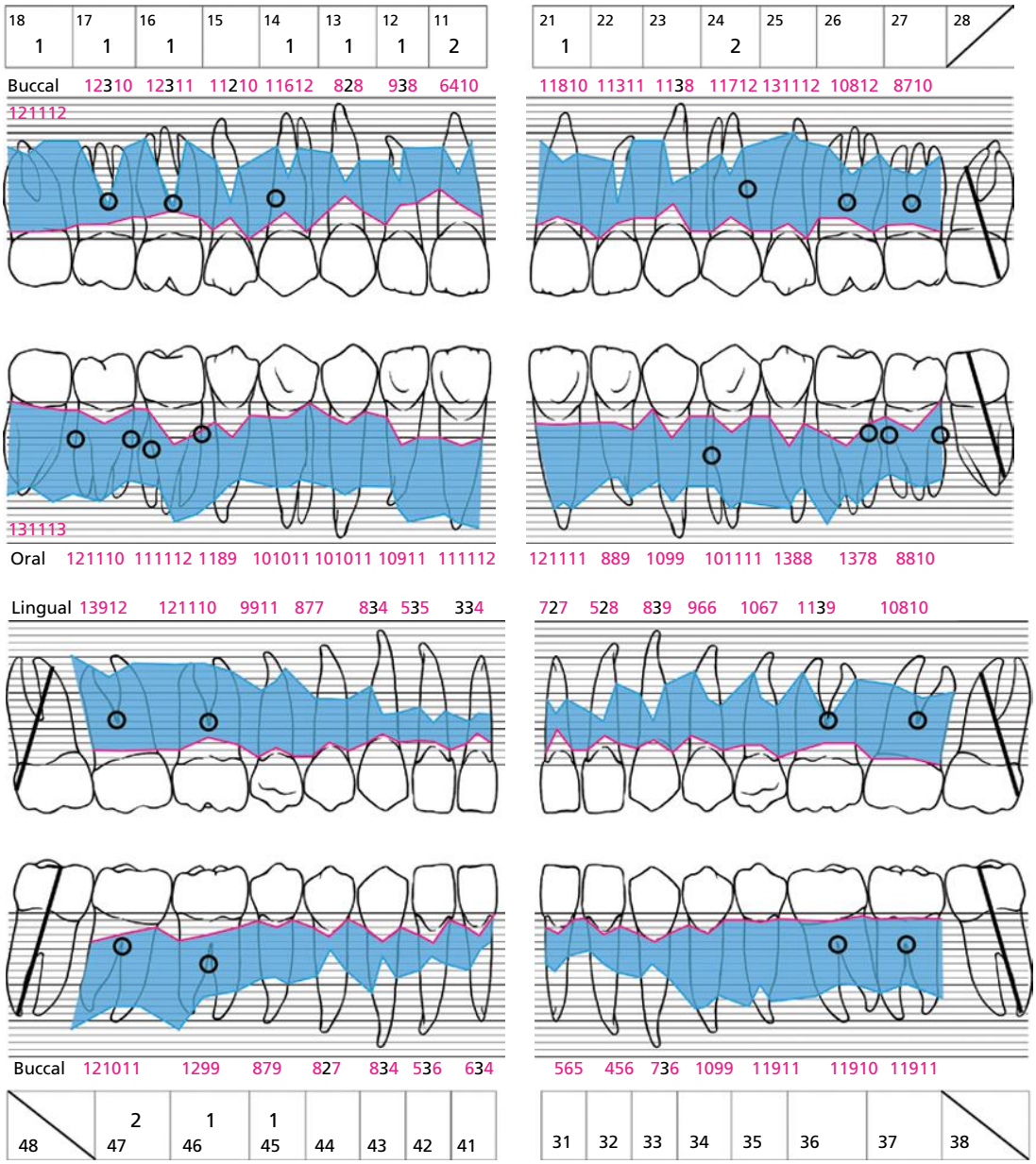

Fig. 29-8 Periodontal chart indicating probing pocket depth (PPD) of <4 mm in black numbers and PPD of ≥4 mm in red numbers.

a pocket depth exceeding 3–4 mm represents a "pseudo-pocket". In other situations, an obvious loss of periodontal attachment may have occurred without a concomitant increase of PPD. A situation of this kind is shown in Fig. 29-9, where multiple recessions of the gingiva can be seen. Hence, the assessment of the PPD in relation to the CEJ is an indispensable parameter for the evaluation of the periodontal condition (i.e. PAL).

Assessment of probing attachment level

PAL may be assessed to the nearest millimeter by means of a graduated probe and expressed as the distance in millimeters from the CEJ to the bottom of the probeable gingival/periodontal pocket. The clinical assessment requires the measurement of the distance from the free gingival margin (FGM) to the CEJ for each tooth surface. After recording this, PAL may be calculated from the periodontal chart (i.e. PPD – distance CEJ–FGM). In cases with gingival recessions, the distance CEJ–FGM turns negative and, hence, will be added to the PPD to determine PAL.

Errors inherent in periodontal probing

The distances recorded in a periodontal examination using a periodontal probe have generally been assumed to represent a fairly accurate estimate of the PPD or PAL at a given site. In other words, the tip of the periodontal probe has been assumed to identify the

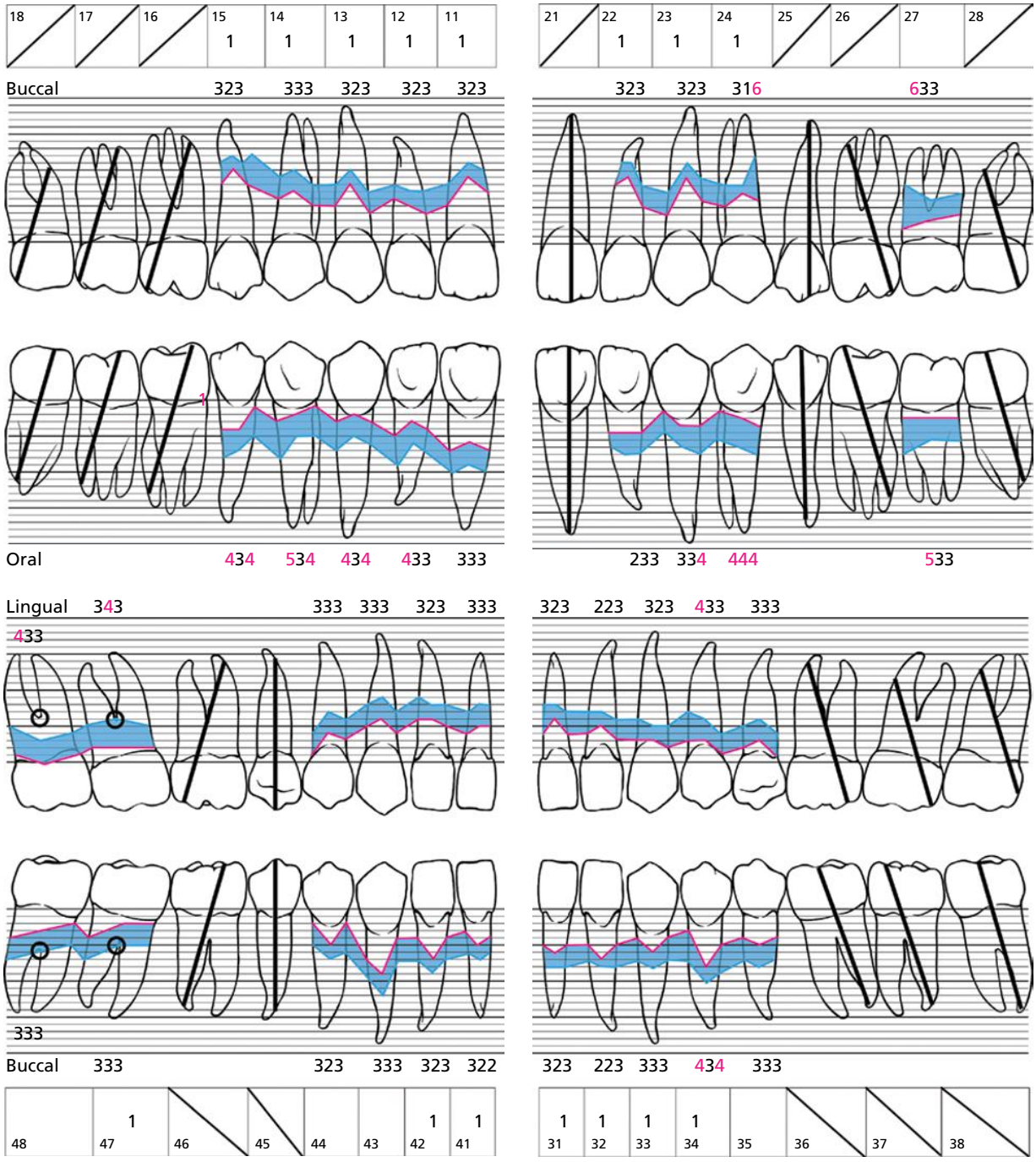

Fig. 29-9 Periodontal chart indicating that attachment loss has occurred without a concomitant increase of probing pocket depth. Multiple buccal/labial as well as palatal/lingual gingival recessions can be seen.

level of the most apical cells of the dentogingival (junctional) epithelium. Results from research, however, have indicated that this is seldom the case (Saglie *et al*. 1975; Listgarten *et al*. 1976; Armitage *et al*. 1977; Spray *et al*. 1978; Robinson & Vitek 1979; van der Velden 1979; Magnusson & Listgarten 1980; Polson *et al*. 1980). A variety of factors influence measurements made with periodontal probes, including the (1) thickness of the probe used; (2) angulation and positioning of the probe due to anatomic features such as the contour of the tooth surface; (3) graduation scale of the periodontal probe; (4) pressure applied on the instrument during probing; and (5) degree of inflammatory cell infiltration in the soft tissue and accompanying loss of collagen. Therefore, a distinction should be made between the histologic and the clinical PPD to differentiate between the depth of the actual anatomic defect and the measurement recorded by the probe (Listgarten 1980).

Measurement errors as a result of factors such as the thickness of the probe, contour of the tooth surface, and incorrect angulation and graduation scale of the probe can be reduced or avoided by the selection of a standardized instrument and careful management of the examination procedure. More difficult to avoid, however, are errors resulting from variations in probing force and the extent of inflammatory alterations of the periodontal tissues. As a rule, the greater the probing pressure applied, the deeper the penetration of the probe into the tissue. In this context, it should be realized that in investigations designed to disclose the probing pressure (force) used by different clinicians, this was found to range from 0.03 to 1.3 N (Gabathuler & Hassell 1971; Hassell *et al*. 1973), and also to differ by as much as two-fold for the same dentist from one examination to another. In order to exclude measurement errors related to the effect of variations in probing pressure, so-called pressure-sensitive probes have been developed. Such probes enable the examiner to probe with a predetermined pressure (van der Velden & de Vries 1978; Vitek *et al*. 1979; Polson *et al*. 1980). However, over- and under-estimation of the "true" PPD or PAL may also occur when this type of probing device is employed (Armitage *et al*. 1977; Robinson & Vitek 1979; Polson *et al*. 1980). When the connective tissue subjacent to the pocket epithelium is infiltrated by inflammatory cells (Fig. 29-10), the periodontal probe will penetrate beyond the apical termination of the dentogingival epithelium, resulting in an overestimation of the "true" depth of the pocket. Conversely, when the inflammatory infiltrate decreases in size following successful periodontal treatment and a concomitant deposition of new collagen occurs within the previously inflamed tissue area, the dentogingival tissue will become more resistant to penetration by the probe. The probe may then fail to reach the apical termination of the epithelium using the same probing pressure and the "true" PPD or PAL is underestimated. The magnitude of the difference between the probing measurement and the histologic "true" pocket depth (Fig. 29-10) may range from fractions of a millimeter to a couple of millimeters (Listgarten 1980).

From this discussion it should be understood that reductions in PPD and/or gain of PAL, assessed by periodontal probing, following periodontal treatment, do not necessarily indicate the formation of a new connective tissue attachment at the bottom of the treated lesion. Rather, such a change may merely represent a resolution of the inflammatory process and may thus occur without an accompanying histologic gain of attachment (Fig. 29-10). In this context it should be realized that the terms "probing pocket depth" (PPD) and "probing attachment level" (PAL) have replaced the previously used terms "pocket depth" and "gain and loss of attachment". Likewise, the term PAL is used in conjunction with "gain" and/or "loss" to indicate that changes in PAL have been assessed by clinical probing.

Current knowledge of the histopathology of periodontal lesions and healing thereof has thus altered

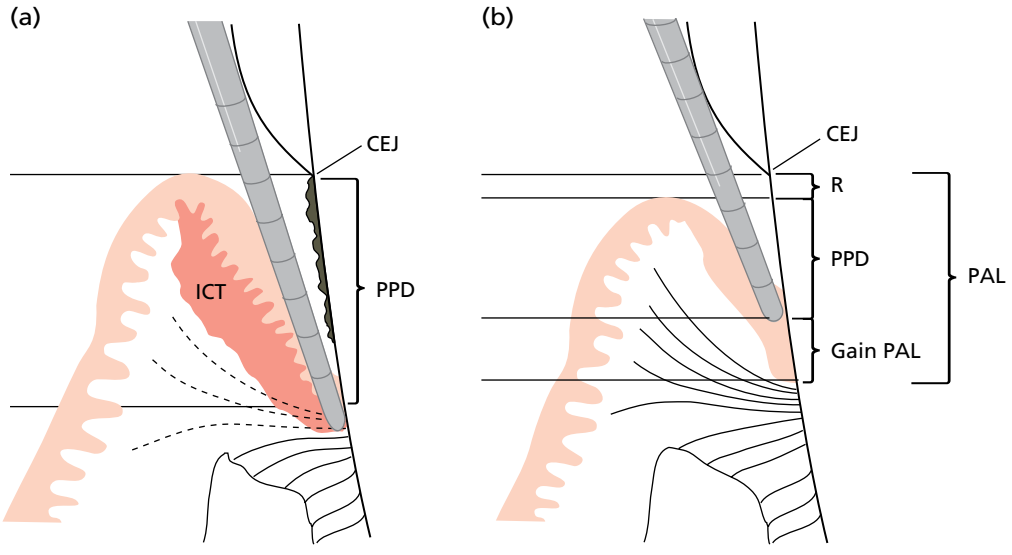

Fig. 29-10 (a) In the presence of an inflammatory cell infiltrate (ICT) in the connective tissue of the gingiva, the periodontal probe penetrates apically to the bottom of the histologic pocket. (b) Following successful periodontal therapy, the swelling is reduced and the connective tissue cell infiltrate is replaced by collagen. The periodontal probe fails to reach the apical part of the dentogingival epithelium. (CEJ, cementoenamel junction; PPD, probing pocket depth; PAL, probing attachment level; R, recession; Gain PAL, recorded false gain of attachment ("clinical attachment").)

confidence in the validity of periodontal probing. However, despite difficulties in interpreting the significance of PPD and PAL measurements, such determinations still give the clinician a useful estimate of the degree of disease involvement, particularly when the information obtained is related to other findings of the examination procedure, such as BoP and changes in alveolar bone height.

In recent years, periodontal probing procedures have been standardized to the extent that automated probing systems, for example the Florida Probe™, provides periodontal charts which document PPD, PAL, BoP, FI, and TM (Gibbs *et al*. 1988). Also, repeated examinations allow the comparison of parameters and, hence, an assessment of the healing process (Fig. 29-11).

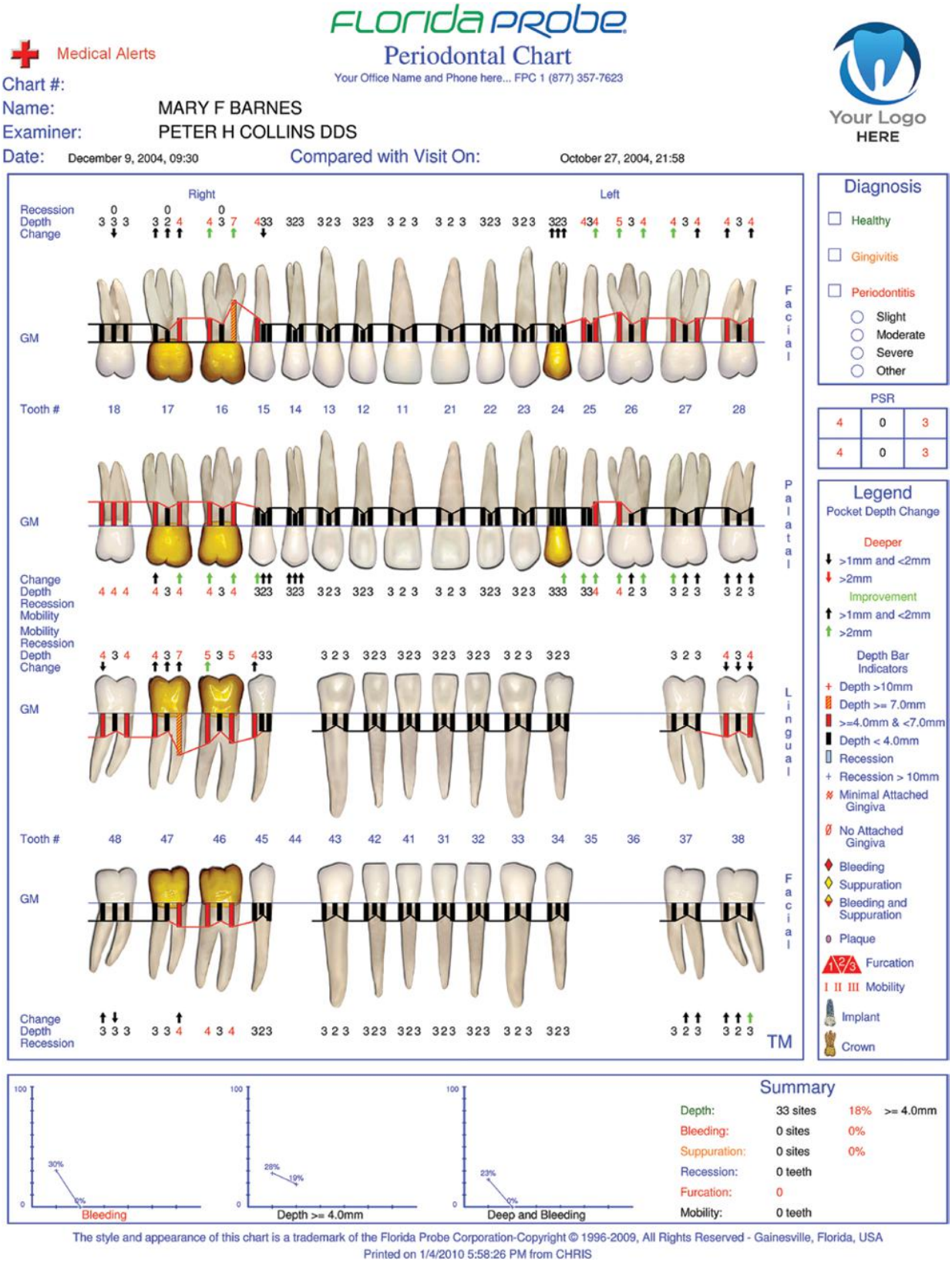

Fig. 29-11 Periodontal chart using an automated probing system (Florida Probe™). Source: Florida Probe Corporation. (c) Copyright 1996 to 2009.

Assessment of furcation involvement

The progression of periodontitis around multirooted teeth may involve the destruction of the supporting structures of the furcation area (Fig. 29-12). In order to plan the treatment of such involvement, a detailed and precise identification of the presence and extent of periodontal tissue breakdown within the furcation area is of importance for proper diagnosis.

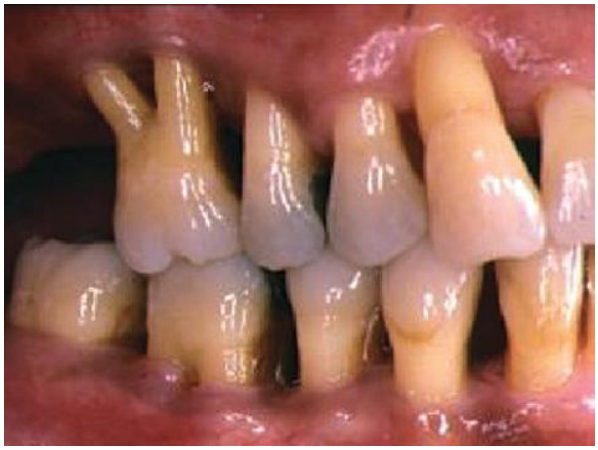

Fig. 29-12 Superficial (tooth 46) and deep (tooth 16) periodontal tissue destruction in the buccal furcation areas.

FI is assessed from all the entrances of possible periodontal lesions of multirooted teeth, that is buccal and/or lingual entrances of the mandibular molars. Maxillary molars and premolars are examined from the buccal, distopalatal, and mesiopalatal entrances. Owing to the position of the first maxillary molars within the alveolar process, the furcation between the mesiobuccal and the palatal roots is best explored from the palatal aspect (Fig. 29-13).

FI is explored using a curved periodontal probe with 3-mm graduations (Nabers furcation probe; Fig. 29-14). Depending on the penetration depth, the FI is classified as "superficial" or "deep":

- *Class I*: horizontal probing depth of ≤3 mm from one or two entrances
- *Class II*: horizontal probing depth of >3 mm from at most one entrance and/or in combination with a FI class I

(a) (b)

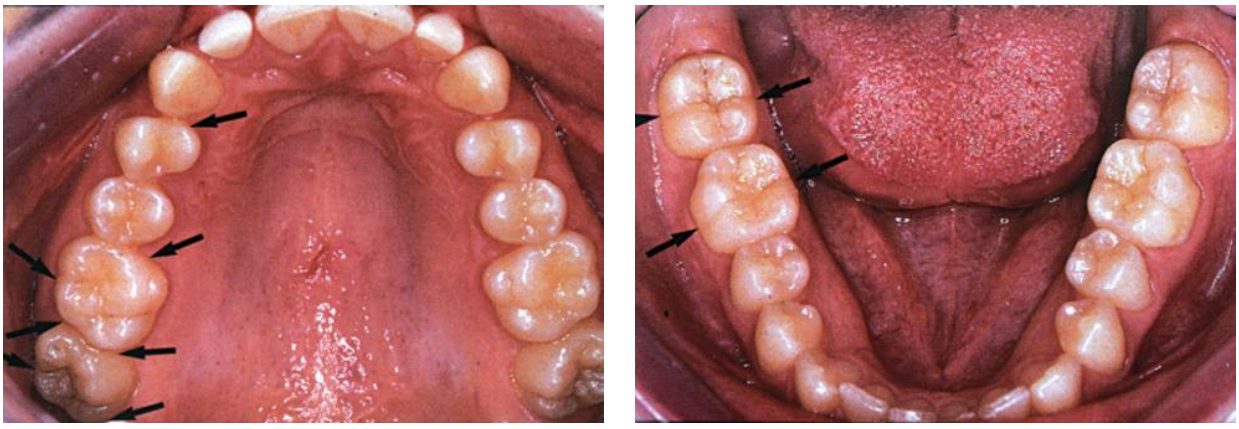

Fig. 29-13 (a, b) Anatomic locations (arrows) for the assessment of furcation involvement in the maxilla and in the mandible.

(a) (b)

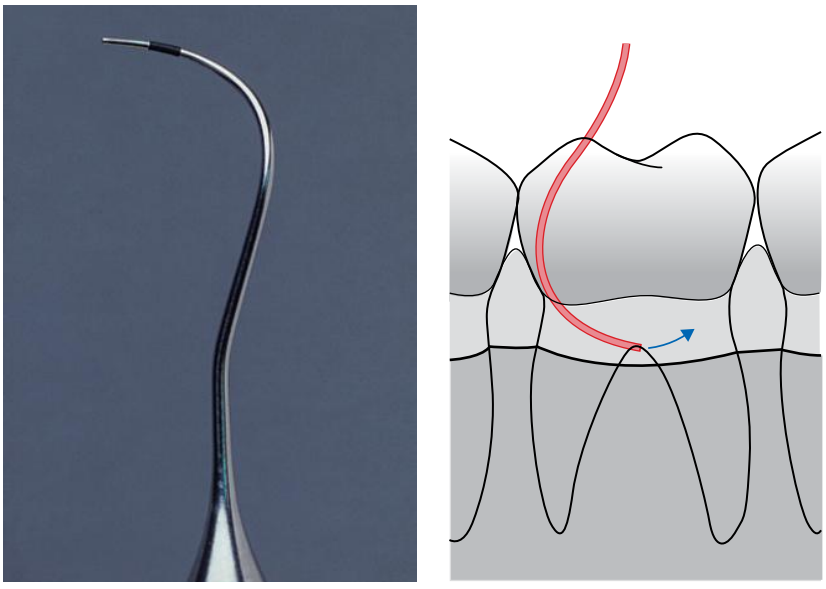

Fig. 29-14 (a, b) Furcation involvement is explored using a curved periodontal probe with 3-mm graduations (Nabers furcation probe).

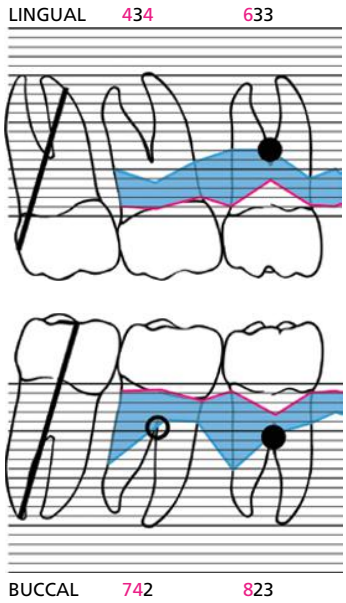

Fig. 29-15 Furcation involvement (FI) shown in the periodontal chart. Open circles represent a superficial FI (i.e horizontal probe penetration of < 3 mm), whereas filled black circles represent a deep FI (i.e. horizontal probe penetration of ≥ 3 mm).

- *Class III*: horizontal probing depth of >3 mm from two or more entrances usually represents a "through-and-through" destruction of the supporting tissues in the furcation.

The FI class is presented on the periodontal chart (Fig. 29-15) together with a description of which tooth surface the involvement has been identified on. The effects of various therapeutic approaches to the management of multirooted teeth with FI has been systematically appraised (Huynh-Ba *et al*. 2009). A detailed description of the management of furcation-involved teeth is presented in Chapter 40.

Assessment of tooth mobility

Increased TM may be classified according to Miller (1950):

- *Degree 0*: "physiologic" mobility measured at the crown level. The tooth shows mobility of 0.1–0.2 mm in the horizontal direction within the alveolus
- *Degree 1*: increased mobility of the crown of the tooth of at the most 1 mm in the the horizontal direction
- *Degree 2*: visually increased mobility of the crown of the tooth exceeding 1 mm in the horizontal direction
- *Degree 3*: severe mobility of the crown of the tooth in both horizontal and vertical directions, and impinging on the function of the tooth.

The continuous loss of the supporting tissues during progressionn of plaque-associated periodontal disease progression may result in increased TM. However, it must be understood that plaque-associated periodontal disease is not the only cause of increased tooth mobility. For instance, overloading of teeth and trauma from occlusion may result in tooth hypermobility. Increased TM can frequently also be observed in conjunction with periapical lesions or immediately following periodontal surgery. From a therapeutic point of view it is important, therefore, to assess not only the degree of increased TM, but also the cause of the observed hypermobility (see Chapters 16 and 58).

All data collected from measurements of PPD and PAL, as well as assessments of FI and TM, are included in the periodontal chart (see Fig. 29-8). The various teeth in this chart are denoted according to the two-digit system adopted by the World Dental Federation (FDI) in 1970.

Alveolar bone

Radiographic analysis

Radiographs provide information on the height and configuration of the interproximal alveolar bone (see Fig. 29-3). Obscuring structures such as tooth roots often make it difficult to identify the outline of the buccal and lingual alveolar bony crest. The analysis of the radiographs must, therefore, be combined with a detailed evaluation of the periodontal chart in order to correctly estimate the "horizontal" and " angular" bony defects.

Unlike the periodontal chart, which represents a sensitive diagnostic estimate of the lesions, the radiographic analysis is a specific diagnostic test yielding few false-negative results and, hence, confirms the periodontal chart (Lang & Hill 1977).

To enable meaningful comparative analysis, a reproducible radiographic technique should be used: a long-cone paralleling technique (Updegrave 1951) is recommended (Fig. 29-16).

Radiographic evaluation of implant recipient sites

In order to evaluate vertical bone height at potential implant recipient sites, panoramic radiography is a reliable diagnostic tool to determine the preoperative implant length in premolar and molar mandibular areas (Vazquez *et al*. 2013). Furthermore, to accurately determine the bone volume and morphology at future implant recipient sites, cone-beam computed tomography (CBCT) may offer valuable information in select indications such as implant placement in conjunction with sinus floor elevation (Harris *et al*. 2012).

Diagnosis of periodontal lesions

Based on the information regarding the condition of the various periodontal structures (i.e. the gingiva, periodontal ligament, and alveolar bone) obtained

through the comprehensive examination presented above, the periodontal condition of the patient as well as each tooth may be classified according to four different tooth-based diagnoses (Fig. 29-17, Table 29-1).

Gingivitis

This diagnosis is applied to teeth displaying BoP. The sulcus depth usually remains at 1–3 mm irrespective of the level of clinical attachment. "Pseudopockets" may be present in cases of slightly increased probing depth without concomitant attachment and alveolar bone loss and presence/absence of BoP. The diagnosis of gingivitis usually characterizes lesions confined to the gingival margin.

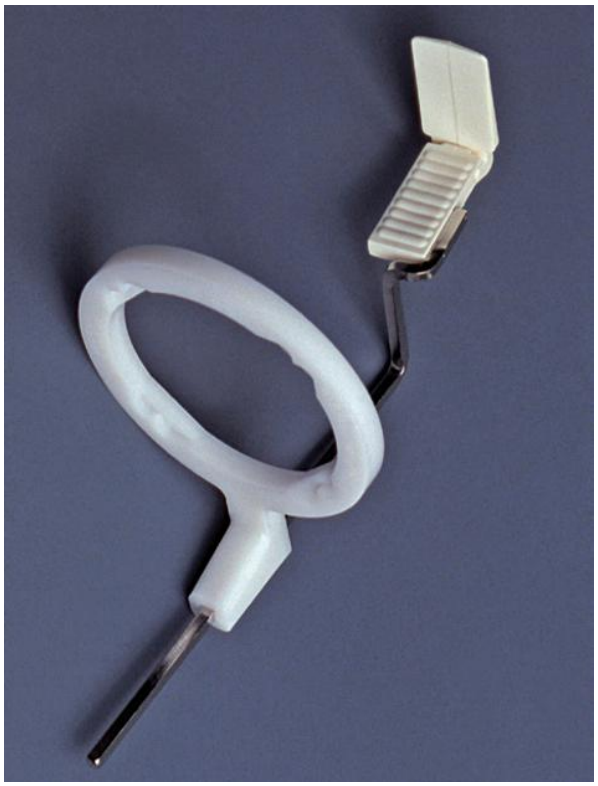

Fig. 29-16 Use of a Rinn film holder and a long-cone paralleling technique yields reproducible radiographs.

Parodontitis

Paradontitis superficialis (mild-to-moderate periodontitis)

Gingivitis in combination with attachment loss is termed "periodontitis". If the PPD does not exceed 6 mm, a diagnosis of mild-to-moderate periodontitis is given irrespective of the morphology of the periodontal lesions. This diagnosis may, therefore, be applied to teeth with "horizontal" loss of supporting tissues, thus representing suprabony lesions, and/or to teeth with "angular" or "vertical" loss of supporting tissues, thus representing infrabony lesions. "Infrabony" lesions include "intrabony one-, two- and three-wall defects", as well as "craters" between two adjacent teeth.

Parodontitis profunda (advanced periodontitis)

If the PPD exceeds 6 mm, a diagnosis of advanced periodontitis is given irrespective of the morphology of the periodontal lesions. As for mild-to-moderate periodontitis, angular as well as horizontal alveolar bone loss are included in this diagnosis. The distinction between mild-to-moderate and advanced periodontitis is based on increased PPD alone.

Parodontitis inter-radicularis (periodontitis in the furcation area)

Adjunctive diagnoses may be attributed to multirooted teeth with FI (see earlier): superficial FI if the horizontal PPD is ≤3 mm (parodontitis inter-radicularis superficialis) and deep FI for horizontal PPD of >3 mm (parodontitis inter-radicularis profunda).

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Gingivitis																
Parodontitis superficialis																
Parodontitis profunda	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Parodontitis interradicularis		x	x		x							x		x	x	
Parodontitis interradicularis		x	x											x	x	
Parodontitis profunda		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Parodontitis superficialis																
Gingivitis																
	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Fig. 29-17 Chart of the individual tooth diagnoses of the patient presented in Fig. 29-1.

In the presence of necrotizing and/or ulcerative lesions, these terms may be added to tooth-related diagnoses of both gingivitis and periodontitis (Chapter 22). Acute lesions, including gingival and periodontal abscesses, are diagnosed as indicated in Chapter 24.

The various teeth of the patient whose clinical status is shown in Fig. 29-1, radiographs in Fig. 29-3, and periodontal chart in Fig. 29-8 received the diagnoses described in Fig. 29-17.

Oral hygiene status

In conjunction with examination of the periodontal tissues, the patient's oral hygiene practices must also be evaluated. Absence or presence of plaque on each tooth surface in the dentition is recorded in a dichotomous manner (O'Leary *et al*. 1972). The bacterial deposits may be stained with a disclosing solution to facilitate their detection. The presence of plaque is marked in appropriate fields in the plaque chart (Fig. 29-18). The mean plaque score for the dentition is given as a percentage in correspondence with the system used for BoP (see Fig. 29-6).

Alterations with respect to the presence of plaque and gingival inflammation are monitored in a simple way by the repeated use of the combined BoP (see Fig. 29-6) and plaque (Fig. 29-18) charts during the course of treatment. Repeated plaque recordings alone (Fig. 29-18) are predominantly indicated during the initial phase of periodontal therapy (i.e. infection control) and are used for improving self-performed plaque control. Repeated BoP charts alone (Fig. 29-6), on the other hand, are predominantly recommended during supportive periodontal therapy (SPT).

Table 29-1 Diagnoses of periodontal tissue conditions around each tooth in the dentition according to main criteria (i.e. the periodontal chart and radiographic analysis) and additional criteria (i.e. bleeding on probing).

Diagnosis	Main criteria	Additional criteria
Gingivitis	BoP No loss of PAL and alveolar bone PPD ≤3 mm Pseudo-pockets	
Parodontitis superficialis (mild-to-moderate periodontitis)	PPD ≤5 mm irrespective of the morphology of the periodontal lesion Angular and/or horizontal alveolar bone loss	BoP
Parodontitis profunda (advanced periodontitis)	PPD ≥6 mm irrespective of the morphology of the periodontal lesion Angular and/or horizontal alveolar bone loss	BoP
Parodontitis inter-radicularis (periodontitis in the furcation area)	Horizontal PPD ≤3 mm: superficial FI Horizontal PPD >3 mm: deep FI	BoP

PAL, probing attachment level; PPD, probing pocket depth; BoP, bleeding on probing; FI, furcation involvement.

Additional dental examinations

In addition to the assessment of plaque, retentive factors for plaque, such as supra- and sub-gingival calculus and defective margins of dental restorations, should be identified. Furthermore, the assessment of tooth sensitivity is essential for comprehensive treatment planning. Sensitivity to percussion may indicate acute changes in pulp vitality and lead to emergency treatment prior to systematic periodontal therapy. It is obvious that a complete examination and assessment of the patient will need to include a search for carious lesions, both clinically and radiographically.

A screening for functional disturbances may be performed using a short (i.e. 1/2 minute) test (Shore 1963). In this test, harmonious function of the jaws with simultaneous palpation of the temporomandibular joints during opening, closing, and excursive movements is verified. Maximal mouth opening is assessed and finally, the lodge of the lateral pterygoid muscles is palpated for muscle tenderness. Further morphologic characteristics of the dentition as well as occlusal and articulating contacts may be identified.

Conclusion

The methods described in this chapter for the examination of patients with periodontal diseases and candidates for implant therapy provide a thorough analysis of the presence, extent, and severity of disease in the dentition. The periodontal classification of the patient and the correct diagnosis for each individual tooth should form the basis for a pretherapeutic prognosis and treatment planning for the individual patient.

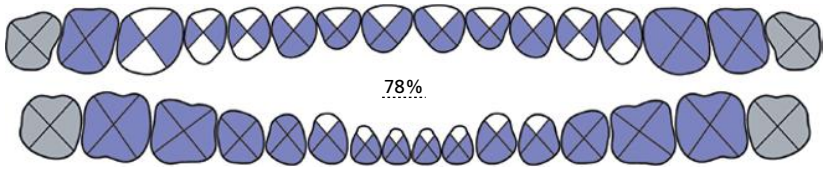

Fig. 29-18 Presence of bacterial deposits is marked in the appropriate fields in the plaque chart.

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Chapter 30

Diagnostic Imaging of the Periodontal and Implant Patient

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Introduction

Our understanding of periodontal diseases and implant dentistry continues to grow exponentially. Similarly, the options and techniques available for their radiologic examination continue to evolve rapidly. The modern-day clinician must be suitably equipped with sufficient and accurate information to be able to prescribe the appropriate radiologic test. The practice of dentistry, especially orofacial implantology, based solely on traditional intraoral and panoramic radiography is no longer considered an acceptable standard of care in many parts of this world. The clinician of today must consider all available modalities and carefully weigh the diagnostic benefit against the potential biologic cost of diagnostic imaging; the ALARA (as low as reasonably achievable) principle should be considered in making these decisions. It is recognized that certain imaging modalities may not be readily available in some parts of the world. The monetary cost of some imaging techniques may also be relatively high and potentially prohibitive, although this must be weighed against the financial cost of the potential treatment. Typically, the financial cost of diagnostic imaging, including advanced modalities, is a fraction of the cost of the implant prosthesis or periodontal therapy and maintenance over time. Ultimately, it is the clinician who makes the decision as to which modality is best employed, based on the clinical findings. It is also the clinician's responsibility to ensure that the imaging is performed optimally or referred to radiologists who are appropriately skilled in orofacial imaging. Most importantly, the clinician must ensure that the imaging dataset is evaluated in entirety and interpreted by appropriately skilled persons.

It is of paramount importance that clinicians remain up to date and it is recognized that technological

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advances typically outstrip the publication of studies related to the technology.

Interpretation of the radiologic examination

Prescribing the appropriate imaging modality and ensuring optimal imaging protocols and techniques are used will produce optimal images to aid in diagnosis. In many ways, the interpretation of the images created is the most important aspect of diagnostic imaging. This applies to the practice of radiology generally and certainly includes diagnostic imaging in relation to the periodontal and implant patient. Failure to ensure thorough and accurate interpretation denies the diagnostic benefit to the patient who has received ionizing radiation associated with the radiologic study. Therefore, this chapter dedicates a section to the key aspects of radiologic interpretation, with particular reference to periodontology and implant dentistry.

For periodontal bone loss, appropriate interpretation is required to confirm that the bone loss is inflammatory in nature and not related to another disease process. The morphology and severity of the periodontal defects as well as the associated contributing factors are also important. In addition, other dentoalveolar findings including caries, periapical disease, and the state of the existing restorative therapy, must be evaluated so that an overall diagnosis, prognosis, and treatment plan can be made.

In implant dentistry, diagnostic imaging firstly provides an opportunity to evaluate the site(s) of an intended implant and the adjacent bony and soft tissues for the presence and nature of pathology (Figs. 30-1, 30-2). The relevant findings with regards to the suitability and planning for implants are obviously crucial. It is also important that the remaining dentoalveolar structures are thoroughly evaluated so that the planning of the implant is not performed in isolation; in other words, implant therapy must be planned as part of the overall orofacial treatment plan.

The ability to perform morphologic analyses (e.g. the shape and extent of a periodontal defect) and plan surgical procedures (e.g. implant planning) with a specific imaging modality is not the same as the skill set required to evaluate radiologic images for the presence of disease and interpret the radiologic features of a lesion. Radiologic interpretation is based upon the knowledge of disease processes and the behavior of diseases within a specific anatomic region. It involves the application of an algorithm which requires a specific knowledge base and skill set. These allow the identification of normal structures and presence of abnormalities. Combined with an understanding of the specific radiologic characteristics of various pathologies, this contributes substantially to diagnosis.

In dentistry, the observer may also be the examining clinician and often has a preconception as to the likely diagnosis. In these scenarios, there is potential for a quick perusal of the radiologic study to confirm clinical suspicions rather than a thorough evaluation of the radiologic study. An example is where preliminary clinical findings suggest the presence of an inflammatory periodontal defect and radiologic interpretation effectively ends as soon as a lucent appearance is noted in association with the roots. A thorough radiologic evaluation to identify the features of an inflammatory lesion is not carried out, potentially leading to misdiagnosis. Clinicians are encouraged to avoid this inappropriate application of diagnostic imaging.

It is important that the diagnostic imaging and interpretation is completed prior to biopsy or other surgical intervention. Appropriate radiologic interpretation can assist in identifying the optimal and/or safe site(s) for biopsy. Also, some lesions should be excluded prior to biopsy or surgical intervention. Of note are the vascular malformations. In addition, surgical procedures and biopsies often significantly

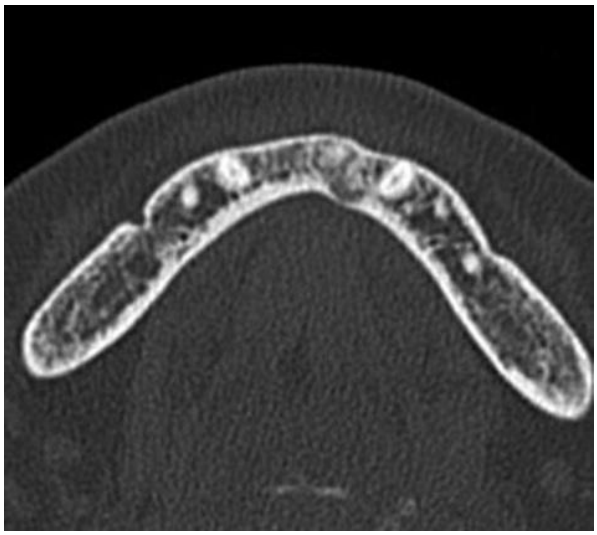


Fig. 30-1 Axial low-dose MCT image demonstrates the presence of cementosseous dysplasia at the 32 region where an implant was planned. Note the sclerotic borders.

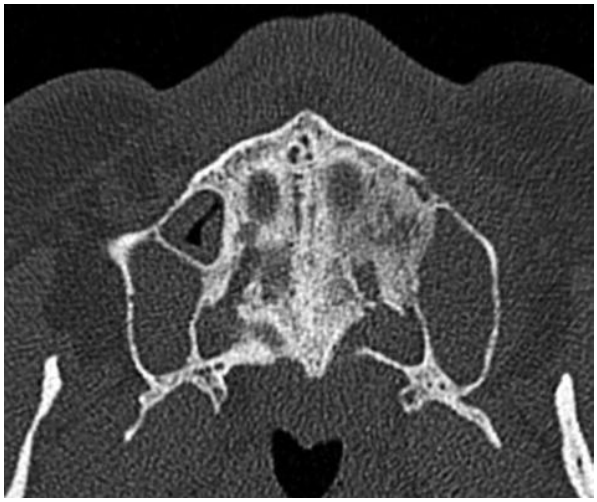


Fig. 30-2 Axial low-dose CBCT axial image demonstrates a left maxillary fibrous dysplasia in an area intended for implant placement. Note the internal ground-glass appearances.

alter the radiologic appearances of a lesion by introducing inflammatory changes, potentially compromising diagnosis.

The clinician responsible for the radiologic examination must ensure that all the information obtained in the radiologic study is thoroughly evaluated, not just the region of interest, for example the dentoalveolar structures only. If the clinician responsible for the study does not have appropriate and recognized training in the interpretation of a particular study, the clinician must then ensure that the radiologic study is interpreted by radiologists who have the appropriate training and skill set. It must be recognized that the knowledge and skill involved in the interpretation of intraoral and panoramic radiographic images is not the same as that for the interpretation of volumetric data, including multislice/multidetector computed tomography (MCT) and cone-beam computed tomography (CBCT).The medicolegal right that general and specialist dentists have to perform complex surgery does not imply that they have had appropriate training nor the skill set to carry out the procedure competently. Similarly, it must be remembered that the legal right to operate a particular radiologic machine does not imply sufficient knowledge to interpret the information captured. The associated ethical and medicolegal implications require consideration.

A thorough discussion of radiologic interpretation is not within the scope of this chapter and, while there are useful publications on this topic (White & Pharoah 2009; Koong 2012), clinically-based guided training is required to develop a competent level of interpretive skill. However, the generic key requirements and steps will be briefly discussed, followed by a section which will apply these principles to periodontology and implantology.

Basic prerequisites

Radiologic anatomy

A detailed understanding of three-dimensional anatomy and how structures appear radiologically, depending on the imaging modality employed, is essential. Knowledge of normal variants and their radiologic appearances in the various modalities is also a requirement. Obviously, larger field of view (FOV) two-dimensional (2D) images will include more structures, requiring a broader knowledge base. The radiologic anatomy as depicted on plain 2D images differs from that seen in volumetric datasets from modalities such as MCT and CBCT. The ability to identify the presence of disease is extremely limited if the clinician is not thoroughly familiar with radiologic appearances of all anatomic structures and normal morphologic variants. It must be emphasized that not all abnormalities present as overt opacities or lucencies (Fig. 30-3).

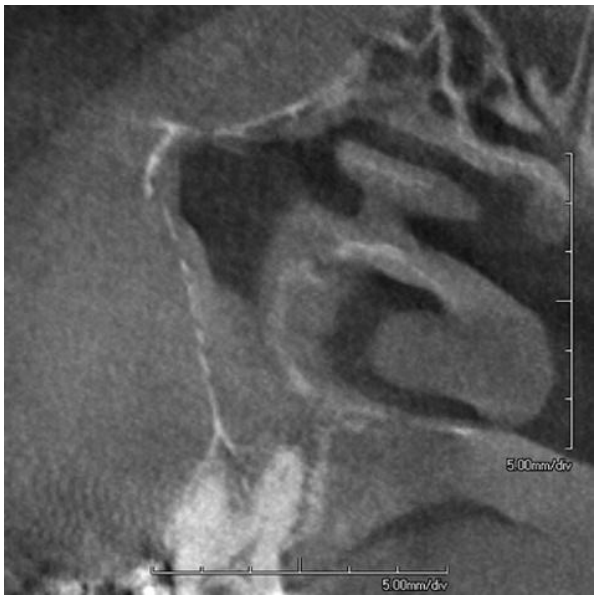


Fig. 30-3 Low-dose CBCT corrected sagittal image demonstrates small cortical erosions related to an infiltrative lesion such as a lymphoma. The patient had presented with facial swelling and discomfort, originally thought to be of dentoalveolar origin.

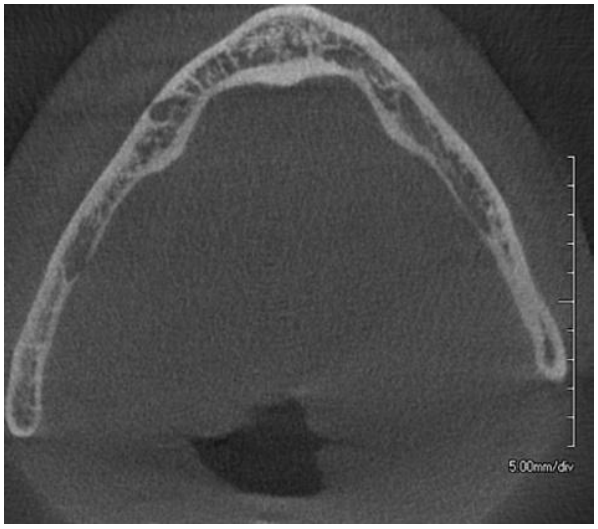


Fig. 30-4 Low-dose CBCT axial image of a left-sided pharyngeal mass, proven to be a squamous cell carcinoma.

Pathology

The person carrying out the interpretation must possess knowledge of diseases which are potentially associated with all structures included in the radiologic study. Appreciation of the clinical significance of these various diseases is also crucial. Many imaging techniques capture a significant proportion of the orofacial structures. Panoramic and cephalometric projections obviously include many other facial structures, apart from the dentoalveolar structures. To varying degrees, MCT and CBCT scans include the paranasal sinuses, pharyngeal air spaces, skull base, cervical spine, and upper neck (Fig. 30-4). All structures included in a radiologic examination must

be evaluated for the presence of pathology, by persons with appropriate and recognized training.

Imaging modality

There are numerous imaging techniques which can be applied in the radiologic examination of the orofacial structures, including intraoral radiographs, other plain 2D views, the panoramic tomograph, MCT, CBCT, MRI, ultrasound, and nuclear medicine. The clinician of today must be familiar with all available modalities, including their various strengths and limitations. This will allow the selection of the optimal modality, while minimizing the radiation dose delivered to the patient. Recognition of the limitations of a particular technique is essential when interpreting a radiologic study. The effects of the various protocols employed on image quality must also be understood. Importantly, just because a specific structure can be seen in a radiologic examination does not mean that it is sufficiently well demonstrated for accurate interpretation. A different modality may be required. A description and comparison of the key features of the various radiologic modalities commonly applied in dentistry is provided in a later a section.

Viewing conditions

Optimal viewing conditions are essential for the identification of all relevant features within the radiologic images. A subtle change in the radiologic appearance of an anatomic structure can be related to a significant abnormality. Ambient light must be kept to a minimum and extraneous light from a viewing box should be obscured. Digital images viewed on a computer monitor can be manipulated. The quality of the computer monitor must be of sufficient standard. For analog images, optical magnification and use of a brighter light source can be critical. The interpretation of plain 2D radiographic digital images printed on paper can be problematic. Even an image printed onto high quality paper from a high quality printer does not demonstrate the same optical range as film or good quality monitors. Optimal imaging is assumed and the technical aspects are well described in many texts.

Key steps in interpretation

Recognizing the presence of an abnormality

The practitioner/radiologist is responsible for interrogating all structures within a FOV/entire volume of a radiologic examination, not just for the primary focus of the study, such as implant planning (Carter *et al*. 2008). The process of interrogating radiologic images for abnormalities varies, depending on the modality (Koong 2010). For example, the algorithm and skill set required to accurately and thoroughly analyze MCT and CBCT data (using multiplanar reformatted images) differ from those employed for intraoral and panoramic images. Every normal anatomic structure captured in the study must be specifically identified and evaluated. This is essential since not all lesions are always obvious. For example, the absence of a cortical boundary of a structure can reflect the presence of significant disease (Fig. 30-3). The appearance of a wide stylomandibular notch (seen on CBCT or MCT examination of a maxilla or mandible) is a radiologic feature of a mass associated with the deep lobe of the parotid gland. This is important since deep lobe parotid masses are often not clinically symptomatic until they are relatively large. This feature is of particular relevance in CBCT as the soft tissue mass itself is not evident or poorly demonstrated.

Radiologic evaluation of a lesion

The following describes a series of steps which assists in the identification of the important radiologic characteristics of a lesion. This provides information on the behavior and nature of the lesion. These features are also important from a surgical viewpoint.

Location

First, prior to focusing on a known or obvious lesion, the entire FOV or scan must be analyzed for the presence of related lesions. It is important to identify if the disease is multifocal or generalized, rather than solitary. Another key point in this step is to attempt to identify the point at which the lesion originated. The location and extent of the lesion can provide useful information about the likely tissues involved. For example, a lesion centered below the mandibular canal is unlikely to be odontogenic in nature.

Shape and contour

The shape of the lesion can provide useful information regarding its nature. True cysts such as the dentigerous cyst are generally spherical or ovoid and expansile (Fig. 30-5). In contrast, a keratocystic odontogenic tumour often demonstrates a scalloped peripheral morphology and is non-expansile within the body of the mandible. An osteoma typically presents as an expansile, homogenous, well-defined bony prominence with a smooth convex periosteal surface, while an osteochondroma tends to demonstrate a more irregular surface with more heterogenous internal appearances. A bone island typically demonstrates a well-defined homogenous non-expansile opaque appearance, isodense with cortical bone (Fig. 30-6).

Border

The first part of this step is to identify if the border of a lesion is well defined or poorly defined. If a lesion is well defined, this border has to be further examined

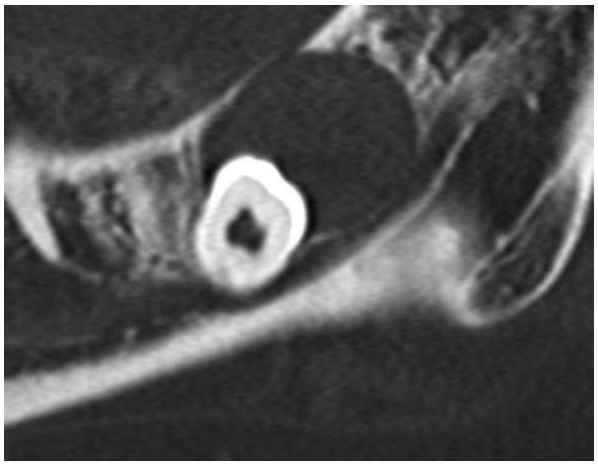


Fig. 30-5 Low-dose MCT corrected sagittal image demonstrates a dentigerous cyst related to an impacted third molar. Note the corticated margin and compression of the superior aspect of the mandibular canal.

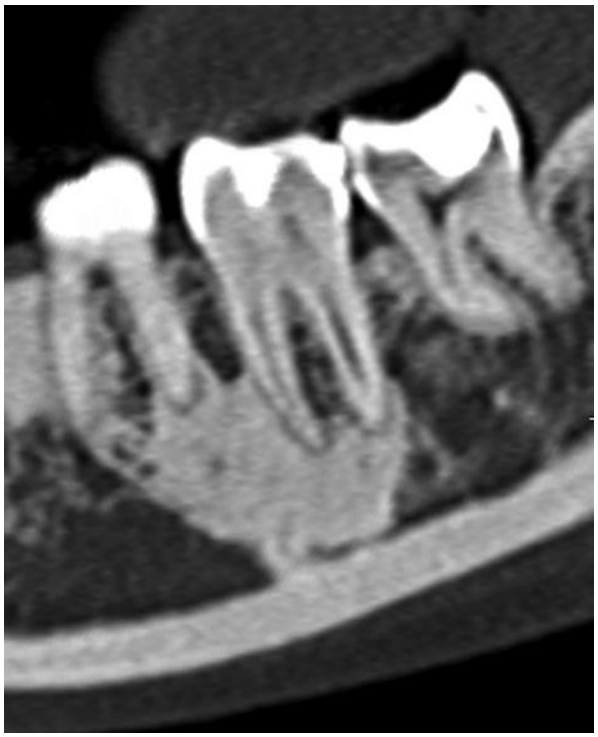


Fig. 30-6 Low-dose MCT corrected sagittal image demonstrates a bone island with well-defined margins.

and subcategorized. Most well-defined borders fall into one of the following descriptions:

- *Sharp delineation* between normal and abnormal, with no other appreciable features. These lesions are commonly referred to as "punched out". Multiple myeloma is a classic example.
- *Corticated border*. This describes a sharp, opaque, usually curved line (Fig. 30-5).
- *Sclerotic border*. This refers to an opaque border which is thicker (to varying extents) and much less uniform than a corticated border. Most chronic inflammatory bony lesions, including plaque-related inflammatory periodontal diseases, demonstrate sclerotic margins, which reflect the reaction of the surrounding trabecular bone to the inflammatory lesion (Fig. 30-7). However, other lesions, such as cemento-osseous dysplasia (Fig. 30-1) and some malignant lesions (Fig. 30-8), can also demonstrate sclerotic margins.
- *Surrounding lucent margin*. This is typically only seen in association with opaque and mixed-density lesions. In most cases, this lucent margin reflects the presence of layer of soft tissue surrounding the lesion.

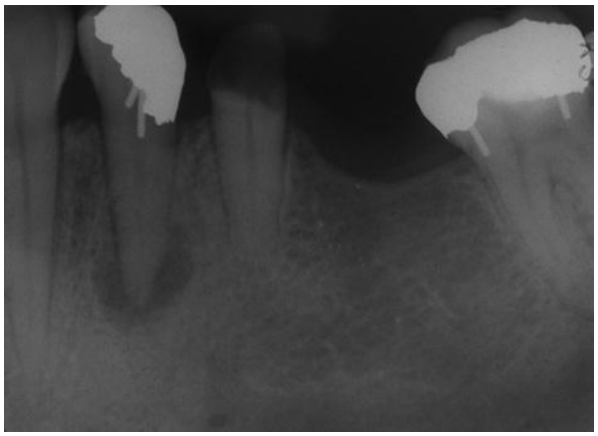


Fig. 30-7 Periapical radiograph demonstrates a periapical hypodense inflammatory lesion associated with tooth 34. There are focal regions where the margins appear better defined, related to chronicity. The sclerotic margins are evident, also related to the chronic nature of this lesion. Note the sclerotic appearance at the apical aspect of tooth 35, which likely reflects reactive sclerosis related to an inflammatory lesion, although the apical periodontal ligament is not obviously widened (likely obscured by the sclerosis on this 2D view).

An ill-defined border should be further analyzed and categorized into one of the following:

- *Gradual change from abnormal to normal*. Acute inflammatory lesions, including plaque-related inflammatory periodontal bone loss, are good examples. However, it should be noted that the borders of more chronic inflammatory lesions tend to appear better defined, especially on plain 2D imaging (Fig. 30-7).
- *Aggressive margin*. Malignant lesions display these borders. Aggressive and infiltrative margins include the appearance of lytic extensions into the adjacent bone. Unusual enlargement of adjacent marrow spaces is another feature. Irregular widening of the periodontal ligament spaces with focal multiple regions of destruction of the lamina dura is an example of the leading edge of an infiltrative lesion spreading around tooth roots. These dentoalveolar malignant lesions are easily misinterpreted for inflammatory diseases if appropriate analysis is not performed. (Fig. 30-8).

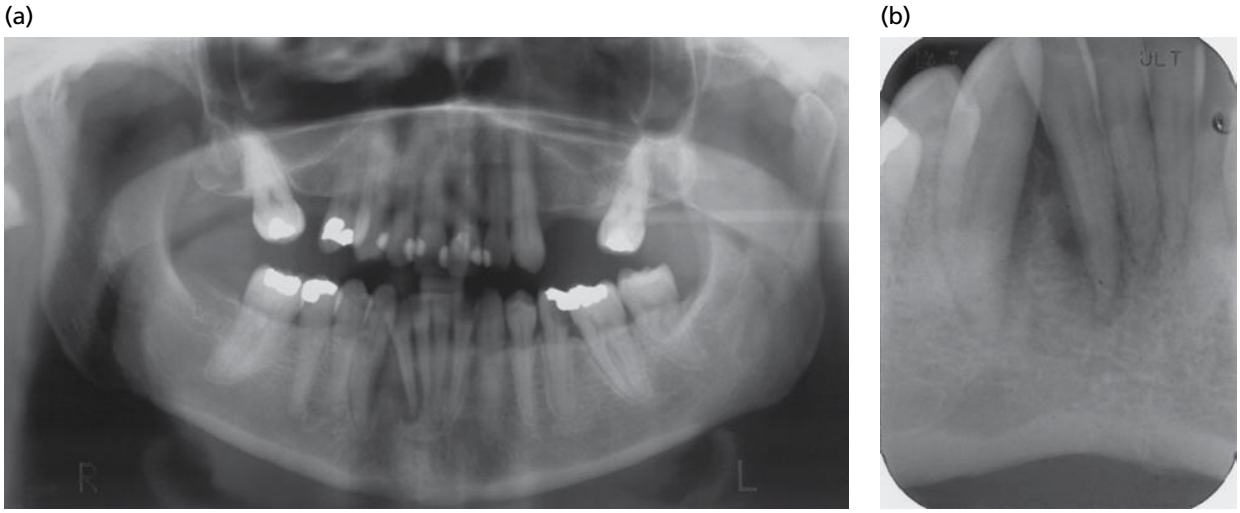


Fig. 30-8 (a) Panoramic and (b) periapical radiographs demonstrate a malignant breast metastatic lesion at the 43–41 region. Note the irregular widening of the perioidontal ligament spaces with focal lucencies extending further in the periapical view. These features are not well demonstrated on the panoramic radiograph, related to the typical limitations of this view. The adjacent sclerosis is also evident, which is typical of these lesions.

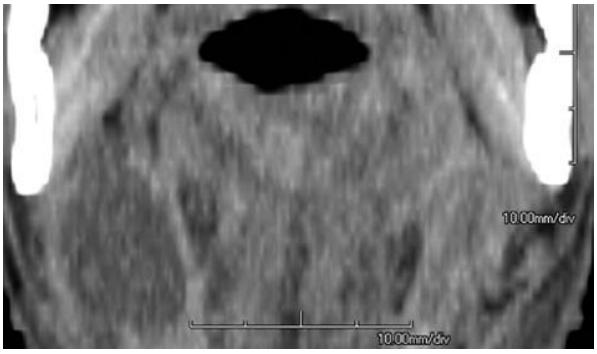


Fig. 30-9 Low-dose MCT coronal image demonstrates fluid collection within the right submandibular space, related to abscess collection from a dentoalveolar infection. This is of urgent surgical relevance and cannot be identified with present day CBCT.

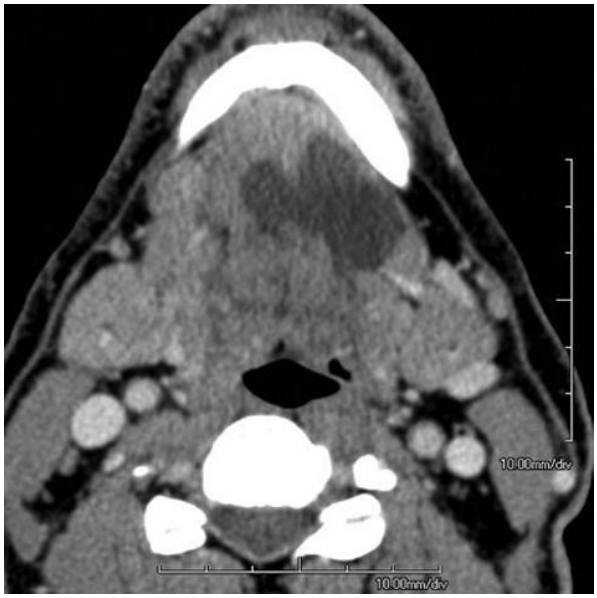


Fig. 30-10 Reduced dose axial MCT image demonstrates left-sided fluid density collection related to a ranula. This would not be appreciated with present day CBCT.

Internal appearances

A complete lucent lesion seen on plain 2D views usually reflects the presence of air/gas, fluid or soft tissue. Inflammatory periodontal lesions are classically lucent internally. Typically, air/gas appears more lucent than fluid and soft tissue on plain 2D imaging. MCT has far superior soft tissue contrast resolution and can demonstrate density differences between different types of soft tissues (Figs. 30-9, 30-10). Currently, CBCT is unable to demonstrate these differences sufficiently well. It is important to note that soft tissues lesions are often best evaluated with MRI.

The density of completely opaque lesions should first be identified, for example, isodense with cortical bone. The degree of homogeneity or heterogeneity should then be identified and any consistent pattern recognized. Fibrous dysplasia classically demonstrates a ground-glass appearance internally (Fig. 30-1). Bone islands are usually homogenous internally and isodense with cortical bone (Fig. 30-6).

There are also lesions which appear both lucent and opaque internally. In these cases, it is necessary to identify the nature of the opacities, for example bony, odontoid or dystrophic calcification. The pattern and distribution of these internal opacities are also important, since many lesions often demonstrate particular patterns. For example, a multilocular ameloblastoma classically demonstrates coarse curvilinear septae, while central giant cell granulomas often reveal much finer septae. Osteomyelitis can demonstrate heterogenous internal appearances, with focal irregular lucent and sclerotic foci.

Adjacent anatomic structures

The way in which normal anatomic structures influence the growth, expansion, and spread of a lesion, and the effects of a lesion on these anatomic structures are important. These features provide clues to the behavior of the lesion. For example, all true cysts (including radicular cysts) displace the mandibular canal (Fig. 30-5), while periodontal inflammatory lesions do not. Displacement of teeth is a characteristic of a lesion with mass effect that is usually benign in nature, although it must be recognized that there are other causes of tooth movement, for example occlusal forces on teeth with reduced alveolar bone support.

Effacement of cortical boundaries can occur with a variety of lesions, including inflammatory lesions. This requires special attention as malignant lesions often demonstrate this feature (Fig. 30-3).

Interpretation of the findings

Many lesions demonstrate similar features. Also, specific lesions do not always present classically and often only demonstrate a few or even just one classical characteristic. Therefore, in addition to identifying the key radiologic features of a lesion, the observer has to weigh the various features which have been identified. This requires knowledge of the classical radiologic features of the possible pathologies as well as training and experience in the interpretation of this information. For example, periodontal and periapical lucent lesions are often inflammatory in nature. However, malignant lesions can be associated with teeth and are also lucent. Furthermore, some malignancies demonstrate adjacent sclerosis which can appear similar to the reactive sclerosis typically seen in chronic inflammatory lesions. In these cases, the invasive features of margins become critical for appropriate diagnosis (Fig. 30-8).

As mentioned earlier, fibrous dysplasia classically presents with ground-glass appearances internally (Fig. 30-1). However, it is not uncommon that it demonstrates a more heterogenous internal appearance (Fig. 30-11). In these cases, other features, such as the particular nature of the expansion, must be recognized for appropriate interpretation and diagnosis.

Radiologic interpretation in relation to inflammatory periodontal disease

The radiologic examination of the patient with periodontal disease is primarily employed to provide information on the supporting bony structures of teeth.

Key radiologic features

Applying the principles described above, the key radiologic characteristics of inflammatory periodontal disease are discussed.

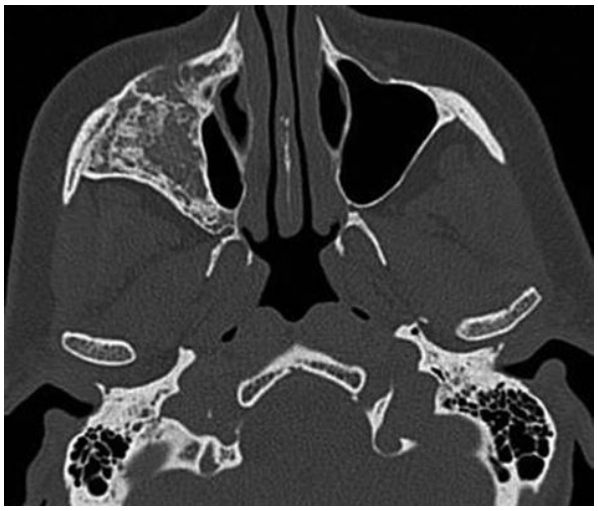


Fig. 30-11 Reduced dose axial MCT image demonstrates a right maxillary fibrous dysplasia. Note the less typical heterogenous internal appearance of this expansile lesion.

Location, origin, and distribution

Plaque-related inflammatory periodontal bone loss originates at the alveolar crest. A lesion that does not demonstrate morphology compatible with this requires further careful analysis and potentially additional tests. Malignant lesions of the alveolar process can resemble inflammatory periodontal defects, although careful analysis will usually reveal that the appearances are not typical of a lesion that originated at the alveolar crest (Fig. 30-8). Langerhans cell histiocytosis is another example of a lesion involving the alveolar process that can appear similar to periodontitis, except that it often appears to be centered at the mid-root region rather than the alveolar crest. Periodontitis can be limited to focal region(s) (involving one or a few teeth) or widely distributed (involving most or all teeth).

More aggressive forms of periodontal disease tend to be seen in younger patients (usually under 30 years of age), often beginning in puberty. The periodontal bone loss is usually rapid and may roughly correlate with tooth eruption, favoring the incisors and first molars. These aggressive forms may also present with more generalized periodontal bone loss, not limited to the incisors and molars (Brown *et al*. 1996).

Severity of periodontal bone loss

Severity of bone loss can be classified as follows:

- *Early bone loss* ranges from slight blunting, loss of cortex, decreased density or a less defined or irregular appearance of the alveolar crests, to bone loss of up to 1 mm (Fig. 30-12)
- *Moderate bone loss* ranges between 1 mm of periodontal bone loss up to the mid-root point (Fig. 30-13)
- *Severe bone loss* extends beyond the mid-root or the bony defect involves a furcation (Figs. 30-14, 30-15, 30-16, 30-17, 30-18).

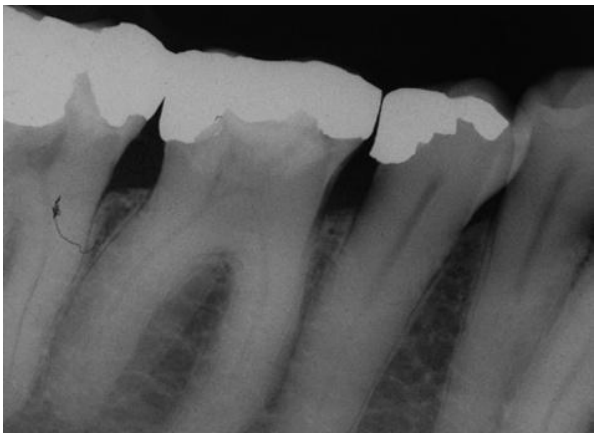


Fig. 30-12 Cropped periapical radiograph demonstrates early moderate periodontal bone loss. Note the overhang at the distal aspect of tooth 45.

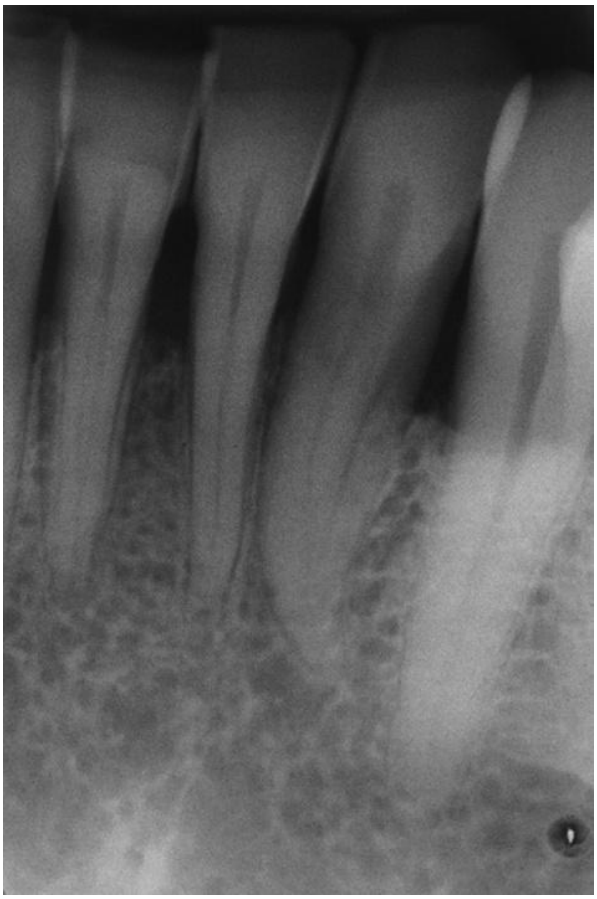


Fig. 30-13 Periapical radiograph demonstrates moderate horizontal periodontal bone loss. Note the absence of the interdental alveolar crest.

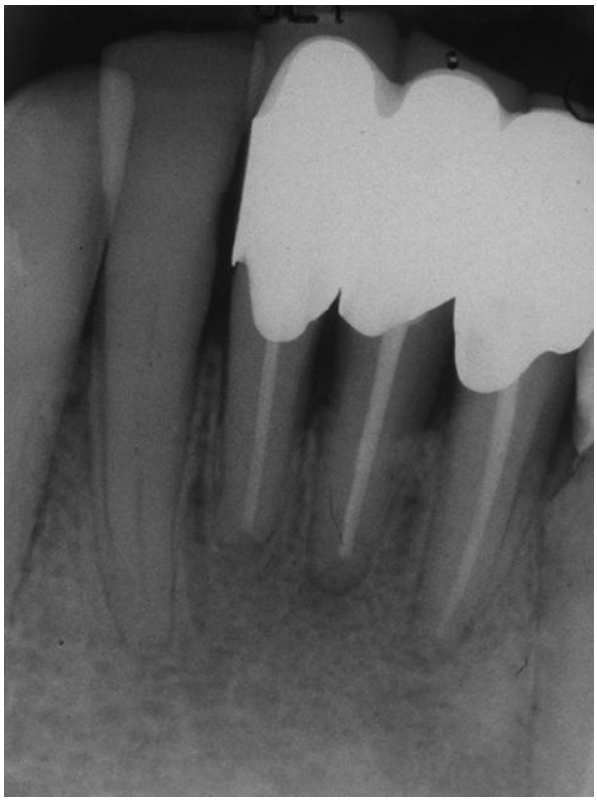


Fig. 30-14 Periapical radiograph demonstrates moderate-to-severe periodontal bone loss. Note the slight overhang at the distal aspect of tooth 41.

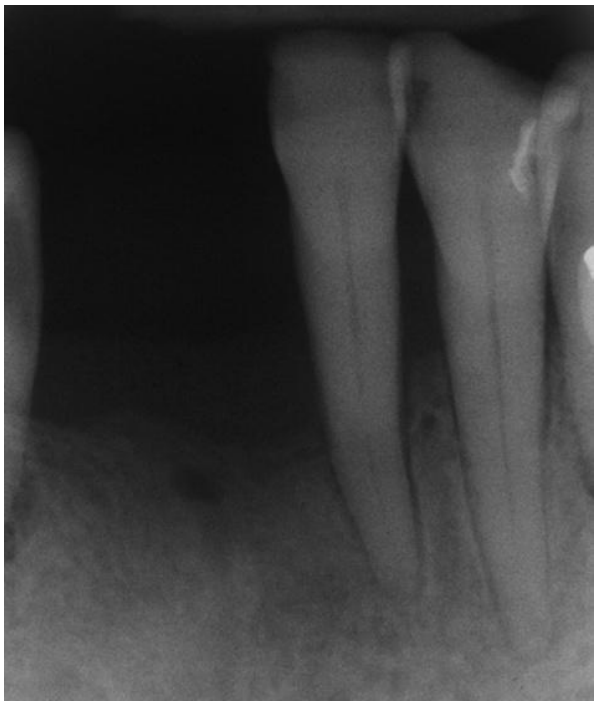


Fig. 30-15 Periapical radiograph demonstrates moderate-to-severe periodontal bone loss with widened periodontal ligament spaces, especially at tooth 31, related to increased mobility.

It should be recognized that radiologically detectable periodontal bone loss is preceded by clinically detectable inflammatory periodontal disease (Goodson *et al*. 1984). It must also be noted that the presence of periodontal bone loss, or indeed the severity in itself, does not indicate the presence of disease activity; in other words, the bone loss may be related to previous disease activity that has been controlled by appropriate therapy. The limitations of the radiographic examination of periodontal bone loss, especially intraoral and panoramic radiography, must be recognized and correlation with clinical findings is important (Mann *et al*. 1985; Khocht *et al*. 1996).

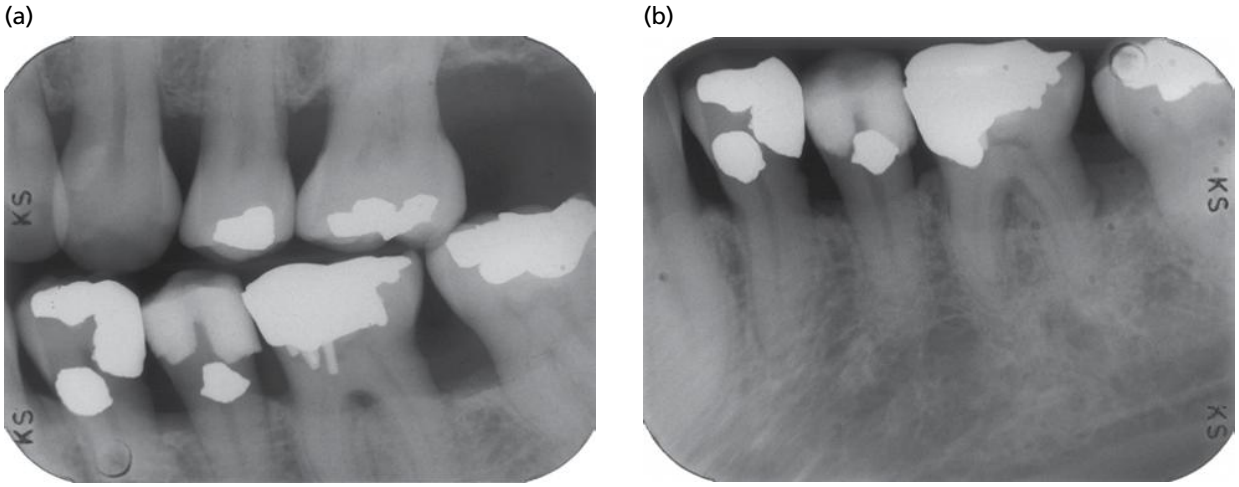


Fig. 30-16 (a) Bitewing radiograph demonstrates primarily horizontal bone loss. The furcation lucency of tooth 36 likely reflects severe periodontal bone loss at tooth 36. Note that this tooth 36 furcation lucency is not well appreciated on the periapical radiograph (b) with appearance of widened periodontal ligament space, suggesting minimal furcation involvement, related to a slightly different vertical projection angle. Also related to variation in projection angle, the horizontal bone loss between teeth 36 and 37 demonstrated on the bitewing appears as a hypodense focus in the periapical radiograph, raising the possibility of a crater defect, or that the bone loss is more severe buccally or lingually, with absence of either cortex. There is a distal overhang associated with tooth 35; this is seen on the bitewing radiograph but is not as obvious on the periapical view. Note the mesial angular defect of tooth 26, likely largely a two-walled defect.

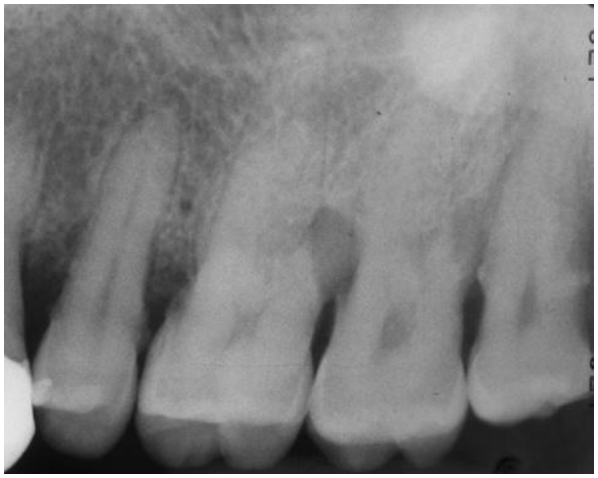


Fig. 30-17 Periapical radiograph demonstrates the "J-shaped" lucent appearance associated with tooth 26, suggesting a furcation defect. A similar appearance, but more subtle, is associated with tooth 27. When clinically indicated, these defects are best identified and the morphology better appreciated with MCT and CBCT.

Morphology of periodontal bone loss

Horizontal bone loss

The bone loss is parallel with the cementoenamel junction (CEJ), usually involving multiple teeth (Figs. 30-12, 30-16).

Angular/vertical defects

The bone loss is uneven and oblique, centered upon one tooth more than the adjacent tooth (Figs. 30-16, 30-18, 30-19).

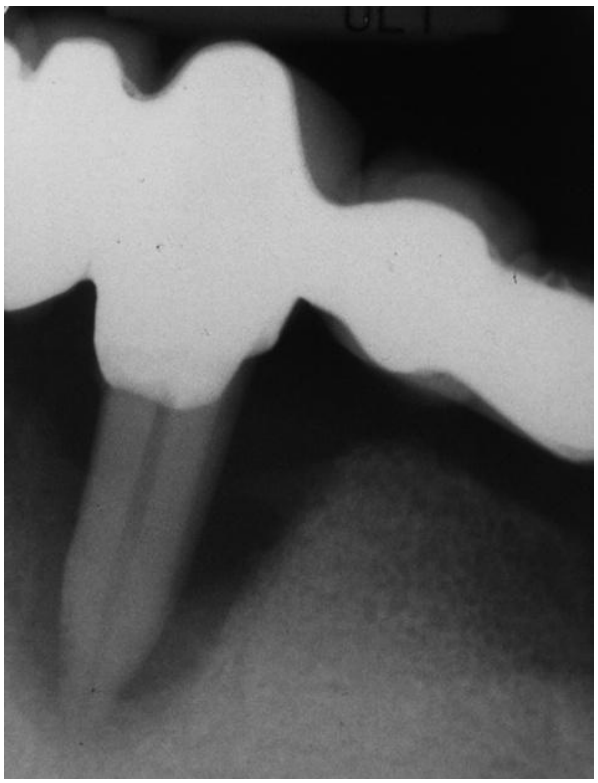


Fig. 30-18 Periapical radiograph demonstrates severe angular periodontal bone loss. The appearance of the distal angular defect suggests a largely two-walled defect; there may be a focal region superiorly where it is single-walled and likely a three-walled defect at the apical third of this root. The appearance of the mesial angular defect suggests a three-walled defect. A perio-endo defect is also suspected. The absence of periapical bone apically may be obscured by residual buccal and lingual bone. Note the adjacent substantial reactive sclerosis, related to chronicity. Where clinically indicated, these defects are best evaluated with MCT and CBCT.

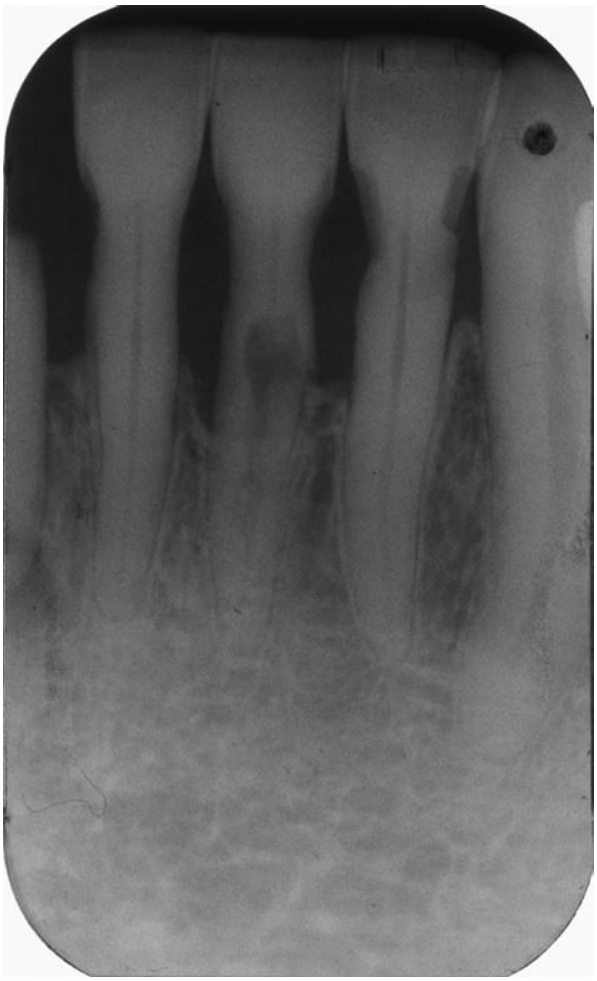


Fig. 30-19 Periapical radiograph demonstrates minor-to-moderate largely horizontal periodontal bone loss with an angular defect at the mesial aspect of tooth 31, likely a single-walled defect. This angular defect likely extends lingually or labially. Note the lucent radicular appearance of tooth 31, related to internal resorption.

Interdental crater defect

These occur at the crest where it is usually a two-walled defect, with relative preservation of the buccal and lingual cortex. It is often not appreciated on plain 2D imaging, but may appear as a focal hypodense region at the superior aspect of the interdental bone. Figures 30-16 and 30-20 demonstrate the difficulty in identifying these defects with intraoral radiography.

Infrabony defects

These refer to focal bone loss which extends along a root surface apically. This defect can be:

- *Three-walled*, where both buccal and lingual cortices are preserved (Fig. 30-18)
- *Two-walled*, where a buccal or lingual cortex is effaced (Figs. 30-16, 30-18)
- *Single-walled*, where both buccal and lingual cortices are effaced (Figs. 30-18, 30-19).

In the intraoral 2D projection, the single-walled defect appears lucent and well defined, and the three-walled defect appears hypodense rather than completely lucent with borders that can appear less well defined.

The identification of the presence of periodontal defects and appreciation of the defect morphology, including vertical defects, is best appreciated with volumetric imaging techniques, including MCT and CBCT (Figs. 30-21, 30-22, 30-23, 30-24, 30-25, 30-26) (Langen *et al*. 1995; Fuhrmann *et al*. 1995, 1997; Mengel *et al*. 2005; Misch *et al*. 2006; Mol & Balasundaram 2008; Vandenberghe *et al*. 2008) It should be noted that vertical defects can be associated with a specific local cause or contributing factor, for example a vertical root fracture (Figs. 30-23, 30-24, 30-26) and overhang.

(a) (b)

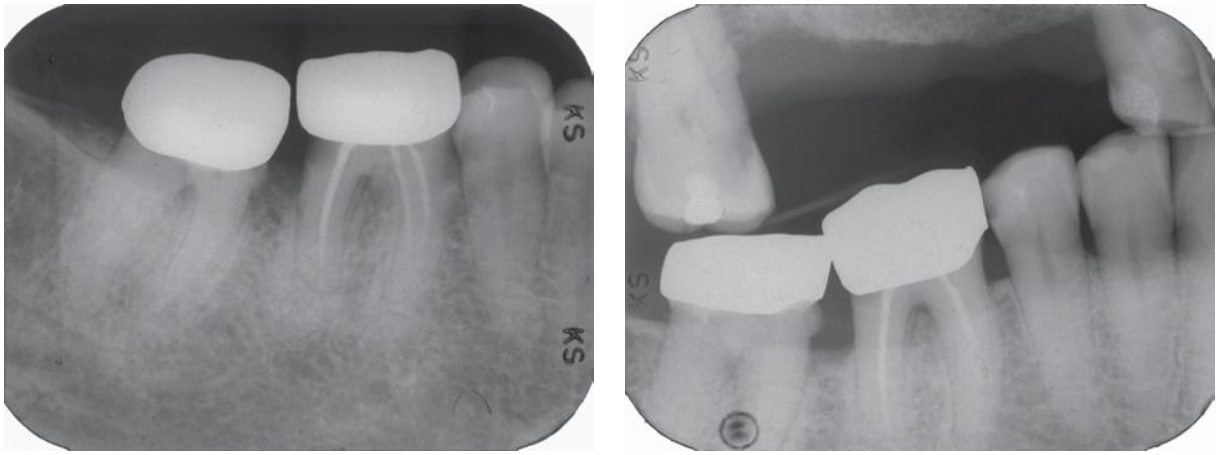


Fig. 30-20 (a) Periapical and (b) bitewing radiographs demonstrate the difference in appearance of the periodontal defects, especially between teeth 46 and 47. The horizontal defect between both these molars is well demonstrated on the bitewing view, but the periapical view only demonstrates a hypodense appearance, which could be misinterpreted as a slight decrease in density or a crater defect. This is related to the difference in vertical projection angle. Interestingly, the mesial calculus deposit of tooth 47 is not as well demonstrated on the periapical view, while the distal cervical caries of tooth 46 is not well demonstrated on the bitewing view. The distal deficiency associated with the tooth 45 restoration is not as well appreciated on the periapical view, related to a difference in the horizontal projection angle. Note the appearance of a slightly widened periodontal ligament space at the tooth 46 furcation, raising the possibility of an early furcation defect.

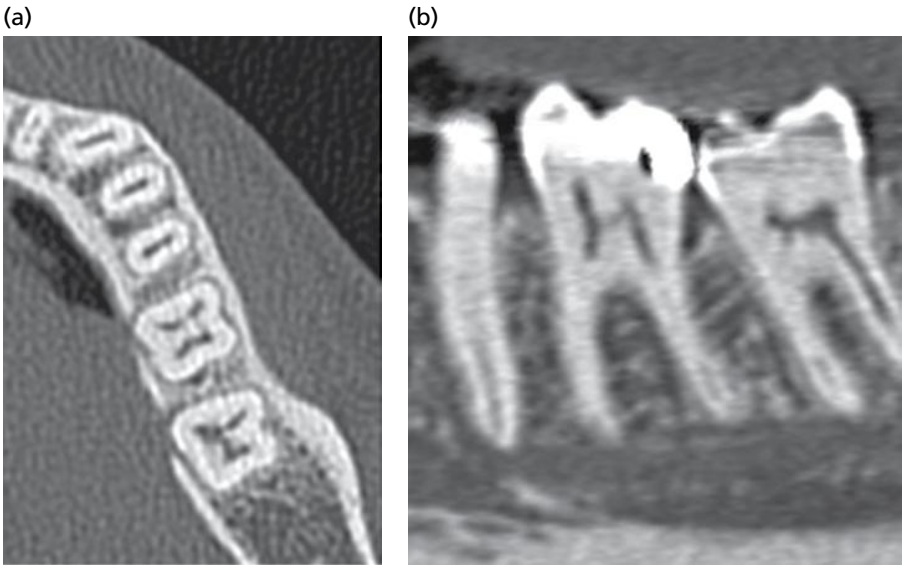


Fig. 30-21 (a) Axial and (b) corrected sagittal low-dose MCT images demonstrate a focal distal angular defect of tooth 36, which is narrow buccolingually. This would not be appreciated on an intraoral radiograph, as this narrow defect would be obscured by projection of the buccal and lingual bone.

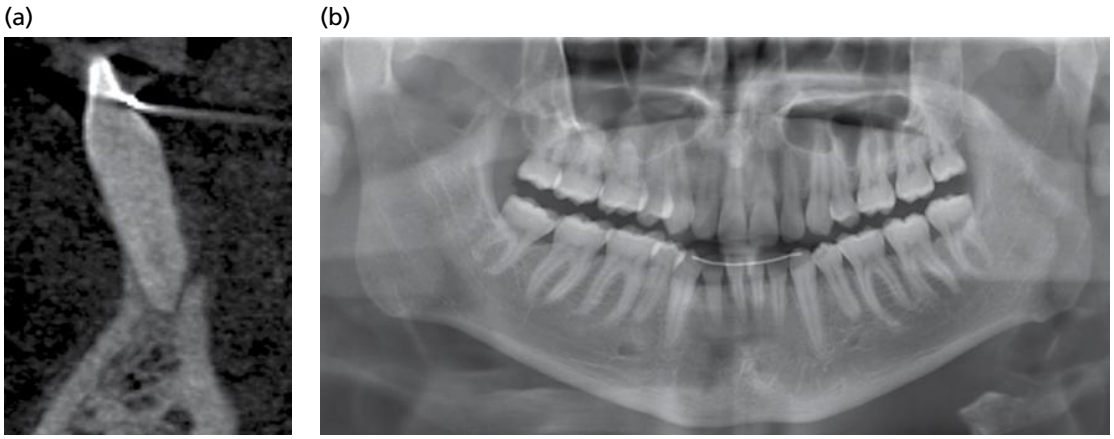


Fig. 30-22 (a) Sagittal low-dose CBCT image demonstrates focal severe lingual periodontal defect of tooth 41 with lingual cortical dehiscence approaching the apex. Note also the widened apical periodontal ligament space which is likely related to increased mobility, although it is difficult to completely exclude early pulpal involvement. (b) This tooth 31 periodontal defect is not well demonstrated on the panoramic radiograph.

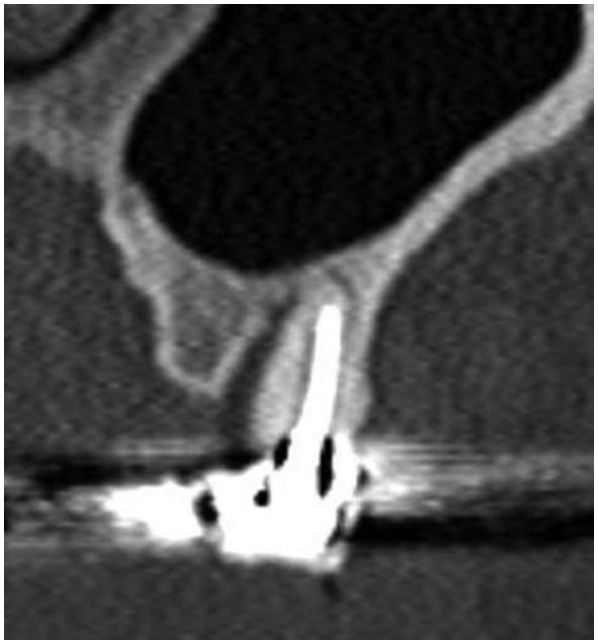


Fig. 30-23 Low-dose coronal MCT image demonstrates a severe narrow palatal vertical periodontal defect associated with this root of tooth 16. This is likely related to a vertical root fracture. Undisplaced root fractures can be subresolution and not detected with MCT or CBCT. This palatal periodontal defect would not be detected on an intraoral radiograph. Note the adjacent reactive sclerosis, likely related to the chronic nature of the lesion.

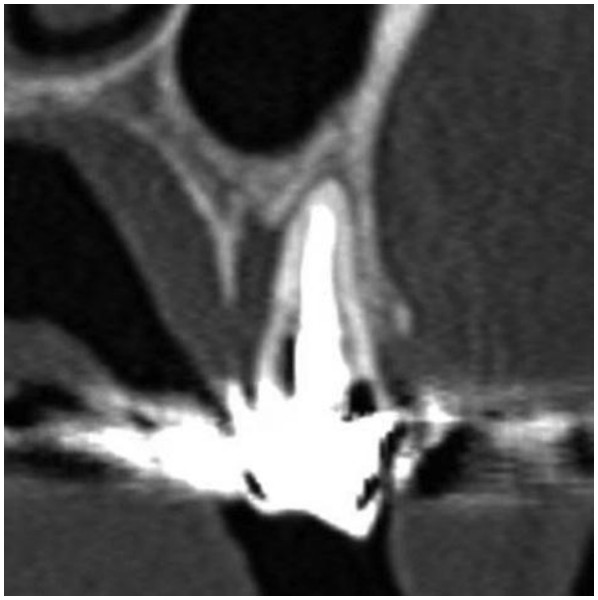


Fig. 30-24 Low-dose coronal MCT image demonstrates a vertical palatal periodontal defect of the endodontically treated tooth 25, with some residual palatal cortex. This would not be appreciated on intraoral or panoramic radiography. This appearance raises the possibility of a vertical root fracture. Undisplaced root fractures can be subresolution and not identified with MCT or CBCT.

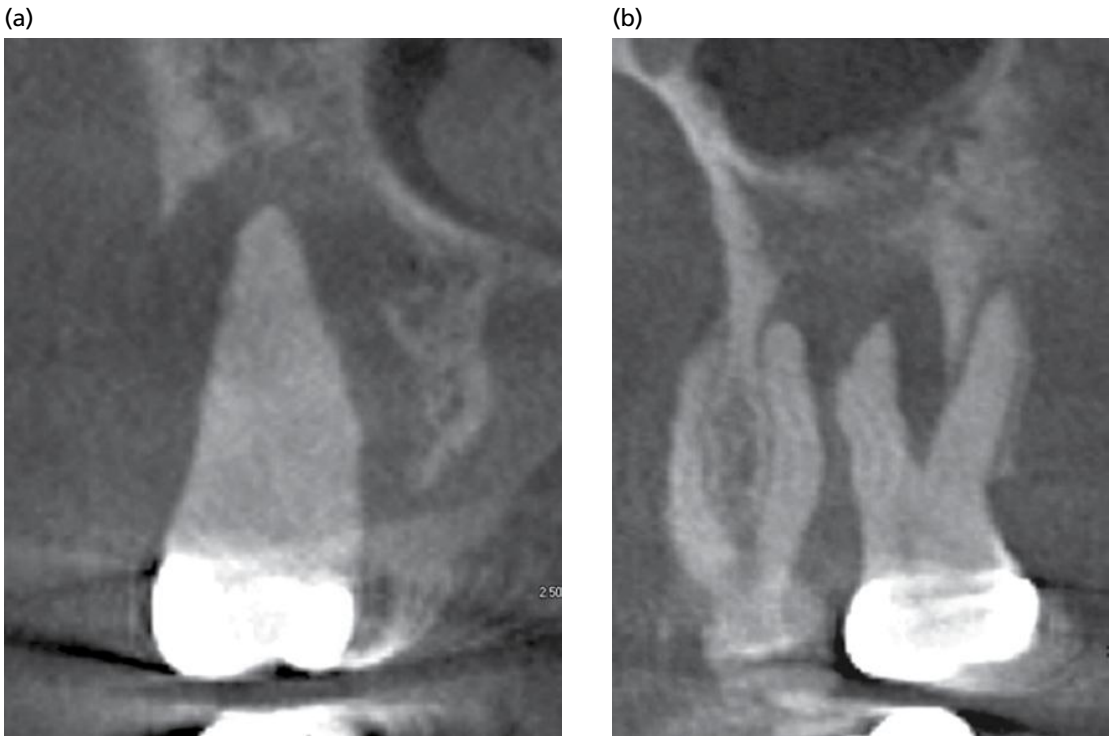


Fig. 30-25 (a) Low-dose coronal and (b) sagittal CBCT images demonstrate severe angular and perio-endo defects involving both tooth 26 distobuccal and tooth 27 mesiobuccal roots. The coronal image of the tooth 16 mesiobuccal root shows the associated buccal cortical dehiscence while also demonstrating preservation of the residual palatal bone of the alveolar process adjacent to the perio-endo defect. The morphology of these defects is best appreciated with multiplanar reformatted (MPR) images on a computer.

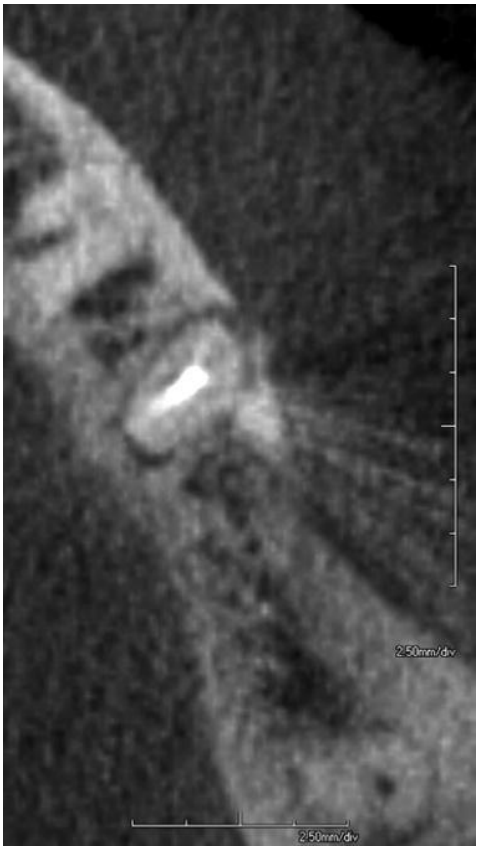


Fig. 30-26 Axial low-dose CBCT image demonstrates narrow buccal and distopalatal periodontal defects, likely associated with vertical root fracture of this endodontically treated tooth 35. Undisplaced root fractures can be subresolution, not identified with CBCT or MCT. Note the substantial beam hardening associated with the non-metallic obturation of this premolar.

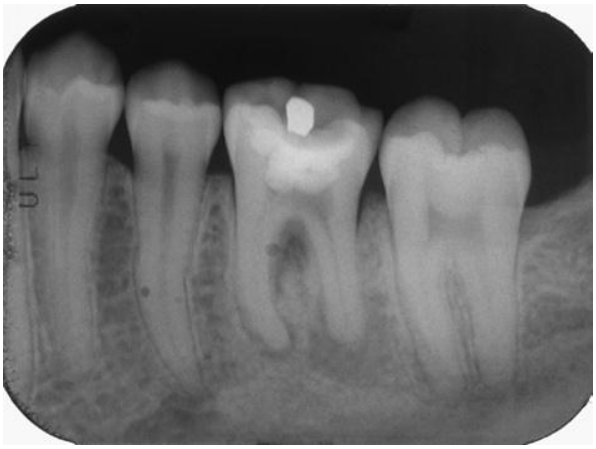


Fig. 30-27 Periapical radiograph demonstrating lucent lesions at the furcation and root apices, likely inflammatory. The adjacent substantial sclerosis is likely reactive, related to chronicity. It is suspected that the furcation lesion is of pulpal origin, rather than periodontal. There is likely ongoing endodontic management of this molar.

Furcation defects

On intraoral 2D views, early inflammatory disease involvement of a furcation usually presents radiologically as a widened periodontal ligament space at the furcation (Figs. 30-16, 30-20). As the disease progresses, a lucent bony defect is visualized at the furcation (Fig. 30-16). It should also be noted that an inflammatory furcation lesion may also be of pulpal origin, related to accessory pulpal canals, root resorption or iatrogenic perforation (Figs. 30-27, 30-28).

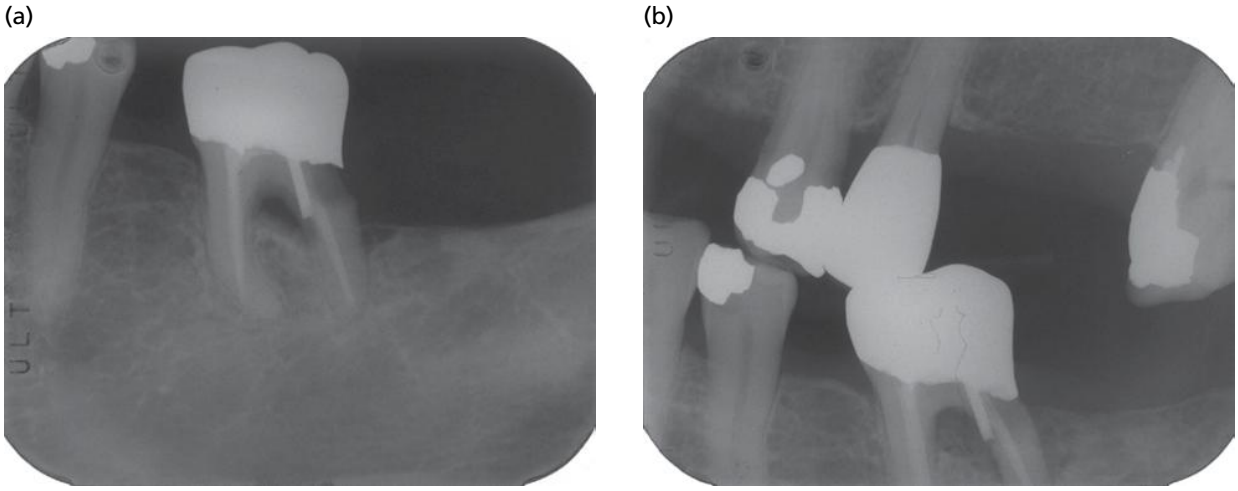


Fig. 30-28 (a) Periapical and (b) bitewing radiographs demonstrate a lucent furcation inflammatory lesion, more obvious on the periapical view. This is likely related to perforation associated with the post of the distal root, more definitively demonstrated on the bitewing view. Interestingly, the distal cervical caries is also better demonstrated on the periapical view.

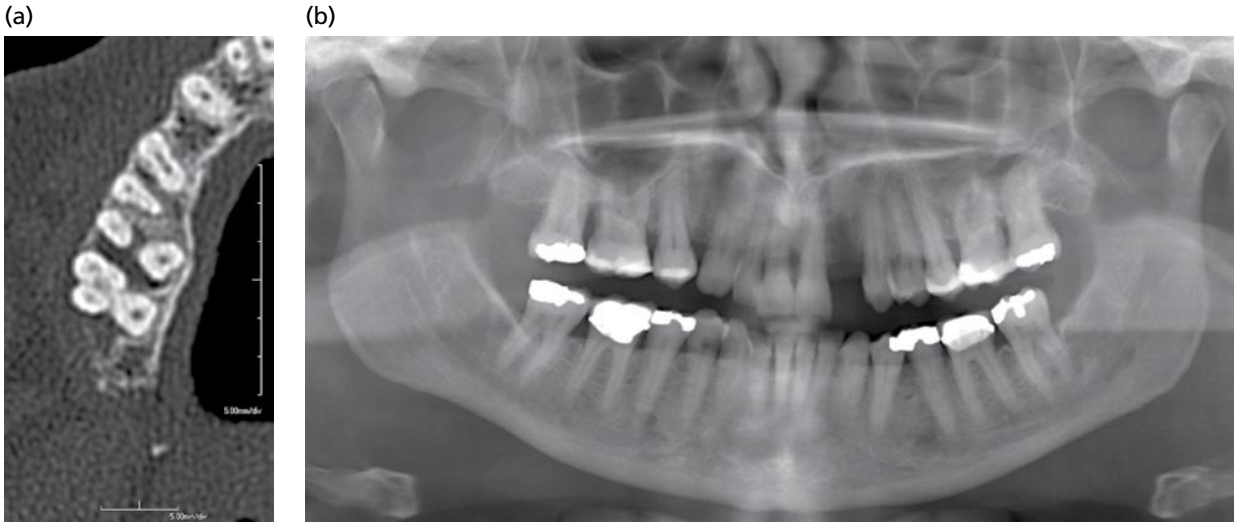


Fig. 30-29 (a) Low-dose axial MCT image demonstrates the precise morphology of the severe periodontal bone loss of tooth 16 with bony furcation involvement. (b) Panoramic radiograph does not demonstrate this defect, although the degree of periodontal bone loss would raise the possibility of a furcation defect. Note that this defect morphology is best appreciated by interrogating the MCT dataset with multiplanar reformatted (MPR) images on a computer.

On plain 2D imaging, lucent and relatively well-defined mandibular molar furcations are usually only seen when there is destruction of either the buccal or lingual cortical plates, or both. If both or one of cortices are preserved, the mandibular molar furcation defect appears as a focal region of varying hypodensity and definition. With limitations, multiple projections with application of parallax principles can be helpful in identifying if the furcation defect is centered buccally or lingually. In some cases, the buccal or lingual cortical loss extends further than at the furcation, resulting in a hypodense appearance at the furcation region where the periodontal ligament space can appear slightly widened. This appearance of a widened furcation periodontal ligament space may be related to less attenuation of the X-ray photons from the normally present buccal and/or lingual cortices, rather than to true furcation disease.

Precise plain 2D radiographic examination for furcation defects is limited, especially of the maxillary molars, largely because of the presence of the palatal root. The classically described "J-shaped" lucent appearance is sometimes seen (Fig. 30-17). The precise location, extent, and morphology of periodontal defects, including furcation defects, is better appreciated with MCT and CBCT (Figs. 30-29, 30-30, 30-31, 30-32, 30-33) (Langen *et al*. 1995; Fuhrmann *et al*. 1995, 1997; Mengel *et al*. 2005; Misch *et al*. 2006; Mol & Balasundaram 2008; Vandenberghe *et al*. 2008).

Perio-endo defects

These are lucent lesions extending from the crestal bone to the apex of a tooth root, but are not always clearly apparent on plain 2D imaging, often because of the projection of the adjacent tooth and bony structures. MCT or CBCT better demonstrate these defects (Figs. 30-18, 30-25, 30-32, 30-33, 30-34).

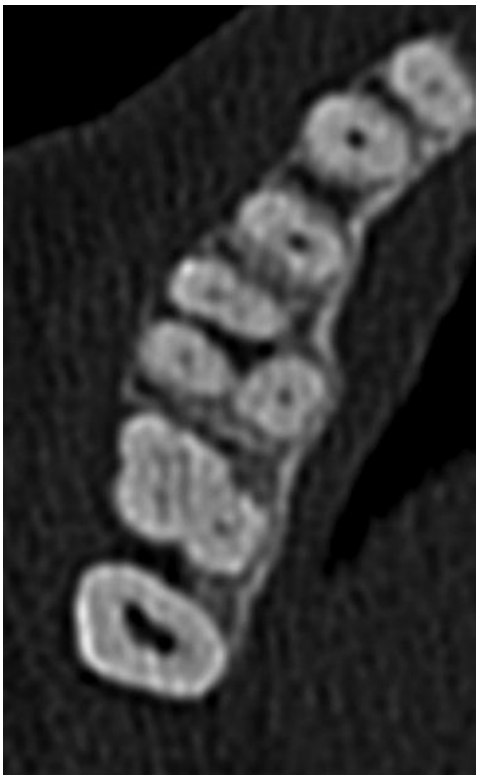


Fig. 30-30 Low-dose MCT axial image demonstrates a furcation defect of tooth 16, where the buccal roots are in close proximity. Access and debridement of this trifurcation defect would be very difficult, if not impossible, without root surgery. Note the extension of the distal periodontal bone loss of tooth 17 to the distal concavity. The morphology of these defects is more precisely evaluated with multiplanar reformatted (MPR) images on a computer.

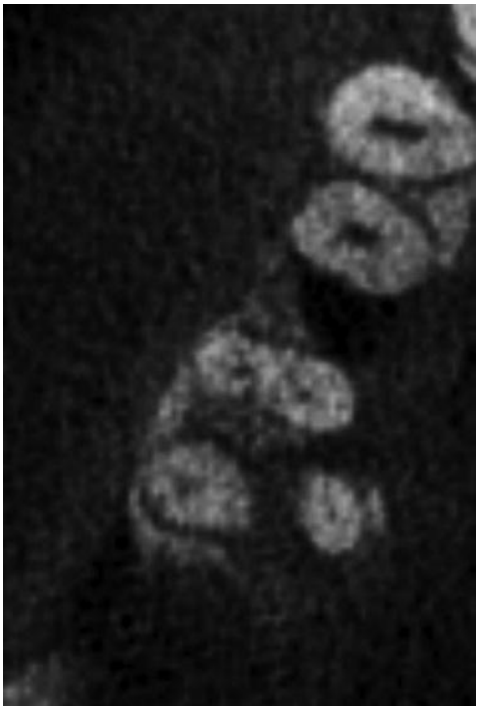


Fig. 30-31 Low-dose CBCT axial image demonstrating a class III bony furcation defect of the tri-rooted tooth 46, extending from the distal to the lingual aspect. The reduced image quality is related to the patient's head size and the low-dose protocol and unit employed. The morphology of this defect is best appreciated with multiplanar reformatted (MPR) images on a computer.

These defects may reflect contiguity of periodontal and periapical inflammatory lesions, where both lesions are sufficiently large that they essentially merge to form one larger lesion. These perio-endo defects could also be primarily or solely of periodontic or endodontic origin. Radiologically, it can be difficult to distinguish between the various causes, although the morphology of the lesion may provide useful clues which can be correlated with the clinical findings. For example, an inflammatory perio-endo defect involving a root, where the apical aspect of the defect is much larger and the periodontal bone loss elsewhere is more limited, may raise the suspicion that this lesion is at least primarily of pulpal origin.

Similar to vertical defects, perio-endo defects can also be associated with a specific local cause or contributing factor, such as a vertical root fracture.

Acute periodontal abscess

This acute inflammatory lesion is usually not seen on plain 2D radiography and CBCT. The lesion identified on these views often largely reflects the chronic bony destruction, which has taken some time to occur. An abscess and/or inflammatory infiltrate can extend into the adjacent soft tissues (see later).

Border

While inflammatory lesions are classically relatively ill defined, inflammatory periodontal bone loss is usually chronic in nature. Therefore, the margins often appear relatively well defined.

Internal appearances of periodontal defects

Inflammatory periodontal bony lesions are lucent internally. Occasionally, oral debris is seen.

Adjacent structures

Hypodense or lucent appearances adjacent to an inflammatory lesion often reflect a loss of trabecular bone related to progression of the disease. This less dense appearance is related to a decrease in the density as well as the number of trabeculae.

Sclerosis of the adjacent bone (increased density) is quite commonly seen. This is a reaction of the adjacent trabecular bone to the inflammatory lesion, with deposition of bone on the trabeculae resulting in thicker trabeculae and smaller marrow spaces. This takes time and reactive sclerosis therefore reflects the chronic nature of the dentoalveolar inflammatory lesion (Figs. 30-7, 30-18, 30-23, 30-27, 30-34). Substantially sclerotic mandibular appearances are not infrequently seen. It is also important to recognize that this sclerosis may persist following successful therapy, usually for extended periods; that is, this sclerosis is residual and does not indicate ongoing active disease.

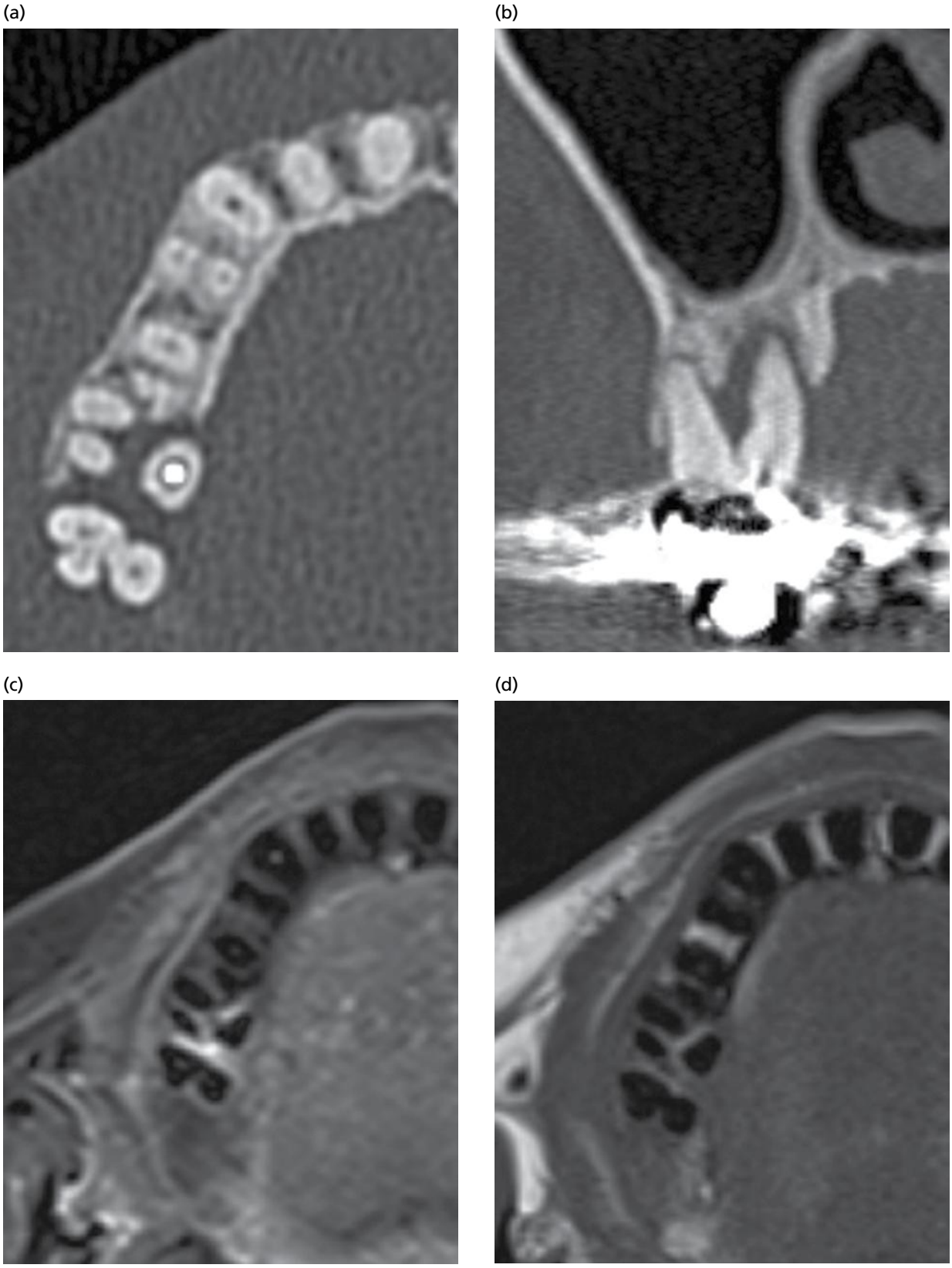


Fig. 30-32 (a) Low-dose axial and (b) coronal MCT images demonstrating a class III bony furcation defect of tooth 16, with perio-endo defect of the palatal root (coronal image). Note the extension of the periodontal bone loss of tooth 17 to the inter-radicular grooves. The morphology of these defects is best evaluated on computer, with multiplanar reformatted (MPR) images. (c) Axial MRI STIR sequence demonstrates the edema between teeth 16 and 17, and also associated with the furcation defect of tooth 16. (d) Axial MRI T1 sequence demonstrates normal fatty marrow interdentally between the premolars and also anteriorly. These features are not demonstrated with MCT or CBCT.

Periapical and severe periodontal inflammatory lesions affecting the maxillary posterior teeth often induce a reactive change at the maxillary sinus bases. Apical inflammatory lesions and periodontal inflammatory lesions which approximate the root often result in a focal reaction of the periosteum, a focal periostitis. Radiologically, this appears as a focal dome-shaped, curvilamina opacity over the inflammatory lesion at the sinus base (Fig. 30-34). These inflammatory lesions may thin, elevate or even focally efface the cortical floor of the maxillary sinus. In addition, periapical and periodontal inflammatory lesions which closely approximate the maxillary antral bases almost always induce a reactive mucosal thickening at the maxillary sinus floor (Fig. 30-34).

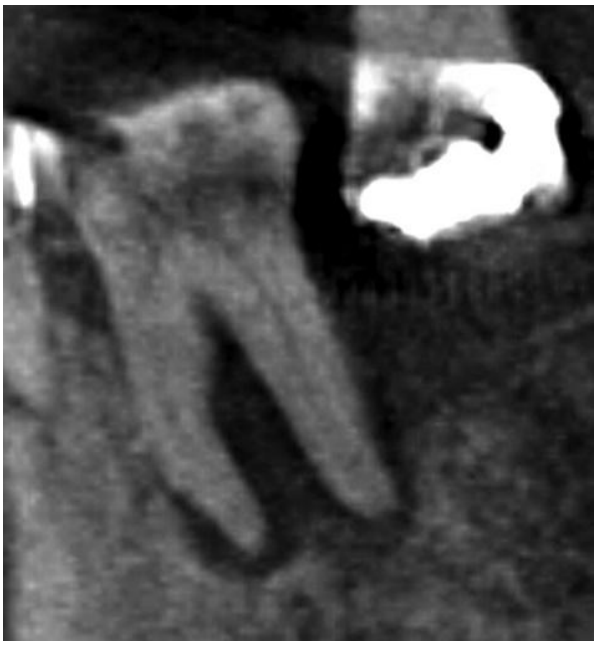
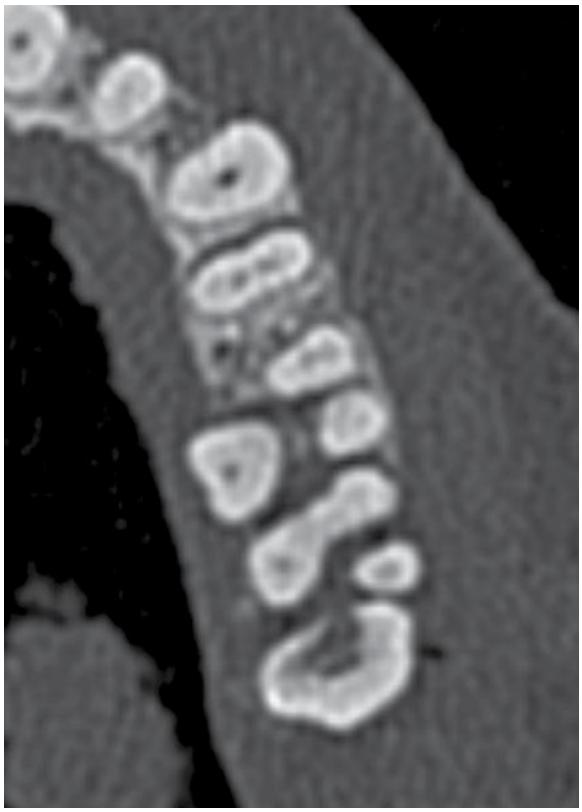


Fig. 30-33 Sagittal low-dose CBCT image demonstrates furcation and perio-endo defects of tooth 36.

When inflammatory lesions extend to cortical boundaries, the inflammatory products can extend through the cortex (which clinically and radiologically appear preserved) to elevate the periosteum. This elevated periosteum lays down a lamina of bone, often referred to as periosteal response or periosteal new bone formation. Radiologically, a bony curvilamina opacity adjacent and largely parallel to the cortex is seen. In cases where there are multiple chronic and acute phases, multiple opaque lamina are seen. Periosteal response is often seen in osteomyelitis, but is rarely seen with periodontal disease, except where this is severe and aggressive.

When there is frank extension of periodontal and periapical inflammatory lesions into the adjacent soft tissues, there is usually radiologically evident effacement of the bony cortex, however small. These

(a)



(b)

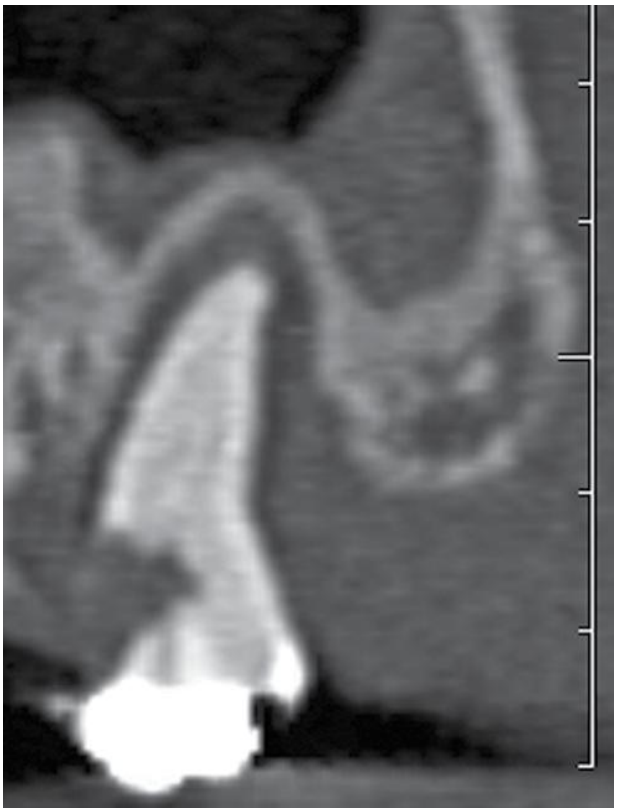


Fig. 30-34 (a) Axial and (b) sagittal low-dose MCT image: There is a class III bony furcation defect of tooth 27 extending from the distal to the buccal aspects (axial image). There is also a perio-endo defect of tooth 28 with associated focal periostitis and reactive mucosal thickening at the left maxillary antral base. The adjacent sclerosis is likely also reactive. Note also the early distal bony furcation involvement of tooth 26 and mesial caries of tooth 28.

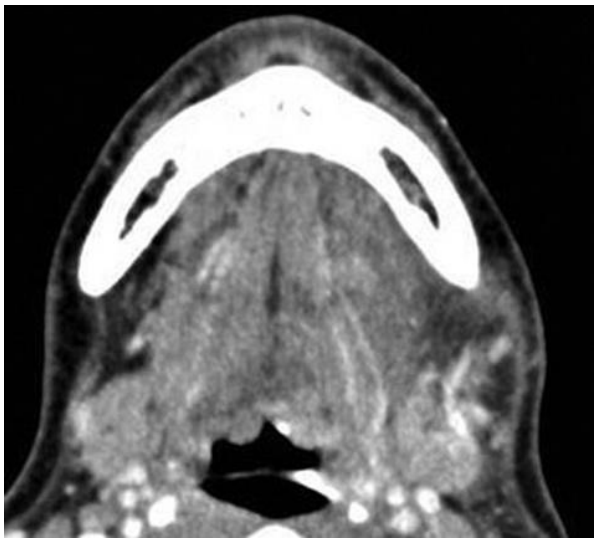


Fig. 30-35 MCT axial soft tissue window image (with intravenous contrast) demonstrates inflammatory infiltrate within the left submandibular space from a left mandibular periapical lesion. Note the minimal prominence of the left lateral pharyngeal wall. When severe, compromise of the airway can be life threatening.

cortical defects often appear as lucencies on 2D views, more lucent if both cortices are involved. However, these lucencies may not be appreciated on 2D imaging when projected over more opaque structures, such as the tooth root itself. These cortical defects are best visualized with MCT or CBCT. However, infection within the soft tissues cannot be examined with plain 2D radiography or CBCT, and MCT, often with intravenous contrast, is then the modality of choice. The details of these examinations are beyond the scope of this text. MCT features, including the presence of inflammatory infiltrate, fat streaking, contrast enhancement, abscess collection, and periosteal new bone formation, can be useful in the evaluation of an acute periodontal inflammatory lesion. The location and extent of cellulitis and extent of abscess collection as well as airway patency are findings with potentially urgent clinical and surgical relevance (Figs. 30-9, 30-35).

Related factors

There are many factors which influence inflammatory periodontal disease. Many of the locally related factors are sometimes identified radiologically. However, it must be recognized that these factors may not be identified radiologically, particularly when subtle and especially with 2D radiography. Local factors include:

- Calculus deposits (Figs. 30-20, 30-36)
- Restorative therapy-related factors, including overhangs, deficiencies, open margins, incorrect contours, and open contacts (Figs. 30-12, 30-14, 30-16)
- Caries occurring or extending cervically (Figs. 31-20, 31-28, 30-34)

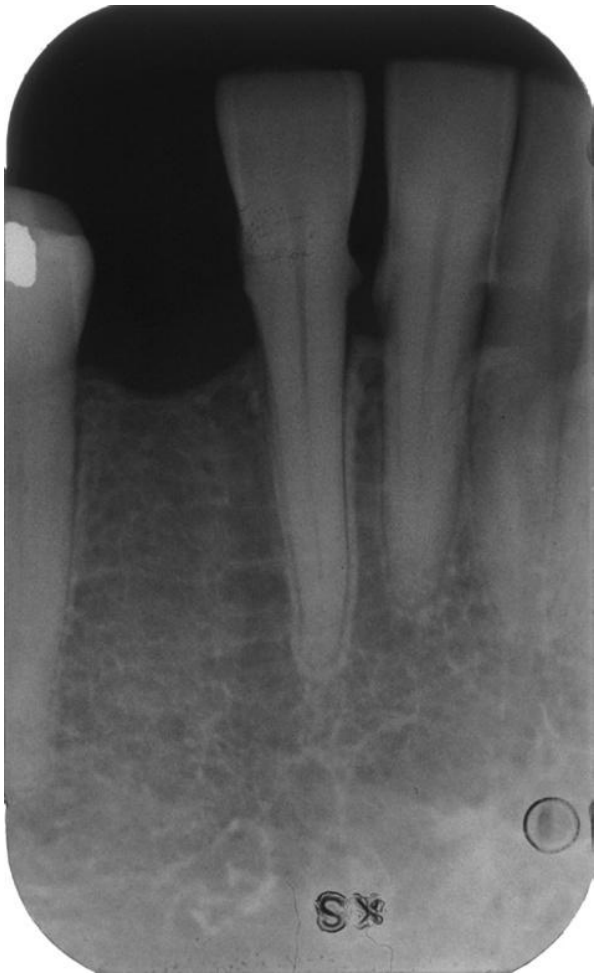


Fig. 30-36 Periapical radiograph demonstrates horizontal bone loss and calculus deposits.

- Root fractures (Figs. 30-23, 30-26)
- Perforations related to endodontic therapy and post preparations (Fig. 30-28)
- Increased mobility and/or increased occlusal loading, usually presenting with widened periodontal ligament spaces (Fig. 30-15). This widening can involve the entire root or be seen only apically and cervically. A thickened lamina dura is sometimes evident
- Hypercementosis is often idiopathic but can also be related to increased loading
- Crown-to-root ratio of a tooth may be relevant to the prognosis
- Presence of apical inflammatory lesions (Figs. 30-7, 30-27) may affect the prognosis and treatment planning.

Differential diagnosis

Essentially, any lesion which results in the loss of periodontal bone can resemble plaque-related inflammatory bone loss.

A malignant lesion, for example squamous cell carcinoma or adenoid cystic carcinoma, can resemble periodontitis. Malignant metastatic lesions such as adenocarcinoma from the breast can also resemble

periodontitis. However, there are almost always differences in the radiologic appearances. Most importantly, the appearance of infiltrative and invasive margins and of the leading edge are key radiologic features (Fig. 30-8). When occurring within the alveolar process, Langerhans cell histiocystosis can also resemble periodontitis-related bone loss. However, these lesions tend to be centered at the mid-root, in contrast to inflammatory periodontal bone loss which begins at the alveolar crest. Benign tumors can also occasionally resemble periodontal bone loss, although mass effect is often seen with these and may result in unusual tooth displacement.

If suspicious appearances are noted on a 2D radiographic image, further evaluation with MCT must be considered. Malignant lesions are not optimally evaluated with CBCT, because of the limitations of this technique, including poor visualization of the soft tissues. Intravenous contrast is usually required for these examinations. Sometimes, the malignant features are not obvious, especially on 2D radiography, requiring a high level of interpretive skill to identify them. Specialist radiologic opinion should be considered.

As a general rule, focal moderate-to-severe periodontal defects, where the periodontium elsewhere is essentially within normal limits, should be evaluated carefully. Biopsy should be considered if there is clinical suspicion that the lesion is not inflammatory. If the clinical and radiologic findings support the presence of inflammatory bone loss and there is no pretreatment indication for biopsy or other tests, post-management clinical and radiologic review should be considered.

Pathology involving other regions of the jaws and adjacent structures

Appropriate radiologic examination also provides an opportunity to identify other pathology within the jaws or affecting the adjacent structures. These findings, even if not directly related to the inflammatory periodontal disease, may affect the overall diagnosis and treatment planning.

Frequency of periodontal radiologic examinations

The frequency of radiologic examination for the patient with periodontal disease is dependent on the clinical findings and treatment response. Radiologic documentation of the disease sites prior to periodontal treatment is important, both for diagnosis and also as a baseline in the evaluation of interval change. It is important to emphasize that the presence and severity of periodontal bone loss does not indicate the presence of active disease. Clinical evaluation and radiologic evidence of interval change are important in this regards.

Implant imaging

The importance of and the key steps involved in evaluating the region intended for implant placement for presence of pathology have been discussed earlier. The importance of evaluating other dentoalveolar and oral structures in relation to an overall treatment plan was also recognized.

An appropriate radiologic study also obviously provides an opportunity to evaluate the site(s) in relation to the implant placement itself. Preliminary radiologic studies often contribute to the initial diagnosis and clinical decision as to whether implant therapy is the optimal choice in the overall management. To varying extents and to varying levels of accuracy, the various imaging techniques aid in the selection of the optimal implant and planning of the most favorable location and orientation, and also facilitate surgical planning. It is critical that radiologic diagnostic information is maximized and appropriately applied to achieve the best possible outcome, and minimize complications and failures. It must be emphasized that the radiologic findings must be combined with the clinical information in the planning of the implant. For example, while there may appear to be sufficient bone volume at a particular site, the angulation of the implant required for a satisfactory result may still require bone augmentation. Some of the key parameters in implant planning where appropriate imaging (Figs. 30-37, 30-38, 30-39, 30-40, 30-41 30-42, 30-43, 30-44, 30-45) can contribute are:

- Bone height (craniocaudal dimension)
- Faciolingual/faciopalatal width
- Mesiodistal dimension
- Bone morphology
- Presence and prominence of anatomic features:
  - Sublingual and submandibular fossae
  - Incisive and canine fossae
- Neurovascular canals and foramina, including:
  - Mandibular canal and the mental foramen
  - Incisive canal and foramen
  - Mandibular lingual canals and foramina (Laboda 1990; Mason *et al*. 1990; Katakami *et al*. 2009; Tagaya *et al*. 2009; Givol *et al*. 2000)
  - Greater palatine canal and foramen
- Cortical thickness and density
- Extent and morphology of the alveolar recesses of the maxillary sinus bases.

Normal variants of anatomy must be kept in mind and appropriate imaging applied so that these are identified. Substantial variations in many anatomic structures are well known, such as the degree of extension of the alveolar recesses of the maxillary sinuses into the maxillary alveolar process. Large variations in the location of the mandibular canal and mental foramina, the location and size of the maxillary incisive canals, as well as prominences of the

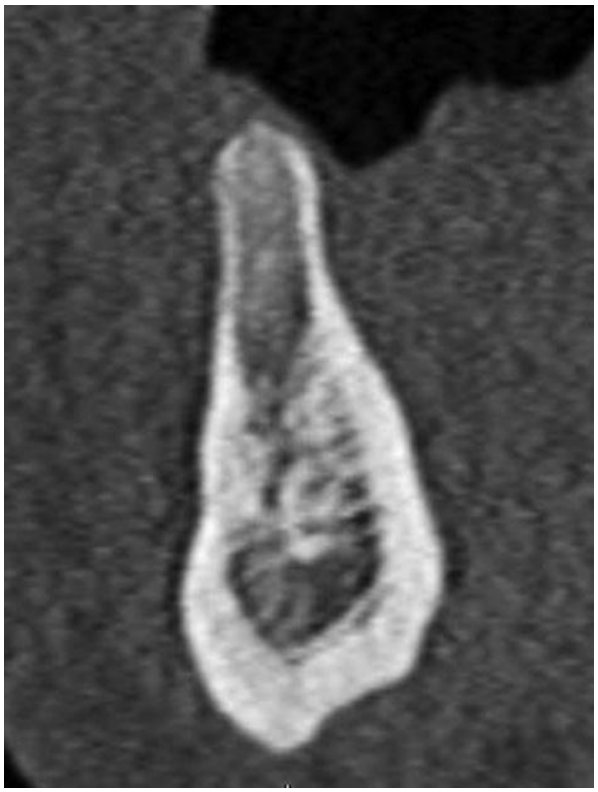


Fig. 30-37 Low-dose cross-sectional MCT image of the tooth 43 site demonstrates new bone formation, with some remodeling, within the tooth socket.

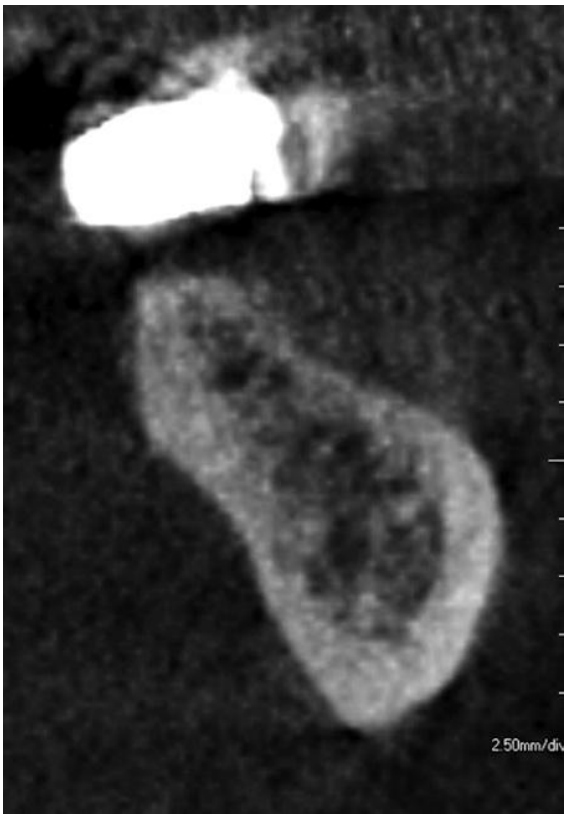


Fig. 30-39 Low-dose reformatted cross-sectional image of a tooth 36 site. There has been postextraction bony remodeling. Note the slight-to-moderate submandibular concavity. The mandibular canal is visualized.

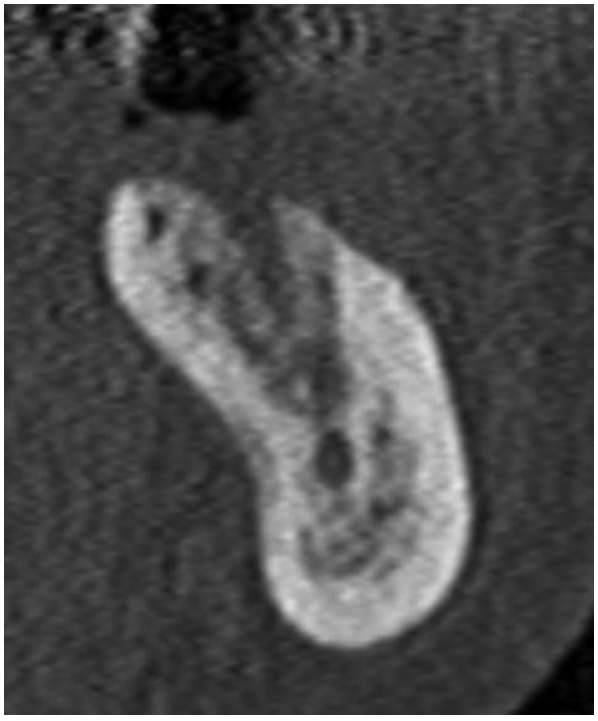


Fig. 30-38 Low-dose cross-sectional MCT image of a tooth 36 site demonstrates substantial peripheral new bone formation. The mandibular canal is visualized at the apical aspect of the healing socket. Note the slight-to-moderate submandibular concavity.

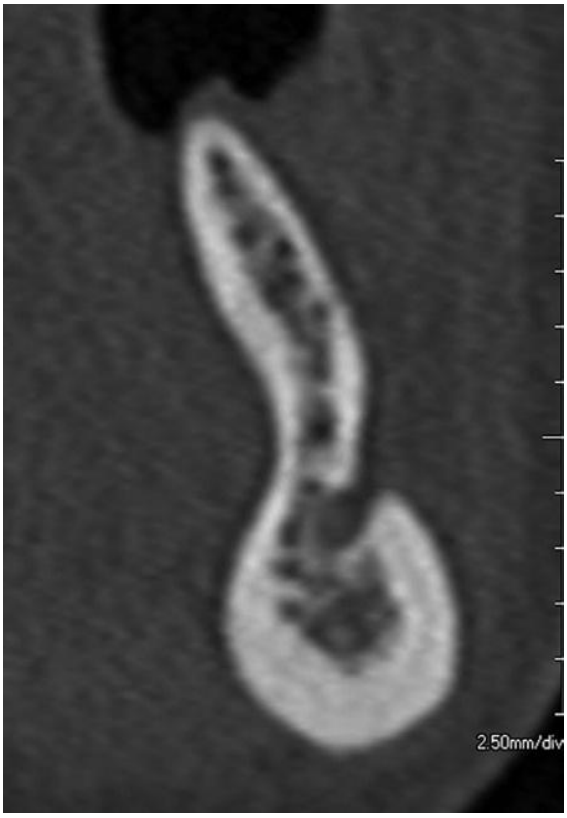


Fig. 30-40 Low-dose cross-sectional MCT image of a premolar site demonstrates the mental foramen and adjacent mandibular canal. Note the relatively narrow residual ridge and the moderately prominent sublingual concavity.

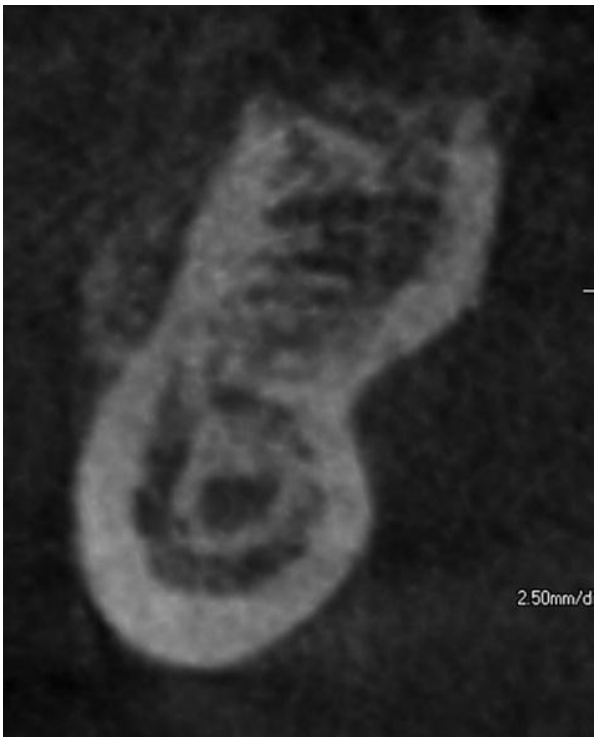


Fig. 30-41 Low-dose cross-sectional CBCT image of a mandibular molar site demonstrates a moderate submandibular concavity. The mandibular canal is visualized.

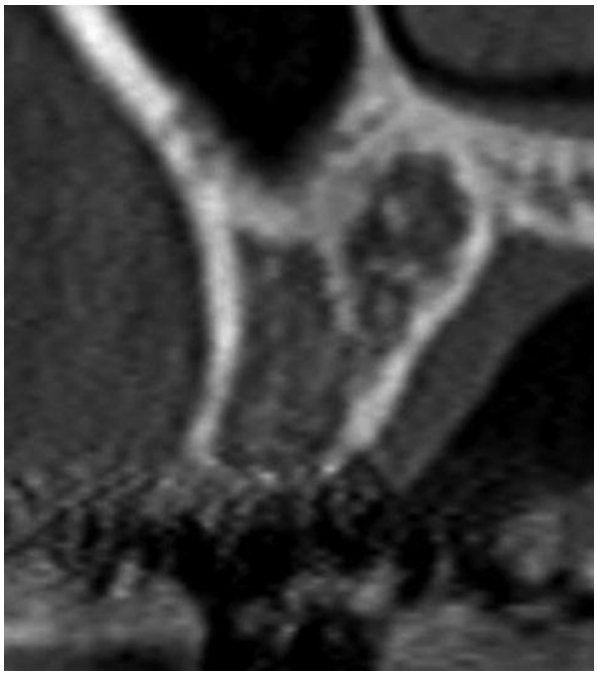


Fig. 30-42 Low-dose cross-sectional MCT image of site 15. Note the proximity of the maxillary antral base at the buccal aspect.

(a) (b)

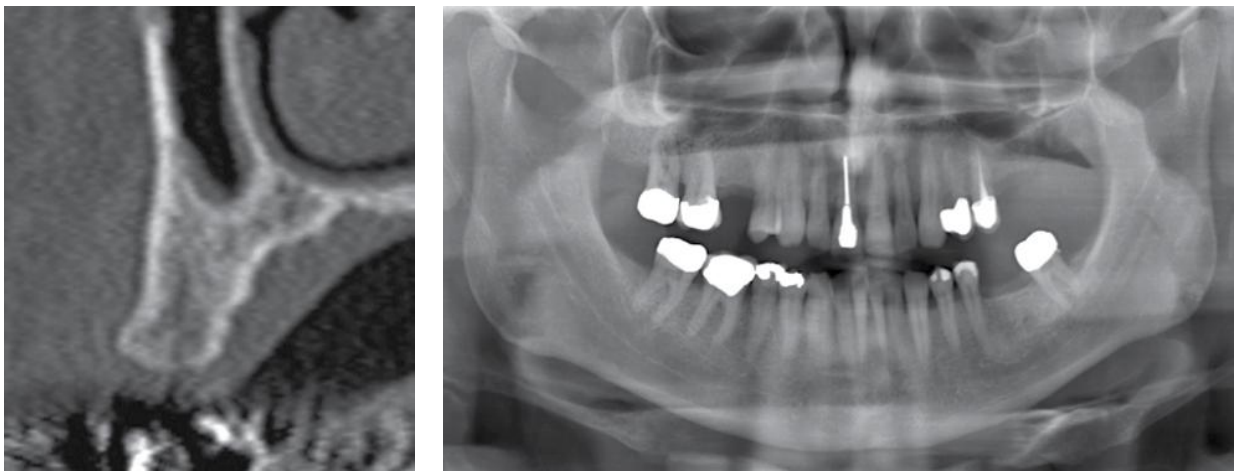


Fig. 30-43 (a) Low-dose cross-sectional MCT image demonstrating the buccolingual concaved morphology of the maxillary antral base at site 15. (b) This is not appreciated on the panoramic view, giving the false impression of a larger bone height.

sublingual and submandibular fossae are also well known. Multiple mental foramina and mandibular canals as well as variation in the length and extent of the anterior loop of the canal leading to the mental foramen have also been described (Arzouman *et al*. 1993; Naitoh *et al*. 2009a; Uchida *et al*. 2009; Kuribayashi *et al*. 2010; Apostolakis & Brown 2012; de Oliveira-Santos *et al*. 2012). The presence of lingual canals and foramina of the mandible have also been commonly reported and considered potentially life threatening in relation to the surgical placement of implants (Laboda 1990; Mason *et al*. 1990; Givol *et al*. 2000; Katakami *et al*. 2009; Tagaya *et al*. 2009). It is essential that the imaging modality selected is capable of accurately demonstrating these critical structures. These normal variants are discussed in further detail in the section on MCT and CBCT below.

Imaging modalities

Intraoral radiographs

Intraoral radiographs represent a series of small FOV 2D images. Essentially, 3D structures are projected over each other onto a flat detector. This is a high-resolution modality, available in almost all dental

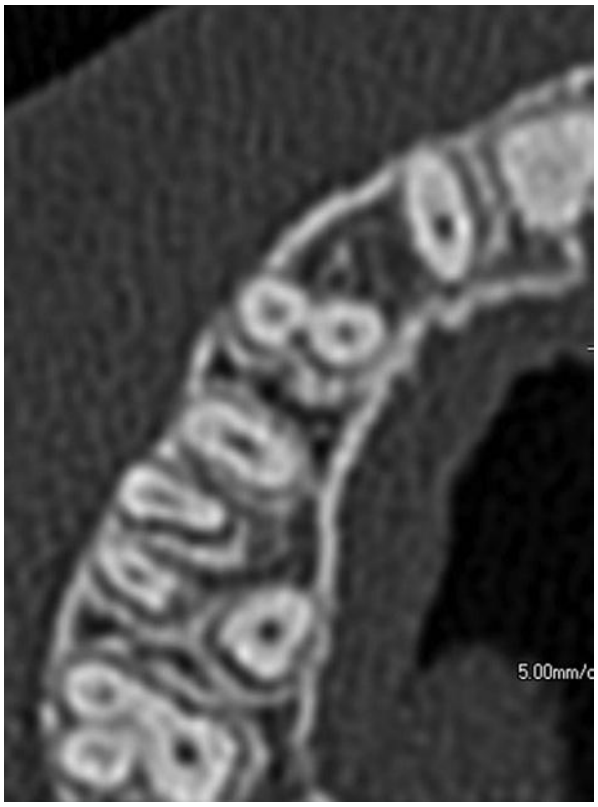


Fig. 30-44 Axial low-dose MCT image demonstrates the tooth site 13. The mesiodistal dimension at this site is smaller palatally, which would not be appreciated on 2D radiography. Note that these interdental dimensions are best evaluated on axial images, rather than cross-sectional and panoramic slices.

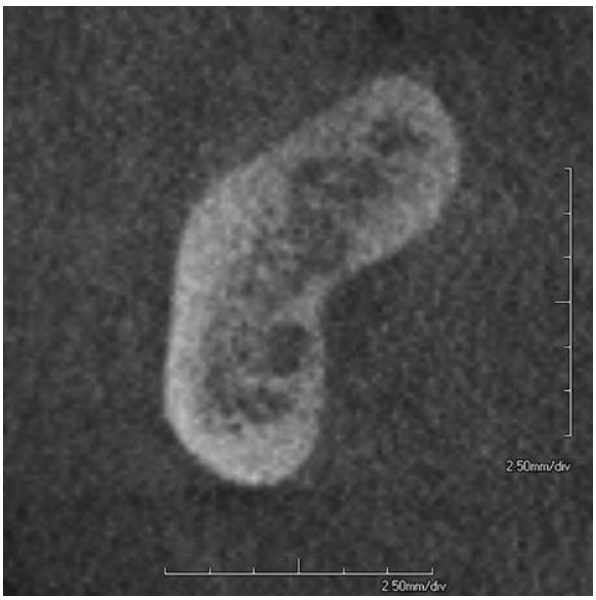


Fig. 30-45 Cross-sectional low-dose CBCT image of a mandibular molar site demonstrates a prominent submandibular concavity. The mandibular canal is visualized.

settings, and can be relatively inexpensive. However, the limitations must be recognized.

In relation to the periodontal patient, only the proximal structures are sufficiently well visualized. Alterations in density may provide only limited information regarding the status of buccal/labial and lingual/palatal periodontal bone (Fig. 30-23). Multiple projections employing parallax principles can be useful, although the true 3D morphology of a periodontal bony defect is not demonstrated on intraoral radiography. Obviously, a certain level of bone demineralization or loss must occur before bony change is detected radiologically. This is particularly true with plain 2D imaging, including intraoral radiography, where a lesion must cause sufficient loss of osseous structure to be visualized. In other words, the lesion must cause sufficient decrease in bone density and/or bony destruction, especially in the faciolingual dimension, to be identified on 2D imaging. For example, narrow vertical periodontal defects are often not detected on intraoral views (Figs. 30-21, 30-26). Many lesions are not identified on 2D radiography until buccal or lingual cortices are effaced. Soft tissues are not examined with this technique, although the profile of the overlying soft tissue, for example the operculum over an impacted third molar, is occasionally seen. Projection of dense or thick bony structures over the area of interest on intraoral radiography may obscure a periodontal defect, for example an external oblique ridge and the inferior cortex of the zygomatic process of the maxilla.

Whenever possible, the paralleling technique must be employed for periapical radiography. Interestingly, the bitewing projection is usually more accurate in the evaluation of periodontal bone loss, as the primary beam is more perpendicular to the long axis of the teeth. This may be the projection of choice where the periodontal bone loss is not expected to be severe. There is often compromise in the projection angles in periapical imaging, which can result in the inaccurate reflection of the true periodontal bone levels (Figs. 30-16, 30-20). However, the opposite can sometimes be true (Fig. 30-28). Therefore, it is crucial that the observer is aware of the precise angle of projection. Detailed examination of the other anatomic structures in the FOV can be helpful in identifying the projection. One method is to evaluate the coronal morphology, where the degree of superimposition of cusps of posterior teeth upon each other provides clues to the vertical angle of projection. Obviously, the degree of overlap of proximal crown surfaces may provide clues to the horizontal projection angle.

Several associated techniques have been explored to assist in the comparison of images to evaluate for bony changes. Grids and subtraction radiography both rely on exact detector placement and projection angle, which is not easily achieved and rather impractical in the clinical setting.

In the evaluation of periodontal bone loss, periapical radiography is not as accurate as CBCT and MCT (Furhmann *et al*. 1995; Langen *et al*. 1995; Mol & Balasundaram. 2008; Vandenberghe *et al*., 2008). It has also been shown that the presence and the morphology of periodontal defects is more accurately identified by CBCT and MCT (Fuhrmann *et al*. 1995;

Langen *et al*. 1995; Fuhrmann *et al*. 1997; Misch *et al*. 2006), as discussed in the relevant section below. The need to employ CBCT or MCT in the evaluation of periodontal defects remains dependent on the clinical findings of each individual case. For example, CBCT may be indicated in a case with moderate periodontal disease where there is suspicion of narrow vertical or furcation defects which are not obvious clinically. CBCT may also be preferable to a full-mouth intraoral series or multiple periapical radiographs. To arrive at the optimal decision, the clinician must be thoroughly acquainted with the capabilities of MCT and CBCT, as well as the associated radiation doses (see relevant section below).

The presence and extent of periapical disease is also obviously of importance to the overall diagnosis of the periodontal patient. Volumetric imaging modalities like MCT and CBCT have been shown to be significantly superior in identifying the presence of periapical lesions than periapical radiographs (Velvart *et al*. 2001; Huumonen *et al*. 2006; Lofthag-Hansen et al. 2007; Stavropoulos & Wenzel 2007; Low *et al*. 2008; Estrela *et al*. 2008). Volumetric imaging provides more information with regards to the radiologic features of a periapical lesion and has been shown to be more accurate with regards to the diagnosis of the periapical lesion (Simon *et al*. 2006).

In dental implantology, periapical radiography can provide a useful initial view. However, the limitations of this application must be well understood. These 2D views obviously provide no cross-sectional information. For example, submandibular and sublingual fossae and the morphology of the alveolar recess of a maxillary sinus base are not accurately appreciated, but are well demonstrated with MCT and CBCT (Figs. 30-38, 30-39, 30-40, 30-41, 30-42, 30-43). Assuming a paralleling technique, the residual ridge and implant orientation may not be at the same "angle" as the intended implant. Only a small area of jaw is imaged unless multiple views are obtained. The relative inaccuracy of periapical radiography generally, compared to MCT and CBCT, must be recognized (Furhmann *et al*. 1995; Langen *et al*. 1995; Williams *et al*. 2006; Mol & Balasundaram 2008; Vandenberghe *et al*. 2008). CBCT and MCT have also been shown to more accurately identify the mandibular canal than the periapical radiograph (Klinge *et al*. 1989; Lindh *et al*. 1992). While appreciating the availability of radiologic equipment, it should be noted that the planning of an implant solely based upon a periapical radiograph is no longer considered an appropriate standard of care in several parts of the world.

The periapical radiograph remains an important technique in post-implant imaging, although the difficulties in obtaining these views are recognized. While it has been shown to accurately demonstrate peri-implant defects (De Smet *et al*. 2002; Corpas Ldos *et al*. 2011), only the proximal bone is demonstrated, unlike with volumetric techniques (Figs. 30-46, 30-47). However, it has the advantage of absence of image artifacts associated with implants, unlike as often seen on CBCT (Pauwels *et al*. 2013) and also MCT studies (Figs. 30-48, 30-49). If clinically indicated, the periapical radiograph can still be useful even if the entire implant cannot be included in the

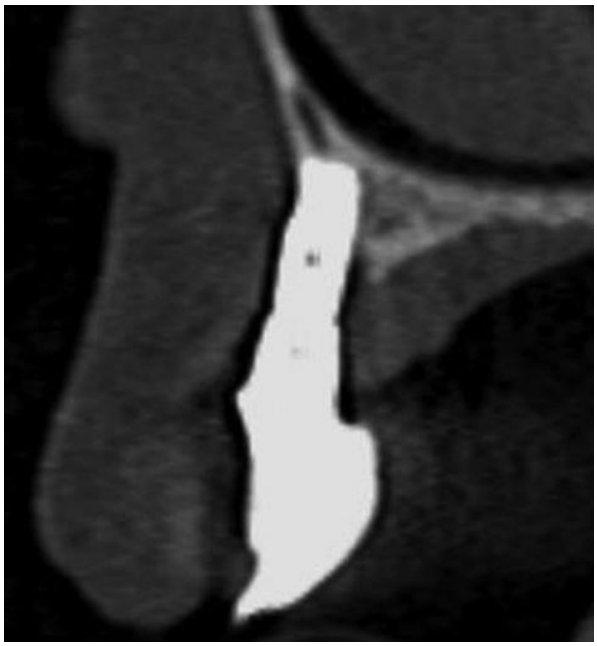


Fig. 30-46 Cross-sectional low-dose MCT image demonstrates moderate-to-severe peri-implant bone loss associated with the tooth site 13 implant.

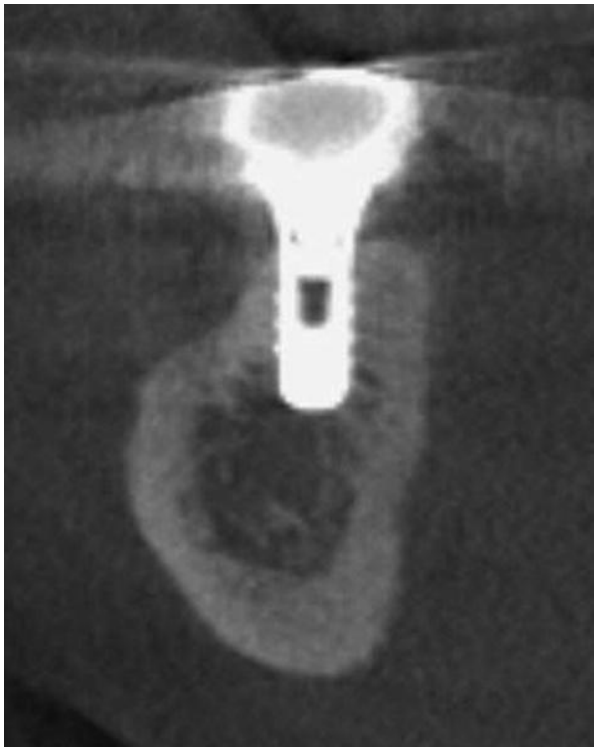


Fig. 30-47 Cross-sectional low-dose CBCT image of a mandibular posterior implant, demonstrating no associated focal osseous abnormality buccally and lingually. The separation of the implant apex and the mandibular canal is accurately appreciated.

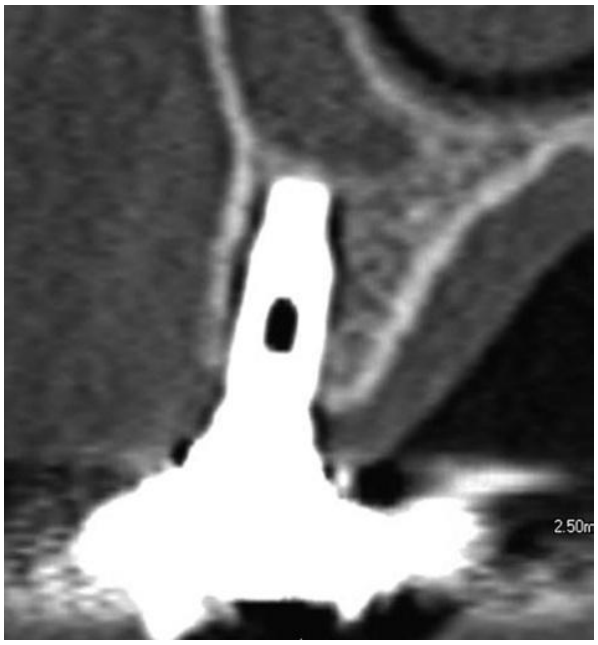


Fig. 30-48 Cross-sectional low-dose MCT image of a tooth site 15 implant demonstrates the lucent artifact immediately adjacent to the implant.

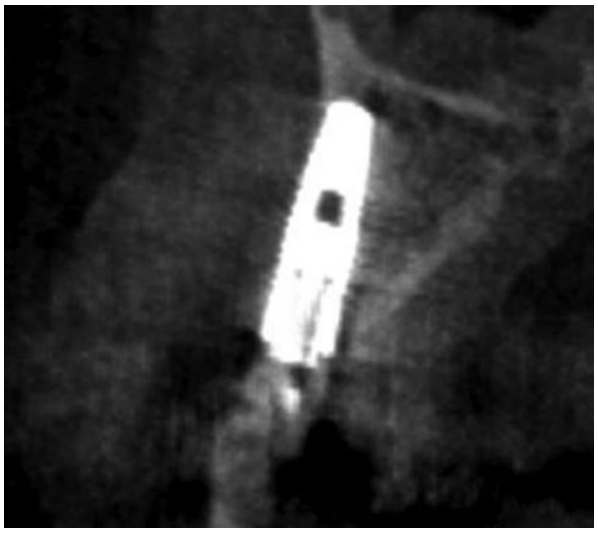


Fig. 30-49 Cross-sectional low-dose CBCT image of a tooth site 12 implant demonstrates largely absent labial bone over this implant. Note the beam hardening artifact typical of CBCT.

FOV, as long as the detector is parallel to the implant and the central X-ray beam is perpendicular to both. MCT and CBCT should be considered if the intraoral radiograph does not provide the information required for diagnosis, as discussed in the relevant section below.

With some implant systems, intraoral radiographs can be useful in confirming the optimal position of the abutments. An optimal paralleling technique is required.

Panoramic radiographs

The panoramic radiograph is a unique form of conventional tomography. Like conventional tomography, this technique relies on motion of the detector and the X-ray tube during image capture. Motion unsharpness results in more blurring of the structures that are not in the plane of interest. The panoramic radiograph is essentially a thick curvilinear tomogram where the plane of interest is curved along the line of the alveolar arches. Therefore, it only provides 2D information, with no cross-sectional information for the arches.

In addition to the limitations of 2D views already discussed in relation to intraoral radiography, there are further well-known and substantial limitations of panoramic radiography, including:

- Lower resolution
- Overlapping structures, for example C-spine, soft tissues, air spaces
- Objects outside the focal trough are not imaged
- Ghost images
- Double images
- Magnification:
  - Machine dependent
  - Unpredicatable, even with the same patient in the same machine
  - Uneven magnification within one single image
- Image distortion
- Objects nearer the film/detector (buccal) are narrowed
- Lingual objects appear more superior
- Varying foreshortening and elongation
- No 3D information on:
  - Ridge width and orientation
  - Submandibular fossa
  - Incisive fossa
  - Mandibular canal location
  - Mental foramen
  - Incisive canal and foramen
  - Maxillary sinus
  - Floor of nasal cavity.

The challenges associated with the accurate interpretation of a panoramic radiograph are often underestimated, and incorrect interpretation is often related to a lack of understanding of the many limitations. For example, many structures depicted on a panoramic radiograph are not sufficiently well demonstrated to rule out the presence of pathology nor evaluate the nature of the disease (Figs. 30-8, 30-50). Another common error arises from lack of understanding of the specific projection angle at one specific point of the image, which changes throughout and is usually horizontally and vertically oblique. For example, the orientation of an impacted tooth seen on a panoramic radiograph is often not a true reflection (Fig. 30-51). Limited knowledge of the radiologic anatomy and insufficient knowledge of all pathologies (including the radiologic features) which could arise or manifest within the orofacial structures included in these views, also contribute to potentially erroneous interpretation.

In addition to the limitations associated with intraoral radiography, the substantial limitations of

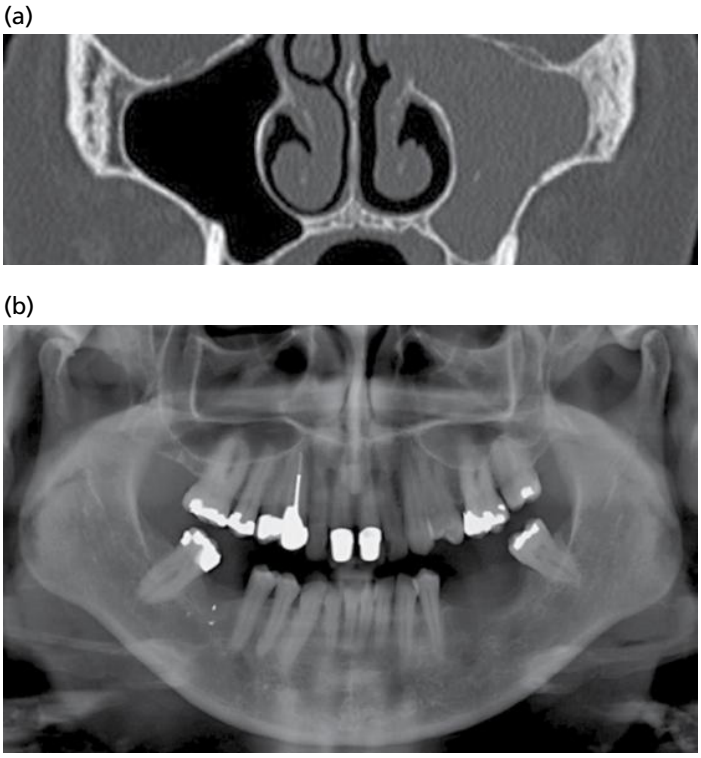


Fig. 30-50 (a) Opacified left maxillary sinus extending into the left ostiomeatal unit with sclerotic sinus walls and internal opacities is demonstrated on the coronal MCT image. This appearance is compatible with chronic inflammatory disease where there may be fungal superinfection. (b) This left maxillary sinus disease is not appreciated on the panoramic radiograph, highlighting the many and substantial limitations of panoramic radiographs, including for evaluation of the maxillary sinuses.

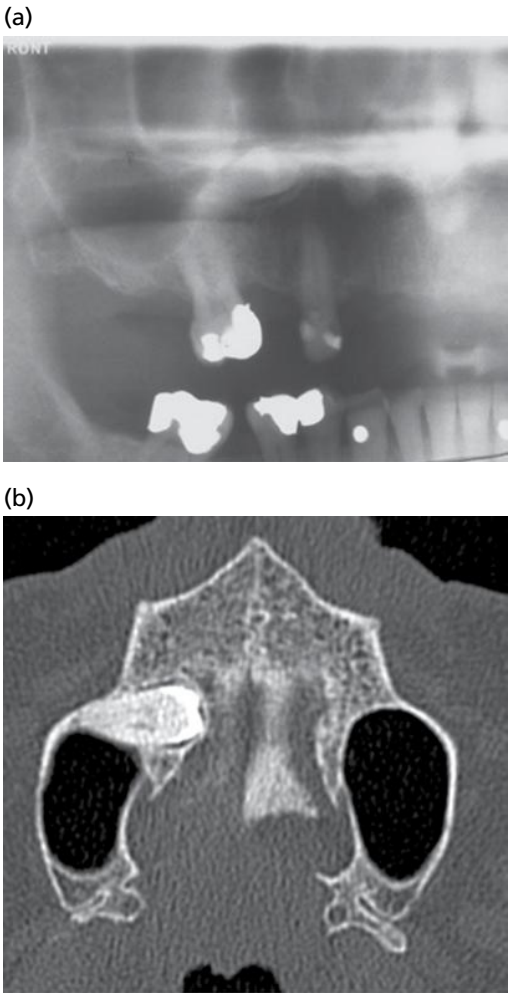


Fig. 30-51 (a) Cropped panoramic radiograph demonstrates an impacted right maxillary premolar with the crown directed mesially, which does not reflect the true orientation, related to the obliquity of the projection typical of these views. (b) True orientation of this premolar, with crown directed medially, is demonstrated on the axial low-dose MCT image.

the panoramic radiograph described also apply in the evaluation of periodontal bone (Fig. 30-29). Also of note, the vertical magnification of teeth varies within the single panoramic image (Thanyakarn *et al*. 1992), which can result in incorrect estimates of periodontal bone loss.

While the panoramic radiograph is useful in providing a rough estimate of the size of a lesion within a jaw, it has substantial limitations when a more accurate evaluation of the 3D relationship of structures and dimensional accuracy is required (Thanyakarn *et al.* 1992; Bou Serhal *et al*. 2002; Sharan & Madjar 2006). Its application in final implant planning is therefore limited. It had been suggested that, if a larger error is allowed for measurements, panoramic views remain useful for final implant planning (Vazquez *et al*. 2008). However, not being able to appreciate structures in the third dimension remains a significant issue. Examples include the inability to accurately appreciate important morphologic variations such as the submandibular, sublingual, and other fossae (Figs. 30-40, 30-41, 30-45), and variations in the extent and morphology of the alveolar recesses of the maxillary sinuses (Fig. 30-43).

It is also well known that the mandibular canal is not infrequently difficult to identify on a panoramic view. In addition, on the panoramic view, a mandibular canal which is located towards the buccal aspect of the body of the mandible will give the impression of a larger available vertical distance from the ridge crest. This is related to the typically negative vertical angle of the X-ray tube. It has been shown that MCT is superior in accurately identifying the precise location of the mandibular canal (Klinge *et al*. 1989; Lindh *et al*. 1992) and the normal variants of these canals (Naitoh *et al* 2007). The superiority of MCT and CBCT over the panoramic radiograph in implant planning is more thoroughly discussed in the section on MCT and CBCT below.

While recognizing that access to imaging equipment and appropriate radiologic support can be the limiting factor, it should be noted that the planning of implants from just panoramic and intraoral radiograph is no longer considered the appropriate standard of care in many parts of the world. The possibility of complications, including inferior alveolar nerve injury and life-threatening hemorrhage, should be considered given the relatively elective nature of implant placement, in contrast to, for example, the surgical excision of a tumor or enucleation of a cyst.

With regards to post-implant imaging, the discussed limitations of the panoramic radiograph also apply, in addition to those associated with intraoral radiography. The panoramic radiograph may provide a useful initial evaluation of peri-implant bone, with the view to further periapical radiographic, CBCT or MCT examinations, as indicated.

The importance of identifying the presence of other dentoalveolar diseases in the radiologic examination of the periodontal and implant patient has already been discussed. It is accepted that periapical lesions are not as well identified on panoramic radiographs as on periapical radiographs (Rohlin *et al*. 1989). Indeed, MCT and CBCT are superior to periapical and panoramic radiographs in identifying these lesions (Velvart *et al*. 2001; Huumonen *et al*. 2006; Lofthag-Hansen *et al*. 2007; Stavropoulos & Wenzel 2007; Estrela *et al*. 2008; Low *et al*. 2008). It should also be recognized that the intraoral radiographs are superior to panoramic radiographs in the identification of caries, the bitewing being superior to the periapical radiograph (Akarslan *et al*. 2008).

In summary, the panoramic radiograph remains a useful modality, especially for initial overall evaluation. However, its substantial limitations must be well understood. Incorrect interpretation and inappropriate application of this view, without due regard to the significant inaccuracies, can lead to erroneous diagnosis with disastrous consequences.

Conventional tomography

As described earlier, conventional tomography relies on the motion of both the detector and the X-ray tube during image capture. The motion unsharpness results in most blurring of the structures furthest from the plane of interest and least blurring for those within the plane in interest. It has traditionally been applied to the study of high-contrast structures, for example the temporomandibular joint, and in implant planning.

While providing information in the cross-sectional plane, conventional tomography has now been largely superseded by MCT and CBCT. The limitations of conventional tomography include:

- Low resolution
- Parasite lines in linear tomography
- Objects close to the plane of interest are less blurred and may still be seen, for example an adjacent mandibular torus
- Thin slices (e.g. 1 mm) are not practical and resultant images are usually not diagnostic
- Thick slices (e.g. 3 mm or thicker) can result in:
  - Increased superimposition of adjacent structures
  - Phantom images: apparent structures that do not exist, related to superimposition of repetitive structures outside the of plane of interest, for example trabeculae and teeth
- Time consuming and patient discomfort.

The angle of the tomographic section at the site of interest is decided by the radiographer. There is no reliable way in which the clinician can verify this angle, which may not be the same as the angle intended for implant placement. Errors and need for repeats with this technique are not uncommon, related to the precision required for implant planning. Compared to modern-day low-dose CBCT and MCT (with appropriate protocols), the potential benefit of the lower radiation dose levels associated with conventional tomography is questionable. Conventional tomograms for implant planning require careful interpretation as the anatomic structures are not always easily identified. The position of the mandibular canal is more accurately identified on MCT (Klinge *et al*. 1989; Ylikontiola *et al*. 2002).

Multislice/multidetector computed tomography and cone-beam computed tomography

In any discussion regarding radiographic equipment, the pace of evolution of this technology and the relative lag in peer-reviewed published studies must be recognized. While this applies to most technologies, it is particularly true of MCT and CBCT.

In simple terms, MCT uses finely collimated, flat, fan-shaped beams which rotate around the patient in a helical progression to acquire slices of image data. In contrast, CBCT machines employ a divergent cone/pyramidal-shaped beam, obtaining multiple planar projections (similar to traditional 2D radiographic images) in a single rotation. These cone-shaped beams are similar to those of X-ray units for 2D radiography. With both MCT and CBCT, computers are used to reconstruct 3D information from the acquired raw data, typically employing a back-projection algorithm. Many modern MCT machines are able to employ iterative reconstruction, which may allow for even lower dose imaging.

Review papers comparing CBCT and MCT technology (Koong 2010) provide more detail; the essential considerations are discussed below.

Presently, CBCT machines have been reported to produce images with a voxel resolution range of 0.076–0.4 mm (Scarfe *et al*. 2008; White 2008). However, this higher resolution of CBCT compared to MCT can be significantly reduced by other factors (Draenert *et al*. 2007; Sanders *et al*. 2007; Watanabe *et al*. 2011).

MCT scans are performed with patients in a supine position, while most of the presently used orofacial

CBCT units acquire image data with patients standing or sitting. In addition, for a similar volume, MCT scans acquire data faster than CBCT. Therefore, the potential motion-related image degradation is higher with CBCT.

With CBCT, a substantially larger volume of orofacial structures is irradiated during each planar basis projection and large area detectors are used. These result in a much larger amount of Compton scatter, significantly increasing image noise compared to MCT. This noise, combined with the typically lower energy photons of CBCT, result in a significantly lower signal-to-noise ratio compared to MCT. Therefore, CBCT images can be more difficult to evaluate, since the structures of interest do not "stand out" as much from the increased "background noise", compared to MCT. This smaller variation between usually more radiodense and less radiodense structures is typical of CBCT images; in other words the image is "flatter". This must be considered when interpreting CBCT studies. For example, sclerosis may not be as easily appreciated on CBCT compared to MCT.

Beam hardening is usually a significant disadvantage of CBCT compared to MCT (Draenert *et al*. 2007; Sanders *et al*. 2007), again related to the typically low signal nature of CBCT. X-ray beams are typically polychromatic, with a range of photon energies. As the beam traverses the human body, low energy photons are absorbed first, altering the quality of the beam This contributes to the appearance of shadows and bands associated with dense structures. In contrast, beam hardening associated with dense nonmetallic objects is usually not significant on MCT scans of the orofacial structures. For example, these beam hardening artifacts related to gutta percha associated with endodontic therapy are often seen on CBCT (Fig. 30-26) but not on MCT (Fig. 30-24). Beam hardening increases with patient head size and denser structures, especially where these structures are in close proximity (see Fig. 30-60).

Metal artifact (extreme attenuation) from metallic restorations is more significant with MCT than CBCT. However, considering the described limitations of CBCT, including beam hardening (Draenert *et al*. 2007; Sanders *et al*. 2007), the overall weakness in relation to metallic restorations is similar for both techniques (Figs. 30-23, 30-47)

It must be noted that CBCT and MCT image quality varies between different makes and models. However, it is generally accepted that this variation in image quality from different MCT makes and models is smaller. Importantly, it must be recognized that MCT machines offer a far larger range of protocols. Therefore, a substantially larger range in image quality can be delivered by the same MCT unit. CBCT machines typically offer a significantly smaller range of imaging protocol options.

With regard to diagnostic imaging for the planning of implants, both MCT and CBCT allow superior 3D appreciation of the morphology and relevant structures, as well as more accurate measurements of the various relevant dimensions for implant placement, compared to common dental views, including panoramic and intraoral radiography (Klinge *et al*. 1989; Lindh *et al*. 1992, 1997; Ylikontiola *et al*. 2002; Hanazawa *et al*. 2004; Kobayashi *et al*. 2004; Marmulla *et al*. 2005; de Morais *et al*. 2007; Nickenig *et al*. 2007; Naitoh *et al*. 2007; Loubele *et al*. 2008; Suomalainen *et al*. 2008; Kamburoglu *et al*. 2009).

The differences between CBCT and MCT discussed earlier should be considered. With particular relevance to implant planning, measurements for common dental procedures performed on images from MCT and CBCT scans have been shown to be similar and sufficiently accurate (Klinge *et al*. 1989; Hanazawa *et al*. 2004; Kobayashi *et al*. 2004; Loubele *et al*. 2005; Marmulla *et al*. 2005; Suomalainen *et al*. 2008; Kamburoglu *et al*. 2009; Nickenig *et al*. 2010). It is generally accepted that the error is ± 1 mm. However, it should be recognized that studies also demonstrate that, for a small percentage of scans, the error is larger than ± 1 mm. It is suspected that many factors, including observer variations, viewing methods, and the window levels and widths selected, can contribute to these errors. Extreme care to ensure correct imaging and reformatting of MCT and CBCT studies, as well as precise and careful measurements made on the appropriate multiplanar images, are recommended. MCT and CBCT have been shown to be more accurate in identifying important structures (e.g. mandibular canal) and allow for more accurate measurement compared to panoramic and intraoral 2D radiography (Klinge *et al*. 1989; Lindh *et al*. 1992; Ylikontiola *et al*. 2002; Howe 2009; Kamburoglu *et al*. 2009).

Variations in normal anatomy, some of which are well known, have been mentioned previously. The large variation in the morphology of the base of the maxillary sinuses and various extensions of the alveolar recesses are examples. It is well accepted that this variation is much more accurately demonstrated with MCT and CBCT (Fig. 30-43), compared to common dental views, including panoramic and intraoral radiography. Similarly, large variations in the prominences of the submandibular and sublingual fossae are not appreciated on 2D radiography (Figs. 30-38, 30-40, 30-41, 30-45). Life-threatening hemorrhage related to vascular damage at implant surgery following perforation of the mandibular cortex has been reported, emphasizing the importance of precise preimplant knowledge of the mandibular lingual morphology of each specific case (Laboda 1990; Mason *et al*. 1990; Givol 2000).

The considerable variation in the 3D location of the mandibular canal is well known. This canal is more accurately examined with volumetric imaging (Klinge *et al*. 1989; Lindh *et al*. 1992). Other normal variations of neurovascular bundles and the unpredictability of these variants have also been reported, including bifid mandibular canals (Naitoh *et al*. 2009a; Kuribayashi *et al*. 2010; de Oliveira-Santos *et al*. 2011) (Figs. 30-52). The panoramic radiograph does not reliably identify the presence of bifid mandibular

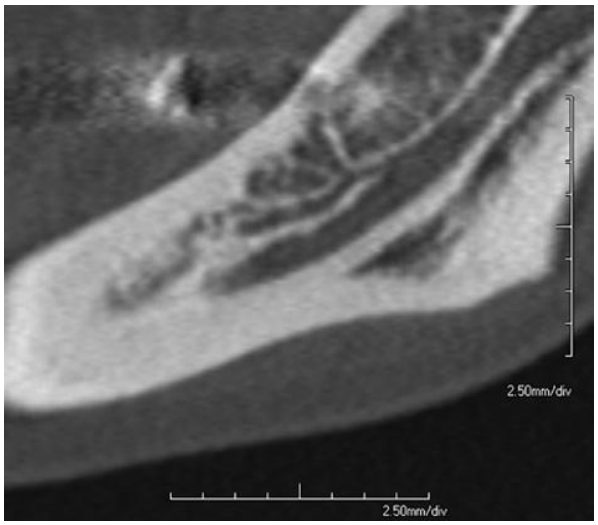


Fig. 30-52 Corrected sagittal low-dose MCT image partially demonstrates a bifid mandibular canal. Multiplanar images are required to fully appreciate this, best performed on a computer.

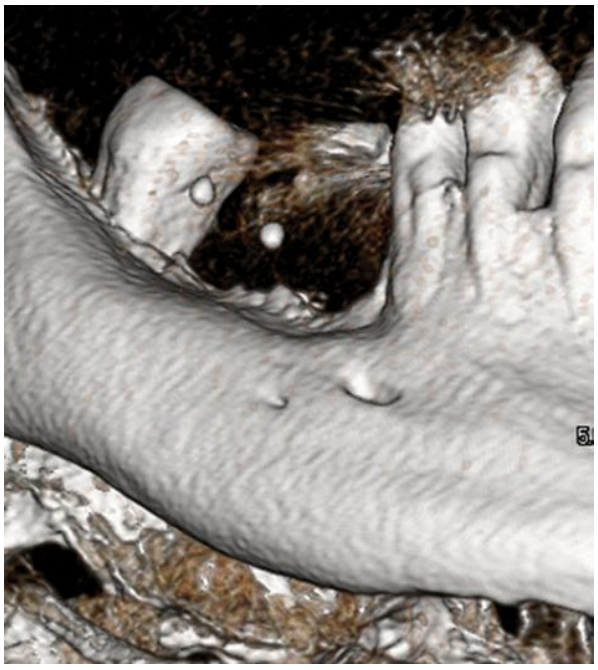


Fig. 30-53 Surface rendered low-dose MCT image demonstrates two right mental foramina.

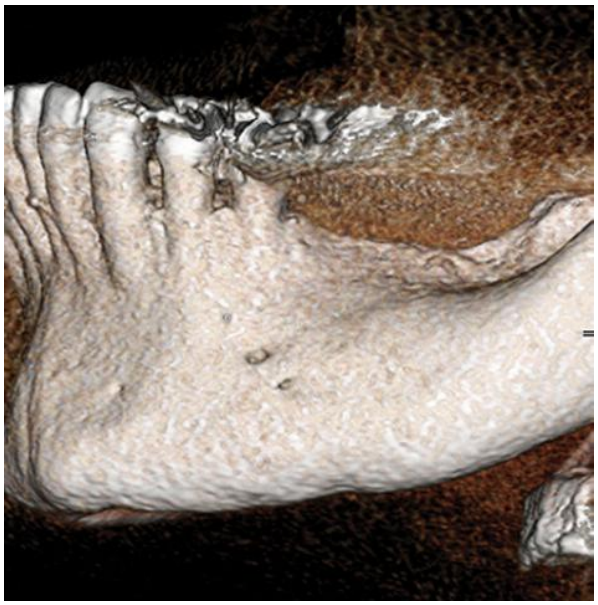


Fig. 30-54 Surface rendered low-dose MCT image demonstrates two left mental foramina.

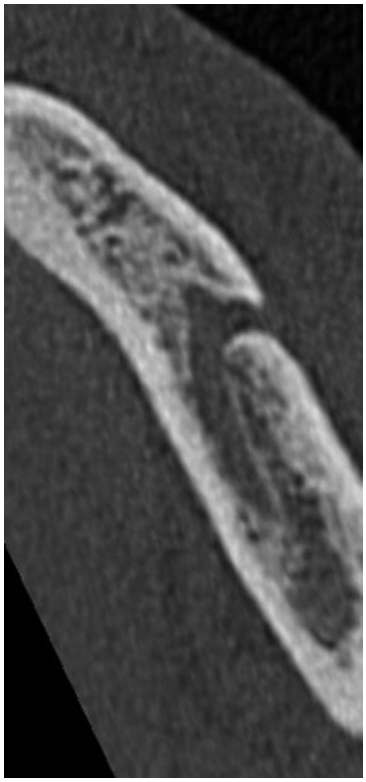


Fig. 30-55 Corrected axial low-dose MCT image demonstrates the anterior loop of the left mandibular canal as it leads to the mental foramen.

canals and volumetric imaging is superior in this respect (Naitoh *et al*. 2007; Kuribayashi *et al*. 2010; Fukami *et al*. 2011; Kim *et al*. 2011). The presence of bifid mandibular canals is more prevalent than generally realized, potentially occurring in between 10% and 20% of the population (Kuribayashi *et al*. 2010; de Oliveira-Santos et al. 2011). This author's experience suggests that the presence of multiple mental foramina is also more common than is generally expected and not appreciated in the panoramic radiograph (Figs. 30-53, 30-54). The anterior aspect of the mandibular canal often traverses anteriorly prior to curving posterobucally and often superiorly to the mental foramen. There is large and unpredictable variation in the extent of this anterior loop of the mandibular canal, and it has been shown that this is not reliably evaluated with the panoramic radiograph (Arzouman *et al*. 1993; Uchida *et al*. 2009; Apostolakis & Brown 2011). This author's experience supports these findings, which can only be accurately evaluated with volumetric techniques (Fig. 30-55).

Lingual neurovascular canals and foramina of the body of the mandible are present in most people (Figs. 30-56, 30-57), with substantial variation in their

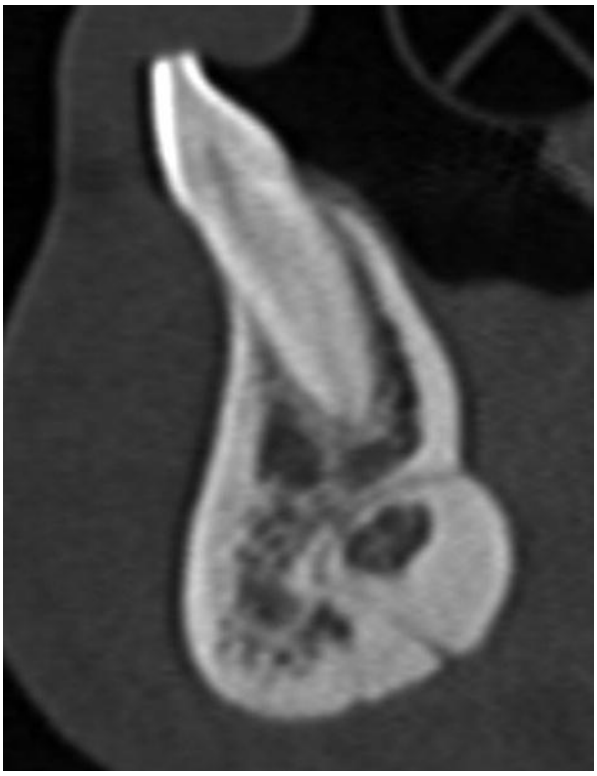


Fig. 30-56 Sagittal low-dose MCT image demonstrates two lingual canals and foramina at the mandibular symphyseal region.

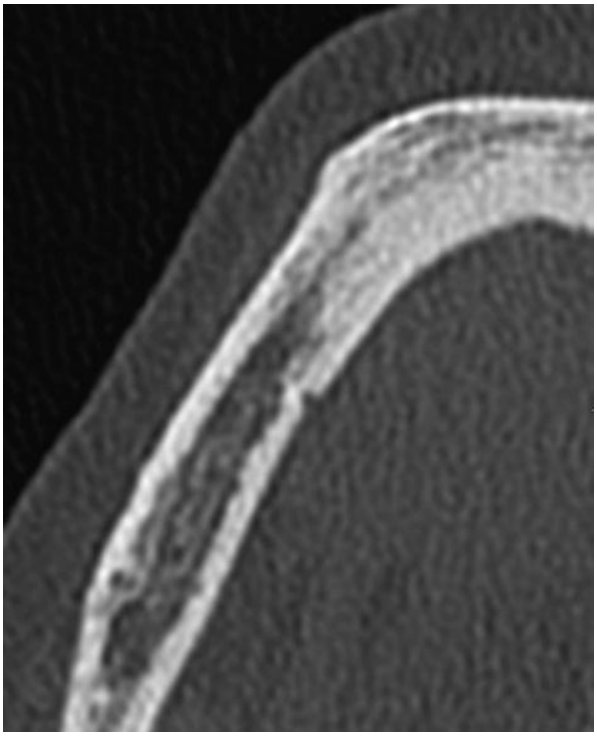


Fig. 30-57 Axial low-dose MCT image demonstrates a lingual canal and foramen of the right body of the mandible. This accessory canal and foramen is best fully appreciated with multiplanar reformatted (MPR) images using a computer.

locations, which is considered to be of surgical relevance because of the possibility of vascular trauma (Liang *et al*. 2006; Vandewalle *et al*. 2006; Liang *et al*. 2007; Katakami *et al*. 2009; Tagaya *et al.* 2009). It is therefore considered important that these lingual canals are identified, and it has been demonstrated that these canals and foramina can only be visualized with MCT and CBCT (Katakami *et al*. 2009; Tagaya *et al.* 2009).

The location of the mandibular incisive canal has been considered to be potentially relevant to implant placement (Jacobs *et al*. 2007); complication from implant placement involving this canal has been reported (Kohavi & Bar-Ziv 1996). Variations in the morphology and width of the maxillary incisive canal are well known (Jacobs *et al*. 2007).

The MCT pixel/voxel value (Hounsfield/CT number) has an almost linear correlation with density (Araki & Okano 2011), and is therefore a useful tool in evaluating bone density in relation to implant placement. In contrast, CBCT voxel values are not absolute and do not have a linear correlation with density (Araki & Okano 2013). This is probably related to the various limitations of CBCT described earlier, including beam hardening and adjacent structures. While some authors suggest that the evaluation of CBCT pixel/voxel density values may still be of some use (Naitoh *et al*. 2009b, 2010a, b; Isoda *et al*. 2012), caution is recommended. CBCT pixel density values perhaps have some application as an extremely rough estimate of bone density.

In post-implant imaging, the limitations of CBCT (Pauwels *et al*. 2013) in relation to adjacent artifacts is recognized. Implant-related artifacts associated with MCT also exist. However, both MCT and CBCT have been shown to accurately evaluate peri-implant defects (Mengel *et al*. 2006). The peri-implant bone density is not well examined with CBCT (Corpas Ldos *et al*. 2011). This author's experience, to date, is that varying degrees of artifact associated with implants are usually seen on MCT and CBCT scans (with machine- and protocol-dependent differences) (Figs. 30-48, 30-49, 30-58, 30-59) Therefore, it is likely that, to varying extents, narrow and subtle peri-implant defects may not be detected and it is often difficult to evaluate peri-implant bone levels. With CBCT, the beam hardening artifact is substantial between two or more implants in close proximity (Fig. 30-60). In this respect, intraoral radiography is superior. The panoramic radiograph may be a useful initial view although, in relation to intraoral radiography, the typical additional limitations apply. While only proximal bone is demonstrated and the entire implant length may not be included in the periapical FOV, it still remains useful, assuming paralleling technique. If imaging is clinically indicated, especially if there is suspicion for the presence of buccal or lingual defects, a need to evaluate the implant position in the buccolingual dimension, unexplained complications or concern for the presence of associated undiagnosed adjacent pathology, MCT or CBCT should be considered (Fig. 30-61).

Periodontal bone loss is more accurately identified and the morphology of the defects is better examined

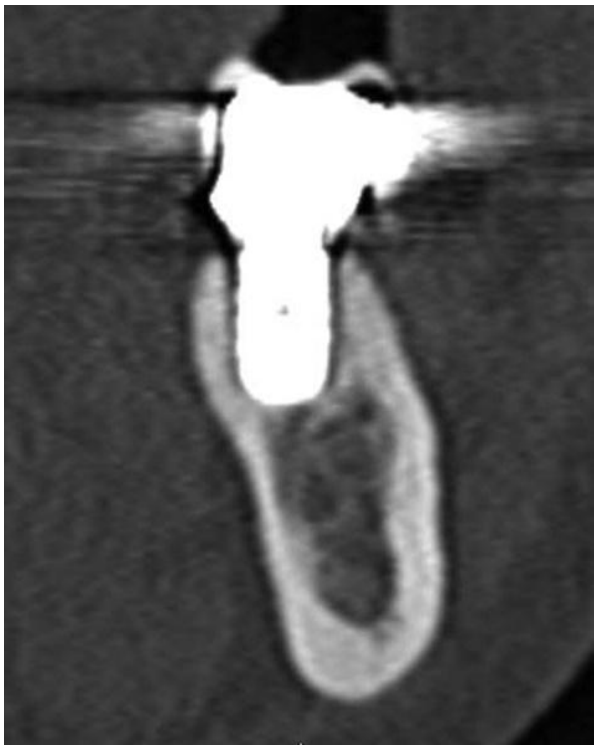


Fig. 30-58 Coronal low-dose MCT image demonstrates the lucent artifact adjacent to the left mandibular implant.

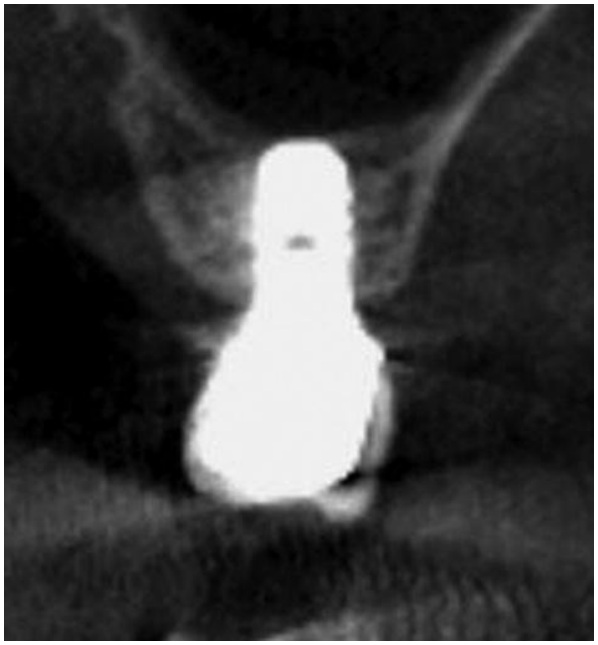


Fig. 30-59 Coronal low-dose CBCT image demonstrates the beam hardening artifact associated with the implant and restoration.

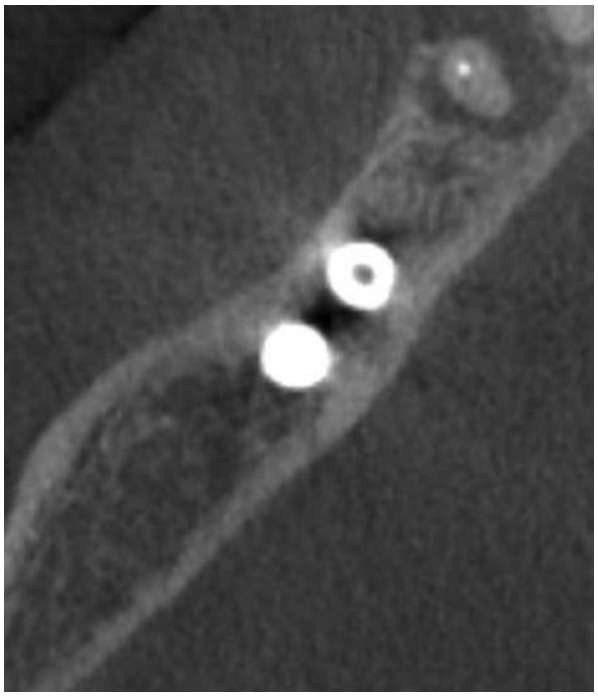


Fig. 30-60 Axial low-dose CBCT image demonstrates the substantial beam hardening artifact between two dense structures; in this case, the two right mandibular implants.

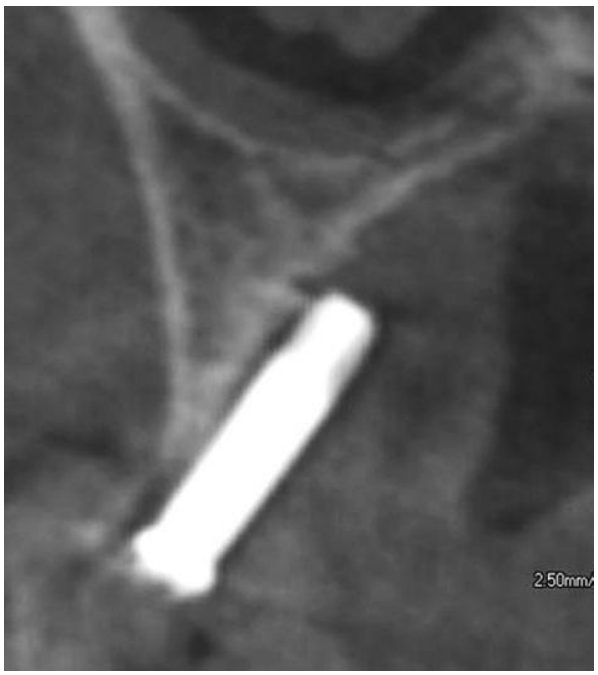


Fig. 30-61 Corrected low-dose CBCT image demonstrates a palatally placed implant which would not be appreciated on 2D radiography. It would be clinically difficult to palpate this implant in view of the thick overlying palatal soft tissue (note the visualized palatal soft tissue profile).

by MCT and CBCT than periapical radiography (Fuhrmann *et al*. 1995; Langen *et al*. 1995; Fuhrmann *et al*. 1997; Mengel *et al*. 2005, Misch *et al*. 2006; Mol *et al*. 2008; Vandenberghe *et al*. 2008). This significant advantage of volumetric imaging over plain 2D radiography and the limitations of the latter have been discussed in earlier sections. The prescription of the optimal modality is based upon the clinical findings and diagnostic needs of a specific case. The importance of thorough knowledge of the various modalities has also been mentioned earlier (refer to the sections on Intraoral radiography and Panoramic radiography).

It is beyond the scope of this chapter to discuss all the potential specific applications of MCT and CBCT. However, the importance of identification of other

dentoalveolar diseases in the radiologic evaluation of the periodontal and implant patient has been discussed. Both MCT and CBCT are superior to periapical radiography in the diagnosis of periapical disease and endodontics (Velvart *et al*. 2001; Huumonen *et al*. 2006; Simon *et al*. 2006; Lofthag-Hansen *et al*. 2007; Mora *et al*. 2007; Nair & Nair 2007; Patel *et al*. 2007; Stavropoulos *et al*. 2007; Low *et al*. 2008).

The inability of CBCT to evaluate caries in the presence of metallic or even radiodense restorations is obvious. In the absence of restorations, studies evaluating the role of CBCT in caries diagnosis seem promising (van Daatselaar *et al*. 2004; Akdeniz *et al*. 2006; Kalathingal *et al*. 2006; Tsuchida *et al*. 2007; Haiter-Neto *et al*. 2008). However, further research studies, especially *in vivo* studies, are required. At present, it remains prudent to employ bitewing radiography when there is an indication for radiologic evaluation for caries.

The soft tissue contrast resolution of current CBCT is poor and is much better with MCT (Watanabe *et al*. 2011). MCT allows evaluation of various soft tissue structures, soft tissue lesions, and also soft tissue changes related to bony lesions. This important diagnostic advantage can be further enhanced with the use of intravenous contrast. This visualization of the soft tissues with MCT can be of significant diagnostic value. For example, orofacial soft tissue lesions (including infections) can present clinically similar to dental infections, which can be demonstrated on an MCT scan but not a CBCT scan. Indeed, MCT can occasionally assist in the identification of the infected tooth, where CBCT and 2D radiography cannot, by demonstrating the location of a soft tissue centred periapical infection, where there are focal cortical fenestrations over a few root apices with no evidence of intrabony periapical lesion. MCT imaging for implant planning can demonstrate adjacent soft tissue lesions with direct surgical relevance to implant planning (e.g. an adjacent arteriovenous malformation with no cutaneous manifestations) and also identify the presence of adjacent serious disease. It should be noted that many soft tissue lesions may be best examined with MRI.

MCT currently remains a more powerful and flexible imaging modality than CBCT in orofacial diagnosis. The advantages of MCT can be critical in the diagnosis of orofacial disease, including dentoalveolar inflammatory disease. It seems prudent to continue evaluating more complex and diagnostically challenging dentoalveolar cases and more serious/significant pathologies with MCT rather than with CBCT. CBCT should be considered in the daily practice of modern clinical dentistry, although there is varying clinical scientific evidence supporting the overall benefits of using CBCT. While the advantages seem obvious, further clinically-based studies are required to confirm these benefits of CBCT, especially in relation to intraoral 2D radiography, panoramic radiography, and MCT. The use of optimal CBCT protocols to produce diagnostic images remains critical. Associated costs, accessibility, and other related factors also require consideration. Rather than replacing other modalities, CBCT complements intraoral 2D radiography, panoramic radiography, MCT, and other techniques, including MRI, ultrasound, and nuclear medicine (Koong 2010). CBCT is not the modality of choice in many clinical scenarios. Indeed, for all cases where CBCT is considered, all other modalities, especially MCT, must also be considered.

Both CBCT and MCT units can export data in DICOM file format standard. This allows both MCT and CBCT data to be viewed with a range of third-party software used for diagnostic and treatment planning purposes, including the creation of 3D models and various applications related to image-guided surgery.

A variety of computer-assisted implant surgery systems based on MCT and CBCT data are available. There is some variation in the application and accuracy of the various computer-guided systems, which are largely favorable, although the final implant position usually does not perfectly correlate with the virtually planned implant position (Eggers *et al*. 2009; Jung *et al*. 2009; Valente *et al*. 2009; Barnea *et a*l. 2010; Pettersson *et al*. 2010; Widmann *et al*. 2010). It is prudent that the clinician is familiar with the accuracy and limitations of any particular system employed. Appropriate training is crucial and the application of this technology does not negate the practice of the usual surgical principles and precautions.

Magnetic resonance imaging

Unlike the other modalities discussed in this chapter, MRI does not employ ionizing radiation. It involves the alignment of the nuclei of many atoms in a strong magnetic field. Radiofrequency pulses are applied, rotating the protons away from the direction induced by the magnet. At the end of the pulse sequence, relaxation occurs and the energy released, in the form of radiofrequency signals, is detected by a receiver coil. The image is then reconstructed (Fourier transform) by a computer.

There are no known biologic side effects associated with MRI. It is particularly useful in the evaluation of soft tissue, generally superior to MCT. Note that soft tissue lesions cannot be evaluated with CBCT. Various MRI sequences can be employed to visualize and highlight different types of tissues and also changes within tissue. For example, it can demonstrate edema within bone marrow, which cannot be identified with MCT or CBCT. The use of intravenous gadolinium allows for further radiologic characterization of lesions.

MRI generally has a lower spatial resolution compared to modern-day MCT and CBCT. More subtle bony changes may be subresolution and not detected. MCT remains the imaging modality of choice for osseous lesions, especially subtle changes. Small

calcific deposits may be undetected on MRI. It can overestimate the extent of tumors, due to the response of adjacent tissues.

Compared to MCT and CBCT, MRI generally involves longer imaging times. Claustrophobia can be an issue for some patients, although modern wider and shorter bore machines have significantly reduced this problem. The presence of ferromagnetic metals usually contraindicates an MRI scan, for example cardiac pacemakers, cerebral aneurysmal clips, and a foreign body within the orbit.

The periodontal bone loss demonstrated on MCT and CBCT studies does not, in itself, mean that the disease is active. MRI can demonstrate the edema associated with current inflammation (Fig. 30-32). On implant imaging, the mandibular canal borders are sometimes not visualized with MCT or CBCT. In these cases, MRI can be useful in identifying the precise location of the inferior alveolar neurovascular bundle.

Comparison of radiation dose levels

The International Commission on Radiological Protection (ICRP) released new tissue weight recommendations for calculating effective doses in 2007 (ICRP 2007). The key change from the previous 1990 recommendations in relation to oral and maxillofacial imaging is the inclusion of the salivary glands (0.01). Therefore, calculated effective doses for orofacial imaging using the 2007 tissue weights are higher than if the 1990 tissue weighting factors are used. Interestingly, this increase is particularly dramatic for the panoramic radiograph, related to the focus of the rotational centers during imaging (Gijbels *et al*. 2001; Ludlow & Ivanovic 2008) Care must be taken when evaluating the literature. For ease of comparison with previous investigations, it may remain necessary to refer to dose calculations based on the 1990 ICRP recommendations, although it must be recognized that these are now not considered to be as accurate as calculations based on the 2007 recommendations.

The range of reported effective doses delivered by orofacial CBCT units is extremely wide; from 6 to 806 μSv (1990 tissue weights) and 27–1073 μSv (2007 tissue weights) (Ludlow *et al*. 2003; Schulze *et al*. 2004; Ludlow *et al*. 2006; Kumar *et al*. 2007; Ludlow *et al*. 2008; Scarfe *et al*. 2008; White 2008; Okano *et al*. 2009; Roberts *et al*. 2009; Suomalainen *et al*. 2009; Davies *et al*. 2012). Compared to MCT, there is substantially less control over CBCT protocols and the wide range of CBCT doses delivered is largely unit specific. Also of importance, some small FOV units deliver larger doses than some larger FOV units. The difficulties associated with making a detailed comparison of the radiation dose levels from various units in published studies is recognized (De Vos *et al*. 2009). This is due to a variety of factors, including variation in device properties, FOV, quality of detectors, frame rates, and image quality. Some of these factors are not easily quantified and it can be overly complex to study and report a comparison of every possible combination of factors associated with various units. Attempts to report these findings in simple tables can be misleading. For example, a study may report that two CBCT units deliver similar doses for approximately the same FOV (i.e. similar volume). However, there may be differences in image quality. The "standard" dose reported for one machine may not produce the optimal image quality for practical clinical application and most operators may routinely employ a different protocol which delivers a much higher dose level than the one reported. Also, one machine may be able to substantially decrease the dose delivered while maintaining diagnostic image quality, while the other is not able to achieve this.

MCT studies of the jaws have been reported to deliver effective doses between 180 and 2100 μSv (1990 tissue weights) and 474–1410 μSv (2007 tissue weights), with substantial variation in scanning protocols (Ngan *et al*. 2003; Loubele *et al*. 2005; Ludlow *et al*. 2008; Loubele *et al*. 2009; Suomalainen *et al*. 2009). While there are differences between various MCT units, the doses delivered for jaw examinations are very much dependent on the imaging protocols.

In comparing MCT and CBCT, it should be noted (from the information provided above) that, where appropriate MCT low-dose protocols are employed, the doses delivered can be lower than those from several CBCT units. It has been demonstrated that appropriate MCT protocols can be employed which substantially reduce radiation dose levels without significantly compromising image quality (Loubele *et al*. 2005). It has also been demonstrated that low MCT doses can indeed be comparable to those delivered by some CBCT units and that MCT may be the imaging modality of choice, given its advantages (Rustemeyer *et al*. 2004). This author's experience supports these findings and indicates that a variety of low-dose MCT protocols can produce diagnostic images for many purposes in dentistry. However, there are currently a few CBCT units which are able to deliver doses that are lower than those achievable with modern-day MCT machines, for the same volume, while maintaining diagnostic image quality. This will, no doubt, change as both CBCT and MCT technology continues to evolve.

The reported effective dose levels delivered by panoramic radiographic machines also vary significantly, with a range of 4.7–54 μSv (ICRP 1990) (Ludlow *et al*. 2003; Ngan *et al*. 2003; Kobayashi *et al*. 2004; Gijbels *et al*. 2005; Gavala *et al*. 2009). Note is made of the dose calculations based on the 1990 ICRP tissue weight recommendations in this instance, to facilitate comparison with older studies. Variation in the curve of the rotational centers likely contributes to the substantial variation between machines (Kaeppler 2008). It should be noted that some recent CBCT units can deliver doses that are lower than those delivered by some panoramic machines, generally the older analog models.

A full-mouth 2D intraoral radiographic series with round collimation has been reported to deliver effective radiation dose levels between 170.7 and 388 μSv (ICRP 2007; Ludlow *et al*. 2008-). It is noted that, based upon the available dose data discussed above, some ultra low-dose CBCT units are able to deliver lower doses than an intraoral 2D radiographic series, depending on the number of 2D projections, technique, and detector employed. Where CBCT is indicated, the employment of ultra low-dose CBCT units is crucial.

The constant and relatively rapid evolution of imaging technology is recognized. It is crucial to emphasize the importance of remaining up to date with these technological advances. Critical evaluation of peer-reviewed publications is necessary, although it has been noted that the comparison of different modalities, makes, and models is a complex task. Simplified summaries and tables usually do not truly reflect the intricacies, full capabilities, and weaknesses of particular makes and models. The lag between published literature and the availability of newly developed technology is also recognized. Therefore, an in-depth understanding of the technology, combined with a review of available valid studies, provides the best opportunity for a balanced evaluation of imaging technology.

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Chapter 31

Patient-Specific Risk Assessment for Implant Therapy

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Introduction

From a patient's perspective, the successful implant is esthetically acceptable, comfortable, low cost, and functional. Practitioners usually discuss implant success in terms of level of marginal bone and absence of deep probing depths and mucosal inflammation. Although the two sets of criteria are not in conflict, they emphasize different points of view. During the consultation visit, before any care is delivered, the practitioner should discuss, based on patient-centered outcomes, what can be expected from the placement of the implant.

A final comprehensive treatment plan should be presented to the patient that includes all recommended dental therapy and alternative treatment options. The patient should also be informed about the sequence of the clinical procedures, risks and costs involved, and the anticipated total treatment time. This discussion between practitioner and patient is critically important in lowering the overall risk of treatment problems. Patients who understand what will be done, and why, are more likely to cooperate with the recommended treatment.

Systemic factors

Patient-based risk assessment begins with taking comprehensive medical and dental histories, as well as conducting a complete examination of the candidate for implant therapy.

A comprehensive medical history should include past and present medications and any substance use or abuse. A standard medical history form filled out and signed by the patient is an efficient way to collect basic information. This should always be followed by an interview to explore in more detail any potential medical risks of implant therapy. If any uncertainties remain regarding the patient's health after the interview, a written medical consultation should be obtained from the patient's physician.

Medical conditions

Osteoporosis

Osteoporosis is a complex group of systemic skeletal conditions characterized by low bone mass and microarchitectural deterioration of bone tissue. Osteoporotic

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bone is fragile and has an increased susceptibility to fracture. Primary osteoporosis is a common condition and is diagnosed when other disorders known to cause osteoporosis are not present. Secondary osteoporosis is diagnosed when the condition is related to, or occurs as a consequence of, osteoporosis-inducing circumstances. These might include diet (e.g. starvation, calcium deficiency), congenital conditions (e.g. hypophosphatasia, osteogenesis imperfecta), drugs (e.g. alcohol abuse, glucocorticoids), endocrine disorders (e.g. Cushing's syndrome), and certain systemic diseases (e.g. diabetes mellitus, rheumatoid arthritis). Osteoporosis is assessed using bone densitometry in which a patient's bone mass or bone mineral density (BMD) is determined. BMD refers to grams of bone mineral per square centimeter (g/cm^2) of bone cross-section.

Scientific evidence indicates that there are no convincing findings that dental implant placement is contraindicated in the osteoporotic patient (Otomo-Corgel 2012). Implants placed in individuals with osteoporosis appear to successfully osseointegrate and can be retained for years (von Wowern & Gotfredsen 2001). However, in cases of secondary osteoporosis there are often accompanying illnesses or conditions that increase the risk of implant failure (e.g. poorly controlled diabetes mellitus, corticosteroid medications). Therefore, in the patient-specific risk assessment, the presence of osteoporosis should alert the clinician to the possible presence of osteoporosis-associated circumstances that are known to increase the risk of implant failure.

Diabetes mellitus

Although there is a slight tendency for more failures of implants in a population with diabetes compared to a non-diabetic population, the increased risk is not substantial in patients who are under good metabolic control (Shernoff *et al*. 1994; Kapur *et al*. 1998; Balshi & Wolfinger 1999; Fiorellini *et al*. 2000; Morris *et al*. 2000; Olson *et al*. 2000).

Patients with diabetes under suboptimal metabolic control often experience wound-healing difficulties and have an increased susceptibility to infections due to a variety of problems associated with immune dysfunctions. Solid clinical evidence, however, for the association of glycemic control with implant failure is lacking (Oates *et al*. 2013). In the risk evaluation of patients with diabetes, it is important to establish the level of metabolic control of the disease. A useful test to determine the level of control over the last 90 days is a blood test for glycosylated hemoglobin (HbA1c). This is a test for the percentage of hemoglobin to which glucose is bound. Normal values for a healthy individual or a patient with diabetes under good metabolic control are HbA1c of <6–6.5% and fasting blood glucose of <6.1 mmol/L (110 mg/dL). Paients with diabetes with HbA1c values of >8% are under poor control and have an elevated risk of encountering wound-healing problems and infection if dental implants are placed.

Immunosuppression

In the early years of the acquired immune deficiency syndrome (AIDS) epidemic, placement of dental implants was ill advised since affected patients developed major life-threatening oral infections. With the advent of effective HAART (i.e. highly active antiretroviral therapy) regimens, most human immunodeficiency virus (HIV)-positive patients who take their medications live for many years without developing severe opportunistic infections. There have been no controlled studies dealing with the risk of dental implant failures in HIV-positive individuals. However, several case reports suggest that placement of dental implants in HIV-positive patients is not associated with elevated failure rates (Rajnay & Hochstetter 1998; Baron *et al*. 2004; Shetty & Achong 2005; Achong *et al*. 2006). Low T-helper (CD4) cell counts (i.e. <200/μL) do not appear to predict increased susceptibility to intraoral wound infections or elevated failure rates of dental implants (Achong *et al*. 2006). Although more studies are needed, it appears that it is safe to place dental implants if the patient's HIV disease is under medical control.

History of radiation therapy to the jaws

Patients who have received radiation (i.e. absorbed dose of ≥60 Gy) to the head and neck as part of the treatment for malignancies are at an increased risk of developing osteoradionecrosis (ORN). Most cases of this complication of cancer treatment are triggered by the extraction of teeth or other oral surgery procedures such as insertion of implants. Implant failure rates of up to 40% have been reported in patients who have a history of radiation therapy (Granström *et al*. 1993; Beumer *et al*. 1995; Lindquist *et al*. 1988; Granström *et al*. 1999). At one time it was believed that ORN was due to vascular derangement and hypoxia of bone cells caused by the tissue-damaging effects of radiation (Teng & Futran 2005). Based on this hypothesis, it has been recommended that oral surgical procedures in patients at risk of ORN be performed in conjunction with hyperbaric oxygen (HBO) therapy. Indeed, Granström *et al*. (1999) reported that use of HBO therapy improved implant survival rates. However, the value of HBO therapy for the management of ORN has been called into question partly based on a placebo-controlled, randomized clinical trial (Annane *et al*. 2004) and other reports showing no advantage from HBO interventions (Maier *et al*. 2000; Gal *et al*. 2003). In addition, a systematic review by Coulthard *et al*. (2008) indicated that there is no high-quality evidence that HBO therapy improves implant survival in irradiated patients.

It is now believed that the pathogenesis of ONR is much more complex than a simple hypoxia-related

phenomenon related to poor vascularity of irradiated tissues. Current evidence supports the view that ONR is a fibroatrophic process (Teng & Futran 2005). From the perspective of risk-assessment procedures for implant placement, patients who have a history of irradiation to the jaws should be considered at high risk for implant failure and HBO interventions will probably not lower that risk.

Hematologic and lymphoreticular disorders

A number of hematologic and lymphoreticular disorders carry an increased susceptibility to periodontitis and other infections (Kinane 1999). Among these disorders are agranulocytosis, acquired neutropenias, cyclic neutropenias, leukocyte adherence deficiency, and aplastic anemia (e.g. Fanconi's syndrome). Since patients with these diseases frequently lose teeth early in life, they often have extensive prosthetic needs that can be met by the placement of dental implants. In the risk-assessment process prior to implant placement, the major concern to be considered is the increased susceptibility to infections that could occur around any implants that might be placed. There are no well-controlled studies of the success rates of implants placed in patients with these disorders. However, implants can be placed if the patient's disease is under control or in remission and a regular supportive therapy program must be an integral part of the overall treatment plan.

Medications

Bisphosphonates

Bisphosphonates are a widely prescribed class of drugs used for the treatment of osteoporosis and to reduce the bone-lytic effects of certain malignancies such as multiple myeloma and metastatic breast cancer (Woo *et al*. 2006). These pyrophosphate drugs are potent inhibitors of osteoclast activity that also have antiangiogenic effects by inhibiting the production of vascular endothelial growth factor (VEGF). The drugs have a high affinity for hydroxyapatite, are rapidly incorporated into all parts of the skeleton, and have a very long half-life (i.e. decades). Relative potencies of the agents depend on their formulation. A complication associated with the use of bisphosphonates is the increased risk of developing osteonecrosis of the jaws [i.e. bisphopsphonate-related osteonecrosis of the jaws (BRONJ)] (Ruggiero *et al*. 2004; Marx *et al*. 2005; Braun & Iacono 2006). The vast majority of cases of BRONJ occur in cancer patients who have received high-potency aminobisphosphonates (e.g. zoledronate, pamidronate) given intravenously to decrease the osteolytic effects of multiple myeloma or malignancies that have metastasized to bone (e.g. breast or prostate cancer).

Of major concern to the prospective implant patient who has been taking an oral bisphosphonate for osteoporosis is the possible risk of developing BRONJ after implant placement. Oral bisphosphonates have been reported to be associated with implant failure (Starck & Epker 1995) and BRONJ (Ruggiero *et al*. 2004; Marx *et al*. 2005; Kwon *et al*. 2014). Since bisphosphonates tightly bind to hydroxyapatite and have a very long half-life, it is likely that the length of time a patient has been taking oral bisphosphonates is important in determining the level of risk. Since oral bisphosphonates slowly accumulate in bone with time, an osteoporosis patient who has been taking the drug for 1 year is at a lower risk of developing BRONJ or implant failure than someone who has been on the drug for many years. It should be kept in mind that bone-remodeling processes are inhibited in patients who have been chronically taking oral bisphosphonates for osteoporosis. Collectively, the duration, route (i.e. oral or intravenous), type of bisphosphonate, and dosage of the medication play an important role in the development of BRONJ (Bornstein *et al*. 2009; Madrid & Sanz 2009a; Otomo-Corgel 2012).

Anticoagulants

Patients who have blood coagulation disorders or are taking high doses of anticoagulants are at an elevated risk of experiencing postoperative bleeding problems after implant surgery. Some patients with coagulation disorders may be at an elevated risk of implant failure (van Steenberghe *et al*. 2003), whereas other patients who chronically take oral anticoagulants can safely receive dental implants (Weischer *et al*. 2005). Patients who are on continuous oral anticoagulant therapy (e.g. coumarin derivatives) to reduce the risk of thromboembolic events and require dental implants for optimal restorative care should be evaluated on a case-by-case basis. Most of these patients can safely continue their warfarin or other anticoagulant therapy when they have standard dental implant surgery (Madrid & Sanz 2009b). In such patients, local bleeding after the placement of dental implants can usually be well controlled by conventional hemostatic methods. The risk of developing life-threatening bleeding or bleeding that cannot be controlled using local measures following placement of dental implants is so low that there is no need to stop oral anticoagulant therapy (Beirne 2005). In addition, the risk of discontinuing anticoagulant medication prior to implant surgery, thereby increasing the probability of thromboembolic events, must be accounted for (Madrid & Sanz 2009b).

Therapeutic levels of an anticoagulant drug such as warfarin are measured by the international normalized ratio (INR), which is the patient's prothrombin time (PT) divided by the mean normal PT for the laboratory (i.e. the PTR). The PTR is then adjusted for the reagents used to arrive at a standardized INR value that will be comparable anywhere in the world. A higher INR reflects a higher level of anticoagulation

with an attendant increased risk of hemorrhage (Herman *et al*. 1997). Although there are insufficient data to draw any evidence-based conclusions, placement of single implants is regarded as safe when the INR target values are 2.0–2.4 (Herman *et al*. 1997).

Cancer chemotherapy

Oral cancer patients are frequently candidates for the placement of dental implants since prostheses designed to replace missing portions of the jaws need to be anchored to implants. Since antimitotic drugs used as chemotherapy for cancer might affect wound healing and suppress certain components of the immune system, it is important to know if these drugs interfere with osseointegration and success of dental implants. In a retrospective study, implant success was compared in 16 oral cancer patients who had no chemotherapy with that in 20 patients who received postsurgical adjuvant chemotherapy with either cisplatin or carboplatin and 5-fluorouracil (Kovács 2001). It was found that these drugs did not have any detrimental effects on the survival and success of implants placed in the mandible. It has also been reported that some cancer patients who received cytotoxic antineoplastic drugs experienced infections around existing dental implants (Karr *et al*. 1992). Therefore, it is important to recognize that many anticancer drugs suppress or kill cells necessary for optimal innate and adaptive immunity. Patients who are receiving cancer chemotherapy should have thorough periodontal and supportive therapy in order to minimize the development of biologic complications.

Immunosuppressive agents

Any medication that interferes with wound healing or suppresses components of innate and adaptive immunity (e.g. corticosteroids) can theoretically increase the risk of implant failure. These drugs are potent anti-inflammatory agents that are widely used for the management of a wide variety of medical conditions, such as after liver transplants (Gu & Yu 2011). They can interfere with wound healing by blocking key inflammatory events needed for satisfactory repair. In addition, through their immunosuppressive effects on lymphocytes, they can increase the rate of postoperative infections. In general, these undesirable effects are greatest in patients who take high doses of the drugs for long periods of time.

Age

In adult patients, age is usually not considered an important risk factor for implant loss. Indeed, most longitudinal studies of survival rates of implants include some subjects who are well over 75 years of age (Dao *et al*. 1993; Hutton *et al*. 1995; Nevins & Langer 1995; Davarpanah *et al*. 2002; Becktor *et al*. 2004; Fugazzotto *et al*. 2004; Karoussis *et al*. 2004; Fransson *et al*. 2005; Herrmann *et al*. 2005; Quirynen *et al*. 2005; Mundt *et al*. 2006; Wagenberg & Froum 2006). An upper age limit is usually not listed as an exclusion criterion in such studies. Several reports indicate that there is no statistically significant relationship between the age of the patient and implant failure (Dao *et al*. 1993; Hutton *et al*. 1995; Bryant & Zarb 1998; Fransson *et al*. 2005; Herrmann *et al*. 2005; Mundt *et al*. 2006; Wagenberg & Froum 2006). It cannot be excluded that there may have been some selection bias in these studies since older patients might have been excluded for medical reasons. On the other hand, older individuals included in these studies may be atypical in that they were healthy enough to be good candidates for implant placement.

In one retrospective study of the success of 4680 dental implants placed by a single surgeon over a 21-year period in 1140 patients, it was reported that increasing age was strongly associated with implant failure (Moy *et al*. 2005). A univariate analysis of the data indicated that compared to patients younger than 40 years (n = 181), patients in the 60–79-year age group (n = 499) yielded a significantly higher risk of implant failure (relative risk 2.24; $P = 0.05$). However, in a multivariate analysis of the data from the entire study population, age was not a significant predictor of implant failure (Moy *et al*. 2005).

Growth considerations

At the other end of the spectrum, a potential problem associated with the placement of dental implants in still-growing children and adolescents is the possibility of interfering with growth patterns of the jaws (Op Heij *et al*. 2003). Osseointegrated implants in growing jaws behave like ankylosed teeth in that they do not erupt and the surrounding alveolar housing remains underdeveloped. Dental implants may be of great help to young people who have lost teeth due to trauma or have congenitally missing permanent teeth. However, because of the potential deleterious effects of implants on growing jaws, it is highly recommended that implants are not placed until craniofacial growth has ceased or is almost complete (Thilander *et al*. 2001).

Untreated periodontitis and oral hygiene habits

The association between self-performed oral hygiene levels and peri-implantitis has been shown to be dose-dependent (Ferreira *et al*. 2006). Partially edentulous patients with very poor and poor oral hygiene are at statistically significantly higher risks of developing peri-implant mucositis and peri-implantitis compared with patients with proper plaque control (Ferreira *et al*. 2006). A direct cause–effect relationship between a 3-week period of abolished oral hygiene practices with experimental plaque accumulation

and the development of peri-implant mucositis has been shown in humans (Pontoriero *et al*. 1994; Zitzmann *et al*. 2001; Salvi *et al*. 2012). A period of 3 weeks of resumed oral hygiene practices followed the experimental plaque accumulation period (Salvi *et al*. 2012). Despite resumed optimal plaque control, however, 3 weeks of wound healing were insufficient to re-establish pre-experimental levels of peri-implant mucosal health (Salvi *et al*. 2012). Furthermore, it has been shown that partially edentulous patients with high plaque scores before implant placement experience more implant losses than those with lower plaque levels (van Steenberghe *et al*. 1993).

Based on this evidence, it may be postulated that, if left untreated, peri-implant mucositis may lead to progressive destruction of peri-implant marginal bone (i.e. peri-implantitis) and, eventually, implant loss.

Moreover, high percentages of implants diagnosed with peri-implantitis are associated with the presence of iatrogenic factors such as cement remnants (Wilson 2009) and with an inadequate access for self-performed oral hygiene (Serino & Ström 2009). These findings indicate that, in addition to insufficient oral hygiene habits, plaque-retentive factors are related to the presence of peri-implantitis.

Based on this evidence any patient-specific risk assessment should include an evaluation of the patient's ability to maintain high levels of self-performed plaque control (Salvi & Lang 2004).

History of treated periodontitis

Periodontitis-susceptible patients treated for their periodontal conditions may experience more biologic complications and implant losses compared with non-periodontitis patients (Hardt *et al*. 2002; Karoussis *et al*. 2003; Ong *et al*. 2008; De Boever *et al*. 2009; Matarasso *et al*. 2010; Aglietta *et al*. 2011). This observation is of special interest in patients treated for aggressive periodontitis and rehabilitated with dental implants (De Boever *et al*. 2009; Swierkot *et al*. 2012). One implication of these findings is that patients who have lost their teeth because of periodontitis might also be more susceptible to peri-implant infections.

Outcomes from long-term clinical studies of patients with treated periodontal conditions indicated that residual pocket probing depths (PPD) of ≥6 mm, full-mouth bleeding on probing (BoP^+) ≥30%, and heavy smoking (i.e. ≥20 cigarettes/day) represented risk factors for periodontal disease progression and tooth loss over a mean period of 11 years of supportive periodontal therapy (SPT) (Matuliene *et al*. 2008). Moreover, findings from two clinical studies indicated that residual PPD of ≥5 mm and BoP^+ after completion of periodontal therapy represented risk factors for the survival and success rates of implants placed in periodontally compromised patients (Lee *et al*. 2012; Pjetursson *et al*. 2012). In a retrospective case–control study, the effects of periodontal conditions on the outcomes of implant therapy were evaluated in periodontally compromised patients stratified according to the presence of one or more residual PPD of ≥6 mm after a mean follow-up period of 8.2 years (Lee *et al*. 2012). Patients with one or more residual PPD of ≥6 mm displayed a significantly greater mean peri-implant PPD and radiographic bone loss compared with both periodontally healthy and periodontally compromised patients without residual PPD, respectively (Lee *et al*. 2012). Moreover, patients with one or more residual PPD of ≥6 mm had significantly more implants with a PPD of ≥5 mm, BoP^+, and radiographic bone loss compared with either of the other two groups of patients (Lee *et al*. 2012). Residual PPD of ≥5 mm at the end of active periodontal therapy represented a significant risk for the onset of peri-implantitis and implant loss over a mean follow-up period of 7.9 years (Pjetursson *et al*. 2012). In addition, patients enrolled in regular SPT and developing periodontal re-infections were at greater risk for peri-implantitis and implant loss compared with periodontally stable patients (Pjetursson *et al*. 2012).

From a microbiologic point of view, a similar composition of the subgingival microbiota was found in pockets around teeth and implants with similar probing depths (Papaioannou *et al*. 1996; Sbordone *et al*. 1999; Hultin *et al*. 2000; Agerbaek *et al*. 2006). Moreover, evidence exists that periodontal pockets might serve as reservoirs of bacterial pathogens (Apse *et al*. 1989; Quirynen & Listgarten 1990; Mombelli *et al*. 1995; Papaioannou *et al*. 1996; Fürst *et al*. 2007; Salvi *et al*. 2008) that may be transmitted from teeth to implants (Quirynen *et al*. 1996; Sumida *et al*. 2002). Therefore, the risk assessment of patients with a history of treated periodontitis should emphasize the increased risk of developing peri-implantitis and highlight the importance of successful periodontal therapy and regular SPT.

Compliance with supportive periodontal therapy

Based on the fact that biologic implant complications are characterized by etiologic factors similar to those involved in the development of periodontal diseases (Heitz-Mayfield & Lang 2010), it may be assumed that long-term survival and success rates of dental implants can be achieved by applying the same principles used during SPT of natural teeth. Findings from long-term clinical studies demonstrated that compliance with SPT is an essential component for the prevention of disease recurrence (e.g. caries and periodontitis) and tooth loss (Lindhe & Nyman 1984, Ramfjord 1987; Kaldahl *et al*. 1996; Rosling *et al*. 2001; Axelsson *et al*. 2004). Patients treated for advanced periodontitis and subsequently enrolled in a regular SPT program experienced a mean incidence of tooth loss ranging between 2% and 5% over an observation

period of 10 years (Lindhe & Nyman 1984; Yi *et al*. 1995; Rosling *et al*. 2001; König *et al*. 2002; Karoussis *et al*. 2004). On the other hand, lack of compliance with SPT was associated with disease progression and higher rates of tooth loss (Axelsson *et al*. 2004; Ng *et al*. 2011; Costa *et al*. 2012a). In the majority of patients complying with SPT, periodontal disease progression and tooth loss occurred rarely (Ng *et al*. 2011). In non-compliant patients, however, a seven-fold increase in tooth loss due to periodontitis was reported compared with compliant patients (Ng *et al*. 2011). Despite the evident benefits of SPT, however, only a minority of patients complied with the recommended recall intervals (Mendoza *et al*. 1991; Checchi *et al*. 1994; Demetriou *et al*. 1995).

Peri-implant mucositis represents a common finding among patients not enrolled in a regular SPT program including anti-infective preventive measures (Roos-Jansåker *et al*. 2006). Lack of adherence of partially edentulous patients with dental implants to a regular SPT program was associated with a higher incidences of peri-implantitis and implant loss compared with those of compliant patients (Roccuzzo *et al*. 2010; Costa *et al*. 2012b; Roccuzzo *et al*. 2012). In partially edentulous patients, pre-existing peri-implant mucositis in conjunction with lack of SPT was associated with a higher incidence of peri-implantitis over a 5-year follow-up period (Costa *et al*. 2012b). The outcomes of that study (Costa *et al*. 2012b) yielded a 5-year incidence of peri-implantitis of 18.0% in the group of patients with SPT and of 43.9% in the group without SPT. The logistic regression analysis revealed that lack of SPT within the overall patient sample was significantly associated with peri-implantitis with an odds ratio (OR) of 5.92. Moreover, a diagnosis of periodontitis was significantly associated with the occurrence of peri-implantitis in the overall patient sample (OR 9.20) and particularly in patients without SPT (OR 11.43) (Costa *et al*. 2012b). Patients with a history of moderate-to-severe periodontitis and erratic compliance with SPT yielded a significantly higher incidence of implant losses and peri-implant bone loss of ≥3 mm compared with compliant patients after a follow-up period of 10 years (Roccuzzo *et al*. 2010, 2012, 2014). On the other hand, low incidences of peri-implant bone loss and high implant survival rates were reported in patients treated for periodontal disease and enrolled in regular SPT (Wennström *et al*. 2004; Rodrigo *et al*. 2012). Patients attending a SPT program two to three times a year over the 5 years following implant placement experienced a high implant survival rate (i.e. 97.3%), a low amount of bone level changes during the final 4 years (0.02 mm/year), and a low percentage (11%) of implants with >2 mm of bone loss (Wennström *et al*. 2004).

Outcomes of a prospective cohort study with a 5-year follow-up indicated that implants placed in patients with treated periodontal conditions and enrolled in SPT yielded a 20% prevalence of mucositis (Rodrigo *et al*. 2012). In that study (Rodrigo *et al*. 2012), upon diagnosis of mucositis or peri-implantitis, all implants with the exception of one were successfully treated according to a cumulative interceptive anti-infective protocol (Lang *et al*. 1997). In addition, data indicated that patients susceptible to periodontitis who received dental implants as part of their oral rehabilitation displayed a higher rate of compliance with scheduled SPT appointments compared with patients who underwent periodontal surgery without receiving dental implants (Cardaropoli & Gaveglio 2012). Hence, in order to achieve high long-term survival and success rates of dental implants, enrolment in regular SPT including anti-infective preventive measures should be implemented (Salvi & Zitzmann 2014). Therapy of peri-implant mucositis should be considered as a preventive measure for the onset of peri-implantitis.

Smoking history

Smoking is now generally accepted as an important modifiable risk factor for the development and progression of periodontitis (Johnson & Hill 2004). The reasons that smokers are more susceptible to both periodontitis and peri-implantitis are complex, but usually involve impairment of innate and adaptive immune responses (Kinane & Chestnutt 2000; Johnson & Hill 2004) and interference with wound healing (Johnson & Hill 2004; Labriola *et al*. 2005). Based on data from several longitudinal studies on implant survival, cigarette smoking has been identified as a statistically significant risk factor for implant loss (Bain & Moy 1993; Strietzel *et al*. 2007). In addition, smoking has been associated with increased risk for peri-implant marginal bone loss (Lindquist *et al*. 1997; Galindo-Moreno *et al*. 2005; Nitzan *et al*. 2005, Aglietta *et al*. 2011) and postoperative complications after sinus floor elevation and placement of onlay bone grafts (Levin *et al*. 2004). Smoking is such a strong risk factor for implant failure that smoking-cessation protocols are implemented as part of the treatment plan for implant patients (Bain 1996; Johnson & Hill 2004).

Although smoking does not represent an absolute contraindication for implant placement, smokers should be informed that they are at increased risk of implant loss and development of peri-implantitis with OR ranging from 3.6 to 4.6 (Heitz-Mayfield & Huynh-Ba 2009).

Genetic susceptibility traits

Genetic polymorphisms are small variations in base-pair components of DNA that occur with a frequency of approximately 1–2% in the general population (Kornman & Newman 2000). These small variations in genes are biologically normal and do not cause disease. However, gene polymorphisms can affect in subtle ways how different people respond to

environmental challenges. Within the context of risk assessment for implant therapy, they affect how people respond to a microbial challenge and how efficiently their wounds heal.

Polymorphisms in the interleukin-1 (*IL-1*) gene cluster on chromosome 2q13 have been associated with a hyper-responsive inflammatory reaction to a microbial challenge. A specific composite genotype of *IL-1A* and *IL-1B* polymorphisms, consisting of allele 2 of both *IL-1A* −889 (or the concordant +4845) and *IL-1B* +3954 was associated with an increased risk of severe chronic periodontitis in non-smokers (Kornman *et al*. 1997). Several investigators have attempted to determine whether this composite *IL-1* genotype can serve as a risk marker for biologic complications such as marginal bone loss or even implant loss (Wilson & Nunn 1999; Rogers *et al*. 2002; Feloutzis *et al*. 2003; Gruica *et al*. 2004; Jansson *et al*. 2005). All of these reports found that being positive for the composite *IL-1* genotype was not associated with an increased risk of marginal bone loss or other implant-related problems. Hence, based on available evidence, it may be considered premature to recommend a systematic genetic screening of patients who are candidates for implant therapy (Huynh-Ba *et al*. 2008; Dereka *et al*. 2012).

Conclusion

Patient-based risk-assessment represents a process in which an attempt is made to identify factors or indicators increasing the risk of complications that eventually lead to implant loss. Risk assessment of the implant patient is a critically important preamble to treatment planning and if properly done, can minimize the complications associated with dental implants. In many cases, early identification of these factors or indicators makes it possible to avoid or eliminate them, thereby increasing the chances of long-term implant survival and success. Most of the systemic risk factors for implant complications are those that increase the patient's susceptibility to infections or those that interfere with wound healing. Important risk factors that can interfere with wound healing around dental implants are long-term use of bisphosphonates, history of radiation therapy of the jaws, and poor metabolic control of diabetes mellitus. Additional factors such as parafunctional habits (e.g. bruxism) and relationships of the jaws (e.g. vertical and sagittal dimensions) should be included in a comprehensive patient-based risk assessment.

Based on the fact that untreated oral infections can lead to implant complications, it is highly recommended that any endodontic, periodontal, and other oral infections be treated prior to implant placement.

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Part 10: Treatment Planning Protocols

Chapter 32

Treatment Planning of Patients with Periodontal Diseases

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Introduction

Caries and periodontal diseases represent opportunistic infections associated with biofilm formation on the surfaces of teeth. Factors such as bacterial specificity and pathogenicity as well as the disposition of the individual for disease, for example local and general resistance, may influence the onset, rate of progression, and clinical characteristics of the plaque-associated dental disorders. Findings from animal experiments and longitudinal studies in humans, however, have demonstrated that treatment, including the elimination or the control of the biofilm infection and the introduction of careful plaque control measures, in most, if not all, cases results in dental and periodontal health. Even if health cannot always be achieved and maintained, the arrest of disease progression following treatment must be the goal of modern dental care.

The treatment of patients affected by caries and periodontal disease, including symptoms of associated pathologic conditions such as pulpitis, periapical periodontitis, marginal abscesses, tooth migration, etc., may be divided into four different phases:

1. Systemic phase of therapy, including smoking counseling
2. Initial (or hygienic) phase of periodontal therapy, that is cause-related therapy
3. Corrective phase of therapy, that is additional measures such as periodontal surgery and/or endodontic therapy, implant surgery, restorative, orthodontic, and/or prosthetic treatment
4. Maintenance phase (care), that is supportive periodontal therapy (SPT).

Treatment goals

In every patient diagnosed with periodontitis, a treatment strategy including the elimination of the opportunistic infection must be defined and followed. This treatment strategy must also define the clinical outcome parameters to be reached through therapy. Such clinical parameters include:

- Reduction or resolution of gingivitis [bleeding on probing (BoP)]: a full-mouth mean BoP of ≤25% should be reached

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

- Reduction in probing pocket depth (PPD): no residual pockets with a PPD of >5 mm should be present.
- Elimination of open furcations in multirooted teeth: furcation involvement should not exceed 2–3 mm in the horizontal direction
- Absence of pain
- Individually satisfactory esthetics and function.

It must be emphasized that risk factors for periodontitis that can be controlled must be addressed as well. The three main risk factors for chronic periodontitis are improper plaque control, cigarette smoking, and uncontrolled diabetes mellitus (Kinane *et al*. 2006).

Systemic phase

The goal of this phase is to eliminate or decrease the influence of systemic conditions on the outcomes of therapy and to protect the patient and the dental care providers against infectious hazards. Consultation with the patient's physician or specialist should enable appropriate preventive measures to be taken, if necessary. Efforts must be made to stimulate a smoker to enroll in a smoking cessation program. Additional aspects are discussed in Chapters 35 and 36.

Initial (hygienic) phase

This phase represents the major cause-related therapy. Hence, the objective of this phase is the achievement of clean and infection-free conditions in the oral cavity through complete removal of all soft and hard deposits and their retentive factors. Furthermore, this phase should aim at motivating the patient to perform optimal plaque control. The initial phase of periodontal therapy is concluded by a re-evaluation and a planning of both additional and supportive therapies.

Corrective phase (additional therapeutic measures)

This phase addresses the sequelae of the opportunistic infections and includes therapeutic measures such as periodontal and implant surgery, endodontic therapy, restorative and/or prosthetic treatment. The volume of corrective therapy required and the selection of means for the restorative and prosthetic therapy can be determined only when the level of success of the cause-related therapy has been properly evaluated. The patient's willingness and ability to cooperate in the overall therapy must determine the content of the corrective treatment. If this cooperation is unsatisfactory, it may not be worth initiating treatment procedures and there will be no permanent improvement of oral health, function, and esthetics. The validity of this statement can be exemplified by the results of studies aimed at assessing the relative value of different types of surgical methods in the treatment of periodontal disease. Thus, a number of clinical trials (Lindhe & Nyman 1975; Nyman *et al*. 1975; Rosling *et al*. 1976a, b; Nyman *et al*. 1977; Nyman & Lindhe 1979) have demonstrated that gingivectomy and flap procedures performed in patients with proper plaque control levels often result in gain of alveolar bone and clinical attachment, while surgery in plaque-contaminated dentitions may cause additional destruction of the periodontium.

Maintenance phase (supportive periodontal therapy)

The aim of this treatment is the prevention of reinfection and disease recurrence. For each individual patient a recall system must be designed that includes (1) assessment of deepened sites with bleeding on probing, (2) instrumentation of such sites, and (3) fluoride application for the prevention of dental caries (see Chapter 60). In addition, this treatment involves the regular control of prosthetic restorations incorporated during the corrective phase of therapy. Tooth sensitivity testing is to be applied to abutment teeth owing to the fact that loss of vitality represents a frequently encountered complication (Bergenholtz & Nyman 1984; Lang *et al*. 2004; Lulic *et al*. 2007). Based upon the individual caries activity, bitewing radiographs should be incorporated in SPT at regular intervals.

Screening for periodontal disease

A patient seeking dental care is usually screened for the presence of carious lesions by means of clinical and radiographic tools. Likewise, it is imperative that such a patient is screened for the presence of periodontitis as well, using a procedure termed the basic periodontal examination (BPE) [or periodontal screening record (PSR)].

Basic periodontal examination

The goal of the BPE is to screen the periodontal conditions of a new patient and to facilitate treatment planning. BPE scoring will allow the therapist to identify a patient with:

- Reasonably healthy periodontal conditions, but in need of long-term preventive measures
- Periodontitis and in need of periodontal therapy.

In the BPE, the screening of each tooth or implant is evaluated. For this purpose, the use of a thin graduated periodontal probe is recommended. At least two sites per tooth/implant (i.e. mesiobuccal and distobuccal) should be probed using a light force (i.e. 0.2 N). Each dentate sextant within the dentition is given a BPE code or score, whereby the *highest* individual site score is used.

BPE system code

- *Code 0*: PPD ≤3 mm, BoP⁻, no calculus or overhanging fillings (Fig. 32-1a)
- *Code 1*: PPD ≤3 mm, BoP⁺, no calculus or overhanging fillings (Fig. 32-1b).
- *Code 2*: PPD ≤3 mm, BoP⁺, presence of supra- and/or sub-gingival calculus and/or overhanging fillings (Fig. 32-1c).
- *Code 3*: PPD >3 mm but ≤5 mm, BoP⁺ (Fig. 32-1d).
- *Code 4*: PPD >5 mm (Fig. 32-1e).

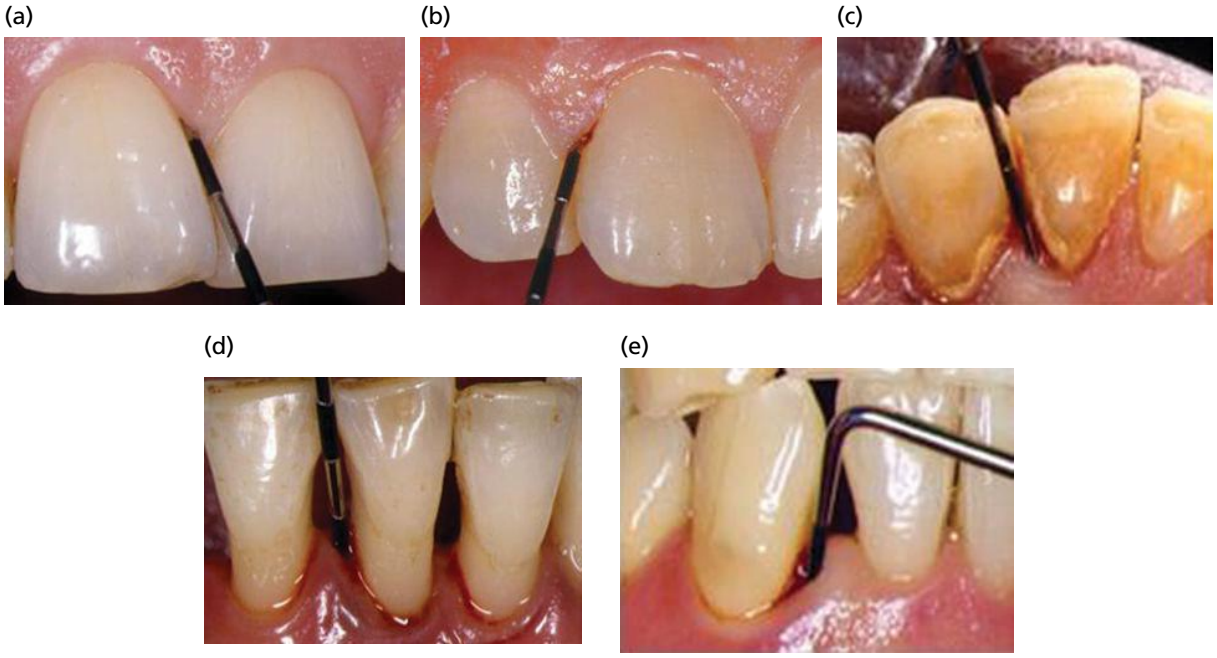


Fig. 32-1 Clinical illustration of the basic periodontal examination scores: (a) code 0, (b) code 1, (c) code 2, (d) code 3, (e) code 4.

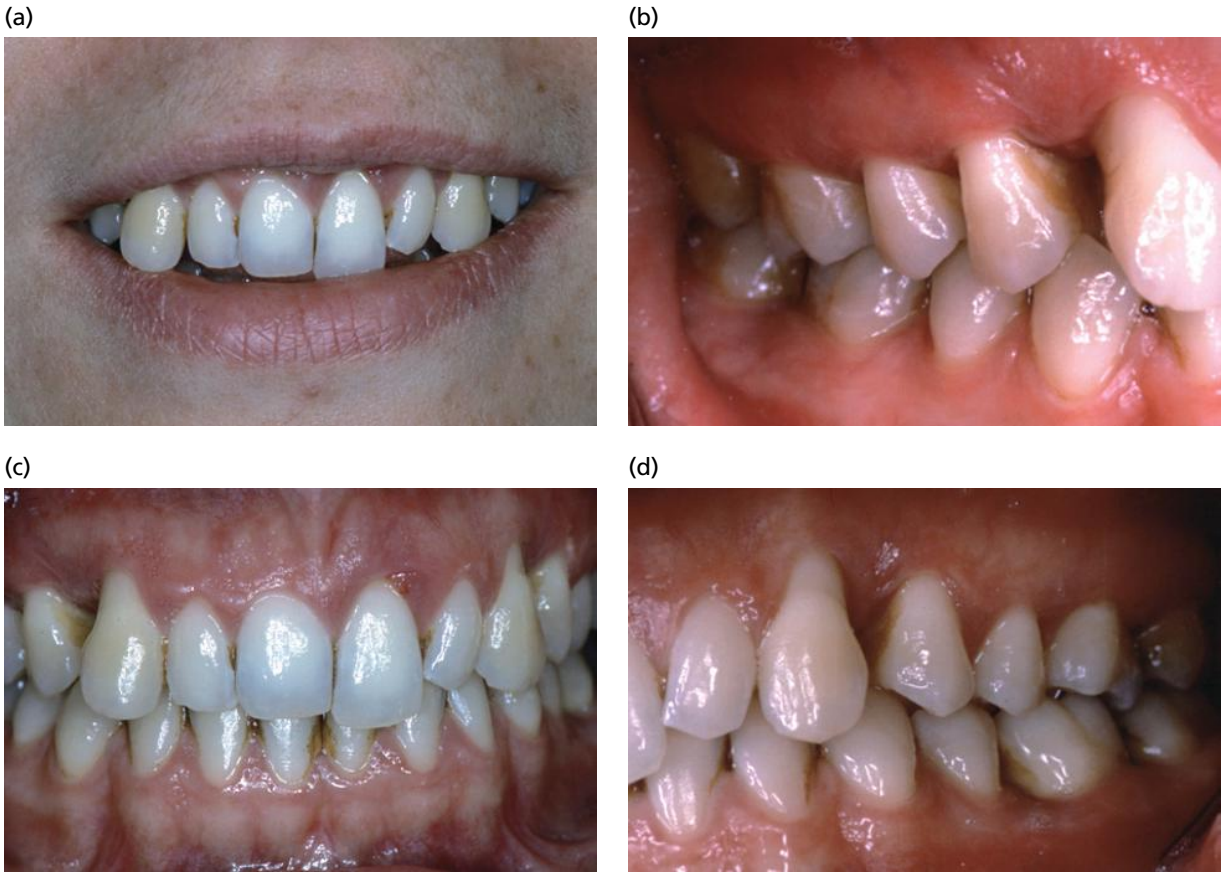


Fig. 32-2 (a–d) Clinical status of a 27-year-old female patient (S.B.) diagnosed with generalized aggressive periodontitis with furcation involvement.

If an examiner identifies one single site with a PPD of >5 mm within a sextant, the sextant will receive a code of 4, and no further assessments are needed in that particular sextant. Patients with sextants given codes of 0, 1 or 2 belong to the relatively periodontally healthy category. A patient exhibiting a sextant with codes of 3 or 4 must undergo a more comprehensive periodontal examination (for details see Chapter 29).

The aim of the following text is to explain the overall objectives of the treatment planning of patients with BPE codes of 3 and 4 undergoing a comprehensive diagnostic process.

Diagnosis

The basis for the treatment planning described in this chapter is established from the clinical data collected from the patient's examination (see Chapter 29). As an example, a 27-year-old female patient (S.B.), who was systemically healthy and a non-smoker, was examined with respect to her periodontal condition: gingival sites displaying signs of *BoP* were identified, *PPD* were measured, the *periodontal attachment level* was calculated, *furcation involvements* were graded, *tooth mobility* was assessed, and the radiographs were analyzed to determine the *height* and *outline* of the *alveolar bone crest*.

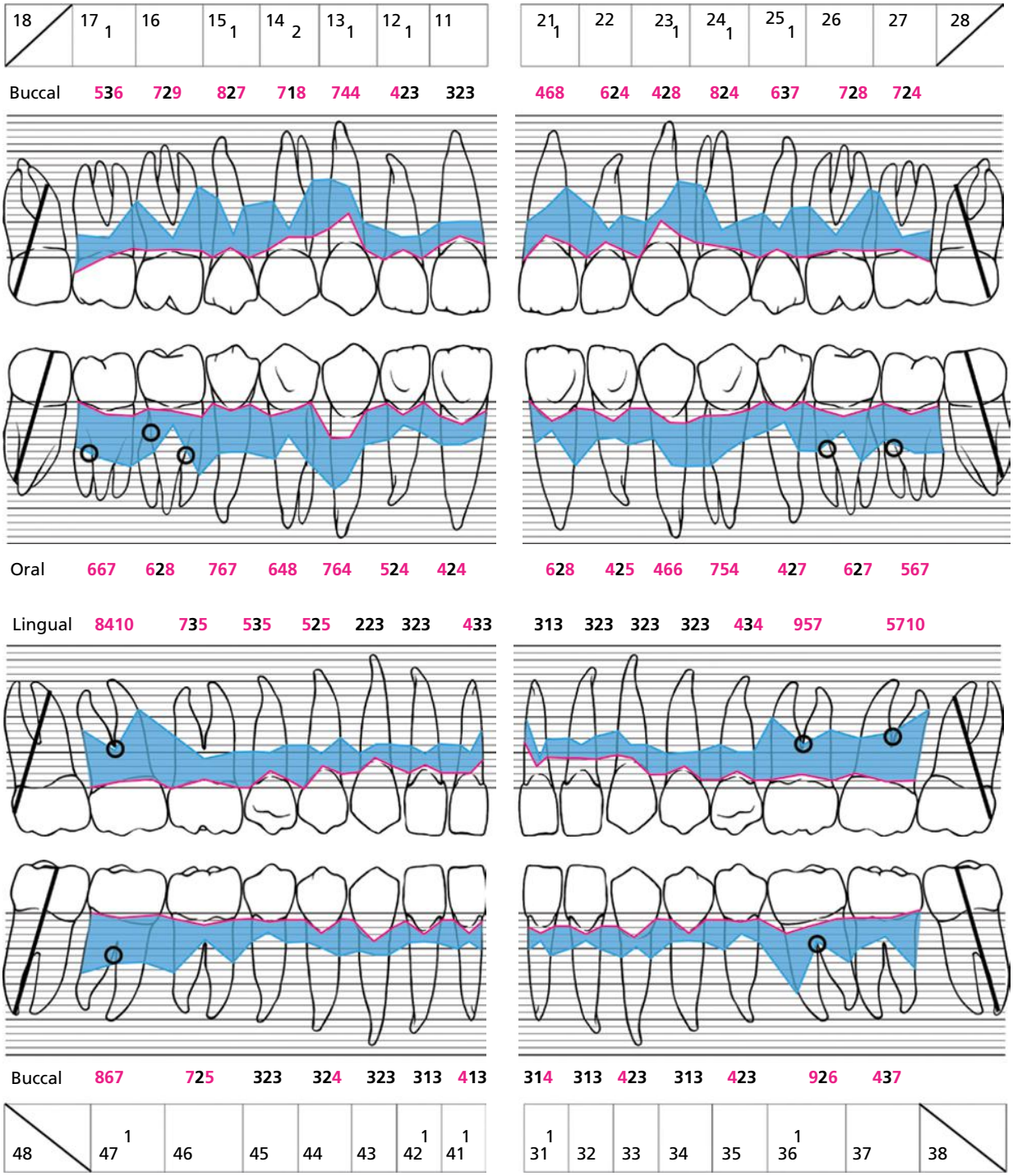


Fig. 32-3 Periodontal chart of the patient presented in Fig. 32-2.

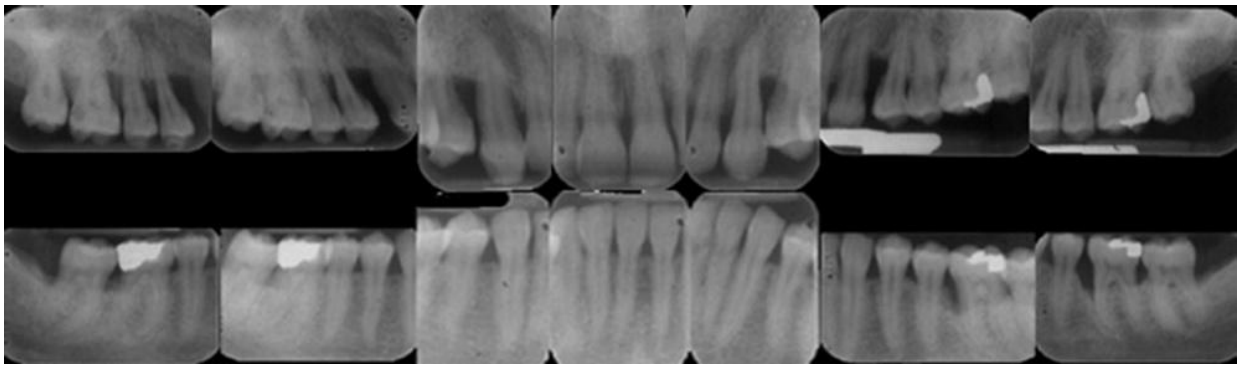


Fig. 32-4 Radiographs of the patient presented in Fig. 32-2.

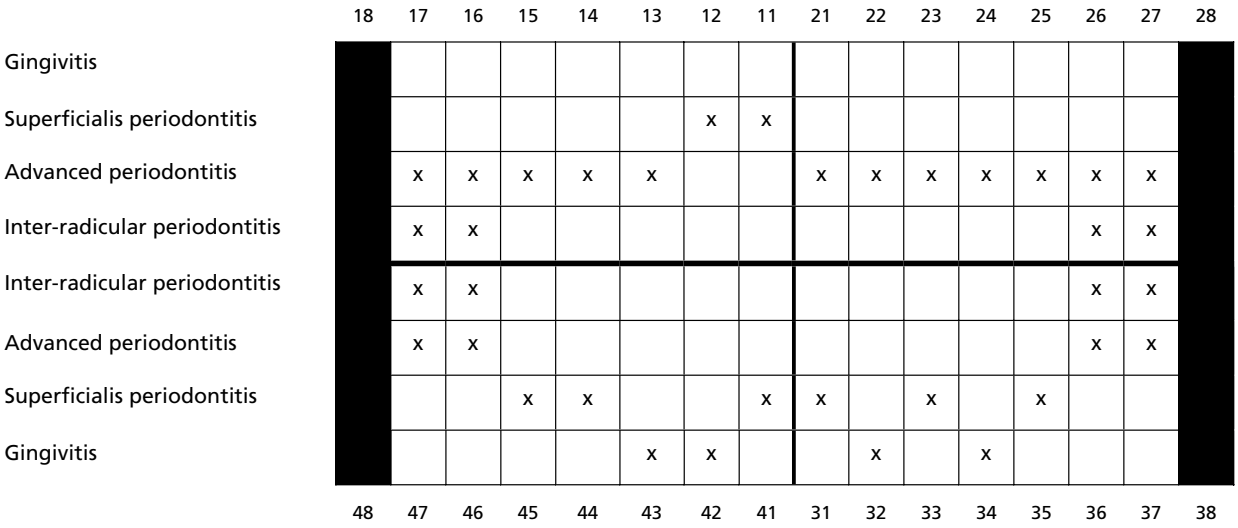


Fig. 32-5 Single tooth diagnosis of the patient presented in Fig. 32-2.

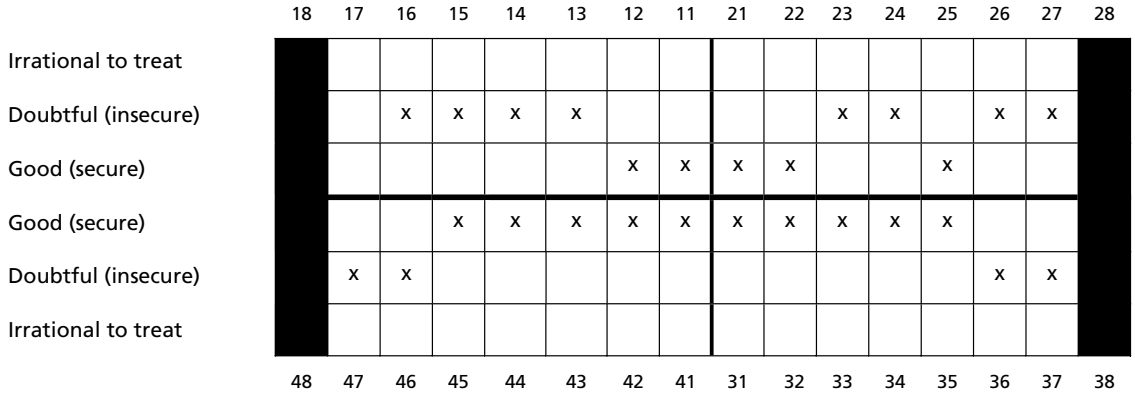


Fig. 32-6 Pretherapeutic single-tooth prognosis of the patient presented in Fig. 32-2.

The clinical characteristics of the dentition of this patient are shown in Fig. 32-2. The periodontal chart and the radiographs are presented in Fig. 32-3 and Fig. 32-4, respectively. Based on these findings, each tooth in the dentition was given a diagnosis (Fig. 32-5) and a pretherapeutic prognosis (Fig. 32-6). In addition to the examination of the periodontal condition, detailed assessments of primary and recurrent caries were made for all tooth surfaces in the dentition. Furthermore, the patient was examined with respect to endodontic and occlusal problems as well as temporomandibular joint dysfunctions.

Treatment planning

Initial treatment plan

Provided that the patient's examination has been completed (see Chapter 29) and a diagnosis of all pathologic conditions has been made, an initial treatment

plan can be established. At this early stage in the management of a patient, it is, in most instances, impossible to make definite decisions regarding all aspects of the treatment sequence, because:

1. *Degree of success of initial therapy is unknown*. The re-evaluation after initial, cause-related therapy forms the basis for the selection of the type of additional therapy. The degree of disease elimination that can be reached depends on the outcome of subgingival instrumentation, but also on the patient's ability and willingness to exercise proper plaque control and to adopt adequate dietary habits.
2. *Patient's "subjective" need for additional (periodontal and/or restorative) therapy is unknown*. When the dentist has completed the examination of the patient and an inventory has been made regarding periodontal disease, caries, pulpal disease, and temporomandibular joint disorders, the observations are presented to the patient (i.e. "the case presentation"). During the case presentation session it is important to find out if the patient's subjective need for dental therapy coincides with the dentist's professional appreciation of the kind and volume of therapy that is required. It is important that the dentist understands that the main objective of dental therapy, besides *elimination of pain, is to satisfy the patient's demands regarding chewing function (comfort) and esthetics*, demands that certainly vary considerably from one individual to another.
3. *Result of some treatment steps cannot be predicted.* In patients exhibiting advanced forms of caries and periodontal disease, it is often impossible to anticipate whether or not all teeth that are present at the initial examination can be successfully treated, or to predict the result of certain parts of the intended therapy. In other words, critical and difficult parts of the treatment must be performed first, and the outcome of this treatment must be evaluated before all aspects of the definitive corrective treatment can be properly anticipated and described.

Pretherapeutic single tooth prognosis

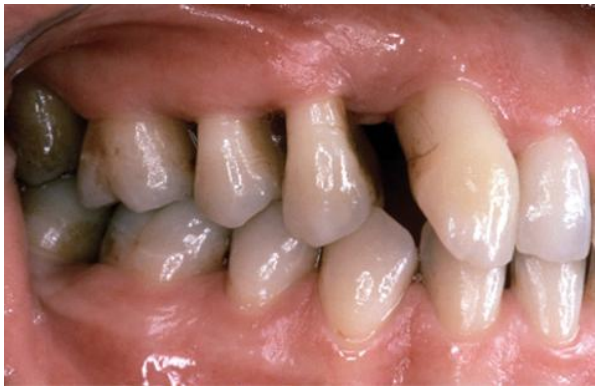
Based on the results of the comprehensive examination, including assessments of periodontitis, caries, tooth sensitivity, and the resulting diagnosis, as well as consideration of the patient's needs regarding esthetics and function, a pretherapeutic prognosis for each individual tooth (root) is made.

Three major questions are addressed:

1. Which tooth/root has a "*good" (safe)* prognosis?
2. Which tooth/root is "*irrational-to-treat*"?
3. Which tooth/root has a "*doubtful" (insecure)* prognosis?

Teeth with a *good* prognosis will require relatively simple therapy and may be regarded as secure abutments for function.

(a)



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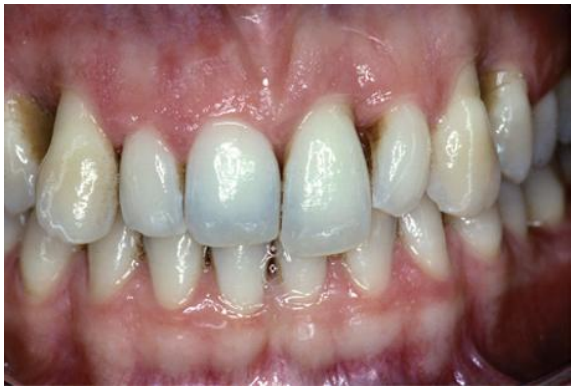

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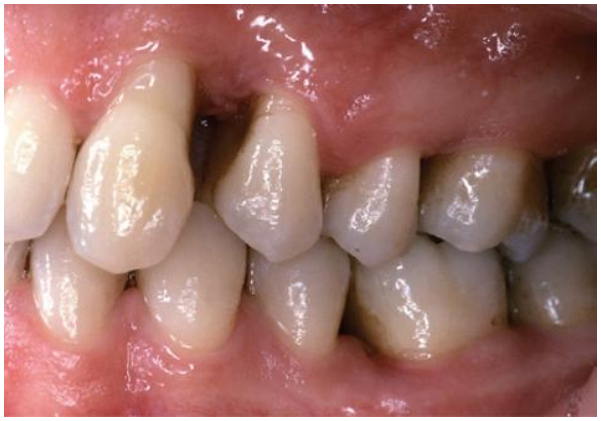


Fig. 32-7 (a–c) Clinical front and lateral views of the patient presented in Fig. 32-2 at re-evaluation after initial periodontal therapy.

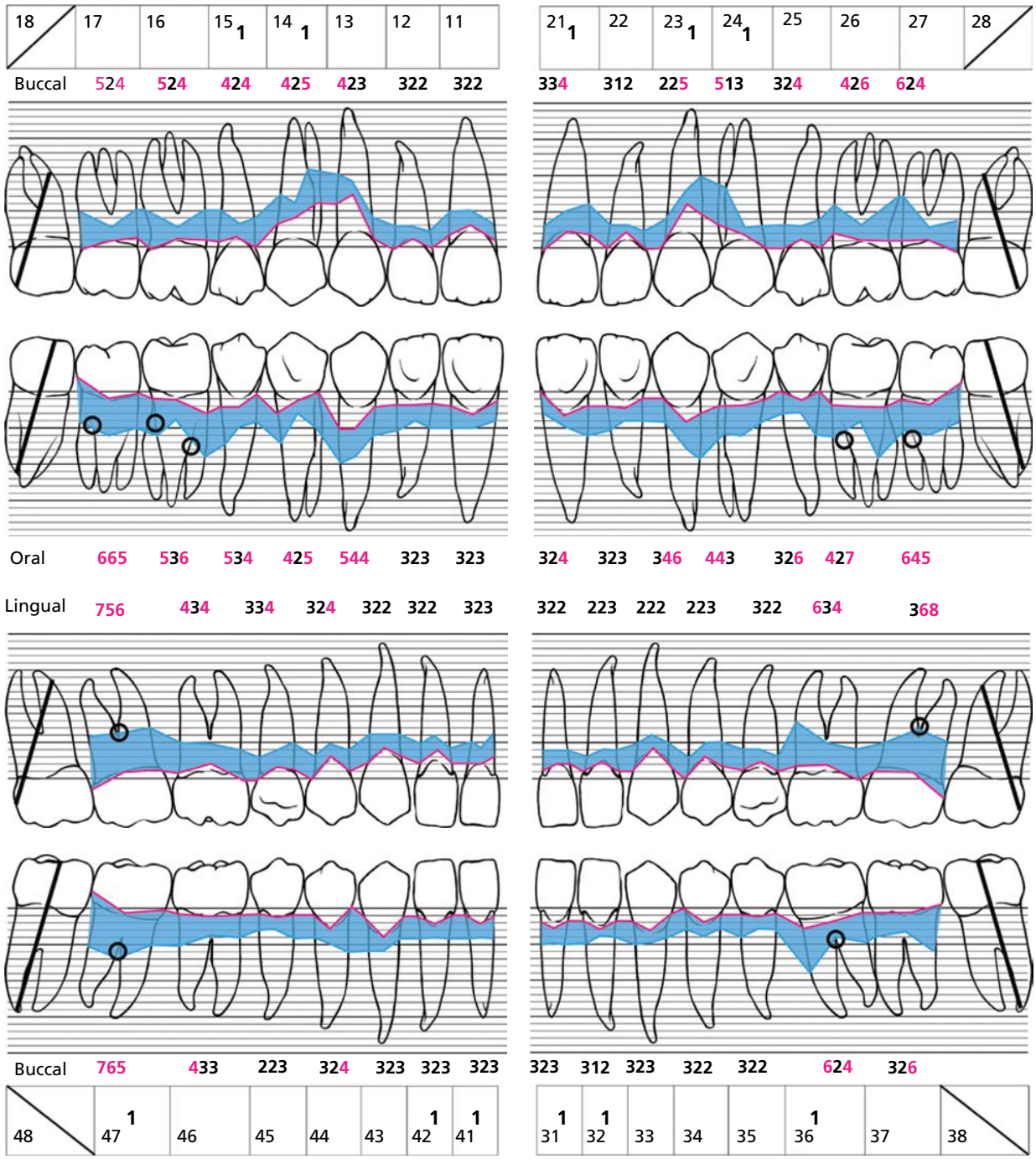


Fig. 32-8 Periodontal chart of the patient presented in Fig. 32-2 at re-evaluation after initial periodontal therapy.

Teeth that are considered "*irrational-to-treat*" should be extracted during initial, cause-related therapy. Such teeth may be identified on the basis of the following criteria:

- *Periodontal*:
  - Recurrent periodontal abscesses
  - Combined periodontal–endodontic lesions
  - Attachment loss to the apical region
- *Endodontic:*
  - Root perforation in the apical half of the root
  - Extensive periapical lesions (diameter >6 mm)
- *Dental*:
  - Vertical fracture of the root (hairline fractures)
  - Oblique fracture in the middle third of the root
  - Caries lesions extending into the root canal
- *Functional*:
  - Third molars without antagonists and with periodontitis/caries.

Teeth with a *doubtful* prognosis are usually in need of comprehensive therapy and must be brought into the category of teeth with a *good* prognosis by means of additional therapy. Such teeth may be identified on the basis of the following criteria:

- *Periodontal*:
  - Furcation involvement (class II or III)
  - Angular (i.e. vertical) bony defects
  - "Horizontal" bone loss involving >⅔ of the root

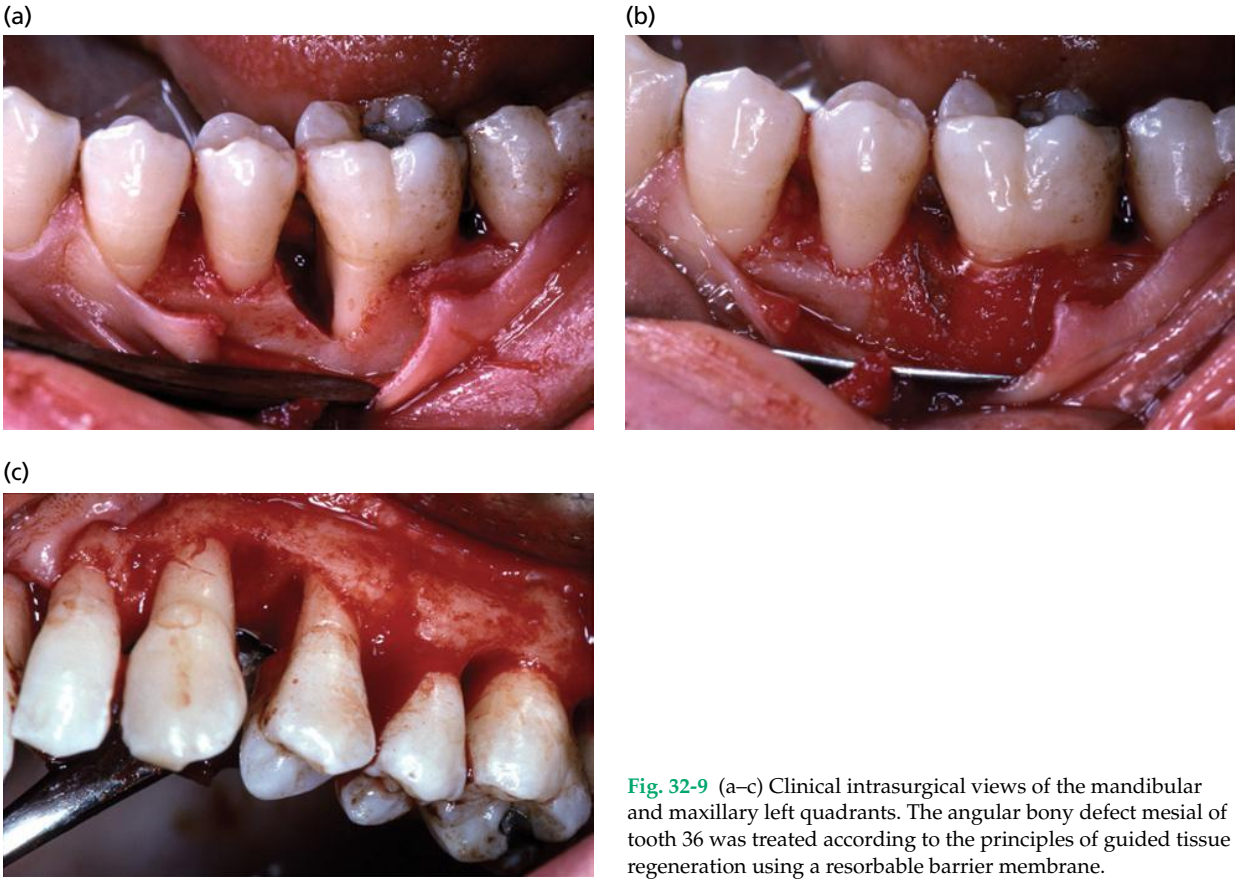


Fig. 32-9 (a–c) Clinical intrasurgical views of the mandibular and maxillary left quadrants. The angular bony defect mesial of tooth 36 was treated according to the principles of guided tissue regeneration using a resorbable barrier membrane.

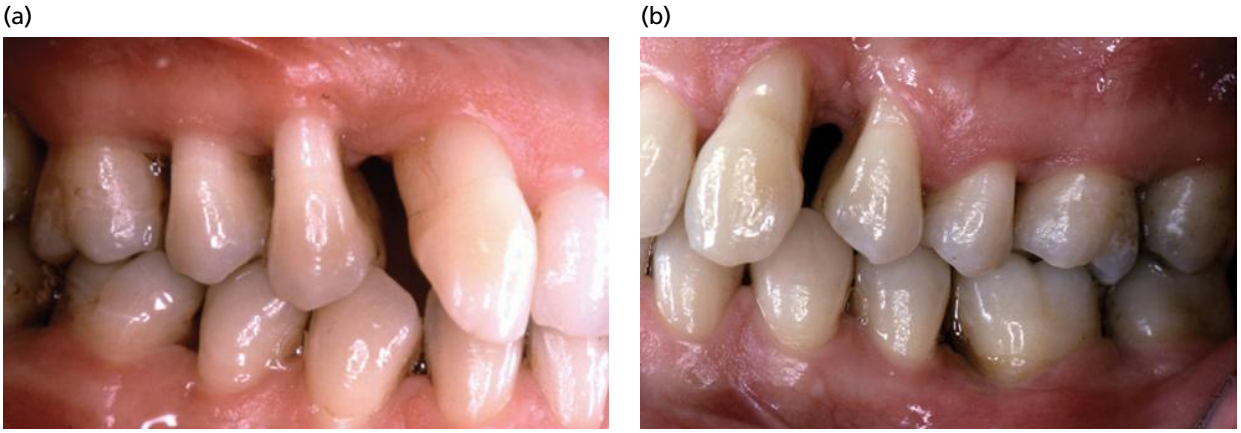


Fig. 32-10 (a, b) Clinical lateral views of the patient presented in Fig. 32-2 at re-evaluation after periodontal surgery.

- *Endodontic*:
  - Incomplete root canal therapy
  - Periapical pathology
  - Presence of voluminous posts/screws
- *Dental*:
  - Extensive root caries.

Case presentation

The "case presentation" is an essential component of the initial treatment plan and must include a description for the patient of different therapeutic goals and the modalities by which these may be reached. At the case presentation for patient S.B., the following treatment plan was described:

- Teeth 12–22 and 45–35 in the dentition will probably not confront the dentist with any major therapeutic challenges. For the remaining teeth in the dentition, however, the treatment plan may involve several additional measures.

Expected benefits inherent to a certain treatment plan versus obvious disadvantages should always be explained to and discussed with the patient. His/her attitude to the alternatives presented must guide the dentist in the design of the overall treatment plan.

Based on the pretherapeutic single-tooth prognosis (Fig. 32-6), following detailed treatment plan described below was presented to the patient.

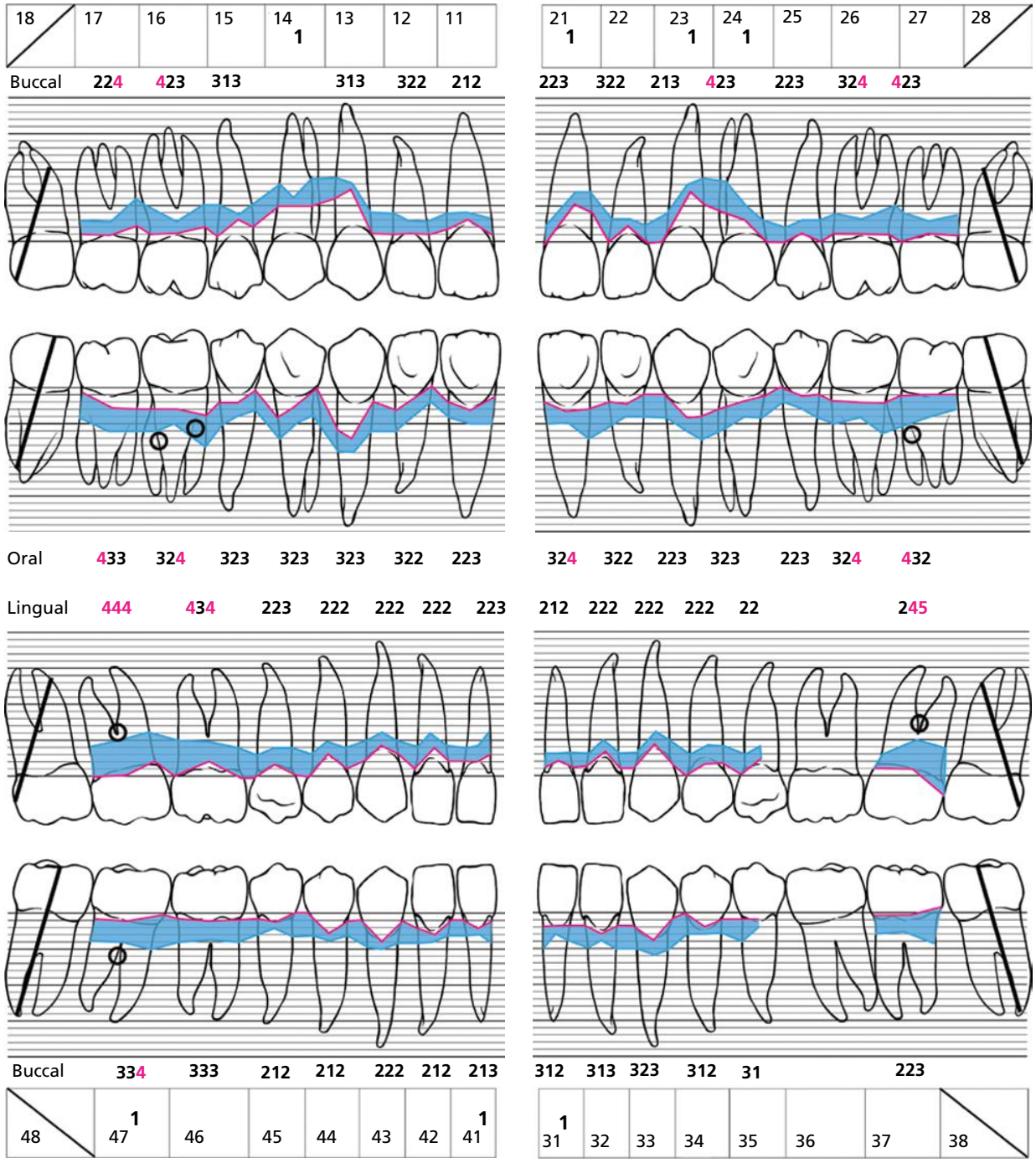


Fig. 32-11 Periodontal chart of the patient presented in Fig. 32-2 at re-evaluation after periodontal surgery.

Systemic phase

Owing to the fact that the patient was systemically healthy and a non-smoker, no medical examination or smoking cessation counseling was required.

Initial phase (cause-related therapy)

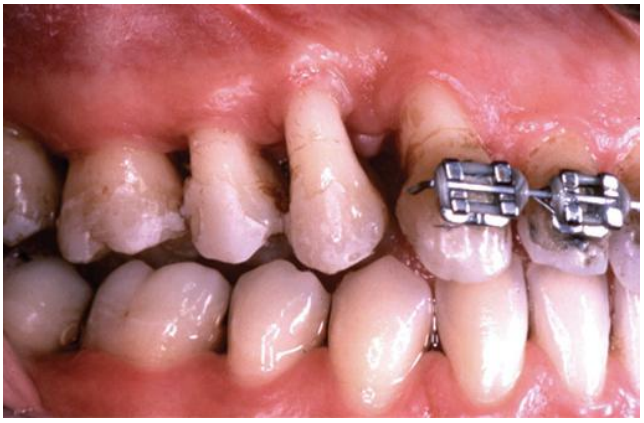
The treatment was initiated and included the following measures to eliminate or control the bacterial infection:

1. *Motivation* of the patient and *instruction* in oral hygiene practices with subsequent check-ups and re-instruction.
2. *Scaling and root planing* under local anesthesia in combination with removal of plaque retentive factors (and teeth irrational to treat, if any).
3. *Excavation and restoration* of carious lesions (teeth 16 and 26).
4. *Endodontic treatment* of tooth 46.

Re-evaluation of treatment

The initial phase of therapy is completed with a thorough analysis of the results obtained with respect to the elimination or degree of control of the dental infections. This implies that a re-evaluation of the patient's periodontal conditions and caries activity must be performed. The results of this re-evaluation

(a)



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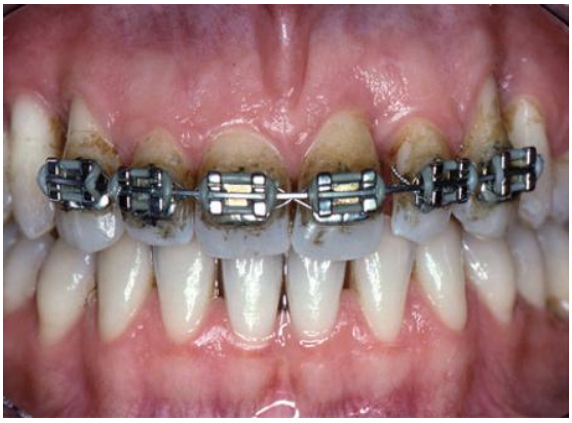


(c)

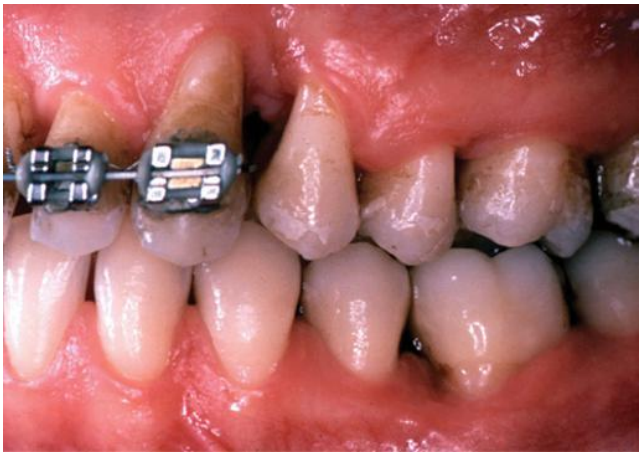
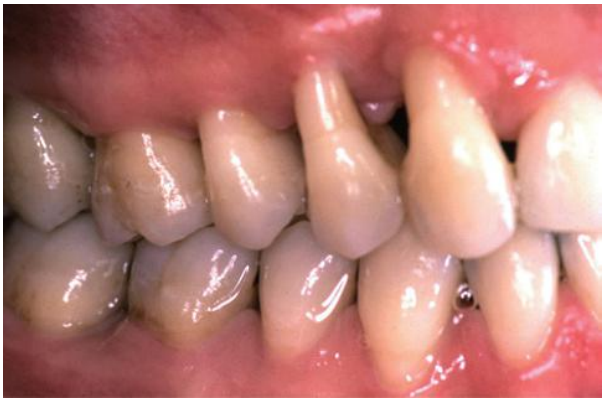


Fig. 32-12 (a–c) Clinical front and lateral views of the patient presented in Fig. 32-2 during orthodontic therapy of the maxillary front teeth.

(a)



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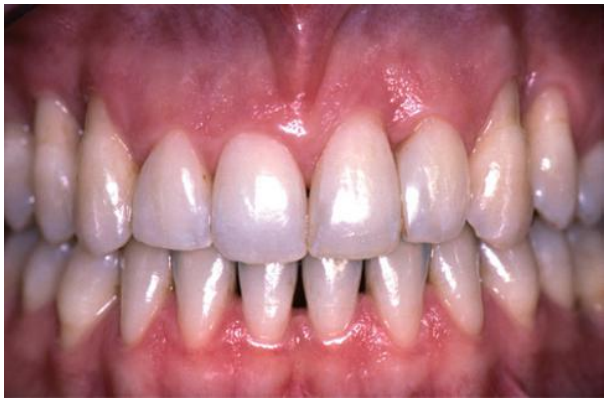

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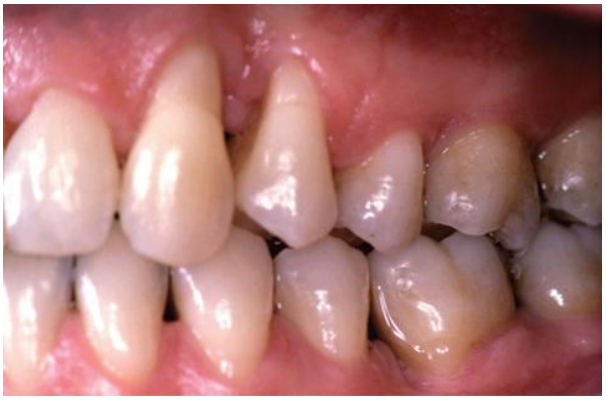


Fig. 32-13 (a–c) Clinical front and lateral views of the patient presented in Fig. 32-2 at the final re-evaluation. To improve the esthetic outcome, the maxillary front teeth were restored with composite fillings.

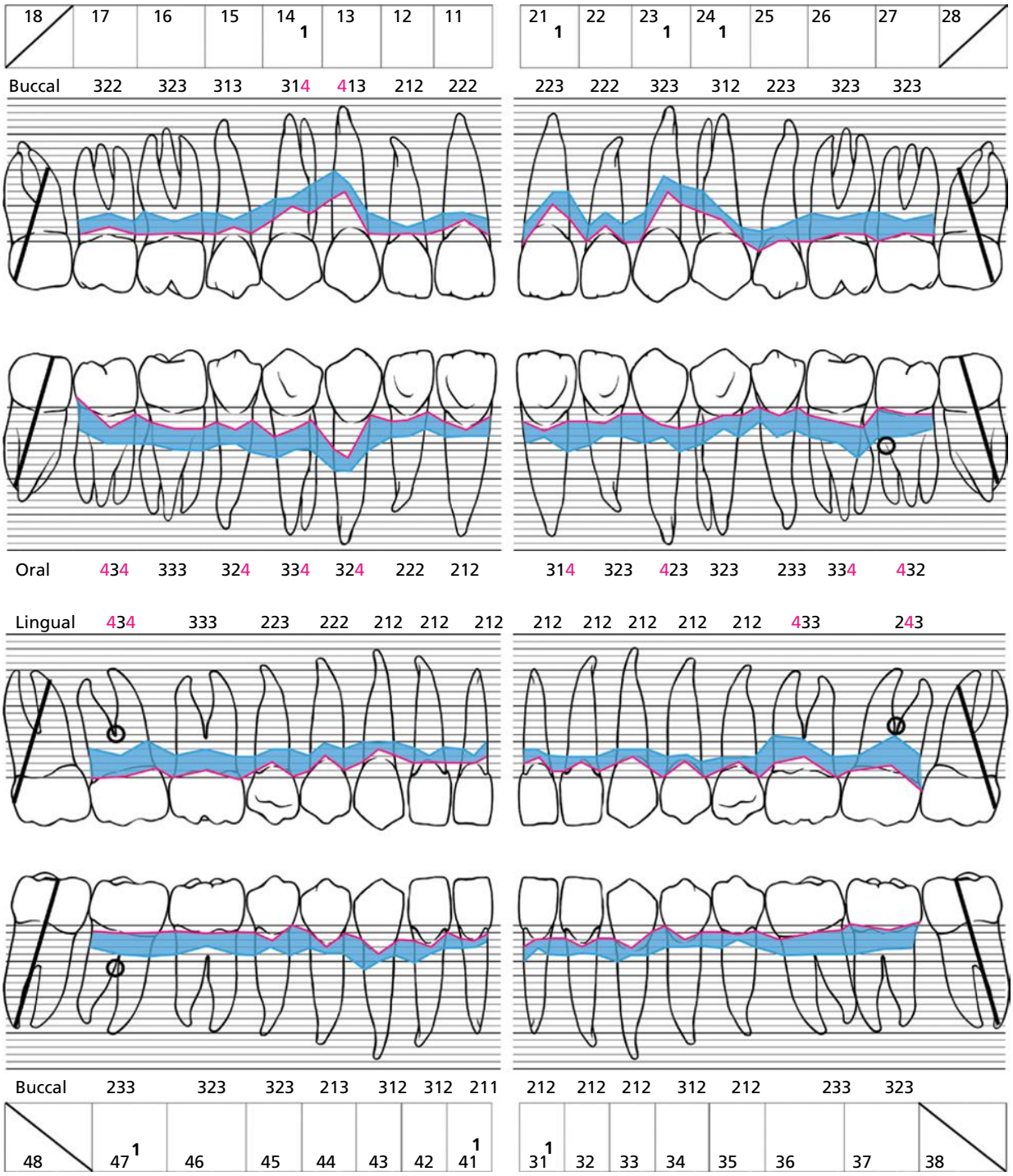


Fig. 32-14 Periodontal chart of the patient presented in Fig. 32-2 at the final re-evaluation.

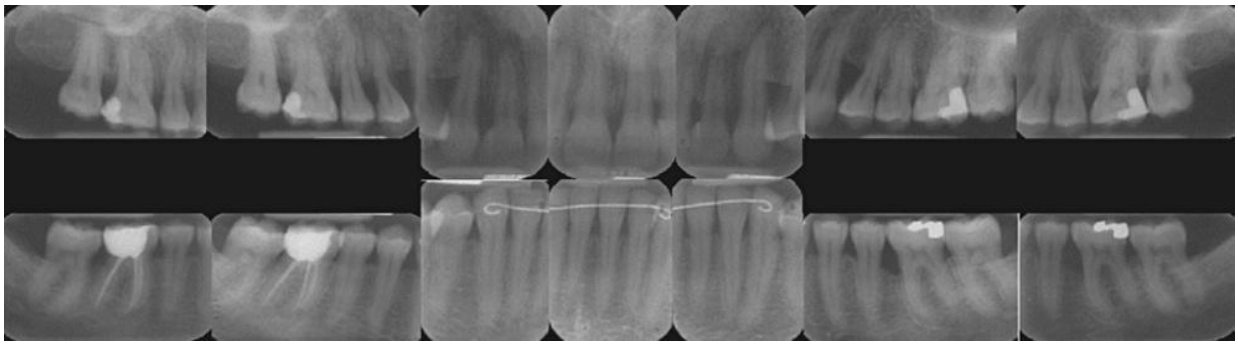


Fig. 32-15 Radiographs of the patient presented in Fig. 32-2 at the final re-evaluation.

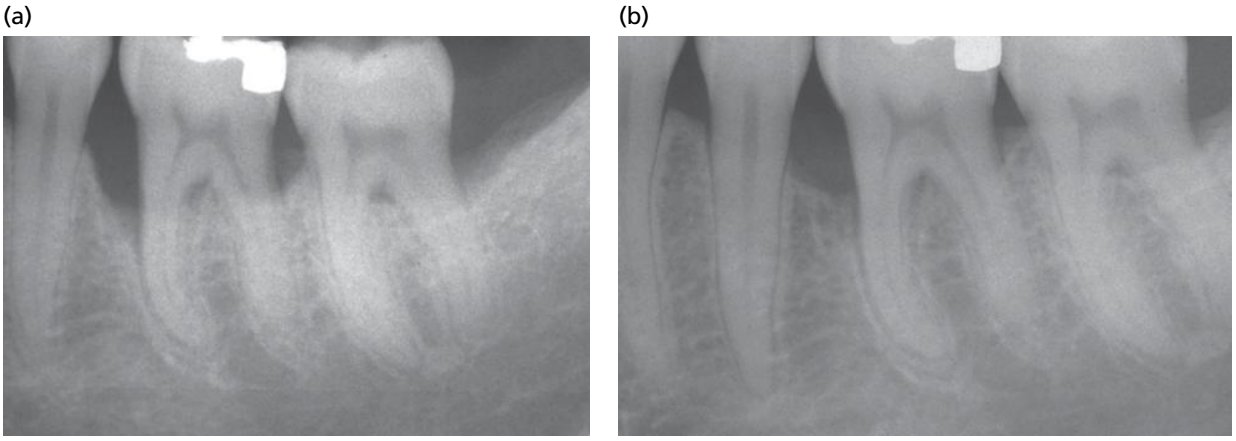


Fig. 32-16 (a, b) Radiographs of tooth 36 of the patient presented in Fig. 32-2 before and after regenerative periodontal therapy according to the principles of guided tissue regeneration.

(Figs. 32-7, 32-8) form the basis for the selection, if necessary, of additional corrective measures to be performed in the phase of definitive treatment (i.e. corrective phase). In order to provide time for the tissues to heal, the re-evaluation should be performed not earlier than 6–8 weeks following the last session of instrumentation.

Planning of the corrective phase (i.e. additional periodontal therapy)

If the results from the re-evaluation, made 6–8 weeks after the termination of the initial treatment phase, show that periodontal disease and caries have been brought under control and the treatment goals (*see* above) have either been reached completely or have been approached substantially, the additional treatment may be carried out. The main goal of this phase is to correct the sequelae caused by oral infections (i.e. periodontal disease and caries). The following procedures may be performed:

- *Additional endodontic treatment with/without post-and-core build-ups.*
- *Periodontal surgery*: type (i.e. open flap debridement, regenerative or resective surgery) and extent of surgical treatment should be based on PPD measurements, degree of furcation involvement, and "BoP" scores assessed at re-evaluation. Periodontal surgery is often confined to those areas of the dentition where the inflammatory lesions were not resolved by root instrumentation alone, in areas with angular bony defects or in furcation-involved molars.
- *Installation of oral implants*: in regions of the dentition where tooth abutments are missing, implant therapy for esthetic and functional reasons may be considered. It is essential to realize that implant therapy must be initiated when all dental infections are under control, that is after successful periodontal therapy.
- *Definitive restorative and prosthetic treatment*, including fixed or removable dental prostheses.

Corrective phase (additional therapy)

Patient S.B. exhibited, after initial therapy, low plaque and gingivitis scores (i.e. 5–10%) and no active carious lesions. The corrective phase, therefore, included the following components:

1. *Periodontal surgery (i.e. open flap debridement)* in the maxillary left and right quadrants as well as in the mandibular molar regions (Fig. 32-9)
2. *Guided tissue regeneration (GTR)* for tooth 36
3. *Re-evaluation* after periodontal surgery (Figs. 32-10, 32-11)
4. *Orthodontic therapy* in the maxillary front area (Fig. 32-12)
5. *Restorative therapy* in the maxillary front area for esthetic reasons (Fig. 32-13).

Re-evaluation after corrective phase

The corrective phase of therapy is completed with a thorough analysis of the results obtained with respect to the elimination of the sequelae of periodontal tissue destruction (Figs. 32-14, 32-15, 32-16). This implies that a re-evaluation of the patient's periodontal and peri-implant conditions must be performed. The results of this re-evaluation form the basis for the assessment of the residual periodontal risk. The outcomes of the periodontal risk assessment (PRA), in turn, will determine the recall frequency of the patient during the maintenance phase.

Maintenance phase (supportive periodontal therapy)

Following completion of cause-related therapy, the patient must be enrolled in a recall system aimed at preventing the recurrence of oral infections (i.e. periodontitis, caries, and peri-implantitis). *Supportive periodontal therpay* (SPT) should be scheduled at the re-evaluation after initial therapy and independently of the need for additional therapy. The time interval between the recall appointments should be based on a PRA (see Chapter 60) established at the re-evaluation

after corrective phase. It has been well established that self-performed plaque control combined with regular attendance of maintenance care visits following active periodontal treatment represent effective means of controlling gingivitis and periodontitis and limiting tooth mortality over a 30-year period (Axelsson *et al*. 2004). It is important to emphasize, however, that the recall program must be designed to meet the individual needs of the patient. According to a PRA performed after completion of active therapy, some patients should be recalled every 3 months, while others may need to be checked only once a year (Lang & Tonetti 2003).

At the recall visits the following procedures should be carried out:

1. Update of the medical and smoking history
2. Soft tissue examination as a cancer screening
3. Recording of the full-mouth PPD of ≥5 mm with concomitant BoP
4. Re-instrumentation of bleeding sites with a PPD of ≥5 mm
5. Polishing and fluoridation for the prevention of dental caries.

Patient S.B., who is presented to describe the guiding principles of treatment planning, was, during the first 6 months after active treatment, recalled twice (i.e. every 3 months) and subsequently only once every 6 months based on the individual PRA.

Concluding remarks

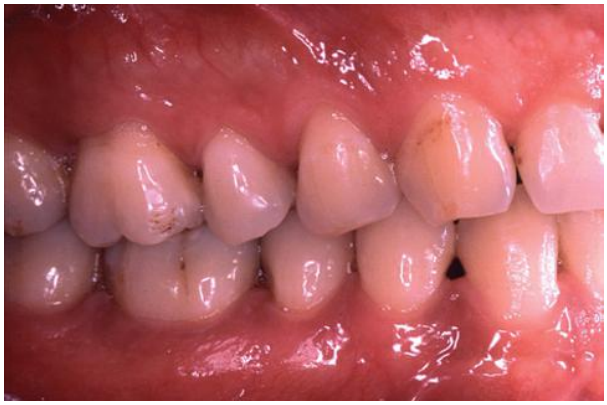
The overall treatment plan and the sequence of the different treatment procedures used for patient S.B. were selected for presentation in order to illustrate the following principle: *in patients exhibiting a generalized advanced breakdown of the periodontal tissues, but with an intact number of teeth, considerable efforts should be made to maintain all teeth*. Extraction of a single tooth in such a dentition will frequently call for the extraction of several others for "prosthetic reasons". The end result of such an approach thus includes a prosthetic rehabilitation that, if the treatment planning had been properly done, could have been avoided.

The large variety of treatment problems that different patients present may obviously require deviations from the sequence of treatment phases (i.e. systemic phase, initial cause-related therapy, corrective therapy, and maintenance care) discussed above. Such deviations may be accepted as long as the fundamental principles characterizing the treatment phases are understood.

Case report

A patient is presented below together with a brief description of his specific dental problems and the treatment delivered in order to demonstrate the rationale behind such treatment phases.

(a)



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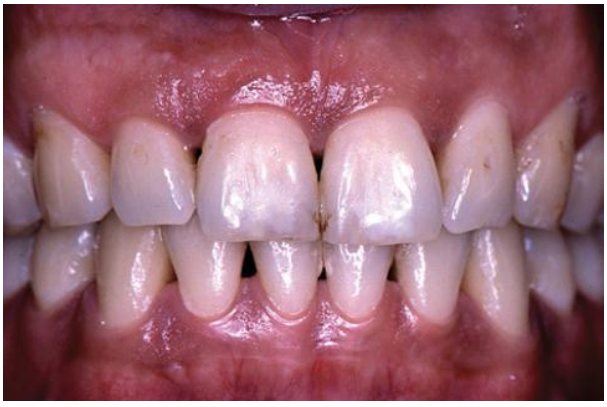

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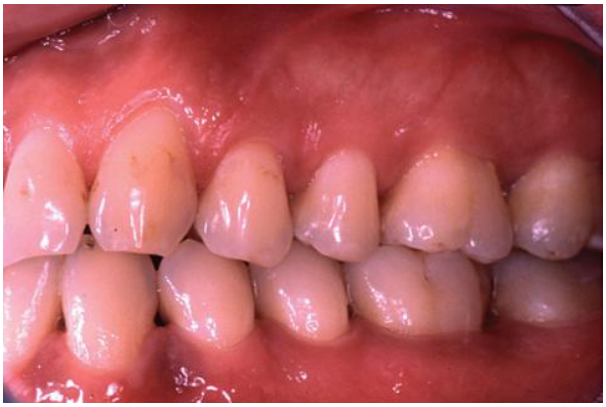


Fig. 32-17 (a–c) Clinical front and lateral views of patient S.K. at initial examination.

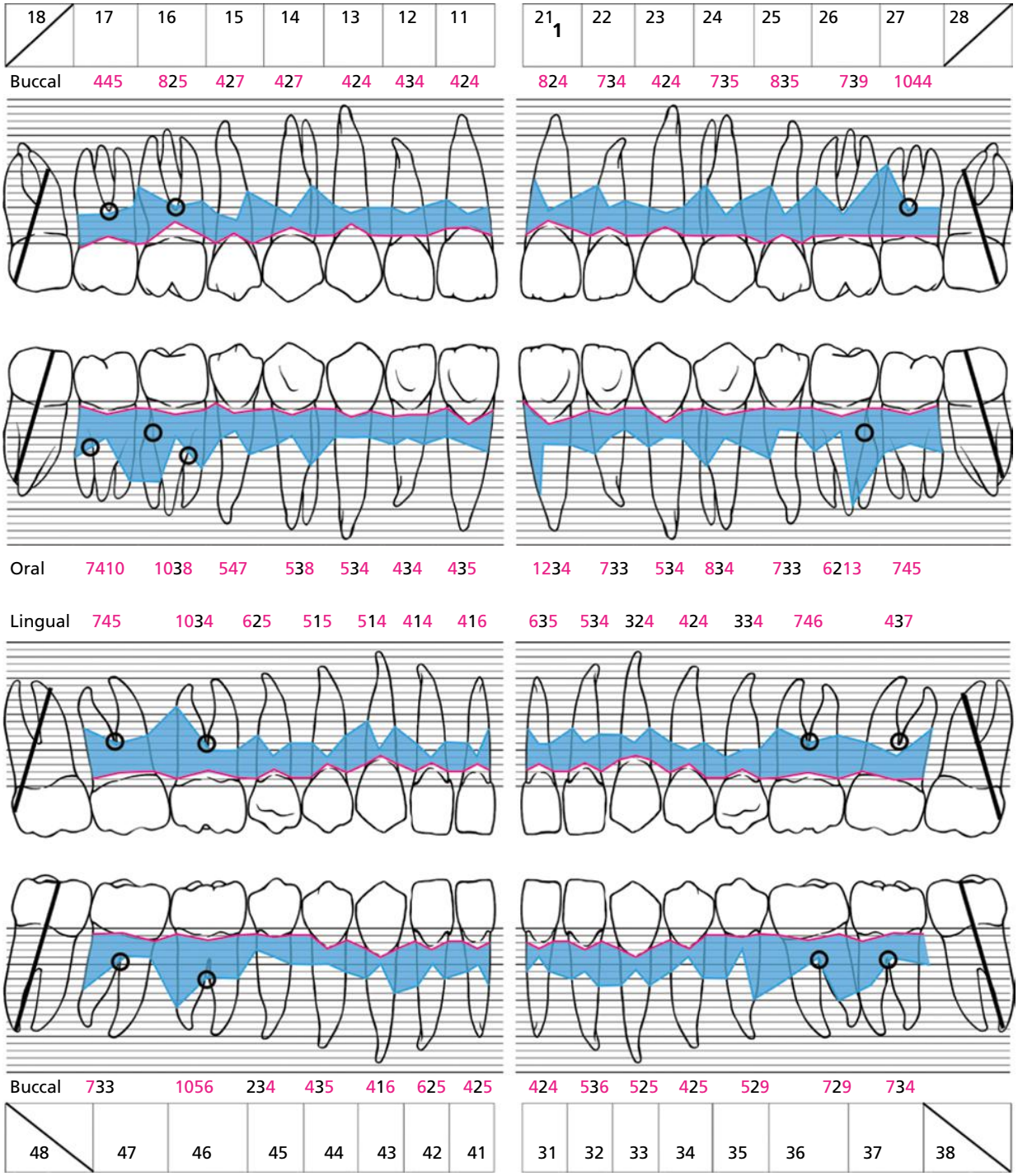


Fig. 32-18 Periodontal chart of the patient presented in Fig. 32-17.

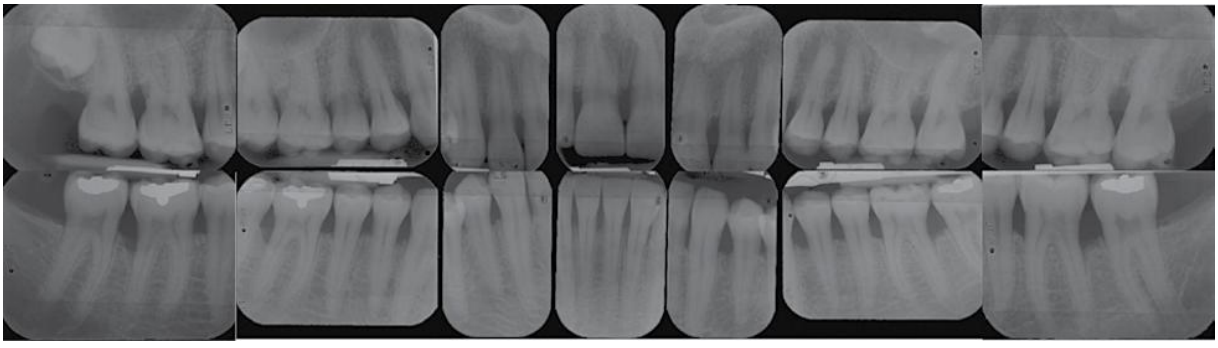


Fig. 32-19 Radiographs of the patient presented in Fig. 32-17.

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Irrational to treat	x															
Doubtful (insecure)		x	x	x	x				x	x		x	x	x	x	
Good (secure)						x	x	x			x					
Good (secure)				x	x	x	x	x	x	x	x	x	x			
Doubtful (insecure)		x	x											x	x	
Irrational to treat																
	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Fig. 32-20 Pretherapeutic single-tooth prognosis of the patient presented in Fig. 32-17.

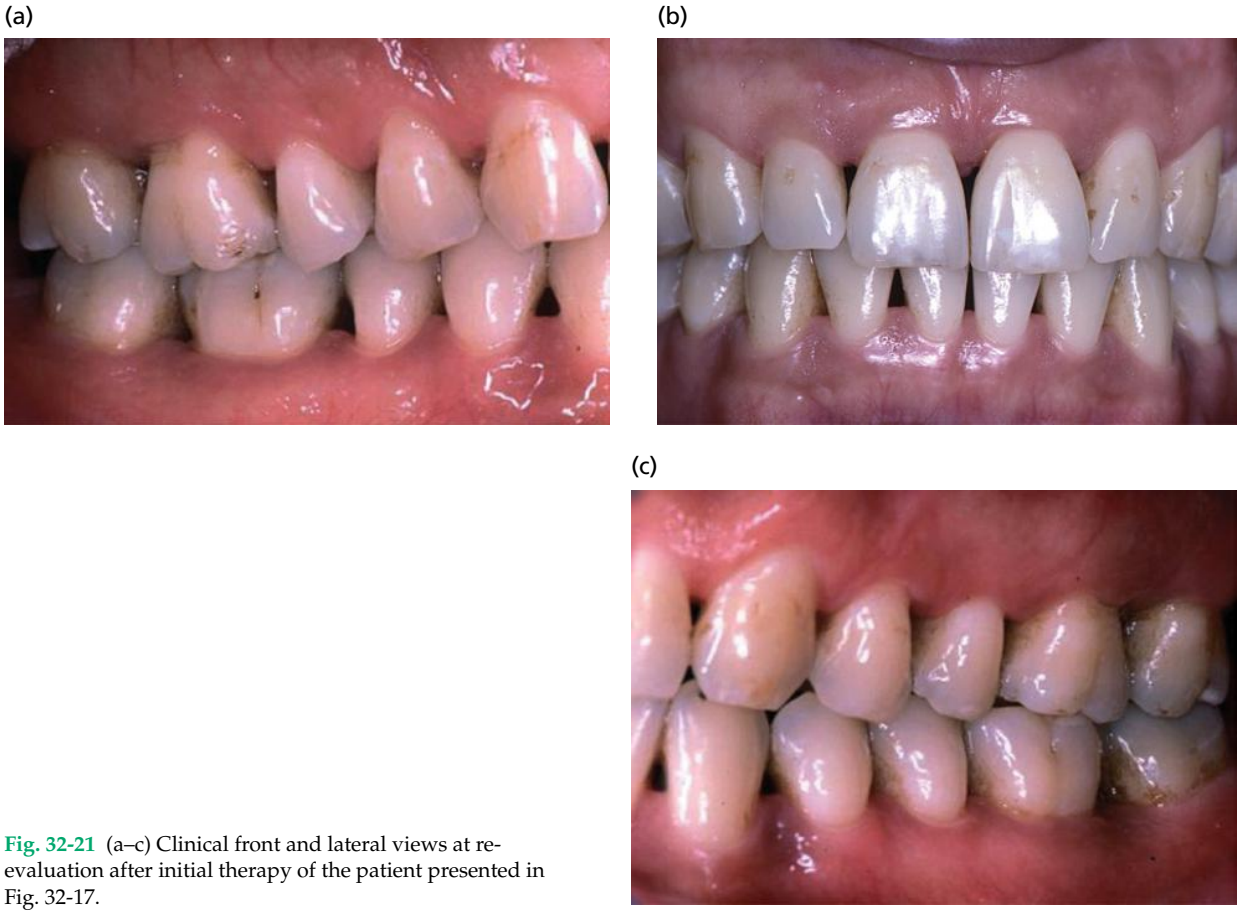


Fig. 32-21 (a–c) Clinical front and lateral views at re-evaluation after initial therapy of the patient presented in Fig. 32-17.

Patient S.K. (male, 35 years old)

Initial examination

The chief complaint of the patient was the slightly increased mobility of tooth 21. The periodontal conditions (i.e. PPD, furcation involvements, tooth mobility, and periapical radiographs) from the initial examination are shown in Fig. 32-17.

The data obtained from the initial examination disclosed the presence of an advanced destruction of the supporting tissues in most parts of the dentition (Fig. 32-18) and the presence of several angular bony defects (Fig. 32-19). The full-mouth plaque score (FMPS) and full-mouth bleeding score (FMBS) were 32% and 86%, respectively. The patient was systemically healthy and a former smoker.

Diagnosis

The patient was diagnosed with a generalized chronic periodontitis with furcation involvement.

Etiology

The supra- and sub-gingival bacterial deposits were identified as the main etiologic factors. Past cigarette smoking was considered a modifying factor.

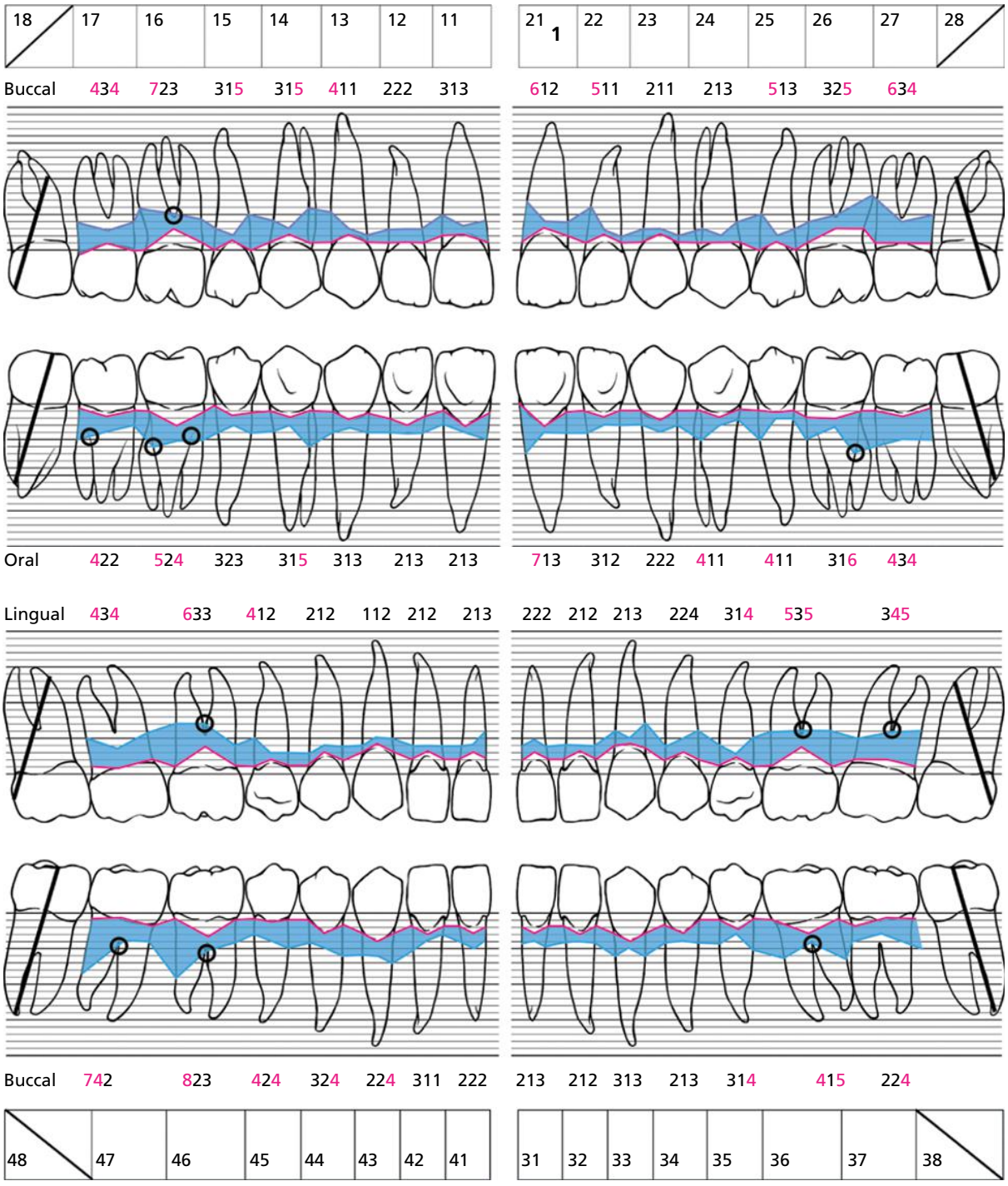


Fig. 32-22 Periodontal chart at re-evaluation after initial therapy of the patient presented in Fig. 32-17.

Pretherapeutic single-tooth prognosis

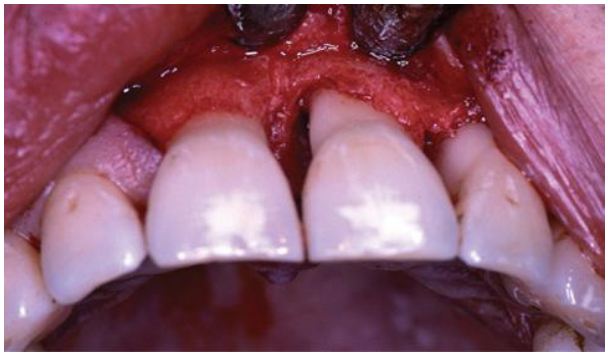
Teeth 28, 38, and 48 were missing. Tooth 18 was impacted and considered irrational to treat. Teeth 13, 12, 11, and 23 in the maxilla and 45–35 in the mandible were classified as secure. A doubtful prognosis was assigned to teeth 17, 16, 15, 14, 21, 22, 24, 25, 26, and 27 in the maxilla and to teeth 36, 37, 46, and 47 in the mandible (Fig. 32-20).

Treatment planning

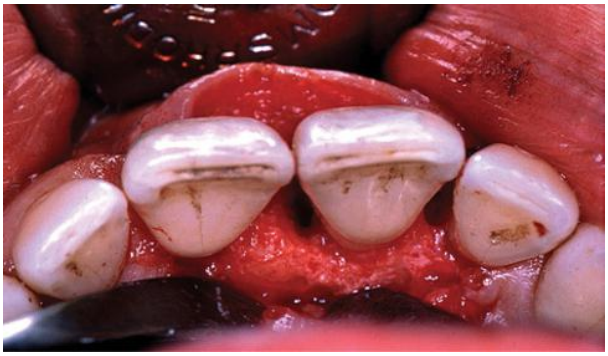
In the treatment planning of this relatively young patient, it seemed reasonable to anticipate the retention of all teeth of his periodontally compromised dentition. The prerequisites for a good long-term prognosis after therapy included (1) optimal self-performed plaque control, (2) proper healing of the periodontal tissues following non-surgical and surgical therapy, and (3) a carefully monitored maintenance care program. As stated above, tooth 21 displayed increased mobility, but this did not disturb the chewing comfort of the patient.

In such a relatively young patient, extensive efforts were made to properly treat inflammatory periodontal disease in the entire dentition, in order to avoid tooth extraction and subsequent prosthetic rehabilitation.

(a)



(b)



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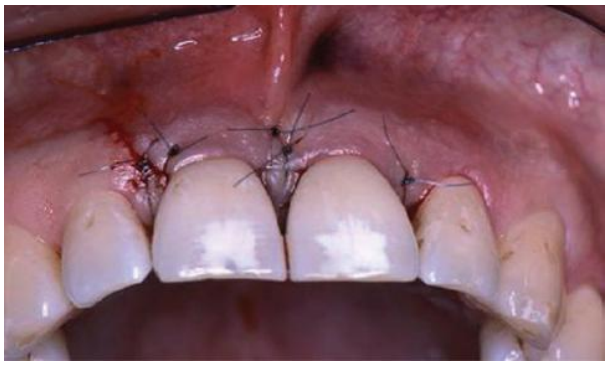
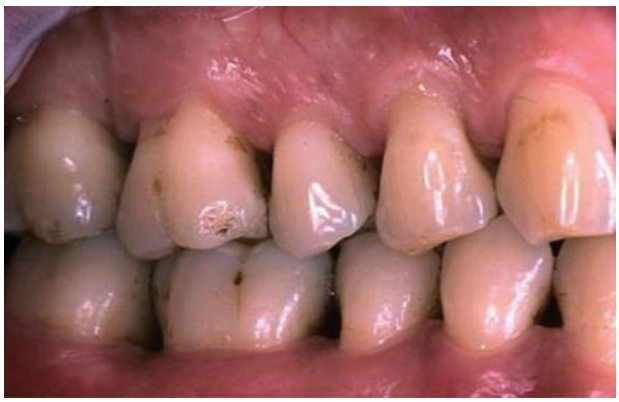


Fig. 32-23 (a–c) Intra- and post-surgical views of the upper front area of the patient presented in Fig. 32-17.

(a)



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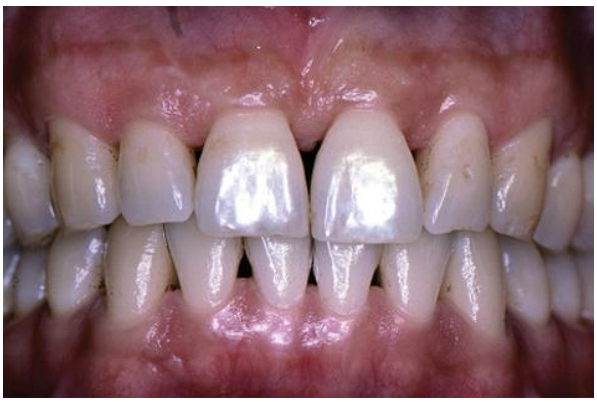

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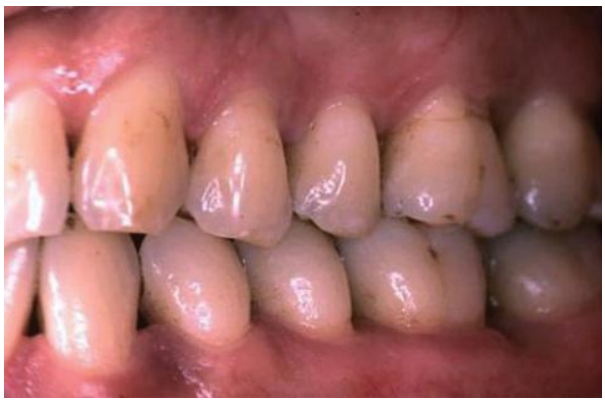

Fig. 32-24 (a–c) Clinical front and lateral views at the final examination of the patient presented in Fig. 32-17.

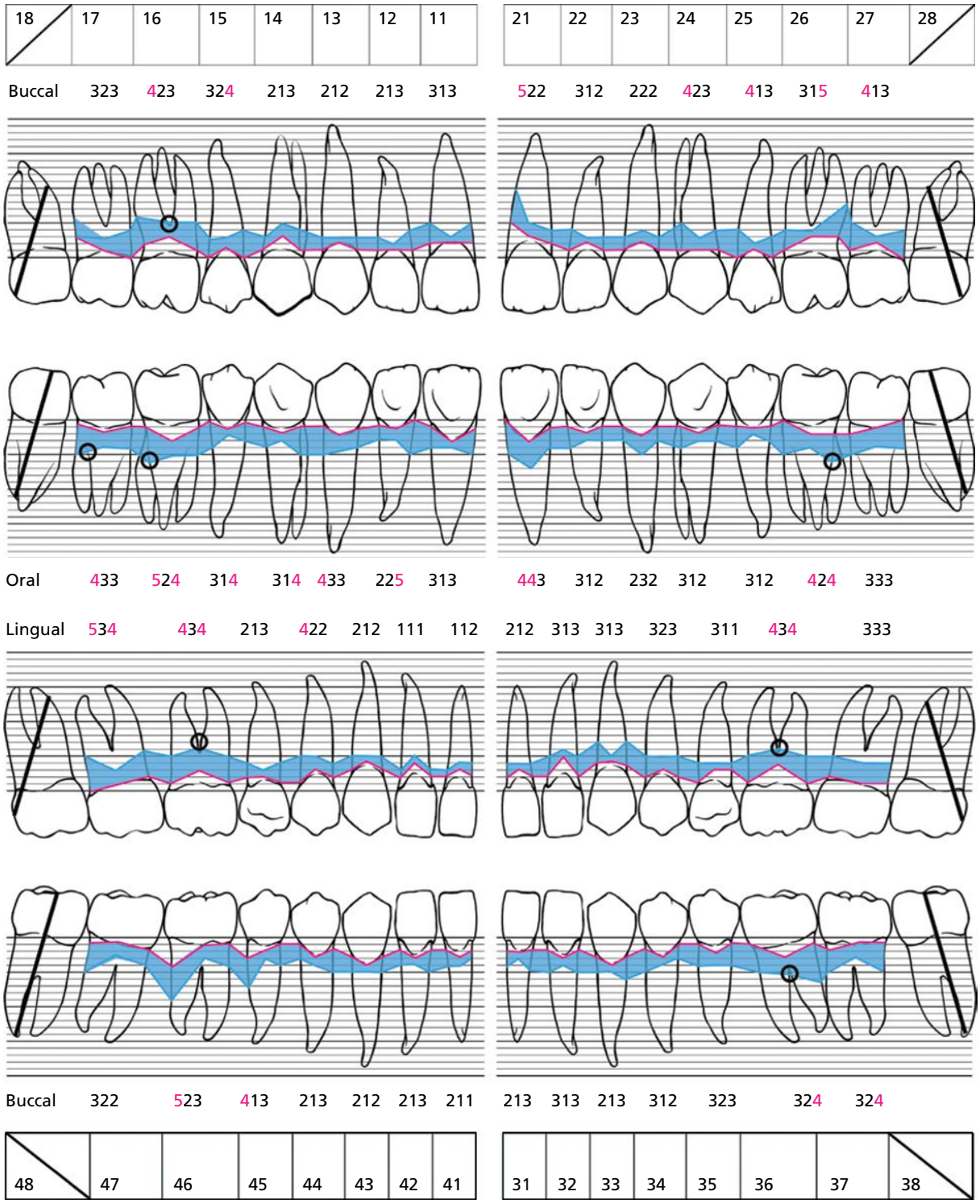

Fig. 32-25 Periodontal chart at the final examination of the patient presented in Fig. 32-17.

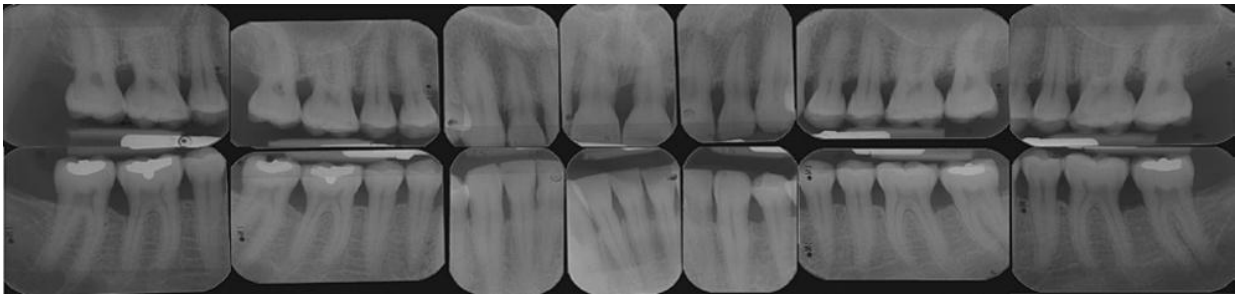

Fig. 32-26 Radiographs at the final examination of the patient presented in Fig. 32-17.

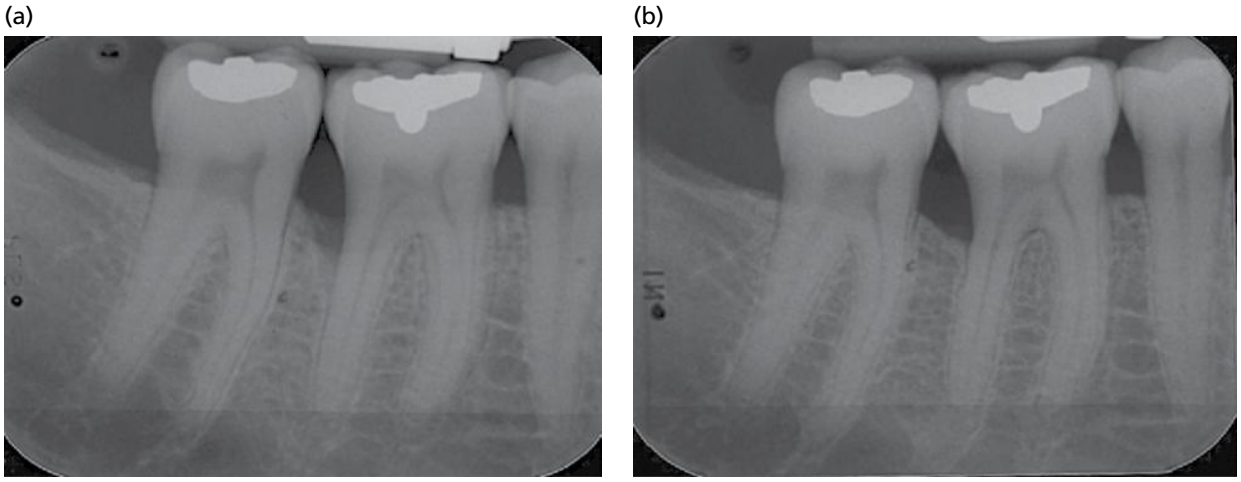

Fig. 32-27 Radiographs (a) before and (b) after periodontal regeneration of the angular bony defect on the distal aspect of tooth 46 of the patient presented in Fig. 32-17.

Treatment

Subsequent to initial examination, the patient was given a detailed "case presentation" and information regarding the alternative goals of and prerequisites for the overall treatment. This information included a description of the role of dental biofilms in the etiology of periodontal disease and the significance of optimal plaque control for a successful outcome of therapy. A treatment program was subsequently planned which aimed at maintaining all teeth. The overall treatment was performed in the following sequence.

Initial cause-related therapy

The patient was counseled not to start smoking again. After thorough motivation, the patient was instructed in the toothbrushing technique according to Bass (1954) and in the use of interdental brushes. Scaling and root planing of all teeth was performed under local anesthesia. The front and lateral views as well as the periodontal chart at re-evaluation after initial therapy are shown in Figs. 32-21 and 32-22, respectively.

Additional therapy

The need for additional therapy was based on the re-evaluation after initial therapy (Fig. 32-22). Periodontal surgery in conjunction with regenerative procedures was deemed necessary in all quadrants. During access flap surgery in the first quadrant extending from tooth 13 to 17, tooth 18 was extracted. Between the upper front teeth 11 and 21, the modified papilla preservation technique (Cortellini *et al*. 1995) was chosen in the surgical procedure to gain access to the angular bony defect of tooth 21 (Fig. 32-23). In this area, the application of enamel matrix derivatives (i.e. Emdogain®) aimed at regenerating the lost periodontal tissues on the mesial aspect of tooth 21.

In the third quadrant, the surgical access flap extended from tooth 35 to 37. In the fourth quadrant, flap surgery in conjunction with the simplified papilla preservation technique (Cortellini *et al.* 1999) was applied to gain access to the angular bony defect on the distal aspect of tooth 46. In this area, the application of enamel matrix derivatives (i.e. Emdogain®) aimed at regenerating the lost periodontal tissues. Six months after completion of the corrective phase (Fig. 32-24), a re-evaluation of the periodontal conditions (Fig. 32-25), including on radiographs (Figs. 32-26, 32-27), followed by a PRA were performed.

Supportive periodontal therapy

After completion of initial and corrective therapy, the patient was recalled for maintenance care every 3 months. During recall appointments, sites bleeding on probing and with a PPD of ≥5 mm were re-instrumented. If necessary, the patient was re-motivated and re-instructed in oral hygiene procedures. Fluoride was regularly applied in order to prevent the onset of dental caries.

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Chapter 33

Treatment Planning for Implant Therapy in the Periodontally Compromised Patient

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[3] Center of Dental Medicine, University of Zurich, Zurich, Switzerland

The use of dental implants for replacement of missing teeth is a viable option in the rehabilitation of the periodontally compromised patient, and certainly the availability of this treatment option may also influence decisions regarding the preservation of teeth with varying degrees of periodontal tissue destruction.

Prognosis of implant therapy in the periodontally compromised patient

Global data on survival rates of dental implants indicate a rather low incidence of implant loss. The question is, however, whether the long-term prognosis for implants is better than that for teeth. In a systematic review by Berglundh *et al.* (2002), including 16 studies reporting data on implant-supporting fixed partial dentures (FPDs), the overall 5-year failure rate was about 5%. In the few studies that included a follow-up of 10 years, the overall rate of implant loss was about 10%. It should be noted, however, that these studies did not specifically address the prognosis of implant therapy in periodontally compromised patients. Hardt *et al.* (2002) reported from a 5-year retrospective study that 8% of the implants were lost in patients who at the time of implant placement presented advanced loss of periodontal support at their natural teeth. The corresponding figure in patients without periodontal tissue destruction was only 3% (Table 33-1). In the periodontally compromised patients, most of the implants that were lost were so-called late failures. Furthermore, after 5 years 64% of the periodontally compromised patients showed a mean bone loss at the implants of >2 mm compared to only 24% of the non-compromised patients. Karoussis

Table 33-1 Percentage of implants lost in relation to experience of destructive periodontal disease.

Authors	Follow-up (years)	No history of destructive periodontal disease (%)	History of destructive periodontal disease (%)
Hardt *et al.* (2002)	5	3.3	8.0
Karoussis *et al.* (2003)	10	3.5	9.5
Ruccuzzo *et al.* (2010)	10	3.4	10

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

Table 33-2 Percentage of teeth lost in patients treated for advanced destructive periodontal disease and maintained in supportive care programs.

Authors	Mean follow-up (years)	Teeth lost (%)	Teeth lost per 10 years (%)
Lindhe & Nyman (1984)	14	2.3	1.6
Yi *et al.* (1995)	15	8	5
Rosling *et al.* (2001)	12	1.9	1.6
König *et al.* (2002)	12	3.1	2.6
Karoussis *et al.* (2004)	10	5	5
Ng *et al.* (2011)	10	3.9	3.9

et al. (2003) found a failure rate of 10% after 10 years in patients who had been treated for periodontitis before implant placement, compared to 4% in patients who had received implant therapy because of tooth loss for reasons other than periodontal disease. Roccuzzo *et al.* (2010) reported from a 10-year prospective longitudinal study an implant loss of 10% among periodontally compromised patients, compared to 3% among periodontally healthy patients. Moreover, periodontally compromised patients who did not completely adhere to the regular supportive care program presented an even higher implant failure rate. Taken together the data reported above indicate that there is an increased risk for implant failure in individuals susceptible to periodontitis.

A question of concern in relation to treatment decisions in a periodontally compromised patient is whether or not the failure rate of implants is different from that of teeth. In order to answer this question the incidence of tooth loss in periodontally treated patients needs to be known. Based on data from studies involving patients who have been treated for advanced periodontal disease and thereafter been provided with regular supportive periodontal therapy (SPT), the average incidence of tooth loss during a 10-year period can be estimated to be between 2% and 5% (Table 33-2). These percentages, in comparison with the data for implant loss presented above, indicate that the prognosis for long-term survival of implants is not better than that for properly treated periodontitis-affected teeth. Furthermore, evidence is accumulating that suggests that longitudinal bone loss at implants is positively correlated with periodontal disease susceptibility (Hardt *et al.* 2001; Matarasso *et al.* 2010; Roccuzzo *et al.* 2010) and that implant therapy in the periodontally compromised patient may not be as successful as the global data for implant therapy in general has indicated.

Strategies in treatment planning

A comprehensive clinical and radiographic examination forms the basis for the treatment planning of the periodontally compromised patient. In relation to implant therapy, careful risk assessments should also be made (see Chapter 31) and additional radiographic examinations may be required (see Chapter 30). The goal of treatment is to satisfy the patient's demands regarding chewing comfort and esthetics, with a favorable long-term prognosis of the restoration. The use of implants as a means to restore chewing function and esthetics in the periodontitis-susceptible patient has to be carefully evaluated in relation to the patient's standard of infection control. In partially dentate patients with remaining periodontal lesions, implants are rapidly colonized by periodontal pathogens, which indicates that periodontal pockets may act as reservoirs for microbial colonization of implants (see Chapter 10). Since there is no evidence that the host response to the microbial challenge is altered when a tooth is substituted with an implant, it should be anticipated that a periodontitis-susceptible individual with improper infection control will face similar risk for disease-induced bone loss at implants and teeth.

Elimination of periodontitis lesions before implant placement and the establishment of a high standard of infection control are consequently decisive factors for the success of implant therapy. Regular recalls for supportive care and monitoring with regard to the occurrence of clinical signs of periodontal/peri-implant infections should be scheduled after the completion of the therapy (see Chapter 60). Provided such a treatment program is firmly adhered to, the long-term success of implant therapy in the periodontally compromised patient is enhanced (Wennström *et al.* 2004; Roccuzzo *et al.* 2010).

Treatment decisions: Case reports

Posterior segments

In the periodontally compromised patient, the posterior segments of the dentition are usually those that are most severely affected by the disease and tooth loss. Figure 33-1 shows the clinical and radiographic status of a 53-year-old male following the completion of basic periodontal therapy for the establishment of infection control. Following periodontal treatment, the patient, originally diagnosed with severe chronic periodontitis, demonstrated a high standard of self-performed infection control and all lesions in the periodontal tissues had been resolved. Because of the severity of the periodontal destruction, remaining teeth posterior to the canines in the maxilla as well as one remaining mandibular molar had to be removed. Hence, the dentition was markedly reduced, not only with regard to the number of teeth but also in terms of the amount of remaining periodontal support. From a chewing comfort point of view, the patient was in

need of prosthetic rehabilitation, particularly in the posterior segments of the maxilla. The treatment options available included (1) a removable prosthesis or (2) implant-supported FPDs. Considering that the remaining teeth showed slightly increased mobility, implant-supported FPD seemed the more appropriate. In addition, the patient, if possible, preferred to have fixed prosthetic reconstructions.

Clinical and radiographic evaluation of the posterior jaw segments of the maxilla revealed that two implants might be placed in quadrant 1 between the canine and the anterior border of the maxillary sinus, while the dimension of the bone inferior to the sinus was judged inadequate for placement of implants (Fig. 33-1b, c). If the implant in position 15 was placed along the anterior wall of the sinus cavity and angulated slightly distally, space might be available to insert a pontic between the two implants and to provide the patient with a three-unit FPD. In quadrant 2, the bone dimensions were more favorable and it was judged feasible to install three implants. Hence, by providing the patient with two three-unit implant-supported FPDs in the posterior segments of the maxilla, a premolar occlusion could be established. The patient considered this treatment solution to be satisfactory with regard to his demands for improved chewing function. He had no requests for improved esthetics in the anterior segments, most likely because

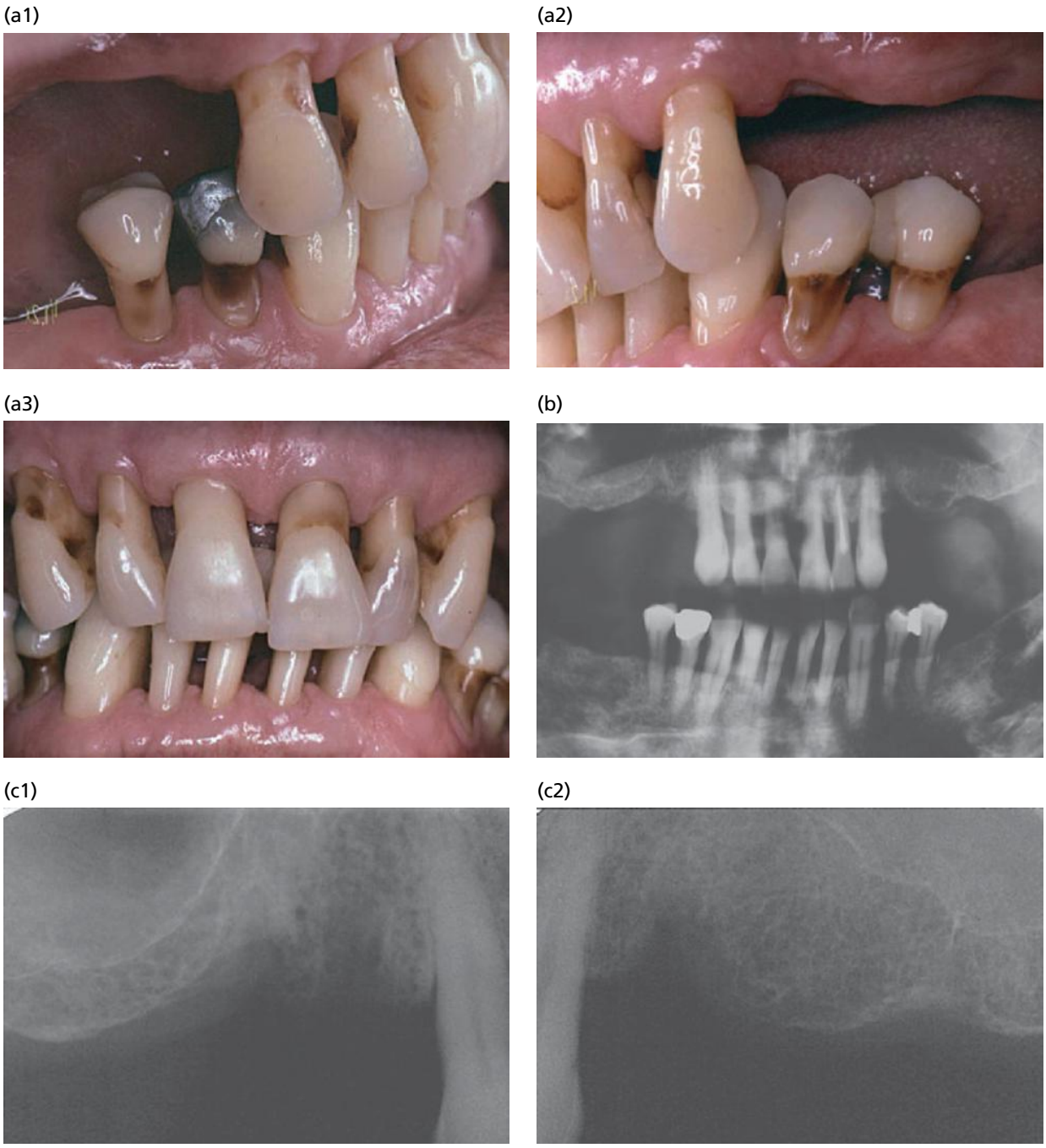
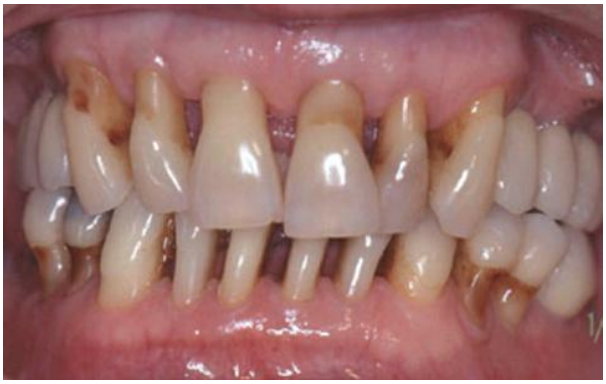
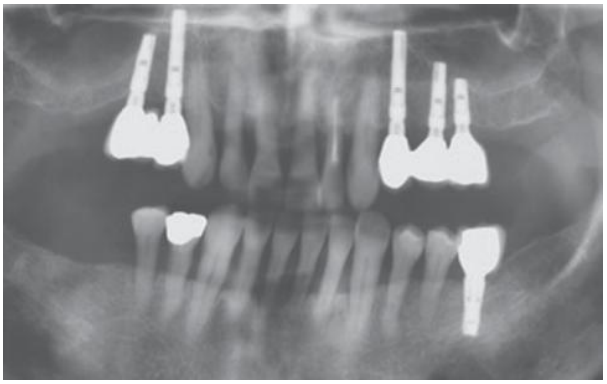


Fig. 33-1 53-year-old male patient with periodontally compromised dentition. (a–c) Clinical and radiographic status after periodontal treatment and establishment of infection control.

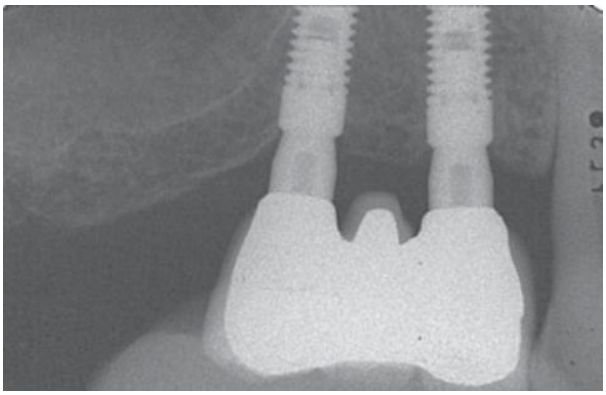
(d)



(e)



(f1)



(f2)

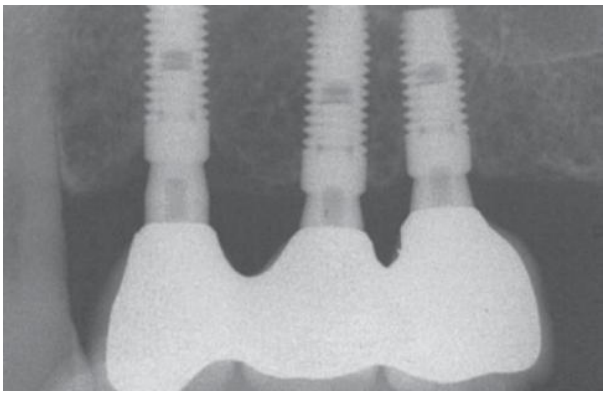
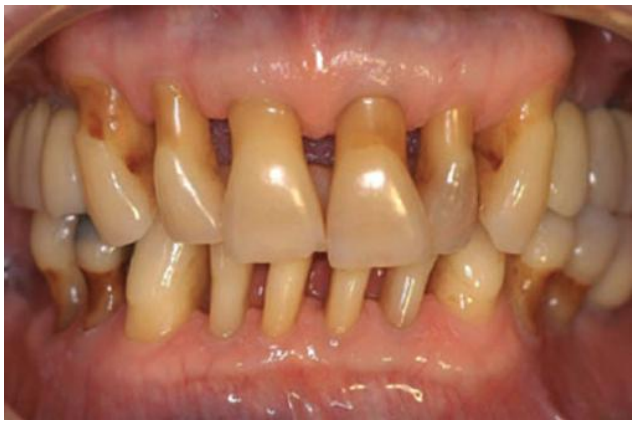
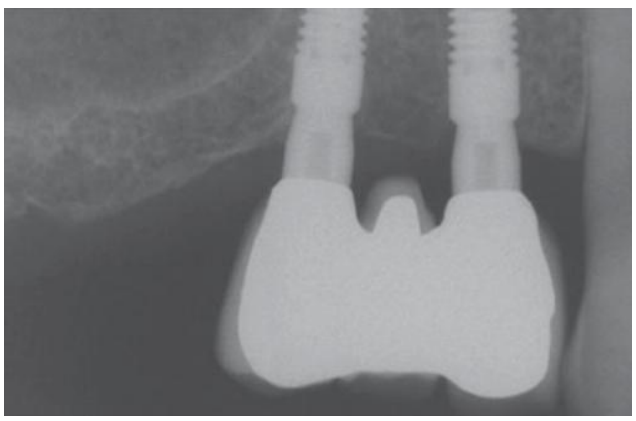


Fig. 33-1 (*Continued*) (d–f) Clinical and radiographic status after completion of the implant treatment.

(g)



(h1)



(h2)

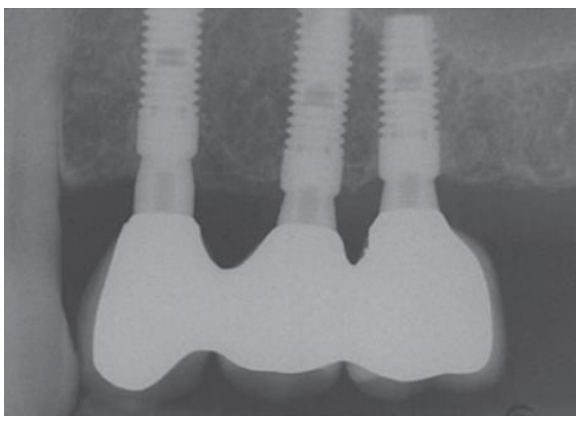


Fig. 33-1 (*Continued*) (g, h) Clinical and radiographic status 10 years after completion of the implant treatment. Note that there is no loss of bone support at the implants.

of a low lip line and because he only exposed the incisial half of the crown when smiling.

Figure 33-1d–f shows the outcome of the restorative treatment. In order to further improve the patient's chewing comfort, a single implant was inserted in the left side of the mandible, after the second premolar had been tilted mesially. After completion of the restorative treatment, the patient was enrolled in a maintenance care program, including recalls once every 6 months to secure a high standard of infection control and to provide preventive means to reduce the risk for development of root caries. The 10-year follow-up status (Fig. 33-1g, h) revealed healthy marginal tissues and no loss of supporting structures at both the implants and the teeth. The standard of self-performed infection control was excellent throughout the follow-up period.

Conclusion

The treatment outcome in this case clearly illustrates that the periodontitis-susceptible patient can be successfully treated with the use of implants and without signs of peri-implant bone loss over time, provided proper infection control is established and maintained. The recall visits for supportive therapy must include careful evaluation of both the periodontal and the peri-implant tissues for detection of signs of pathology, and proper decisions regarding indicated treatment (see Chapter 60).

Tooth versus implant

Treatment decisions regarding implant therapy or advanced periodontal therapy often relate to a single tooth. Figure 33-2 shows such a case. A 67-year-old woman presented with a localized advanced periodontal lesion at an abutment tooth in a three-unit FPD. The FPD was about 15 years old and the patient had no esthetic or functional complaints with regard to the FPD. Tooth 15 had a 10-mm deep pocket at the mesial aspect. The pocket was associated with a wide angular bone defect, and the tooth was positioned with its root in close proximity to the anterior wall of the maxillary sinus. If the tooth was extracted, a marked remodeling of the ridge in the area could be anticipated, and the amount of bone available in the region might become insufficient for implant placement to support a new FPD, unless sinus elevation and bone grafting procedures were performed.

The question in the treatment planning with regard to tooth 15 was whether there was a reasonable chance of saving tooth 15 and maintaining the FPD with periodontal therapy, or whether the tooth should be extracted and implants placed to support a new FPD? Considering the great functional value of the tooth, it was decided to perform flap elevation and to evaluate the potential for tissue regeneration. Following debridement (Fig. 33-2c), it was observed that the defect was wide and had the morphology of a combined one-/two-/three-wall defect. A regenerative approach (application of enamel matrix proteins; see Chapter 45) was selected. The healing resulted in a 6 mm gain in clinical attachment level and radiographic bone fill. The amount of soft tissue recession was minimal, as can be seen in the 6-year follow-up documentation (Fig. 33-2d, e).

Conclusion

Considering that implant therapy in this case most likely would have required sinus elevation and bone grafting to satisfy the patient's demands for esthetics and chewing function, the maintenance of tooth 15 through proper periodontal therapy was of great benefit to the patient.

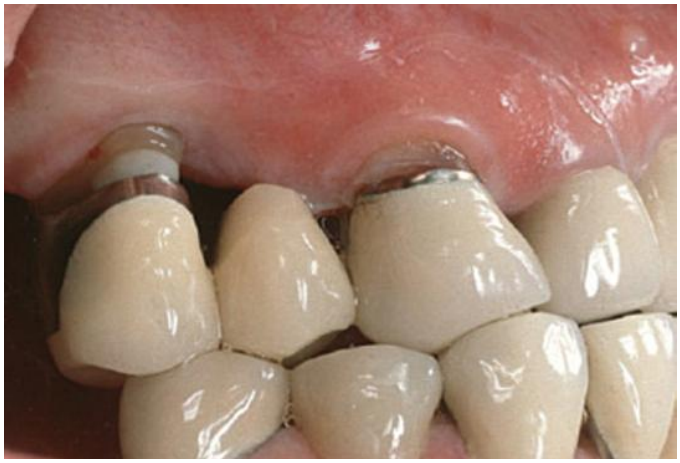
Aggressive periodontitis

Figure 33-3 shows a 22-year-old female patient diagnosed with aggressive periodontitis. The first molar in the maxillary right quadrant and in the mandibular left quadrant had already been lost due to advanced periodontal destruction. The patient asked for prosthetic replacement of the missing teeth. The clinical examination also disclosed the presence of deep angular defects at the first molar in the mandibular right quadrant and at the second premolar in the maxillary right quadrant. It seemed reasonable to plan for implant-supported restorations to replace the missing teeth 16 and 36. The more difficult question, however, related to the treatment of the periodontally compromised teeth 15 and 46 (Fig. 33-3c, d): Was it possible to successfully eliminate the periodontal lesions at teeth 15 and 46 with a good long-term prognosis for the teeth? Or should the teeth be removed and replaced with implant-supported restorations? Extraction of tooth 15 may be seen as a rational decision since implant therapy was planned in the region of tooth 16. However, from an esthetic perspective, it was preferable to maintain tooth 15 because the crown was intact and there was no loss of attachment or soft tissue height at the mesial aspect of the tooth (Fig. 33-3b).

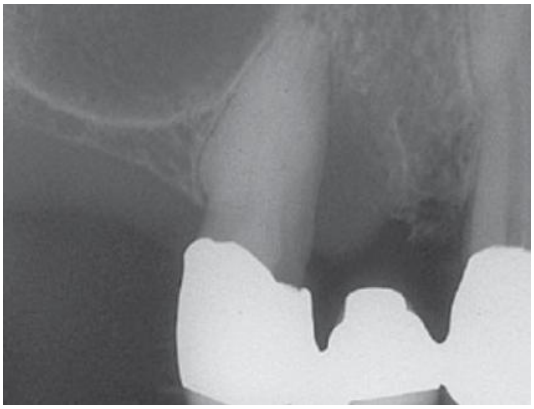
Patients with aggressive periodontitis can be successfully treated, as is well documented in the literature. Further, by applying a regenerative method in the surgical treatment of deep angular defects like those at teeth 15 and 46, the chance of attachment gain of a magnitude of >4 mm is markedly increased (Giannobile *et al.* 2003; Murphy & Gunsolley 2003). Hence, the treatment decisions made in this case were to first establish proper infection control and then to apply a regenerative surgical approach (guided tissue regeneration) in the periodontal treatment of the lesions at teeth 15 and 46.

Evaluation of the periodontal healing revealed closure of the pockets and *de novo* bone tissue formation. Single implant-supported restorations were subsequently performed to address the loss of teeth

(a)



(b)

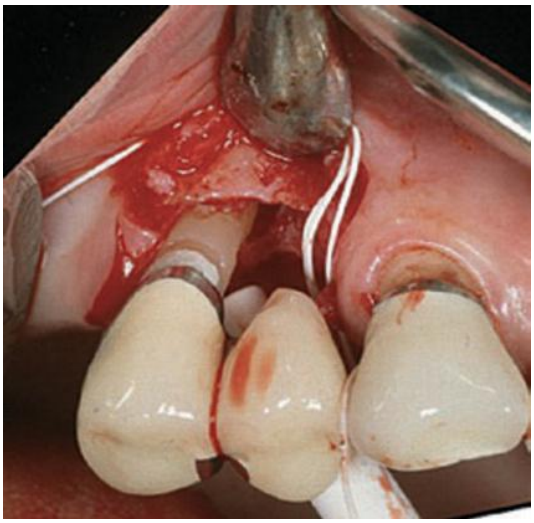


(c)

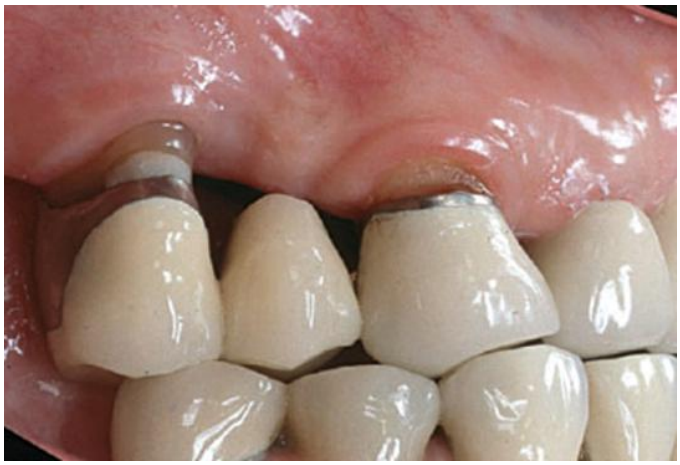
Clinical charting

Tooth	Probing depth				Mob
	m	b	d	l	
-					
15	10	4		6	
-					
13			4		
12					

(d)



(e)



(f)

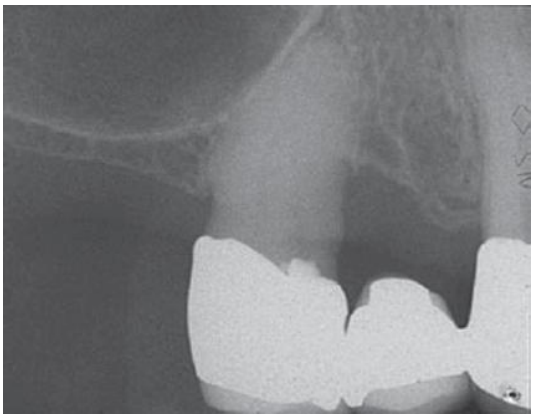


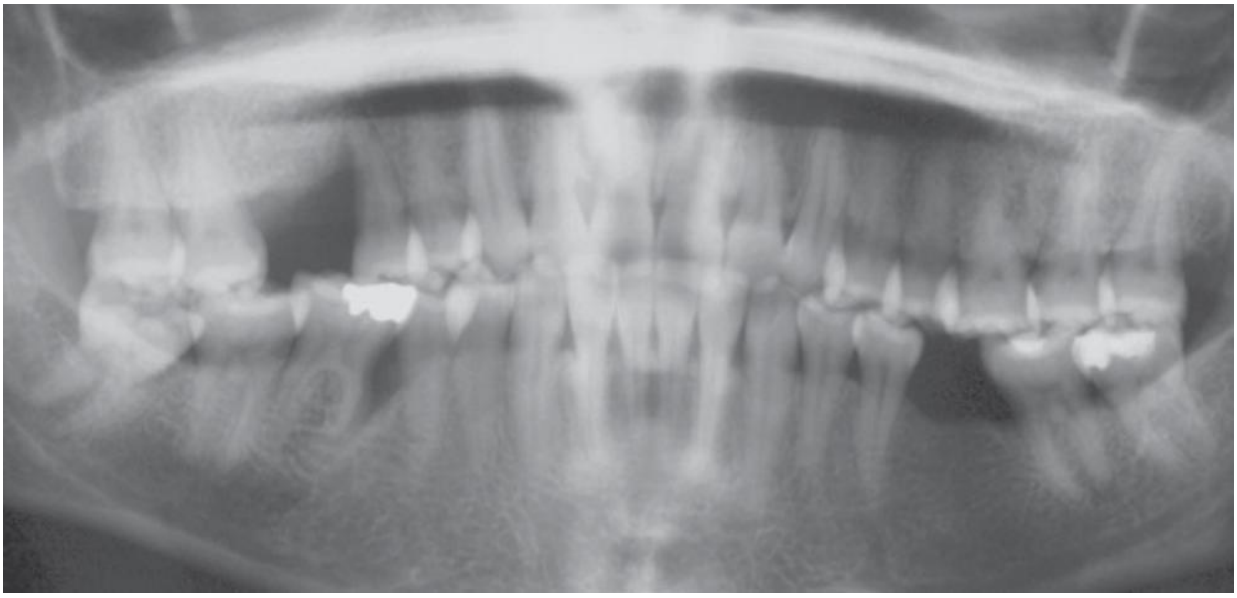
Fig. 33-2 67-year-old female patient with a localized advanced periodontal defect at tooth 15. (a–c) Clinical and radiographic status at the initial examination. (d) Flap elevated and the morphology of the defect can be determined as a wide combined one-/two-/three-wall defect. (e, f) Clinical and radiographic status 6 years after active treatment. (Courtesy of G. Heden.)

16 and 36 (Fig. 33-3e). After completion of the active treatment, the patient was assigned to a supportive care program with recall appointments once every 6 months. Figure 33-3f–i shows the outcome at 12 years post treatment. The regained height of the periodontal tissue support at teeth 15 and 46 following the active treatment was maintained over the years, and optimal bone height is seen around the single implants. The good long-term prognosis in this case is attributed to a high quality of infection control and careful monitoring during the maintenance period.

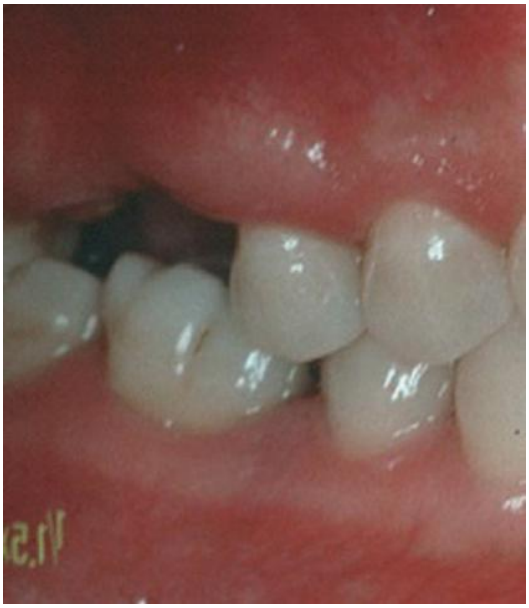
Furcation problems

Even if the goal of the treatment of patients with periodontitis is preservation of teeth, there may be situations when this goal seems less meaningful

(a)



(b)



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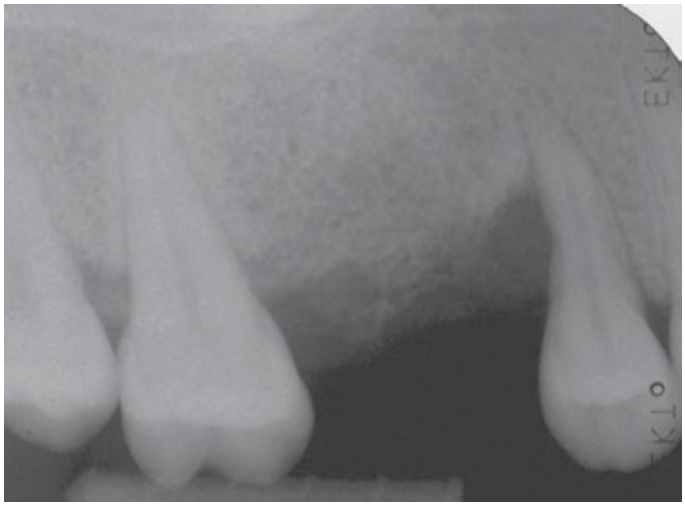
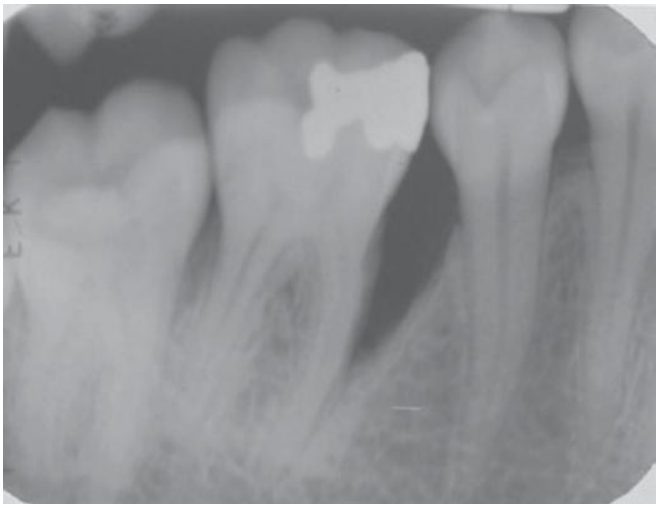


(d)



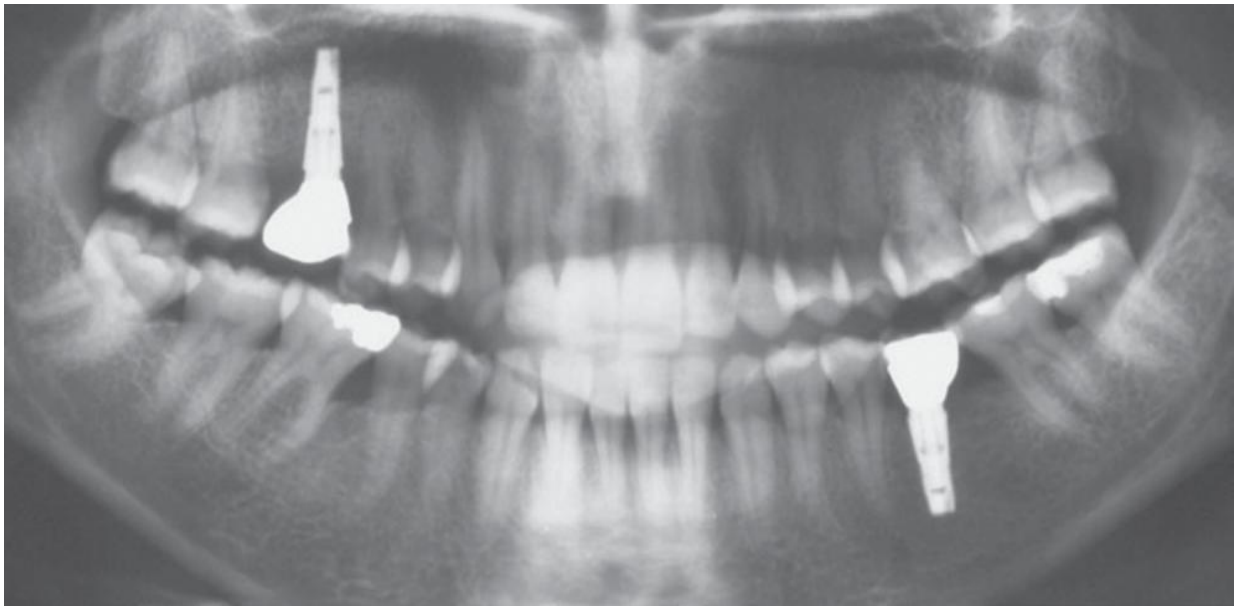
(e)

Clinical charting

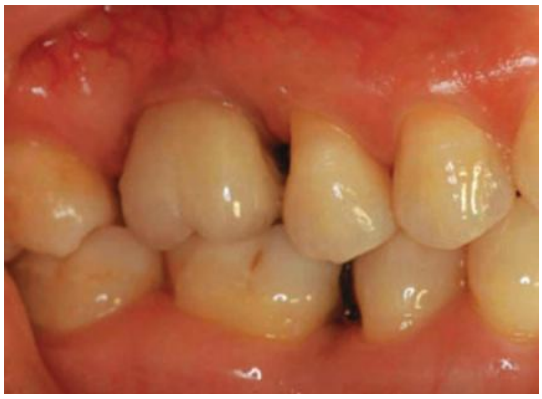
Tooth	Probing Depth				Mob
	m	b	d	l	
17	4		4		
-					
15			9	5	
14					
47			4		
46	10		4	5	
45					
44					

Fig. 33-3 22-year-old female patient diagnosed as a case of aggressive periodontitis. (a–e) Clinical and radiographic status at the initial examination. Localized advanced periodontal lesions are diagnosed at teeth 15 and 46.

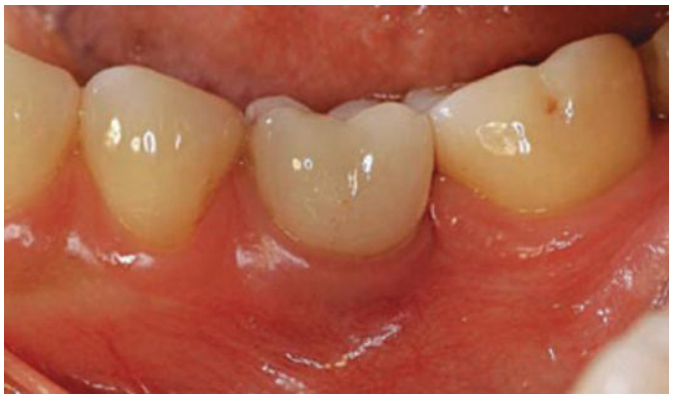
(f)



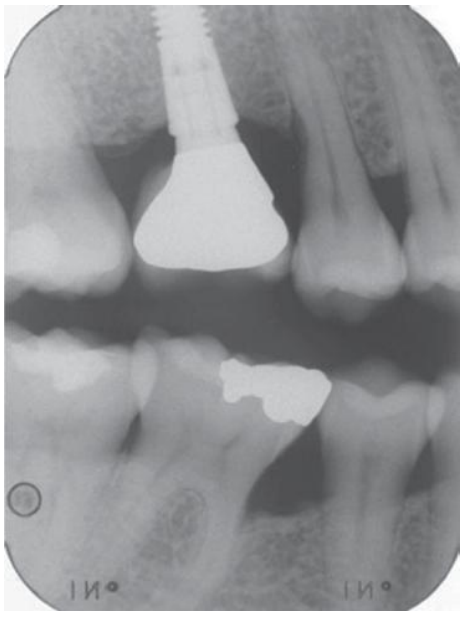
(g)



(h)



(i)



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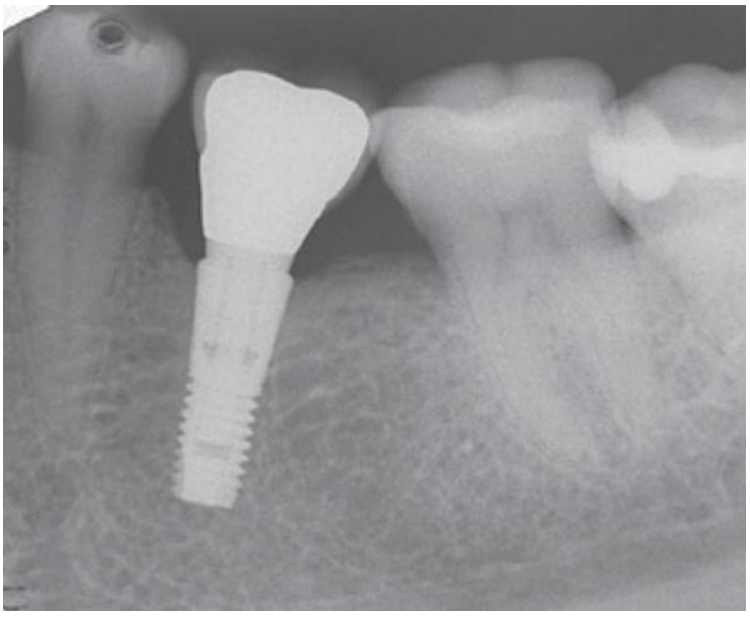
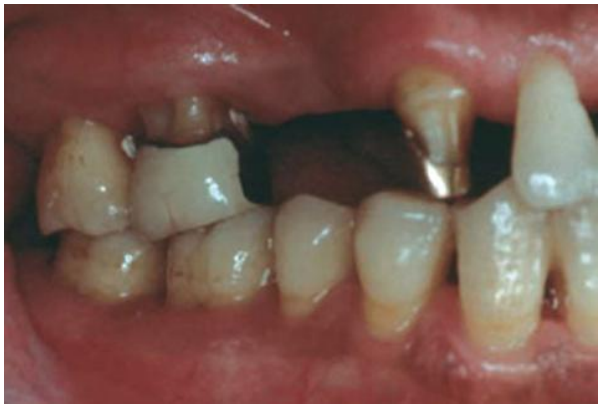


Fig. 33-3 (*Continued*) (f) Radiographic view after periodontal and implant treatment. (g–j) Clinical and radiographic status 12 years after active treatment.

(a)

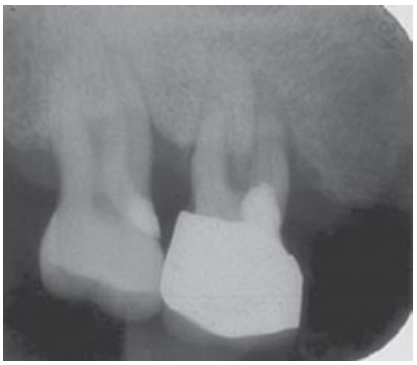


(b)

Clinical charting

Tooth	Probing Depth m	b	d	l	Furc	Mob
-						
17	7	6	6	4	mbd III	
16	6	6	5	5	mbd III	1
-						
-						
13			4			

(c)



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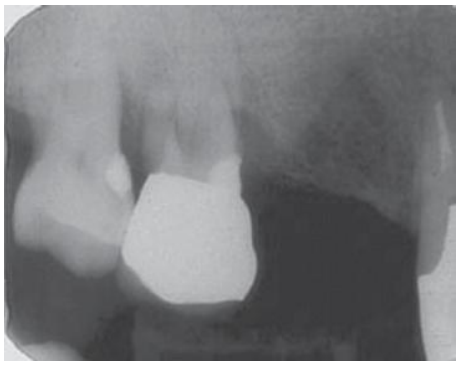

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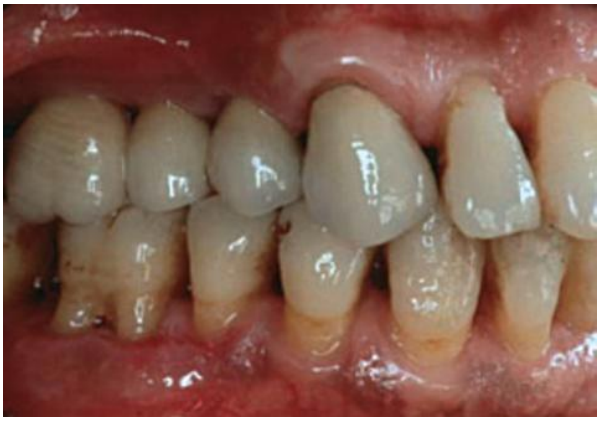

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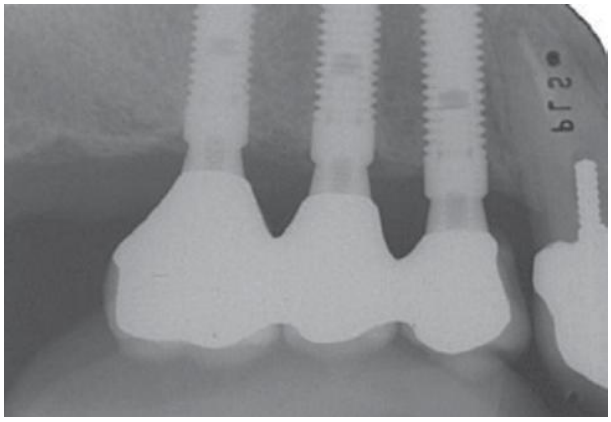


Fig. 33-4 52-year-old male patient with advanced periodontal destruction at the remaining molars in the maxillary right quadrant. (a–d) Clinical and radiographic status at the initial examination. (e, f) Clinical and radiographic status 2 years after active treatment.

in relation to the patient's need for prosthetic rehabilitation. Such a situation is illustrated in Fig. 33-4. The patient was missing the two premolars in the first quadrant and the molars present had advanced periodontal destruction and through-and-through furcation involvement (class III). The patient requested a fixed restoration to substitute for the missing premolars. A possible treatment solution following periodontal therapy could involve root separation of the molars, after proper endodontic therapy, and the maintenance of, for example, the palatal roots of the molars to be used as posterior abutments in a fixed tooth-supported prosthesis 17 … 13. However, advanced inter-radicular periodontal destruction was identified by furcation probing, indicating that the palatal roots might not have enough remaining periodontal support in order to provide functional stability of a straight FPD (17 … 13). The clinical and radiographic examination revealed that the alveolar process in the premolar–molar region had proper dimensions for implant placement. An alternative treatment solution to

satisfy the patient's demands for improved function and esthetics could therefore include implant placement to support an FPD.

The decision in this case was to extract the two molars and, following proper periodontal treatment of the remaining dentition and establishment of adequate infection control, to provide the patient with a three-unit implant-supported FPD and a single-crown restoration on tooth 13 (Fig. 33-4e, f). After completion of active treatment, this patient was enrolled in a maintenance care program including recall appointments once every 4 months.

Single-tooth problem in the esthetic zone

Figure 33-5 shows the maxillary front tooth region of a 45-year-old female patient diagnosed with generalized chronic periodontitis. The right central incisor has severe periodontal destruction with probing pocket depths (PPDs) of 10–11 mm and obvious signs of inflammation at its distal and palatal surfaces. The tooth responded positively to sensibility testing. Interdental black triangles can be seen in the entire anterior tooth region because of approximal loss of periodontal attachment and soft tissue recession. Based on the results of the comprehensive examination, tooth 11 was judged to have a questionable prognosis, whereas it would be possible to resolve the periodontal lesions at the other anterior teeth by non-surgical means and improved self-performed infection control. Since the patient had a high lip line, potential recession of the soft tissue margins as a consequence of the treatment was a factor that had to be considered, particularly in relation to the treatment decision for the severely affected right central incisor. Regenerative therapy may have allowed the tooth to be maintained, but would the treatment result in acceptable esthetics? The facts that the defect had a wide extension (buccolingually) and that the adjacent teeth presented with approximal attachment loss indicated that there was an obvious risk for loss of tissue height during healing following a surgical intervention. An alternative treatment approach could include the extraction of tooth 11 and installation of a single implant. This alternative solution would also offer the possibility of correcting the position of the crown of tooth 11. In discussing the different treatment alternatives and their consequences with the patient, it was apparent that she preferred to have the position of the tooth corrected as part of the treatment. Hence, based on the careful analysis of the esthetic problems associated with the treatment of the tooth, it was decided to extract the tooth and make an implant-supported restoration. By using the crown together with a portion of the root as a pontic, support to the surrounding soft tissues during initial healing of the extraction socket was provided (Fig. 33-5f).

Evaluation of the outcome of the cause-related phase of therapy, which included oral hygiene instructions, plaque control evaluations, and full-mouth pocket/root debridement, disclosed no remaining pathologically deepened pockets in the front tooth region (Fig. 33-5g). The radiographic evaluation of the extraction site 2 months after the removal of tooth 11 (Fig. 33-5h) showed a preserved bone height at the neighboring approximal tooth sites and gain of bone in the extraction socket. Clinically, only minor changes had taken place in the position of the soft tissue margin at the extraction site. A single implant was installed and after 3 months the prosthetic therapy was completed.

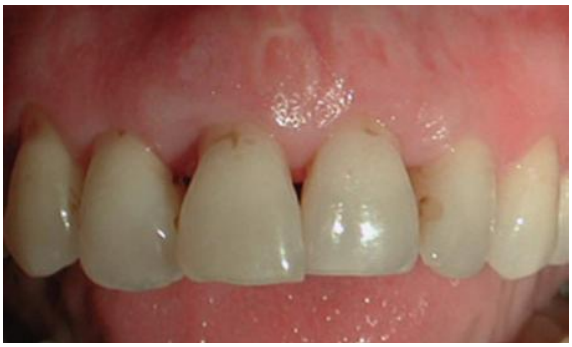
Following the completion of the active treatment, the patient was scheduled for supportive care every 6 months. Figure 33-5i–k shows the clinical and radiographic status at the 1-year follow-up examination. The position of the soft tissue margin was at a similar level at the implant-supported crown and the contralateral incisor. Compared to the pretreatment conditions (Fig. 33-5a), only minimal changes in the position of the soft tissue margins at the implant-borne restoration were evident. Overall some recession of the soft tissue margin had occurred as a consequence of the establishment of healthy marginal tissues.

Conclusion: Although it may be possible to maintain a tooth with severe local periodontal destruction by regenerative periodontal surgery, soft tissue recession as a consequence of the treatment may render the treatment outcome unsatisfactory from an esthetic perspective. Selection of a treatment approach involving tooth extraction and implant therapy instead of periodontal therapy should be based on a careful evaluation of the potential of the various treatment approaches to satisfy the patient's demands for esthetics.

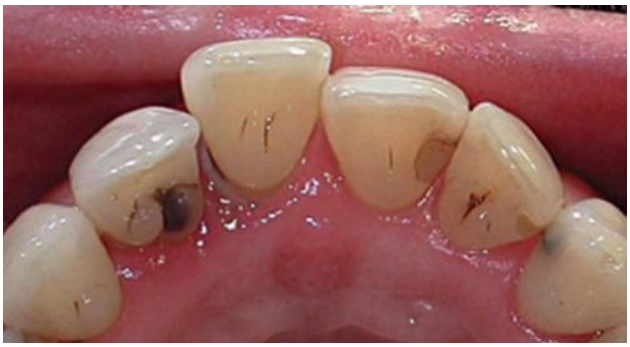
Conclusion

The prognosis for the properly treated periodontitis-affected tooth is at least as good as that for the implant. An increased risk of failure of implant therapy has been reported for periodontitis-susceptible patients. Proper infection control is a critical factor for the long-term success of implant therapy in the periodontally compromised patient. Regular recalls for monitoring with regard to clinical signs of pathology and supportive care should be an integral part of the implant treatment protocol for the periodontally compromised patient.

(a)



(b)



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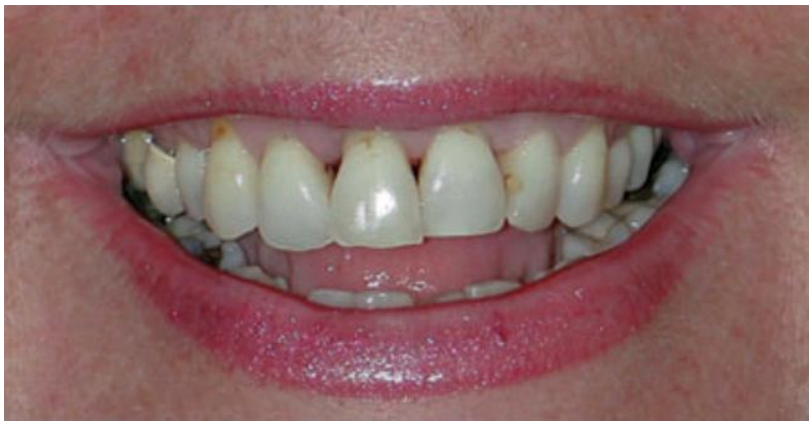

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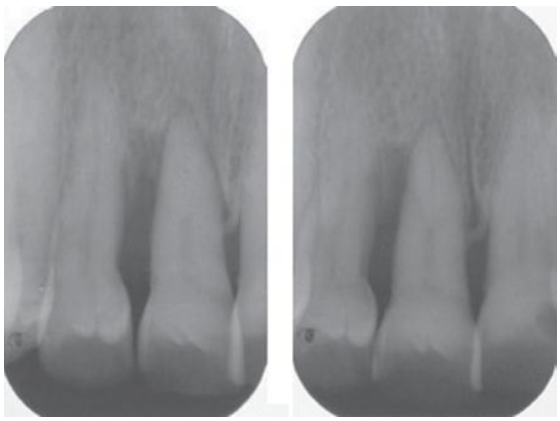
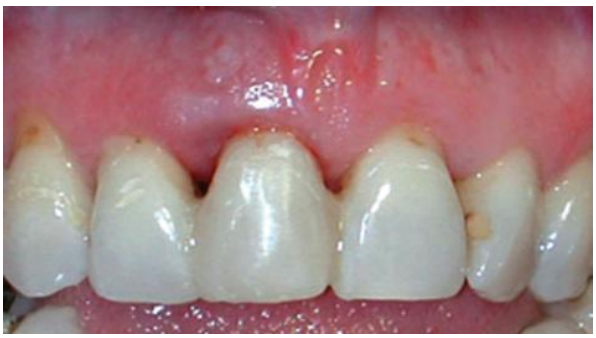


(e)

Clinical charting

Tooth	Probing Depth				Mob
	m	b	d	l	
13	4				
12	5		4	4	
11	4	5	11	10	1
21	5				
22	4				
23			4		

(f)



(g)

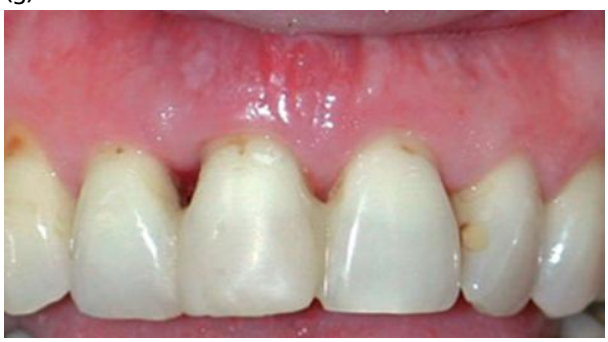
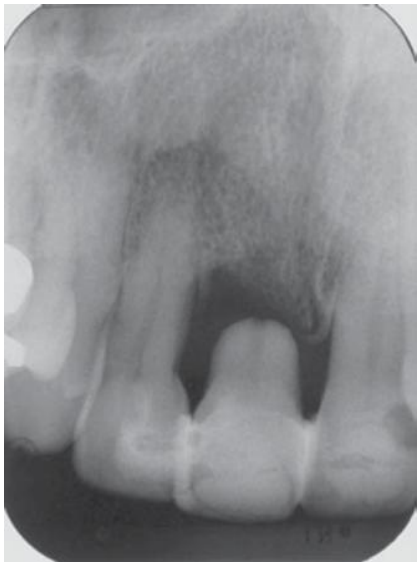
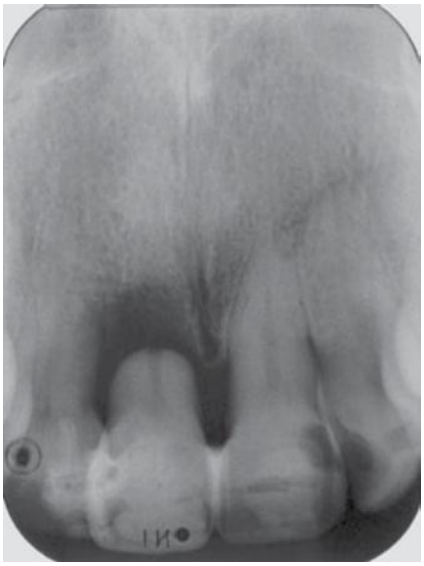


Fig. 33-5 45-year-old female patient with generalized chronic periodontitis. (a–e) Clinical and radiographic status of the maxillary anterior teeth at the initial examination. The right central incisor has severe periodontal destruction with probing pocket depths of 10–11 mm. (f) Tooth 11 was extracted and the tooth was reshaped and fixed to the neighboring teeth to support the soft tissues during the initial healing of the extraction socket. (g, h) Clinical and radiographic status 2 months post extraction when the implant placement surgery was performed.

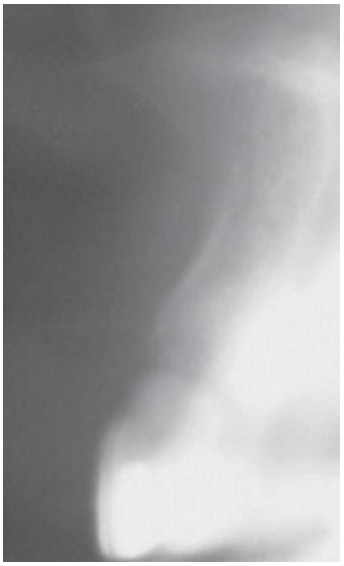
(h1)



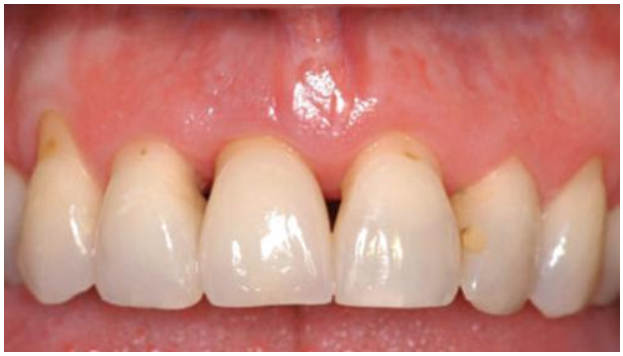
(h2)



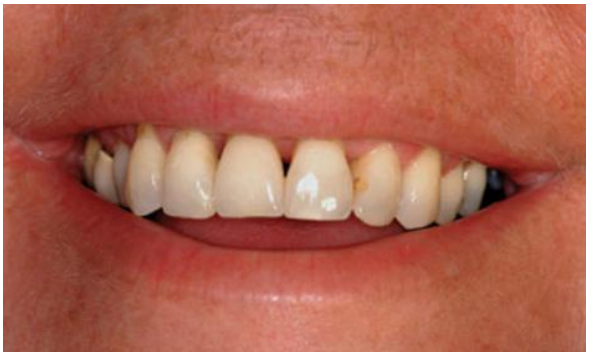
(h3)



(i)



(j)



(k)

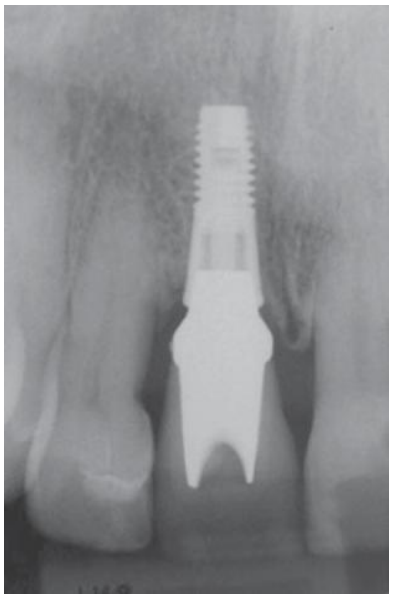


Fig. 33-5 (*Continued*) (i–k) Clinical and radiographic status 1 year after completion of the periodontal and implant treatment.

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Chapter 34

Systemic Phase of Therapy

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Introduction

The systemic phase of periodontal therapy should be concerned with general health implications of periodontal diseases and periodontal treatment. While the former aspects are described in Chapters 14, 15, 18, and 23, the latter aspects are presented in this chapter.

The systemic phase of periodontal therapy is designed to protect the patient against unforeseen systemic reactions, to prevent complications affecting the general health of the patient, and to protect the healthcare providers from (predominantly infectious) hazards in conjunction with the treatment of patients at risk.

In order to adequately plan the systemic phase, results from a health questionnaire (see Chapter 26) filled in by the patient in the waiting area, the family and social history, the general medical, and, in particular, the tobacco use history have to be evaluated. Also, any extra- and intra-oral findings pertinent to the patient's systemic health have to be considered.

The systemic phase of periodontal therapy encompasses:

- Precautions for protecting the general health of the dental team and other patients against infectious and contagious diseases
- Protection against potentially harmful systemic effects of routine therapy
- Making allowances for systemic diseases or disorders that may influence the etiology of the patient's periodontal conditions, the healing potential, and the systemic response to therapy
- Controlling anxiety and low pain threshold
- Risk assessment and considerations of systemic supportive therapy
- Smoking counseling and instituting tobacco use cessation programs.

Protection of the dental team and other patients against infectious diseases

As a general principle, routine periodontal therapy should be postponed in a patient with an active contagious state of a disease until he/she has received adequate medical treatment. Given the fact that patients may not always be aware of such a state or that all manifestations of disease may have abated, but the patient may still be a carrier of infectious agents, routine dental treatment should be carried out under special precautions against transmission of the most serious diseases that can be transmitted orally. These include infectious hepatitis (Levin *et al*. 1974), human immunodeficiency virus (HIV) infection, and venereal diseases (Chue 1975). Hygiene in the dental office, therefore, has to address the most contagious level of infective agents, the hepatitis viruses, and cope with the prevention of the transmission of these infections.

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

As a minimal precaution, the wearing of rubber gloves and a mouth mask is highly recommended for all dental therapy in all patients. Also, protective glasses for both the therapist and the patient should be worn during procedures generating aerosols.

Herpes simplex virus (Nahmias & Roizman 1973) and tuberculosis are further infectious diseases with a high transmission potential. Special precautions should be observed in patients with a recent history (2–3 years) of infectious hepatitis, although the dental team may be vaccinated against hepatitis. If the medical history and the oral examination reveal that the patient may have overt or hidden systemic disease, he/she should be referred for medical examination prior to being enrolled into comprehensive periodontal care.

Protection of the patient's health

A number of systemic conditions may affect treatment planning, although they may have no direct relevance to the pathogenesis and healing potential of periodontal lesions. Since over 50% of all patients over 40 years of age may have systemic conditions or take medications affecting periodontal therapy, these aspects have to be carefully appraised prior to instituting further therapeutic measures.

For patients with life-threatening systemic conditions, such as coronary insufficiency or hypertensive heart disease, their physicians should be consulted about appropriate management and whether treatment should be performed in a hospital or clinic rather than a private practice setting. If the dental office is considered to be an adequate environment for treating these patients, shorter appointments should be scheduled. The treatment should be performed with complete pain control using local anesthesia without any or with minimal vasoconstrictive substitutes.

Prevention of complications

The complications most commonly encountered in the dental office are:

- Infection
- Bleeding
- Cardiovascular incidents
- Allergic reactions
- Specific medications: bisphosphonates.

These may be prevented if appropriate precautions are taken. Hence, gaining awareness of possible complications from a medical history is an important step in treatment planning and comprehensive patient care.

Infection, specifically bacterial endocarditis

Patients with cardiac disease or disorders involving the endocardium are susceptible to endocarditis as a result of blood-borne infection. Such conditions include rheumatic heart disease, congenital valvular heart defects, aortic valvular diseases, and collagen diseases involving the endocardium. Patients wearing prosthetic valves belong to a special high-risk group. In addition, patients wearing prosthetic heart appliances belong to this risk group.

The major procedures thought to be the cause of bacterial endocarditis are extractions and scaling and/or root planing, possibly leading to significant bleeding and bacteremia (Durack 1995). Hence, it is not surprising that national societies have issued guidelines for antibiotic prophylaxis against bacterial endocarditis: USA (Dajani *et al*. 1997) and UK (Gould *et al*. 2006; Federation Dentaire Internationale 1987). The common belief is that bacteremia occurs only when dental procedures cause bleeding and not when there is no bleeding. Hence, procedures such as extractions, root instrumentation, and periodontal and implant surgical procedures would require antibiotic prophylaxis, while, for example, the placement of fillings does not. This hypothesis was addressed in a study in children for whom 14 various dentogingival manipulative procedures were evaluated (Roberts *et al*. 1997). It was clearly demonstrated that there was no relationship between the existence of bleeding and bacteremia. However, the number of oral organisms isolated from the blood was statistically significantly higher when bleeding was present. It was concluded that the cumulative exposure to bacteremia is significantly greater from "everyday" procedures, compared to dental procedures, and hence, the cause of bacterial endocarditis may be attributable to such cumulative everyday exposures that are often thousands to millions of times greater than that occurring following surgical procedures, such as extractions of teeth (Roberts 1999).

Antibiotic prophylaxis to prevent bacterial endocarditis is predominantly based on anecdotal and circumstantial evidence, and hence, the cause of bacterial endocarditis is much more likely to be due to such cumulative everyday exposures which occur much more often than dental procedures (Baltch *et al*. 1982). A case study, however, did not identify a link between endocarditis and dental treatment (Guntheroth 1984; Strom *et al*. 1998). Moreover, accumulating evidence suggests that bacteremia may easily be produced, for example by toothbrushing or chewing gum, rather than by single procedures causing bleeding. Hence, understanding of endocarditis causation has shifted from procedure-related bacteremia to cumulative or "everyday" bacteremia (Gould *et al*. 2006).

Indeed, a systematic review by the Cochrane Collaboration (Oliver *et al*. 2004) concluded that there was no conclusive evidence to support the use of prophylactic penicillin to prevent bacterial endocarditis in invasive dental procedures. This review did not identify any randomized controlled clinical trials, any controlled clinical trials or any cohort studies. From a total of three case–control studies (Imperiale & Horowitz 1990; Van der Meer *et al*. 1992; Lacassin

Table 34-1 Recommendations of the British Society for Antimicrobial Chemotherapy (BSAC) for the prophylaxis of high-risk bacterial endocarditis.

Population	Age			Timing of dose before procedure
	>10 years	≥5 to <10 years	>5 years	
General	Amoxicillin 2 g *per os*	Amoxicillin 1.5 g *per os*	Amoxicillin 750 mg *per os*	1 hour
Allergic to penicillin	Clindamycin 600 mg *per os*	Clindamycin 300 mg *per os*	Clindamycin 150 mg *per os*	1 hour
Allergic to penicillin and unable to swallow capsules	Azithromycin 500 mg *per os*	Azithromycin 300 mg *per os*	Azithromycin 200 mg *per os*	1 hour

Where a course of treatment involves several visits, the antibiotic regimen should alternate between amoxicillin and clindamycin.
Preoperative mouth rinse with chlorhexidine gluconate 0.2% (10 mL for 1 minute).
Source: Gould *et al.* (2006). Reproduced with permission from Oxford University Press.

et al. 1995), only one study (Van der Meer *et al*. 1992) complied with the inclusion criteria. Details of 349 individuals who developed definite native-valve endocarditis in the Netherlands within a 2-year period were collected. Controls had not been diagnosed with endocarditis, but had one of the cardiac conditions and were outpatients of one of five hospitals. Controls were matched for age and had undergone a dental procedure within 180 days of their interview. No significant protective effect of antibiotic prophylaxis was seen against endocarditis.

It has to be acknowledged, however, that clinicians feel bound by guidelines and medicolegal considerations to provide antibiotic prophylaxis rather than by the best available evidence. Ethically, practitioners need to discuss the potential benefits and harms of antibiotic prophylaxis with patients and their cardiologists before the decision is made to administer antibiotics (Oliver *et al*. 2004). Considering the change in paradigms regarding bacterial endocarditis, a task force of the British Society for Antimicrobial Chemotherapy published new guidelines (Gould *et al*. 2006) (Table 34-1). According to these, the practice of giving antibiotics is reserved for those patients with a history of healed bacterial endocarditis, prosthetic heart valves, and surgically constructed conduits, while patients with other cardiac abnormalities should no longer receive antibiotic prophylaxis before dental procedures. The American Heart Association has recently issued similar guidelines (Lockhart *et al.* 2013; Costantinides *et al.* 2014). An information summary for the patient has been published by the British Society for Antimicrobial Chemotherapy (Table 34-2).

Table 34-2 British Society for Antimicrobial Chemotherapy (BSAC) Prevention of Infective Endocarditis Guidelines. Information for Patients and Parents (February 2006).

A BSAC group of experts has spent a lot of time carefully looking at whether dental treatment procedures are a possible cause of infective endocarditis (IE) [sometimes called bacterial endocarditis (BE)], which is infection of the heart valve.

After a very detailed analysis of all the available evidence they have concluded that there is no evidence that dental treatment procedures increase the risk of these infections.

Therefore, it is recommended that the current practice of giving patients antibiotics before dental treatment be stopped for all patients with cardiac abnormalities, except for those who have a history of healed IE, prosthetic heart valves and surgically constructed conduits.

The main reasons for this are the lack of any supporting evidence that dental treatment leads to IE and the increasing worry that administration of antibiotics may lead to other serious complications such as anaphylaxis (severe allergy) or antibiotic resistance.

The advice from the BSAC is that patients should concentrate on achieving and keeping a high standard of oral and dental health, as this does reduce the risk of endocarditis. Help for this will be provided by your Dental Professional.

Source: Gould *et al*. (2006). Reproduced with permission from Oxford University Press.

Bleeding

Due consideration must be given to patients on anticoagulant medication or on preventive anticoagulant drugs such as salicylates. For the first group of patients, a consultation with their physician is indispensable. Especially prior to periodontal or implant surgical procedures, intake of anticoagulant medication should be temporarily adjusted in cooperation with the physician. Careful planning and timing of these procedures are mandatory.

Salicylate therapy does not generally create issues for routine dental therapy, including surgical procedures, although consultation with the patient's physician is still advisable.

Individuals with known cirrhosis of the liver, or even patients with high alcohol consumption over many years without diagnosed cirrhosis, are at a potential risk for bleeding complications during periodontal and/or implant surgery, as their clotting mechanisms may be affected (Nichols *et al*. 1974). Again, medical consultation is recommended prior to periodontal treatment of such patients.

Extra precautions against bleeding should be taken when treating patients with any kind of blood dyscrasia or hemophilia. Following mandatory consultation with the patient's physician, it is

recommended to render treatment in small segments (only a few teeth being instrumented at each visit) and to apply periodontal dressings over the treated area, even if the treatment only consisted of root instrumentation. With systematic periodontal treatment and institution of efficacious oral hygiene measures, the annoying symptom of oral bleeding can often be controlled irrespective of the patient's bleeding disorder.

Cardiovascular incidents

Cardiac patients are often treated with anticoagulants and, hence, may develop bleeding problems (as indicated above), especially if the given drugs (e.g. aspirin, indomethacin, sulfonamide, tetracycline) interact with coagulation. Other cardiovascular drugs (antihypertensives, antiarrhythmics, diuretics) are often given to these patients and may increase the danger of hypotensive episodes during dental treatment.

Stress associated with dental procedures may precipitate anginal pain or congestive heart failure in patients with cardiovascular disease. Therefore, every effort should be made in this patient population to keep dental appointments brief and to control anxiety and pain.

Allergic reactions and drug interactions

Full awareness of the patient's known allergies and the medications he/she is taking is essential before any drug is prescribed or administered during treatment. The most common allergic reactions encountered in the dental office are those to some local anesthetics (Novocain®), penicillins, sulfa derivatives, and disinfectants, such as iodine. In case of known allergies, such drugs must be avoided. A consultation with the patient's physician is advisable to discuss the possible administration of replacement drugs.

Many patients – over 90% over the age of 60 years – regularly take medications for various systemic conditions. Special attention has to be devoted to possible drug interactions, especially in the elderly. Drugs prescribed as part of periodontal therapy or used during treatment may interfere with the effectiveness of drugs the patient is already taking, possibly creating a hazardous interaction. Hence, no new drugs should be prescribed without fully understanding their possible interaction with drugs already in use. Dentists should never change an existing drug therapy without prior discussion with and preferably written consent from the physician.

Many patients regularly take tranquilizers and antidepressant drugs that have the potential for summation and synergistic effects with drugs that may be used during periodontal therapy. Moreover, the interaction and potentiation of these drugs with alcohol should be discussed with the patient.

Systemic diseases, disorders or conditions influencing pathogenesis and healing potential

All possible attempts should be made to alleviate the effects of systemic diseases, such as blood disorders and diabetes mellitus, before any periodontal treatment is initiated. However, cause-related therapy may easily be carried out and generally results in remarkable success even during active stages of these systemic conditions. How far the treatment plan should progress with respect to pocket reduction and/or regenerative procedures depends on the seriousness of the patient's systemic involvement and likewise, to a great extent, on the potential threat to the patient's health from incomplete periodontal therapy.

Diabetes control, as an example, may be facilitated by successful control of the periodontal infection (Grossi *et al*. 1997; Genco *et al*. 2005). Thus, periodontal treatment may have a beneficial effect on the systemic health of the patient (see Chapter 23). Palliative treatment of advanced periodontitis with furcation involvement and residual deep pockets that cannot be reduced should not be undertaken for such patients. Rather, the involved teeth with repeated abscesses and pus formation should be extracted if necessary to accomplish infection control.

Clinical experience indicates that the healing response of the periodontal tissues is as good in patients with diabetes as in healthy individuals provided that the diabetes is fairly well controlled. However, juveniles with diabetes may have angiopathic changes associated with a lowered resistance to infection that may require the use of antibiotics following periodontal or implant surgery. With controlled diabetes, premedication with antibiotics is not indicated. Hypoglycemia may be aggravated by the stress of periodontal surgery and, hence, precautions have to be taken to avoid hypoglycemic reactions in such patients.

Therapeutic doses of cortisone over a long period of time may cause considerable metabolic effects with systemic manifestations of a reduced rate of fibroblastic activity and hence, a lowered resistance to infection during wound healing. Nevertheless, such patients can be treated successfully by regular cause-related therapy with no significant delay in healing. The use of antibiotics is not recommended for these patients, unless there is a serious infectious condition in the mouth associated with the development of fever.

Specific medications: Bisphosphonates as a threat to implant therapy

More than 10 years ago it was discovered that nitrogen-containing bisphosphonates inhibit an enzyme that controls osteoclastic function. The inhibition of this enzyme also inhibits the migration of the cells

responsible for osseous healing. Hence, it is most likely that osteonecrosis may result from the inhibition of cell migration in case of surgically exposed bone such as in implant installation. Bisphosphonate-related osteonecrosis of the jaws (BRONJ), therefore, represents a risk that should not be underestimated even in patients who are taking *oral* bisphosphonates. It should be a warning to all dentists that BRONJ has been observed as early as 1 year after the *oral* administration of biphosphonates (Sedghizadeh *et al*. 2009). Following the reporting of these results, a new pharmacokinetic model was developed to assess drug accumulation at 1 year. In this model, the accumulated concentration of bisphosphonates in bone appeared to predict toxic levels that lead to poor healing following exposure of jaw bone as a result of surgical therapy (Landesberg *et al.* 2008). In this model, the relevant toxicity level does not necessarily affect osteoclasts as hitherto believed, but it affects keratinocytes, endothelial cells, fibroblasts, macrophages, osteoblasts, osteoclast precursor bone marrow cells, and T cells. All these cells are heavily involved in the healing of surgically denuded bone. Hence, it is most likely that nitrogen-containing bisphosphonates impair osseous wound healing and this leads to BRONJ. Non-nitrogen bisphosphonates do not cause BRONJ.

The *in vitro* threshold for inhibition of keratinocyte migration (0.1 µM) was used as the toxic bisphosphonate level for wound healing inhibition in cases of surgically denuded bone. By administering an equivalent of 70 mg of Fosamax® weekly, the number of doses resulting in toxic threshold levels could be calculated for various bone masses. The size of an individual's skeleton may therefore be the determining factor for the risk of BRONJ. Since the total quantity of bone mineral in which nitrogen-containing bisphosphonates are stored affects the toxic threshold of a patient, it is obvious that the skeleton of smaller patients will reach toxic levels sooner than that of larger patients. Once the toxic threshold for nitrogen-containing bisphosphonates in bone is surpassed, osteoclastic resorption will release enough drug to inhibit the ingrowth of the cells indispensable for healing of denuded bone.

In patients on bisphosphonate medication, it is of utmost importance to carefully evaluate the history of the medication and relate it to the habitus of the patient before making decisions on possible implant or other surgical therapy. Consulting with the patient's physician is highly recommended.

Control of anxiety and pain

Many patients interested in maintaining a healthy dentition do not regularly seek dental care because of anxiety and apprehension related to such treatment. A recent study conducted in Australia revealed a prevalence of dental fear in adults ranging from 7.8% to 18.8% and of dental phobia ranging from 0.9% to 5.4% (Armfield 2010). Modern dentistry now offers a variety of effective means for controlling pain and apprehension. This, in turn, means that dental treatment should no longer be as feared by these patients. During the history taking and oral examination, the patient's profile regarding anxiety and pain thresholds should be considered.

Prior to therapy, it may be indicated to premedicate an apprehensive patient using diazepams (benzodiazepine, Valium®, 2–5 mg) taken the night before, in the morning, and half an hour before an extensive and/or surgical procedure. Painless dental care can be achieved by carefully applying local anesthetics.

Postoperative analgesic medication, such as nonsteroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties, are recommended. Diclofenac potassium, the active ingredient of Voltaren® Rapide, inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. Following any kind of periodontal and implant surgery, 50 mg twice daily of Voltaren® Rapide is administered for 3 days. In addition, further adjunctive pain killers (mefenaminic acid, e.g. Ponstan® or Mephadolor® 500 mg not more frequently than every 6–8 hours) may be prescribed depending on the individual patient's need and pain threshold.

Favorable interactions between the patient, the therapist, and the entire office staff may contribute to the control of anxiety, but may require more time and consideration than that allocated to the routine patient.

Tobacco cessation counseling

Second to poor oral hygiene habits, cigarette smoking constitutes the most important modifiable risk factor in the etiology and pathogenesis of periodontal diseases (Ramseier 2005). A careful assessment of the patient's smoking history has therefore become indispensable for comprehensive periodontal care.

In order to support periodontal patients to quit tobacco use, it is helpful for the clinician to have a proper understanding of the genesis of tobacco dependence. The term *tobacco dependence* refers to the condition of tobacco users suffering from both psychological tobacco use dependence and physical addiction to nicotine. Therefore, in order to predictably help smokers to quit, all approaches supporting tobacco use cessation should include both behavioral support to address the psychological component of the dependence and pharmacotherapy to treat the physical symptoms of withdrawal.

Today, professional evidence-based methods for tobacco use cessation predominantly consist of professional behavioral change counseling applying the so-called "5A method" (Ask, Advise, Assess, Assist and Arrange) in combination with pharmacotherapy. It has been shown that the success rates for smoking cessation counseling are generally dependent on (1) the amount of time spent counseling the individual and (2) the prescribed drug. The success rates achieved by counseling lasting for 1–3 minutes, 4–30 minutes,

31–90 minutes, and >90 minutes are 14.0%, 18.8%, 26.5%, and 28.4 %, respectively (Fiore *et al*. 2008).

For practical reasons, periodontal care of smokers includes brief tobacco use interventions lasting 3–5 minutes at each appointment, while focusing on the following strategy (Ramseier *et al*. 2010):

1. *Ask*: It is well recognized that the general medical history form plays a critical role in asking all patients about their tobacco use history. Asking all patients on a regular basis allows a non-threatening introduction to the ensuing conversation between the oral healthcare professional and the patient.
2. *Assess*: When further asked about their readiness to quit smoking, tobacco users often reply that they want to quit smoking "sometime" but that the time is not yet right. There are certain things they need to do first, which are seen as more important than giving up smoking. Even if the patient feels that he/she is ready to quit smoking, there still may be some uncertainty about the next steps. He/she may experience a lack confidence to achieve this goal and feel under prepared to make a quit attempt. Behind this attitude is often the fear of failure, potential change to social habits, or worry about unwanted weight gain.
3. *Assist and refer*: As mentioned above, providing assistance to the patient who wants to quit tobacco requires a combination of behavioral modification techniques and pharmacologic support. Making the arrangements for ongoing support either via the dental office or other healthcare agencies may provide the patients with valuable resources as they undertake a quit attempt. When available, referral to professional tobacco cessation counseling services, whether in-house (including suitably trained dental personnel) or external (i.e. www.quitline.com) should be pursued.

Conclusion

The goals of the systemic phase of periodontal therapy are to appraise aspects that both the dental team and the systemic health of the patient may need to be protected against. Infection control in the dental office plays a central role. Protecting the patient against presumptive complications, such as infection, especially bacterial endocarditis, bleeding, cardiovascular incidences, and allergies, requires in-depth knowledge of the patient's medical history and oral examination.

Bacterial endocarditis prophylaxis is nowadays reserved for those patients with a history of a healed bacterial endocarditis, prosthetic heart valves or surgically constructed conduits, while the use of antibiotics before dental treatment is unnecessary for patients with other cardiac abnormalities. Patients with systemic diseases such as diabetes mellitus or cardiovascular diseases usually are treated with a number of medications that may interact with drugs prescribed during periodontal therapy. Precautions should be taken, and consultation with the patient's physician prior to systematic periodontal therapy is recommended.

It has to be realized that periodontal treatment may have a beneficial effect on the systemic health of the patient as well. Glycemic control may be facilitated in patients with diabetes if proper periodontal therapy is rendered.

Finally, smoking counseling is part of modern periodontal treatment owing to the fact that, after inadequate oral hygiene standards, cigarette smoking constitutes the second most important risk factor for periodontitis.

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Part 11: Initial Periodontal Therapy (Infection Control)

Chapter 35

Motivational Interviewing

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Health behavior change counseling in periodontal care

Periodontal health is supported by appropriate behaviors such as regularly self-performed plaque control, avoidance of tobacco, and glycemic control with diabetes mellitus type 2. Inadequate oral hygiene, tobacco use, and uncontrolled glucose levels, on the other hand, have a destructive impact on periodontal tissues. The prevention and control of periodontal disease needs to be addressed at both the population and the individual level. The dental community involved with oral health care should gain an understanding of the health effects of inappropriate behaviors in order to successfully target prevention and disease control. As a consequence, services for primary and secondary prevention at an individual level oriented towards the change of inappropriate behavior become a professional responsibility for all oral healthcare providers.

Data from epidemiologic studies consistently reveal the prevalence of periodontal disease to be >50% in the adult population (Albandar *et al*. 1999; Albandar 2002). In addition to the causal relationship with dental biofilms, a positive association between periodontal disease and tobacco use has been documented (Bergstrom 1989; Haber *et al*. 1993; Tomar & Asma 2000). Tobacco use contributes to the global burden of public health with almost one-third of the adult population using various forms of tobacco and an increasing number of annual deaths from tobacco-related diseases. Moreover, dietary factors have been shown to significantly impact chronic diseases, including obesity, cardiovascular diseases, diabetes type 2, cancer, osteoporosis, and oral diseases (Petersen 2003).

There is growing evidence that the patient's individual behavior is influential or even critical for the success of periodontal therapy since its results appear to be limited in patients lacking appropriate behavior. In a literature review by Ramseier (2005), it was shown that second to plaque control, smoking cessation was the most important measure for the management of chronic periodontitis. Therefore, it appears to be reasonable in clinical concepts for periodontal care to (1) include assessments of patient behavior, and, if necessary, (2) apply effective behavior change counseling methods.

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The challenge

Traditional periodontal care includes instruction on proper oral hygiene methods. In practice, as an example, a demonstration of a suitable toothbrushing method is given to the patient, followed by recommendations for both the frequency and the time spent per brushing. Past and recent studies on the effectiveness of oral hygiene instructions have consistently revealed that patient adherence to a proper daily oral hygiene regimen generally remains poor (Johansson *et al*. 1984; Schuz *et al*. 2006). The reinforcement of oral hygiene habits through additional appointments can, to some degree compensate for the ineffectiveness of one-off or repeated oral hygiene instructions. However, due to weak patient adherence, visits for supportive periodontal care are often cancelled, resulting in a lack of professional maintenance care and the further potential for recurrence of periodontal disease (Wilson *et al*. 1984; Demetriou *et al*. 1995; Schuz *et al*. 2006).

Unfortunately, many health education approaches seem to be inefficient in accomplishing long-term change, potentially leading to frustration for both the patient and the clinician. The following hypothetical dialog between a clinician (Dr) and a patient (P) illustrates how using a directive advice-oriented method for behavior change counseling may lead to an unproductive conversation and little likelihood of change by the patient:

Dr "Are you flossing regularly?"
P "Yes, but not as often as I should."
Dr "I strongly recommend that you floss every day. As you probably know, there are serious consequences if you don't floss frequently enough."
P "I know I should do it more often, but…"
Dr "It's not something that is optional. It is very important!"
P "I know … … but I don't have the time!"

Since the clinician does not offer the patient a chance to discuss the reasons to floss, as well as the patient's perceived barriers to flossing, the conversation reaches an impasse and behavior change will be unlikely. In certain cases, the patient may even be blamed for poor compliance and further oral health education may be seen to be pointless.

In order to achieve reliable, effective outcomes in periodontal care, hypothetically, it may be necessary to apply different behavior change counseling methods for each individual and behavior. According to the standard of care for oral hygiene instructions, for example the correct use of a cleaning device, may be repeatedly demonstrated, while for tobacco use cessation, in addition to pharmacotherapy, the 5As method (Ask, Advise, Assess, Assist, Arrange) may be used (Fiore 2000). From a practical point of view, however, it may be complicated and even discouraging to approach the periodontal patient with a variety of different methods targeting the same purpose, that is establishing appropriate behavior to improve the outcomes of both periodontal therapy and long-term supportive periodontal care.

Hence, aiming for simplicity, it may be preferable to apply approaches based upon *one single method* for behavior change counseling in periodontal care that is shown to be effective in both primary and secondary prevention of oral diseases. This method should be:

- Based on the best available evidence
- Applicable to oral hygiene behavior, tobacco use prevention and cessation, and dietary counseling
- Suitable for implementation by the dental practice team in a cost-effective way.

Communication with the periodontal patient

Different styles of communication are used – even sometimes unconsciously – when interacting with other people in everyday life. For communication with the periodontal patient, however, it seems appropriate that the dental clinician from time to time specifically adapts his/her manner to the individual behavioral needs of the patient and to the patient's own way of communicating his/her chief complaints. Rollnick *et al.* (2007) presented a three-styles (directing, guiding or following) model for healthcare clinicians to use in communicating with their patients in daily practice:

- *Directing* style: includes the delivery of expert advice and support. This has traditionally been a standard approach within dental care settings. Directing is appropriately used where there is a good rapport between the clinician and the patient. The advice should be well timed, personally relevant, and delivered in such a way as to engage the patient. A directing style can be used after the patient has said something like: "What can I do to stop the need to descale every time I come back here?"
- *Following* style: needs listening skills and is appropriately used when situations require sensitivity (such as when a patient is sad or upset). The goal of a clinician using a following style is not to solve the patient's problem immediately, but to provide support and encouragement. As an example, the following style can be used after the patient has said something like: "There's so much going on in my life. I am discouraged to worry about my teeth too?"
- *Guiding* style: the clinician collaborates with the patient to help him/her identify his/her own goals, and how he/she might best achieve them. This style is most appropriate when talking to patients about making health behavior changes – especially to patients who may be ambivalent about changing. The guiding style can be used after the patient has said something like: "I know that smoking isn't good for me, but it's the only pleasure I have in life."

When it comes to health behavior change issues, some patients may require "direction" – particularly those who have stated that they want further advice or support. Others may have more pressing concerns and therefore need to be "followed". Those patients who appear to know what they need to do, but have not managed to do it yet, will be most receptive to a "guiding" style (Rollnick *et al*. 2007).

During patient communication, in general, it is important to be sensitive to the patient's reaction to a particular style of communication. If the clinician feels that his/her rapport with the patient seems to be wavering, this should be an alert that a particular style does not appear to be working and another style should be tried to maintain the rapport.

In all communication with the patient it should be remembered that the patient should only be asked questions when it is comfortable for him/her to respond (i.e. without interference from instruments and/or the clinician). Without this consideration, communication success will be challenged as the patient may feel a loss of control.

OARS

There are four primary activities to be considered when communicating with the periodontal patient. These can be summarized with the acronym OARS: Open-ended questions, Affirm the patient, Reflect, and Summarize.

- *Ask open-ended questions*. Approaching the patient with multiple closed-ended questions (those that will be answered with a "yes" or "no") gives the patient a rather passive role. In contrast, open-ended questions invite thought, collaboration, and effort on the part of the patient. Example: "How do you feel about your smoking?"
- *Affirm the patient*. It is human nature to presume a negative attitude when one's own behavior is scrutinized. Acknowledging the patient's strengths and appreciation of his/her honesty will decrease defensiveness, increase openness, and the likelihood of change. Example: "You have been clear about why you're not very concerned about your toothbrushing and I appreciate that honesty."
- *Reflect what the patient is communicating*. Reflection is the primary way to demonstrate empathy (ability to understand another person's perspective). Appropriate reflection includes the genuine effort to understand the patient's perspective. It (1) captures the underlying meaning of the patient's words, (2) is concise, (3) is spoken as an observation or a comment, and (4) conveys understanding rather than judgment. Example: "You really seem to have lost hope that you ever really can quit smoking."
- *Summarize*. Summarizing demonstrates interest, organizes the interview, and gets things back on track if necessary. It involves the compilation of the thoughts on change that the patient has expressed during the counseling. Example: "So there's a big part of you that doesn't feel ready to change right now. You really enjoy smoking, but you have been a little worried by the way some people react when they find out that you smoke. Is that about right?"

Understanding motivational interviewing

As discussed, health *education* efforts provided by practitioners are frequently ineffective in changing patient behavior. Considerable behavioral research suggests that the root of this common problem can be traced back to a false assumption inherent in the health education approach. Specifically, it is assumed that behavior change is simply a function of a patient having the requisite knowledge or understanding, and all that is required is for the practitioner to provide the relevant information. Motivational interviewing (MI), in contrast, is based on a different assumption of human behavior change. It assumes that knowledge is insufficient to bring about behavior change and that, instead, sustained behavior change is much more likely when change is connected to something the individual values. In other words, motivation is elicited "from within the patient" rather than externally imposed upon the patient by a practitioner. In MI it is assumed that individuals have "within them" their own reasons for changing and that the role of the practitioner is to elicit and reinforce these reasons.

MI originated in the field of alcohol addictive behavior, but has increasingly been applied to a wide variety of other behavior change problems, including tobacco use, diet, and exercise (Burke *et al*. 2004; Hettema *et al*. 2005). The method was developed by William Richard Miller in response to his observations of the confrontational approach that was standard treatment for patients with alcohol problems in the 1970s. In contrast, he observed that the research literature suggested that positive outcomes were related to a strong bond or "therapeutic alliance" between counselor and patient. Miller developed an empathy-centered treatment which used the *therapeutic alliance* and *empathy* to engender the client's inherent motivation to change (Miller 1983). Subsequently, Miller met Stephen Rollnick, the co-founder of the MI method, who had been concentrating on ambivalence, or the extent to which the client envisioned the pros and cons of changing. Miller and Rollnick began to explore the use of language during MI, concentrating on the elicitation of client "change talk" to promote behavior change. In 1991, Miller and Rollnick published the first edition of *Motivational Interviewing: Preparing People to Change Addictive Behaviors* in which they provided a detailed description of the approach. Since then, there has been an explosion in the research and application of MI, with many researchers addressing the applicability

of the method to addressing health behavior change (Resnicow *et al*. 2002). Recently, various approaches to the implementation of MI in the dental setting have been published (Ramseier & Suvan 2010).

MI has been defined as "a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence" (Miller & Rollnick 2002). The client-centered element refers to the emphasis that is placed on understanding and working from the perspective of the patient and his/her view of what it means to make a behavior change. For example, rather than a clinician simply telling a patient about the benefits of quitting smoking (from the practitioner perspective), the practitioner invites the patient to describe *his/her own view* of the advantages of quitting and disadvantages of continuing to smoke. Although the patient's perspective is central, because MI is also directive, the practitioner takes deliberate steps to facilitate a particular behavioral outcome. For example, without ignoring patient concerns about changing, the practitioner selectively reinforces and encourages elaboration of any patient statements that are oriented toward the possibility or benefits of making a change. By eliciting and elaborating upon the patient's own reasons for change, the motivation to change that is fostered is intrinsic or internal, rather than externally imposed. This approach rests on the assumption that individuals are almost always ambivalent about changing their behavior (i.e. it is almost always the case that individuals can identify both pros and cons of changing). MI practitioners therefore attempt to enhance intrinsic reasons for change by facilitating an exploration and resolution of the patient's underlying ambivalence.

General principles

Although MI methods and techniques provide a wealth of guidance on what to do and what not to do when counseling patients, Miller and Rollnick have emphasized that to be an effective MI practitioner it is more important to embody the underlying philosophy than to be able to apply the collection of techniques. They have identified four general principles that capture the underlying philosophy of the method:

1. A practitioner should *express empathy* for the patient's behavior change dilemma. In other words, the practitioner should communicate acceptance of the patient's perspective, providing and *expressing* full acknowledgement of the patient's feelings and concerns.
2. *Discrepancy* should be developed between the patient's current behavior and how he/she would ideally like to behave to be consistent with his/her broader goals and values. For example, the goal of being strong or responsible, or a good spouse or parent, can often be linked to being healthy and suggests the need for improved health behaviors.
3. *Roll with resistance*. When patients argue against change there is a strong tendency to fall into the trap of providing counter arguments. As a result, the patient expends all of his/her energy arguing against change, which is precisely the opposite of what is desired and may make him/her more resistant to change. MI practitioners therefore avoid arguing and instead use MI methods to "roll with resistance".
4. *Support self-efficacy* or the patient's confidence in his/her ability to make a change. Patients are unlikely to succeed in making a change, even if they are motivated, when they do not know how to change or do not believe they can. MI practitioners therefore make efforts to enhance patient confidence through such means as expressing their belief in the patient's ability to change or pointing out past successes or steps in the right direction.

Giving advice

Although we have highlighted the distinction between advice-oriented health education and MI, it is important to recognize that at times it is appropriate to provide information to address a patient's questions, misapprehensions, or lack of knowledge. The MI skill code (Moyers *et al*. 2003), which is used to assess a practitioner's adherence to the principles of MI, distinguishes between giving advice *without* permission, which is proscribed, and giving advice *with* permission, which is consistent with MI principles. In essence, providing information when the patient is willing and interested in receiving it is consistent with MI. Practitioners commonly err by providing advice too early in an encounter with a patient, resulting in the patient perceiving the practitioner as having an agenda that he/she is trying to "push". In contrast, it is common in MI practice to find that the process of eliciting the patient's perspective reveals gaps in knowledge, questions, concerns, and misapprehensions that the patient would appreciate receiving more information about. The practitioner can then provide particularly relevant information that is much more likely to be well received. Rollnick *et al.* (1999) have outlined a three-step process that serves as a useful framework for providing advice in an MI consistent style:

- Step 1: *elicit* the patient's readiness and interest in hearing the information. For example, a practitioner might say to a patient "I have some information related to that [topic] that you may be interested in. Would you be interested in hearing more about that?"
- Step 2: *provide* the information in as neutral a fashion as possible. For example, a practitioner might say "Research indicates that…" or "Many of my

patients tell me that…" This allows factual information to be presented in a manner that supports the patient's autonomy.

- Step 3: *elicit* the patient's reaction to the information presented. Follow-up will often help the patient integrate the new information in a way that brings about a new perspective and increases motivation to change. Alternatively, follow-up may reveal further gaps in knowledge or misunderstandings that can be addressed. If a patient "rejects" the information, it is important not to enter into a debate about this. It is generally better to simply acknowledge the patient's perspective with statements such as "This information doesn't fit with your experience" or "This information doesn't seem relevant to your situation" and then move on to a more productive area of conversation.

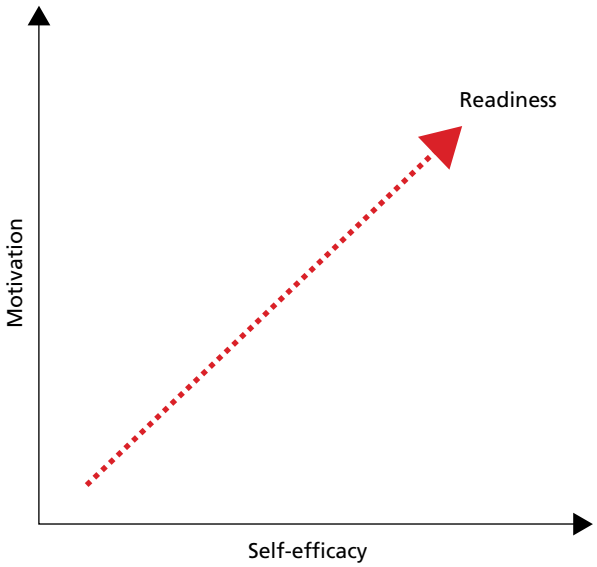

Fig. 35-1 Readiness to change. (Source: Rollnick *et al*. 1999. Adapted with permission from Elsevier.)

Agenda setting

It is often the case that there is more than one health behavior affecting the patient's oral health. Achieving small changes can make a patient feel more able and confident to make other changes (Bandura 1995). In these situations, it is important to start where the patient feels most comfortable, and to encourage him/her to suggest what area he/she would like to talk about, rather than simply selecting what the dental clinician feels is the most pressing issue. One clinical tool that can help with this task is an "agenda setting chart" (Rollnick *et al*. 1999).

The agenda setting chart contains a number of circled picture representations of different issues in oral health, and some blank circles for other factors to be inserted by the patient. The patient then selects the issue that he/she would like to talk about first.

Readiness scale

It may take a number of dental appointments before patients make significant health behavior change. Only relatively small steps towards change are likely to be accomplished following one brief encounter. Dental clinicians who understand how to limit their expectations following each appointment may ultimately feel less inclined to push the patient. By taking a long-term perspective, they may be more aware of what they can accomplish in a relatively short amount of time, and therefore feel less frustration with highly ambivalent patients.

Clinicians usually cannot expect their periodontal patients to be ready to change their oral hygiene habits or tobacco use simply because they would like to have good oral health (Miller & Rollnick 2002). Assessing the patient's readiness to change involves learning about both the patient's motivation and self-efficacy to change (Rollnick *et al*. 1999). Using two questions on motivation and self-efficacy (see below), the clinician can form a rather complete picture of a patient's position regarding readiness to change within a short amount of time.

When assessing both motivation and self-efficacy, the clinician seeks to discover the patient's specific motivators and values, in order to link these to the desired behavior change (Fig. 35-1). As described by Koerber (2010), the readiness scale can be used, particularly in brief interventions in dental settings. It consists of the motivation scale and the self-efficacy scale, as described by Rollnick *et al*. (1999):

- Motivation (importance) scale (Fig. 35-2): consists of three questions. For example:
  - "On a scale from 1 to 10, where 10 is absolutely important and 1 is not at all important, how would you rate the importance of brushing your teeth regularly?"
  - "Why did you rate it as (X) instead of 1?"
  - "Why did you rate it as (X) instead of a 10?"

  Note that the second question reveals the patient's motives, and the third question reveals the patient's ambivalence.
- Self-efficacy (confidence) scale (Fig. 35-2): consists of the following questions:
  - "If you were convinced that brushing your teeth regularly was very important, on a scale from 1 to 10, how confident are you that you could do it? 1 means not at all confident and 10 means completely confident."
  - "Why did you rate it as (X) instead of 1?"
  - "Why did you rate it as (X) instead of 10?"

  Note that the second question reveals a patient's strengths to make the change, and the third question reveals the barriers.

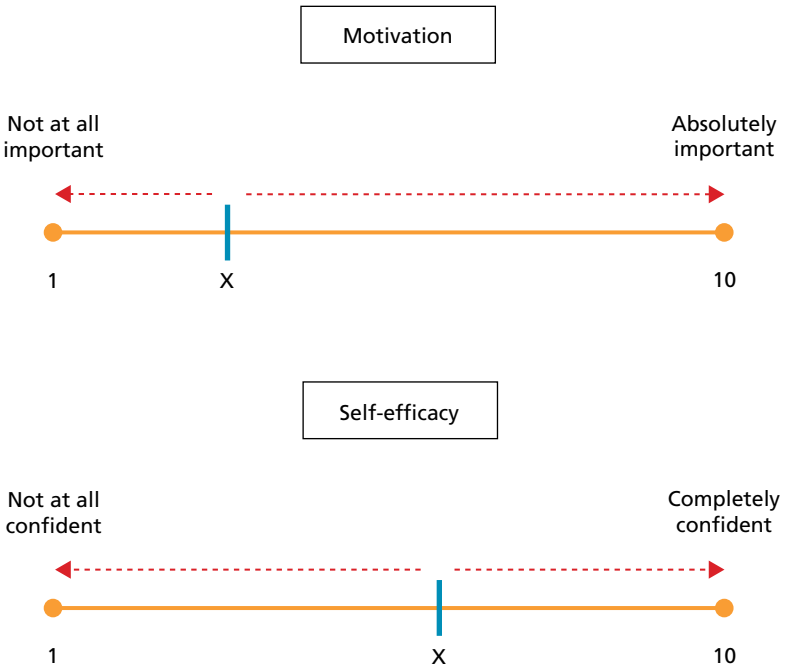

Fig. 35-2 Motivation (importance) and self-efficacy (readiness) scale.

Evidence for motivational interviewing

Evidence in general health care

Because MI was initially developed for the treatment of addictive behavior, particularly alcohol addiction, the bulk of empirical studies has been conducted in this area. Nevertheless, the explosion in the application of MI to other areas of behavior change has generated numerous published meta-analyses (Burke *et al*. 2003, 2004; Hettema *et al*. 2005; Rubak *et al*. 2005; Lundahl *et al*. 2010), the most recent of which include nearly 120 clinical trials. Generally, the meta-analyses indicate that MI-based interventions are at least equivalent to other active treatments and superior to no treatment or placebo controls for problems involving addictive behavior (drugs, alcohol, smoking, and gambling), health behaviors such as diet and exercise, risk behaviors, and treatment engagement, retention, and adherence. Effect sizes are on average in the small-to-medium range (Hettema *et al*. 2005; Lundahl *et al*. 2010). Of particular relevance to dental settings where only brief counseling is feasible is the finding that MI-based interventions are just as efficacious as alternative active interventions despite involving significantly less contact time, suggesting that MI may be a particularly efficient method of counseling in dental settings (Burke *et al*. 2004; Lundahl *et al*. 2010). Rubak *et al*. (2005) reported that of studies evaluating the effectiveness of brief encounters of 15 minutes, 64% showed an effect. In addition, when the intervention was delivered by physicians, an effect was observed in approximately 80% of studies, suggesting that it is feasible for professionals who are not counseling experts to effectively deliver MI in brief encounters.

Studies of MI for tobacco use cessation are also of particular relevance. Recent meta-analyses indicate modest positive effects of MI for smoking cessation (Lai *et al*. 2010; Lundahl *et al*. 2010) and there is evidence that MI leads to significantly more quit attempts (Wakefield *et al*. 2004; Borrelli *et al*. 2005), greater reductions in smoking level, and greater advances in readiness to quit (Butler *et al*. 1999).

Another particularly relevant target behavior for oral health is dietary habits. As already indicated, meta-analyses indicate that MI has significant effects on changing diet: overall dietary intake (Mhurchu *et al*. 1998), fat intake (Mhurchu *et al*. 1998; Bowen *et al*. 2002), carbohydrate consumption (Mhurchu *et al*. 1998), cholesterol intake (Mhurchu *et al*. 1998), body mass index (BMI) (Mhurchu *et al*. 1998), weight (Woollard *et al*. 1995), salt intake (Woollard *et al*. 1995), alcohol consumption (Woollard *et al*. 1995), and consumption of fruit and vegetables (Resnicow *et al*. 2001; Richards *et al*. 2006).

Evidence in dental care

One early study investigating the impact of MI in oral care examined the effect of its use compared to traditional health education on motivating 240 mothers of young children with high risk for developing dental caries to use dietary and non-dietary behaviors for caries prevention (Weinstein *et al*. 2004, 2006). An MI session and six follow-up phone calls over a year in addition to an educational pamphlet and video was more effective than the pamphlet and video alone in preventing new dental caries among the children after 2 years. This result is consistent with the results of meta-analyses that have found MI to be efficacious for dietary change (Burke *et al*. 2003; Hettema *et al*. 2005; Lundahl *et al*. 2010).

Related to clinical periodontology, both short- and long-term studies have demonstrated a positive impact on oral hygiene, as measured by plaque indices, and gingival inflammation, as assessed by gingival indices. Almomani *et al.* (2009) were able to demonstrate a significant positive impact on oral hygiene in a 2-month trial. Jönsson *et al.* (2009b) followed two patients over 2 years to assess the impact of an individually tailored oral hygiene program on periodontal indices (Fig. 35-3). Following MI sessions using

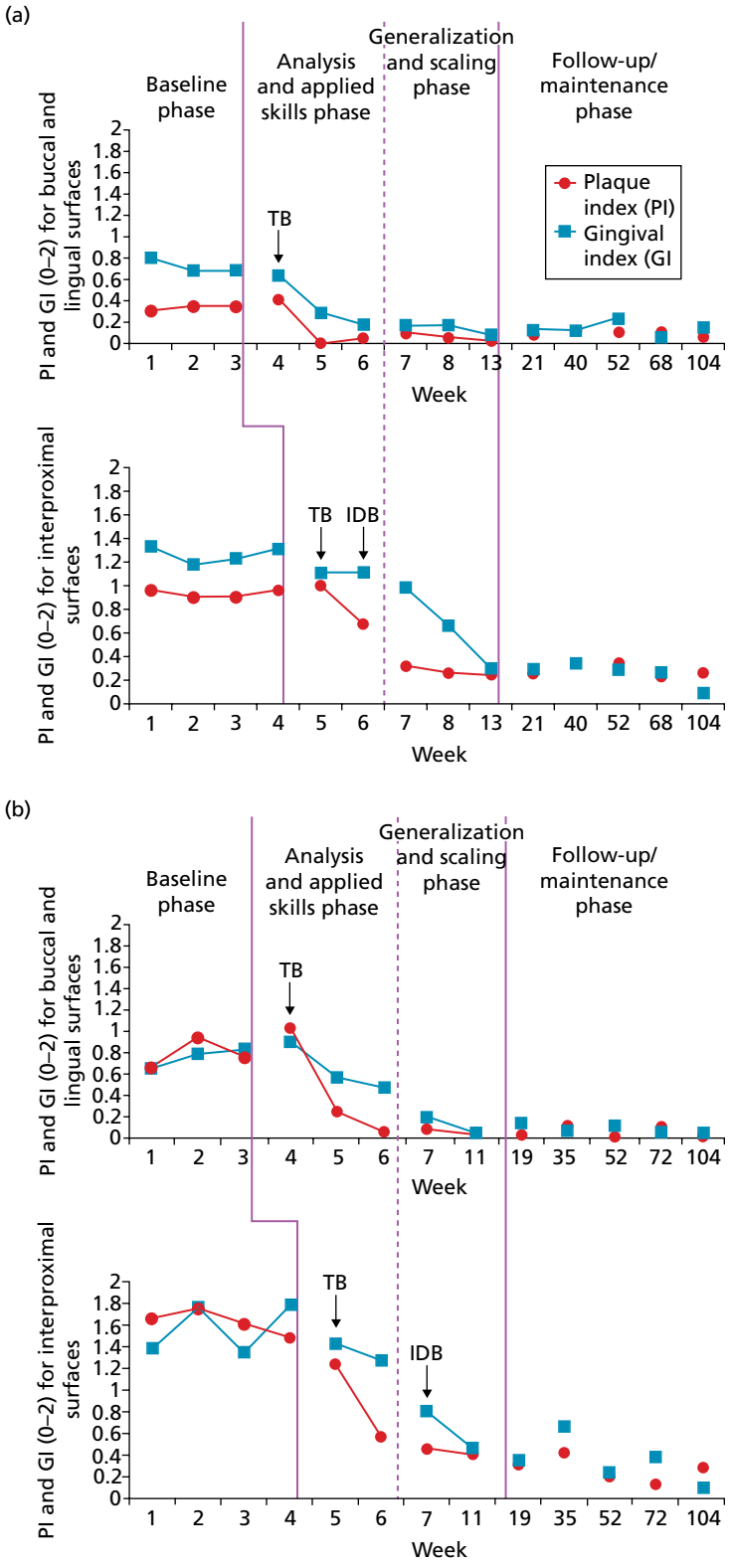

Fig. 35-3 (a) Female patient and (b) male patient. Following an individually tailored treatment program for improved oral hygiene, both full mouth and interproximal Plaque Index and Bleeding Index for both patients dropped significantly over an observation period of 104 weeks. (TB, Toothbrush; TP, toothpick; IDB, interdental brush.) (Source: Jönsson *et al.* 2009b. Reproduced with permission from John Wiley & Sons.)

Table 35-1 Clinical trials evaluating the impact of motivational interviewing (MI) on oral hygiene (as measured by plaque indices specified).

Study	Design	n	Duration (months)	Test method	Primary outcome variables	Plaque scores
Almomani *et al.* (2009)	RCT	27 test, 29 control	2	MI + education	Full-mouth modified Quigley–Hein plaque index	*Test* Baseline 3.6, 8 weeks 1.9 *Control* Baseline 3.3, 8 weeks 2.5
Jönsson *et al.* (2009b)	Case	2	24	MI + education	Interproximal plaque index (Silness and Löe), bleeding index (Löe and Silness)	*Patient A* Baseline 1, 24 months 0.2 *Patient B* Baseline 1.6, 24 months 0.1
Jönsson *et al.* (2009a)	series	57 test, 56 control	12	MI + education	Interproximal plaque index (Silness and Löe), bleeding index (Löe and Silness)	*Test* Baseline 1.01, 12 months 0.23 *Control* Baseline 0.99, 12 months 0.49
Godard *et al.* (2011)	RCT	27 test, 24 control	1	MI only	Plaque index (O'Leary)	*Test* Baseline 35%, 1 month 18% *Control* Baseline 37%, 1 month 27%

RCT, randomized controlled trial.

the techniques described in this chapter, as well as oral hygiene instructions on an individual basis as described in Chapter 36, both patients succeeded in improving their oral hygiene and gingival health over 2 years.

The same authors subsequently demonstrated the positive impact of MI in a lager study of 113 patients over a period of 12 months (Jönsson *et al.* 2009a, 2010). In a recent study by Godard *et al.* (2011), the improvement of oral hygiene was accompanied by greater patient satisfaction in the group of patients receiving MI.

Conclusion: There is a wealth of support for MI as an effective method of counseling for behavior change (Table 35-1). MI has also been shown to be successfully delivered by medical practitioners. In areas of specific relevance to oral health practitioners, MI has either already been shown to be efficacious or offers significant promise.

Patient activation fabric

Implementing MI in a dental setting requires consideration of how to ensure the collaborative and empathetic spirit of the method (Ramseier & Suvan 2010). A specific patient activation fabric was presented by Suvan *et al.* (2010). This model attempts to capture the interdependent elements of the dental visit using the concept of interwoven threads (Suvan *et al.* 2010). Communication and information exchange blend with clinical assessment and treatment (Fig. 35-4).

Band I: Establish rapport

The goal of establishing rapport is to quickly engage the patient and create an environment where both conventional dental treatment and health behavior change counseling can occur. Accomplishing this depends on much more than the amount of time taken. A warm, courteous greeting is a critical start in creating an environment of mutual trust and respect. Furthermore, such basic matters as how the patient and practitioner are seated can contribute to the patient feeling like he/she is truly being invited to engage in a dialog as a partner (Fig. 35-5), rather than feeling he/she is the recipient of expert advice (Fig. 35-6). These simple actions give the perception that the patient and clinician have equal control of the situation, rather than one being dominant. Beginning with an open question that elicits the patient's chief complaint or reason for attending the visit is another simple and valuable step. These opening moments set the scene for the remainder of the

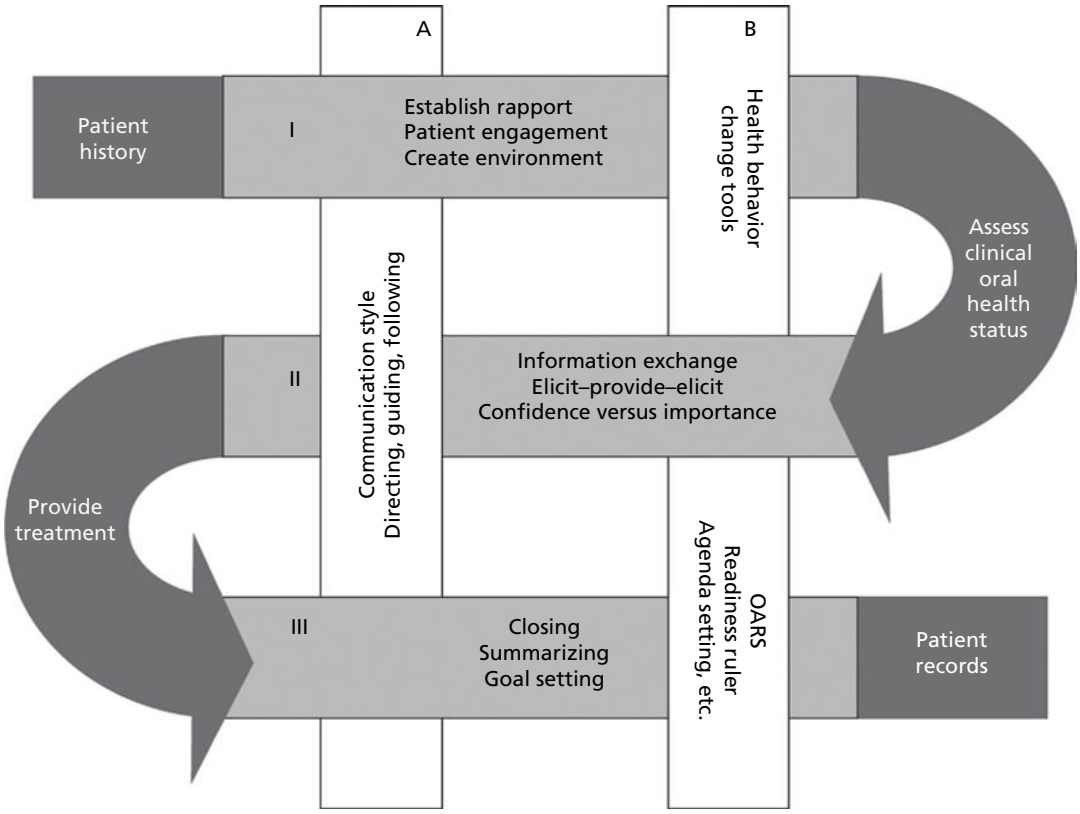

Fig. 35-4 Patient activation fabric for the dental visit (implementation model). The patient history and patient records at the start and the end of a dental visit depict the critical elements of documentation that serve to weave one dental visit into the next. The horizontal bands depict the three core strands of conversations constituting the visit. These bands (I–III) transition directly into the ribbons (A and B) that represent the clinical assessment or treatment that takes place between the conversations as part of the flow of the appointment. The bands are woven together through the vertical ribbons that signify the specific elements of the communication and interaction characterizing the approach. These vertical ribbons represent communication style and health behavior change tools and are consistent, yet flexible, recurring throughout the appointment to provide stability. (OARS, Open-ended questions, Affirm the patient, Reflect, and Summarize.) (Source: Suvan *et al*. 2010. Reproduced with permission from John Wiley & Sons.)

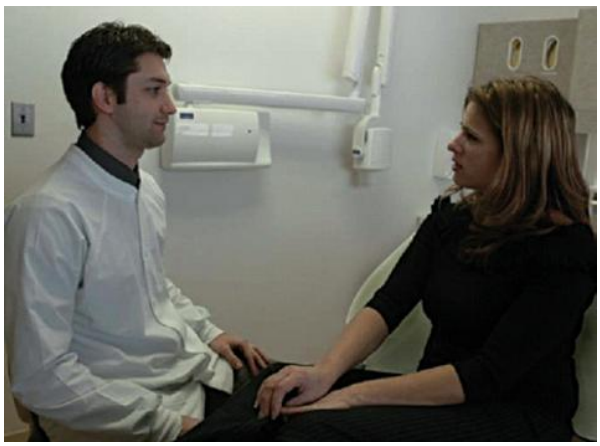

Fig. 35-5 Appropriate position for a conversation: the clinician is facing the patient at the same seating level.

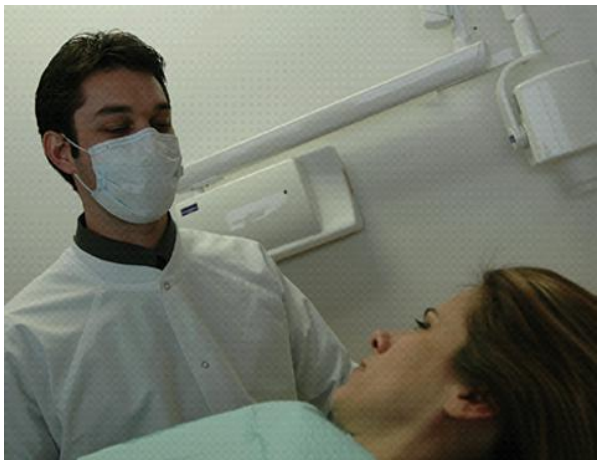

Fig. 35-6 Inappropriate position for a conversation: the clinician is wearing a face mask and is at a level higher than the supine patient.

visit and can save the clinician valuable time later in the session.

Before proceeding with the clinical assessment, it is important to briefly list the elements of the procedure for the patient, and then to ask the patient if he/she is happy for this to be conducted at that time. Asking permission is a simple way to engage the patient while simultaneously encouraging a sense of autonomy. It may be helpful to explain to the patient the relevance of the information that he/she may hear being given to the assistant. These small actions help to keep the patient engaged in the consultation, rather than allowing him/her to shift to a passive role of simply lying on the dental chair throughout the assessment procedure.

Band II: Information exchange

This second part of the interaction most often takes place following initial clinical assessment of the patient's oral health status. This exchange of information allows both clinician and patient to understand the other's perspective and creates a more accurate picture of the clinical problem and approaches to effective management. This discussion can take many different forms.

One approach to providing information is for the practitioner to maintain the focus on patient engagement using the elicit–provide–elicit method. Starting with what the patient already knows (elicit) immediately encourages patients to think, reflect, and acknowledge their own expertise. From that starting point and with permission, the information offered to patients can be tailored (provide). Perhaps the most important step is the question that follows to explore the sense the patient makes of the information provided (elicit). This question can open the door to dialog rich with opportunity for discussions about change.

Leading into and moving on from this middle phase of the visit, a number of clinical tasks can be performed, including assessment and treatment. Conversations about behavior change are most valuable when the clinician and the patient are able to speak freely. These conversations should not be conducted when the patient is unable to be an equal participant, such as when he/she is physically incapable of speaking, or may be feeling pain or discomfort during or after clinical procedures.

Band III: Closing

The third band takes place and functions as a closure to the visit. It may involve a brief summary of the clinical treatment that has been provided and any expected side effects or post-treatment discomfort. An equally important function is to briefly summarize behavior change discussions. This provides the clinician with the opportunity to review the agreed goals or plan of action suggested by the patient in Band II. To ensure this discussion is collaborative, the clinician should ask the patient if there is anything he/she would like to add to the plan and check with the patient that the most important points have been covered. Further treatment options may also be discussed if the patient is not too tired. However, this is not typically the best time for most patients to discuss important facts as they are usually focused on leaving the dental chair as soon as the appointment has concluded.

Ribbon A: Communication style

Earlier in this chapter, styles of communication were presented, highlighting that a spectrum exists with directing and following at its extremes and guiding in the middle as an intermediary style engaging both parties equally. A skillful movement between the three styles constitutes the well-managed interaction with the patient. In the model, communication style is labeled as a vertical ribbon interwoven through the entire visit. This portrays that at certain times during the visit, a particular style will tend to be more advantageous than the others. Maximum patient engagement without compromising the clinician's responsibility and ability to provide important information will be facilitated through use of a guiding style. Fundamental communication techniques such as asking open questions can encourage the two-way communication that characterizes a guiding style. However, this does not infer that it is the only style of communication used during the visit.

Ribbon B: Health behavior change tools

The second vertical ribbon represents the many behavior change tools that can facilitate patient activation or interaction throughout the visit. Like Ribbon A, clinicians may choose the tool they feel will be most beneficial at certain points in the visit or conversation. The choice is driven by the goal to provide a relaxed atmosphere where conversations can be spontaneous and individualized to each patient.

Case examples

Oral hygiene motivation I

Using the following case example, MI for oral hygiene motivation is demonstrated in a dialog between a periodontist (Dr) and a patient (P) diagnosed with chronic periodontitis, at the beginning of periodontal therapy.

Dr "Would you mind if we talk about methods to improve your oral hygiene during and after your gum treatment?" (*raising the topic/asking permission*)
P "No, I don't mind."
Dr "Good. Could you let me know a little bit about how you usually clean your teeth?" (*asking open questions to elicit what the patient already does*)
P "I usually brush once or twice a day."
Dr "So you brush your teeth regularly? What are you using when you clean your teeth?"
P "I use a toothbrush and toothpaste."
Dr "Very good. Could you let me know how you use your toothbrush?"
P "I brush all upper and lower teeth on the outside and the inside as I was shown a long time ago."
Dr "And how do you feel about brushing your teeth that way?"
P "I generally feel quite good about it. But since I have been told I have gum disease, I'm wondering if I haven't been brushing enough?"

Dr "So you have been making efforts to keep your teeth clean but you're worried that maybe you haven't been brushing enough. (*reflective listening*)

It can be difficult to get to all the areas of your teeth and gums to remove the plaque that causes gum disease. (*showing empathy*)

I have some information related to prevention of gum disease that you might be interested in. Would you like to hear about it?" (*asking permission*)

P "Yes."

Dr "The chronic gum or periodontal disease you are diagnosed with was caused by bacterial plaque that has attached to your teeth over time. Plaque has to be entirely removed from all the tooth surfaces on a daily basis in order to prevent and control this disease. (*providing information*)

How confident are you that you were cleaning all the surfaces on a regular basis?" (*assessing confidence*)

P "Not so much, although I thought that I was doing enough."

Dr "Well actually, research indicates that using a toothbrush alone is not sufficient to clean between the teeth. In order to clean these areas, an interdental device is needed such as a dental floss, a toothpick, or an interdental brush. (*providing information*)

Are you using any one of these devices?"

P "Yes, I've tried using dental floss."

Dr "How did you find the use of dental floss?" (*asking open questions*)

P "I had some trouble getting to some of the spaces between my teeth. In other areas, the floss used to rip up too, so I quit using it."

Dr "I am sorry to hear that you had trouble using the dental floss. (*showing empathy*)

The floss can rip up at the edges of dental fillings or crowns. In spaces with extensive tartar build-up, the gap between your teeth may even be blocked with tartar.

Are you using anything else for cleaning?" (*asking open questions*)

P "Yes, I use a toothpick whenever I have something stuck between my teeth."

Dr "So in addition to your regular brushing with toothpaste you are also using a toothpick from time to time to clean your teeth?" (*reflective listening*)

P "That's right."

Dr "Good. During gum treatment, fillings and crowns with rough edges will be smoothed over and tartar can be removed which should make it easier to use things like dental floss or a toothpick between your teeth. (*providing information*)

Thinking of a 10-point scale where 0 is not at all important and 10 is extremely important, how important is it to you to floss or use a toothpick every day to clean the gaps between your teeth? (*using readiness ruler on importance*)

P "Probably a 7."

Dr "That sounds quite important. What makes this so important to you?"

P "I want to do everything necessary to keep my teeth. However, I am not quite sure if I will be able to keep doing it over time."

Dr "So you are quite motivated now because you want to look after your teeth, but you are worried about the long term.

If you were to use the same 10-point scale to rate how confident you are that you can do it over the long term, where would rate yourself?" (*using readiness ruler on importance*)

P "I would be at a 6."

Dr "That sounds fairly confident. What gives you that level of confidence?"

P "Well, taking care of my teeth and gums is part of my routine already so this would just need to be added to it. But it does take extra effort, so it's a matter of realizing that it's really important for my gums."

Dr "So, the fact that it can be part of your existing routine will help. But perhaps I can help you remain motivated in the long run by showing you at your follow-up visits the benefits you are achieving by doing the treatment regularly. How do you think that might help you to stick with it over time?" (*supporting self-efficacy*)

P "Well, yes I think that would probably help a lot to see or learn from you that it really is making a difference to the success of my treatment."

Dr "Great! So let me summarize what we have discussed. You plan to keep brushing on a regular basis with a toothbrush and toothpaste and you will start to use a device for cleaning the gaps between your teeth after the issues with the rough filling and crown margins have been resolved. Then, each time you visit we'll see how you are progressing with your cleaning at home and see if we need to find any other ways to help. Does that sound like it would work for you?" (*summarizing*)

P "Yes, that sounds like it would work."

Oral hygiene motivation II

In this second example dialog, MI is used in a conversation about oral hygiene at a visit for supportive periodontal therapy (SPT).

Dr "From looking at your plaque index, I noticed today that compared to your last visit 3 months ago that there is more plaque around the areas between your teeth. I was wondering if you could tell me a little bit about how you find the cleaning between your teeth." (*raising the topic/asking permission*)

P "Oh… I guess that I don't do it as often as I should. I barely have time now to do it every day, you know."

Dr "I understand. It takes time to clean all the areas between your teeth, you are right. (*showing empathy*)

May I ask you a few questions about your current oral hygiene habits so I can understand your situation better?" (*asking permission*)

P "Sure you can."

Dr "Good. So what do you use to clean your teeth currently?" (*asking open questions to elicit what the patient already does*)

P "I am using an electric toothbrush and the interdental brushes you showed me."

Dr "OK. How often do you use these?"

P "I use the electric toothbrush every day and I use the interdental brushes from time to time."

Dr "So you are using the toothbrush on a regular basis, but only occasionally using the interdental brushes. What is prompting you when you do decide to use the interdental brushes?"

P "Well, sometimes I just feel guilty that I haven't been using them and sometimes I can see the tartar on my teeth and am reminded to use them again."

Dr "So you sometimes worry that you are not using them enough and sometimes you can see from your teeth that you are not using them enough." (*reflecting on ambivalence*)

P "Right, I suppose I should be doing better."

Dr. "Well, let me ask you this. If you had to rate how important it is for you to use the interdental brushes every day on a scale from 0 to 10, 0 being not important at all and 10 being very important, where would you place yourself?" (*using readiness ruler on importance*)

P "I guess the use of these brushes is pretty important. I'd say an 8."

Dr "Well that sounds very motivated. What makes it that important for you?"

P "Well, I don't want to have a lot of problems with my teeth – I hate having fillings and of course I don't want to lose any teeth in the long run."

Dr "So, avoiding pain and discomfort and keeping your teeth is important to you. So how confident are you that you can use the brushes on a daily basis? Where would you rate yourself on that 0–10 scale?" (*using readiness ruler on importance*)

P "As I said, I know that I should use them more often, but finding the time is hard and I even just forget sometimes. I'd give it a 3."

Dr "Using them daily seems quite hard for you. Out of curiosity, though, it seems you do have a little bit of confidence in doing this. May I ask you why gave a score of 3 instead of 0 or 1?"

P "Well, I just think that I would use them more often if they became a part of my routine tooth cleaning, you know? I used to have toothpicks on my dinner table too and so I used them whenever I saw them sitting there. I could think about putting my interdental brushes on my sink next to my toothbrush to remind myself to use them after brushing my teeth with the electric toothbrush."

Dr "That sounds like a really good plan. Can you see any problems with doing that?" (*supporting self-efficacy*)

P "No, not really. Once I have that reminder in place it's just a matter of staying committed to doing it."

Dr "Very good. So if I can summarize, it sounds like you feel quite motivated to use the interdental brushes every day, and that you think that if you put your interdental brushes on your sink next to your electric toothbrush that would help you remember to actually use them." (*summarizing*)

P "Yes, that's right."

Dr "Well does that sound like something you want to do?"

P "Yes, I'll do that tonight."

Tobacco use cessation

In this example, MI is used in a brief intervention for tobacco use cessation at the beginning of periodontal therapy.

Dr "According to your tobacco use history, you are currently smoking cigarettes. May I ask you a few questions about your smoking?" (*raising the topic/asking permission*)

P "Yes."

Dr "Could you tell me how you feel about your smoking?" (*asking open questions to elicit what the patient already knows*)

P "Well I know I should quit. I know it's not good for my health. But I don't want to quit right now."

Dr "So, you don't feel that you want to quit right now, but you do have some concern about the health effects." (*rolling with resistance*)

P "Yes."

Dr "Well, tell me more about what concerns you?"

P "Well, mainly that I would get lung cancer or something."

Dr "So you worry a bit about getting cancer because of smoking. Is there anything else that you don't like about smoking? "

P "Well if I quit my clothes would stop smelling."

Dr "So, the smell of tobacco smoke is something you would like to be rid of?"

P "Yes, but I've smoked for many years, you know and I tried to quit once before."

Dr "So, even though you would like to be a non-smoker for health and other reasons you haven't had much success quitting." (*reflecting on ambivalence*)

P "Yes, and right now I'm enjoying smoking so there's not much motivation to try and quit."

Dr "Well, it sounds like even though you have some important reasons to quit, you're not very confident you could succeed and you don't feel ready to take on this challenge right now.

I wonder if it would be OK for us to talk about this again next time to see where you are with it and whether I could help?" (*summarizing*)

P "Yes, that sounds fine."

Conclusion

Chronic unhealthy behaviors not only affect an individual's general and oral health, but also impact the burden of disease at a community level. Hence, primary and secondary prevention services at an individual level oriented towards the change of inappropriate behavior is a professional responsibility for all oral healthcare providers. MI is a useful method that can be incorporated into the periodontal treatment plan to encourage the modification of all common risk behaviors for periodontal diseases, such as insufficient oral hygiene, tobacco use, unhealthy dietary habits, and alcohol abuse.

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Chapter 36

Mechanical Supragingival Plaque Control

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Importance of supragingival plaque removal

People brush their teeth for a number of reasons: to feel fresh and confident, to have a nice smile, and to avoid bad breath and disease. Oral cleanliness is important for the preservation of oral health because it removes microbial plaque, preventing it from accumulating on the teeth and gingiva (Löe *et al.* 1965). Dental plaque is a bacterial biofilm that is not easily removed from the surface of the teeth. Biofilms consist of complex communities of bacterial species that reside on tooth surfaces or soft tissues. It has been estimated that between 400 and 1000 species can, at various times, colonize oral biofilms. In these microbial communities, there are observable associations between specific bacteria, due in part to synergistic or antagonistic relationships and in part to the nature of the available surfaces for colonization or nutrient availability (see Chapter 10). The products of biofilm bacteria are known to initiate a chain of reactions leading not only to host protection but also to tissue destruction (see Chapter 13). Plaque can be supragingival or subgingival and can be adherent or non-adherent to teeth or tissue. In addition, the microbial composition of plaque varies from person to person and from site to site within the same mouth (Thomas 2004). Maintenance of effective plaque control is the cornerstone of any attempt to prevent and control periodontal disease. In fact, without the continuous collaboration of patients, periodontal treatment has little success and results obtained do not last long.

Supragingival plaque is exposed to saliva and to the natural physiologic forces existing in the oral cavity. Natural self-cleansing mechanisms include tongue movement, by which the tongue makes contact with the lingual aspects of the posterior teeth

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and, to a lesser extent, also cleans their facial surfaces. The cheek covers the buccal aspects of the posterior maxillary teeth and can thereby help to prevent the copious build-up of dental plaque on these surfaces. Saliva flow has some limited potential for cleaning debris from interproximal spaces and occlusal pits, but it is less effective in removing and/or washing out plaque. Friction through mastication might have a limiting effect on occlusal and incisal extensions of plaque. These defenses can best be classified as superficial actions in controlling or mediating plaque build-up. Natural cleaning of the dentition is virtually non-existent. To be controlled, plaque must be removed frequently by active methods. Hence, the dental community continues to encourage proper oral hygiene and more effective use of mechanical cleaning devices (Cancro & Fischman 1995; Löe 2000).

Therefore, to maintain oral health, regular personal plaque removal measures must be undertaken. The most widespread means of actively removing plaque at home is toothbrushing. There is substantial evidence that demonstrates that toothbrushing and other mechanical cleansing procedures can reliably control plaque, provided that this cleaning is sufficiently thorough and is performed at appropriate intervals. Evidence stemming from large cohort studies has demonstrated that high standards of oral hygiene ensure the stability of periodontal tissue support (Hujoel *et al*. 1998; Axelsson *et al*. 2004). Based on a longitudinal study of the natural history of periodontitis in a dentally well-maintained male population (Schätzle *et al*. 2004), Lang *et al.* (2009) concluded that persistent gingivitis represents a risk factor for periodontal attachment loss and tooth loss.

Given the great importance that has been placed on plaque and personal oral hygiene in the periodontal therapy hierarchy, evidence is needed to support this leading role. In a review, Hujoel *et al.* (2005) systematically searched for evidence from randomized controlled trials regarding whether improved personal oral hygiene was associated with a decreased risk of periodontitis initiation or progression. These reviewers were unable to find randomized controlled trial evidence indicating that improved personal oral hygiene prevented or controlled chronic periodontitis. By itself, this finding is not surprising because, based on common sense, it would be unethical to provide periodontal treatment without oral hygiene instruction. Furthermore, almost 60 years of experimental research and clinical trials in different geographic and social settings have confirmed that effective removal of dental plaque is essential for dental and periodontal health (Löe 2000). The reduction of plaque mass through good oral hygiene will reduce the injurious load on these tissues.

As meaningful as oral hygiene measures are for disease prevention, they are relatively ineffective when used *alone* for the treatment of moderate and severe forms of periodontitis (Loos *et al*. 1988; Lindhe *et al*. 1989). Without an adequate level of oral hygiene in periodontitis-susceptible subjects, periodontal health tends to deteriorate once periodontitis is established, and further loss of attachment can occur (Lindhe & Nyman 1984).

Meticulous, self-performed plaque removal measures can modify both the quantity and composition of subgingival plaque (Dahlén *et al*. 1992). Oral hygiene acts as a non-specific reducer of plaque mass. This therapeutic approach is based on the rationale that any decrease in plaque mass benefits the inflamed tissues adjacent to bacterial deposits. The Socransky group (Haffajee *et al.* 2001) reported that a permanent optimal supragingival plaque control regimen could alter the composition of the pocket microbiota and lower the percentage of periodontopathic bacteria.

Currently, both primary prevention of gingivitis and primary and secondary prevention of periodontitis are based on the achievement of sufficient plaque removal. The concept of primary prevention of gingivitis is derived from the assumption that gingivitis is a precursor of periodontitis and that maintenance of healthy gingiva will prevent periodontitis. Consequently, preventing gingivitis could have a major impact on periodontal care expenditure (Baehni & Takeuchi 2003). Primary prevention of periodontal diseases includes educational interventions for periodontal diseases and related risk factors, and regular, self-performed plaque removal and professional, mechanical removal of plaque and calculus. Optimal oral hygiene requires appropriate motivation of the patient, adequate tools, and professional oral hygiene instruction.

There is a lack of evidence with regard to the most effective self-performed oral hygiene around dental implants. Self-care at present can therefore only be based on the knowledge that is available with regard to home-based care of natural teeth. However, because the anatomic structure of the marginal gingival tissues is different from that around natural teeth, the authors strongly suggest further well-performed clinical trials in the near future to examine various aspects of oral hygiene around dental implants.

Self-performed plaque control

Maintenance of oral health has been an objective of humans since the dawn of civilization. Self-care has been defined by the World Health Organization as all of the activities that the individual undertakes to prevent, diagnose, and treat poor personal health though self-support activities or referral to healthcare professionals for diagnosis and care. Personal oral hygiene refers to the effort of the patient to remove supragingival plaque. The procedures used to remove supragingival plaque are as old as recorded history. The use of mechanical devices for the cleaning of

teeth dates back to the ancient Egyptians 5000 years ago, who made brushes by fraying the ends of twigs. People often chewed on one end of a stick until the fibers of the wood formed a brush, which was then rubbed against the teeth to remove food. These chewing sticks were the ancestors of the *miswak,* which is still used today and is especially popular in Muslim communities. The Chinese are believed to have invented the first toothbrush in approximately 1600 BC. This primitive toothbrush was made of natural hog bristles from pigs' necks with the bristles attached to a bone or bamboo handle (Carranza & Shklar 2003). In his writings, Hippocrates (460–377 BC) included commentaries on the importance of removing deposits from the tooth surfaces. The observation that self-performed plaque removal is one of the foundations of periodontal health was clearly described in 1683 by the well-known Dutch scientist Antonie van Leeuwenhoek, who wrote, "Tis my wont of a morning to rub my teeth with salt and then swill my mouth out with water; and often, after eating, to clean my back teeth with a toothpick, as well as rubbing them hard with a cloth; wherefore my teeth, back and front, remain as clean and white as falleth to the lot of few men of my years, *and my gums never start bleeding*" (Carranza & Shklar 2003). Van Leeuwenhoek examined under the lens of an early microscope the scrapings from his own teeth. He observed tiny moving organisms floating and spinning through the soft mass. This centuries-old discovery seems primitive by today's standards, but this early description of the dental biofilm was the basis for modern-day microbiology.

Currently, toothbrushes of various kinds are important aids for mechanical plaque (dental biofilm) removal, and their use is almost universal. Furthermore, a fluoridated dentifrice is an integral component of daily home oral care. Over the past 50 years, oral hygiene has improved; in industrialized countries, 80–90% of the population brushes its teeth once or twice a day (Saxer & Yankel 1997). The use of interdental cleaning devices, mouth rinses, and other oral hygiene aids is less well documented, but the available evidence tends to suggest that only a small percentage of the population uses such additional measures on a regular basis (Bakdash 1995). The benefits of optimal home-use plaque-control measures include the opportunity to maintain a functional dentition throughout life; reduction of the risk of loss of periodontal attachment; optimization of esthetic values, such as appearance and breath freshness; and a reduced risk of complex, uncomfortable, and expensive dental care (Claydon 2008). There is increasing public awareness in the Western world of the value of good oral health practices. This fact has been demonstrated by the recorded increases in both public spending on oral hygiene products (>$3.2 billion per year in the US) and industry spending on consumer-related advertising (>$272 million per year in the US) (Bakdash 1995).

Brushing

Different cleaning devices have been used in different cultures over the centuries (toothbrushes, chewing sticks, chewing sponges, tree twigs, strips of linen, bird feathers, animal bones, porcupine quills, etc.). Toothbrushing is currently the most commonly implemented measure in oral hygiene practices. The toothbrush, when used properly, has no side effects, is easy to use, and is inexpensive. Used with toothpaste it removes tooth stain and is the vehicle to deliver therapeutic agents in toothpaste. According to the Lemelson-MIT Invention Index (2003), the toothbrush was selected as the number 1 invention that Americans could not live without; when they were asked to select from among five choices — toothbrush, automobile, personal computer, cell phone, and microwave — more than one-third of teens (34%) and almost half of adults (42%) cited the toothbrush. Toothbrushing alone, however, does not provide adequate interdental cleaning because a toothbrush can only reach the facial, oral, and occlusal tooth surfaces. It was suggested (Frandsen 1986) that the outcomes of toothbrushing are dependent on: (1) the design of the brush; (2) the skill of the individual using the brush; (3) the frequency of brushing; and (4) the duration of brushing. Also, the uniformity of the dentition and a person's attitude and commitment towards brushing play a role, and together mean that there is no single toothbrush suitable for all populations. Dental professionals must become familiar with the variety in shapes, sizes, textures, and other characteristics of available toothbrushes to provide their patients with proper advice. From the numerous products currently available on the market, only a few should be selected for any individual patient. It is important that the dental care provider understands the advantages and disadvantages of the various toothbrushes (and other aids) to provide the patient with proper information during oral hygiene instruction sessions. It is quite possible that a given patient will obtain better results with one particular toothbrush than with another. Therefore, the provision of oral hygiene information should be tailored to the individual.

Motivation

Oral hygiene education is essential to the primary prevention of gingivitis. Improvement in a patient's oral hygiene is often accomplished through cooperative interaction between the patient and the dental professional. The role of the patient is to seek education regarding efficient self-performed plaque removal and to undergo regular check-ups to ensure a high level of oral hygiene. The patient must be involved in maintaining the health of the tissues, interested in a proposed treatment plan, and motivated to participate. Without compliance, which has been described as the degree to which a patient

follows a regimen prescribed by a dental professional, a good treatment outcome will not be achieved. In this context, it should be realized that compliance with treatment recommendations is generally poor, particularly in patients with chronic diseases for which the risk of complications is not immediate or life threatening. Also, compliance with oral hygiene recommendations is generally poor (Thomas 2004).

Thus, however effective any toothbrushing method is, it will only be of any real value if the patient is prepared to use the technique on a regular basis (Warren & Chater 1996). The patient's positive attitude toward treatment can have positive long-term effects on her/his tooth cleaning efforts. Thus, well-motivated patients who are compliant with professional advice and instructions are likely to achieve and sustain ideal levels of plaque control. Good oral hygiene should form an integral part of overall health practices, along with regular exercise, stress management, diet and weight control, smoking cessation, and moderation in alcohol consumption. If the clinician can establish the link between oral health and general health for the patient, then the individual might be more willing to establish proper oral hygiene measures as part of her/his lifestyle. The issue of changing a patient's lifestyle is the more difficult part of motivational sessions (see Chapter 35). The principles of brushing and flossing are easy to learn. Integrating them into a person's daily routine is far more difficult. This difficulty can become a source of frustration for the clinician who has provided a patient with information about the necessity of personal oral hygiene measures.

Oral hygiene instruction

Oral hygiene education consists not only of knowledge transfer; it must also consider current habits and personal skills. Patients often present with non-specific brushing techniques and need sufficient support to establish methods that are appropriate for their respective needs. Ganss *et al.* (2009a) assessed toothbrushing habits in uninstructed adults and observed that when using a strict definition of appropriate brushing habits (defined as brushing at least twice daily for 120 seconds with a brushing force not exceeding 3 N and with circling or vertical sweeping movements), only 25.2% of the participants fulfilled all of the criteria.

Twice-daily brushing with fluoridated toothpaste is now an integral part of most people's daily hygiene routines in Western societies. However, it appears that most patients are unable to achieve total plaque control at each cleaning. A systematic review (Van der Weijden & Hioe 2005) was initiated to assess the effect of mechanical plaque control and was then refined to address the effect of manual toothbrushing on plaque and gingivitis parameters. It was concluded that in adults with gingivitis, the quality of self-performed mechanical plaque removal was not sufficiently effective and needed to be improved. Based on studies of 6 months or longer in duration, it appears that a single oral hygiene instruction session, during which the use of a mechanical toothbrush is described, in addition to a single professional session of "oral prophylaxis" at baseline, had a significant, albeit small, positive effect on the reduction of gingival inflammation in adults with gingivitis. A recent study evaluated the effects of yearly oral hygiene instructions during dental check-ups of 284 patients over a 5-year period (Furusawa *et al.* 2011). It was shown that these repeated instructions significantly contributed to improved plaque control compared to control in patients not receiving these instructions. Jönsson *et al.* (2009) reported that an individually tailored oral health educational program, based on an integrated cognitive/behavioral and oral health approach, was more effective than standard treatment in achieving proper long-term oral hygiene behavior resulting in reduced plaque and gingivitis, specifically interproximally.

Toothbrushing

Manual toothbrushes (see Box 36-1)

The exact origins of mechanical devices for cleaning teeth in the Western world are unknown. The Chinese are given credit for developing the first handheld bristle toothbrush, as the earliest record of a toothbrush was found in Chinese writing from approximately 1600 BC. A century later, the nobility were using toothbrushes fashioned from silver. In 1698, Cornelis van Solingen, a doctor from The Hague, published a book in which he presented the first illustration of a toothbrush in Europe (Fig. 36-1). Over the past 350 or so years, toothbrushes have been crafted with bone, wood, or ivory handles that held the stiff bristles of hogs, boars, or other animals.

The first mass-produced toothbrush was made by William Addis of Clerkenwald, England, circa 1780. The idea of the bristle bone toothbrush came

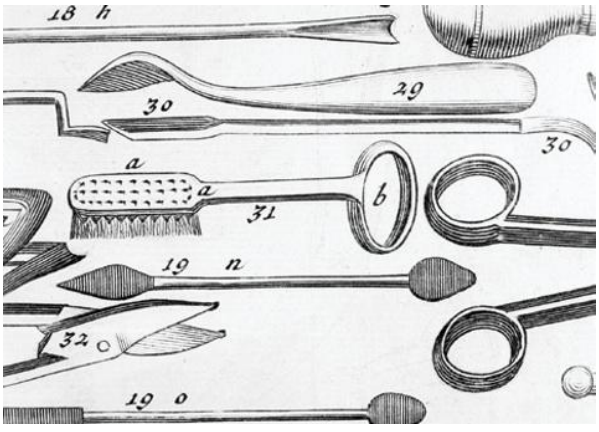


Fig. 36-1 Illustration of a toothbrush and tongue scraper from a book by Cornelis van Solingen. (Courtesy of the University Museum of Dentistry in Utrecht, the Netherlands.)

to William Addis while in prison. Boredom and necessity drove Addis to take a bone left behind from his dinner and to borrow bristles from a guard. The Addis version of the toothbrush had a bone handle and holes for the placement of natural hog bristles, which were held in place by wire. While acceptable at the time and no doubt efficacious in terms of plaque removal, natural products are inherently unhygienic, as the bristle fibers allow the accumulation and proliferation of orally-derived bacteria. The first American to patent a toothbrush was H. N. Wadsworth (in 1857), and many American companies began to produce toothbrushes after 1885. In the early 1900s, celluloid began to replace the bone handle, a change that was hastened by World War I when bone and hog bristles were in short supply. Nylon filaments were introduced in 1938 by Du Pont de Nemours because World War II prevented the exportation of wild boar bristles from China. Nearly all current toothbrushes are made exclusively of synthetic materials (Wilkins 1999). Their nylon filaments and plastic handles are easy to manufacture and are therefore more affordable. This ease of manufacture has made toothbrushing a common practice in most societies. Some unique designs have been developed, including multiple brush heads to allow simultaneous cleaning of tooth surfaces.

During toothbrushing, the removal of dental plaque is achieved primarily through direct contact between the filaments of the toothbrush and the surfaces of teeth and the soft tissues. At the European Workshop on Mechanical Plaque Control, it was agreed that the features of an ideal manual toothbrush are (Egelberg & Claffey 1998):

- Handle size appropriate to user's age and dexterity so that the brush can be easily and efficiently manipulated
- Head size appropriate to the size of the individual patient's requirements
- End-rounded nylon or polyester filaments not larger than 0.23 mm (0.009 inches) in diameter
- Soft filament configurations, as defined by the acceptable international industry standards (ISO)
- Filament patterns that enhance plaque removal in the appropriate spaces and along the gum line.

Additional characteristics could include an inexpensive price, durability, imperviousness to moisture, and easy to clean.

Modern toothbrushes have reached a certain stage of sophistication, and they are designed to be appealing to use. To improve patient comfort, over time the shape of the brush head, the filaments, and the placement of filaments in the handles has changed. Modern toothbrushes have filament patterns designed to enhance plaque removal from hard-to-reach areas of the dentition, particularly from proximal areas. A major shortcoming of the conventional flat-trim toothbrushes has been the "blocking effect" of tight bristle tufts, which prevents individual tufts from reaching interproximal areas. Cross-placed filaments and crimped and tapered filaments are the most recent improvements. The designs are based on the premise that the majority of subjects in any population use a simple horizontal brushing action. Multiple tufts of filaments, sometimes angled in different directions, are also used (Jepsen 1998). These multilevel toothbrushes have alternating rows of taller and shorter bristle tufts acting independently, so they are not influenced by the adjacent bristles during brushing. Once independent motion is achieved, the longer bristles can effectively reach further between the teeth. Multilevel or angled toothbrush designs (Fig. 36-2) yield genuinely improved performance characteristics when compared with flat-headed brushes (Cugini & Warren 2006; Slot *et al.* 2012). Double- and triple-headed toothbrushes have been proposed to reach the lingual surfaces more easily, especially in molar areas, which are normally the tooth surfaces hardest to reach with regular toothbrushes. Although some studies have indicated that the use of such multiheaded toothbrushes might improve plaque control in lingual areas (Agerholm 1991; Yankell *et al.* 1996), their use is not widespread.

Fig. 36-2 Flat-trim, multilevel and angled manual toothbrush bristle tuft design.

Whereas handles used to be straight and flat, round and curved handles are more common today. The modern toothbrush has a handle size that is appropriate to the hand size of the prospective user, and greater emphasis has been placed on new ergonomic designs (Löe 2002). Several studies have investigated differences in plaque removal between brushes with different handle designs. In such studies, brushes with long and contoured handles appear to remove more plaque than brushes with traditional handles (Saxer & Yankell 1997).

Obviously, there can be no single "ideal" toothbrush for all populations. The choice of brush is usually a matter of individual preference, rather than governed by a demonstrated superiority of any one type. In the absence of clear evidence, the best toothbrush is the one that is (properly) used by the patient (Cancro & Fischman 1995; Jepsen 1998).

For a toothbrush company to qualify a toothbrush for the American Dental Association (ADA) Seal of Acceptance, it must be shown that:

- All of the toothbrush components are safe for use in the mouth
- Bristles are free of sharp or jagged edges and end points
- Handle material is manufacturer tested to show durability under normal use
- Bristles will not fall out with normal use
- Toothbrush can be used without supervision by the average adult to provide a significant decrease in mild gum disease and plaque
- Size and shape of the brush should fit in the mouth comfortably, allowing the user to reach all areas easily.

A company earns the ADA seal for its product by producing scientific evidence that the product is safe and effective, claims that are evaluated by an independent body of scientific experts – the ADA Council on Scientific Affairs – according to objective guidelines.

Efficacy

Toothbrush manufacturers have made great efforts to consider many different aspects when designing new models to meet the challenges of enhancing plaque biofilm removal through improved toothbrushing efficacy. Few toothbrush manufacturers have also attempted to evaluate toothbrush efficacy. The enthusiastic use of a toothbrush is not synonymous with a high standard of oral hygiene. Adults, despite their apparent efforts, do not appear to be as effective in their plaque removal as might be expected. The daily experience in dental practice is that patients exhibit plaque even though they reportedly engage in oral hygiene practices. De la Rosa *et al.* (1979) studied the patterns of plaque accumulation and removal with daily toothbrushing over a 28-day period following dental prophylaxis. On average, approximately 60% of the plaque remained after self-performed brushing. Morris *et al*. (2001) reported on the 1998 UK Adult Dental Health Survey and observed that the mean proportions of teeth with plaque deposits were 30% in the 25–34-year-old age group and 44% in those aged 65 years and older. Brushing exercise studies are commonly used for toothbrush evaluations. This study model provides useful indications of the plaque removal capacity of toothbrushes and facilitates the control of confounding variables, such as compliance.

Recently, a systematic review was initiated by Slot *et al.* (2012) to assess the effect of a single brushing exercise using a manual toothbrush. In total, 212 brushing exercises as separate legs of experiments in 10 806 participants, were used to calculate a weighted mean overall percentage plaque reduction score. The sheer magnitude of the number of participants and the heterogeneity observed in the various study designs yielded results of particular value because they reflected what might be generally expected from a routine oral hygiene exercise as encountered among patients in everyday practice. Based on the baseline and end scores, a plaque reduction percentage was calculated for each of the eligible experiments taken from the selected studies. Using these data, a weighted mean difference was calculated as a 42% reduction in plaque index scores from baseline indices.

An interesting aspect of this analysis was that the estimated magnitude of the effect size of toothbrushing appeared to be dependent on the plaque index score used to assess the magnitude of the effect. Compared to the Quigley & Hein plaque index, the estimate with the Navy index resulted in a greater difference between pre- and post-brushing scores: 30% versus 53%, respectively.

The Navy plaque index (Elliott *et al.* 1972) and the Quigley & Hein plaque index (Quigley & Hein 1962) and their modifications are the two indices most commonly used for assessing plaque removal efficacy with toothbrushes. Although these indices score plaque in different ways, there appears to be a strong correlation between them (Cugini *et al.* 2006). The Quigley & Hein plaque index emphasizes the differences in plaque accumulation in the gingival third of the tooth, and it tends to overscore the incisal half of the crown at the expense of the gingival margin. The Navy plaque index gives greater weight to plaque in the immediate gingival area. The scores from both indices are descriptive. They do not represent strictly linear scales; rather, they ascend in severity. A score of 0 is given when no plaque is found. Higher scores are assigned in ascending order, corresponding roughly to increasing areas of tooth surfaces covered by plaque. Because plaque is colorless, it is usually visualized by staining prior to scoring. Plaque is then defined, in an operational sense, as "stainable material" (Fischman 1986). Such practices do not result in precise estimates of the dental biofilm because they fail to evaluate qualitative features.

Methods of toothbrushing

There is no single oral hygiene method that is correct for every patient. The morphology of the dentition (crowding, spacing, gingival phenotype, etc.), the type and severity of periodontal tissue destruction, and the patient's own manual dexterity determine what kind of hygiene aids and cleaning techniques should be recommended. It should also be realized that during the course of periodontitis therapy, the techniques might have to be changed or adapted to the morphologic situation (longer teeth, open interdental spaces, exposed dentin).

The ideal brushing technique is the one that allows for complete plaque removal in the least

possible time, without causing any damage to tissues (Hansen & Gjermo 1971). Different toothbrushing methods have been recommended over time and some have also been abandoned. Such methods can be classified based on the position and motion of the brush.

Horizontal brushing is probably the most commonly used toothbrushing method. It is most frequently used by individuals who have never had instruction in oral hygiene techniques. Despite the efforts of the dental profession to instruct patients to adopt other, more efficient brushing techniques, most individuals use horizontal brushing because it is simple. The head of the brush is positioned perpendicular to the tooth surface, and then a horizontal back-and-forth scrubbing movement is applied (Löe 2000). The occlusal, lingual, and palatal surfaces of the teeth are brushed with an open mouth. To reduce the pressure of the cheek on the brush head, the vestibular surfaces are cleaned with the mouth closed.

Vertical brushing [Leonard (1939) technique] is similar to the horizontal brushing technique, but the movement is applied in the vertical direction, using up-and-down strokes.

Circular brushing [Fones (1934) method] is performed with the teeth closed, the brush placed inside the cheek, and a fast circular motion applied that extends from the maxillary gingiva to the mandibular gingiva, using light pressure. Back-and-forth strokes are used on the lingual and palatal tooth surfaces.

The *scrubbing method* includes a combination of horizontal, vertical, and circular strokes.

Sulcular brushing [Bass (1948) method] (see Box 36-1) emphasizes cleaning of the area directly beneath the gingival margin. The head of the brush is positioned in an oblique direction toward the apex. The filament tips are directed into the sulcus at approximately 45° to the long axis of the tooth. The brush is moved in a back-and-forth direction using short strokes, without disengaging the tips of the filaments from the sulci. On the lingual surfaces in the anterior tooth regions, the brush head is kept in the vertical direction. The Bass method is widely accepted as an effective method for removing plaque, not only at the gingival margin but also subgingivally. A few studies have been conducted on teeth affected with periodontal disease and scheduled for extraction, in which the gingival margin was marked with a groove, and the depth of subgingival cleaning was measured. These studies showed that with the use of this brushing method, plaque removal could reach a depth of approximately 1 mm subgingivally (Waerhaug 1981a).

The *vibratory technique* [Stillman (1932) method], was designed for the massage and stimulation of the gingiva and for cleaning the cervical areas of the teeth. The head of the brush is positioned in an oblique direction toward the apex, with the filaments placed partly in the gingival margin and partly on the tooth surface. Light pressure, together with a vibratory (slight rotary) movement, is then applied to the handle, while the filament tips are maintained in position on the tooth surface.

The *vibratory technique* [Charters (1948) method] was originally developed to increase cleansing effectiveness and gingival stimulation in the interproximal areas. Compared to the Stillman technique, the position of the brush head is reversed. The head of the brush is positioned in an oblique direction, with the filament tips directed toward the occlusal or incisal surfaces. Light pressure is used to flex the filaments and gently force the tips into the interproximal embrasures. A vibratory (slight rotary) movement is then applied to the handle, while the filament tips are maintained in position on the tooth surface. This method is particularly effective in cases with receded interdental papillae because the filament tips can easily penetrate the interdental space and in orthodontic patients (Fig. 36-3).

With the *roll technique*, the head of the brush is positioned in an oblique direction toward the apex of the teeth, with the filaments placed partly in the gingival margin and partly on the tooth surface. The sides of the filaments are pressed lightly against the gingiva. Next, the head of the brush is rolled over the gingiva and teeth in an occlusal direction.

Finally, the *modified Bass/Stillman technique* emerged because the Bass and Stillman methods were both designed to concentrate on the cervical portion of the teeth and the adjacent gingival tissues and could be modified to add a roll stroke. The brush is positioned similarly to in the Bass/Stillman technique. After activation of the brush head in a back-and-forth direction, the head of the brush is rolled over the gingiva and teeth in the occlusal direction, making it possible for some of the filaments to penetrate interdentally.

In the 1970s, several investigators compared various methods of brushing. Because of varying experimental conditions, the outcomes of these studies are difficult to compare. To date, no method of toothbrushing has been shown to be clearly superior to others. As early as 1986, Frandsen commented on this issue, stating, "Researchers have realized that improvement in oral hygiene is not as dependent upon the development of better brushing methods as upon improved performance by the persons using any one of the accepted methods." Therefore, because no particular toothbrushing method has been found to be clearly superior to the others, there is no reason to introduce a specific toothbrushing technique with each new periodontal patient. In most cases, small changes in the patient's own method of toothbrushing will suffice, always bearing in mind that more important than the selection of a certain method of toothbrushing is willingness and thoroughness on the part of the patient to clean his/her teeth effectively. Implementation of the toothbrushing methods described above must be made according to a patient's needs. For example, because the Bass method has been associated with gingival recession

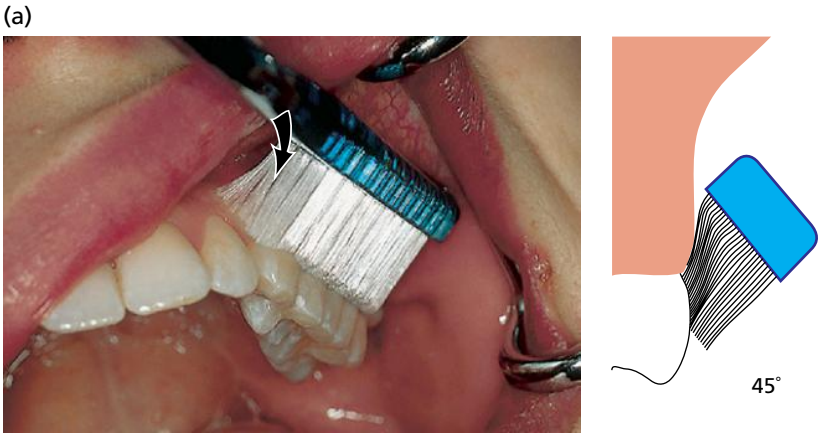


Fig. 36-3 (a) Charters method of toothbrushing. The head of the toothbrush is placed in the left maxilla. Note the angulation of the bristles against the buccal tooth surfaces. The bristles are forced into the interproximal areas. (b) Palatal aspect of the incisor region in the maxilla, illustrating the penetration of the bristles through the interproximal spaces (arrows).

(O'Leary 1980), it is not be indicated in individuals with energetic toothbrushing habits who also have a thin gingival biotype.

Frequency of use

Although the ADA recommends that teeth should be brushed twice per day with a fluoride toothpaste and cleaned in between daily with floss or an interdental cleaner, there is no true consensus as to the optimal frequency of toothbrushing. How often teeth must be brushed and how much plaque must be removed to prevent dental disease from developing are not known. The majority of individuals, including periodontal patients, are usually unable to remove dental plaque completely with daily brushing. However, complete plaque removal does not seem to be necessary. Theoretically, the proper level of oral hygiene is the extent of plaque removal that prevents gingivitis/periodontal disease and tooth decay in the individual patient. The prevention of gingival inflammation is important because inflammatory conditions of soft tissues also favor plaque accumulation (Lang *et al*. 1973; Ramberg *et al*. 1994; Rowshani *et al*. 2004).

Results from cross-sectional studies have been equivocal when the self-reported frequency of tooth cleaning has been related to caries and periodontal disease. A survey, using a questionnaire to assess oral hygiene practices, observed no statistically significant differences in periodontal health measurements (gingival inflammation, probing pocket depth, attachment loss) between subjects performing acceptable (brushing at least once a day) and unacceptable self-reported brushing behavior (Lang *et al.* 1994). However, correlation coefficients have revealed a weakly positive, but significant, relationship between the frequency of tooth brushing and oral hygiene and gingival health (Addy *et al*.1990). Disease appears to be related more to the quality of cleaning than to its frequency (Bjertness 1991). Kressin *et al.* (2003) evaluated the effect of oral hygiene practices on tooth retention in a longitudinal study with 26 years of follow-up. They observed that consistent brushing (at least once per day) resulted in a 49% reduction in the risk of tooth loss, compared to a lack of consistent oral hygiene habits.

If plaque is allowed to accumulate freely in the dentogingival region, subclinical signs of gingival inflammation (gingival fluid) appear within 4 days (Egelberg 1964). The minimum frequency of tooth cleaning needed to reverse experimentally induced gingivitis is once every day or every second day. Bosman and Powell (1977) induced experimental gingivitis in a group of students. Signs of gingival inflammation persisted in those students who removed plaque only every third or fifth day. In the groups who properly cleaned their teeth once per day or every second day, the gingiva healed within 7–10 days.

Based on the observation that the onset of gingivitis appears to be more closely related to the maturation and age of the plaque than to its amount, the minimum frequency of brushing needed to prevent the development of gingivitis was investigated in a prospective study. Dental students and young dental faculty members with healthy periodontal conditions were assigned to study groups with different cleaning frequencies over periods of 4–6 weeks. The results indicated that students who thoroughly removed plaque once daily or even every second day did not develop clinical signs of gingival inflammation over a 6-week period. This tooth cleaning included the use of interproximal aids (dental floss and woodsticks) and toothbrushes (Lang *et al*. 1973). Caution should be exercised in extrapolating the results obtained from studies including dentally aware subjects to the average patient.

As a point of principle, it is reasonable to state that meticulous mechanical removal of plaque by toothbrushing, combined with the removal of interdental plaque once every 24 hours, is adequate to prevent the onset of gingivitis and interdental caries (Axelsson 1994; Kelner *et al*. 1974). From a practical standpoint, it is generally recommended that patients brush their teeth at least twice daily, not only to remove plaque but also to apply fluoride through the use of a dentifrice to prevent caries. This advice also considers feelings of oral freshness. For most patients, it might be desirable to perform all necessary procedures (e.g. brushing and interdental cleaning) at the same time and in the same manner each day. Unfortunately, for subjects who live busy, stressful lives, this level of dedication can be difficult to achieve (Thomas 2004). Despite most individuals claiming to brush their teeth at least twice per day, it is clear from both epidemiologic and clinical studies that mechanical oral hygiene procedures, as performed by most subjects, are insufficient to control supragingival plaque formation and to prevent gingivitis and more severe forms of periodontal disease (Sheiham & Netuveli 2002).

Duration of brushing

Patients usually believe that they spend more time on toothbrushing than they actually do (Saxer *et al*. 1998). The least amount of time spent on brushing was observed in a study performed on English school children; in the 13-year-old group, the children spent approximately 33 seconds on brushing (Macgregor & Rugg-Gunn 1985). Approximately one-third of the studies that were reviewed reported an average brushing time of <56 seconds, whereas two-thirds of the studies reported brushing times of between 56 and 70 seconds. Two investigations reported an average brushing time of ± 90 seconds (Ayer *et al*. 1965; Ganss *et al*. 2009a). MacGregor and Rugg-Gunn (1979) reported that of a mean 50-second brushing time, only 10% of that time was spent on the lingual surfaces.

The best estimates of actual manual brushing time range between 30 and 60 seconds (Van der Weijden *et al*. 1993; Beals *et al.* 2000). Some caution regarding these estimates should be exercised, as the act of measuring brushing time has been shown to affect brushing behavior (MacGregor & Rugg-Gunn 1986).

The toothbrushing in the study by Van der Weijden *et al.* (1993) was performed by a dental professional. This study compared the effect of brushing time on plaque removal using manual and electric toothbrushes, utilizing five different brushing times (30, 60, 120, 180, and 360 seconds). The results indicated that 2 minutes of electric toothbrushing was as effective as 6 minutes of manual toothbrushing. The authors furthermore observed that at 2 minutes, an optimum in plaque-removing efficacy was reached with both manual and electric toothbrushes. Recently, in their systematic review, Slot *et al.* (2012) evaluated in a subanalysis the effect of a single brushing exercise with a manual toothbrush relative to the toothbrushing time. Based on the Quigley & Hein plaque index scores, the estimated weighted mean efficacy as represented in plaque score reduction was 27% after 1 minute and 41% after 2 minutes.

Six studies have been identified in the literature that address the question of whether, in adult patients, the duration of toothbrushing correlates with the efficacy of plaque removal. Three of these studies evaluated the use of electric toothbrushes (Van der Weijden *et al*. 1996a; McCracken *et al*. 2003, 2005). One study compared manual toothbrushes with electric toothbrushes (Preber *et al*. 1991), while two studies evaluated only manual toothbrushes (Hawkins *et al*. 1986; Gallagher *et al.* 2009). The results from all six studies indicated that the duration of brushing was consistently correlated with the amount of plaque that was removed.

Based on the above observations, the duration of toothbrushing is likely to be an important determinant of plaque removal in the general population; therefore, it should be stressed during toothbrushing instruction sessions. As plaque removal is strongly correlated with brushing time for any given toothbrush, brushing for 2 minutes or longer should be encouraged, regardless of the brush used. Brushing time is also likely the most easily controlled parameter of effective everyday brushing.

Brushing filaments

The characteristics of an effective toothbrush correspond to the primary functional properties of the filaments. Most modern toothbrushes have nylon filaments. The end of a toothbrush filament can be cut in either a blunt or a rounded manner (see Filament end-rounding below). Today, many manufacturers vary the length or diameter of the filaments mounted in the head. The degrees of hardness and stiffness of a toothbrush depend on the filament characteristics, such as material, diameter, and length.

Toothbrushes with thinner filaments are softer, while thicker-diameter filaments are stiffer and less flexible. Curved filaments can be more flexible and less stiff than straight filaments of equal length and diameter. Also, the density of the filaments in a tuft influences its stiffness, as each filament provides support to adjacent filaments, and each tuft provides support to adjacent tufts. Consequently, the number of filaments per tuft also determines the hardness of a toothbrush. Increased stiffness will prevent the filament ends from bending back during brushing, avoiding the potential risk of damaging the gums. However, the filament must be sufficiently stiff so that during brushing, sufficient pressure (shear force) is exerted to allow for proper plaque removal.

Concern about toothbrush filaments relates primarily to the potential for hard and soft tissue abrasion. Consider that a rod represents a filament of a toothbrush. While brushing, a vertical upward load is exerted, which, in turn, exerts an effect of the same order of magnitude on the oral mucosa. The force of the brush, acting on the individual filament, is thus always as great as the load exercised by the filament on the mucosa. If the load is increased, then the load on the mucosa increases to the same extent. Consequently, the risk of soft tissue damage increases as the filament's tip can penetrate into the mucosa. However, elastic rods demonstrate a peculiarity in their behavior. They suddenly fold back laterally when a certain load limit is exceeded. When folding back, the rod suddenly gives way elastically (without breaking), and the load on the oral mucosa diminishes abruptly. Thus, a load greater than this fold-back limit cannot be transferred to the mucosa by the rod via its tip.

As late as 1967, most people were buying hard brushes (Fanning & Henning 1967). The shift in preference to soft brushes of a specific design paralleled the change that occurred in oral health care when calculus was identified as the prime etiologic agent in periodontal disease (Mandel 1990). The concentration on plaque, especially in the crevicular area, and attention to intrasulcular brushing strongly influenced the change from hard to soft filaments, primarily because of the concern for trauma to the gingival tissues (Niemi *et al.* 1984). Soft filaments are universally recommended for sulcular brushing, such as with the Bass method. Patients can brush at the cervical areas without fear of discomfort or soft tissue laceration. However, various studies have shown that subjects cleaned significantly better with medium and hard brushes than with soft-bristled brushes (Robertson & Wade 1972; Versteeg *et al.* 2008a). Therefore, it appears that the filaments must have a degree of stiffness to create sufficient abrasion to dislodge plaque deposits. There is no point in using a brush with very thin filaments that merely stroke across the tooth and, as a result of the lack of load, no longer clean the tooth surface. However, to avoid damaging the gums when positioning the toothbrush, they must not be too hard: the harder the toothbrush filaments, the greater the risk of gingival abrasion (Khocht *et al.* 1993). People also tend to prefer medium-to-hard brushes because they feel that their teeth are cleaner after brushing with a stiffer brush. Versteeg *et al.* (2008a) showed that when there is no clinical indication for a soft toothbrush, the professional advice with regard to effectiveness should indeed be for a toothbrush of medium stiffness. Soft-filament brushes are particularly recommended for brushing shortly after periodontal surgery for patients with highly inflamed gingiva and for patients with naturally finely textured atrophic or sensitive mucosa. However, the topic of filament stiffness should not be addressed by itself; brush–toothpaste interaction should also be considered. The capacity of a toothbrush to hold and move polish/abrasive over the tooth surface affects the amount of hard tissue abrasion (see Toothbrush abrasion below).

Filament end-rounding

End-rounding has become increasingly common in the toothbrush-manufacturing process to reduce gingival abrasion (Fig. 36-4). The logic that smooth filament tips would cause less trauma than filament tips with sharp edges or jagged projections has been validated in both animal and clinical studies (Breitenmoser *et al.* 1979). Danser *et al.* (1998) evaluated two types of end-rounding and observed their effects on the incidence of abrasion. However, the form to which the ends were rounded had no effect on the level of plaque removal. Tapered filaments (Fig. 36-5) have endings in the shape of an extreme rotational ellipsoid instead of a hemisphere. This shape has been suggested to give the filaments very soft endings, combined with good stability of the filament corpus. As a result, more flexibility is

Fig. 36-4 Tapered toothbrush filaments.

Fig. 36-5 Filament end-rounding.

introduced into the filaments, which are presumably less harmful. The efficacy of tapered toothbrush filaments has been tested in laboratory studies, and it has been found that they were able to reach into the interproximal areas of the teeth, under the gum line and into the fissures. The outcomes of clinical studies comparing end-rounded filaments with flat-trimmed toothbrush head configurations have been equivocal (Dörfer *et al*. 2003; Versteeg *et al*. 2008b).

Wear and replacement

Common sense dictates that toothbrushes should be replaced because the filaments and tufts do not retain their shape forever. Completely worn brushes lose the capacity to remove plaque effectively. This result most likely occurs because of a loss of shear force, as the tips of the filaments can no longer disrupt the plaque adequately. The exact moment at which a toothbrush should be replaced is difficult to determine. In general, dental associations, professionals, and the oral care industry advocate toothbrush replacement every 3–4 months. While this advice would seem reasonable, there is little actual clinical proof that this recommendation is correct. Patients do not appear to heed this advice; the evidence indicates that the average age at which a toothbrush is replaced ranges from 2.5 to 6 months (Bergström 1973). On average, each person in the US purchases three toothbrushes every 2 years.

Common sense would suggest that a worn toothbrush with splayed or frayed filaments loses its resilience and is less likely to be as effective in removing plaque as a new brush. Because of the variability in subjects' brushing techniques and the force applied to the teeth while brushing, the degree of wear varies significantly from subject to subject. It is also likely that different brushes, made from various materials, would exhibit differences in longevity.

Because many patients use their brushes for periods significantly longer than the recommended time of 3 months, it is important to know whether excessive wear is of clinical relevance. There is inconclusive evidence about the relationship between toothbrush wear and plaque removal. The age of the toothbrush by itself appears not to be the critical parameter that is crucial to plaque removal efficacy. Studies with laboratory-worn toothbrushes have reported that such toothbrushes had inferior plaque removal efficacy compared to new brushes (Kreifeldt *et al*. 1980; Warren *et al*. 2002). However, artificially worn toothbrushes might not properly mimic the characteristics of naturally worn brushes. The wear of laboratory-worn toothbrushes will inevitably be highly uniform and will not reflect the variations in wear seen in normal toothbrush use. Most studies in which naturally worn toothbrushes were studied reported no statistically significant decreases in the reduction of whole-mouth plaque scores after brushing compared to when using new toothbrushes (Daly *et al*. 1996; Sforza *et al*. 2000; Tan & Daly 2002; Conforti *et al*. 2003; Van Palenstein Helderman *et al*. 2006). In a recent study with a parallel design, Rosema *et al.* (2013) evaluated the plaque-removing efficacy of new and used manual toothbrushes and found that wear rate seemed to be the determining factor with regard to loss of efficacy.

Thus, the replacement advice should be related more to wear than to the age of the toothbrush. In this respect, wear, as can be observed by the consumer, is considered to be bending, splaying, or matting of the filaments rather than the tapering effect of the filament ends. Kreifeldt *et al.* (1980) studied tapering of toothbrush filaments with regard to toothbrush wear and reported that new brushes were more efficient in removing dental plaque than old brushes. They also examined worn toothbrushes and observed that, as a result of wear, the filaments exhibited tapering that proceeded from the insertion to the free end. For example, filaments were seen that tapered from 0.28 mm at one end to 0.020–0.015 mm at the free end. They concluded that, among wear factors tapering contributed the most to loss of effectiveness. Their explanation for this observation was that as tapering results in a reduction of filament diameter, the brush will become softer and remove less plaque. Based on this tapering phenomenon, some commercially available brushes have filaments that change color after a certain amount of use. These wear indicator filaments serve to remind patients that it is time to replace the brush.

Electric (power) toothbrushes (see Box 36-2)

In well-motivated and properly instructed individuals who are willing to invest the necessary time and effort, mechanical measures using traditional toothbrushes and adjunctive manual (interdental) devices are effective in removing plaque. Maintaining

a dentition that is close to plaque-free is not easy, however. The high prevalence of gingivitis indicates that toothbrushing is not as effective in practice as it is in supervised studies. The electric toothbrush represents an advance that has the potential to enhance both plaque removal and patient motivation. Electric toothbrushes have been around since the 1940s, starting with devices such as the Motodent (circular brush head) and the Toothmaster (straight brush head). An example of the latter can be found in the National Museum of Dentistry in Baltimore, Maryland. The first successfully marketed electric toothbrushes were introduced more than 50 years ago. In 1954, the Swiss inventor Dr Philippe Guy E. Woog invented an oscillating, motorized electric toothbrush. This toothbrush was further developed by Bemann & Woog and first appeared in 1956 in Switzerland. In 1959, it was introduced in the US as the Broxodent at the centennial celebration of the ADA by E.R. Squibb and Sons. This early electric brush was a plug-in device that featured bristles that moved from side to side. In 1961, a cordless, rechargeable model was introduced by General Electric, the so-called Automatic Toothbrush, which soon took the lead in what was turning out to be a very competitive market.

The first electric toothbrushes were basically mechanized versions of manual toothbrushes, with the bristles moving back and forth in an imitation of the way people brushed by hand. Studies of the use of these early electric toothbrushes showed that there was no difference in plaque removal when compared with manual toothbrushes, although they had mixed effects on gingivitis. In 1966, the consensus from the research reports on toothbrushing of the World Workshop in Periodontics stated, "in non-dentally oriented persons, in persons not highly motivated to oral health care, or in those who have difficulty in mastering suitable hand brushing technique, the use of an electric brush with its standard movements may result in more frequent and better cleansing of the teeth".

Since the 1980s, tremendous advances have been made in the technology of electrically powered toothbrushes. Various electric toothbrushes have been developed with unique motions to improve the efficiency of plaque removal, using increased filament velocity and brush stroke frequency, and various filament patterns and motions. Whereas older electric toothbrushes used a combination of horizontal and vertical movements, mimicking closely the back-and-forth motion of traditional brushing methods, the more recent designs have incorporated a variety of actions, such as vibrating at ultrasonic frequencies, and have heads that rotate, heads that move from side to side, or sets of bristles that move one way and then the other way. The electric toothbrush that in the 1980s successfully steered away from a conventional brushing mode and instead mimicked the small round rotating brush head of dental prophylaxis instruments was the Rotadent (Zila, Fort Collins, CO, USA) (Boyd *et al*. 1989). It was sold with three different brush heads in different shapes to facilitate access to all areas of the oral cavity. However, the consumer found it difficult to control. In the 1980s the Interplak was introduced (Conair, Stamford, CT, USA), with independent tufts of bristles that performed rotary and counter-rotary movements (Van der Weijden *et al*. 1993). Although being effective it lost popularity because of the complicated gearing system which could not cope with the abrasive nature of toothpaste.

The development of an oscillating rotating round brush head by Braun (Kronberg, Germany) made control of the brush easier. Oscillating-rotating brushes are designed with round heads that move back and forth, with alternating one-third turns clockwise and counterclockwise. The original oscillating-rotating toothbrush, the Braun Oral-B Plaque Remover (D5), featured a small, round brush head that made rotating and oscillating movements at a speed of 2800 oscillating rotations/min. A further development of this brush, the Braun Oral-B Ultra Plaque Remover (D9), maintained the oscillating–rotating action but at an increased speed (3600 rotations/min). A clinical study with the D9 demonstrated equivalence in safety and a trend toward greater plaque removal (Van der Weijden *et al*. 1996b). Newer developments in oscillating–rotating brush technology are the addition of high-frequency vibrations in the direction of the bristles, creating three-dimensional movements during brushing. This modification was developed to enhance penetration and the removal of plaque from the proximal spaces of the dentition. Studies have shown that the three-dimensional movements performed by the brush are safe and more efficient regarding plaque removal (Danser *et al*. 1998).

Another advance in this technology has been the development of sonic toothbrushes, which have a high frequency of filament movement in excess of approximately 30 000 strokes/min. For example, the rechargeable Oral-B Sonic Complete® (Oral-B Laboratories, Boston, MA, USA) and the Philips Sonicare® Elite (Philips Oral Healthcare, Snoqualmie, WA, US) both use a side-to-side motion operating at a frequency of 260 Hz, but are based on different technologies. Toothbrushes with bristle motion at a high frequency can generate a turbulent fluid flow in the oral cavity. This flow can cause hydrodynamic forces (wall shear forces) that act parallel to a surface. The vibration of toothbrush bristles could further enable energy transfer in the form of sound pressure waves. *In vitro* studies have indicated that non-contact biofilm reduction can be obtained by these hydrodynamic effects. However, *in vivo*, the additional beneficial effects of higher amounts of non-contact biofilm removal have not yet been shown clinically (Schmidt *et al*. 2013).

The electric toothbrush should not be considered a substitute for a specific interdental cleaning method, such as flossing, but it can offer advantages in terms of an overall approach to improved oral hygiene.

Fig. 36-6 Overview of the development of electric toothbrushes, from brushes mimicking a manual toothbrush to high-frequency brush head movement. From left to right: the Braun D3® (courtesy of Braun), Rotadent® (courtesy of Rotadent), Interplak® (courtesy of Conair), Braun/Oral-B Triumph® (courtesy of Braun and Oral-B), and Sonicare Elite® (courtesy of Philips).

Electric brushes versus manual toothbrushes

To some extent, modern design features of electric brushes have overcome the limitations of manual dexterity and skill of the user (Fig. 36-6). These modern toothbrushes remove plaque in a shorter time than a standard manual brush. It takes 6 minutes to remove the same percentage of plaque using a manual toothbrush that is removed in 1 minute using a powered toothbrush in the hands of a professional operator (Van der Weijden *et al*. 1993, 1996a). The new generation of electric brushes has better plaque removal efficacy and gingival inflammation control on the proximal tooth surfaces (Egelberg & Claffey 1998). Of this latter aspect the superiority was clearly demonstrated in a study conducted on extracted teeth (Rapley & Killoy 1994).

The collective evidence, which has been summarized in two independent, systematic reviews, has indicated that oscillating–rotating toothbrushes have superior efficacy over manual toothbrushes in reducing plaque and gingivitis (Sicilia *et al*. 2002; Robinson *et al*. 2005). Electronic toothbrushes with this mode of action reduced plaque by 7% and gingival bleeding upon probing by 17% over the long term, when compared with manual brushes (Robinson *et al*. 2005). The conclusion from a Cochrane Oral Health Group review (Robinson *et al*. 2005) was that there is consistent evidence only for oscillating–rotating brushes to consider them clinically superior to manual brushes and that they offer greater plaque and gingivitis reductions. Any reported side effects were localized and temporary. Sensitivity analyses revealed the results to be robust when selecting trials of high quality, and there was no evidence of publication bias.

Some clinical studies have shown sonic technology to be comparable to or more effective than manual toothbrushes in removing plaque and reducing gingival inflammation (Johnson & McInnes 1994; Tritten & Armitage 1996; Zimmer *et al*. 2000; Moritis *et al*. 2002). Tritten and Armitage (1996) compared the Sonicare Advance to a traditional manual toothbrush in a 12-week parallel group study and concluded that both brushes were equally effective in reducing gingival inflammation.

Modern electric toothbrushes are known to enhance long-term compliance. In a study involving periodontitis patients with persistently poor compliance, Hellstadius *et al.* (1993) found that switching from a manual to an electric toothbrush reduced plaque levels and that the reduced levels were maintained over a period of between 12 and 36 months. The electric brush significantly improved compliance, and patients expressed a positive attitude toward the new brush. Another study reported 62% of people continuing to use their electric toothbrushes on a daily basis 36 months after purchase (Stålnacke *et al.* 1995). In a survey conducted in Germany, most dentists stated that the time their patients spent on toothbrushing was too short (Warren 1998). Approximately half of the dentists stated that they recommended that their patients use an electric toothbrush, and the vast majority of the dentists believed that changing to an electric toothbrush would improve the condition of their patients' teeth and gums. The findings from a US practice-based study, involving a large number of subjects who switched from manual toothbrushes to the Braun Oral-B Ultra Plaque Remover (D9), confirmed those from a German study (Warren *et al*. 2000).

Comparison of different electric toothbrushes

Today's marketplace is crowded with dozens of electric brushes. The choices range from inexpensive, disposable, battery-operated, rotating brushes to sophisticated, rechargeable electric brushes.

Two studies, using the same experimental gingivitis model, compared an earlier Sonicare device and the Oral-B oscillating–rotating toothbrush. In both studies, the oscillating–rotating brush was more effective in improving the level of gingival health (Putt *et al*. 2001; Van der Weijden *et al*. 2002a). These findings confirmed the findings of an earlier 6-week cross-over study (Isaacs *et al*. 1998), in which the improvement in gingival condition was 8.6% greater with the oscillating–rotating brush. Rosema *et al.* (2005) compared the Sonicare Elite to the Oral-B Professional Care 7000 and again found that the oscillating–rotating pulsation brush was more effective.

To establish the superiority of electric brushing over any other mode, the most recent review, performed in collaboration with the Cochrane Oral Health Group, assessed the collective evidence on efficacy of electric brushes and their effects on oral health (Deacon *et al.* 2011). The selection criteria were studies that were randomized, involved at least 4 weeks of unsupervised brushing, enrolled participants who had no impairment of manual dexterity, and compared two or more electric brushes with different

modes of action. Brushes with a rotation–oscillation action reduced plaque and gingivitis more than those with side-to-side action in the short-term. However, the difference was small and its clinical importance unclear. Due to the low numbers of trials using other types of electric brushes, no other definitive conclusions can be drawn regarding the superiority of one type of electric toothbrush over another. However, it must be emphasized that absence of evidence is not evidence of absence, and it might be that future trials show the superiority of specific toothbrush designs. Further research is required before evidence-based advice concerning the relative performances of different electric toothbrushes can be provided by healthcare professionals to the public.

Safety

The safety of electric toothbrushes has been a concern of dental care professionals. One fear was that they would be used excessively and compulsively. For example, enthusiastic electric brush users could apply too much force and compromise their gingival tissues, thereby promoting recession. In a recent systematic review of the effects of oscillating–rotating and manual brushes on hard and soft tissues, the authors determined the safety of this design of electric toothbrush as comprehensively as possible (Van der Weijden *et al.* 2011). They searched the existing literature, using a variety of electronic databases, for any study that compared the safety of rotation–oscillation brushes to that of manual brushes, including all but the weakest levels of evidence. Having extracted the relevant data from the 35 most appropriate original papers, the data were grouped by research design (randomized controlled trials with safety as the primary outcome, trials in which safety was a secondary outcome, studies that used a surrogate marker of safety, and laboratory-based studies). Within these groups, the designs of the original studies were usually so diverse that it was impossible to bring the results together into a single statistical analysis. Nevertheless, the original data consistently failed to indicate problems with the safety of rotation–oscillation brushes. However, the majority of the trials considered safety as a secondary outcome. Therefore, the evidence was usually anecdotal rather than quantitative. The review authors concluded, "This systematic review of a large body of published research in the preceding two decades consistently showed oscillating–rotating toothbrushes to be safe when compared with manual brushes, and collectively indicated that there is no evidence that they do pose a clinically relevant concern to either hard or soft tissues". The outcomes were consistent with the observations of Robinson *et al.* (2005) and Deacon *et al.* (2011) in reviews reporting only minor and transient side effects. Currently, there are no systematic reviews of the safety of any other types of electric brushes.

Electrically active (ionic) toothbrush

Several toothbrushes (ionic, electronic, and electrically active) have been marketed over the years that are designed to send a small, imperceptible electronic current through the brush head onto the tooth surfaces, presumably to disrupt the attachment of dental plaque and to damage the electrostatic bonding of plaque proteins to tooth surfaces. Thus, these currents could enhance the efficacy of brushes in plaque elimination. Electrons should eliminate H^+ ions from the organic acid in the plaque, which could result in decomposition of the bacterial plaque (Hoover *et al.* 1992). The first record of a charged toothbrush, "Dr. Scott's Electric Toothbrush," was found in the February 1886 issue of *Harper's* weekly magazine. The handle of Dr Scott's toothbrush was purportedly "charged with an electromagnetic current which acts without any shock, immediately upon the nerves and tissues of the teeth and gums…arresting decay…and restoring the natural whiteness of the enamel."

Hotta and Aono (1992) studied an electrically active manual toothbrush that was designed with a piezoelectric element in the handle. This brush generated a voltage potential corresponding to the bending motion of the handle as the teeth were brushed. In this study, no difference in the amount of remaining plaque after brushing was observed between the placebo and the electrically active brush. Other toothbrushes that have claimed an "electrochemical" effect on dental plaque have had semiconductors of titanium oxide (TiO_2) incorporated into the brush handle. In the presence of light, saturated low-energy electrons in the wet semiconductor are transformed into high-energy electrons. An electron current of approximately 10 nA was measured to run from the semiconductor to the tooth (Weiger 1988). Some short-term clinical studies of the use of these kinds of brushes have documented beneficial effects in terms of plaque reduction and gingivitis resolution (Hoover *et al.* 1992; Galgut 1996; Weiger 1998; Deshmukh *et al.* 2006), while others have failed to do so (Pucher *et al.* 1999; Moreira *et al.* 2007). One 6-month study reported lower plaque scores and improvement of gingivitis with the ionic brush compared to the control, but these findings were not substantiated in subsequent 6- and 7-month studies (Van der Weijden *et al.* 1995, 2002b).

Interdental cleaning

There is confusion in the literature regarding the definitions of the proximal, interproximal, interdental, and proximal sites. Commonly used indices are not suitable for assessing interdental plaque (directly under the contact area), thereby limiting the interpretation of interdental plaque removal. In 1998, the European Workshop on Mechanical Plaque Control proposed the following definitions. *Proximal* areas are the visible spaces between teeth that are not under

the contact area. These areas are small in healthy dentition, although they can increase after periodontal attachment loss. The terms *interproximal* and *interdental* can be used interchangeably and refer to the area under and related to the contact point.

The rationale for considering interdental cleaning under a separate heading is related to toothbrushing alone being considered optimally capable of thoroughly cleaning the *flat* surfaces of the teeth, that is the buccal, lingual, and occlusal surfaces, with the exceptions of pits and fissures. Toothbrushes do not reach the proximal surfaces of teeth as efficiently, nor do they reach into the interproximal areas between adjacent teeth. Therefore, measures for interdental plaque control should be selected to complement plaque control by toothbrushing (Lang *et al*. 1977; Hugoson & Koch 1979). The interdental gingiva fills the embrasure between two teeth apical to their contact point. This is a "sheltered" area which is difficult to access when the teeth are in their normal position. In populations that use toothbrushes, the interproximal surfaces of the molars and premolars are the predominant sites of residual plaque. The removal of plaque from these surfaces remains a valid objective because in patients susceptible to periodontal diseases, gingivitis and periodontitis are usually more pronounced in these interdental areas than on the oral or facial aspects (Löe 1979). Dental caries also occur more frequently in the interdental region than on the oral or facial smooth surfaces. A fundamental principle of prevention is that the effect is greatest where the risk of disease is greatest. Therefore, interdental plaque removal, which cannot be achieved with a toothbrush, is of critical importance for most patients.

A number of interdental cleaning methods have been developed, ranging from flossing to the more recently introduced electrically powered cleaning aids. Flossing is the most universally applicable method. However, not all interdental cleaning devices suit all patients or all types of dentitions. Factors such as the contour and consistency of the gingival tissues, the size of the interproximal embrasures, tooth position and alignment, and the ability and motivation of the patient should be taken into consideration when recommending an interdental cleaning method. The most appropriate interdental hygiene aids must be selected for each individual patient. The selection made from among the numerous commercially available devices is dependent for the most part on the size and shape of the interdental space and on the morphology of the proximal tooth surfaces. In subjects with normal gingival contours and embrasures, dental floss or tape can be recommended. At sites where soft tissue recession has become pronounced, flossing becomes progressively less effective. Thus, an alternative method (either woodsticks or interdental brushes) should be recommended. In addition, it should be borne in mind that the advice offered might need to change as the effectiveness of treatment and improved oral hygiene change the shapes of the interproximal regions.

Table 36-1 Interdental cleaning methods recommended for particular situations in the mouth.

Situation	Interdental cleaning method
Intact interdental papillae; narrow interdental space	Dental floss or small woodstick
Moderate papillary recession; slightly open interdental space	Dental floss, woodstick or small interdental brush
Complete loss of papillae; wide open interdental space	Interdental brush
Wide embrasure space; diastema, extraction diastema, furcation or posterior surface of most distal molar, root concavities or grooves	Single-tufted/end-tufted brush or gauze strip

A review of interdental cleaning methods (Warren & Chater 1996) concluded that all conventional devices are effective, but each method should be suited to a particular patient and to a particular situation in the mouth (Table 36-1). Furthermore, for maximum effectiveness, the level of oral hygiene advice delivered to the patient must contain enough information to enable the patient to be able to identify each site in turn, to select a device, and to clean all interdental surfaces effectively (Claydon 2008). The starting point is an evaluation of existing products. An ideal interdental cleaning device should be user-friendly, remove plaque effectively, and have no deleterious soft tissue or hard tissue effects. Gingival bleeding during interdental cleaning can be the result of trauma, such as lacerations and gingival erosions, or it can be an indication of inflammation. Patients must be aware that bleeding *per se* is not a sign that interdental cleaning should be avoided, but is more likely an indicator of inflammation that needs to be treated (Gillette & Van House 1980).

Dental floss and tape (see Box 36-3)

Of all the methods used for removing interproximal plaque, dental flossing is the most frequently recommended. Levi Spear Parmly, a dentist based in New Orleans, is credited with being the inventor of modern dental floss. As early as 1815, Parmly recommended tooth flossing with a piece of silk thread. In 1882, the Codman and Shurtleft Company of Randolph, Massachusetts, started to mass-produce unwaxed silk floss for commercial home use. In 1898, the Johnson & Johnson Company of New Brunswick, New Jersey, was the first to patent dental floss. Dr Charles C. Bass developed nylon floss as a replacement for silk floss during World War II. He was also responsible for making teeth flossing an important part of dental hygiene.

Dental floss and tape – the latter a type of broader dental floss – are most useful where the interdental papillae completely fill the embrasure space. When properly used, effective flossing removes up to 80% of proximal plaque. Even subgingival plaque can be removed because dental floss can be introduced 2–3.5 mm beyond the tip of the papilla (Waerhaug 1981b). Several types of floss (waxed, unwaxed) are available. Studies have shown no difference in the effectiveness of unwaxed versus waxed dental floss. Unwaxed dental floss is generally recommended for patients with normal tooth contacts because it slides through the contact area easily. It is the thinnest type of floss available, yet when it separates during use it covers a larger surface area of the teeth than waxed floss. Waxed floss is recommended for patients with tight proximal tooth contacts.

Ease of use is the most important factor that influences whether patients will use floss on a daily basis. Using dental floss is a complicated skill that many people find difficult to master. Unlike toothbrushing, few people have learned how to properly use dental floss. However, like any other skill, flossing can be taught, and those patients who are given appropriate instruction will increase their flossing frequency (Stewart & Wolfe 1989). Patients benefit from step-by-step instructions (see Box 36-3) and frequent re-instruction and reinforcement in the use of floss are necessary. Because many people think that the purpose of flossing is to remove particles of food, they must be advised that the objective is to remove plaque that adheres to the tooth surface.

To facilitate flossing, a special floss holder can be used. These holders can be re-used and are normally made of a plastic that is durable, lightweight, and easy to clean. Research has revealed that reductions in bacterial plaque biofilm and gingivitis are equivalent with either hand flossing or the use of a floss holder. Powered flossing devices have been introduced. In comparison with manual flossing, no differences were found in terms of plaque removal or gingivitis reduction, although patients preferred flossing with the automated device (Gordon *et al*. 1996).

Flossing is also time-consuming. When a patient is unwilling to use dental floss, alternative interdental hygiene aids should be recommended, even if these aids are less efficient. If a patient finds a particular method or device more appealing to use, long-term compliance becomes an achievable goal. Although it is clear that flossing, when properly used, removes plaque in a very efficient manner, there is no evidence that flossing in adult patients with preserved interproximal periodontal tissues should be routinely indicated (Burt & Eklund 1999).

Two systematic reviews are available concerning the efficacy of dental floss. The first, by Berchier *et al.* (2008), evaluated the collective evidence to determine the effectiveness of dental floss, in combination with toothbrushing, on plaque and the clinical parameters of gingivitis in adults. The majority of the included studies showed that there was no benefit from flossing. The meta-analysis of plaque and gingival index scores also showed no significant differences between groups. Advocacy for flossing as an interdental cleaning method hinges, in large part, on common sense. However, common sense arguments are the lowest level of scientific evidence. A more recent Cochrane review included a variety of floss-related products and, based on the combined evidence, concluded that there was some evidence that flossing, in addition to toothbrushing, reduced gingivitis compared to toothbrushing alone (Sambunjak *et al*. 2011). Thus, there is weak, very unreliable evidence that flossing plus toothbrushing could be associated with a small reduction in plaque.

That dental floss has no additional effects on toothbrushing is apparent from more than one review. Hujoel *et al.* (2006) found that flossing was only effective in reducing the risk of interproximal caries when applied professionally. High-quality professional flossing, performed in first-grade children on school days, reduced the risk of caries by 40%. In contrast, self-performed flossing failed to show a beneficial effect. The lack of an effect on caries and the absence of an effect on gingivitis in the systematic review by Berchier *et al.* (2008) were most likely the consequences of plaque not being removed efficiently.

That flossing does not appear to be effective in the hands of the general public does not preclude its use. For instance, in interdental situations that only allow for the penetration of a string of dental floss, floss is the best available tool. Although floss should not be the first tool recommended for cleaning open interdental spaces, if the patient does not like any other tool, flossing could still be part of oral hygiene instruction. The dental professional should realize that proper instruction, sufficient motivation of the patient, and a high level of dexterity are necessary to make the flossing effort worthwhile. Routine instruction in using floss is not supported by scientific evidence.

Woodsticks (see Box 36-4)

While flossing is the most widely advocated interdental cleaning method, picking of teeth may well be one of humanity's oldest habits and the toothpick one of our earliest tools. The toothpick might date back to the days of cave people, who probably used sticks to pick food from between their teeth. The ancient Romans made use of toothpicks fabricated from bone and metal. Saxon women carried ivory toothpicks. The evolution of the primitive toothpick took a second pathway in more acquisitive societies, becoming part of personal care kits, along with depilatory tweezers and earwax scoops (Mandel 1990). In 1872, Silas Noble and J. P. Cooley patented the first toothpick-manufacturing machine.

Originally, dental woodsticks were advocated by dental professionals a "gum massagers" used to massage inflamed gingival tissue in the interdental areas, to reduce inflammation, and to encourage keratinization of the gingival tissue (Galgut 1991).

The key difference between a toothpick and a woodstick (wooden stimulator/cleaner) relates to the triangular (wedge-like) design of the latter. Woodsticks should not be confused with toothpicks, which are simply intended to remove food debris after meals (Warren & Chater 1996). Woodsticks are inserted interdentally, with the base of the triangle resting on the gingival side (see Box 36-4). The tip should point occlusally or incisally, with the triangle against the adjacent tooth surfaces. Triangular, wedge-like woodsticks have been found to be superior in plaque removal compared to round or rectangular woodsticks, because they fit the interdental area more snugly (Bergenholtz *et al*. 1980; Mandel 1990). Woodsticks are usually made of soft wood to prevent injury to the gingiva. Their tapered form makes it possible for the patient to angle the woodstick interdentally and even clean the lingually localized interdental surfaces. Unlike floss, woodsticks can be used on the concave surfaces of the tooth roots. Some are handheld, while others are designed to be mounted in a handle, which facilitates access to the interdental areas in the posterior region of the mouth (Axelsson 2004). The wood can store fluoride crystals, both on the surface and in the porosities. These crystals readily dissolve when woodsticks are moistened with saliva (Axelsson 2004).

Woodsticks have the advantage that they are easy to use and can be used throughout the day, without the need for special facilities, such as a bathroom or a mirror. A national dental survey showed that the Swedish population prefers using woodsticks to dental floss for the removal of interdental plaque: approximately 46% of adults used woodsticks sporadically and 12% used woodsticks daily. In contrast, dental floss was used occasionally by 12% of adults and daily by only 2%. In other words, adults used woodsticks as oral hygiene aids four to six times more frequently than dental floss (Axelsson 1994). Woodsticks can be used in primary prevention, including in posterior areas, even in cases of poor manual dexterity. To use woodsticks, there must be sufficient interdental space available; in these cases, woodsticks are an excellent substitute to dental floss. Woodsticks can clearly be recommended for patients with open interdental spaces for secondary prevention of periodontal diseases.

During use, the soft wood can become splayed. As soon as the first signs of splaying are evident, the woodstick should be discarded.

Although woodsticks have good cleansing capacity in the central part of the interproximal surfaces of teeth in contact, their effect is reduced on the lingual side of these surfaces. Woodsticks are somewhat difficult to use in the far posterior regions of the jaws because of the lack of accessibility and because the triangular cross-section must pass into the embrasure space at a specific angle (Bassiouny & Grant 1981). When used in healthy dentition, woodsticks can depress the gingival margin. Long-term use can cause permanent loss of the papilla and opening of the embrasure, which can have important esthetic implications for the anterior dentition.

Hoenderdos *et al.* (2008) performed a systematic review to evaluate and summarize the available evidence on the effectiveness of using triangular woodsticks in combination with toothbrushing, to reduce both plaque and clinical inflammatory symptoms of gingival inflammation. The heterogeneity of the data prevented quantitative analysis and only allowed for a descriptive analysis. In seven studies, improvement in gingival health represented a significant incremental benefit realized by the use of triangular woodsticks. None of the studies that scored visible interdental plaque demonstrated any significant advantage of using woodsticks, as opposed to alternative methods (toothbrushing only, dental floss or interdental brushes), in patients with gingivitis.

A series of histologic investigations in patients with periodontitis has shown that the papillary area with the greatest inflammation corresponds to the middle of the interdental tissue. It is difficult to assess the mid-interdental area clinically, as it is usually not available for direct visualization (Walsh & Heckman 1985). When used on healthy dentition, woodsticks depress the gingiva by up to 2–3 mm (Morch & Waerhaug 1956) and therefore clean part of the subgingival area. Thus, woodsticks can specifically remove subgingivally located interdental plaque that is not visible and therefore not evaluated by the plaque index. This physical action of woodsticks in the interdental area could produce a clear, beneficial effect on interdental gingival inflammation.

The studies included in the review by Hoenderdos *et al.* (2008) showed that changes in gingival inflammation were as apparent as changes in bleeding tendency as indicators of disease. Numerous studies have shown that sulcular bleeding is a very sensitive indicator of early gingival inflammation. Bleeding following the use of woodsticks can also be used to increase patient motivation and awareness of gingival health. Several studies have illustrated the clinical effectiveness of gingival self-assessment (Walsh *et al.* 1985). The presence of bleeding provides immediate feedback on the level of gingival health. The dental care professional can also easily demonstrate the gingival condition to the patient, using an interdental bleeding index for this obvious clinical manifestation. This monitoring device could encourage patients to include woodsticks as part of their oral hygiene regimens.

Interdental brushes (see Box 36-5)

Interdental brushes were introduced in the 1960s as an alternative to woodsticks. They are effective in the removal of plaque from the proximal tooth surfaces

(Bergenholtz & Olsson 1984). Interdental brushes consist of soft nylon filaments twisted into a fine stainless steel wire. This "metal" wire can prove uncomfortable for patients with sensitive root surfaces. For such patients, the use of plastic-coated metal wires might be recommended. The support wire is continuous or inserted into a metal/plastic handle. Interdental brushes are manufactured in different sizes and forms. The most common forms are cylindrical or conical/tapered (like a Christmas tree).

The length of the bristles in cross-section should be tailored to the interdental space. Interdental brushes are available for the smallest to the largest interdental spaces (Fig. 36-7). Although unconfirmed in the scientific literature, it is believed that the most efficient cleaning is achieved if the brush selected is slightly larger than the embrasure space. Therefore, patients require interdental brushes of various sizes. Schmage *et al*. (1999) assessed the relationship between the interdental space and the position of the teeth. Most of the interproximal spaces in the anterior teeth were small and of an appropriate size for the use of floss. Premolars and molars have larger interproximal spaces and are accessible with interdental brushes. The brush can be inserted obliquely into the interdental space from the apical direction. As the posterior proximal spaces have wider lingual embrasures, conical-shaped interdental cleaners are not the first choice. Approaching then from the lingual side will result in more effective plaque removal, but this technique is not easy. Cleaning is performed with a back-and-forth motion. The interdental brush is the aid of choice when root surfaces with concavities or grooves have been exposed. Interdental brushes are also the most suitable cleaning devices for "through-and-through" furcation defects.

Like woodsticks, interdental brushes are easy to use, although they can have some drawbacks, including different types perhaps being needed to fit differently sized, open interproximal spaces. When not used properly, interdental brushes can elicit dentin hypersensitivity. To minimize the risk of hard tissue abrasion, interdental brushes should be used without dentifrice except in special cases, and then only for the short term. They can also be used as carriers to apply fluoride or antimicrobial agents, for example chlorhexidine gel, into the interdental space to prevent caries or the recolonization of residual pockets. Brushes should be discarded when the filaments become loose or deformed.

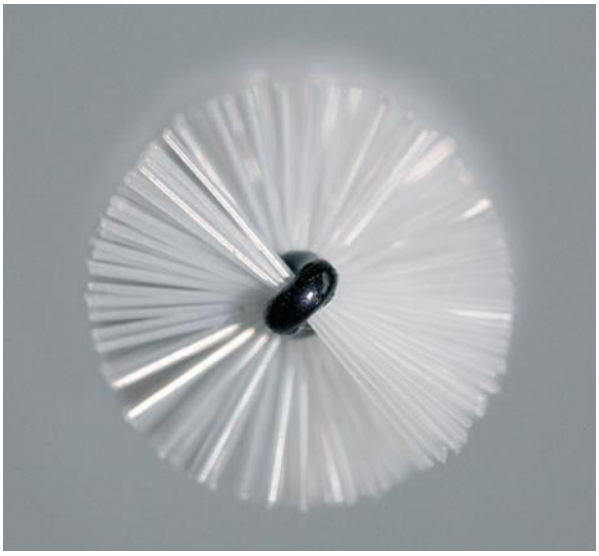


Fig. 36-7 With interdental brushes, the diameter of the metal wire core is a determining factor with regard to access. A close fit of the brushing filaments influences the cleaning capacity.

Interdental brushes represent the ideal interdental cleaning tool, especially for periodontitis patients. Waerhaug (1976) showed that individuals who habitually used interdental brushes were able to maintain supragingival proximal surfaces free of plaque and to remove some subgingival plaque below the gingival margin. In a more recent study in patients with moderate-to-severe periodontitis, Christou *et al.* (1998) demonstrated that interdental brushes were more effective than dental floss in the removal of plaque and in promoting pocket reduction. Patients reported that the use of interdental brushes was easier than using dental floss. This finding is in agreement with those of previous studies (e.g. Wolffe 1976). Additionally, the perception of efficacy was better for interdental brushes. Significantly fewer patients reported problems with using interdental brushes. Even if the efficacy of interdental brushes were not better than that of floss, the long-term use of interdental brushes might be more easily implemented in patients' routines than floss. Patient acceptance is a major issue to be considered when it comes to the long-term use of interdental cleaning devices. Interdental brushes are considered to be less time-consuming and more efficacious than floss for interdental plaque removal.

Slot *et al.* (2008) systematically reviewed the literature to determine the effectiveness in patients with gingivitis or periodontitis of interdental brushes used as adjuncts to toothbrushes in terms of plaque and clinical parameters of periodontal inflammation. The majority of the studies showed a positive significant difference in plaque index when using interdental brushes compared to floss. No differences were identified for gingival or bleeding indices. Meta-analysis revealed a significant effect with the Silness and Löe plaque index in favor of the interdental brush group compared to the floss group. Most of the included studies did not discuss the different interdental brush sizes, nor did they indicate whether interdental brushes were used in all available proximal sites. Two of the included studies showed a significant effect on pocket depth reduction with the use of interdental brushes compared to the use of floss. Jackson *et al.* (2006) proposed that the reduced pocket depth might have been related to the reduction in swelling with concomitant recession. However, the effect on pocket depth cannot readily be explained by a reduction in the level of gingival inflammation (Slot *et al.* 2008). As an alternative explanation for the observed effect,

which seems conceivable, Badersten *et al.* (13) suggested that mechanical depression of the interdental papilla is induced by interdental brushes, which, in turn, causes recession of the marginal gingiva. This result, together with the good plaque removal, could have been the origin of the improved reduction in pocket depth.

A recent development is the Soft-pick, introduced by the GUM Company (Sunstar Europe S.A., Etoy, Switzerland). Its plastic core with soft elastomeric bristles is said to massage the gum and dislodge food. It is presented as an alternative to flossing and should improve patient compliance. It has only been studied in one clinical study to date. Regarding plaque removal or gingival bleeding tendency, no significant differences were observed after 6 weeks of use compared to dental floss; however, a significant difference in favor of interdental brushes was noted (Yost *et al*. 2006).

Single-tufted/end-tufted brushes (see Box 36-6)

Single-tufted brushes have smaller brush heads, which have a small group of tufts or a single tuft. The tuft can be 3–6 mm in diameter and can be flat or tapered. The handle can be straight or contra-angled. Angled handles permit easier access to lingual and palatal aspects. The filaments are directed into the area to be cleaned and are activated with a rotating motion. Single-tufted toothbrushes are designed to improve access to the distal surfaces of the posterior molars and to tipped, rotated or displaced teeth; to clean around and under fixed partial dentures and pontic, orthodontic appliances or precision attachments; and to clean teeth affected by gingival recession and irregular gingival margins or furcation involvement. Little research has been performed with this type of brush. A cross-over study compared the single tuft to a flat-trim toothbrush. The results indicated that the single-tuft brush was effective in removing plaque from relatively hard-to-reach sites. More plaque was removed on the buccal side of the maxillary molars and on the lingual interproximal side of the mandibular molars (Lee & Moon 2001).

Adjunctive aids

Additional oral hygiene aids have been developed in an attempt to augment the effects of toothbrushing on reducing interdental plaque.

Dental water jets/oral irrigators (see Box 36-7)

The dental water jet was developed by a hydraulic engineer, John Mattingly, and a dentist, Gerald Moyer. It was introduced to the dental profession in 1962 and has been studied extensively for the past several decades. Prior to 1964, Mattingly built the units at home, and they were sold exclusively through Dr Moyer's practice. In 1964, a patient who loved the device raised thousands of dollars to help make the units available in stores. A few years later, Water Pik devices could be found in drug stores and department stores. In 2001, the American Academy of Periodontology stated, "Among individuals who do not perform excellent oral hygiene, supragingival irrigation with or without medicaments is capable of reducing gingival inflammation beyond that normally achieved by toothbrushing alone. This effect is likely due to the flushing out of subgingival bacteria". The pulsating, hydrodynamic forces produced by irrigators can rinse away food debris from interdental spaces and plaque-retentive areas. It has been reported that a pulsating stream of water is better than a continuous flow. Irrigation is not, however, a monotherapy but an adjunct designed to supplement or enhance other home oral care methods (brushing and flossing) intended for mechanical plaque removal (Hugoson 1978; Cutler *et al*. 2000) (Fig 36-8).

Husseini *et al.* (2008) performed a systematic review of the existing literature to evaluate the effectiveness of oral water irrigation as an adjunct to toothbrushing on plaque and clinical parameters of periodontal inflammation compared to toothbrushing alone or to regular oral hygiene. The heterogeneity of the data prevented quantitative analysis; therefore, a descriptive approach was undertaken. None of the included studies showed a significant difference between toothbrushing and the use of a dental water jet in combination with toothbrushing. When observing visual signs of gingival inflammation, three of the four studies reported a significant effect with the use of a dental water jet as an adjunct to regular oral hygiene. Two of the four studies showed a significant reduction in probing depth as a result of using a dental water jet as an adjunct to regular oral hygiene. The authors concluded that there is evidence that suggests a positive tendency toward improved gingival health when using a dental water jet as an adjunct to toothbrushing, as opposed to regular oral hygiene (i.e. self-performed oral hygiene without any specific instructions). A recent 4-week evaluation showed (within the limits of this short evaluation period) that when combined with manual toothbrushing, the daily use of an oral irrigator is significantly more

Fig. 36-8 Dental water jet. Fluid flow can be either continuous or pulsated.

effective in reducing gingival bleeding scores than the use of dental floss (Rosema *et al.* 2011).

The selected papers for this systematic review reported no statistically significant reduction in plaque with use of a dental water jet (Husseini *et al.* 2008). Plaque reduction is a prerequisite for an oral hygiene device to be considered valuable. Despite the lack of an effect on the plaque index, these studies did find a significant effect on the bleeding index. The mechanisms underlying these clinical changes in the absence of a clear effect on plaque are not understood. Different hypotheses have been put forward by authors to explain the results. One hypothesis is that when patients with gingivitis perform supragingival irrigation on a daily basis, the populations of key pathogens (and their associated pathogenic effects) are altered, reducing gingival inflammation (Flemmig *et al.* 1990). There is also the possibility that water pulsations alter specific host–microbial interactions in the subgingival environment and that inflammation is reduced independent of plaque removal (Chaves *et al.* 1994). Another possibility is that the beneficial activity of a dental water jet is at least partly due to removal of food deposits and other debris, flushing away of loosely adherent plaque, removal of bacterial cells, interference with plaque maturation, and stimulation of immune responses (Frascella *et al.* 2000). Other explanations include mechanical stimulation of the gingiva or a combination of previously reported factors. Irrigation can reduce plaque thickness, which might not be easily detected using two-dimensional scoring systems. This fact could explain the absence of an effect on plaque but a positive effect on gingival inflammation.

Irrigation devices can increase the delivery of fluid beneath the gingival margin (Flemmig *et al.* 1990). Greater penetration of a solution into periodontal pockets was achieved by patient-applied supragingival irrigation compared to mouth rinsing (Flemmig *et al.* 1995). Studies evaluating the capacity of supragingival irrigation to project an aqueous solution subgingivally have determined that supragingival irrigation with a standard irrigation tip was capable of delivering water or a medicinal fluid 3 mm subgingivally or to approximately half the probing depth of a 6-mm pocket (Larner & Greenstein 1993). Irrigation devices can be used with water or with disinfectant solutions (Lang & Räber 1982). The use of chlorhexidine in suboptimal concentrations (e.g. 0.06%) has resulted in improved plaque inhibition and has had anti-inflammatory effects (Lang & Räber 1982; Flemmig *et al*. 1990).

Success with pulsating oral irrigators with regular tips is limited to the subgingival area and periodontal pockets (Wennström *et al*. 1987). With a specially designed tip (Pik Pocket® subgingival irrigation tip; WaterPik Technologies, Fort Collins, CO, USA), the pulsating stream of fluid can penetrate more deeply into the pocket areas (Cobb *et al*. 1988). These blunt-ended cannulas can also be used to inject antimicrobial agents into shallow-to-moderate periodontal pockets.

Supragingival irrigation applies considerable force to the gingival tissues. Irrigation was shown to have the potential to induce bacteremia. However, given the collective evidence, it appears that irrigation is safe for healthy patients (Husseini *et al.* 2008).

A recent development (2010) is the Sonicare AirFloss (Philips Oral Healthcare, Snoqualmie, WA, USA), which uses a spray of microbubbles and a small dose of fluid to generate the interdental cleaning action, through which it is claimed it disrupts plaque biofilm structures. The nozzle tip is designed to act as a guide to the spaces between teeth. Two studies have reported that the oral irrigator is significantly more effective than the AirFloss in reducing plaque and gingivitis (Sharma *et al.* 2012a, b). There is clearly a need for more published clinical research studies regarding this device to establish its clinical value.

Tongue cleaners (see Box 36-8)

Regular tongue cleaning has been used since ancient times and is still used by the native populations of Africa, the Arab countries, India and South America. Many ancient religions emphasized the cleanliness of the entire mouth, including the tongue. Indian people's daily ritual of oral hygiene was not confined to brushing of the teeth; the tongue was also scraped, and the mouth was rinsed with concoctions of betel leaves, cardamom, camphor or other herbs.

The dorsum of the tongue, with its papillary structure, furrows and crypts, harbors a great number of microorganisms. It forms a unique ecologic oral site with a large surface area (Danser *et al*. 2003). The tongue is said to act as a reservoir, which permits the accumulation and stagnation of bacteria and food residues (Outhouse *et al*. 2006). Tongue bacteria can serve as a source of bacterial dissemination to other parts of the oral cavity, for example the tooth surfaces, and can contribute to dental plaque formation. These bacteria make the greatest contribution to the bacteria found in the saliva. Therefore, tongue brushing has been advocated as part of daily home oral hygiene, together with toothbrushing and flossing (Christen & Swanson 1978). Tongue brushing has also been advocated as a component of the so-called "full-mouth disinfection" approach in the treatment of periodontitis, with the aim of reducing possible reservoirs of pathogenic bacteria (Quirynen *et al*. 2000).

A large variety of tongue cleaners are commercially available. A modern tongue-scraping instrument can consist of a long strip of plastic ribbon. This strip is held in both hands and is bent so that the edge can be pulled down over the dorsal surface of the tongue. Brushing also appears to be an easy method of cleaning the tongue, provided that the gag reflex can be controlled. However, in a systematic review, it was concluded that scrapers or cleaners are more effective than toothbrushes for tongue cleaning

(Outhouse *et al*. 2006) and with them the gag reflex is reduced (Van der Sleen *et al.* 2010). Patients should be informed that it is most important to clean the posterior portion of the tongue dorsum, but in reality, it is likely that many patients do not reach far enough to contact the posterior dorsum during tongue cleaning because extended reaching causes the gag reflex.

Tongue cleaning is a simple and fast procedure that helps to remove microorganisms and debris from the tongue. When tongue cleaning is practiced on a daily basis, the process becomes easier. Eventually, the patient can indeed feel "unclean" when tongue debris is not removed on a regular basis. In a study by Gross *et al.* (1975), the test group was instructed to brush the tongue as an adjunct to normal oral hygiene measures. The control group was not instructed to clean the tongue. A reduction of 40% in the presence of tongue coating was noted in the test group compared to the control group.

Some studies have shown that tongue brushing, in combination with other methods of oral hygiene, is an effective method for reducing the formation of dental plaque. In contrast, Badersten *et al.* (1975) found no difference in *de novo* plaque accumulation between a 4-day period of tongue brushing and a 4-day period of no oral hygiene procedures. The authors suggested that the majority of the important plaque-forming bacteria might not originate from the tongue. Another reason for not finding an effect of tongue brushing on plaque formation might be that brushing the posterior part of the dorsum of the tongue is difficult due to inaccessibility and discomfort.

Yaegaki and Sanada (1992) observed six times more tongue coating in patients with periodontal problems than in those who were periodontally healthy. Consequently, individuals with periodontal diseases will likely present with microbial flora more favorable to exacerbating the formation of volatile sulfur compounds than healthy individuals. Over the years, oral malodor has become a topic of interest to both the scientific community and to people who suffer from it. Regular mechanical tongue cleaning can play a role in controlling bacterial numbers and removing tongue coating. Individuals with coated tongues showed significantly higher malodor scores than individuals with non-coated tongues (Quirynen *et al.* 2004). Van der Sleen *et al.* (2010) demonstrated in their systematic review that mechanical approaches, such as tongue brushing or tongue scraping, to clean the dorsum of the tongue have the potential to reduce tongue coating and oral malodor. This systematic review detected only one study that included patients with chronic oral malodor, with an unknown evaluation period and a high potential risk of bias. This study stood in contrast to the other included studies, which evaluated the effect of tongue cleaning in cases of morning bad breath. Consequently, no firm statement can be made as to whether mechanical tongue cleaning contributed to a reduction in oral halitosis. More research is needed to assess the effect of mechanical tongue cleaning, particularly in true halitosis populations.

Foam brushes, swabs or tooth towelettes

Tooth towelettes are being marketed as a method of plaque removal when toothbrushing is not possible. Their use is not meant to replace a daily toothbrushing regimen.

Finger brushes, such as the I-Brush®, are mounted on the index finger of the brushing hand and use the agility and sensitivity of the finger to clean the teeth. Consequently, the pressure with which they are applied can be well controlled because the finger can actually feel the tooth and gingival surfaces and help position the brush for more effective scrubbing. During a 3-week clinical trial (Graveland *et al*. 2004), no adverse effects were found with the I-Brush®. The results showed that the finger brush removed less plaque than a regular manual toothbrush. In particular, proximal plaque reduction was poor in comparison with manual toothbrushing. Based on these results, it was concluded that there were no beneficial effects of the finger brush in comparison with regular manual toothbrushes.

Foam brushes resemble a disposable soft sponge on a stick, and they have been dispensed to hospital patients for intraoral cleansing and refreshing since the 1970s. They are used in particular for oral care in medically compromised and immunocompromised patients to reduce the risk of oral and systemic infection (Pearson & Hutton 2002). Lefkoff *et al.* (1995) studied the effectiveness of such a disposable foam brush on plaque. In this study, regular manual toothbrushes were found to be significantly more effective in retarding the accumulation of plaque from a plaque-free baseline on both facial and lingual surfaces. However, the foam brush did show some plaque-preventive capabilities by maintaining plaque formation below 2 mm at the cervical margin of the tooth. Nevertheless, according to most authors, foam brushes should not be considered a substitute for regular toothbrushes. In a study by Ransier *et al.* (1995), foam brushes were saturated with a chlorhexidine solution. The authors found foam brushes that had been soaked in chlorhexidine to be as effective as regular toothbrushes in controlling plaque and gingivitis levels. Therefore, if hospitalized patients cannot use a toothbrush, an alternative could be the use of chlorhexidine applied with a foam brush.

Dentifrices

The use of a toothbrush is usually combined with that of a dentifrice, with the intention of facilitating plaque removal and applying agents to the tooth surfaces for therapeutic or preventive reasons, to produce fresh breath, and to make the toothbrushing procedure more pleasant. The term dentifrice is derived from the Latin words *dens* (tooth) and *fricare* (to rub). A simple, contemporary definition of a dentifrice is a mixture

used on the tooth in conjunction with a toothbrush. Dentifrices are marketed as powders, pastes, and gels. Dentifrice was used as early as 500 BC in both China and India; modern toothpastes were developed in the 1800s. In 1824, a dentist named Peabody was the first person to add soap to toothpaste. John Harris first added chalk to toothpaste in the 1850s. Colgate mass-produced the first toothpaste in a jar. In 1892, Dr Washington Sheffield of Connecticut manufactured toothpaste in a collapsible tube (Dr. Sheffield's Creme Dentifrice). Advancements in synthetic detergents made after World War II have allowed the replacement of the soap used in toothpaste with emulsifying agents, such as sodium lauryl sulfate. Later, fluoride was added.

Traditionally, it was believed that dentifrices should contain an abrasive. The addition of abrasives supposedly facilitated plaque and stain removal without producing gingival recession/tooth abrasion or altering the remaining components of the dentifrice. For many decades, abrasive systems, such as calcium carbonate, alumina, and dicalcium phosphate, have been used. Today, most dentifrices contain silica. Although more expensive, silica can be combined with fluoride salts, and it is very versatile. It has also been shown to increase the abrasiveness of dentifrices, resulting in even more plaque removal (Johannsen *et al.* 1993).

Conflicting reports have been published concerning the added value of using dentifrice for plaque removal. Studies by de la Rosa *et al.* (1979) and by Stean and Forward (1980) validated the use of dentifrice because they found that there was a reduction in plaque growth after brushing with a dentifrice as opposed to brushing with water. Similarly, Eid and Talic (1991) reported overall reductions in plaque of 67% for manual toothbrushing with a dentifrice and 59% for toothbrushing with water. In contrast, in a study by Gallagher *et al.* (2009), the use of 1.5 g of dentifrice showed no additional effect after 1 minute of brushing compared to brushing without dentifrice. Paraskevas *et al.* (2006) also studied whether dentifrice had a beneficial effect on plaque removal and whether an abrasive additive was a contributor. Their results showed that among 40 subjects using three different hydrated, silica-based dentifrices in a cross over study, the difference in abrasiveness (RDA 80 and 200) did not play a role in plaque removal. Moreover, significantly more plaque (3%) was removed when the brushing procedure was performed without dentifrice. In another study by Paraskevas *et al.* (2007), the group that used dentifrice removed a significant 6% less plaque compared to the group that did not use dentifrice. Furthermore, in a study by Jayakumar *et al.* (2010), a 9% difference in plaque removal, in favor of the non-dentifrice group, was observed. The results of a recent study by Rosema *et al.* (2013) showed a difference in plaque removal of 2% in favor of the non-dentifrice group. Although this difference in plaque score reduction did not reach the level of significance, it is noteworthy that the use of dentifrice did not seem to increase the amount of "instant" plaque removal (i.e. the immediate effect of brushing, as opposed to prolonged effects beyond the brushing exercise). These results are also supported by a report from the ADA Division of Science (American Dental Association 2001), which accepts that "plaque removal is associated minimally with abrasives." The effectiveness of plaque removal during toothbrushing with dentifrice appears to be essentially a function of the access of brush filaments, rather than dentifrice abrasives (Gallagher *et al.* 2009).

Another factor that might be involved in the process of plaque removal is the detergent (or surfactant) contained in the dentifrice formulation. Detergents are surface-active compounds that are added to the formulation because of their foaming properties. This foaming effect could be beneficial in clearing loosened plaque from the teeth and also in providing the pleasant feeling of cleanness. Today, dentifrice formulations also contain ingredients that could help improve oral health. Fluoride is almost omnipresent in commercially available toothpastes. Problems with dentifrice formulation have involved finding compatible constituents to combine with the active ingredients in dentifrice formulas. Over the years, many dentifrice formulations have been tested and become well established because of their antiplaque and/or antigingivitis properties. For additional information, see Chapter 37.

Some substances in dentifrices can induce local or systemic side effects. Chlorhexidine in dentifrices can foster tooth staining. Pyrophosphates, flavorings, and detergents, especially sodium lauryl sulfate which is present in most commercially available dentifrices, have been implicated as causative factors in certain oral hypersensitive reactions, such as aphthous ulcers, stomatitis, cheilitis, burning sensations, and oral mucosal desquamation. In such cases, the dental professional should identify these conditions and advise the patient to discontinue use of the suspected dentifrice.

Side effects

Brushing force

In a study evaluating toothbrushing habits in unin-structed adults, the mean brushing force was 2.3 ± 0.7 N, with a maximum of 4.1 N (Ganss *et al.* 2009a). Brushing force with electric toothbrushes has consistently been shown to be lower than that with a manual toothbrush (by approximately 1.0 N) (Van der Weijden *et al.* 1996c). McCracken *et al.* (2003) observed, for a range of pressures from 0.75 to 3.0 N, that the improvement in plaque removal when forces in excess of 1.5 N with an electric toothbrush were used was negligible. In a feedback study, a professional brusher was asked to brush with a pressure of 1.0 N, 1.5 N, 2.0 N, 2.5 N, and 3.0 N, during which time the efficacy with regard to brushing force was determined. An increase in efficacy was observed when

the brushing force was raised from 1.0 N to 3.0 N (Van der Weijden *et al*. 1996c). Hasegawa *et al.* (1992) evaluated the effects of different toothbrushing forces on plaque reduction by brushing at 100-g force intervals on a scale from 100 to 500 g. The results of their study corroborated the findings of earlier studies that with increasing force, more plaque is removed. In addition, they observed that 300 g seemed to be the most effective brushing force when using a manual toothbrush for both children and adults. Forces exceeding 300 g caused pain and gingival bleeding in the test patients. As shown in a manual brushing study in which efficacy was plotted against brushing force, the relationship between force and efficacy does not appear to be linear (Van der Weijden *et al*. 1998a). Using a manual toothbrush, a positive correlation was identified between efficacy and force (up to 4.0 N). The greater the force used, the more effective was the plaque removal. However, efficacy decreased when forces of >4.0 N were used. Indeed, there appeared to be a negative correlation. The hypothesis is that this negative correlation was due to the distortion of the brushing filaments. Beyond 4.0 N, brushing was no longer performed with the tip of the filament but, due to bending, with its side, indicating that brushing force is not the sole factor that determines efficacy. Other factors, such as the action of the brush, the size of the brush head, brushing time, and manual dexterity, could be of greater importance.

Excessive brushing force has been mentioned as a factor that is partly responsible for toothbrush trauma (gingival abrasion). For patients who use excessive force, manual and electric toothbrush manufacturers have introduced toothbrush designs that can limit the amount of force used and thus reduce the chance of damage to soft and hard tissues. However, there is no linear correlation between brushing force and gingival abrasion. A recent *in vitro* experiment revealed that under severe erosive conditions, neither total mineral loss nor the spatial loss of mineralized dentin (measured using profilometry) significantly increased after brushing, regardless of the force applied. The demineralized organic dentin matrix was strikingly resistant to mechanical impact, although it was compressed with greater brushing forces (Ganss *et al.* 2009b).

Mierau and Spindler (1989) performed a quantitative assessment of patterns of toothbrushing habits in 28 subjects over nine sessions. The least variations among individuals were observed with regard to brushing force. Brushing force ranged from 1.0 to 7.4 N between individuals. The authors did not observe any (visual) lesions from brushing in those individuals using a brushing force of <2 N. If the brushing force was >2 N, co-factors such as brushing time, brushing method, and frequency of brushing appeared to be associated with acute brushing lesions. Burgett and Ash (1974) argued that the potentially detrimental effect of brushing is related to the force applied at a particular point, that is the pressure. It should be recognized that the head of a manual brush is larger than the head of an electric brush. Because the forces are given as a total of the force over the entire brush, it could be that the unit pressure is less for manual brushes than for electric brushes. Van der Weijden *et al.* (1996c) observed no difference in pressure between soft manual (11.32 g/mm^2) and electric toothbrushes (11.29 g/mm^2), demonstrating that the pressures for the electric and the manual brushes were similar.

Toothbrush abrasion

Because various mechanical products are used in personal control of supragingival plaque, the possibility exists that some deleterious effects can occur as a consequence of these oral hygiene practices (Echeverría 1998). The simple act of removing deposits from teeth requires that the toothbrush–dentifrice combination possess some level of abrasiveness. The filaments must have a sufficient degree of stiffness to create abrasion to dislodge plaque deposits. This stiffness must be balanced against potentially detrimental effects on dental hard and soft tissues. The wear on a tooth consists of a combination of attrition (tooth-to-tooth contact wear), erosion (acid-mediated surface softening), and abrasion (wear because of toothbrushing with toothpastes). Toothbrush abrasion is modified by toothbrush filament stiffness (Wiegand *et al.* 2008).

It has long been known that toothbrushing can have some unwanted effects on the gingiva and hard tooth tissues (Kitchin 1941). Trauma to hard tissues leads to cervical abrasion of the tooth surfaces (Fig. 36-9). These lesions have been associated with toothbrush stiffness, the method of brushing, and brushing frequency. Cervical tooth abrasions have a multifactorial etiology, but in most cases, they are the consequence of toothbrushing with excessive brush pressure and an excessive number of toothbrushing episodes/time. Both situations are likely linked to personality traits (*compulsive brushers*). Tooth wear has also been associated with toothbrush characteristics, especially with the finishing and hardness of the filaments (Fishman 1997). It has been stated that hard tissue damage is mainly caused by the abrasives in dentifrice (Axelsson *et al*. 1997; Meyers *et al*. 2000). The capacity of a toothbrush to hold and move polish/abrasive over the tooth surface particularly affects the amount of hard-tissue abrasion. In a recent study, the influence of the type of toothbrush was negligible when water was used as a substrate, but when toothpaste was added: the abrasion values diverged by more than ten-fold depending on the toothbrush. A softer toothbrush might have caused similar or even more abrasions than a harder brush (Tellefsen *et al.* 2011).

In many instances, *tooth abrasion* is found in combination with *gingival recession*. Whereas gingival recession is associated with different etiologic/risk factors, for example periodontal inflammation, smoking, gingival biotype or repeated periodontal instrumentation, inadequate use of the toothbrush is likely the most significant cause (Björn *et al*. 1981). Clinical

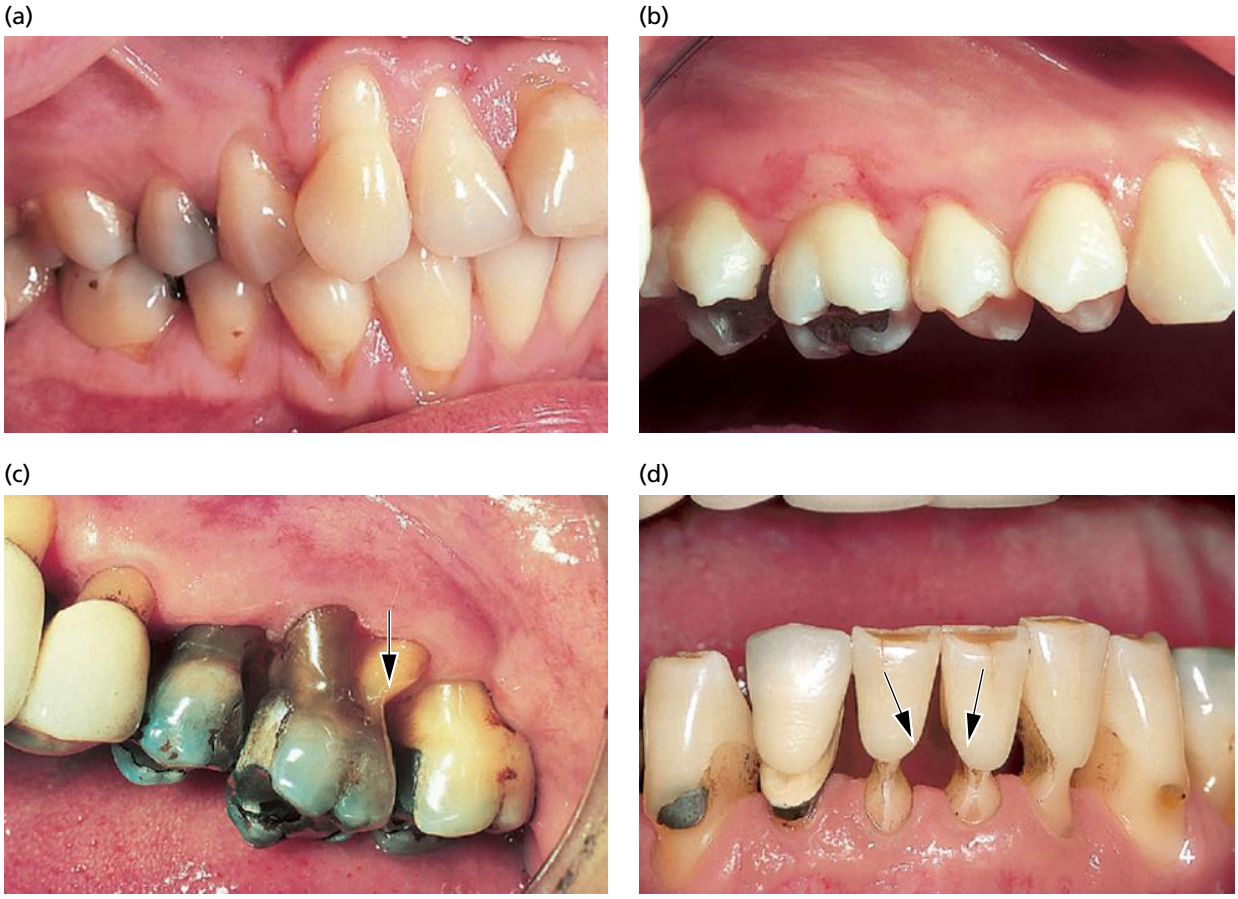


Fig. 36-9 (a) Soft tissue damage as a result of extensive toothbrushing. Note the gingival recession on the buccal gingival surface of tooth 13. (b) Note the multiple ulcerations of the buccal gingival margin in the right maxilla. (c, d) Hard tissue damage (arrows) has resulted after extensive use of interdental brushes.

experience supports the idea that, with improper use, toothbrushing can cause superficial damage to the gingival tissues. Patients with good oral hygiene have been found to have more gingival recession and more dental abrasions than patients with poor oral hygiene. Unfortunately, there have been few studies in the dental literature concerning gingival lesions resulting from toothbrushing. Thus, the extent to which oral hygiene procedures can traumatize the gingival tissues is not clear.

Gingival abrasions as a result of brushing are often reversible, localized, superficial lesions. It is unlikely that gingival abrasion is induced by a single factor. One factor, which has already been mentioned as related to gingival abrasion, is brushing force. In the literature, other factors have been suggested, such as brushing method (e.g. the Bass method), abusive toothbrush use, toothbrushing duration, manual or powered toothbrushing, toothbrush grip, brush head shape, stiffness of the filaments, end-rounding of toothbrush filaments, and toothbrushing frequency (Van der Weijden & Danser 2000).

Toothbrushes with hard bristles remove plaque better but can also cause more soft-tissue trauma compared to brushes with softer bristles. Zimmer *et al.* (2011) investigated the effectiveness and potential harmfulness of manual toothbrushes of the same type but with different bristle stiffnesses. Based on their observations, they suggested that for subjects with poor oral hygiene, a toothbrush with hard bristles should be considered. If a patient already shows soft tissue damage, a soft toothbrush should be recommended. If the patient cannot be classified, a toothbrush with medium stiffness might be the solution (Versteeg *et al.* 2008a). Sharp-edged and unacceptably rounded filament tips represent a greater threat to dental tissues. Breitenmoser *et al.* (1979) evaluated the effects of filament end forms on the gingival surface. It was found that manual toothbrushes with cut filament ends resulted in significantly greater gingival lesions than rounded ends. Further research has shown in several studies that filaments with sharp edges can cause soft tissue injury. The depth of epithelial lesions caused by toothbrushing was influenced by the quality of filament end-rounding (Plagmann *et al.* 1978). Non–end-rounded filaments were approximately twice as abrasive to soft tissues as rounded filament tips (Alexander *et al.* 1977).

The pattern of toothbrushing is that most right-handed people begin on the buccal surfaces of the anterior teeth on the left side. Accordingly, the most severe gingival recession and abrasion defects are localized to the buccal surfaces on the left side (MacGregor & Rugg-Gunn 1979).

Interestingly, there has been little debate regarding the role of dentifrice in the abrasion of soft tissues. This fact is somewhat surprising when abrasion of dental hard tissues is almost entirely a function of dentifrice. Detergents in dentifrice, agitated over a mucosal surface, can enhance the removal of the protective salivary glycoprotein layer and exert cytotoxic action on the overlying epithelial cells (Addy & Hunter 2003). No statistically significant differences in the incidence of gingival abrasions were identified between brushing with dentifrice or without dentifrice (Versteeg *et al*. 2005; Rosema *et al.* 2013). This finding was in agreement with those of Alexander *et al.* (1977), who used hamster cheek pouch tissue that was brushed mechanically for various intervals. The results showed that the dentifrice/polishing agent applied to the tissue with a brush did not increase the abrasive effects of the brush (using protein removed during brushing as an index of tissue abrasion). Meyers *et al.* (2000) investigated the effects of three commercially available dentifrices on tooth and gingival surfaces by means of scanning electron microscopy (SEM) quantification. The results indicated that none of the dentifrices tested was harmful to teeth or soft tissues.

Importance of instruction and motivation in mechanical plaque control

A fundamental principle for all preventive action is that the effect is greatest when the risk of the development of disease is greatest. Needs-related instruction in oral hygiene should therefore aim to intensify mechanical plaque removal on those individual teeth and surfaces that are at risk. A prerequisite for establishing needs-related tooth-cleaning habits is a well-motivated, well-informed, and well-instructed patient (Axelsson 2004). Mechanical plaque control demands active participation of the individual subject; therefore, the establishment of proper home oral care habits is a process that greatly involves and depends on behavioral changes. When implementing behavioral changes, dental professionals should try to ensure that the patient recognizes his/her oral health status and the role of his/her personal oral hygiene procedures in the prevention of caries and periodontal diseases. The patient should be informed about the casual relationship that led to the disease process and should be encouraged to take responsibility for his/her own oral health. The dental team has numerous opportunities to demonstrate to the patient the soft tissue alterations elicited by inflammation and the responsible etiologic factors. Most commonly, as with sports coaching, a one-to-one professional–patient approach should be employed.

Many patients spend too little time brushing, or they brush haphazardly. The importance of thorough plaque removal should be stressed. Toothbrushing instruction for a patient involves teaching what, when, where, and how. A recommended toothbrushing regimen should take into account the characteristics of the toothbrush and dentifrice, and the individual's behavior with regards to brushing frequency, duration, pattern, force, and method. Toothbrushing habits are locally acquired at home and can be supplemented periodically with more formal instruction from the dental professional. In addition, instruction should also involve a description of specific toothbrushing methods, the grasp of the brush, the sequence and amount of brushing, the areas of limited access, and supplementary brushing for occlusal surfaces and the tongue. The possible detrimental effects from improper toothbrushing and variations for special conditions can be described (Wilkins 1999). The design of toothbrushes or a specific toothbrushing method is of secondary importance to the skills of the individual in using the brush (Frandsen 1986). The simplest, least time-consuming procedures that will effectively remove bacterial plaque and maintain oral health should be recommended. If a patient prefers a specific oral hygiene strategy, the clinician can evaluate this and modify the technique to maximize effectiveness rather than changing it. Although it is necessary to give all patients honest feedback on their plaque removal efforts, it is also important to reward positive performance and not entertain unrealistic expectations, so that the patient will not dread each maintenance visit.

Oral hygiene instruction should also include components such as self-assessment, self-examination, self-monitoring, and self-instruction. With this purpose, several devices and chemical agents have been used to make dental plaque more evident to the patient. The interested patient can be informed and motivated, for example, through the use of disclosing agents to visualize plaque at the gingival margin or in the interdental spaces. Disclosing agents are chemical compounds, such as erythrosine, fuchsine or fluorescein-containing dye, that stain dental plaque and thus make it fully evident to the patient using either regular or ultraviolet light. Erythrosine has been used for many years as a means of motivating patients and evaluating the effectiveness of oral hygiene, and it has received Food and Drug Administration (FDA) approval (Arnim 1963) (Fig. 36-10). When applied immediately before toothbrushing, the patient can identify the amount of plaque formed since the last toothbrushing episode, thus receiving immediate feedback about his/her cleaning performance. This procedure is useful during the early phase of plaque control. Later, the disclosing agent should be applied after toothbrushing, which allows the patient to identify those areas needing additional cleaning efforts. Disclosing solution is available in liquid and tablet forms. The liquid form might offer some advantages in that the operator can ensure that all surfaces are adequately covered. Red disclosing solution remains in the mouth for some time and can temporarily stain the lips and gingiva. This may create an esthetic

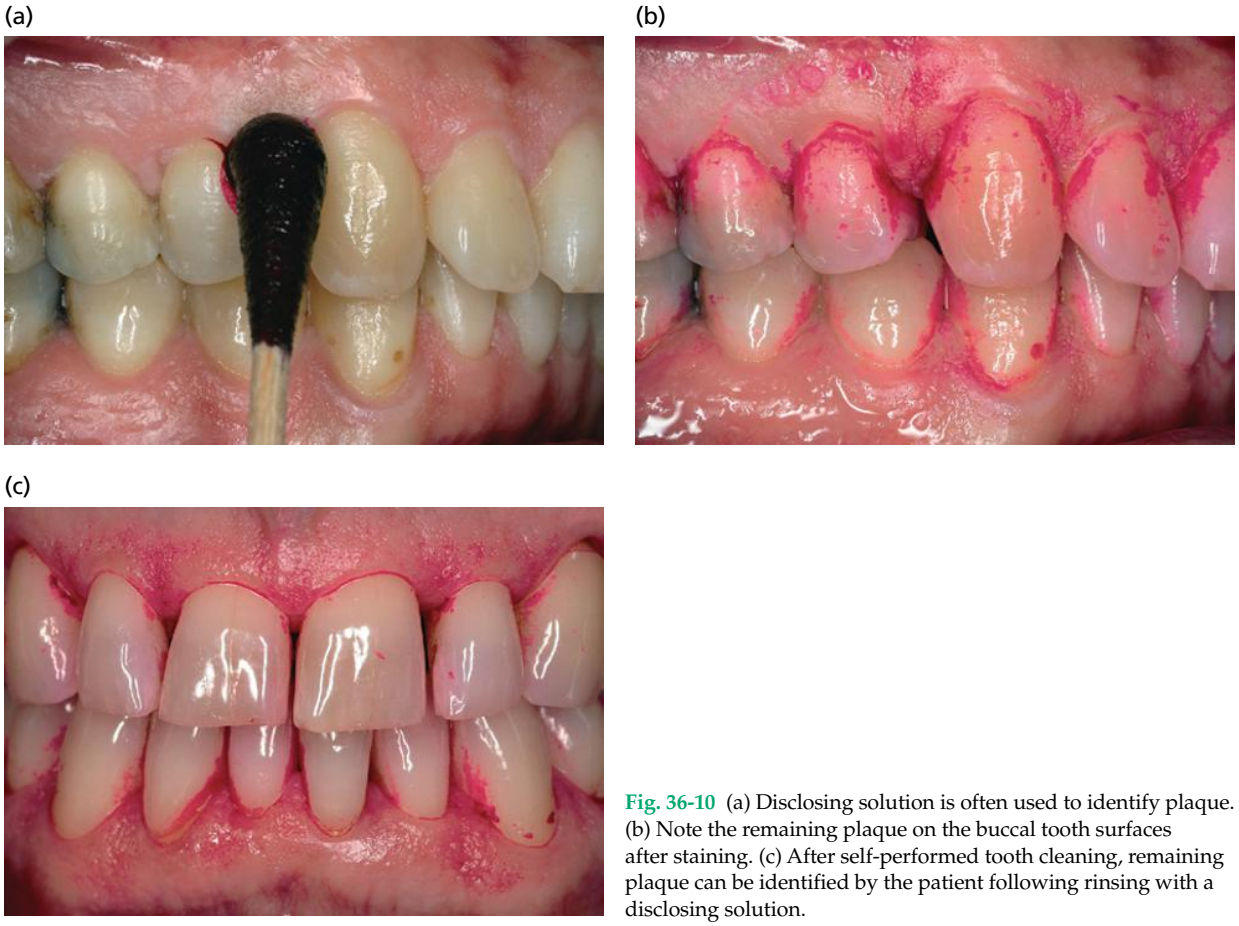


Fig. 36-10 (a) Disclosing solution is often used to identify plaque. (b) Note the remaining plaque on the buccal tooth surfaces after staining. (c) After self-performed tooth cleaning, remaining plaque can be identified by the patient following rinsing with a disclosing solution.

problem for some patients, but can be eliminated by protecting the lips with petroleum jelly. Two-tone agents (containing methylene blue and erythrosine) are also available that distinguish an old plaque accumulation from a more recent one.

Disclosing plaque in the patient's mouth is usually not sufficient to establish good oral hygiene habits. Other factors might influence the individual to modify or determine his/her behavior. These factors could be more or less beyond the control of the dental professional (such as social and personal factors, environmental settings, and past dental experiences), or they may lie within the control of the professional (such as the conditions of treatment and the instruction and education of the patient). All of these factors should be considered in the design of an individualized oral hygiene program.

A variety of methods can be used to deliver advice and instructions. The effects of various oral hygiene instruction programs, administered individually or in groups, have been evaluated in a number of clinical studies. These studies have evaluated whether instruction given during one visit only is similar to step-by-step instruction provided over several visits, and whether the use of pamphlets or videotapes is superior to self-instruction manuals and to personal instruction given by a dental professional. In a study by Renton-Harper *et al.* (1999), an instructional video for an oscillating rotating electric toothbrush was evaluated. The subjects who followed the instructional video benefited significantly and considerably in terms of plaque removal compared to subjects who received only written instructions. Different types and amounts of feedback given to the patients using disclosed plaque scores and phase-contrast demonstrations have also been investigated. These studies have usually reported similar improvements in plaque and gingivitis scores, irrespective of the mode of instruction. However, these results should be interpreted with caution because the subjects participating in these studies were examined at regular intervals; therefore, it is difficult to separate the effects of repeated examinations from the effects of the instructions (Renvert & Glavind 1998).

If oral hygiene motivation, information, and instruction are combined with professional tooth cleaning, the effects in terms of reduction of plaque levels and levels of gingival inflammation can persist even after 6 months. A systematic review concluded, based on ≥6-month–long studies, that a single oral hygiene instruction describing the use of a mechanical toothbrush, in addition to a single professional "oral prophylaxis" provided at baseline, had significant, albeit small, positive effects on the reduction of gingivitis (Van der Weijden & Hioe 2005).

Rylander and Lindhe (1997) recommended that oral hygiene instruction be provided over a series of

visits, allowing for the possibility of giving the patient immediate feedback and reinforcing the patient in his/her home oral care activities. The protocol below is based on the one used in several clinical trials by Lindhe and Nyman (1975), Rosling *et al.* (1976) and Lindhe *et al.* (1982) in which the role of plaque control in preventing and arresting periodontal diseases was clearly demonstrated.

First session

1. Apply a plaque-disclosing solution to the teeth and, with the aid of a hand mirror, demonstrate all sites with plaque to the patient (see Fig. 36-10b). The plaque score should be recorded using a plaque control record (Fig. 36-11).
2. Ask the patient to clean his/her teeth using his/her traditional technique. With the aid of a hand mirror, demonstrate the results of the toothbrushing to the patient, again identifying all sites with plaque (see Fig. 36-10c).
3. Without changing the technique, ask the patient to clean the surfaces with plaque.

Depending on the plaque remaining after this second toothbrushing, the dental professional should either improve the technique or introduce an alternative system of toothbrushing. So as not to overload the patient with too much information during the first session, the use of adjunctive devices for interproximal cleaning can be introduced or improved in the second session.

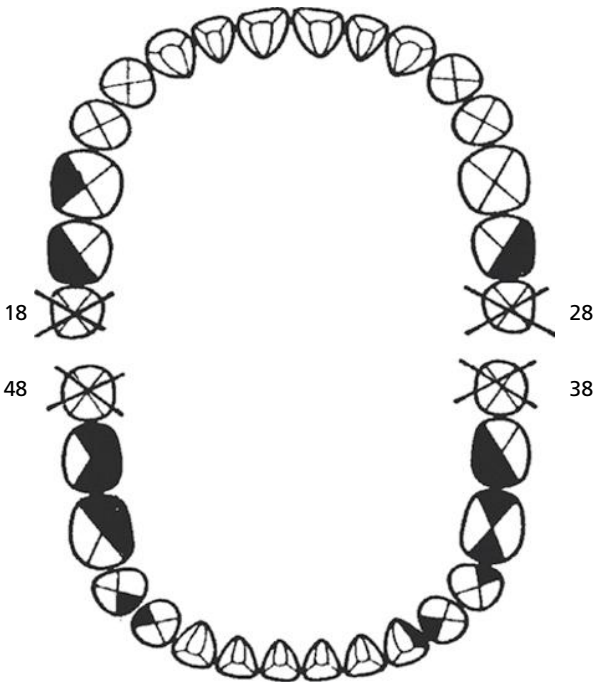


Fig. 36-11 Chart showing the teeth and tooth surfaces in the maxilla and mandible. The distribution of tooth surfaces with dental plaque (shadowed areas) is identified. In this case, the plaque score is 17%.

Second session

1. A few days after the first session, the disclosing solution is again applied. The results, in terms of plaque deposits, are identified in the mouth, recorded in the plaque control record, and discussed with the patient.
2. The patient is then invited to clean his/her teeth, according to the directions previously provided during the first session, until all staining is removed. In many cases, toothbrushing instructions will need to be reinforced. Positive recognition should be given to the patient at the same time.

If necessary, the use of interproximal cleaning aids can now be introduced or improved.

Third and subsequent sessions

1. One or 2 weeks later, the procedure used in the second session is repeated. However, the efficacy of self-performed plaque control should be evaluated and presented to the patient at each appointment. This repeated instruction, supervision, and evaluation aims to reinforce the necessary behavioral changes.

The long-term results of oral hygiene instruction are dependent on behavioral changes. Patients might fail to comply with given instructions for many reasons, ranging from unwillingness to perform oral self-care, poor understanding, lack of motivation, poor dental health beliefs, and unfavorable dental health values due to stressful life events or poor socioeconomic status. Although the use of behavior-modification techniques can offer an advantage over traditional instruction techniques, there is limited research in this area to clarify the relationship between health beliefs and compliance.

Conclusion

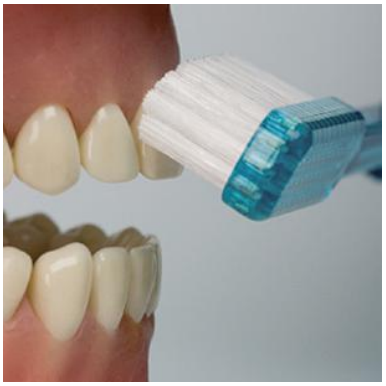
- Ultimately, the goal of a patient's self-care program is to prevent, arrest, and control periodontal disease and caries. The patient's ability to remove plaque from all areas, including interproximal areas, is an essential part of this.
- Oral hygiene instruction should be tailored to each individual patient on the basis of his/her personal needs and other factors.
- The patient should be involved in the instructional process.
- An individualized maintenance program should follow basic oral hygiene instruction.

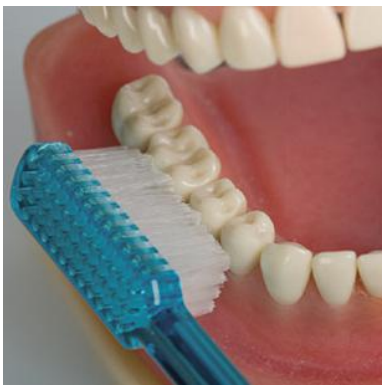
Acknowledgments

All of the figures illustrating the procedures in Boxes 36–1 to 36–8 are used with permission from the Paro Praktijk Utrecht.

Box 36-1 Instructions for manual toothbrushing.

It is of the utmost importance, in addition to using the correct toothpaste and also brushing for at least 2 minutes, to brush the teeth in a set sequence. This technique prevents certain areas from being missed. Areas untouched by the brush will allow plaque to continue to grow. Try to choose a brush with medium or soft bristles and a small head.

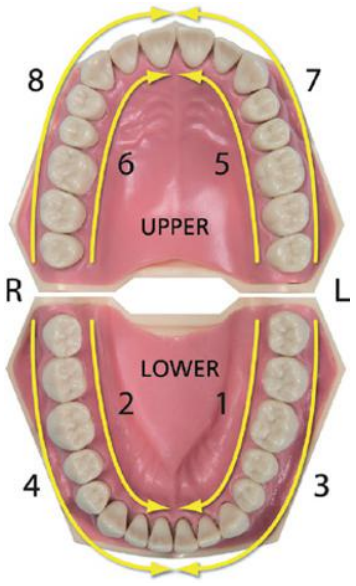




Instructions

- Hold the brush firmly and place the bristles at an angle against the edge of your gums (use a 45° angle). Take care to ensure that the bristles are in contact with a small part of the gum margin.
- Place the brush against the molar or tooth at the back of the mouth and make short back-and-forth scrubbing movements. Brush from the back to the front of the mouth, and try to overlap the strokes. Do not brush more than two teeth simultaneously. Always start at the back and work slowly forward.
- Always hold the brush head horizontally when cleaning the outside surfaces of the teeth. It is easier to hold the head vertically when brushing the inside surfaces of the top and bottom teeth.
- Avoid too much pressure and fast movements, and be aware of feeling contact with the gum margin. Also, avoid brushing too vigorously, thereby preventing damage to the gums.

When cleaning the teeth, keep using the same sequence of brushing. For example, brush the inside of the lower left jaw (15 seconds) and then the inside right (15 seconds). Then, brush the left on the outside (15 seconds), followed by the right on the outside (15 seconds). Repeat the same sequence in the upper jaw. Finally, brush the chewing surfaces with small scrubbing movements. Replace the brush when the bristles start to bend or splay.



Box 36-2 Instructions for electric (power) toothbrushes.

The importance of using a set sequence of brushing movements is applicable when using an electric toothbrush. The question of whether or not an electric brush is better than a manual one has been asked many times. Both brushes allow a high level of oral hygiene to be achieved. However, research has shown that electric toothbrushes are more efficient, and many people report that they are easier to use.

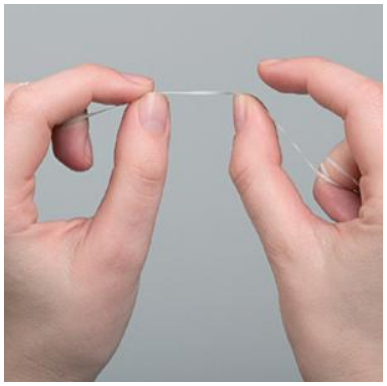
Instructions

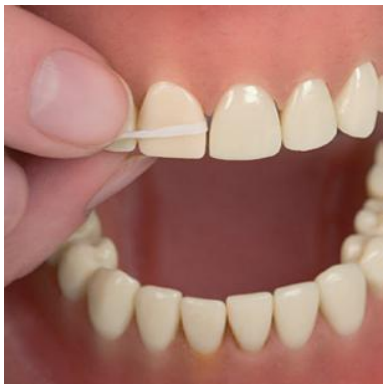
- Place the brush firmly on the hand piece. Grip the brush in the palm so that the bristles of the head are somewhat angled toward the gums (at an angle of approximately 70°). Try to allow the longer bristles to penetrate between the teeth, and take care that the bristles contact your gums.
- Switch on the brush, place the head on the last tooth in the mouth (check the angle), and move the head gradually (over approximately 2 seconds) from the back to the front of this tooth.
- Try to follow the contours of both the teeth and the gums. Place the brush head on the next tooth, and repeat this process.
- Allow the electric toothbrush to do the work. It is not necessary to press hard or make brushing movements.
- Use a timer! Many brushes will provide some form of signal after 30 seconds (the apparatus stops for a moment). This is the point at which to move on to a new part of the mouth.

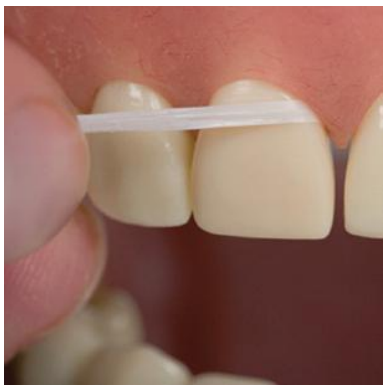
Remember to clean the brush and its head thoroughly when finished.

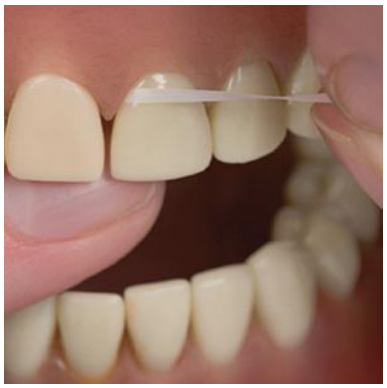
Box 36-3 Instructions for use of dental floss.

The use of dental floss has become part of oral care, in addition to correct, more frequent, and longer tooth brushing. Floss can be purchased in a variety of thicknesses and types and with or without a layer of wax. If there is sufficient space between the front and back teeth, it is advisable to use the somewhat thicker tape rather than the thinner floss.









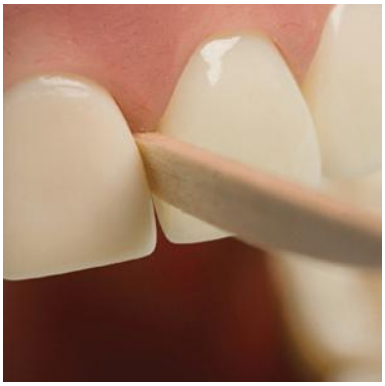
Instructions

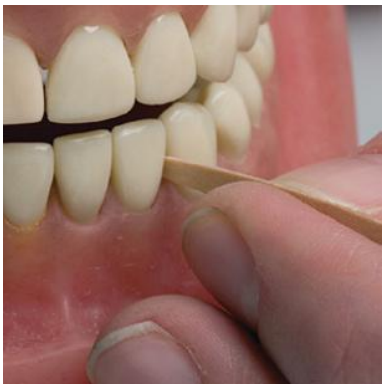
- Take approximately 40 cm of floss and wind the ends loosely around the middle fingers. Allow for 10 cm between the middle fingers. Then, hold the floss taut between the thumb and first finger so that roughly 3 cm remains between the thumbs. Alternatively a loop or circle of dental floss can be created.
- Using a sawing movement, allow the tightly stretched piece of floss to pass between the contact of the front and back teeth. This action might be difficult where the teeth are so close together that the space between them is limited. Avoid allowing the floss to slip so quickly between the teeth because through this "snapping" the gums may be damaged.
- Stretch the floss in a "U" shape around one of the teeth, press firmly against the side of the tooth surface and carefully allow the floss to pass just under the gum, once again with a sawing movement.
- Draw the floss up to the contact point with a sawing movement, and then repeat the process on the other tooth bordering the space filled with gum tissue.
- Remove the floss from between the teeth, once again with a sawing movement, and repeat this process for all of the other spaces in the mouth.
- Use a clean piece of floss for each separate space by unwinding part of it from around one middle finger while winding it around the other middle finger.

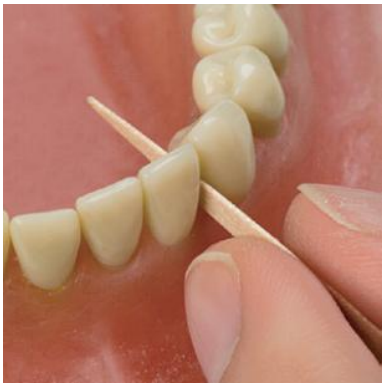
Do not worry if at first your gums bleed slightly. This bleeding will stop after using the floss a number of times. Do not give up!

Box 36-4 Instructions for use of woodsticks.

Most adults have sufficient space available between the incisors and molars to allow woodsticks to be used. These sticks come in differing thicknesses, they are made from wood, and they have a triangular cross-section, mimicking the shape of the space between the teeth. Woodsticks can only be used once and are ideal for use when you have a few spare moments – for example, when sitting in traffic!







Instructions

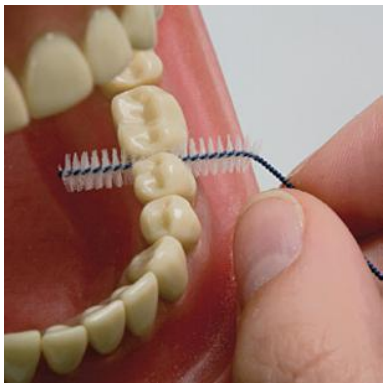
- Hold the woodstick firmly between the thumb and first finger, roughly halfway along its length. When possible, place the other fingers for support on the chin. Moisten the tip of the woodstick by sucking on the point of it, thus making it softer and more flexible.
- Place the flat side of the woodstick (i.e. not the sharp side) against the gum. In the upper jaw, the flat surface will face upward, and in the lower jaw, it will face downward.
- Push the woodstick firmly from the outer side of the space into the space until the stick just becomes wedged. Then, pull it back slightly, and push it back once again, using a light, sawing motion at right angles to the outer surfaces of the teeth. Light pressure can also be applied simultaneously to the gums. Repeat this action a few times, angling the woodstick to contact the surfaces of the teeth enclosing the space.
- When using a woodstick between the premolars and molars, close the mouth slightly to reduce tension in the cheeks, thus making the movements easier.

With this method, all of the spaces between the teeth throughout the mouth can be cleaned. Should the woodstick prick the surface of the gums with the point, angle it a little differently – in the upper jaw, the point will face downward, and in the lower jaw, it will face upward.

Do not be concerned if your gums bleed a little at first – this bleeding will disappear after using the woodsticks repeatedly for a period of time. Do not give up!

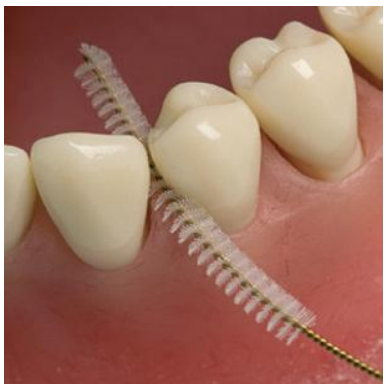
Box 36-5 Instructions for use of interproximal brushes.

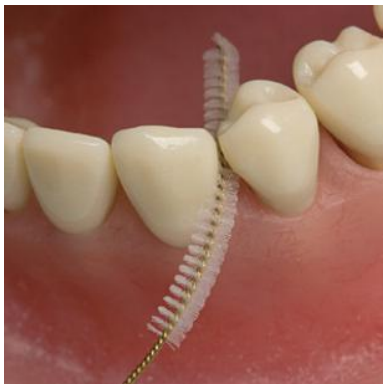
Interdental brushes can be purchased in a variety of sizes, ranging from small (1.9 mm) to very large (14 mm). It is important to choose the correct diameter of the bristle part of the brush. The size of the space between the teeth determines the size of the diameter of the bristles on the brush. Dental professionals can precisely identify which sizes you need and also demonstrate their proper use. A brush that is too small will not completely clean the interdental spaces, and a brush that is too large can injure the gums. The wire of an interdental brush must be thin and the bristles as fine and as long as possible. With such dimensions, the interdental brush will fill the entire space between the teeth quite softly and gently. Tooth spacing varies, so it is often necessary to use a different size of brush within one mouth for optimal cleansing. To remove dental plaque effectively, there should be a slight degree of resistance when the brush is moved back and forth between the teeth.



Instructions

- Always use the interdental brush *without* toothpaste.
- Hold the interdental brush just behind the bristles between the thumb and forefinger. Support can be achieved when necessary by placing your other fingers on your chin. From the outer side of the space, push the interdental brush carefully between the teeth, taking care that the brush remains at a right angle to the teeth.
- You may bend the interdental brush slightly to improve accessibility to the posterior interdental spaces.
- Avoid scraping the center (metal spiral part) of the brush against the teeth.
- Slide the brush in and out of the space using the full length of the bristle part of the brush. This action will remove the dental plaque.
- The area of contact between the brush and the teeth can be somewhat increased by using differing angles of insertion.
- Do not push interdental brushes between the teeth with force. Slight pressure of the brush against the gums should be used, as it will allow the bristles to penetrate slightly underneath the gum margin.
- By slightly closing the mouth, it will be easier to manipulate the brush as the tension in the cheeks is lessened. It might also be helpful to bend the brush slightly to ease insertion.
- Cleanse all areas between the teeth where an interdental brush will fit. Rinse interdental brushes thoroughly after use and allow them to dry out. It is often a good idea to combine the use of interdental brushes and woodsticks.

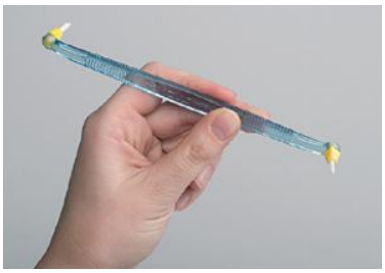


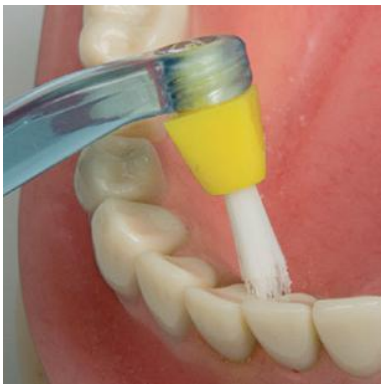


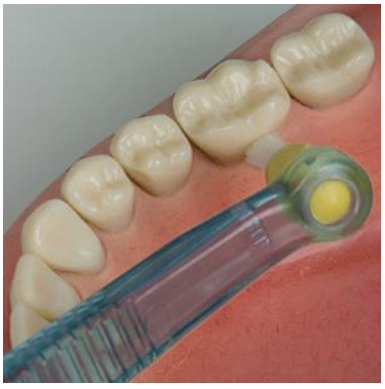
Do not be alarmed if the gums bleed initially. This bleeding does not mean that you have an injury but inflammation, which is caused by concealed, old plaque. This reaction is fairly normal during the first week. Using the interdental brush will soon cure this inflammation, and the bleeding will stop. As the inflammation subsides, the interdental spaces will become slightly larger, and you will most likely need a larger interdental brush. Ask your dental professional.

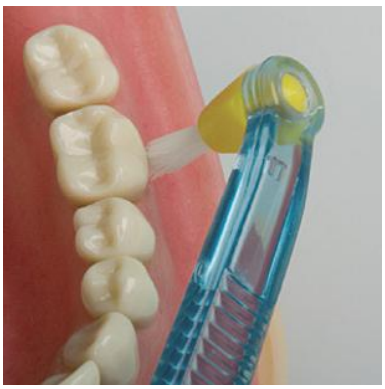
Box 36-6 Instructions for use of single-tufted/end-tufted brushes.

The single-tufted toothbrush is a small brush with a small, single tuft of short bristles attached to the end. The end-tufted brush has a number of small tufts attached in a similar manner. These brushes are an option for cleansing areas of the dentition that cannot be reached with other oral hygiene aids, for example, a lone-standing tooth, the back surface of the last molar or a tooth in the arches, wires and locks of orthodontic braces, grooves or the entrances to areas where the roots have split apart.







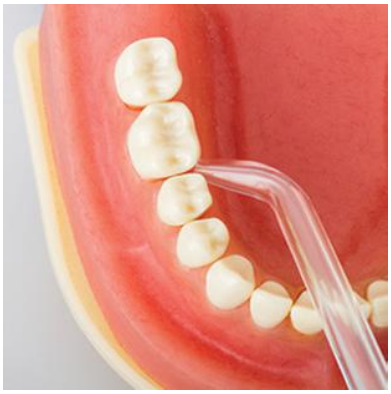


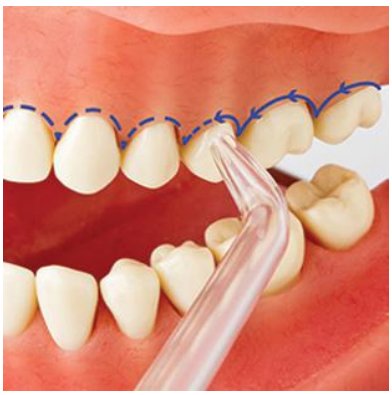
Instructions

- Hold the single-tufted brush as you would hold a pen. This method prevents too much force being applied to the gums.
- Place the single-tufted brush at an angle directed toward the gums (approximately 45°) – this angle allows the bristles to reach just under the gum margin.
- Use small, rotational pencil movements.
- The bristles of the brush will then rotate under and along the gum margin. The brush should then be slowly moved along the tooth surface to cover all areas.

Box 36-7 Instructions for use of oral irrigators.

There are various brands of oral irrigators. Before starting to use a product, it is advisable to read the manufacturer's instructions carefully and to be sure you understand how an oral irrigator works.





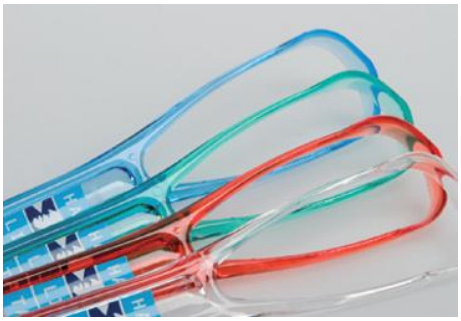
Instructions

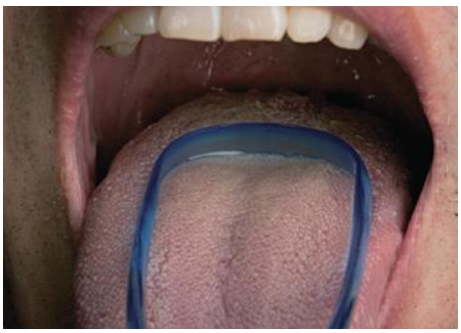
- Fill the water reservoir with lukewarm water, and plug the power cord into the wall outlet. You can use a cup to fill the reservoir. If the unit has removable tips, press the appropriate tip firmly into the irrigator handle. The tip should snap into place because it works under pressure and may shoot away otherwise.
- Test the oral irrigator before use.
- Breathe calmly through your nose. Lean over the sink, and close your lips enough to prevent splashing, while still allowing water to fall from the mouth into the sink.
- Aim the tip just above and toward the gum line at a 90° angle, and press the switch that allows the water to flow.
- *Do not* attempt to watch yourself in the mirror. You will make a mess!
- Starting with the back teeth (where your molars are located), follow the gum line. Take your time to get in between teeth. Continue to work slowly forward until all areas around and between teeth have been cleaned.
- Use the same sequence each time you use the irrigator so that you do not miss any teeth.
- At difficult to reach areas you can adjust the angle of the nozzle, for example while cleaning the brackets of an orthodontic appliance or at root furrows
- Spit out excess water as needed.
- Empty any water remaining in the reservoir after use. Dry thoroughly to avoid bacterial growth. Make sure to unplug the unit before cleaning it.

Irrigating is a technique that relies on your sense of touch. At first, it might take a little longer until you develop a routine and become more comfortable with the oral irrigator. Depending on the power level, you might need to refill the water reservoir. Antiseptics can be added if that has been advised by your dental care professional. If so, a mouth rinse or another antiseptic is added to the water in the reservoir.

Box 36-8 Instructions for use of tongue cleaners.

Tongue cleaning is a useful addition to the daily oral hygiene routine. Many bacteria can be found within the grooves on the back of the tongue, which can cause bad breath. By brushing or scraping the tongue, this problem can be markedly helped or prevented entirely. One of the problems associated with tongue cleaning is that it can stimulate a gag reflex, especially when first applying this procedure. This reflex occurs more frequently with brushing than when using a scraper. Some people find it less of a problem if they clean their tongue in the evening.





Instructions

- There are various types of tongue cleaners: the most effective seems to one having the form of a loop.
- Extend the tongue as far as possible out of your mouth.
- Breathe calmly through your nose.
- Place the tongue cleaner as far back as possible on the tongue, and press lightly with it so that the tongue becomes flattened.
- Ensure full contact of the tongue cleaner with the tongue.
- Pull the tongue cleaner slowly forward.
- Clean the middle part of the tongue, first using the raised edge on one side of the instrument.
- Use the smooth surface of the tongue cleaner on the sides of the tongue.
- Repeat these scraping movements a number of times.
- Rinse the mouth several times.

Remember to clean the tongue cleaner thoroughly after each use.

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Chapter 37

Chemical Oral and Dental Biofilm Control

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Rationale for supragingival biofilm control

Bacteria present in oral biofilms are responsible for the most prevalent diseases of mankind: caries and periodontal diseases. Therefore, control of oral biofilms becomes essential for the prevention of those diseases.

Three levels of prevention of periodontal diseases can be distinguished (Baehni & Takeuchi 2003):

- *Primary prevention*: to protect individuals from pathogens by means of barriers between the pathogens and the host; trying to keep the population in health, avoiding the development of the disease.
- *Secondary prevention*: to limit the progression of the disease once the pathogen has contacted the host; trying to recover health, without damage to the host tissues.
- *Tertiary prevention*: to limit the progression of the disease; trying to restore the host tissues, but with some degree of functional damage.

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

Primary prevention of periodontal diseases is based on supragingival biofilm control by means of mechanical and/or chemical oral hygiene products that are able to limit gingivitis development (Baehni & Takeuchi 2003). Primary prevention of periodontitis assumes that healthy gums (without gingivitis) will not develop periodontitis. Programs for the general population should be implemented to control dental plaque levels and prevent gingivitis with various considerations (Sheiham & Netuveli 2002):

- Toothbrushing must be part of daily personal hygiene habits
- Behavioral factors should be taken into account
- Cleaning methods should be socially acceptable
- Proposed methods should be easy to comply with in daily life
- Hygiene procedures should be simple to perform
- Quality control methods should be part of the program in order to assure its adequate quality.

Secondary and tertiary prevention of periodontal diseases, once disease progression are arrested after proper periodontal therapy of the cause, are achieved by means of supportive periodontal therapy programs that include both individual biofilm control and periodic re-evaluation with professional plaque control (Baehni & Takeuchi 2003).

Oral hygiene products

Thus, supragingival biofilm control is essential in primary, secondary, and tertiary prevention of periodontal diseases. In order to control biofilms in the oral cavity, different oral hygiene products have been developed and marketed. Oral hygiene products refer to "mechanical devices and chemical formulations designed to provide oral health and cosmetic benefits to the user" (Addy & Moran 1997).

Therefore, oral hygiene products include both mechanical devices and chemical formulations.

Mechanical biofilm control

Physical disruption and elimination of dental biofilms can be accomplished by means of manual toothbrushes, different devices for interdental cleaning, powered toothbrushes, etc. (van der Weijden & Slot 2011).

The manual toothbrush is the most widely used method of plaque control (Saxer & Yankell 1997; Hugoson *et al*. 1998), and it has demonstrated efficacy in biofilm control and gingivitis prevention (Hancock 1996; van der Weijden & Hioe 2005). Some powered toothbrushes have also demonstrated efficacy (van der Weijden *et al*. 1998).

Devices for interdental cleaning have also demonstrated efficacy in reducing plaque and gingival indices (Kinane 1998). However, their use is not common due to the lack of proper instruction in their use, difficulties with using them, and limited time and awareness of potential adverse effects. Among the available devices, floss is the most commonly used, but interdental brushes are better accepted.

Mechanical methods of plaque control are covered in detail in Chapter 36.

Limitations

Mechanical devices have demonstrated their efficacy in biofilm and gingivitis control, but different studies (Rugg-Gunn & MacGregor 1978; Lavstedt *et al*. 1982; Addy *et al*. 1986; Albandar & Buischi 1995; Hugoson & Jordan 2004) and systematic reviews (van der Weijden & Hioe 2005) have shown that mechanical control alone may not be enough in a large proportion of the population for the prevention of the onset or the reactivation of periodontal diseases. Different explanations for this can be found:

- Limited time of usage: the normal mean brushing time does not exceed 37 seconds (Beals *et al*. 2000).
- Devices for interdental cleaning are used daily by <10% of the population (Ronis *et al*. 1994); only 2–10% floss daily (Lang *et al*. 1995; Stewart *et al*. 1997; MacGregor *et al*. 1998).
- Even patients instructed in oral hygiene habits tend over time to return to baseline plaque levels (Stewart *et al*. 1997). In most of the studies on mechanical biofilm control, the Hawthorne effect will be present and it may be the case that patients included in a study do not maintain their oral hygiene habits after the end of the study (Johansen *et al*. 1975; Emilson & Fornell 1976; Löe *et al*. 1976; Lindhe *et al*. 1993; Yates *et al*. 1993; Claydon *et al*. 1996; Rosling *et al*. 1997b).
- Lack of control of oral biofilms other than dental plaque, due to lack of adequate instruction on cleaning (tongue dorsum, cheek mucosal surfaces) or access (tonsils) (Quirynen *et al*. 1995; Greenstein 2002, 2004).

In addition, there are circumstances in which adequate mechanical plaque control is not possible, including after oral or periodontal surgery, in patients with intermaxillary fixations, in acute mucosal or gingival infections where pain precludes mechanical hygiene, in mentally or physically handicapped patients, etc. (Storhaug 1977; Nash & Addy 1979; Shaw *et al.* 1984; Zambon *et al*. 1989; Hartnett & Shiloah 1991; Laspisa *et al*. 1994; Eley 1999).

Chemical biofilm control

Chemical plaque control may be necessary in those subjects who are unable to properly control supragingival biofilm with mechanical devices. The use of chemical products should be adjunctive to that of the mechanical devices. The latter reduce the amount of biofilm and disrupt its structure, allowing for a more effective action of the chemical formulations (FDI Commission 2002b). Adjunctive use may be more relevant than sole use, since most chemical agents are only able to act against the most external parts of the

biofilm. However, some agents have demonstrated some capacity for penetration, such as chlorhexidine (CHX) (Netuschil *et al*. 1995) and essential oils (Pan *et al*. 1999, 2000; Fine *et al*. 2001).

The use of chemical formulations (especially antiseptics) to control plaque and gingivitis levels has been widely evaluated, and efficacy for some formulations has been observed in different systematic reviews (Hioe & van der Weijden 2005; Gunsolley 2006; Paraskevas & van der Weijden 2006; Addy *et al*. 2007; Stoeken *et al*. 2007; Gunsolley 2010; Sahrmann *et al*. 2010; Afennich *et al*. 2011; Hossainian *et al*. 2011).

Mechanism of action

Chemical plaque control may be achieved by different mechanisms of action (Fig. 37-1), with a quantitative (reduction of the number of microorganisms)

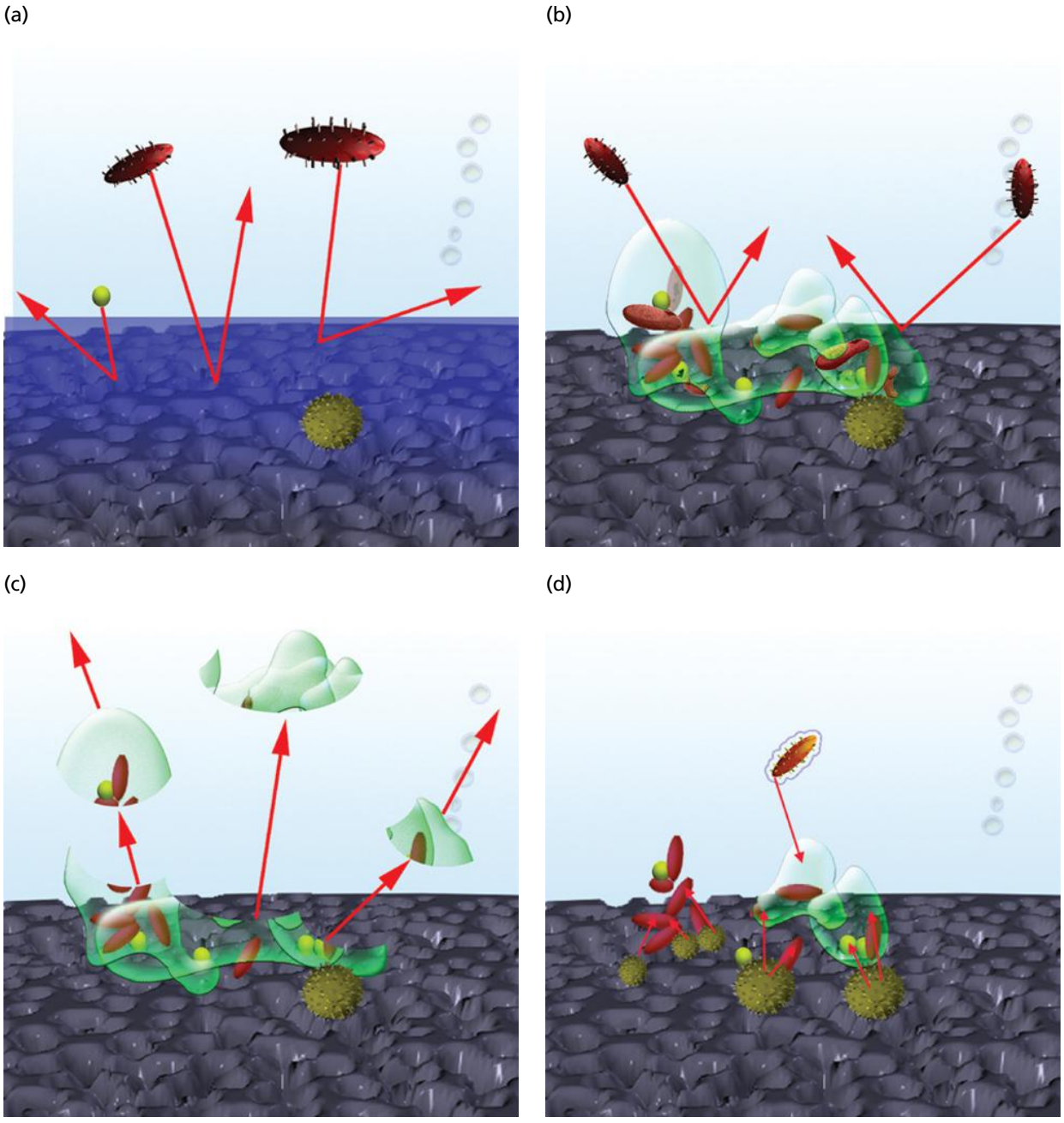

Fig. 37-1 Mechanisms of effect of antiplaque agents on bacterial biofilms (in green). (a) Prevention of bacterial adhesion to tooth surfaces: the active agent forms a pellicle (blue film) over the tooth surface, interfering with bacterial adhesion (red arrows), thus avoiding bacterial colonization. (b) Bactericidal or bacteriostatic effect, avoiding bacterial proliferation and co-aggregation: interference with bacterial division (damaged bacterial cells depicted in red) leads to interference with biofilm formation. In addition, biofilm maturation is also prevented as co-aggregation of new species (red arrows) is impeded, due to the non-favorable environmental conditions. (c) Biofilm disruption from tooth surfaces: "chemical brushing". The agent induces detachment and/or biofilm elimination from the tooth surface by breaking the chemical links between the surface and the biofilms, and by disrupting the biofilm structure (red arrows). (d) Alteration of biofilm pathogenicity or enhancement of host immune systems by different mechanisms: enhanced host defense systems provide more effective biofilm control by the host (short red arrows); or presence of defined bacterial species that may influence biofilm development and maturation, by means of the release of different products, such as bacteriocins, or by competition for nutrients (long red arrow).

and/or qualitative (altering the vitality of the biofilm) effect (FDI Commission 2002b):

- By preventing bacterial adhesion
- By avoiding bacterial growth and/or co-aggregation
- By eliminating an already established biofilm
- By altering the pathogenicity of the biofilm.

Categories of formulations

Formulations for chemical plaque control can be classified according to their effects (Lang & Newman 1997):

- *Antimicrobial agents*: bacteriostatic or bactericidal effects *in vitro*
- *Plaque-reducing/inhibitory agents*: quantitative or qualitative effect on the plaque that may or may not be enough to affect gingivitis and/or caries
- *Antiplaque agents*: affect the plaque sufficiently to show a benefit in terms of gingivitis and/or caries control
- *Antigingivitis agents*: reduce gingival inflammation without necessarily affecting dental plaque, including anti-inflammatory drugs.

These definitions are widely accepted in Europe, but in North America the term "antiplaque" refers more often to agents capable of significantly reducing plaque levels and "antigingivitis" to agents capable of significantly reducing gingivitis levels.

Ideal features

The features of the ideal chemical agent for plaque control have been proposed by different authors (Loesche 1976; van der Ouderaa 1991; Baker 1993; Fischman 1994):

- *Specificity*. Agents and formulations for chemical plaque control should demonstrate a wide spectrum of action, including against bacteria, viruses, and yeasts. More specific products, such as antibiotics, must not be used in the prevention of periodontal diseases, and their use should be limited to the prevention of bacteremia in at-risk patients, and for the treatment of some periodontal conditions (Herrera *et al*. 2008).
- *Efficacy*. Antimicrobial capacity must be demonstrated against microorganisms implicated in gingivitis and periodontitis, in both *in vitro* and *in vivo* studies. Although bactericidal effects may be only achieved at high dosages, antimicrobial effects should also be present at lower dosages (FDI Commission 2002b).
- *Substantivity*. The effects of the chemical formulations do not depend only on the antimicrobial activity *in vitro*. Other factors will influence the *in vivo* activity, among which substantivity may be one of the most relevant. Substantivity has been defined as the duration of the antimicrobial action *in vivo* (FDI Commission 2002b) and as a measurement of the contact time between the agent and the substrate in a defined medium. This time may be longer than expected with simple mechanical deposition (van Abbé 1974) (Fig. 37-2). According to their substantivity, agents have been divided into three distinct generations (Kornman 1986a):
  - First-generation agents show very limited substantivity with limited time of action; examples are phenolic derivatives, plant extracts, fluorides, quaternary ammonium compounds, and oxidizing agents
  - Second-generation agents demonstrate good substantivity; CHX is the best example
  - Third-generation agents include those which interfere or prevent bacterial or biofilm adhesion.

  Since antiseptics are used with the aim of preventing biofilm formation, the longer the duration of their action, the higher their activity. As an example, CHX has demonstrated the highest substantivity and this is associated with its strongest antiplaque effects.
- *Safety*. This must be demonstrated in animal models before use in humans. Due to the chronicity of the conditions to be prevented and the expected long-term use, secondary effects must be minimal.
- *Stability*. Agents must be stable at room temperature for an extended period of time. Care should be taken when mixing different ingredients in a formulation to avoid interference between molecules.

Evaluation of activity of agents for chemical biofilm control

In order to assess the plaque inhibitory and antiplaque activity of chemical compounds, consecutive phases of evaluation have been proposed, with the last being randomized clinical trials of home use with at least 6 months' duration (Addy & Moran 1997).

In vitro studies

Bacterial tests evaluate the antimicrobial activity of a product by measuring the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) against different bacterial species. The information provided is limited (antibacterial activity, spectrum of action), because many other factors will influence the effects *in vivo* and because the bacterial species are usually tested as planktonic cells, while in the mouth they are organized as sessile biofilm cells. However, antibacterial tests are useful for initial screening of products or for evaluation of the effects of the addition of new agents to a formulation.

Uptake studies are *in vitro* studies that assess the adsorption of products on different surfaces, such as hydroxyapatite, enamel, and dentin.

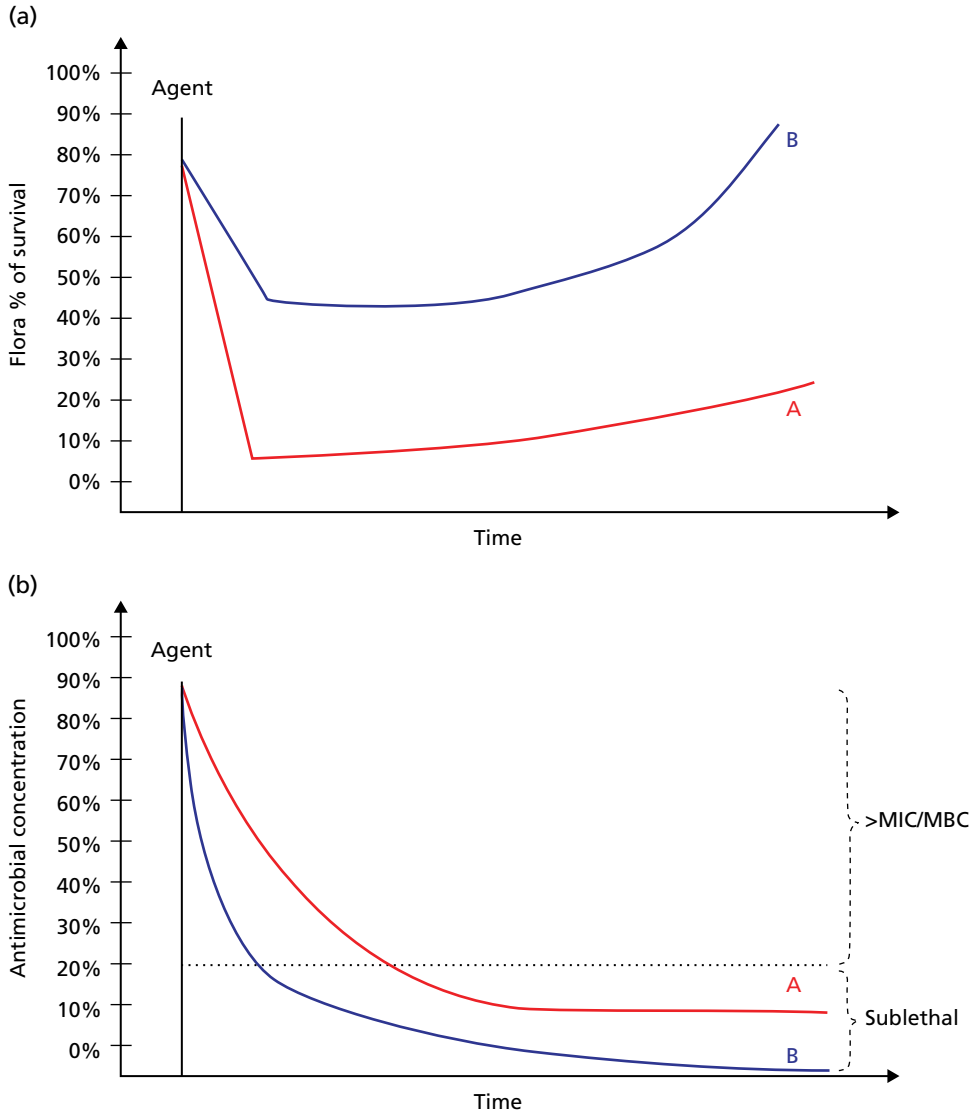

Fig. 37-2 Substantivity. (a, b) Two agents with different substantivity (measurement of the contact time between the agent and the substrate in a defined medium): with time, the concentrations of the products decreases and the bacterial concentration increases. Product A has better substantivity than product B. (a) Time after contact versus percentage bacterial survival. (b) Time after contact versus concentration of the antibacterial agent. (MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration.)

Bioavailability and activity can be assessed by different chemical methodologies, such as spectrophotometry, or by indirect methods, such as staining.

Biofilm models allow formulations to be tested *in vitro* against sessile biofilm bacterial cells, which may better simulate real-life conditions (Xu *et al*. 2000; Shapiro *et al*. 2002; Socransky & Haffajee 2002). However, no standardized and accepted model is available, but several different *in vitro* biofilm models have been proposed (Sanchez *et al*. 2011). In addition to information on the antimicrobial activity, other relevant information, such as the penetration of the agent in the biofilm, can be obtained with these models. Both CHX and essential oils have demonstrated capacity to penetrate and bactericidal action in biofilms (Arweiler *et al*. 2001; Shapiro *et al*. 2002; Arweiler *et al*. 2003; Ouhayoun 2003; Corbin *et al*. 2011; Guggenheim & Meier 2011; Otten *et al*. 2011) (Fig. 37-3).

In vivo studies

Depot studies assess the retention of an agent in the mouth after a single use by measuring the agent level in saliva or in dental plaque. These studies do not provide information on the activity of the product (Rolla *et al*. 1971; Bonesvoll *et al*. 1974a, b; Gjermo *et al*. 1974, 1975; Bonesvoll 1978).

In vivo biofilm study models assess the effects of different formulations on disks of enamel, dentin or other materials inserted into the mouth of patients (with different prosthetic devices) and retrieved for the evaluation of the biofilms formed in their presence (cross-over designs) (Pan *et al*. 2000; Sreenivasan *et al*. 2004).

Antimicrobial tests *in vivo* are designed as cross-over studies (with a placebo and a positive control), with the amount of bacteria in saliva measured before and after (several hours and at different times) a single

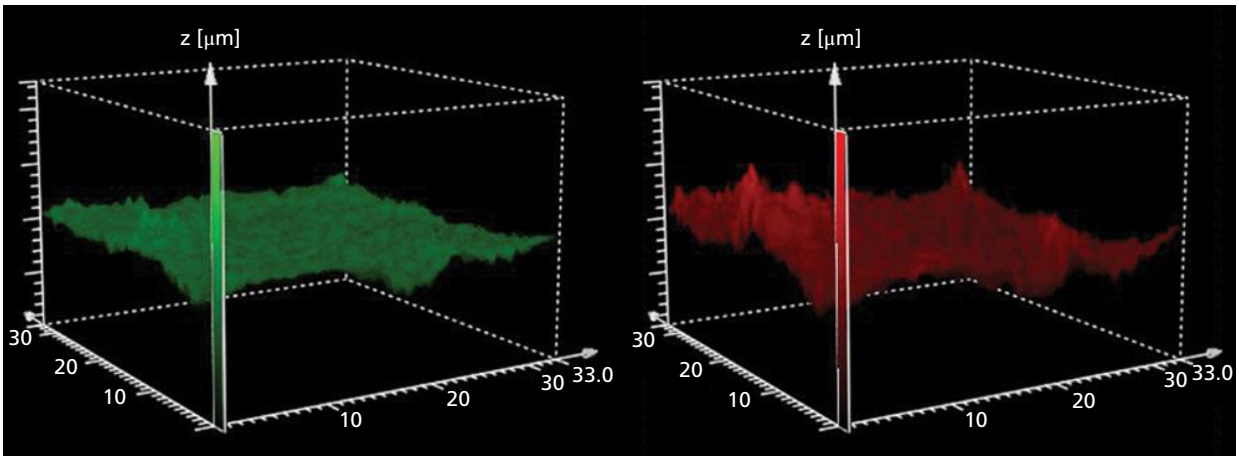

Fig. 37-3 Three-dimensional assessment of cell vitality in a biofilm, with a confocal microscope. Cells in green show vitality and cells with a damaged cytoplasmic membrane appear in red. This tool allows for the assessment of the capacity of biofilm penetration by an antiseptic and its bactericidal activity.

use of a formulation (a mouth rinse, a dentifrice or a dentifrice in an aqueous slurry). This study design has been extensively used since its first use with CHX (Schiøtt *et al*. 1970), and provides information on antimicrobial activity and duration of activity.

Plaque regrowth models are also designed as cross-over studies (with a placebo and a positive control), with the plaque regrowth after professional prophylaxis measured over a period of time (normally 3–4 days) and only the tested formulation allowed for oral hygiene (no mechanical hygiene). Information on the plaque inhibitory capacity of the formulation is obtained (Harrap 1974; Addy *et al*. 1983; Moran *et al*. 1992; Arweiler *et al*. 2002; Pizzo *et al*. 2008).

Experimental gingivitis models have the same design as plaque regrowth models but test the formulation for longer periods of time (typically 12–28 days), allowing for the evaluation of gingivitis indices (Löe 1965; Löe & Schiøtt 1970). No mechanical hygiene is permitted. Parallel studies can be also designed due to the longer duration of the study periods.

Home-use clinical trials

It is a general consensus that plaque inhibitory and antiplaque activities have to be demonstrated in long-term (at least 6 months), home-use, randomized clinical trials, and concomitantly demonstrate safety, based on the lack of relevant side effects. In these studies, the use of the tested formulations is adjunctive to mechanical plaque control. The characteristics of these trials, in order for their conclusion to be valid, have been proposed to be (Council of Dental Therapeutics 1986):

- Double blind (patients and examiner).
- Controlled (negative and/or positive controls). It is not valid to compare the effects of the tested formulation against the baseline values due to the Hawthorne effect (improvement of patients' oral hygiene habits due to their awareness of their presence in the study) and to the performance of a professional prophylaxis at the beginning of these studies (Overholser 1988).
- Minimum of 6 months of duration. This period has a number of advantages: 6 months is the typical period of time between two consecutive supportive periodontal therapy visits; it permits an adequate evaluation of long-term adverse events, including microbiologic effects; and it may compensate for part of the Hawthorne effect, since this effect will slowly disappear as the study progresses (Overholser 1988).
- Microbiologic evaluation to assess the overgrowth of pathogenic, opportunistic or resistant strains.
- Microbiologic sampling and evaluation of plaque and gingival indices should be carried out at the minimum at baseline, the final evaluation, and an intermediate point (e.g. 3 months).

In addition, other factors with regards to the quality of these studies should be considered, such as the selection of a representative population, with study groups homogeneous for different factors (age, smoking, gender, general, oral and periodontal health, etc.). Clinical trials must be clear, comparable, and have internal and external validity (Koch & Paquette 1997).

Based on the availability of at least two independent investigations of 6-month duration demonstrating significant differences, as compared with the negative control, for plaque and gingivitis, different products have received a "seal of approval" for plaque inhibitory and/or antiplaque activity from the American Dental Association (ADA) and the Food and Drug Administration (FDA).

In the following section, the scientific evidence supporting the use of the most common agents is reviewed, with special attention paid to 6-month, home-use, clinical trials and to systematic reviews with meta-analysis of 6-month studies.

Active agents

Antibiotics

Penicillins, tetracyclines, metronidazole, vancomycin, kanamycin, and spiramycin.

- *Characteristics*. When systemically taken, effects are greater due to the maintenance of stable serum levels (also in the gingival crevicular fluid); when topically or locally applied, effects are smaller due to the limited time of action.
- *Evaluation*. Different groups of antibiotics have demonstrated an effect on the dental biofilm.
- *Limitations*. Use against dental plaque is not recommended due to the poor benefit-to-risk ratio, including adverse effects and increase in bacterial resistance (Genco 1981; Kornman 1986b; Slots & Rams 1990; Herrera *et al.* 2000; van Winkelhoff *et al*. 2000).
- *Usefulness, marketed*. Should not be used for chemical plaque control.

Enzymes

Disrupt the biofilm

Dextranase, mutanase, proteases, and lipases.

- *Characteristics*. Very limited substantivity and frequent side effects (Addy 1986).
- *Evaluation*. Use *in vivo* is limited due to side effects. Other enzymes and combinations of enzymes have been evaluated, but only *in vitro* data are available (Johansen *et al*. 1997; Donlan & Costerton 2002).
- *Limitations*. Frequent side effects (Hull 1980; Addy 1986).
- *Usefulness, marketed*. No.

Enhance the host defenses

Glucose oxidase and amyloglucosidase.

- *Characteristics*. Mechanisms of action rely on the catalization of thyocianate into hypothyocianate, through the salivary lactoperoxydase system.
- *Evaluation*. Results for *in vivo* effect on gingivitis have been contradictory and no long-term studies are available (Addy 1986; Moran *et al*. 1989; Kirstila *et al*. 1994; Hatti *et al*. 2007).
- *Limitations*. Limited scientific evidence available.
- *Usefulness, marketed*. Marketed as Zendium® by Opus Health Care AB (Malmö, Sweden) in a mouth rinse with amyloglucosidase, glucosidase and lactoperoxidase, sodium fluoride, xylitol and zinc, and no alcohol; and in toothpaste. Another commercialized toothpaste is Bioxtra® (Bio-X Healthcare, Namur, Belgium), with lactoferrin, lysozyme, and lactoperoxidase.

Amine alcohols

Delmopinol (Fig. 37-4) and octapinol.

- *Characteristics*. Mechanism of action is not fully understood, but they are not antimicrobials and their effect is achieved by the inhibition of biofilm matrix formation or disruption of the biofilm matrix. Delmopinol also inhibits glucane synthesis by *Streptococcus mutans* (Rundegren *et al*. 1992; Elworthy *et al*. 1995) and reduces acid synthesis by bacteria (Simonsson *et al*. 1991).
- *Evaluation*. Delmopinol has been formulated and clinically evaluated as a mouth rinse at 0.1% and 0.2% (Collaert *et al*. 1992; Moran *et al*. 1992; Abbott *et al*. 1994; Claydon *et al*. 1996; Zee *et al*. 1997) and

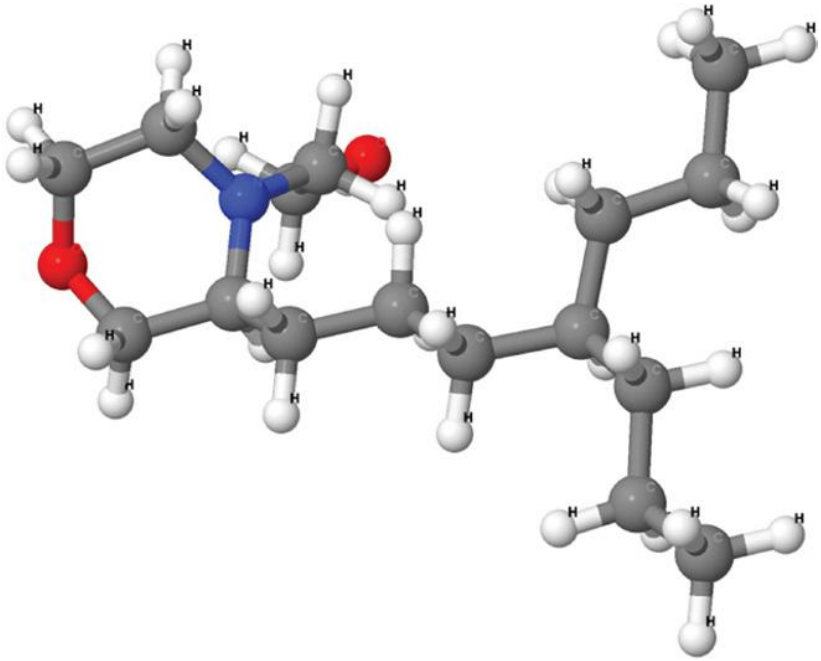

Fig. 37-4 Chemical structure of delmopinol (prepared with Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/).

demonstrated efficacy as an antiplaque agent in a systematic review (Addy *et al*. 2007). It was approved by the FDA in 2005 as a 0.2% mouth rinse indicated in the treatment of gingivitis (Imrey *et al*. 1994).
- *Limitations*. Most relevant side effects are dental staining, a temporary feeling of numbness in the mucosa (e.g. tongue), and a burning sensation.
- *Usefulness, marketed*. Delmopinol has been marketed in several countries by Sinclair Pharma (Paris, France) under the name of Decapinol, both as a 0.2% mouth rinse with 1.5% of alcohol, and as a 0.2% toothpaste with 0.11% sodium fluoride.

Detergents

The most important and frequently used detergent or surfactant (active-surface compounds) is sodium lauryl sulfate (SLS).

- *Characteristics*. SLS has demonstrated substantivity of 5–7 hours. The foaming properties of detergents may help in removing plaque, although there is insufficient evidence to support this statement.
- *Evaluation*. SLS has a limited antimicrobial and plaque-inhibitory effect (Addy *et al*. 1983; Moran *et al*. 1988).
- *Limitations*. SLS has been associated with oral hypersensitivity reactions, including cheilitis, stomatitis or aphthous ulcers, burning sensation, and desquamation (Herlofson & Barkvoll 1996; Chahine *et al*. 1997; Plonait & Reichart 1999).
- *Usefulness, marketed*. SLS is present in many dentifrice and mouth rinse formulations, but has not been formulated as a single active agent product.

Oxygenating agents

Sodium peroxyborate and peroxycarbonate, and hydrogen peroxide.

- *Characteristics*. Exert antimicrobial effects through the release of oxygen.
- *Evaluation*. Peroxyborate and peroxycarbonate have demonstrated some antimicrobial and plaque inhibitory activity (Moran *et al*. 1995). Hydrogen peroxide was evaluated in a systematic review (Hossainian *et al*. 2011) of 10 publications, three of which (one with a 6-month follow-up) had a low risk of bias. No effect was observed in the short term, but the 6-month study demonstrated significant benefits in terms of the modified gingival index (Hasturk *et al*. 2004).
- *Limitations*. No long-term data are available for peroxyborate and peroxycarbonate, and only one study for hydrogen peroxide has been published. At low concentrations (i.e. <1.5%) of hydrogen peroxide, adverse events are not common, but at higher concentrations a painful sensation in the mouth and ulcers may be frequent (Rees & Orth 1986).
- *Usefulness, marketed*. Peroxyborate (Bocasan®, Amosan®) and peroxycarbonate (Kavosan®) were widely marketed by Procter and Gamble (Cincinnati, OH, USA), but they are now only available in some countries. Hydrogen peroxide is available in North America as Rembrant® (Dent-Mat Corp., Santa Maria, CA, USA).

Metal salts

Zinc salts

Zinc lactate, zinc citrate, zinc sulfate, and zinc chloride.

- *Characteristics*. At low concentrations, no adverse effects have been reported.
- *Evaluation*. As sole agents they have limited effects on plaque, but if combined with other active agents, there is an improvement in substantivity and action.
- *Limitations*. No data as individual agents are available.
- *Usefulness, marketed*. In combination with CHX, cetylpyridinium chloride (CPC), triclosan, hexetidine, etc. Combination products have been evaluated for plaque control (zinc lactate with CHX; zinc citrate with triclosan), but some combinations have also been evaluated for halitosis control (zinc lactate with CHX and CPC), tartar control (zinc chloride with essential oils), or ulcer healing (zinc sulfate with triclosan).

Stannous fluoride

Stannous fluoride has been included in dentifrices, mouth rinses, and gels since 1940. Several formulations have been tested, but the two most commonly evaluated are the combination of stannous fluoride with amine fluoride (see below), and different formulations of 0.454% stannous fluoride dentifrice [combined with sodium hexametaphosphate (SHMP) in the most recent formulation].

- *Characteristics*. Combination of tin and fluoride (SnF_2); difficult to formulate in oral hygiene products due to limited stability in aqueous solution (Miller *et al*. 1969). It is not frequently formulated in mouth rinses.
- *Evaluation*. Several 6-month studies have been published, evaluating gel or dentifrice products, most frequently (five investigations) with the 0.454% stannous fluoride formulation (Beiswanger *et al*. 1995; Perlich *et al*. 1995; Mankodi *et al*. 1997; McClanahan *et al*. 1997; Williams *et al*. 1997), but also with stannous fluoride plus SHMP (Mankodi *et al*. 2005a; Mallatt *et al*. 2007; Boneta *et al*. 2010) and older formulations (Boyd & Chun 1994; Wolff *et al*. 1989). Less frequently, mouth rinse products

have been assessed (Leverett *et al*. 1984, 1986). In a systematic review, the 0.454% stannous fluoride formulation provided significant benefits in terms of gingivitis [weighted mean difference (WMD) 0.441; P <0.001, with significant heterogeneity P = 0.010] (Gunsolley 2006). In another systematic review (Paraskevas & van der Weijden 2006), the meta-analysis was limited due to the availability of data, and data pooling was performed at the final study visit, assuming that no differences were found at baseline. In addition, the results combined different stannous fluoride formulations, including the combination with amine fluoride. The results demonstrated significant differences at the final visit (and no differences at baseline) for gingival index (WMD −0.15), modified gingival index (WMD −0.21), and plaque index (WMD −0.31), always with significant heterogeneity.

- *Limitations*. Main limiting factor is dental staining (Brecx *et al*. 1993; Paraskevas & van der Weijden 2006).
- *Usefulness, marketed*. Most recently marketed formulation is Crest Pro-Health (Procter & Gamble, Cincinnati, OH, USA), with 0.454% stannous fluoride with SHMP, zinc lactate, and SLS; approved by the ADA. The earlier formulation with 0.454% stabilized stannous fluoride was marketed as Crest Gum Care or Crest Plus Gum Care (Procter & Gamble).

Stannous fluoride with amine fluoride

Amine fluoride was developed in the 1950s at the University of Zurich.

- *Characteristics*. Stannous fluoride and amine fluoride have both demonstrated bactericidal activity against bacteria, and activity is increased if they are combined. Amine fluoride exerts its antimicrobial action by antiglycolytic effects. The activity of stannous/amine fluoride seems to be greater as a dentifrice, with 8 hours of action following use (Weiland *et al*. 2008).
- *Evaluation*. Six-month studies assessing stannous/amine fluoride as dentifrice (Sgan-Cohen *et al*. 1996; Shapira *et al*. 1999), mouth rinse (Zimmermann *et al*. 1993) or both (Mengel *et al*. 1996; Paraskevas *et al*. 2005) reveal no significant benefit of the dentifrice alone, while the mouth rinse achieved significant plaque and gingivitis reductions. If both products were used in combination, either no significant effects (Mengel *et al*. 1996) or significant effects on plaque, but not on gingivitis (Paraskevas *et al*. 2005), were reported.
- *Limitations*. Tooth staining is the most common adverse effect (Paraskevas *et al*. 2005).
- *Usefulness, marketed*. Both the dentifrice and the mouth rinse are marketed as Meridol® (GABA International AG, Therwil, Switzerland).

Other fluorides

Sodium fluoride and sodium monofluorophosphate.

- *Characteristics*. Usefulness has been demonstrated in reducing caries incidence (Petersson 1993).
- *Evaluation*. Fluoride ion has not demonstrated plaque-inhibitory or antiplaque properties.
- *Limitations*. Not evaluated as individual agents.
- *Usefulness, marketed*. Present in most dentifrices.

Natural products

Sanguinarine extract and other herbal ingredients (camomile, echinacea, sage, myrrh, rhatany, peppermint oil).

- *Characteristics*. Sanguinarine is an alkaloid obtained from the plant *Sanguinaria canadensis*.
- *Evaluation*. Sanguinarine extract has demonstrated low bactericidal capacity in an *in vitro* biofilm model (Shapiro *et al*. 2002), while the clinical evaluation reported contradictory results (Moran 1988; Scherer *et al*. 1998; Quirynen *et al*. 1990). At least six home-use, 6-month oral hygiene trials were performed in the 1980s and early 1990s assessing sanguinarine extract with zinc chloride, as dentifrice (Lobene *et al*. 1986; Mauriello & Bader 1988), as mouth rinse (Grossman *et al*. 1989) or the combined use (Hannah *et al*. 1989; Harper *et al*. 1990; Kopczyk *et al*. 1991). Significant reductions in terms of plaque and gingivitis were reported with combined use.
- *Limitations*: Use of formulations of sanguinarine was associated with oral leukoplakia (Mascarenhas *et al*. 2002).
- *Usefulness, marketed*: Viadent (Colgate-Palmolive Co., Piscataway, NJ, USA), with sanguinarine extract is no longer available. Paradontax (GlaxoSmithKline, Middlesex, UK) contains other herbal components.

Essential oils

Mouth rinse with eucalyptol (0.092%), menthol (0.042%), methyl salicylate (0.060%), thymol (0.064%), and alcohol (26.9% in the original formulation) (Fig. 37-5).

- *Characteristics*. Multiple mechanisms of action have been proposed, such as cell wall disruption, inhibition of bacterial enzymes, extraction of endotoxins derived from lipopolysaccharide (LPS) of Gram-negative bacteria (Fine *et al*. 1985), and anti-inflammatory action based on antioxidant activity (Firatli *et al*. 1994; Sekino & Ramberg 2005).
- *Evaluation*. A mouth rinse with essential oils has demonstrated antimicrobial activity in biofilm models *in vitro* (Fine *et al*. 2001; Shapiro *et al*. 2002), and plaque inhibitory and antiplaque effects in different home-use, 6-month oral hygiene studies (Lamster 1983; Gordon *et al*. 1985; Beiswanger *et al*. 1997; DePaola *et al*. 1989; Grossman *et al*. 1989;

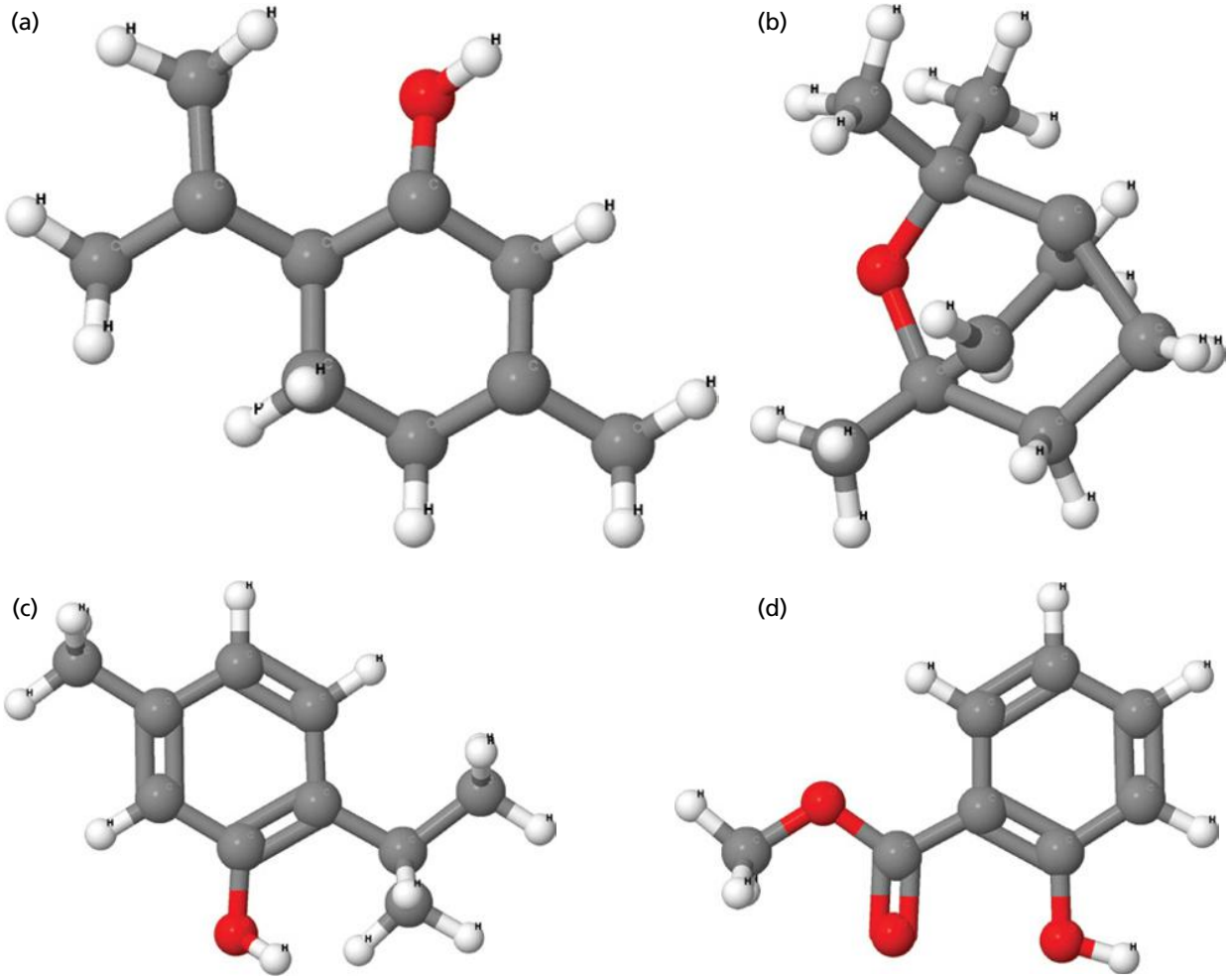

Fig. 37-5 Chemical structure of essential oils. (a) Menthol; (b) eucalyptol; (c) thymol; (d) methyl salicylate (prepared with Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/).

Overholser *et al*. 1990; Charles *et al*. 2001; Sharma *et al*. 2002; Bauroth *et al*. 2003; Charles *et al*. 2004; Sharma *et al*. 2004). In a systematic review (Stoeken *et al*. 2007), including investigations of 6 months or more, 11 papers were included and statistically significant differences in the meta-analysis were found for both plaque (WMD −0.83; P <0.00001; with significant heterogeneity, P <0.00001) and gingivitis index (WMD −0.32, P <0.00001; with significant heterogeneity, P <0.00001).

- *Limitations*. Secondary effects include a burning sensation and tooth staining. There is some controversy concerning the association of alcohol-containing mouth rinses (including Listerine®) and oral cancer (Blot *et al*. 1983). However, critical assessment of the literature does not support an association (Ciancio 1993; Claffey 2003).
- *Usefulness, marketed*. There are different formulations of Listerine® as mouth rinse, including one without alcohol (Johnson & Johnson Healthcare Products, Skillman, NJ, USA).

Triclosan

Triclosan [5-chloro-2-(2,4 dichlorophenoxy) phenol] is a non-ionic bisfenolic, broad-spectrum antibacterial agent (Ciancio 2000) (Fig. 37-6).

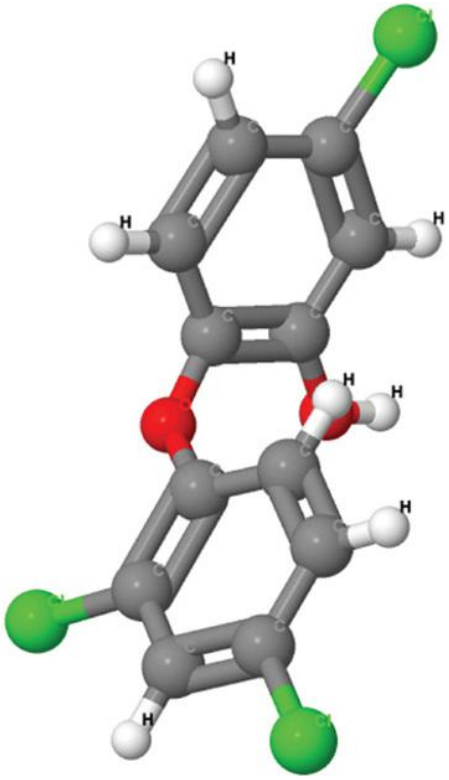

Fig. 37-6 Chemical structure of triclosan (prepared with Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/).

- *Characteristics*. Formulated both in mouth rinses and in dentifrices. In mouth rinses, at 0.2%, there is a limited bactericidal activity (Shapiro *et al*. 2002; Arweiler *et al*. 2003) and a substantivity of approximately 5 hours (Jenkins *et al*. 1991a). As a dentifrice, it can be detected for up to 8 hours in dental plaque following application (Gilbert & Williams 1987). It has normally been formulated in combination with polyvinyl-methyl ether maleic acid co-polymer, zinc citrate or pyrophosphate, in order to improve the substantivity and/or the antimicrobial activity. Triclosan may also induce anti-inflammatory effects (Barkvoll & Rolla 1994; Gaffar *et al*. 1995; Kjaerheim *et al*. 1996) through inhibition of the cyclooxygenase and lipoxygenase pathways, which reduces the synthesis of prostaglandins and leukotrienes.
- *Evaluation*. Home-use, 6-month, oral hygiene studies are available for three distinct triclosan dentifrice formulations (triclosan with co-polymer, triclosan with zinc citrate, triclosan with pyrophosphate), and a mouth rinse with triclosan and co-polymer.
  - A *dentifrice with triclosan and zinc citrate* was extensively evaluated in the 1990s (Svatun *et al*. 1989; Stephen *et al*. 1990; Svatun *et al*. 1990, 1993a, b; Palomo *et al*. 1994; Renvert & Birkhed 1995). Conflicting results were reported and a limited meta-analysis conducted (using end of trial values, rather than changes in values), demonstrating a limited but significant effect on plaque (WMD −0.07; P <0.00001) and a more important effect on bleeding (WMD −10.81%; P <0.00001) (Hioe & van der Weijden 2005). Conversely, no significant differences were observed in another systematic review considering differences between baseline and final visit (Gunsolley 2006).
  - A *dentifrice with triclosan and co-polymer* has also been extensively evaluated in 6-month studies (Garcia-Godoy *et al*. 1990; Cubells *et al*. 1991; Deasy *et al*. 1991; Bolden *et al*. 1992, Denepitiya *et al*. 1992; Mankodi *et al*. 1992; Lindhe *et al*. 1993; Svatun *et al*. 1993a; Palomo *et al*. 1994; Kanchanakamol *et al*. 1995; Triratana *et al*. 1995; Hu *et al*. 1997; McClanahan *et al*. 1997; Charles *et al*. 2001; Allen *et al*. 2002; Winston *et al*. 2002). In a limited meta-analysis of final visit values, a significant effect was observed for the Turesky modification of the plaque index (WMD −0.48; P <0.0001) and for the Talbott modification of the gingival index (WMD −0.24; P <0.0001), in both cases with significant heterogeneity (Hioe & van der Weijden 2005). In another meta-analysis evaluating changes between baseline and the final visit, a significant effect on plaque was observed (WMD 0.823), with significant differences in 14 of the 18 included arms; and for gingivitis (WMD 0.858), in both cases with significant heterogeneity (Gunsolley 2006).
  - A *dentifrice with triclosan and pyrophosphate* has been evaluated less frequently (Palomo *et al*. 1994; Renvert & Birkhed 1995; Grossman *et al*. 2002; Winston *et al*. 2002); results have shown significant heterogeneity and conflicting results (Gunsolley 2006).
  - A *mouth rinse with triclosan and co-polymer* was evaluated in the 1990s in at least four 6-month trials (Worthington *et al*. 1993; Ayad *et al*. 1995; Triratana *et al*. 1995; Schaeken *et al*. 1996), demonstrating statistically significant differences both in plaque and gingival indices. The triclosan and co-polymer mouth rinse formulation has also been tested as a prebrushing agent; a meta-analysis of two 6-month studies gave a WMD of 0.269 (P <0.0001) (Angelillo *et al*. 2002).
- *Limitations*. There are no relevant side effects, but risk of formation of the carcinogenic product chloroform was suggested in an *in vitro* study testing the combination of triclosan and free chlorine present in water (Rule *et al*. 2005). Also, environmental problems from the presence of triclosan in the food chain have been suggested.
- *Usefulness, marketed*. Triclosan (0.30%) with co-polymer and sodium fluoride (0.24%) is marketed as Colgate Total® (Colgate-Palmolive Co.). The formulation of triclosan and co-polymer as mouth rinse has been marketed as Plax®, although different products under this name have been marketed, including formulations with sodium benzoate.

Bisbiguanides

CHX digluconate, alexidine dihydrochloride, and octenidine dihydrochloride.

- *Characteristics*. Symmetric molecules with two chlorophenolic rings and two biguanides groups connected by a central bridge of hexametilene (Fig. 37.7).
- *Evaluation*. Excellent antiplaque agent. CHX is the reference, since the other bisbiguanides show similar or inferior activity (Shapiro *et al*. 2002).
- *Limitations*. Similar among all bisbiguanides, but there are more studies for CHX.
- *Usefulness, marketed*. Many CHX formulations are available on the market.

Chlorhexidine

CHX is the most widely evaluated and the most efficacious agent against oral biofilms. Its activity was first investigated >50 years ago (Schroeder 1969).

CHX is most often formulated in mouth rinses with a concentration of 0.1–0.2% (Löe *et al*. 1976; Segreto *et al*. 1986; Grossman *et al*. 1989; Flemmig *et al*. 1990; Lang *et al*. 1998). These concentrations achieve the ideal CHX dosage of 18–20 mg/application. Clinical activity is observed with dosages of 5–6 mg t.i.d. and higher dosages do not increase the effect (but do increase adverse effects) (Cancro *et al*. 1974). To obtain a 20-mg dosage with a 0.2% formulation, rinsing with 10 mL should last for 30 seconds; with a 0.12% formulation, rinsing with 15 mL should last for 60 seconds.

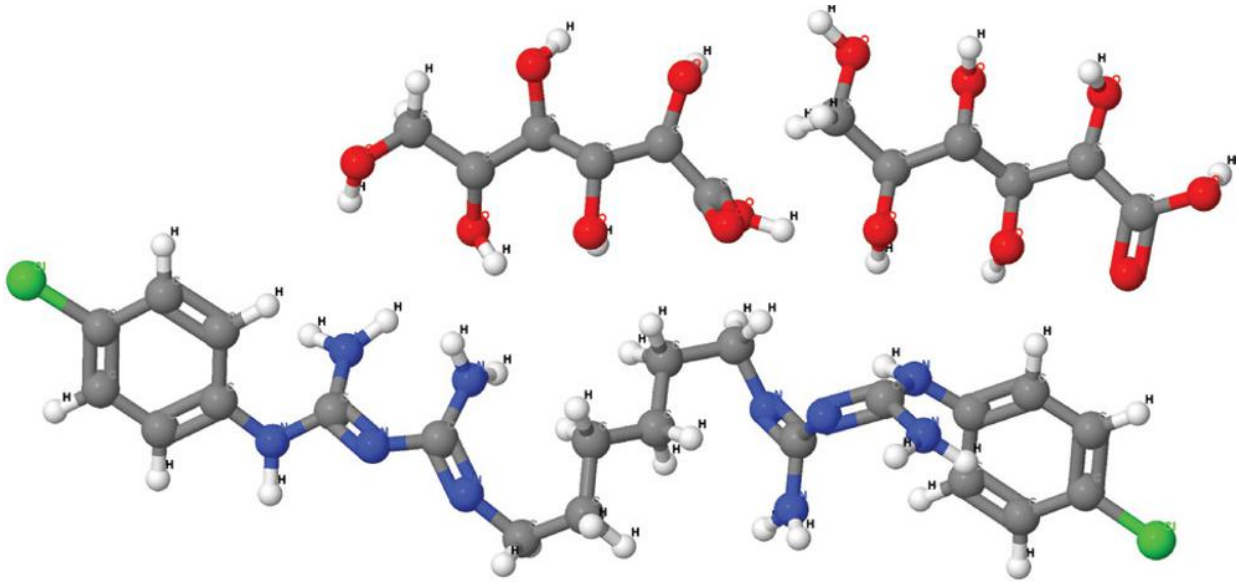

Fig. 37.7 Chemical structure of chlorhexidine digluconate (prepared with Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/).

More recently, mouth rinses with lower concentrations (e.g. 0.05%) have been marketed, aiming to decrease adverse effects. The resulting dosages will be approximately 5 mg per application, which is at the lower limit of clinical activity; therefore, the bioavailability of CHX (which depends on the formulation and the presence of other ingredients) is crucial, and combination with other active agents (triclosan, cetylpyridinium chloride, zinc salts) has been proposed (Joyston-Bechal & Hernaman 1993; Marsh & Bradshaw 1995; Claydon *et al*. 2001; Shapiro *et al*. 2002).

- *Characteristics*. CHX is active against Gram-positive and Gram-negative bacteria, yeast, and viruses, including human immunodeficiency virus (HIV) and hepatitis B virus (Wade & Addy 1989).
  - *Antimicobial effect*. This depends on concentration. At low concentrations, CHX increases the permeability of the plasmatic membrane, leading to a bacteriostatic effect (Hugo & Longworth 1964, 1965). At higher concentrations, it induces precipitation of cytoplasmic proteins and cell death, thus having a bactericidal effect (Hugo & Longworth 1966; Fine 1988). CHX has been shown to penetrate biofilms and to actively act inside the biofilm, altering biofilm formation or having a bactericidal effect (Arweiler *et al*. 2001; Shapiro *et al*. 2002).
  - *Plaque inhibitory effect*. In addition to its antimicrobial effect, CHX molecules adhere to the tooth surface and interfere with bacterial adhesion (Rolla & Melsen 1975; Wolff 1985; Fine 1988; Jenkins *et al*. 1988, 1989). CHX also interacts with salivary glycoproteins, thus leading to reduced salivary pellicle formation. In addition, it has been suggested that CHX affects the activity of bacterial enzymes involved in glucan production (glycosiltranferase C) (Vacca-Smith & Bowen 1996).
  - *Substantivity*. CHX molecules bind reversibly to oral tissues, with a slow release (Bonesvoll *et al*. 1974a, b) that allows for sustained antimicrobial effects (up to 12 hours) (Schiøtt *et al*. 1970).
- *Evaluation*: 6-month studies are available both for mouth rinses and for dentifrices.
  - *Dentifrices.* The difficulties in formulating CHX in dentifrices are well known and due to the high risk of inactivation. However, a 1% CHX dentifrice (Yates *et al*. 1993) and a 0.4% CHX dentifrice with zinc (Sanz *et al*. 1994) both demonstrated significant benefits in terms of plaque and, for the 1% CHX dentifrice, also in gingival inflammation.
  - *Mouth rinses*. Different 0.12% and 0.2% mouth rinse formulations have been evaluated in 6-month studies (Sanz *et al*. 1994; Grossman *et al*. 1986, 1989; Flemmig *et al*. 1990; Overholser *et al*. 1990; Hase *et al*. 1998; Lang *et al*. 1998, Charles *et al*. 2004; Stookey 2004), and each independent study revealed statistically significant benefits in terms of both plaque and gingival indices, with one exception. In a systematic review of 0.12% formulations (six studies, one unpublished), the WMD for the plaque index was 1.040 (P <0.001) and for the gingival index was 0.563 (P <0.001; with significant heterogeneity, P = 0.013) (Gunsolley 2006).

    A systematic review *comparing 0.12% and 0.2% formulations* (Berchier *et al*. 2010) included eight papers (with a study duration of 3–14 days, except for one paper reporting 3-month results). For the Quigley & Hein plaque index (Quigley & Hein 1962), meta-analyses of seven papers revealed a significant difference between the two formulations (WMD 0.10; P = 0.008), although this difference was not considered to be clinically relevant and none of the individual studies showed significant differences. For gingival inflammation, no difference was observed in a meta-analysis of three papers.

    CHX and essential oil mouth rinses have been compared. In a systematic review (van Leeuwen *et al*. 2011) of 19 papers, meta-analyses were

carried out on studies with a follow-up of 4 weeks or more. Significant differences (favoring the CHX groups) were found at the final visit for plaque (four studies, WMD 0.19; $P = 0.0009$), but no significant difference for gingival inflammation (three studies, WMD 0.03; $P = 0.58$). Significantly more staining was observed in the CHX groups (WMD 0.42; $P < 0.000001$). It must be highlighted, however, that the meta-analyses considered final visit values, rather than the changes between the baseline and final visit. In addition, different CHX concentrations and formulations were pooled, as well as different follow-up times. Another meta-analysis only included 6-month studies (Gunsolley 2006) and pooled data from four studies (Segreto & Collins 1993; Grossman *et al*. 1989; Overholser *et al*. 1990; Charles *et al*. 2004). A significant difference ($P = 0.02$) in plaque was reported, favoring 0.12% CHX formulations, with two individual studies demonstrating significant differences. For the gingival index, one study reported significant differences, and the pooled results showed a tendency to significant differences ($P = 0.068$). The authors highlighted that the essential oil mouth rinse showed 60% of the effect of CHX mouth rinses for both parameters.

- *Limitations*. CHX safety has been extensively studied. Only heating for long periods of time can induce the formation of 4-chloroanilinine, which has been shown to be cancerogenic and mutagenic. Despite the low risk of formation of 4-chloroanilinine, CHX formulations are marketed in dark bottles, and should be kept at room temperature, out of direct sunlight. No adverse microbiologic changes, including the overgrowth of opportunistic strains, are induced over long-term use (Schiøtt *et al*. 1970, 1976a, b).

  Reported adverse events include:
  - Hypersensitivity reaction (Beaudouin *et al*. 2004)
  - Neurosensory deafness if the product is placed in the middle ear (Aursnes 1982)
  - Taste alterations (Marinone & Savoldi 2000; Breslin & Tharp 2001), particularly affecting salty and bitter taste; these are reversible and disappear soon after discontinuation of product usage
  - Uni- or bi-lateral parotid tumefaction (Fløtra et al. 1971; van der Weijden *et al*. 2010)
  - Mucosal erosion (Almqvist & Luthman 1988)
  - Healing process alterations. *In vitro* studies have suggested some inhibition of fibroblast proliferation in culture. However, *in vivo* studies of CHX mouth rinses after periodontal surgery have found no interference with the healing process; indeed, a better resolution of inflammation was observed (Sanz *et al*. 1989)
  - Increase in calculus formation (Yates *et al*. 1993)
  - *Staining* of teeth, mucosa, tongue dorsum, or restorations (Fløtra *et al*. 1971). Tooth and tongue staining is the most common adverse effect (Fig. 37-8) and different mechanisms have been proposed to explain staining associated with CHX usage (Watts & Addy 2001):
    - Degradation of the CHX molecule to parachloraniline
    - Catalysis through Maillard reactions
    - Protein denaturation with formation of metal sulfide
    - Precipitation of anionic dietary chromogens.

    The intensity of staining seems to correlate with the frequency of intake of chromogenic products, such as coffee, tea, wine, and tobacco, and also with the concentration of CHX in commercial formulations. In addition, a direct correlation has been observed between staining and antimicrobial effect (Addy *et al*. 1989; Claydon *et al*. 2001).

    In recent years, different methods to decrease the staining associated with CHX have been evaluated, including the use of an antidiscoloration system (ADS). Although equivalent antimicrobial efficacy was claimed on the basis of short-term studies (Cortellini *et al*. 2008; Solís *et al*. 2011), other investigations have shown that ADS also diminishes the efficacy of CHX (Arweiler *et al*. 2006; Guggenheim & Meier 2011).

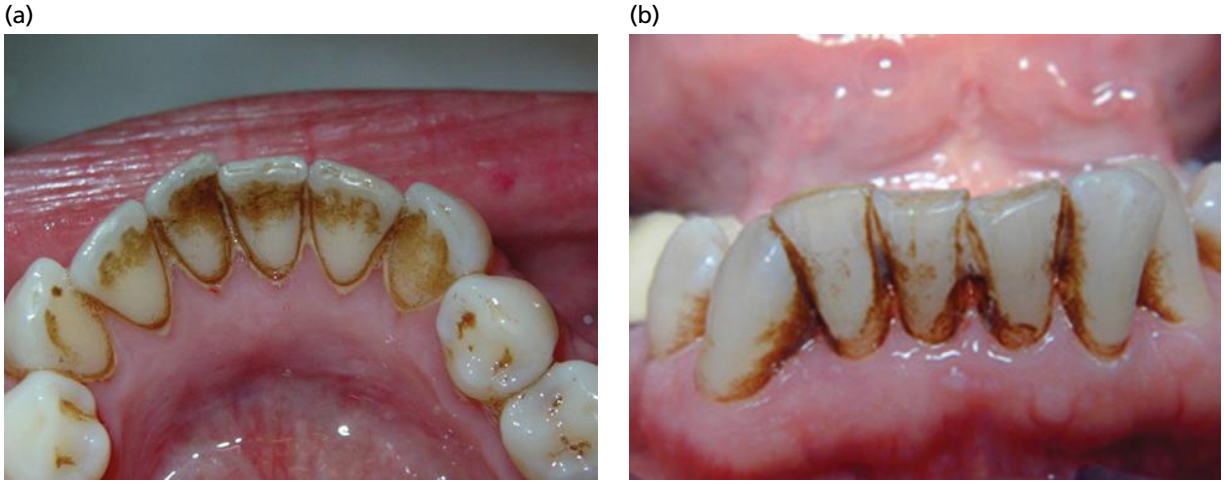

Fig. 37-8 Tooth staining after chlorhexidine use. (a) Lingual aspect; (b) buccal aspect.

- *Usefulness, marketed*. The first CHX formulations in Europe were 0.2% mouth rinses in hydroalcohol vehicle, and the first demonstration of antiseptic activity was in studies of 0.2% products (Löe *et al*. 1976). However, the CHX formulation that obtained the ADA seal was Peridex® (Zila Pharmaceuticals, Phoenix, AZ, USA), which was formulated at 0.12%. Since then, many CHX formulations have been marketed. However, it has been demonstrated that the mere presence of CHX in a product does not assure clinical activity (Harper *et al*. 1995; Herrera *et al*. 2003). Therefore, study models and/or clinical trials are needed to confirm that the activity of a new formulation is similar to that of the reference products. In addition, concerns for adverse effects and the presence of alcohol in mouth rinses, have led to new formulations without alcohol, with lower CHX concentration, and/or combined with other active agents.

Quaternary ammonium compounds

Benzylconium chloride and cetylpyridinium chloride (CPC) (Fig. 37-9).

- *Characteristics*. Monocationic agents that rapidly adsorb to oral surfaces (Bonesvoll & Gjermo 1978). Substantivity approaches 3–5 hours (Roberts & Addy 1981), due to rapid desorption, loss of activity, less retention or neutralization (Bonesvoll & Gjermo 1978). The mechanism of action relies on the hydrophilic part of the CPC molecule interacting with the bacterial cell membrane, leading to the loss of cell components, disruption of cell metabolism, inhibition of cell growth, and finally cell death (Merianos 1991; Smith *et al*. 1991). However, the positive charge of this active hydrophilic part means that it may be inactivated by other products in the formulation, making it crucial that a CPC formulation is evaluated for bioavailability.
- *Evaluation*: Three 6-month trials have been published, one with a 0.05% formulation (Allen *et al*. 1998) and two with 0.07% formulations (Mankodi *et al*. 2005b; Stookey *et al*. 2005). With the addition of four unpublished studies, a meta-analysis demonstrated significant benefits in terms of plaque index (seven studies, two published; P <0.001) and gingivitis index (five studies, two published; P = 0.003), although the studies were highly heterogeneous, and they evaluated different formulations (Gunsolley 2006). In another systematic review, the meta-analysis of the three 6-months studies revealed a WMD of 0.42 (P <0.00001; heterogeneity P = 0.06) for the Quigley & Hein plaque index at the final visit (Haps *et al*. 2008).
- *Limitations*. Safety of CPC formulations, marketed since 1940, has been demonstrated for concentrations of 0.045–0.1% (Nelson & Lyster 1946; Margarone *et al*. 1984; Lin *et al*. 1991; Segreto 2004; Stookey 2004; Federal Register 2004, unpublished studies C.1 and C.2). Adverse effects are less frequent than with CHX formulations, and include tooth and tongue staining, transient gingival irritation, and aphthous ulcers in some individuals (Lobene *et al*. 1979). In addition, no significant changes in the oral microbiota or overgrowth of opportunistic species have been observed (Ciancio *et al*. 1975).
- *Usefulness, marketed*. With 0.05% CPC (Cepacol Combe, White Plains, NY, USA), 0.045% CPC (Scope, Procter & Gamble), and 0.07% CPC (Crest ProHealth, Procter & Gamble; Vitis Xtra Forte, Dentaid;...).

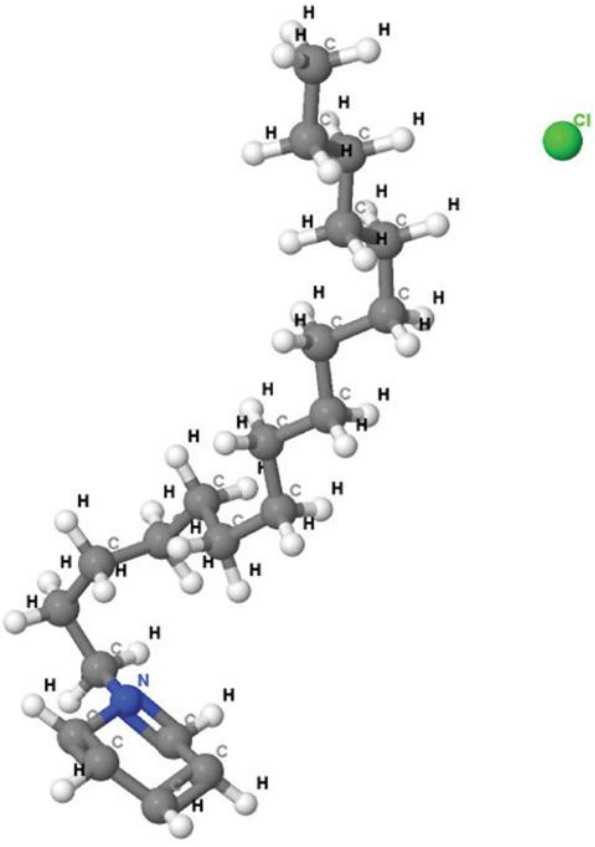

Fig. 37-9 Chemical structure of cetylpyridinium chloride (prepared with Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/).

Hexetidine

Hexetidine is a pyrimidine derivative.

- *Characteristics*: Shows antimicrobial properties against Gram-positive and Gram-negative bacteria and yeast (*Candida albicans*) (Menghini & Sapelli 1980; Jones *et al*. 1997). However, oral retention seems to be limited and antimicrobial activity may not last >90 minutes (McCoy *et al*. 2000).
- *Evaluation*. *In vitro* results suggest some bactericidal activity, even in biofilm models (Shapiro *et al*. 2002), but with a wide variability. In a systematic review (Afennich *et al*. 2011), six randomized controlled trials were identified, but the longest follow-up was 6 weeks. The results demonstrated heterogeneity and therefore, *in vivo* results have not demonstrated plaque inhibitory or antiplaque activity for hexetidine products.

- *Limitations*. Tooth staining, mucosal erosion, and parotid gland swelling, but with low frequency (Addy & Moran 1984; Yusof 1990; van der Weijden *et al*. 2010).
- *Usefulness, marketed*. Normally formulated at 0.1%, with many different brand names (Bactidol, Hexalen, Hexoral, Hextril, Oraldene, Oraldine, and Oraseptic).

Povidone iodine

Iodine is a recognized antibacterial agent, which is combined with the synthetic polymer povidone.

- *Characteristics*. At 1% it has demonstrated substantivity of only 1 hour.
- *Evaluation*. Limited substantivity leads to a very limited plaque inhibitory action (Addy *et al*. 1977; Addy & Wrigth 1978). It has been evaluated combined with 1.5% hydrogen peroxide (5% povidone iodine), both short term (Maruniak *et al*. 1992) and for 6 months (Clark *et al*. 1989), combining rinsing and subgingival irrigation, with clear reductions of gingivitis (Greenstein 1999). Povidone iodine has also been used in the treatment of necrotizing gingivitis (Addy & Llewelyn 1978) and as an adjunct to scaling and root planing, and been shown to significantly decrease pocket depth but with only small clinical significance (Sahrmann *et al*. 2010).
- *Limitations*. No relevant side effects, but it may affect thyroid function.
- *Usefulness, marketed*. Betadine (10% povidone iodine; still available), Perimed (1.5% hydrogen peroxide with 5% of povidone iodine; no longer available).

Other evaluated products

- *Acidified sodium chlorite*. Suggested to have similar activity to CHX (Fernandes-Naglik *et al*. 2001), but with the potential to erode enamel (Pontefract *et al*. 2001).
- *Chlorine dioxide*. Frequently used for oral halitosis; its plaque-inhibitory and antiplaque effects have still to be assessed (Paraskevas *et al*. 2008; Shinada *et al*. 2010).
- *Salifluor*. 5n-octanoyl-3′-trifluormethylsalicylanilide was tested in the late 1990s with acceptable results (Furuichi *et al*. 1996; Nabi *et al*. 1996).
- *Polyhexamethylene biguanide hydrochloride*. Evaluated in study models in the early 2000s at concentrations of 0.04-0.2% and demonstrated the capacity to inhibit plaque regrowth (Rosin *et al*. 2002; Welk *et al*. 2005).
- *Herbal products*. Herbal extracts of tea tree oil (*Melaleuca alternifolia*) have shown conflicting results (Arweiler *et al*. 2000). Also, green tea extracts have been formulated in mouth rinses, but there is limited evidence available assessing their activity (Venkateswara *et al*. 2011).

Future approaches

Molecular signaling

Since signaling molecules (such as acyl homoserine lactones) are involved in biofilm architecture and detachment, future treatment approaches may focus on quorum-sensing systems (Donlan & Costerton 2002). In addition, inhibitors of quorum-sensing processes may reduce the virulence of certain pathogens (Rasch *et al*. 2007; Harjai *et al*. 2010).

Inhibition of transcription genes

If the genes that are activated or repressed during initial biofilm formation are identified and selectively targeted, this may inhibit biofilm formation (Donlan & Costerton 2002).

Probiotics

The use of probiotic products (from bacterial species such as *Streptococcus salivarius*, *Lactobacillus reuteri*, *Lactobacillus salivarius*) may have an effect on biofilm composition, either through competition or release of bacteriocins. Some studies have reported a decrease in pathogenic species (Mayanagi *et al*. 2009) and some improvement in the levels of plaque and gingival inflammation with probiotics (Krasse *et al*. 2006; Shimauchi *et al*. 2008; Harini & Anegundi 2010; Teughels *et al*. 2011).

Delivery formats

Different formats are available to deliver agents for chemical plaque control: rinses, gels, dentifrices, chewing gums, aerosols, varnishes, sustained-release devices, lozenges, and irrigators (Addy & Renton-Harper 1996).

Mouth rinses

Mouth rinses are formulated with different ingredients, including colorings, flavorings, preservatives (sodium benzoate), stabilizers, and active agents.

Among the stabilizers, one of the most frequently used is alcohol. However, some controversy exists with regards to the inclusion of alcohol in mouth rinse formulations, due to the suggested association between alcohol and oropharyngeal cancer. However, critical assessment of the literature does not support the statement (Ciancio 1993; Claffey 2003), but alcohol is not recommended in mouth rinses for use by children, former alcoholics, and patients with conditions affecting the oral mucosae (e.g. lichen planus, leukoplakia). Other suggested problems associated with the presence of alcohol in mouth rinses are:

- Systemic toxicity in children: cases arising from swallowing alcohol-containing mouth rinses have infrequently been reported (Eley 1999)
- Intraoral discomfort: which is probably concentration related (Bolanowski *et al*. 1995).

- Softening of composite hardness: this softening effect can be directly related to the percentage of alcohol in the mouth rinse (McKinney & Wu 1985; Penugonda *et al*. 1994).

Most agents for chemical plaque control have been formulated as mouth rinses, since this vehicle has a number of advantages:

- Favorable pharmacokinetics: easier to reach the effective dosage of the active agent
- Can be used independently of the ability of the patient to perform toothbrushing
- Allows access to difficult-to-reach areas; the tonsils can be reached by gargling
- Easy to use and well accepted by patients.

Dentifrices

Dentifrices represent the ideal delivery format, especially from a preventive perspective, since they are used as an adjunct to the most frequently employed oral hygiene measure, toothbrushing. However, a number of disadvantages can be listed:

- Formulation of some active agents may be difficult
- Pharmacokinetics are less predictable
- Not possible to perform toothbrushing in certain clinical situations, thus limiting the use of a dentifrice: disabled patients, after oral surgery, intermaxillary fixations ...
- Do not reach difficult-to-access areas, such as the tonsils or the dorsum of the tongue.

The different ingredients in a dentifrice formulation are:

- *Abrasives*. These determine the consistency of the dentifrice and ease dental plaque and stain removal. However, higher dentifrice abrasivity does not seem to contribute to increased plaque removal with a manual toothbrush. It appears that the mechanical action of the toothbrush is the main factor in the plaque-removing process (Paraskevas *et al*. 2006). The most common abrasives are calcium carbonate, alumina, dicalcium phosphate, and silica.
- *Detergents*. The most widely used is SLS, which provides some antimicrobial action (Jenkins *et al*. 1991a, b), although no evidence is available to support its effectiveness in plaque removal.
- *Thickeners*. These include silica and gums, and they influence the viscosity of the toothpaste.
- *Sweeteners*, such as sodium saccharin.
- *Humectants*. These prevent the toothpaste from drying up; glycerine and sorbitol are the most commonly used.
- *Flavorings*, such as mint and strawberry.
- *Coloring agents*.
- *Active agents*, including fluorides, triclosan, CHX (with some difficulties in the formulation, due to its interference with anionic detergents and with flavorings), CPC, and other active agents (anticalculus agents, whitening products, desensitizing agents).

Gels

Gels do not include abrasives or detergents. Active agents are formulated more easily in gels than in dentifrices, but other disadvantages are similar: less predictable pharmacokinetics, impossible to use in certain clinical situations, and lack of access to some difficult-to-reach areas.

CHX gels are available in different concentrations, including 0.1%, 0.12%, 0.2%, 0.5%, and 1%, to be used with toothbrushing or applied in trays. For toothbrushing, the amount of CHX delivered is not predictable (Saxén *et al*. 1976). Reduction in the levels of plaque and inflammation has been reported with gel application in a dental tray (Francis *et al*. 1987b; Pannuti *et al*. 2003; Slot *et al*. 2010), although the acceptance by disabled patients and therapy providers was not high (Francis *et al*. 1987a).

CHX gel may also be used for other purposes, such as the prevention of alveolitis after tooth extraction (Hita-Iglesias *et al*. 2008; Minguez-Serra *et al*. 2009). Its use has also been suggested as part of the protocol for full-mouth disinfection, including 1% CHX gel for tongue brushing for 1 minute and subgingival irrigation of pockets (Bollen *et al*. 1996, 1998). More recently, it has been evaluated in peri-implant mucositis therapy (Heitz-Mayfield *et al*. 2011), with limited effects.

Gels containing 0.4% stannous fluoride have also been evaluated, with reported reductions in gingival inflammation and bleeding on probing (Tinanoff *et al*. 1989; Boyd & Chun 1994).

Chewing gums

CHX has been formulated in chewing gums for use as an adjunct to or even short-term replacement of mechanical plaque control. A reduction in the levels of plaque and gingival inflammation has been reported with chewing gum use (Ainamo & Etemadzadeh 1987; Smith *et al*. 1996; Simons *et al*. 2001; Kolahi *et al*. 2008).

Varnishes

CHX varnishes have been used in the prevention of root caries (Clavero *et al.* 2006; Baca *et al*. 2009), although no solid evidence is available to support their use (Bader *et al*. 2001; Zhang *et al*. 2006).

Lozenges

Both CPC and CHX have been formulated as lozenges. For CPC lozenges, interactions with other ingredients of the formulation have been observed (Richards *et al*. 1996). Clinical use is associated with a reduction in levels of plaque and gingival inflammation, although these reductions are smaller than those achieved with a CHX mouth rinse (Vandekerckhove *et al*. 1995). Reductions in plaque and gingivitis levels have also been reported for CHX lozenges. Mean plaque score was reduced by 62.8% (from 2.38 to 0.89; $P < 0.0001$), after 1 week of usage (Kaufman *et al*. 1989).

Irrigators

The use of irrigators has been suggested to remove food debris from teeth and dental restorations. They may help to improve oral health in subjects not using interdental devices (Frascella *et al*. 2000). The use of irrigators is not associated with an improvement in plaque levels, but it may have some effect on gingival inflammation (Husseini *et al*. 2008). Different agents can be used with irrigators and good results have been reported for CHX (Lang & Räber 1981).

Sprays

The advantage of aerosols is that the agent can be applied exactly where it is needed. However, the dosage is not predictable. Aerosols with 0.2% CHX have been used in disabled patients to prevent biofilm formation (Francis *et al*. 1987b; Kalaga *et al*. 1989b). Their use on all dental surfaces is associated with a reduction in plaque level similar to that obtained with mouth rinsing, but the adverse effects are also the same (Francis *et al*. 1987b; Kalaga *et al*. 1989a).

Sustained-release devices

CHX is also formulated in sustained-release devices designed with a therapeutic purpose: chips, gels, and xanthan gels (see Chapter 43 for a review of their effects).

Clinical indications for chemical plaque control: Selection of agents

As it has been reviewed, different agents (alone or in combination) in different delivery format and formulations are available for clinical use. In addition, many different indications for their use have been proposed. Therefore, it may be challenging for the clinician to decide whether or not to prescribe a chemical oral hygiene product, and if one is to be prescribed, which one, as well as which formulation, in which delivery format, at which dosage, and for how long. In this section, some guidelines are provided, based on the scientific evidence available. However, due to the limitations of the evidence, all suggestions should be viewed with caution and each clinical case should be considered individually.

Different clinical situations, depending on the duration of product usage and the main objective of the intervention, are considered: single use, short-term use (either with a preventive or a therapeutic aim), and long-term use (either with a preventive or a therapeutic aim).

Single use

Different objectives may be considered for a single use.

To decrease of the bacterial load

CHX has been shown to reduce the aerolized bacterial load during different oral interventions (e.g. debridement with sonic or ultrasonic devices), decreasing the risk of cross-contamination in a dental setting (Stirrups 1987; Worrall *et al*. 1987; Logothetis & Martinez-Welles 1995). Also, a single rinsing with essential oils has been shown to affect aerolized bacterial load (Fine *et al*. 1993).

To decrease the risk of bacteremia

Different studies have assessed the effect of CHX usage on the risk of bacteremia associated with dental interventions (scaling, tooth extraction), both by means of rinsing (Jokinen 1978; Rahn *et al*. 1995; Lockhart 1996; Brown *et al*. 1998; Tomas *et al*. 2007) or subgingival irrigation (MacFarlane *et al*. 1984). Other active agents have also been evaluated for this indication: essentials oils (Fine *et al*. 1993; DePaola *et al*. 1996; Fine *et al*. 2010) and povidone iodine, both as mouth rinse (Jokinen 1978) or subgingival irrigation (Rahn *et al*. 1995). However, following evaluation of the available evidence, a recent consensus report concluded that CHX, used as an oral rinse, does not significantly reduce the level of bacteremia following dental procedures (Centre for Clinical Practice at NICE (UK) 2008). In addition, the American Heart Association concluded: "topical antiseptic rinses do not penetrate beyond 3 mm into the periodontal pocket and, therefore, do not reach areas of ulcerated tissue where bacteria most often gain entrance to the circulation. On the basis of these data, it is unlikely that topical antiseptics are effective in significantly reducing the frequency, magnitude and duration of bacteremia associated with a dental procedure" (Wilson *et al*. 2007).

To decrease the risk of infection of the surgical area

CHX has been evaluated as a preoperative measure before oral surgery, to decrease bacterial load and the risk of postoperative infection (Worrall *et al*. 1987).

Summary: The general aim of single use is to reduce the bacterial load in the oral cavity before an intervention. The highest bactericidal action is desirable and is demonstrated by CHX formulations both *in vitro* and *in vivo*. Due to the single use, side effects are not common and if present, they rapidly disappear. In case of intolerance, other active agents may be considered, such as CPC (Pitten & Kramer 2001), essentials oils (Fine *et al*. 1993; DePaola *et al*. 1996; Fine *et al*. 2010) or povidone iodine (Jokinen 1978; Rahn *et al*. 1995).

Short-term use for the prevention of dental biofilm formation

In clinical situations in which mechanical control may be limited due to discomfort or postoperative instructions to avoid mechanical contact with a treated area (e.g. following regenerative or mucogingival surgery), use of chemical plaque control may have a preventive objective on a short-term basis. The

most widely used agent for preventive indications (aiming to compensate for the limitations of mechanical biofilm control) is CHX, since side effects will be limited due to the short-term usage.

After scaling and root planing or periodontal surgery

Both CHX (Sanz *et al*. 1989; Christie *et al*. 1998; Eley 1999) and essential oil mouth rinses (Zambon *et al*. 1989; Laspisa *et al*. 1994) have demonstrated benefits. Use of the antiseptic products should be maintained until mechanical biofilm control is again adequate.

Prevention of postsurgical infection

When CHX rinses were used during postsurgical care, a lower infection rate (17 infections in 900 procedures, 1.89%) was observed, compared to that following procedures with no CHX as part of the postsurgical care (five infections in 153 procedures, 3.27%) (Powell *et al*. 2005). In addition, a lower incidence of postextraction alveolitis has been reported with the use of a 0.2% CHX gel (Hita-Iglesias *et al.* 2008; Minguez-Serra *et al*. 2009) or a 0.2% CHX rinse (Tjernberg 1979).

Patients with intermaxillary fixations

After bone fractures or after orthognatic or cosmetic maxillary surgeries when no mechanical hygiene is possible, CHX mouth rinses have been shown to be useful in biofilm formation prevention (Nash & Addy 1979).

Patients with mucosal or gingival acute infections

In these patients, pain precludes mechanical hygiene and CHX mouth rinses may be useful in biofilm formation prevention (Eley 1999).

Short-term use for therapy

Other clinical situations may require the short-term use of antiseptic products with a therapeutic aim. The most widely used agent for therapeutic indications (aiming to control the pathogenic microorganisms) is CHX, since the risk of side effects will be limited due to the short-term usage. Also, any side effects are easily reversible.

Necrotizing gingivitis therapy

Chemical agents alone may have limited antimicrobial activity against an organized biofilm because of the difficulties of penetration. Therefore, chemical agents should be used in conjunction with mechanical debridement. The recommended agent is a CHX mouth rinse (Hartnett & Shiloah 1991). Other agents have been evaluated in necrotizing gingivitis, such as oxygenating agents and iodine povidone (Wade *et al*. 1966; Addy & Llewelyn 1978).

Candidiasis therapy

Use of CHX mouth rinses has been proposed in candidiasis treatment (Ellepola & Samaranayake 2001; Torres *et al*. 2007). However, as sole therapy, complete resolution is not achieved, and they are more effective in combination with specific antifungal agents (e.g. itrakonaxole) (Simonetti *et al*. 1988). However, a possible interaction between CHX and nistatine in combined use has been proposed, due to the formation of a less soluble salt (Barkvoll & Attramadal 1989). As part of candidiasis therapy, the immersion of dental prosthesis in 0.2% CHX is effective in eliminating *Candida* spp. from the prosthesis (Olsen 1975; Uludamar *et al*. 2011). In cases of intolerance to CHX, CPC mouth rinses have been proposed as an alternative (Pitten & Kramer 2001).

Peri-implant mucositis therapy

Treatment strategies have been developed based on mechanical or chemical plaque control, alone or in combination, and some of these have been evaluated in randomized controlled trials. No additive effect (over mechanical control) from the application of a CHX gel was observed (Thone-Muhling *et al.* 2010; Heitz-Mayfield *et al*. 2011), as was also true for irrigation of the sulcus (Porras *et al*. 2002). In one study, CHX irrigation provided better results than CHX rinsing (Felo *et al*. 1997). In home-use studies, an essential oil mouth rinse (Ciancio *et al*. 1995) and a triclosan/co-polymer dentifrice (Ramberg *et al*. 2009) demonstrated better clinical results than the control.

Peri-implantitis therapy

Adjunctive CHX application in the treatment of periimplantitis lesions has been shown to have only limited effects on clinical and microbiologic parameters (Renvert *et al.* 2008).

Periodontitis therapy

The adjunctive use of antiseptics (especially CHX mouth rinses) has been evaluated, most frequently in a full-mouth disinfection approach (Quirynen *et al*. 1995, 2000; Greenstein 2002, 2004). Use of different CHX formulations (including mouth rinse, spray, irrigators, gel for the tongue dorsum) in addition to debridement within 24 hours showed additional clinical benefits in some studies (Quirynen *et al*. 2000). However, systematic reviews have not confirmed these results, although modest benefits favoring full-mouth approaches were observed (Eberhard *et al*. 2008a, b; Lang *et al*. 2008). The use of CHX mouth rinses during basic periodontal therapy may help in

controlling the dental biofilm, resulting in additional benefits in terms of clinical and microbiologic parameters (Faveri *et al*. 2006; Feres *et al*. 2009).

Long-term use for the prevention of dental biofilm formation

Patients carrying fixed or removable orthodontic appliances

The presence of these appliances makes mechanical control more difficult, facilitates plaque retention, and thus promotes gingivitis development (Ristic *et al*. 2007; Levin *et al*. 2008). Additionally, many orthodontic patients, especially children and adolescents, fail to floss because they find this procedure time-consuming and tedious in the presence of orthodontic arch wires (Alexander 1993). A common strategy to improve mechanical plaque removal in these patients is the addition, as part of the oral hygiene regimen, of a chemotherapeutic antimicrobial agent (Ainamo 1977). The efficacy of different active ingredients, such as CHX (Brightman *et al*. 1991; Anderson *et al*. 1997; Chin *et al.* 2006; Olympio *et al*. 2006), essential oils (Tufekci *et al*. 2008), amine/stannous fluoride (Ogaard *et al.* 2006) or sanguinarine (Hannah *et al*. 1989), in the form of mouth rinses, toothpastes or gels has been evaluated in clinical studies. Most have reported significant benefits from the adjunctive use of these products, although the magnitude of the reported benefits might not have a clear clinical relevance. In addition, the use of some of the formulations was associated with adverse effects (such as staining with the use of CHX).

Disabled patients

In physically or mentally disabled patients, the use of CHX improves plaque and gingival health (Storhaug 1977). In these patients, a spray (0.2% CHX) is the preferred vehicle (Francis *et al*. 1987a, b; Kalaga *et al*. 1989b; Clavero *et al*. 2003).

Patients with gingival overgrowth or enlargement

In these patients, mechanical control is difficult and a CHX mouth rinse may be helpful (O'Neil & Figures 1982; Saravia *et al*. 1990; Francetti *et al*. 1991).

Periodontitis patients

Together with an adequate professional supportive periodontal therapy program, chemical agents may be recommended to improve biofilm control and to decrease the risk of disease progression. A careful consideration of the risk-to-benefit ratio should be made, since these patients will be in supportive therapy for life. Low-dose CHX mouth rinses have been evaluated and a formulation of 0.05% CHX and 0.05% CPC has been reported to have beneficial effects with limited adverse events (Soers *et al*. 2003; Santos *et al*. 2004; Quirynen *et al*. 2005; Escribano *et al*. 2010). Also, a dentifrice with triclosan and co-polymer, evaluated for 2 years, demonstrated a significant reduction in the detection of deep pockets and sites with clinical attachment loss and bone loss (Rosling *et al*. 1997a, b; Bruhn *et al*. 2002).

Patients with dental implants

The use of different agents (CHX, triclosan, stannous fluoride, essential oils) has been suggested to favor biofilm control and to decrease the risk of peri-implant diseases (Ciancio *et al*. 1995; Di Carlo *et al*. 2008; Sreenivasan *et al*. 2011). In randomized controlled trials, triclosan with co-polymer significantly improved clinical and microbiologic variables, as compared with a fluoride dentifrice, after 6 months (Sreenivasan *et al*. 2011); conversely, no influence on implant survival and clinical variables was observed with the use of 0.12% CHX mouth rinses in a 5-year study (Truhlar *et al*. 2000).

General population

The main aim in the general population is to maintain periodontal health with the presence of a biofilm in equilibrium with the host response. Different agents have demonstrated an antiplaque effect in 6-month trials, including mouth rinses with CHX (Gunsolley 2006), with essential oils (Stoeken *et al*. 2007), with delmopinol (Addy *et al*. 2007), and with CPC (Gunsolley 2006), or with dentifrices with triclosan and co-polymer (Hioe & van der Weijden 2005; Gunsolley 2006), or with stannous fluoride (Gunsolley 2006; Paraskevas & van der Weijden 2006).

The benefit of the daily usage of antiseptic products in a general population is a subject of controversy. However, the results of available studies reflect clinical benefits beyond those obtained with improvement in mechanical oral hygiene due to oral hygiene instructions. As suggested by the systematic review by Gunsolley (2006), reductions in the placebo groups in plaque (15.7 ± 18.7) and gingivitis (18.5 ± 15.6) are associated with the Hawthorne effect and oral hygiene instructions, and should reflect the efficacy of oral hygiene instructions provided in clinical practice. The added benefit of the adjunctive use of CHX or essential oils mouth rinses were evident and significant (for CHX, 40.4 ± 11.5 in plaque reduction and 28.7 ± 6.5 in gingivitis reduction; for essential oils, 27.0 ± 11.0 and 18.2 ± 9.0, respectively).

Long-term use for the prevention of other oral conditions

Predisposed patients, with high risk of suffering oral infections

In patients with blood dyscrasia or who are immunosuppressed, the use of CHX mouth rinses may help to prevent oral or systemic complications, but they may

not be useful once the infection appears (Eley 1999). In patients on mechanical ventilation, reduction of aerobic pathogens in the oropharyngeal tract was observed in patients using a CHX gel (Fourrier *et al*. 2005). Studies with CHX have demonstrated its capacity to prevent oral complications, such as the occurrence of chronic or opportunistic infections, including *Candida* spp., in high-risk patients (irradiated patients, patients on chemotherapy or bone marrow transplant recipients) (Addy & Moran 1997).

Oral mucositis prevention (associated with radiation or chemotherapy in head and neck cancer patients)

CHX rinses have been proposed as part of the treatment to prevent or treat oral mucositis. CHX mouth rinses for the prevention of oral mucositis have been evaluated in numerous randomized controlled trials (Ferretti *et al*. 1990; Spijkervet *et al*. 1990; Epstein *et al*. 1992; Foote *et al*. 1994; Dodd *et al*. 1996; Pitten *et al*. 2003; Lanzos *et al*. 2010, 2011), but the outcomes differed. Seven studies were included in a meta-analysis (Stokman *et al*. 2006) and showed no effect of CHX in the prevention of mucositis in chemotherapy and radiotherapy patients (odds ratio 0.7; 95% CI 0.43–1.12).

Caries prevention

CHX use has been shown to reduce counts of *S. mutans* in at-risk patients (Ullsfoss *et al*. 1994; Quirynen *et al*. 2005). The best vehicle was varnish, followed by gel and mouth rinse (Emilson & Fornell 1976; Emilson 1994). Also, a reduction in caries incidence was reported for CHX in dentifrice with sodium fluoride (Dolles & Gjermo 1980; FDI Commission 2002a), but other studies have reported poorer results for CHX formulations with sodium fluoride as mouth rinses (Shapiro *et al*. 2002; Herrera *et al*. 2003). Essential oil mouth rinses have also been shown to reduce *S. mutans* levels (Fine *et al*. 2000; Agarwal & Nagesh 2011), but no studies on caries incidence are available. Dentifrices with triclosan and co-polymer or a zinc salt have demonstrated superior anticaries activity than fluoride dentifrices (Panagakos *et al*. 2005), even in long-term studies (Mann *et al*. 2001). In high-risk patients, amine and stannous fluoride may also be recommended, based on their proven remineralization and anticaries action (Tinanoff *et al*. 1980; Paraskevas *et al*. 2004).

Candidiasis prevention

CHX has been evaluated with regards to candidiasis prevention in patients with systemic diseases and in patients with dental prosthesis (Ferretti *et al*. 1987, 1988; Toth *et al*. 1990; Barasch *et al*. 2004; Elad *et al*. 2006).

Prevention of recurrent aphthous ulcers

CHX use may reduce the incidence, duration, and severity of ulcers, including in patients with fixed orthodontic appliances (Shaw *et al*. 1984). Triclosan formulations may also decrease the incidence of oral ulcers (Skaare *et al*. 1996).

Halitosis therapy and secondary prevention

Different chemical agents and formulations have been evaluated with respect to two main aims: antibacterial and interference with the volatilization of odoriferous compounds. Among the most evaluated agents, the following may be highlighted: essential oil mouth rinses (Pitts *et al*. 1983; Kozlovsky *et al*. 1996); triclosan with zinc or co-polymer (van Steenberghe 1997; Sharma *et al*. 1999; Niles *et al*. 2003; Hu *et al*. 2005); or CHX, especially if combined with zinc salts and CPC (Roldán *et al*. 2003b; Winkel *et al*. 2003; Roldán *et al*. 2004). In order to be effective, these agents need to be used in conjunction with adequate oral hygiene and tongue scrapping or brushing (Roldán *et al*. 2003a) (see Chapter 36).

Conclusion

The main aim of supragingival biofilm control is to allow for the presence of a biofilm in equilibrium with the host response, in order to maintain a healthy status. Due to the limitations of mechanical biofilm control, chemical control has been extensively evaluated and is widely used.

Although different delivery formats are available to deliver the active agents, two can be highlighted: mouth rinses, due to their favorable pharmacokinetics and ease of use, and dentifrices, due to their concomitant use with toothbrushing, although their pharmacokinetic profiles are less favorable and they are more difficult to formulate.

Most of the agents are antimicrobials, but other mechanisms of action have been proposed and some marketed effective agents are not antimicrobials (e.g. delmopinol). Substantativity is identified as one of their most relevant characteristics associated with their clinical activity.

In the evaluation of the different agents and formulations, 6-month home-use, randomized clinical trials represent the highest level of evidence, especially when their results are pooled in meta-analyses. Based on the available evidence, CHX mouth rinses achieve the highest reductions in plaque levels, with the lowest heterogeneity among studies (Tables 37-1, 37-2). Triclosan with co-polymer in dentifrice has shown the largest reduction in gingival index, but with a high level of heterogeneity.

However, CHX products are not free from adverse effect, especially tooth staining. Therefore, in a clinical situation in which the product is needed for a

Table 37-1 Summary of meta-analyses of 6-month home-use randomized clinical trials: plaque levels.

Active agent (delivery format)	Study	No. of studies in meta-analysis	WMD	*P* value	95% CI	Heterogeneity *P* value/I^2	Heterogeneity Method
Chlorhexidine (mouth rinse)	Gunsolley (2006)	6	1.040	<0.001	NA	Low/<25%[a]	Fixed??
Essential oils (mouth rinse)	Gunsolley (2006)	20	0.852	<0.0001	NA	Positive/>25%[a]	NA
	Stoeken *et al.* (2007)	7	0.83	<0.00001	0.53–1.13	<0.00001/96.1%	Random
Cetylpyridinium chloride (mouth rinse)	Haps *et al.* (2008)	3	0.42	<0.00001	0.53–0.31	0.06/58.8%	Random
Delmopinol (mouth rinse)	Addy *et al.* (2007)	8	0.34	<0.00001	0.29–0.39	Low/<25%[a]	Fixed
Triclosan and co-polymer (dentifrice)	Gunsolley (2006)	17	0.823	<0.0001	NA	High/>75%[a]	Random
	Hioe & van der Weijden (2005)	9	0.48	<0.0001	0.24–0.73	<0.00001/97.2%	Random
	Davies *et al.* (2004)	11	0.48	<0.00001	0.32-0.64	<0.00001/95.7%	Random
Triclosan and zinc citrate (dentifrice)	Hioe & van der Weijden (2005)	6	0.07	<0.00001	0.05–0.10	0.53/0%	Random
	Gunsolley (2006)	?	NA	NA	NA	NA	NA
Stannous fluoride (dentifrice)	Gunsolley (2006)	5	0.168	Significant	NA	Low/<25%[a]	NA
	Paraskevas *et al.* (2006)	4	0.31	0.01	0.07–0.54	<0.0001/91.7%	Random

[a] Estimated.
WMD, weighted mean difference between test and placebo groups; NA, not available; CI, confidence interval.

Table 37-2 Summary of meta-analyses of 6-month home-use randomized clinical trials: gingivitis levels.

Active agent (delivery format)	Study	No. of studies in meta-analysis	WMD	*P* value	95% CI	Heterogeneity *P* value/I^2	Heterogeneity Method
Chlorhexidine (mouth rinse)	Gunsolley 2006	6	0.563	<0.001	NA	0.013	NA
Essential oils (mouth rinse)	Gunsolley (2006)	8	0.306	0.006	NA	<0.001	NA
	Stoeken *et al.* (2007)	8	0.32	<0.00001	0.19–0.46	<0.00001/96.7%	Random
Cetylpyridinium chloride (mouth rinse)	Haps *et al.* (2008)	3[b]	0.15	0.00003	0.07–0.23	0.0001/87%	Random
Delmopinol (mouth rinse)	Addy *et al.* (2007)	8	0.10	<0.00001	0.06–0.14	Low/<25%[a]	Fixed
Triclosan and co-polymer (dentifrice)	Gunsolley (2006)	16	0.858	<0.001	NA	<0.001	Random
	Hioe & van der Weijden (2005)	8	0.24	<0.0001	0.13–0.35	<0.00001/98.3%	Random
	Davies *et al.* (2004)	14	0.26	<0.00001	0.18–0.34	<0.00001/96.5%	NA
Triclosan and zinc citrate (dentifrice)	Hioe & van der Weijden (2005)	4	10.81%[c]	<0.00001	8.93–12.69	0.48/0%	Random
	Gunsolley (2006)	1	NS	NA	NA	NA	NA
Stannous fluoride (dentifrice)	Gunsolley (2006)	6	0.441	<0.001	NA	0.010	NA
	Paraskevas *et al.* (2006)	6	0.15	<0.00001	0.11–0.20	<0.00001/91.1%	Random

[a] Estimated.
[b] One of the studies was not of 6-month duration.
[c] Effect on bleeding.
WMD, weighted mean difference between test and placebo groups, NS, not significant; NA, not available; CI, confidence interval.

prolonged period of time, the risk-to-benefit ratio should be evaluated. In some clinical situations, the benefits will compensate for the adverse effects (staining), such as in disabled patients or those with high systemic risk. In situations in which the benefits do not compensate for the adverse effects, alternatives with lower effect but also with fewer adverse events should be considered.

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Chapter 38

Non-surgical Therapy

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Introduction

Non-surgical therapy involves various means to control the infection causing pathologic lesions in the periodontal tissues. Pocket/root instrumentation (scaling and root planing), combined with effective self-performed supragingival plaque control measures, serves this purpose by altering the subgingival ecology through disruption of the microbial biofilm, reduction of the amount of bacteria, and suppression of the inflammation. A variety of instruments and approaches to treatment may be utilized in non-surgical therapy.

This chapter outlines the various means and methods used in non-surgical periodontal therapy and their respective merits, shortcomings, and clinical efficacy. Addressed also are considerations in relation to the selection of instruments and treatment approach, as well as re-evaluation after initial non-surgical therapy.

Goal of non-surgical pocket/root instrumentation

Periodontitis is strongly associated with the presence of bacterial biofilms and dental calculus on root surfaces. Hence, the ultimate goal of non-surgical pocket/root instrumentation is to render the root free from microbial deposits and calculus. However, several *in vitro* (e.g. Rateitschak-Pluss *et al.* 1992; Breininger *et al.* 2001) and *in vivo* studies (e.g. Waerhaug 1978; Eaton *et al.* 1985; Caffesse *et al.* 1986; Sherman *et al.* 1990; Wylam *et al.* 1993) have shown that complete removal of hard and soft deposits is not a feasible objective of closed pocket/root instrumentation, even with the most meticulous scaling and root planing procedures (SRP). Nevertheless, non-surgically performed SRP is an effective treatment modality for periodontal disease, as demonstrated by the marked reduction in clinical signs and symptoms of the disease following treatment (Cobb 2002; van der Weijden & Timmerman 2002). Taken together, these observations indicate that there may exist an individual threshold level of bacterial load following instrumentation below which the host can cope with the remaining infection, and hence the goal of non-surgical pocket/root debridement is to reach below this threshold level for all pathologic tooth sites. Besides the quantity and quality of the remaining biofilm, host-related and modifiable environmental factors are to be recognized in this respect, for example diabetes, stress, smoking. While it is not feasible by probing the root surface to determine if adequate debridement has been achieved (Sherman *et al.* 1990), clinical signs of resolution of the inflammatory lesion

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(e.g. lack of bleeding on probing, increased tissue resistance to probing or "pocket closure") are indeed useful assessments to indicate sufficient removal of subgingival biofilms and calculus. Nonetheless, from a practical standpoint, if calculus is detected clinically, the site is more likely to display ongoing inflammation (Sherman *et al*. 1990).

Debridement, scaling, and root planing

Kieser (1994) proposed that, in preference to the traditionally practiced combination of scaling and root planing, pocket/root instrumentation should be performed as three separate stages of treatment – *debridement*, *scaling*, and *root planing* – with objectives pursued in an orderly sequence. According to the author, *debridement* is defined as instrumentation for disruption and removal of microbial biofilms, *scaling* instrumentation for removal of mineralized deposits (calculus), and *root planing* instrumentation to remove "contaminated" cementum and dentin in order to restore the biologic compatibility of periodontally diseased root surfaces. Furthermore, it was advocated that the clinical healing obtained following pocket/root debridement should be assessed before any repeated instrumentation efforts, or proceeding to the next stage of instrumentation. Although the intention of the various stages of instrumentation is different, overlap to some degree is of course inevitable.

Since periodontal diseases are infections caused by bacteria residing in subgingival biofilms, the need to lower the microbial load by disruption/removal of subgingival biofilms is indisputable. Calculus does not in itself induce inflammation, but has a deleterious effect because of its ability to provide an ideal surface for microbial colonization (Waerhaug 1952). In fact, it has been demonstrated that epithelial adherence to subgingival calculus can occur following its disinfection with chlorhexidine (CHX) (Listgarten & Ellegaard 1973). Thus, the rationale for the removal of calculus relates to eliminating, as far as possible, surface irregularities harboring pathogenic bacteria.

The rationale for performing root planing was originally based on the concept that bacterial endotoxins penetrate into the cementum (Hatfield & Baumhammers 1971; Aleo *et al*. 1974), and for this reason it was thought necessary to remove not only biofilms and calculus but also underlying cementum. However, evidence gained from experimental studies demonstrated that endotoxins were only loosely adherent to the surface and did not penetrate into the cementum (Hughes & Smales 1986; Moore *et al*. 1986; Hughes *et al*. 1988; Cadosch *et al*. 2003). Furthermore, animal and human studies revealed similar clinical and histologic healing following treatment of infected root surfaces, previously exposed to the periodontal pocket, in conjunction with flap surgery by polishing only with a low-abrasive paste as following extensive SRP, provided supragingival hygiene was meticulous (Nyman *et al*. 1986, 1988). Hence, aggressive tooth substance removal does not seem warranted and pocket/root instrumentation should preferably be carried out with instruments that cause minimal root substance removal, but are effective in disrupting the biofilm and removing calculus.

Instruments used for non-surgical pocket/root debridement

Non-surgical periodontal treatment may be carried out using various types of instruments, for example hand instruments, sonic and ultrasonic instruments, and ablative laser devices.

Hand instruments

The use of hand instruments allows good tactile sensation, but tends to be more time consuming than other methods, and requires correct and frequent instrument sharpening. A hand instrument is composed of three parts: the working part (the blade), the shank, and the handle (Fig. 38-1). The cutting edges of the blade are centered over the long axis of the handle in order to give the instrument proper balance. The blade is made of carbon steel, stainless steel or tungsten carbide. Instruments with titanium, plastic or carbon fiber blades are also available and used for bacterial biofilm and calculus removal on dental implant surfaces. Depending on the design of the blade, hand instruments are categorized as curettes, sickles, hoes or files.

Curettes are instruments used for debridement and scaling, both supra- and sub-gingivally (Fig. 38-2). The working part of the curette is the spoon-shaped

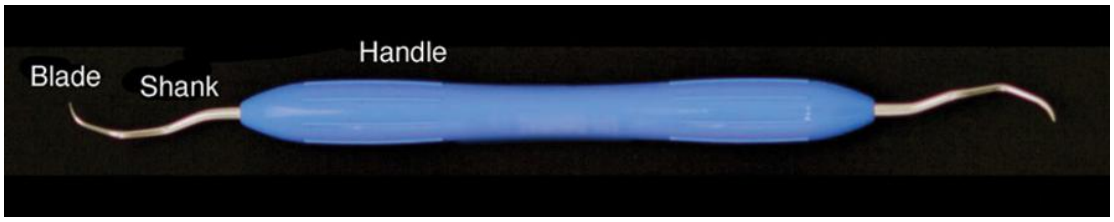


Fig. 38-1 Curette demonstrating the handle, shank, and blade.

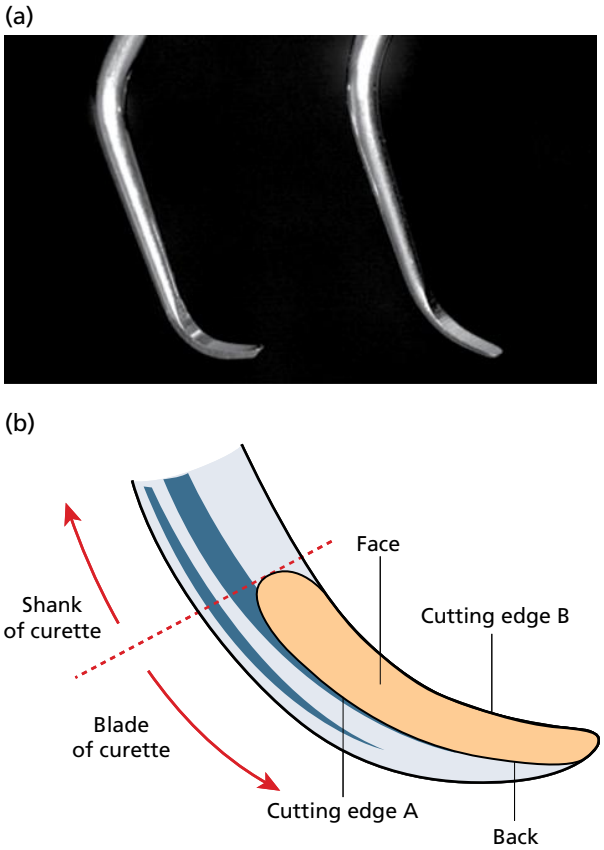


Fig. 38-2 Working end of curettes and schematic illustration of their design with rounded toe, face, and cutting edges.

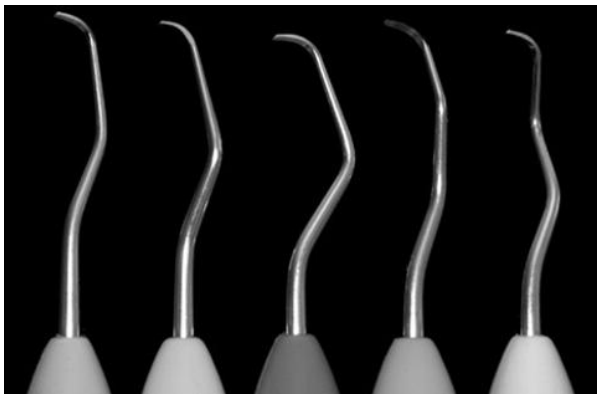


Fig. 38-3 Selection of curettes with varying shank configurations to facilitate debridement of different areas of the dentition.

blade that has two curved cutting edges, united by the rounded toe. The curettes are usually made "double-ended" with mirror-turned blades. The length and angulation of the shank as well as the dimensions of the blade differ between different brands of instruments (Fig. 38-3). Curettes with extended shanks and mini-blades have been designed to improve the efficacy of subgingival instrumentation in deep and narrow pockets.

A *sickle* has either a curved or a straight blade with a triangular cross-section and two cutting edges (Fig. 38-4a). The "facial" surface between the two cutting edges is flat in the lateral direction but may be curved in the direction of its long axis. The "facial" surface converges with the two lateral surfaces of the blade. Sickles are mainly used for debridement/scaling supragingivally or at tooth sites with shallow pockets.

The *hoe* has only one cutting edge. The blade is turned at a 100° angle to the shank with the cutting edge beveled at a 45° angle (Fig. 38-4b). The blade can be positioned at four different inclinations in relation to the shank: facial, lingual, distal, and mesial. The hoe is mainly used for supragingival scaling. Periodontal *files* (Fig. 38-4c) can be useful for smoothing roots in areas of stubborn deposits.

Use of curettes for subgingival debridement/scaling

Subgingival instrumentation should preferably be performed under local anesthesia. The root surface of the diseased site is explored with a probe to identify (1) the probing depth, (2) the anatomy of the root surface (irregularities, root furrows, open furcations, etc.), and (3) the location of the calcified deposits.

The type of hand instrument most suitable for subgingival debridement is the curette. The angulation of the cutting edge of the curette to the tooth surface influences the efficiency of debridement. The optimal angle is approximately 80° (Fig. 38-5a). Too obtuse an angle, as shown in Fig. 38-5b, will result in cratering and consequent roughening of the root surface. Too acute an angle, as shown in Fig. 38-5c, will result in ineffective removal and burnishing of subgingival calculus deposits.

The instrument is held in a modified pen grasp and the blade inserted into the periodontal pocket with the face of the blade parallel to and in light contact with the root. It is important that all root surface instrumentation is performed with a proper finger rest. This implies that one finger – the third or the fourth – must act as a fulcrum for the movement of the blade of the instrument (Fig. 38-6). A proper finger rest serves to (1) provide a stable fulcrum, (2) permit optimal angulation of the blade, and (3) enable the use of wrist–forearm motion. The finger rest must be secured as close as possible to the site of instrumentation to facilitate controlled use of the instrument.

After the base of the periodontal pocket has been identified with the lower edge of the blade, the instrument is turned into a proper working position: that is, the shank is parallel to the long axis of the tooth (Fig. 38-7). The grasp of the instrument is tightened somewhat, the force between the cutting edge and the root surface is increased, and the blade is moved in a coronal direction. Strokes must be made in different directions to cover all aspects of the root surface (cross-wise, back and forth) but, as stated above,

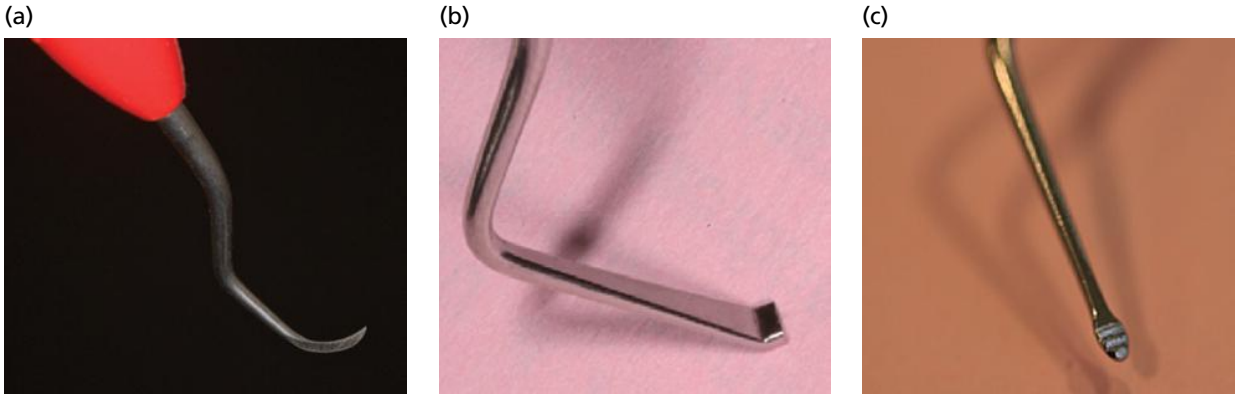


Fig. 38-4 Working end of a (a) sickle, which has a triangular cross-section and two cutting edges, (b) hoe, and (c) file.

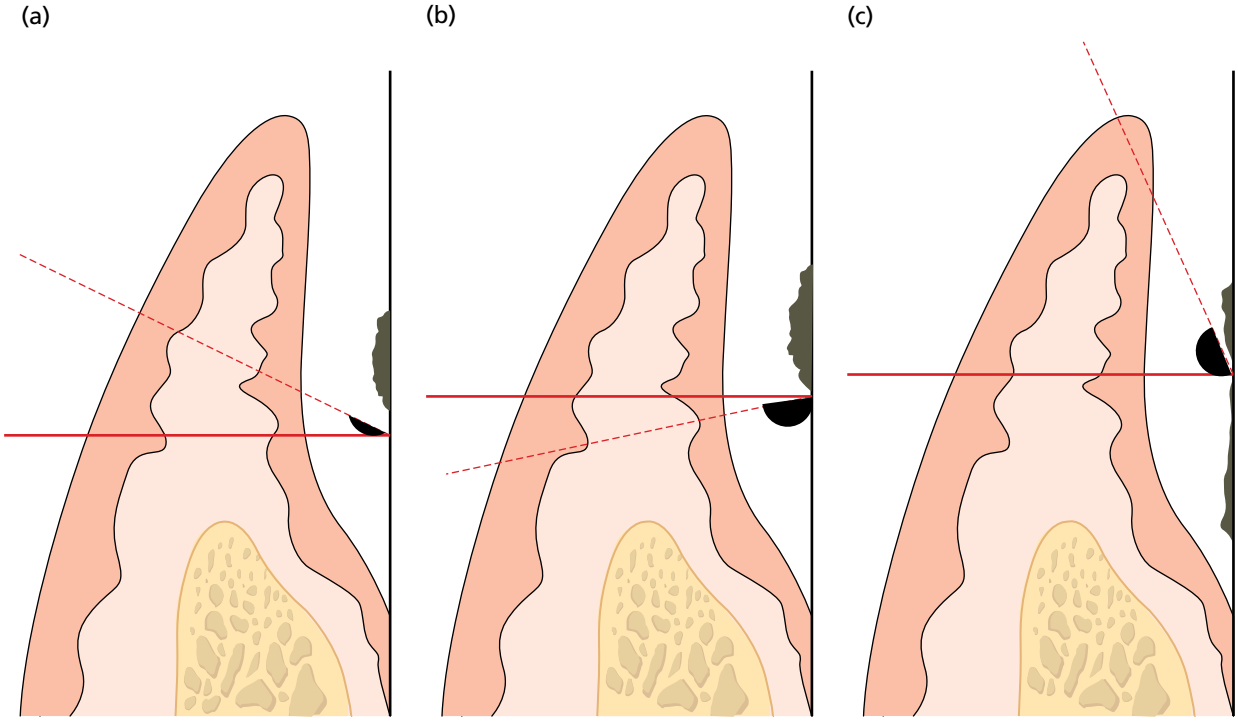


Fig. 38-5 Effect of different angulations of the cutting edge of the curette to the tooth surface. (a) Correct angle of application. (b) Angulation too obtuse resulting in ineffective calculus removal and the possibility of cratering the surface. (c) Angulation too acute resulting in ineffective calculus removal and burnishing of the calculus deposits.

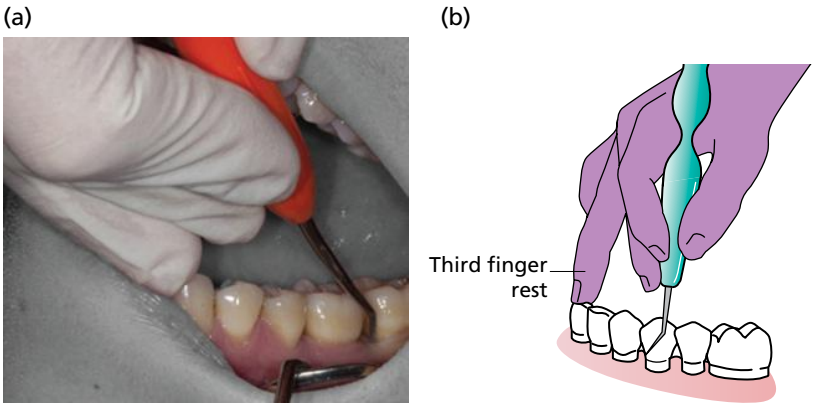


Fig. 38-6 Clinical image and schematic illustration of modified pen grasp and "third finger rest" in the premolar and molar region of the mandible.

strokes should always start from an apical position and be guided in a coronal direction. The probe is inserted into the pocket again and the surface of the root assessed anew for the presence of calculus.

Frequent sharpening of the cutting edge of the instrument is necessary to obtain efficient calculus removal. The angle between the face and the back of curettes must be maintained at approximately 70°

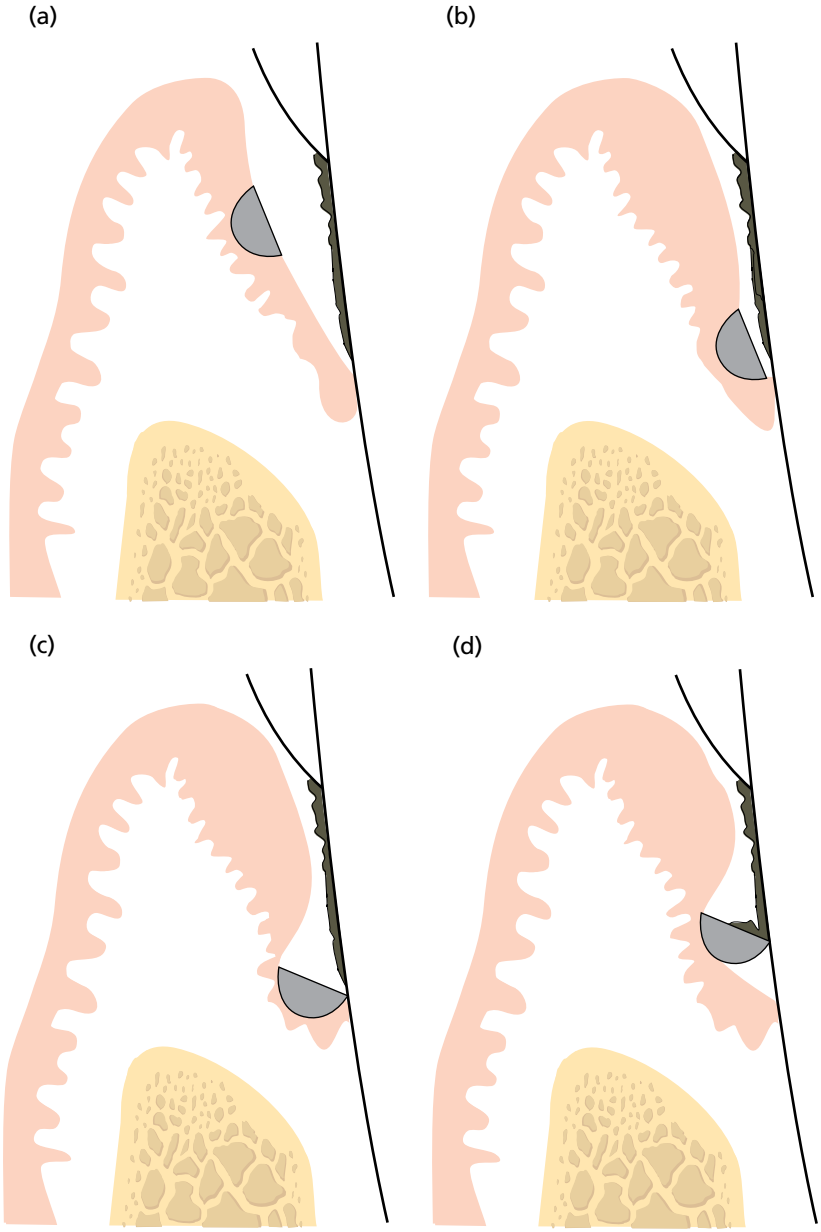


Fig. 38-7 (a) Curette is inserted into the periodontal pocket. Note the near 0° angulation of the face of the curette against the root surface to facilitate access of the pocket. (b) Bottom of the periodontal pocket is identified with the distal edge of the blade of the curette. (c) Curette is turned to a proper cutting position for scaling. (d) Blade is moved along the root surface in a scaling stroke to remove calculus.

during sharpening (Fig. 38-8). A greater angle will result in dulling of the cutting edge. A more acute angle results in a fragile and easily worn cutting edge.

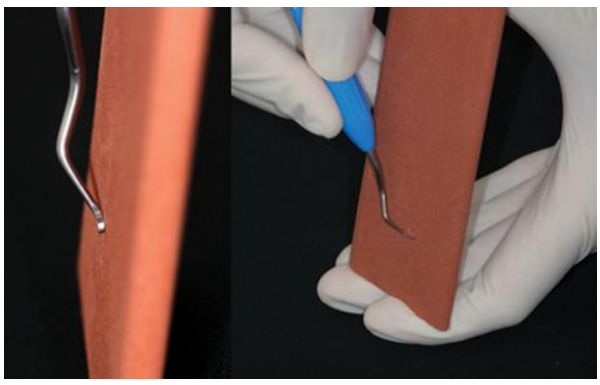


Fig. 38-8 Sharpening of a curette. The original geometry of the cutting edge must be maintained during the sharpening procedure.

Sonic and ultrasonic instruments

A common alternative to hand instrumentation for non-surgical periodontal therapy is the use of sonic and ultrasonic instruments. Sonic devices use air pressure to create mechanical vibration that in turn causes the instrument tip to vibrate; the frequencies of vibration ranging from 2000 to 6000 Hz (Gankerseer & Walmsley 1987; Shah *et al*. 1994). Ultrasonic scalers convert electrical current into mechanical energy in the form of high-frequency vibrations at the instrument

Fig. 38-9 Inserts of different length and curvature for piezoelectric (left) and magnetostrictive (right) ultrasonic devices.

tip; the vibration frequencies ranging from 18 000 to 45 000 Hz and an amplitude range of 10–100 µm.

There are two types of ultrasonic scalers: magnetostrictive and piezoelectric. In *piezoelectric scalers* the alternating electrical current causes a dimensional change in the handpiece that is transmitted to the working tip as vibrations. The pattern of vibration at the tip is primarily linear. In *magnetostrictive scalers* the electrical current produces a magnetic field in the handpiece that causes the insert to expand and contract along its length and in turn causes the insert to vibrate. The pattern of vibration at the tip is elliptical. Modified sonic and ultrasonic scaler tips, for example tiny, thin, periodontal probe type (Fig. 38-9), are available for use in deep pockets. Wear of the ultrasonic tip will affect the working performance of the ultrasonic instrument and therefore the degree of loss of tip dimension should be checked regularly (Fig. 38-10). Water is used as coolant during instrumentation.

Another type of ultrasonic instrument is the Vector system (Sculean *et al*. 2004; Guentsch & Preshaw 2008) which uses a working frequency of 25 000 Hz and a coupling at the head of the handpiece to transfer energy indirectly to the working tip, providing an amplitude of movement of 30–35 µm. These instruments are cooled by a water-based medium containing polishing particles of various sizes dependent on the therapeutic indication. The amount of contaminated aerosol is said to be reduced compared to that produced by other ultrasonic or sonic devices.

Fig. 38-10 Control of wear of the piezoelectric ultrasonic tip. The red line marks the level of wear when the tip should be discarded because of loss of instrument efficacy.

Ablative laser devices

A laser is a device that produces coherent electromagnetic radiation. Laser radiation is characterized by a low divergence of the radiation beam and, with few exceptions, a well-defined wavelength. The term laser is well known as the acronym for "light amplification by stimulated emission of radiation".

Ablative laser therapy has bacteriocidal and detoxification effects, is capable of removing bacterial biofilm and calculus with extremely low mechanical stress and no formation of a smear layer on root surfaces, and can remove the epithelium lining and inflamed tissue within the periodontal pocket (Ishikawa *et al.* 2009). However, with regard to the removal of inflamed tissue, studies have shown that curettage of the soft tissue walls has no added benefit over SRP (Lindhe & Nyman 1985).

Er:YAG lasers are capable of effectively removing calculus from the root surface. To reduce potential damage to the root surface, some Er:YAG laser devices are equipped with a feedback system based on a diode laser that activates the main laser irradiation only if calculus is detected. Er:YAG laser irradiation energy is absorbed by water and organic components of the biologic tissues, which raises the temperature and causes water vapor production, and thus an increase in internal pressure within the calculus deposits. The resulting expansion of the calculus deposits causes their separation from the root surface. Inadvertent irradiation and reflection from shiny metal surfaces may damage a patient's eyes, throat, and oral tissues other than the targeted area. Therefore, care must be taken when using these devices and both patient and operator must use protective eyeglasses (Fig. 38-11). There may also be a risk of excessive tissue destruction from direct ablation and thermal side effects.

Other types of lasers such as carbon dioxide lasers, diode lasers, and Nd:YAG lasers are not effective in removing calculus and hence, their use in periodontal therapy has been primarily as an adjunct therapy to SRP. Carbon dioxide lasers, when used with relatively low energy output in a pulsed and/or defocused mode, have root conditioning, detoxification, and bactericidal effects on contaminated root surfaces. Diode lasers of different wavelength have been introduced as therapy adjunctive to mechanical subgingival debridement to detoxify the root surface or in photodynamic therapy to reduce bacterial load. In photodynamic therapy a photoactive compound such as toluidine blue is placed in the pocket and activated with a laser in order to produce free radical

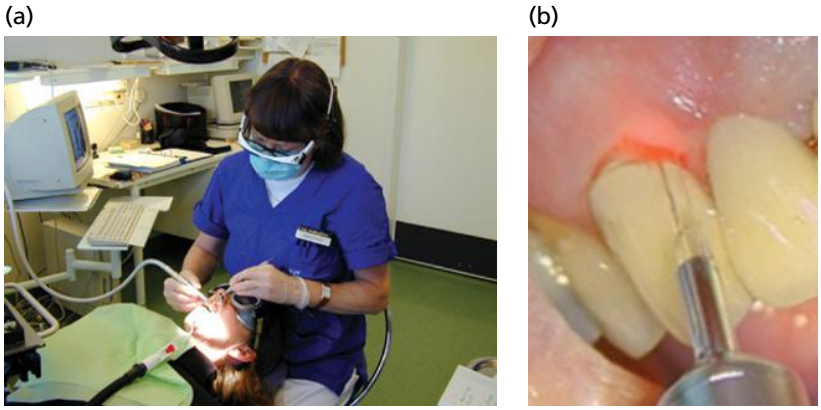


Fig. 38-11 (a) Using laser in periodontal treatment: patient and operator must wear protective eyeglasses. (b) Er:YAG laser tip inserted into the pocket and activated.

ions that have a bactericidal effect (Ishikawa *et al.* 2009). Another potential application for diode lasers is as low-level laser therapy (LLLT), which may stimulate cell proliferation and promote wound healing (Walsh 1997).

Approaches to subgingival debridement

The traditional modality of non-surgical therapy as an initial periodontal treatment phase is pocket/root instrumentation, including root planing, by jaw quadrant or sextant, depending on the extent and severity of the disease, at a series of appointments (Badersten *et al.* 1984). However, various other treatment protocols have also been proposed in the literature as alternatives to this conventional staged approach of SRP for periodontal infection control. In order to prevent re-infection of treated sites from remaining untreated periodontal pockets, Quirynen *et al.* (1995) advocated the benefit of carrying out the pocket/root instrumentation of the entire dentition within a time frame of 24 hours (*full-mouth SRP*). They also considered the risk of re-infection from other intraoral niches such as the tongue and tonsils and therefore also included tongue cleaning and an extensive antimicrobial regimen with CHX (*full-mouth disinfection protocol*). Other proposed treatment protocols that similarly challenge the traditional approach of non-surgical periodontal therapy restrict the number of and the interval between treatment sessions and the time allocated to instrumentation, and may or may not include the adjunctive use of various antimicrobials.

Full-mouth instrumentation protocols

The first full-mouth instrumentation protocol described by Quirynen *et al.* (1995) comprised two sessions of SRP within 24 hours, each covering half of the dentition. However, the total time used for subgingival instrumentation in this approach did not differ from that of the traditional quadrant-wise approach. As already mentioned, the benefit of this treatment protocol was suggested to be a reduced risk of re-infection of treated sites from the otherwise untreated sites, as well as a potential boost to the immunologic response by inoculation of periodontal bacteria into the local vasculature. From the patient's perspective, a tangible benefit of the full-mouth treatment protocol is that fewer appointments, but not necessarily less chair-time for treatment, are required. Apatzidou and Kinane (2004) described a modified protocol in which the SRP of the entire dentition was completed at two sessions on the same day. Another proposed approach consisted of four sessions of SRP on four consecutive days (Eren *et al*. 2002). In all these protocols the time allocated for SRP was 1 hour per jaw quadrant.

Adhering to the concept of differentiation between debridement, scaling, and root planing in non-surgical periodontal therapy (Kieser 1994), modified approaches to the full-mouth instrumentation protocol have been proposed that involve pocket/root debridement by the use of piezoelectric ultrasonic devices in a single-visit, full-mouth procedure, limited to 45–60 minutes to minimize removal of root substance (Wennström *et al*. 2005; Zanatta *et al*. 2006; Del Peloso Ribeiro *et al*. 2008) or without time limit (Koshy *et al*. 2005). Hence, common features of these modified protocols are that the initial subgingival treatment is reduced to one session only and that markedly less time is devoted to instrumentation than that to SRP in the previously described protocols for full-mouth instrumentation.

Full-mouth disinfection protocols

Several intraoral niches, such as the tongue, mucosa, saliva, and tonsils, may act as reservoirs for Gram-negative strains recognized as periodontal pathogens (Beikler *et al*. 2004), and translocation of these bacteria might result in rapid recolonization of a recently instrumented pocket. Hence, as already mentioned, in order to optimize the treatment outcome of the full-mouth SRP approach, Quirynen *et al.* (1995) proposed adjunctive therapy including tongue cleaning and an extensive antimicrobial regimen with CHX (*full-mouth disinfection protocol*). The CHX regimen in conjunction with each treatment session included (1) brushing the dorsum of the tongue for 1 minute with 1% CHX gel, (2) rinsing twice with 0.2% CHX

solution for 1 minute, (3) spraying the tonsils four times with a 0.2% CHX solution, (4) three subgingival irrigations with 1% CHX gel (repeated after 8 days), and (5) instructing the patient to rinse twice daily with a 0.2% CHX solution for 2 weeks. The protocol was later modified by adding the instruction that patients should rinse the mouth and spray the tonsils twice daily with a 0.2% CHX solution for a period of 2 months after the SRP (Mongardini *et al.* 1999).

Other full-mouth instrumentation protocols including adjunctive antimicrobial therapy can be found in the literature, but none is as rigorous as the full-mouth disinfection protocol proposed by the Quirynen group. For example, Koshy *et al.* (2005) included the use of 1% povidone iodine solution as a coolant during the full-mouth ultrasonic debridement session, instruction of patients in careful oral hygiene and brushing of the tongue, as well as mouth rinsing with a 0.05% CHX solution twice daily for 1 month.

Clinical outcomes following various approaches to pocket/root instrumentation

A number of systematic reviews on the efficacy of mechanical non-surgical periodontal therapy have been published (Tunkel *et al*. 2002; van der Weijden & Timmerman 2002; Hallmon & Rees 2003; Suvan 2005; Eberhard *et al.* 2008; Lang *et al.* 2008). There is a consensus among these reviews that pocket/root instrumentation combined with proper supragingival plaque control measures is an effective treatment modality in reducing probing pocket depths (PPDs) and improving clinical attachment levels (CALs) (Figs. 38-12, 38-13), and that there is no major difference in the efficacy of pocket/root instrumentation using hand or power-driven instruments (sonic/ultrasonic). Furthermore, it was deliberated that the data available from published clinical studies are too limited to judge whether the adverse effects of the treatment may vary with the type of instrument used. Table 38-1 shows the mean changes in PPD, CAL, and gingival recession generally observed in clinical studies following an initial treatment phase of *conventional staged quadrant-wise SRP*.

In a Cochrane review (Eberhard *et al.* 2008), a meta-analysis including five studies comparing *full-mouth instrumentation* versus quadrant-wise SRP revealed no statistically significant differences with regard to mean PPD reduction or CAL change. Subgroup analyses of initially moderate (5–6 mm) and deep (>6 mm) pockets at single- and multi-rooted teeth, respectively, disclosed no significant differences for either between the two treatment approaches.

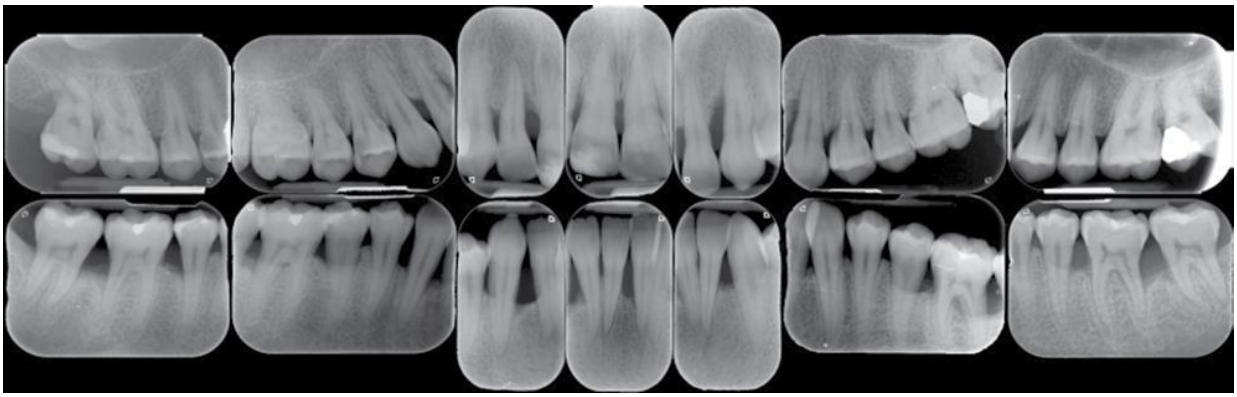
The comparison between *full-mouth disinfection* and quadrant-wise SRP performed in the Cochrane review (Eberhard *et al.* 2008), based on data from three studies, revealed a statistically significant difference in favor of full-mouth disinfection for moderately deep pockets at single-rooted teeth (mean difference 0.53 mm; 95% CI 0.28–0.77), but no difference for deep pockets or for multirooted teeth. With regards to CAL changes for single- and multi-rooted teeth combined (two studies), a significantly greater amount of CAL gain was found for full-mouth disinfection (mean difference 0.33 mm; 95% CI 0.04–0.63), but no significant differences were found in the subgroup analyses. Corresponding analyses in a systematic review by Lang *et al.* (2008) showed outcomes of similar magnitude in favor of the full-mouth disinfection approach. However, none of the systematic reviews found any significant differences for the clinical outcome variables between full-mouth disinfection and full-mouth instrumentation.

Although the analyses performed in the systematic reviews revealed some statistically significant differences favoring the full-mouth disinfection over the quadrant-wise SRP approach, but not in comparison to full-mouth instrumentation, the clinical relevance of the observed improvements with extensive CHX treatment may be questioned.

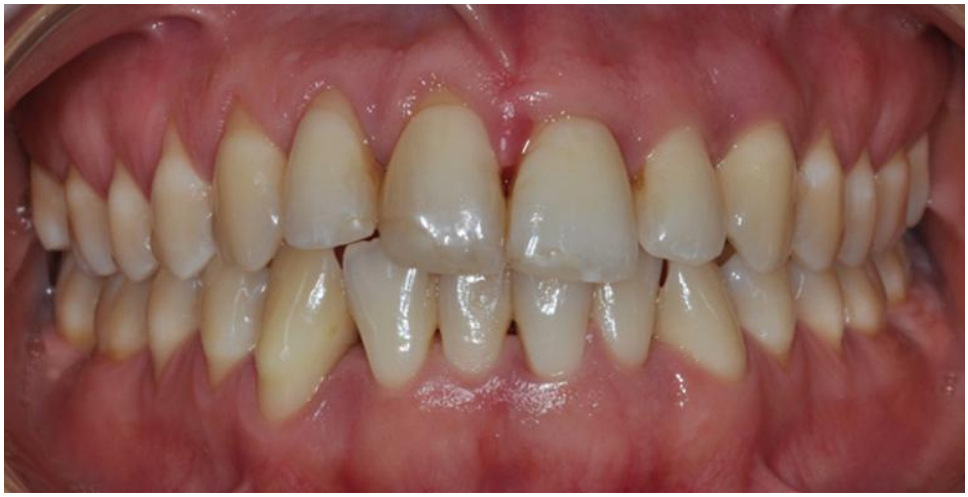
Conclusion: All three non-surgical treatment approaches to periodontal infection control (conventional staged quadrant-wise SRP, full-mouth instrumentation and full-mouth disinfection) result in marked improvements in clinical conditions, and the decision to select one approach over another has to involve also considerations other than just clinical outcomes.

Microbiologic outcomes following various approaches to pocket/root instrumentation

Removal of subgingival plaque and calculus deposits through subgingival debridement in combination with efficient self-performed supragingival infection control alters the ecology of the pockets through reduction in the quantity of microorganisms, resolution of the inflammation, and a decrease in pocket depth, and species that may have flourished in the subgingival environment of the diseased pocket may find the new habitat less hospitable. A decrease in the total bacterial count for sites of >3 mm depth, from 91×10^5 to 23×10^5, has been observed immediately following subgingival debridement (Teles *et al.* 2006). Furthermore, a decrease in the mean counts and number of sites colonized by *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* (Shiloah & Patters 1994), *Tannerella forsythia*, and *Treponema denticola* (Haffajee *et al*. 1997; Darby *et al*. 2005) and an increase in proportion of streptococci (e.g. *Streptococcus gordonni*, *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguinis*) and *Actinomyces* spp., *Eikenella corrodens*, and *Gemella morbillarum* were observed several weeks following subgingival debridement. An increase in the proportions of Gram-positive aerobic cocci and rods is



	Tooth	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
PPD	m						6	7		6		9	6				
	b											6					
	d		7							6						9	
	l		4									6				6	
Furc	m																
	b																
	d		I													I	
	Mobility																



	Tooth	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
PPD	m		6	6			9			6					6	9	
	b															6	
	d		9	9	6		6	6			6			6	10	9	
	l		6	6	6		9							6	6	6	
Furc	b																
	d		II	I													
	Mobility																

Fig. 38-12 Radiographs, clinical image, and probing pocket assessments of a 32-year old female non-smoker with untreated periodontitis, before periodontal therapy.

associated with periodontal health (Cobb 2002). Interestingly, microorganisms do not exist in isolation in the subgingival environment, but rather as members of communities. Socransky *et al*. (1998) identified groups of organisms that were commonly found together and subdivided microorganisms into complexes accordingly. Members of the "red" and "orange" complexes are most commonly identified

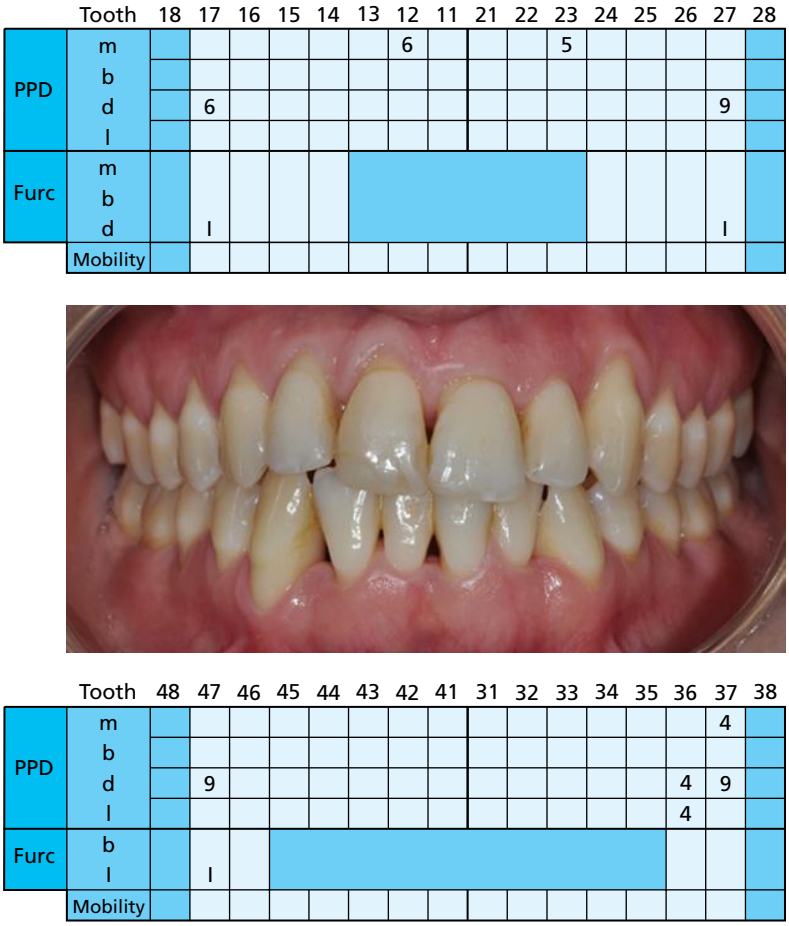


Fig. 38-13 Clinical image and probing pocket assessments of the same patient as in Fig. 39-12, 6 months following initial non-surgical therapy.

Table 38-1 Mean changes (mm) generally observed in studies of bleeding score, probing depth, probing attachment levels, and gingival recession after a single episode of supra- and sub-gingival instrumentation for sites with varying initial probing depths.

	Change (mm)		
Initial probing depth (mm)	**Probing depth**	**Probing attachment level**	**Recession**
≤3	0	–0.5	0.5
4–6	–1–2	0–1	0–1
≥7	–2–3	1–2	1–2

at sites displaying signs of periodontitis. Hence, a re-emergence of species of the red and orange complexes 3–12 months post debridement may indicate lack of resolution of the periodontal lesion (Haffajee *et al*. 2006). It is also important to recognize that in the absence of appropriate home care, the re-establishment of the pretreatment microflora will occur in a matter of weeks (Magnusson *et al*. 1984; Loos *et al*. 1988; Sbordone *et al*. 1990).

In a study comparing the microbiologic outcome of *full-mouth instrumentation* and quadrant-wise SRP (Quirynen *et al.* 2000), it was demonstrated by phase-contrast microscopy and culturing techniques that both treatment approaches reduced the total number of facultative and strict anaerobic species, as well as the number of black-pigmented bacteria, spirochetes, and motile rods in subgingival samples, but also that the reductions were more pronounced following the full-mouth instrumentation. Other studies comparing the microbiologic outcomes following the two treatment approaches using polymerase chain reaction (PCR) techniques (Apatzidou *et al.* 2004; Koshy *et al*. 2005; Jervøe-Storm *et al*. 2007) also reported reductions in presumptive periodontal pathogens, but no detectable differences between the approaches. Hence, these studies failed to support the concept that a full-mouth debridement approach may prevent or delay recolonization of instrumented pockets. Besides the different microbiologic techniques employed in these studies compared to the study by Quirynen *et al.* (2000), the fact that the patients in the former studies showed a high standard of oral hygiene before the initiation of the subgingival instrumentation may explain the contradictory findings. It should be noted that the Quirynen study was primarily designed as a "proof of principle" study, and in order to increase the chance for cross-contamination, interproximal cleaning in the quadrant-wise SRP group was prohibited until the last quadrant had been instrumented.

Studies evaluating microbiologic alterations after *full-mouth ultrasonic instrumentation* with a restricted time protocol (45 minutes of ultrasonic debridement) (Zanatta *et al.* 2006; Del Peloso Ribeiro *et al.* 2008) also showed significant reductions in the frequency and amount of presumptive periodontal pathogens, as evaluated by the use of real-time PCR; reductions were similar to those after conventional quadrant-wise SRP.

More favorable microbiologic changes have been reported following *full-mouth disinfection* as compared to quadrant-wise SRP with respect to decreases in the total amount of motile organisms and spirochetes, total number of facultative or strict anaerobic bacteria, black-pigmented bacteria, as well as frequencies and levels of "red" and "orange" microbial complexes detected using differential phase-contrast microscopy, culturing, and DNA–DNA hybridization technique (Quirynen *et al.* 1999, 2000; De Soete *et al.* 2001). By contrast, Koshy *et al.* (2005) could not detect any added microbiologic benefits as recorded by PCR following their modified full-mouth disinfection approach compared to quadrant-wise instrumentation.

The question of differences in microbiologic outcomes following full-mouth instrumentation, full-mouth disinfection, and conventional staged quadrant-wise SRP has also been addressed in a systematic review (Lang *et al.* 2008). Based on the analysis of seven studies, it was concluded that with the use of modern microbiologic identification methods, no superior reductions in either bacterial load or specific presumptive periodontal pathogens could be identified for any of the three treatment modalities.

Considerations in relation to selection of instruments and treatment approach

Selection of instruments

It has been demonstrated that hand, sonic, and ultrasonic instruments produce similar periodontal healing response with respect to PPD, bleeding on probing, and CAL (Badersten *et al.* 1981, 1984; Lindhe & Nyman 1985; Kalkwarf *et al.* 1989; Loos *et al.* 1987; Copulos *et al.* 1993; Obeid *et al.* 2004; Wennström *et al.* 2005; Christgau *et al.* 2006). With respect to root surface loss, sonic and ultrasonic scalers have been shown to produce less loss than hand instruments (Ritz *et al.* 1991; Busslinger *et al.* 2001; Schmidlin *et al.* 2001; Kawashima *et al.* 2007).

In comparison to hand instrumentation, the use of sonic and ultrasonic instruments may provide better access to deep pockets and furcation areas (Kocher *et al.* 1998; Beuchat *et al.* 2001). In addition, the flushing action of water used as coolant during sonic and ultrasonic instrumentation removes, to a certain extent, debris and bacteria from the pocket area, but the use of antiseptic solutions, for example CHX, iodine and Listerine®, as coolant has shown no greater effects compared to water irrigation (Koshy *et al.* 2005; Del Peloso Ribeiro *et al.* 2006; Leonhardt *et al.* 2006; Del Peloso Ribeiro 2010; Feng *et al.* 2011; Krück *et al.* 2012). However, tactile sensation is reduced, contaminated aerosols are produced (Barnes *et al.* 1998; Harrel *et al.* 1998; Rivera-Hidalgo *et al.* 1999; Timmerman *et al.* 2004), and some patients may find the vibration, sound, and water spray uncomfortable. The use of the Vector ultrasonic system has been shown to result in clinical and microbiologic outcomes comparable to those achieved by manual instrumentation and conventional ultrasonic instruments; however, it may be less efficient in removing large accumulations of calculus (Sculean *et al.* 2004; Christgau *et al.* 2007; Kahl *et al.* 2007; Guentsch & Preshaw 2008).

The use of Er:YAG lasers produces results comparable to those with hand or ultrasonic instrumentation (Schwarz *et al.* 2008; Sgolastra *et al.* 2012). However, no adjunctive benefit of the use of Er:YAG lasers over mechanical debridement alone has been demonstrated (Schwarz *et al.* 2003; Lopes *et al.* 2010; Rotundo *et al.* 2010). The use of other types of lasers has not shown treatment effects comparable to mechanical debridement or any adjunctive effect when used in combination with hand or ultrasonic instrumentation (Ambrosini *et al.* 2005; Schwarz *et al.* 2008; Slot *et al.* 2009). Contradictory findings have been reported with regard to beneficial clinical and microbiologic effects of photodynamic diode laser therapy when used as an adjunct to mechanical debridement (Christodoulides *et al.* 2008; Chondros *et al.* 2009; Lulic *et al.* 2009). There is no evidence of positive healing effects of LLLT when applied following mechanical pocket/root debridement (Lai *et al.* 2009; Makhlouf *et al.* 2012).

Selection of treatment approach

At the VI European Workshop on Periodontology the effects of full-mouth debridement with and without adjunctive use of antiseptics was addressed. Based on evaluation of the systematic reviews by Lang *et al.* (2008) and Eberhard *et al.* (2008), the consensus of the workshop was that *full-mouth debridement* and *full-mouth disinfection* do not provide clinically relevant advantages over the conventional staged quadrant-wise SRP in the treatment of patients with moderate-to-advanced periodontitis (Sanz & Teughels 2008). Furthermore, the clinical recommendations given were that (1) "all three modalities may be recommended for debridement" and (2) "clinicians should choose the modality of debridement according to the needs and preferences of the patient, their personal skills and experience, the logistic setting of the practice and the cost-effectiveness of the therapy rendered. It should be noted that the performance of optimal oral hygiene practices is an inseparable principle to be observed with any protocol of mechanical debridement".

Considering cost-to-benefit issues, it is of interest to note that piezoelectric ultrasonic debridement performed as a single-visit, full-mouth procedure restricted to 45–60 minutes of pocket/root instrumentation has been shown to result in comparable healing outcomes to those of SRP performed in a quadrant-wise manner at weekly intervals (Wennström *et al.* 2005; Zanatta *et al.* 2006; Del Peloso Ribeiro *et al.* 2008). This finding indicates that sufficient removal of subgingival deposits may be attainable using a shorter treatment time than that traditionally allocated to non-surgical pocket/root instrumentation. Calculating the efficiency of the treatment approaches, in this case the time used for instrumentation in relation to the number of pockets reaching the end point of treatment success (PPD ≤4 mm), it was shown that the full-mouth ultrasonic approach was three times more favorable than the quadrant-wise SRP approach (Wennström *et al.* 2005). Hence, tangible benefits of full-mouth ultrasonic debridement as an initial approach to subgingival infection control would be fewer appointments and less chair-time for treatment. Furthermore, available data regarding patients' experience of discomfort/pain related to the treatment do not indicate differences between full-mouth ultrasonic debridement and the quadrant-wise approach. It has to be recognized, however, that it is the quality of the instrumentation, not the time factor, that is the important issue in pocket/root debridement, and that the goal of the instrumentation is to reduce the bacterial load at all tooth sites below the threshold level at which the individual host can cope with the remaining infection. It is important to point out that the studies referred to should not be interpreted to justify a protocol of a defined time for instrumentation in non-surgical periodontal therapy, but merely illustrate that many, but not all, pockets may respond positively to less aggressive instrumentation, which in fact supports the concept proposed by Kieser (1994) that the clinical healing obtained following initial pocket/root debridement should be assessed before more extensive instrumentation efforts, including root planing, are performed.

Re-evaluation following initial non-surgical periodontal treatment

Although recent studies indicate that the conventional quadrant-wise as well as the full-mouth debridement approach, combined with careful instruction in self-performed plaque control methods, are evidence-based and rational initial approaches to the treatment of patients with chronic periodontitis, it is important to be aware that all lesions may not be resolved. Hence, a critical component in the establishment of periodontal infection control is to follow up the initial non-surgical treatment and to perform a re-evaluation examination with regard to sites with remaining clinical signs of pathology.

An increased resistance of the periodontal tissues to probing and absence of bleeding are signs of resolution of the inflammatory lesion related to a sufficient removal of biofilm/calculus. Thus, clinical end points of treatment success may be defined as (1) no bleeding on pocket probing and (2) "pocket closure", that is a probing pocket depth of ≤4 mm. PPD change is a combined result of recession of the gingival margin and decreased probe penetration into the pocket due to resolution of the inflammatory lesion in the bordering soft tissues (Fig. 38-14). Pocket reduction or "pocket closure" as an important outcome variable is validated by data showing that it demonstrates lower risk for disease progression and tooth loss (Westfelt *et al.* 1988; Badersten *et al.* 1990; Claffey & Egelberg 1995; Lang & Tonetti 2003; Matuliene *et al.* 2008). In a retrospective study including 172 subjects followed for a mean of 11 years after active periodontal therapy, Matuliene *et al.* (2008) reported that, compared to a PPD of ≤3 mm, a remaining PPD of 5 mm represented a risk factor for tooth loss with an odds ratio of 7.7. The corresponding odds ratios for a remaining PPD of 6 mm and ≥7 mm were 11.0 and 64.2, respectively. The long-term influence of the variable "bleeding on probing" on tooth loss was addressed in a 26-year longitudinal study of 565 Norwegian males (Schätzle *et al.* 2004), and revealed that teeth that at all examinations were positive for bleeding on probing had a 46 times higher risk of

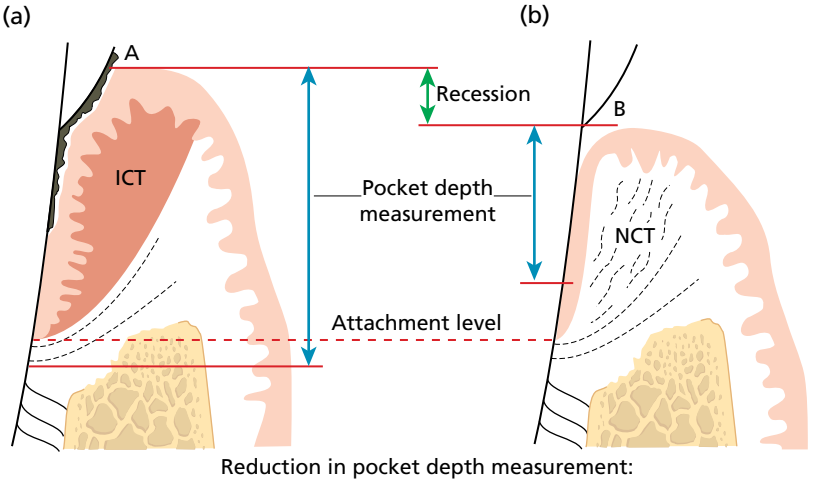


Fig. 38-14 Schematic illustration of a gingival unit (a) before and (b) after periodontal therapy. Probing depth measurements are shown by the blue lines. Dotted line indicates the "histologic" attachment level. Green line shows recession. Location of the gingival margin before therapy (A) and after therapy (B). (ICT, infiltrated connective tissue; NCT, non-infiltrated connective tissue.)

Table 38-2 Predicted probability of pocket closure [probing pocket depth (PPD) ≤4 mm] for sites with different initial PPD.

	Initial PPD		6 mm	7 mm	8 mm
Non-smoker	PL⁻	Single-rooted	84%	63%	36%
		Multi-rooted	70%	43%	19%
	PL⁺	Single-rooted	76%	50%	24%
		Multi-rooted	57%	30%	12%
Smoker	PL⁻	Single-rooted	64%	36%	16%
		Multi-rooted	43%	20%	7%
	Pl⁺	Single-rooted	51%	25%	10%
		Multi-rooted	31%	12%	4%

PL, plaque at site.
Adapted from Tomasi *et al.* (2007), with permission from John Wiley & Sons.

being lost compared to teeth not showing gingival inflammation. Hence, these data justify the use of "pocket closure" and absence of bleeding on probing as clinical end points of treatment success in the re-evaluation following periodontal treatment.

On average about 35% of initially pathologic pockets may not reach the end point of treatment success at re-evaluation following initial non-surgical periodontal therapy, and this percentage is independent of the type of instruments or approach used for subgingival debridement (Wennström *et al.* 2005; Jervøe-Storm *et al.* 2006). Generally, clinical improvement is less pronounced at molars, particularly at furcation sites, than at single-rooted teeth (Lindhe *et al.* 1982; Loos *et al.* 1989). However, there are certainly many other factors related to the patient, the tooth, and the tooth site that might influence the treatment response. The use of multilevel statistical modeling allows the simultaneous investigation of factors at different levels. As an example, in Table 38-2 the probability of "pocket closure" (final probing pocket depth ≤4 mm) following initial non-surgical therapy could be estimated for pockets of various initial PPD, taking into consideration the factors smoking habit, single- or multi-rooted tooth, as well as presence/absence of supragingival plaque at the level of the tooth site (Tomasi *et al.* 2007). The marked difference in probability of pocket closure noted between smokers and non-smokers (e.g. 36% versus 63% for 7-mm deep pockets) places the focus on smoking as a significant factor influencing treatment outcome following non-surgical periodontal therapy. Smoking is proven to negatively affect the outcome of all modalities of periodontal therapy (Labriola *et al.* 2005; Heasman *et al.* 2006) and hence, if the patient is a smoker, inclusion of a smoking cessation program should be considered as an adjunctive measure.

Efficacy of repeated non-surgical pocket/root instrumentation

If the patient fails to maintain an adequate standard of oral hygiene, efforts have to be devoted to improving the patient's motivation. Persisting pathologic pockets, that is with a PPD of ≥5 mm and bleeding on probing, should be subjected to re-instrumentation efforts which now may include also root planing. The patient is then scheduled for a new re-evaluation and a decision regarding potential need for supplementary active treatment options. Whether it will be worthwhile to once again carry out repeated non-surgical instrumentation of a site/tooth that shows poor response to the performed subgingival debridement, or if other treatment modalities (e.g. adjunctive antimicrobial therapy, open-flap debridement, surgical pocket reduction) to achieve the goal of periodontal infection control should be selected, is a delicate decision in which both subject- and site-specific factors, as well as clinical skills and experience, have to be considered. Largely clinical improvements following pocket retreatment by non-surgical SRP are rather limited compared to those following the initial phase of subgingival instrumentation (Badersten *et al.* 1984; Wennström *et al.* 2005). It has been shown that of all sites that respond poorly to initial mechanical debridement, only 11–16% might be brought to a successful treatment end point following mechanical re-instrumentation, and about 50% of the pockets with an initial probing pocket depth of ≥7 mm will remain as non-successful sites (Wennström *et al.* 2005). Another study evaluating the outcome of re-instrumentation of periodontal sites showed that the overall probability of achieving "pocket closure" 3 months after retreatment was about 45%, while for sites with a PPD of >6 mm, the probability was only 12% (Tomasi *et al.* 2008). The fact that pockets associated with molars, furcation sites, and angular bone defects have been shown to respond less favorably to repeated non-surgical instrumentation (e.g. Axtelius *et al.* 1999; D'Aiuto *et al.* 2005; Tomasi *et al.* 2007) should be considered in the decision-making process regarding selection of retreatment procedure and the potential benefit of repeated non-surgical instrumentation.

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Part 12: Additional Therapy

Chapter 39

Periodontal Surgery: Access Therapy

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Introduction

Surgical access therapy must be considered as adjunctive to cause-related therapy (see Chapters 35–38). Therefore, the various surgical methods described in this chapter should be evaluated on the basis of their potential to facilitate removal of subgingival deposits and self-performed infection control, and thereby enhance the long-term preservation of the periodontium.

The decision concerning what type of periodontal surgery should be performed and how many sites should be included is usually made after the effect of initial cause-related measures has been evaluated. The time lapse between termination of the initial cause-related phase of therapy and this evaluation may vary from 1 to several months. This routine has the following advantages:

- Removal of calculus and bacterial plaque will eliminate or markedly reduce the inflammatory cell infiltrate in the gingiva, thereby making assessment of the "true" pocket depths possible.
- Reduction of gingival inflammation makes the soft tissues more fibrous and firmer, which facilitates flap management. The propensity for bleeding is also reduced, making inspection of the surgical field easier.
- The effectiveness of the patient's home care, which is of decisive importance for the long-term prognosis, can be properly evaluated. Lack of effective self-performed infection control is in most cases a contraindication for surgical treatment.

Techniques in periodontal pocket surgery

Over the years, several different surgical techniques have been described and used in periodontal therapy. A superficial review of the literature in this area may give the reader a somewhat confusing picture of the

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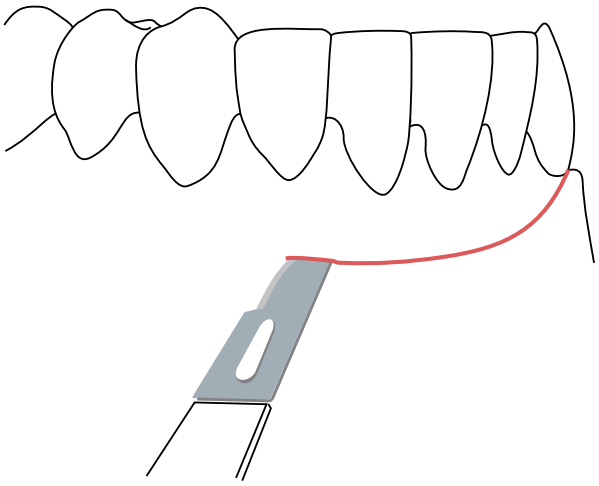

Fig. 39-1 Gingivectomy. Straight incision technique. (Source: Robicsek, 1884, reviewed in 1965 by the American Academy of Periodontology.)

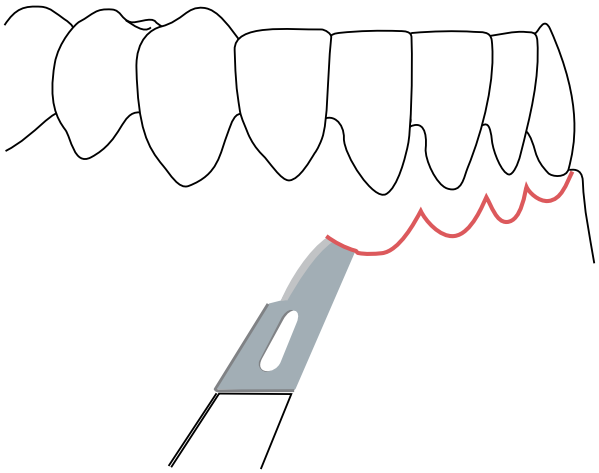

Fig. 39-2 Gingivectomy. Scalloped incision technique. (Source: Zentler 1918. Reproduced with permission of the American Medical Association).

specific objectives and indications relevant to the various surgical techniques. It is a matter of historical interest that the first surgical techniques used in periodontal therapy were described as means of gaining access to diseased root surfaces. Such access could be accomplished without excision of the soft tissue pocket ("open-view operations"). Later, procedures were described by which the "diseased gingiva" was excised (gingivectomy procedures).

The concept that not only inflamed soft tissue but also "infected and necrotic bone" had to be eliminated called for the development of techniques by which the alveolar bone could be exposed and instrumented (flap procedures). Other concepts, such as (1) the importance of maintaining the mucogingival complex (i.e. a wide zone of gingiva) and (2) the possibility for regeneration of periodontal tissues, have also prompted the introduction of "tailor-made" techniques.

This section will describe the surgical procedures which represent important steps in the development of the surgical component of periodontal therapy.

Gingivectomy procedures

The surgical approach as an alternative to "blind" subgingival scaling for pocket therapy was already recognized in the latter part of the 19th century, when Robicsek (1884) pioneered the so-called *gingivectomy* procedure. Gingivectomy was much later defined by Grant *et al*. (1979) as being "the excision of the soft tissue wall of a pathologic periodontal pocket". The procedure, which aimed at "pocket elimination", was usually combined with recontouring of the gingiva to restore its normal architecture.

Robicsek (1884) and later Zentler (1918) described the gingivectomy procedure in the following way. The line to which the gum is to be resected is determined first. Following a straight (Robicsek) (Fig. 39-1) or scalloped (Zentler) (Fig. 39-2) incision, first on the labial and then on the lingual aspect of each tooth, the diseased tissue is loosened and lifted out with a hook-shaped instrument. After elimination of the soft tissue, the exposed alveolar bone is scraped. The area is then covered with some kind of antibacterial gauze or painted with disinfecting solutions. The deepened periodontal pocket is hereby eradicated and a dentition established that can be kept clean more easily.

Technique

The gingivectomy procedure as it is employed today was first described in 1951 by Goldman:

1. When the dentition in the area scheduled for surgery has been properly anesthetized, the depths of the pathologic pockets are identified with a conventional periodontal probe (Fig. 39-3a). At the level of the bottom of the pocket, the gingiva is pierced and a bleeding point is produced on the outer surface of the soft tissue (Fig. 39-3b). The pockets are probed and bleeding points produced at one or more location points around each tooth in the area. The series of bleeding points produced describes the depth of the pockets in the area scheduled for treatment and is used as a guideline for the incision.
2. The primary incision (Fig. 39-4), which may be made with a scalpel (blade No. 12B or 15; Bard–Parker®) in either a Bard–Parker® handle or an angulated handle (e.g. a Blake's handle), or a Kirkland knife No. 15/16, should be planned to give a thin and properly festooned margin of the remaining gingiva. Thus, in areas where the gingiva is bulky, the incision must be placed at a more apical level than in areas with a thin gingiva, where a less accentuated bevel is needed. The beveled incision is directed towards the base of the pocket. In areas where the interdental pockets are deeper than the buccal or lingual pockets, additional amounts of buccal and/or lingual (palatal)

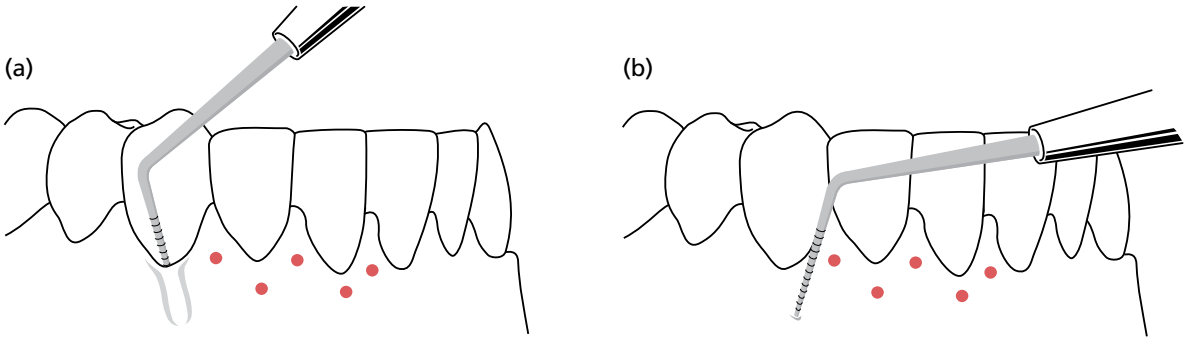

Fig. 39-3 Gingivectomy. Pocket marking. (a) An ordinary periodontal probe is used to identify the bottom of the deepened pocket. (b) When the depth of the pocket has been assessed, an equivalent distance is delineated on the outer aspect of the gingiva. The tip of the probe is then turned horizontally and used to produce a bleeding point at the level of the bottom of the probeable pocket.

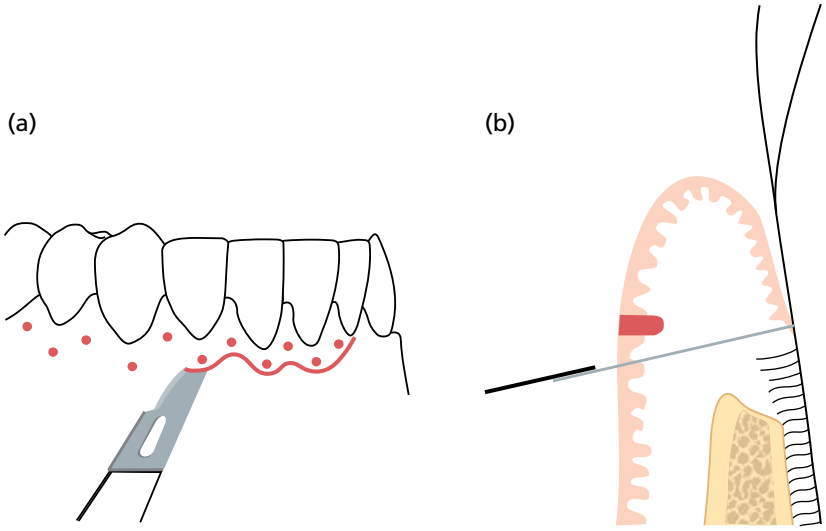

Fig. 39-4 Gingivectomy. (a) Primary incision. (b) The incision is terminated at a level apical to the "bottom" of the pocket and is angulated to give the cut surface a distinct bevel.

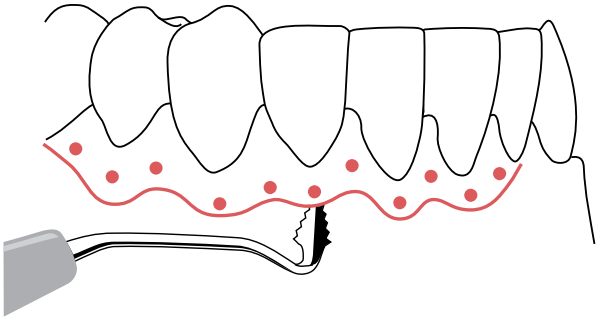

Fig. 39-5 Gingivectomy. The secondary incision through the interdental area is performed with a Waerhaug knife.

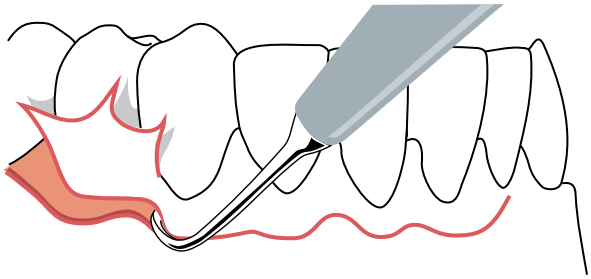

Fig. 39-6 Gingivectomy. The detached gingiva is removed with a scaler.

gingiva must be removed in order to establish a "physiologic" contour of the gingival margin. This is often accomplished by initiating the primary incision at a more apical level.

3. Once the primary incision is completed on the buccal and lingual aspects of the teeth, the interproximal soft tissue is separated from the interdental periodontium by a secondary incision using an Orban knife (No. 1 or 2) or a Waerhaug knife (No. 1 or 2; a saw-toothed modification of the Orban knife) (Fig. 39-5).
4. The incised tissues are carefully removed with a curette or a scaler (Fig. 39-6). Pieces of gauze packs often have to be placed in the interdental areas to control bleeding. When the field of operation is properly prepared, the exposed root surfaces are carefully debrided.
5. Following meticulous debridement, the dentogingival regions are probed again to detect any remaining pockets (Fig. 39-7). The gingival contour is checked and, if necessary, corrected with the use of knives or rotating diamond burs.
6. To protect the incised area during the period of healing, the wound surface must be covered by a periodontal

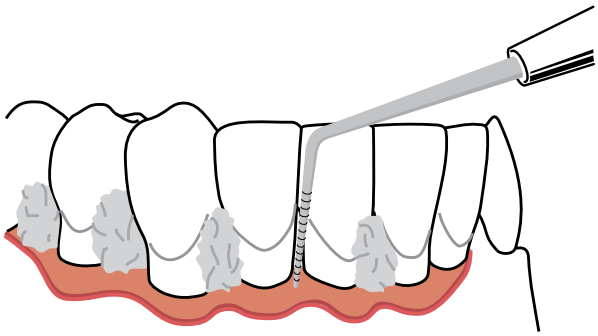

Fig. 39-7 Gingivectomy. Probing for residual pockets. Gauze packs have been placed in the interdental spaces to control bleeding.

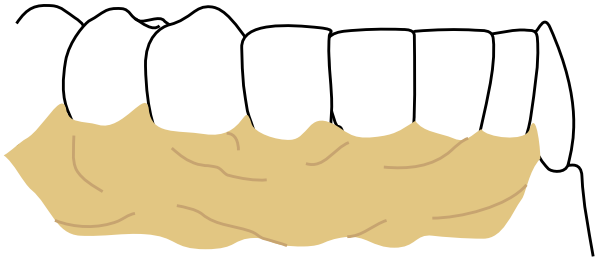

Fig. 39-8 Gingivectomy. The periodontal dressing has been applied and properly secured.

dressing (Fig. 39-8). The dressing should be closely adapted to the buccal and lingual wound surfaces as well as to the interproximal spaces. Care should be taken not to allow the dressing to become too bulky, since this is not only uncomfortable for the patient, but also facilitates its dislodgement.

7. The dressing should remain in position for 10–14 days. After removal of the dressing, the teeth must be cleaned and polished. The root surfaces are carefully checked and remaining calculus removed with a curette. Excessive granulation tissue is eliminated with a curette. The patient is instructed to clean the operated segments of the dentition, which now have a different anatomy compared to the preoperative situation.

Flap procedures

Original Widman flap

In 1918, Leonard Widman published one of the first detailed descriptions of the use of a flap procedure for pocket elimination. In his article "The operative treatment of pyorrhea alveolaris", Widman described a mucoperiosteal flap design that aimed to remove the pocket epithelium and the inflamed connective tissue, thereby facilitating optimal cleaning of the root surfaces.

Technique

1. Sectional releasing incisions are first made to demarcate the area scheduled for surgery (Fig. 39-9). These incisions are made from the mid-buccal gingival margins of the two peripheral teeth of the treatment area and are continued for several millimeters out into the alveolar mucosa. The two releasing incisions are connected by a gingival incision, which follow the outline of the gingival margin and *separate the pocket epithelium and the inflamed connective tissue from the non-inflamed gingiva*. Similar releasing and gingival incisions, if needed, are made on the lingual aspect of the teeth.

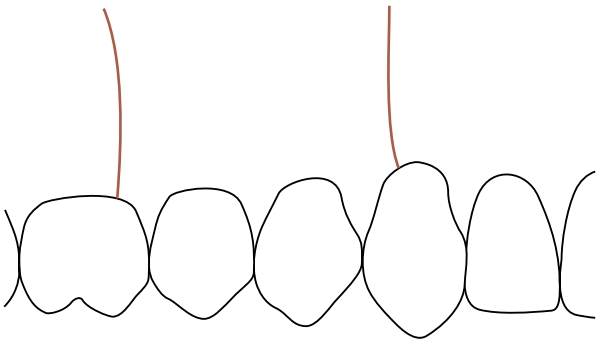

Fig. 39-9 Original Widman flap. Two releasing incisions demarcate the area scheduled for surgical therapy. A scalloped reverse bevel incision is made in the gingival margin to connect the two releasing incisions.

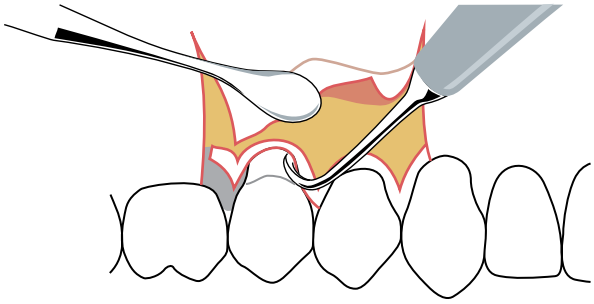

Fig. 39-10 Original Widman flap. The collar of inflamed gingival tissue is removed following the elevation of a mucoperiosteal flap.

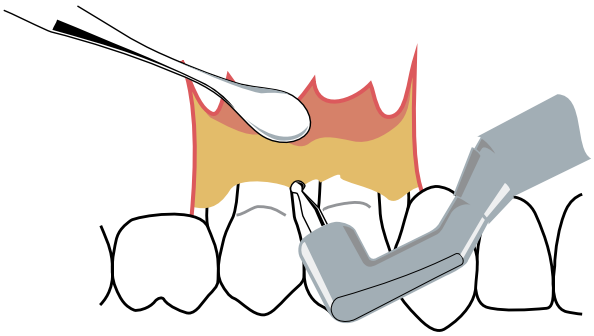

Fig. 39-11 Original Widman flap. By bone recontouring, a "physiologic" contour of the alveolar bone may be re-established.

2. A mucoperiosteal flap is elevated to expose at least 2–3 mm of the marginal alveolar bone. The collar of inflamed tissue around the neck of the teeth is removed with curettes (Fig. 39-10) and the exposed root surfaces are carefully instrumented. Bone recontouring is recommended in order to achieve an ideal anatomic form of the underlying alveolar bone (Fig. 39-11).

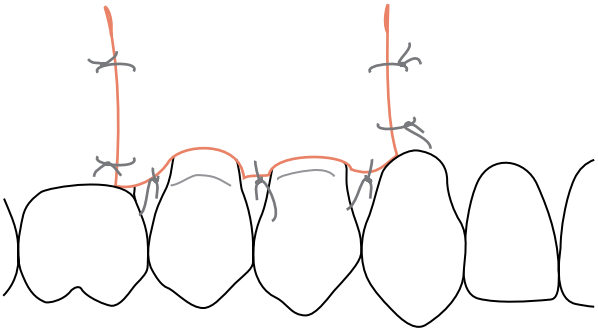

Fig. 39-12 Original Widman flap. The coronal ends of the buccal and lingual flaps are placed at the alveolar bone crest and secured in this position by interdentally placed sutures.

3. Following careful debridement of the teeth in the surgical area, the buccal and lingual flaps are laid back over the alveolar bone and secured in this position with interproximal sutures (Fig. 39-12). Widman pointed out the importance of placing the soft tissue margin at the level of the alveolar bone crest, so that no pockets would remain. Often the interproximal areas are left without soft tissue coverage of the crestal bone.

The main advantages of the "*original Widman flap*" procedure in comparison to the gingivectomy procedure include, according to Widman (1918):

- Less discomfort for the patient, since healing occurred by primary intention
- Possible to re-establish a proper contour of the alveolar bone in sites with angular bony defects.

Neumann flap

Only a few years later, Neumann (1920) suggested the use of a flap procedure, which in some respects was different from that originally described by Widman.

Technique

1. An *intracrevicular incision* is made through the base of the gingival pockets and the entire gingiva (and part of the alveolar mucosa) is elevated in a mucoperiosteal flap. Sectional releasing incisions are made to demarcate the area of surgery.
2. Following flap elevation, the inside of the flap is curetted to remove the pocket epithelium and the granulation tissue. The root surfaces are subsequently carefully debrided. Any irregularities of the alveolar bone crest are corrected.
3. The flaps are then trimmed to allow both an optimal adaptation to the teeth and a proper coverage of the alveolar bone on both the buccal/lingual (palatal) and the interproximal sites. Neumann (1920) pointed out the importance of removing the soft tissue pockets, that is replacing the flap at the crest of the alveolar bone.

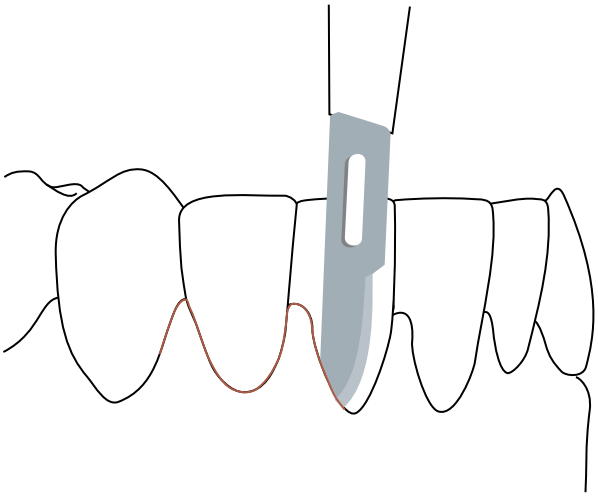

Fig. 39-13 Modified flap operation (the Kirkland flap). Intracrevicular incision.

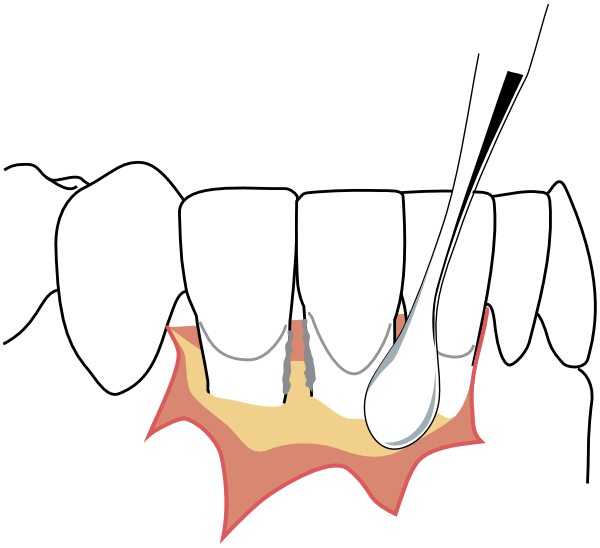

Fig. 39-14 Modified flap operation (the Kirkland flap). The gingiva is retracted to expose the "diseased" root surface.

Modified flap operation

In a publication from 1931, Kirkland described a surgical procedure to be used in the treatment of "periodontal pus pockets". The procedure was called the *modified flap operation*, and is basically an access flap used to allow proper root debridement.

Technique

1. Pocket incisions are made (Fig. 39-13) on both the labial and the lingual aspects of the interdental area. The incisions are extended in a mesial and a distal direction.
2. The gingiva is retracted labially and lingually to expose the diseased root surfaces (Fig. 39-14) which are carefully debrided (Fig. 39-15). Angular bony defects are curetted but no bone is removed.
3. Following the elimination of the pocket epithelium and granulation tissue from the inner surface of the flaps, these are *replaced* at their original position and secured with interproximal sutures (Fig. 39-16).

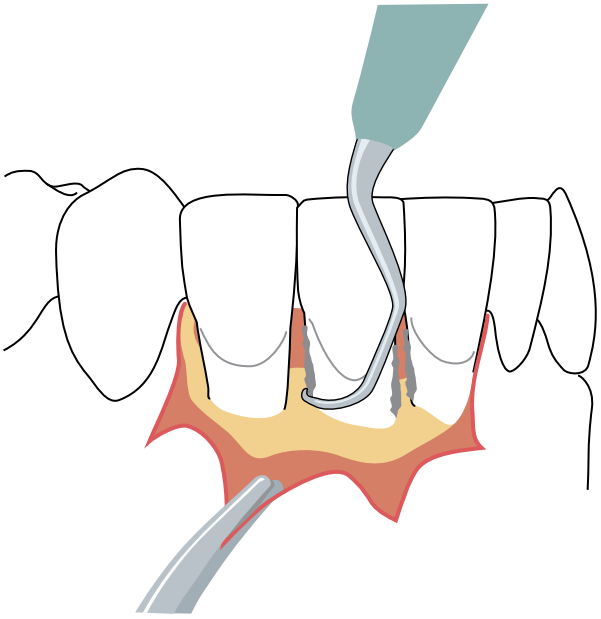

Fig. 39-15 Modified flap operation (the Kirkland flap). The exposed root surfaces are subjected to mechanical debridement.

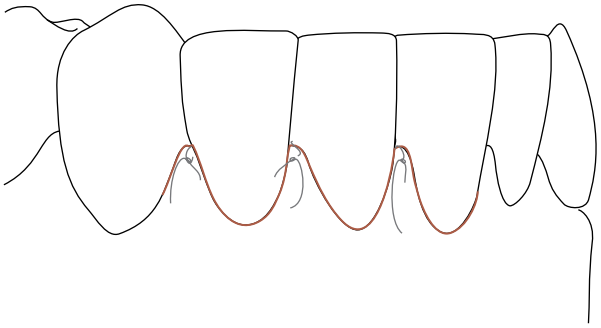

Fig. 39-16 Modified flap operation (the Kirkland flap). The flaps are repositioned at their original position and sutured.

In contrast to the *original Widman flap* as well as the *Neumann flap*, the *modified flap operation* does not include (1) extensive removal of non-inflamed tissues and (2) apical displacement of the gingival margin. The method could be useful in the anterior regions of the dentition for esthetic reasons, since the root surfaces are not markedly exposed. Another advantage of the *modified flap operation* was the potential for bone regeneration in intrabony defects that, according to Kirkland (1931), frequently occurred.

The main objectives of the flap procedures so far described were to:

- Facilitate the debridement of the root surfaces as well as the removal of the pocket epithelium and the inflamed connective tissue
- Eliminate the deepened pockets (the *original Widman flap* and the *Neumann flap*)
- Cause a minimal amount of trauma to the remaining periodontal tissues and a minimum of discomfort to the patient.

Apically repositioned flap

In the 1950s and 1960s new surgical techniques for the removal of soft and, when indicated, hard tissue periodontal pockets were described in the literature. The importance of maintaining *an adequate zone of attached gingiva* after surgery was now emphasized. One of the first authors to describe a technique for the preservation of the gingiva following surgery was Nabers (1954). The surgical technique developed by Nabers was originally denoted "repositioning of attached gingiva" and was later modified by Ariaudo and Tyrrell (1957). In 1962, Friedman proposed the term *apically repositioned flap* to describe more appropriately the surgical technique introduced by Nabers. Friedman emphasized the fact that, at the end of the surgical procedure, the entire complex of the soft tissues (gingiva and alveolar mucosa), rather than the gingiva alone, was displaced in the apical direction. Thus, rather than removing gingiva which would be in excess after osseous surgery (if performed), the whole mucogingival complex was maintained and repositioned apically. This surgical technique was used on buccal surfaces in both upper and lower jaws and on lingual surfaces in the lower jaw, while a bevel flap (see below) technique had to be used on the palatal aspect of maxillary teeth where the lack of alveolar mucosa made it impossible to reposition the flap in an apical direction.

Technique

According to Friedman (1962) the technique should be performed in the following way:

1. A reverse bevel incision is made using a scalpel with a Bard–Parker® blade (No. 12B or No. 15). How far from the buccal/lingual gingival margin the incision should be made is dependent on the pocket depth as well as the thickness and the width of the gingiva (Fig. 39-17). If preoperatively the gingiva is thin and only a narrow zone of keratinized tissue is present, the incision should be made close to the tooth. The beveling incision should be given a scalloped outline, to ensure maximal interproximal coverage of the alveolar bone when the flap subsequently is repositioned. Vertical releasing incisions extending out into the alveolar mucosa (i.e. past the mucogingival junction) are made at each of the end points of the reverse incision, thereby making apical repositioning of the flap possible.
2. A full-thickness mucoperiosteal flap including buccal/lingual gingiva and alveolar mucosa is raised by means of a mucoperiosteal elevator. The flap has to be elevated beyond the mucogingival line in order to be able later to reposition the soft tissue apically. The marginal collar of tissue, including pocket epithelium and granulation tissue, is removed with curettes (Fig. 39-18), and the exposed root surfaces are carefully scaled and planed.

3. The alveolar bone crest is recontoured with the objective of recapturing the normal form of the alveolar crest, but at a more apical level (Fig. 39-19). The osseous surgery is performed using burs and/or bone chisels.
4. Following careful adjustment, the buccal/lingual flap is repositioned to the level of the newly recontoured alveolar bone crest and secured in this position (Fig. 39-20). The incisional and excisional technique used means that it is not always possible to obtain proper soft tissue coverage of the denuded interproximal alveolar bone. A periodontal dressing should therefore be applied to protect the exposed bone and to retain the soft tissue at the level of the bone crest (Fig. 39-21). After healing, an "adequate" zone of gingiva is preserved and no residual pockets should remain.

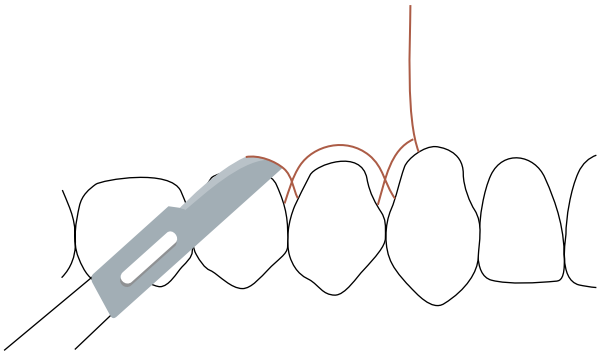

Fig. 39-17 Apically repositioned flap. Following a vertical releasing incision, the reverse bevel incision is made through the gingiva and the periosteum to separate the inflamed tissue adjacent to the tooth from the flap.

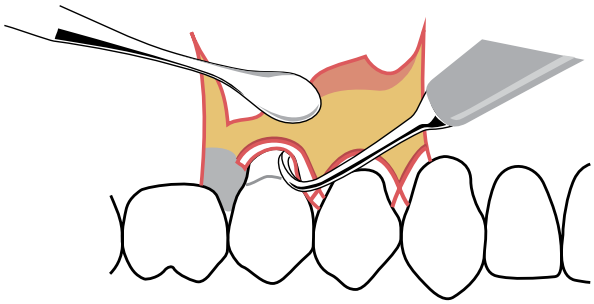

Fig. 39-18 Apically repositioned flap. A mucoperiosteal flap is raised and the tissue collar remaining around the teeth, including the pocket epithelium and the inflamed connective tissue, is removed with a curette.

To handle periodontal pockets on the palatal aspect of the maxillary teeth, Friedman described a modification of the "apically repositioned flap", which he termed the *beveled flap*:

1. In order to allow the tissue at the gingival margin to follow the outline of the alveolar bone crest properly, a conventional mucoperiosteal flap is first elevated (Fig. 39-22).
2. Tooth surfaces are debrided and osseous recontouring is performed (Fig. 39-23).
3. The palatal flap is subsequently replaced and the gingival margin is adjusted to the alveolar bone crest by a secondary scalloped and beveled incision (Fig. 39-24). The flap is secured in this position with interdental sutures (Fig. 39-25).

Among a number of suggested advantages of the *apically repositioned flap* procedure, the following have been emphasized:

- Minimum pocket depth postoperatively
- If optimal soft tissue coverage of the alveolar bone is obtained, the post-surgical bone loss is minimal
- Postoperative position of the gingival margin may be controlled and the entire mucogingival complex may be maintained.

The removal of periodontal tissues by bone resection and the subsequent exposure of root surfaces (which may cause esthetic and root sensitivity problems) are regarded as the main disadvantages of this technique.

Modified Widman flap

Ramfjord and Nissle (1974) described the *modified Widman flap* technique that is also recognized as the *open flap curettage* technique. It should be noted that, while the *original Widman flap* technique included both apical displacement of the flap(s) and osseous recontouring (elimination of bony defects) to obtain proper pocket elimination, the *modified Widman flap* technique is not intended to meet these objectives.

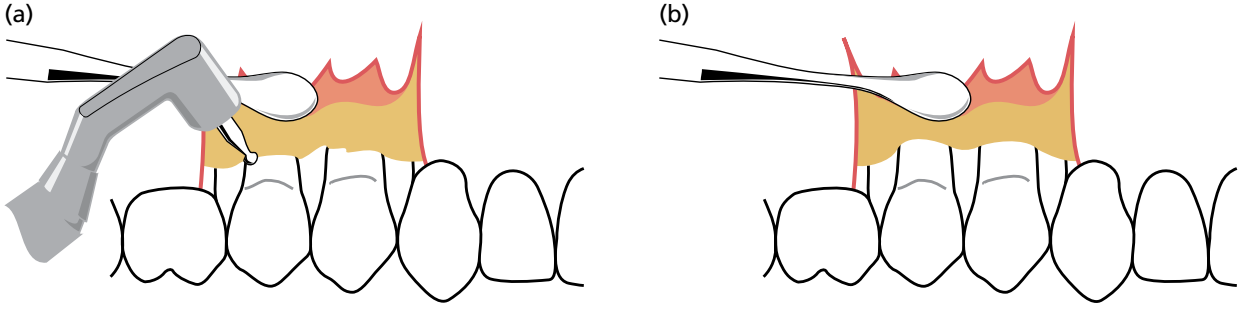

Fig. 39-19 Apically repositioned flap. Osseous surgery is performed with the use of a rotating bur (a) to recapture the physiologic contour of the alveolar bone (b).

Technique

1. According to the description by Ramfjord and Nissle (1974), the *initial incision* (Fig. 39-26), which may be performed with a Bard–Parker® knife (No. 11), should be parallel to the long axis of the tooth and placed approximately 1 mm from the buccal gingival margin in order to properly separate the pocket epithelium from the flap. If the pockets on the buccal aspects of the teeth are <2 mm deep or if esthetic considerations are important, an intracrevicular incision may be made. Furthermore, the scalloped incision should be extended as far as possible in between the teeth, to allow maximum amounts of the interdental gingiva to be included in the flap. A similar incision technique is used on the palatal aspect. Often, however, the scalloped outline of the initial incision may be accentuated by placing the knife at a distance of 1–2 mm from the mid-palatal surface of the teeth. By extending the incision as far as possible in between the teeth, sufficient amounts

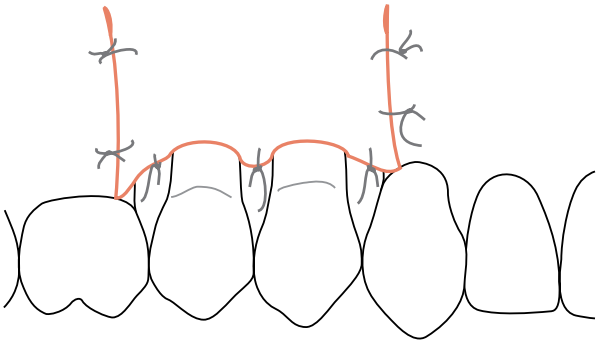

Fig. 39-20 Apically repositioned flap. The flaps are repositioned in an apical direction to the level of the recontoured alveolar bone crest and retained in this position by sutures.

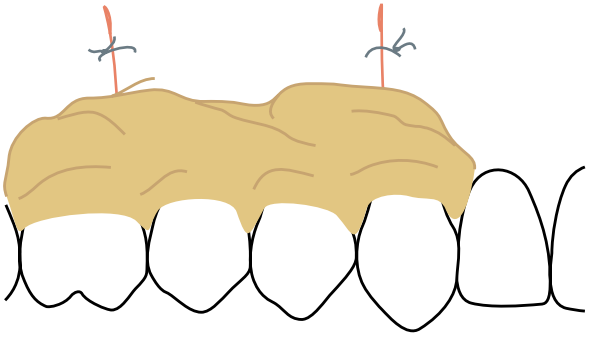

Fig. 39-21 Apically repositioned flap. A periodontal dressing is placed over the surgical area to ensure that the flaps remain in the correct position during healing.

Fig. 39-23 Beveled flap. Scaling, root planing, and osseous recontouring are performed in the surgical area.

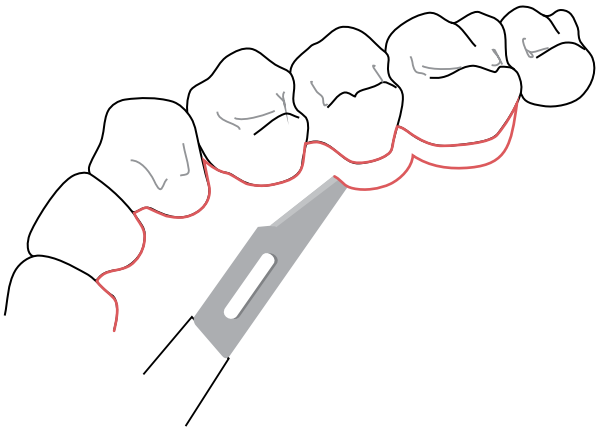

Fig. 39-24 Beveled flap. The palatal flap is replaced and a secondary, scalloped, reverse bevel incision is made to adjust the length of the flap to the height of the remaining alveolar bone.

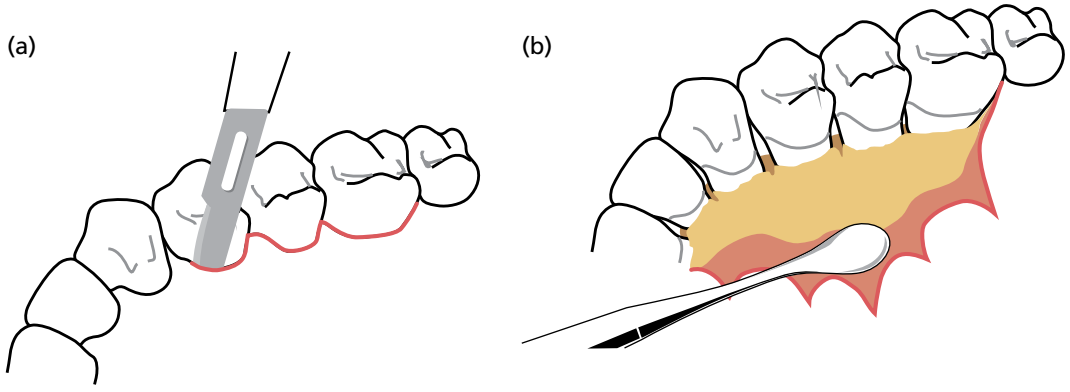

Fig. 39-22 Beveled flap. A primary incision is made intracrevicularly through the bottom of the periodontal pocket (a) and a conventional mucoperiosteal flap is elevated (b).

of tissue can be included in the palatal flap to allow for proper coverage of the interproximal bone when the flap is sutured. Vertical releasing incisions are not usually required.

2. Buccal and palatal full-thickness flaps are carefully elevated with a mucoperiosteal elevator. The flap elevation should be limited and allow only a few millimeters of the alveolar bone crest to become exposed. To facilitate the gentle separation of the collar of pocket epithelium and granulation tissue from the root surfaces, an intracrevicular incision is made around the teeth (*second incision*) to the alveolar crest (Fig. 39-27).
3. A *third incision* (Fig. 39-28) made in a horizontal direction and in a position close to the surface of the alveolar bone crest separates the soft tissue collar of the root surfaces from the bone.
4. The pocket epithelium and the granulation tissues are removed by means of curettes. The exposed roots are carefully scaled and planed, except for a narrow area close to the alveolar bone crest in which remnants of attachment fibers may be preserved. Angular bony defects are carefully curetted.
5. Following the curettage, the flaps are trimmed and adjusted to the alveolar bone to obtain complete coverage of the interproximal bone (Fig. 39-29). If this adaptation cannot be achieved by soft tissue recontouring, some bone may be removed from the outer aspects of the alveolar process in order to

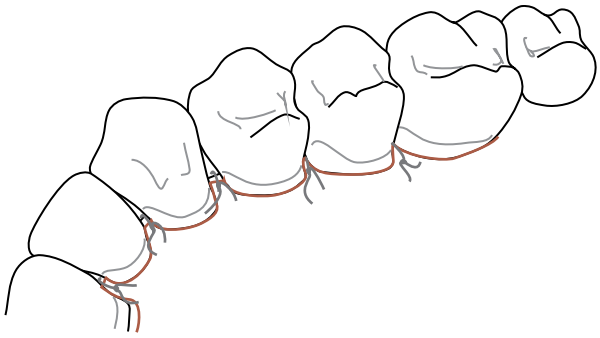

Fig. 39-25 Beveled flap. The shortened and thinned flap is replaced over the alveolar bone and in close contact with the root surfaces.

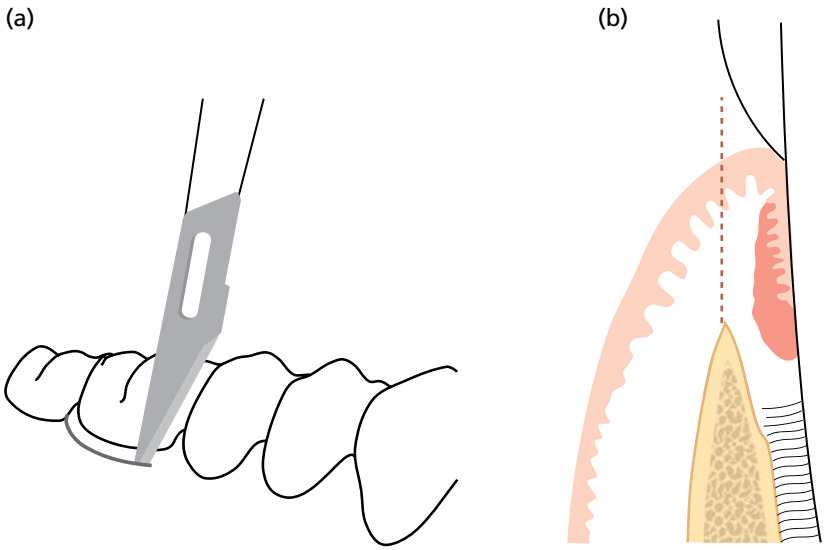

Fig. 39-26 Modified Widman flap. The initial incision is placed 0.5–1 mm from the gingival margin (a) and parallel to the long axis of the tooth (b).

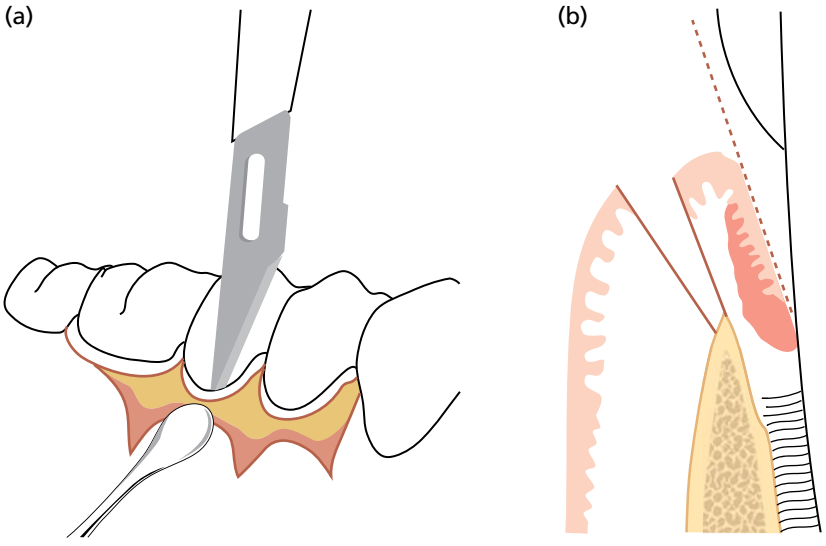

Fig. 39-27 Modified Widman flap. Following careful elevation of the flaps, a second intracrevicular incision (a) is made to the alveolar bone crest (b) to separate the tissue collar from the root surface.

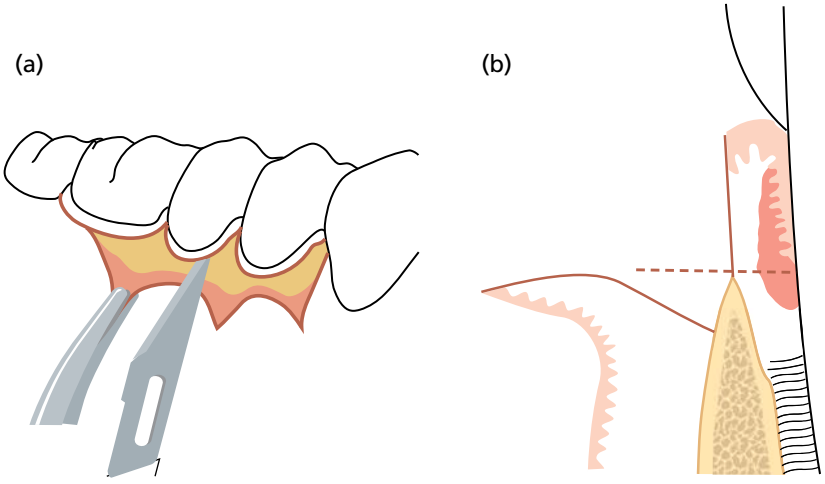

Fig. 39-28 Modified Widman flap. A third incision is made perpendicular to the root surface (a) and as close as possible to the bone crest (b), thereby separating the tissue collar from the alveolar bone.

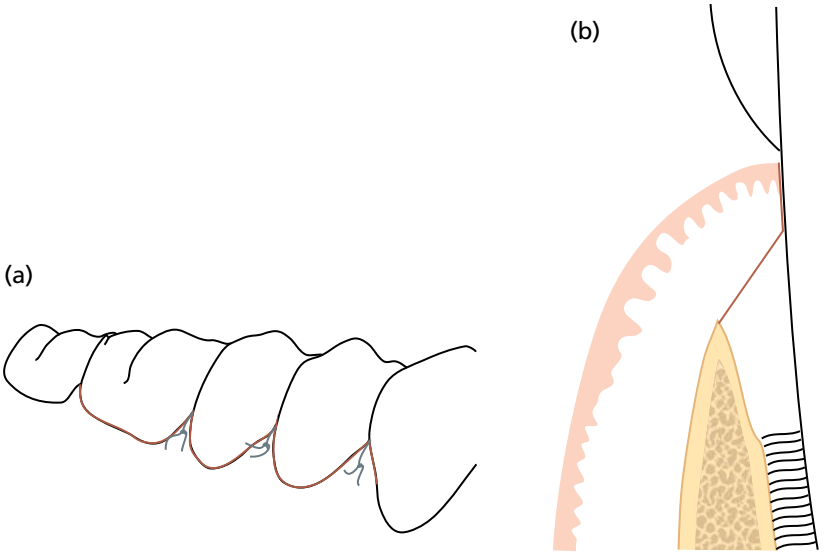

Fig. 39-29 Modified Widman flap. (a) Following proper debridement and curettage of angular bone defects, the flaps are carefully adjusted to cover the alveolar bone and sutured. (b) Complete coverage of the interdental bone as well as close adaptation of the flaps to the tooth surfaces should be accomplished.

facilitate the all-important flap adaptation. The flaps are sutured together with individual interdental sutures. Surgical dressing may be placed over the area to ensure close adaptation of the flaps to the alveolar bone and root surfaces. The dressing, as well as the sutures, is removed after 1 week.

The main advantages of the *modified Widman flap* technique in comparison to the other procedures previously described are, according to Ramfjord and Nissle (1974):

- Possibility of obtaining a close adaptation of the soft tissues to the root surfaces
- Minimum of trauma to which the alveolar bone and the soft connective tissues are exposed
- Less exposure of the root surfaces, which from an esthetic point of view is an advantage in the treatment of anterior segments of the dentition.

Papilla preservation flap

In order to preserve the interdental soft tissues for maximum soft tissue coverage following surgical intervention involving treatment of proximal osseous defects, Takei *et al*. (1985) proposed a surgical approach called *papilla preservation technique*. Later, Cortellini *et al*. (1995b, 1999) and Cortellini and Tonetti (2007) described modifications to the flap design to allow minimally invasive surgical techniques to be used in combination with regenerative procedures. For esthetic reasons, the papilla preservation technique is often utilized in the surgical treatment of anterior tooth regions.

Technique

1. According to the description by Takei *et al*. (1985), the *papilla preservation flap technique* is initiated by an intrasulcular incision at the facial and proximal aspects of the teeth without making incisions through the interdental papillae (Fig. 39-30a). Subsequently, an intrasulcular incision is made along the lingual/palatal aspect of the teeth with a semilunar incision made across each interdental area. The semilunar incision should dip apically by at least 5 mm from the line angles of the teeth, which will allow the interdental tissue to be elevated in the facial flap. In situations where an osseous defect has a wide extension into the lingual/palatal area, the semilunar incision may be placed on the facial aspect of the interdental area to include the papillae in the lingual/palatal flap.

2. A curette or interproximal knife is used to free the interdental papilla carefully from the underlying hard tissue. The detached interdental tissue is pushed through the embrasure with a blunt instrument (Fig. 39-30b).
3. A full-thickness flap is reflected with a periosteal elevator on both facial and lingual/palatal surfaces. The exposed root surfaces are thoroughly debrided and bone defects carefully curetted (Fig. 39-31).
4. While holding the reflected flap, the margins of the flap and the interdental tissue are trimmed to remove pocket epithelium and excessive granulation tissue. In anterior areas, the trimming of granulation tissue should be limited in order to maintain the maximum thickness of tissue.
5. The flaps are repositioned and sutured using cross mattress sutures (Fig. 39-32). Alternatively, a direct suture of the semilunar incisions can be placed as the only means of flap closure. A surgical dressing may be placed to protect the surgical area. The dressing and sutures are removed after 1 week.

Regenerative procedures

In the 1980s, treatment of periodontal pockets was given a new dimension when it was shown that, with specific surgical handling of the periodontal wound, a significant amount of new connective tissue attachment is achievable (Nyman *et al*. 1982; Bowers *et al*. 1989).

Obtaining periodontal regeneration has always been a major challenge to the periodontist and several approaches to periodontal regeneration have been used throughout the years. The earliest attempts involved various bone-grafting procedures, such as the use of autogenous grafts from both extraoral and intraoral

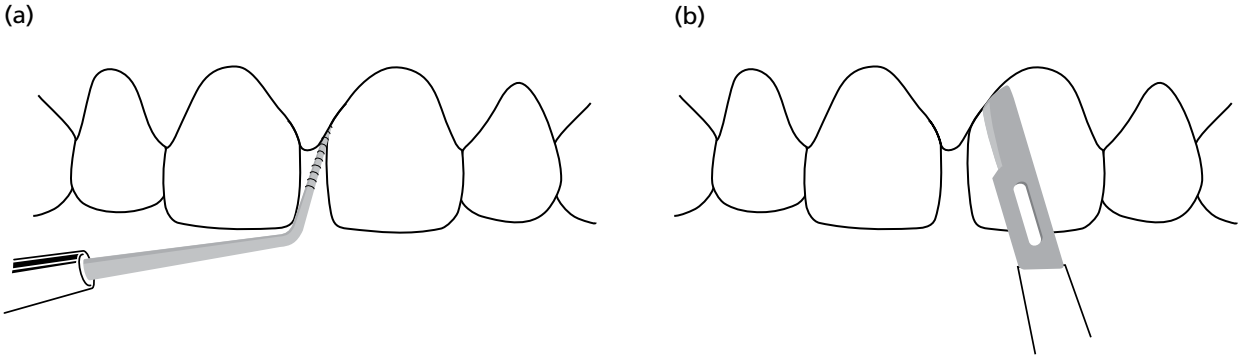

Fig. 39-30 Papilla preservation flap. (a) A deep pocket is present at an approximal tooth site. (b) Intracrevicular incisions are made at the facial and proximal aspects of the teeth.

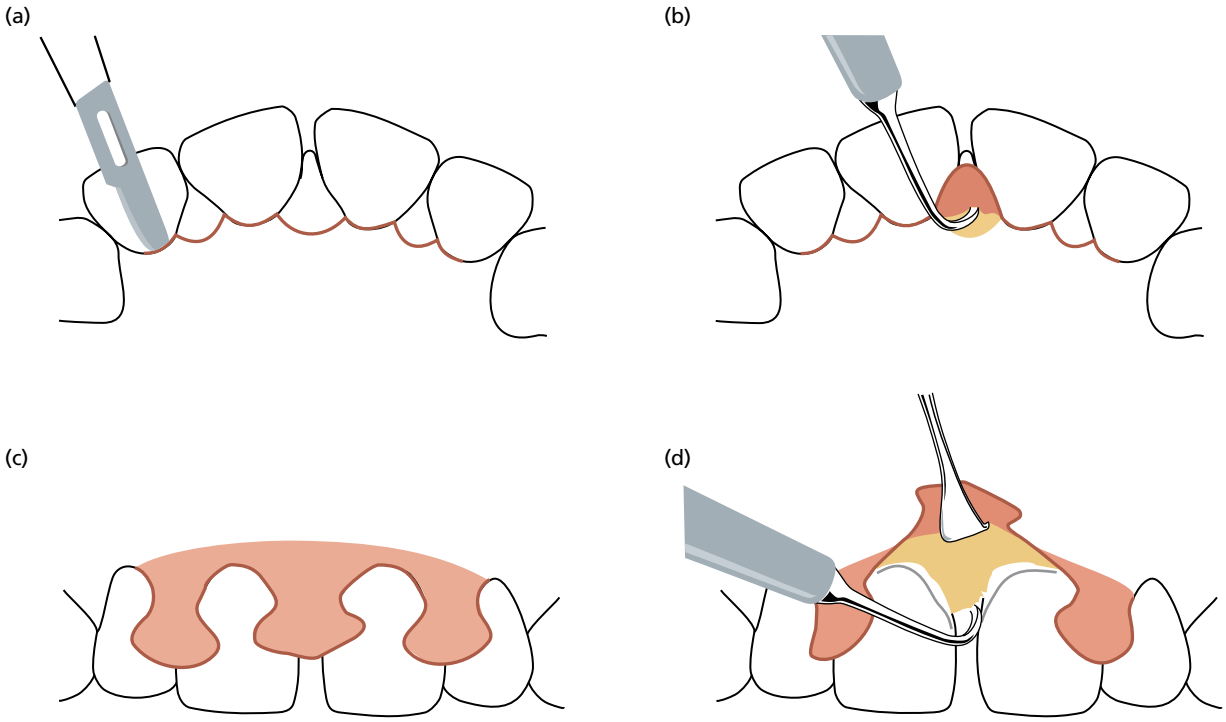

Fig. 39-31 Papilla preservation flap. (a) An intracrevicular incision is made along the lingual/palatal aspect of the teeth with a semilunar incision made across each interdental area. (b) A curette or a papilla elevator is used to carefully free the interdental papilla from the underlying hard tissue. (c, d) Detached interdental tissue is pushed through the embrasure with a blunt instrument to be included in the facial flap.

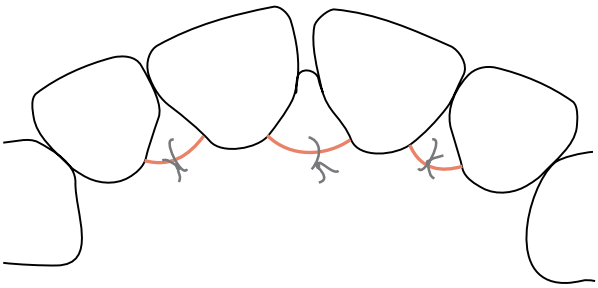

Fig. 39-32 Papilla preservation flap. The flap is replaced and sutures are placed on the palatal aspect of the interdental areas.

donor sites, allogenic grafts, and non-decalcified/decalcified lyophilized bone grafts, or "implant" procedures utilizing slowly resorbable tricalcium phosphate and non-resorbable hydroxyapatite. Other approaches to periodontal regeneration involved the use of citric acid for root surface demineralization or the use of methods for improved root surface biocompatibility or to enhance cellular responses.

The use of physical barriers, such as membranes (non-biodegradable or biodegradable), to retard or prevent apical migration of epithelium as well as exclude gingival connective tissue from the healing wound, formed the basis for the concept known as "guided tissue regeneration" (Gottlow *et al*. 1986). The procedure can be described as a coronally repositioned flap procedure without bone recontouring, with the adjunctive use of a membrane tightened to the tooth to cover the exposed root surface and adjacent intrabony defect before repositioning the soft tissue flaps.

In the late 1990s, a new approach to periodontal regeneration was presented, which involved the use of a derivative of enamel matrix proteins (Hammarström 1997; Heijl *et al*. 1997). These proteins are involved in the embryogenesis of cementum, periodontal ligament, and supporting bone, and when applied to the exposed root surface facing an intrabony periodontal defect, they may mediate regeneration of a new attachment apparatus. The surgical procedure is performed as a coronally repositioned flap procedure without bone recontouring. Before repositioning of the soft tissue flaps, the exposed roots are treated with ethylenediaminetetra-acetic acid (EDTA) for removal of the "smear layer", followed by the application of the derivative of enamel matrix proteins.

Various regenerative procedures for surgical treatment of periodontal lesions, as well as the biologic basis for periodontal regeneration, are discussed in detail in Chapters 28 and 45.

Distal wedge procedures

In many cases the treatment of periodontal pockets on the distal surface of distal molars is complicated by the presence of bulbous tissues over the tuberosity or by a prominent retromolar pad. The most direct approach to pocket elimination in such cases in the maxillary jaw is the gingivectomy procedure. The incision is started on the distal surface of the tuberosity and carried forward to the base of the pocket of the distal surface of the molar (Fig. 39-33).

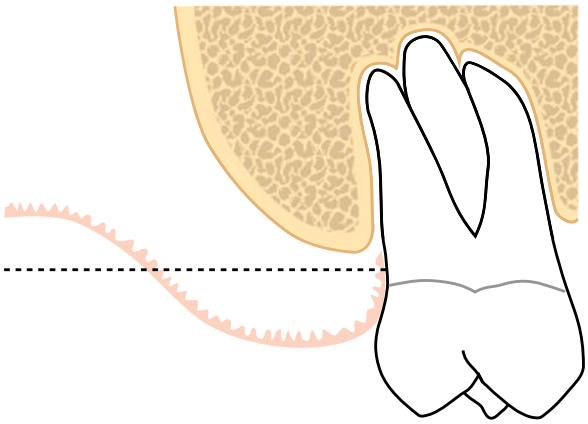

Fig. 39-33 Distal wedge procedure. Simple gingivectomy incision (dashed line) can be used to eliminate a soft tissue pocket and adjacent fibrous tissue pad behind a maxillary molar.

However, when only limited amounts of keratinized gingiva are present, or none at all, or if a distal angular bony defect has been diagnosed, the bulbous tissue should be reduced in size rather than removed *in toto*. This may be accomplished by the *distal wedge procedure* (Robinson 1966). This technique facilitates access to the osseous defect and makes it possible to preserve sufficient amounts of gingiva and mucosa to achieve soft tissue coverage.

Technique

1. Buccal and lingual incisions are made in a vertical direction through the tuberosity or retromolar pad to form a triangular wedge (Fig. 39-34a). The facial and lingual incisions should be extended in a mesial direction along the buccal and lingual surfaces of the distal molar to facilitate flap elevation.
2. The facial and lingual walls of the tuberosity or retromolar pad are deflected and the incised wedge of tissue is dissected and separated from the bone (Fig. 39-34b).
3. The walls of the facial and lingual flaps are then reduced in thickness by undermining incisions (Fig. 39-34c). Loose tags of tissue are removed and the root surfaces are debrided. If necessary, the bone is recontoured.
4. The buccal and lingual flaps are replaced over the exposed alveolar bone, and the edges trimmed to avoid overlapping wound margins. The flaps are secured in this position with interrupted sutures (Fig. 39-34d). The sutures are removed after approximately 1 week.

The original distal wedge procedure may be modified according to individual requirements. Some commonly used modifications of the incision technique are shown in Figs. 39-35, 39-36, 39-37, and 39-38, all having the goals of eliminating the deep pocket and achieving mucosal coverage of the remaining periodontium.

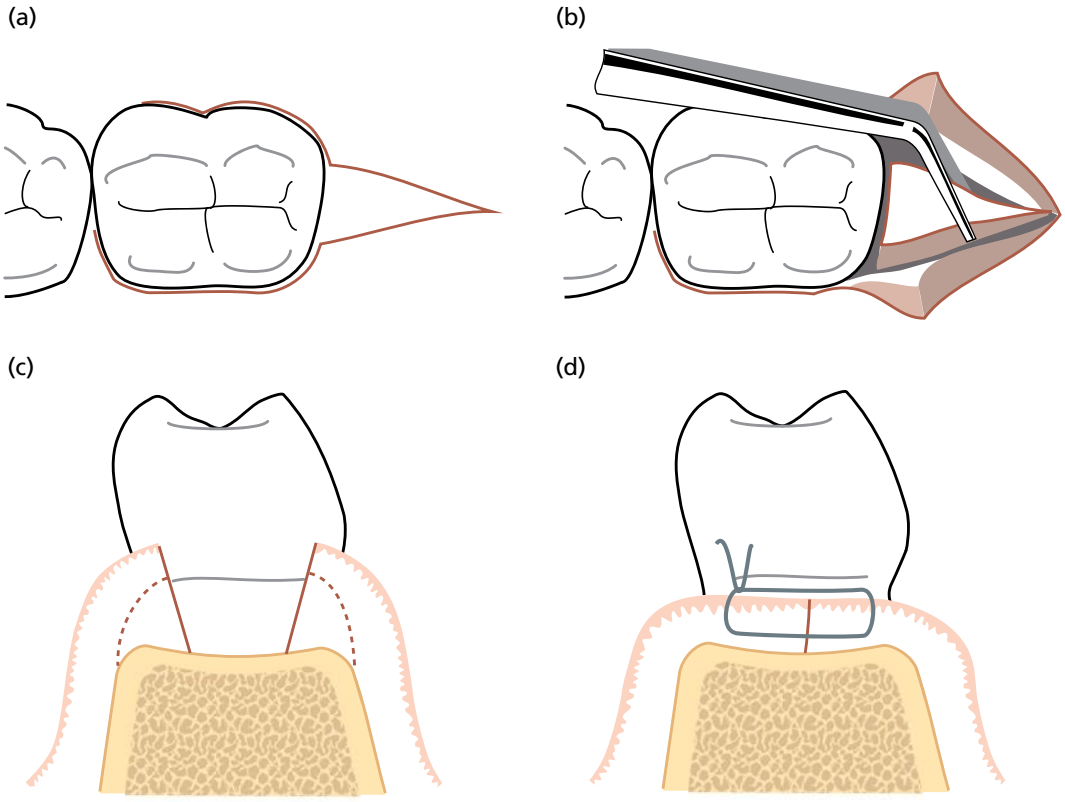

Fig. 39-34 Distal wedge procedure. (a) Buccal and lingual vertical incisions are made through the retromolar pad to form a triangle behind a mandibular molar. (b) Triangular-shaped wedge of tissue is dissected from the underlying bone and removed. (c) Walls of the buccal and lingual flaps are reduced in thickness by undermining incisions (dashed lines). (d) The flaps, which have been trimmed and shortened to avoid overlapping wound margins, are sutured.

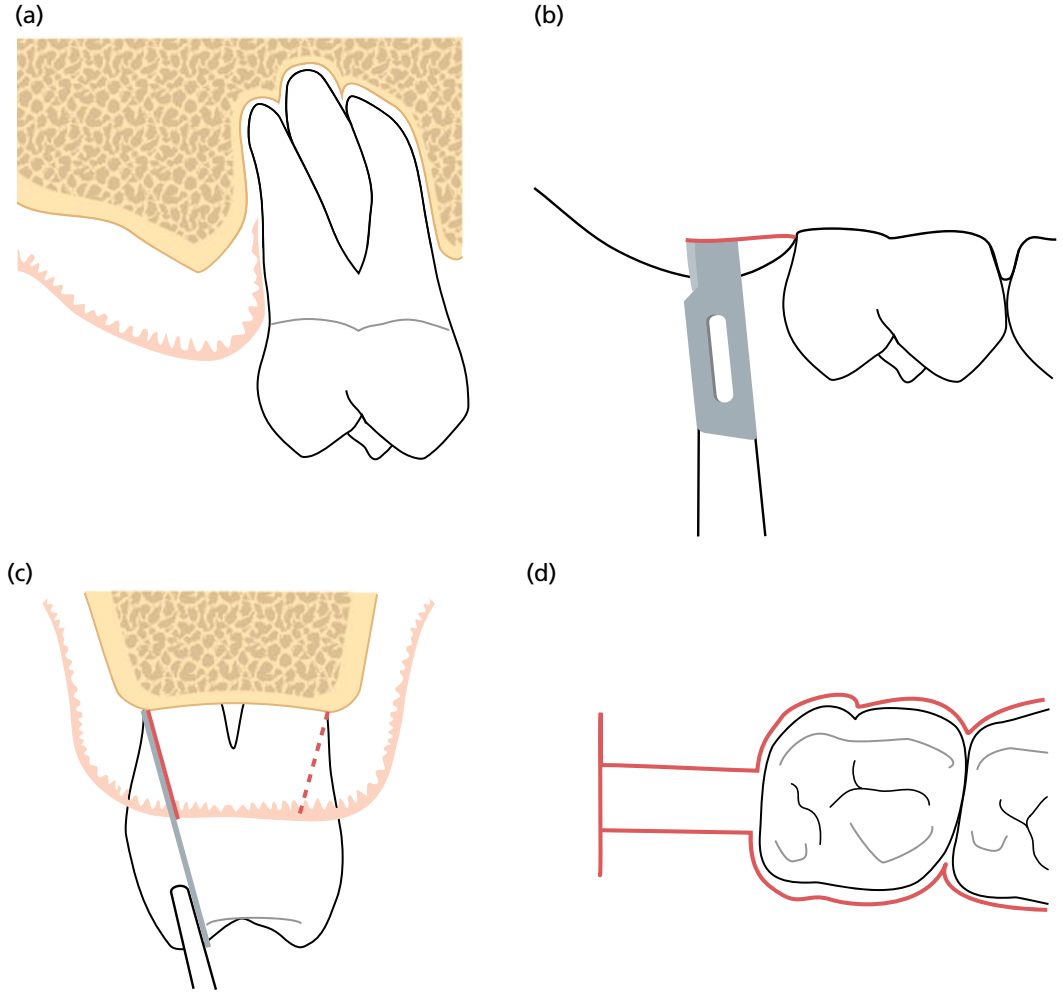

Fig. 39-35 Modified distal wedge procedure. (a) A deep periodontal pocket combined with an angular bone defect at the distal aspect of a maxillary molar. (b–d) Two parallel reverse bevel incisions, one buccal and one palatal, are made from the distal surface of the molar to the posterior part of the tuberosity, where they are connected with a buccolingual incision (d). The buccal and palatal incisions are extended in a mesial direction along the buccal and palatal surfaces of the molar to facilitate flap elevation.

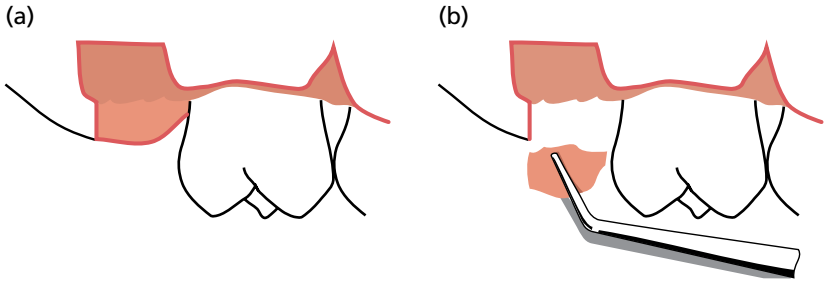

Fig. 39-36 Modified distal wedge procedure. (a) Buccal and palatal flaps are elevated and (b) the rectangular wedge is released from the tooth and underlying bone by sharp dissection and then removed.

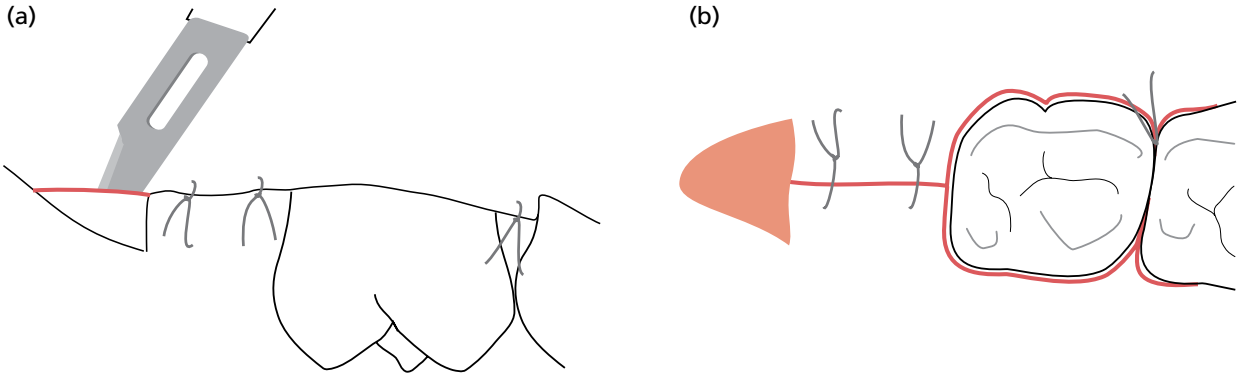

Fig. 39-37 Modified distal wedge procedure. (a, b) Following bone recontouring and root debridement, the flaps are trimmed and shortened to avoid overlapping wound margins and sutured. A close soft tissue adaptation should be accomplished to the distal surface of the molar. The remaining fibrous tissue pad distal to the buccolingual incision line is "leveled" by the use of a gingivectomy incision.

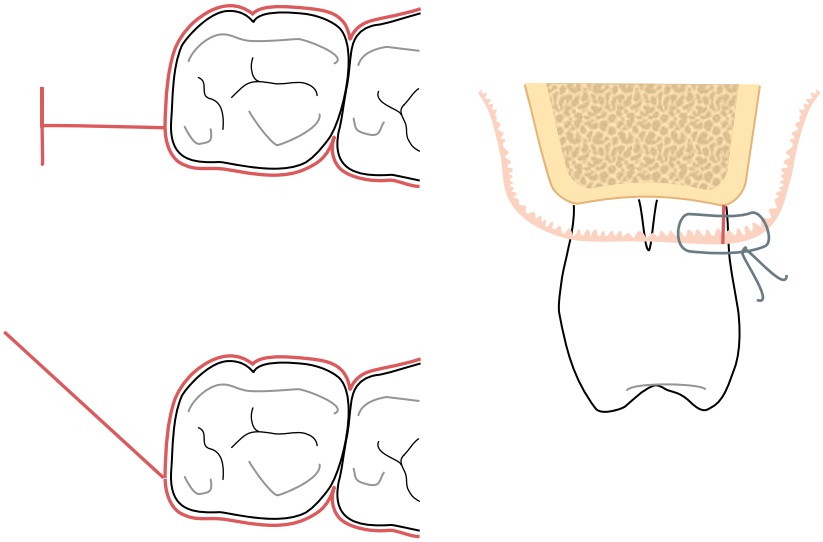

Fig. 39-38 Modified incision techniques in distal wedge procedures. To ensure optimal flap adaptation at the furcation site, the incision technique may be modified. The amount of attached keratinized tissue present as well as the accessibility to the retromolar area has to be considered when placing the incision.

Osseous surgery

The principles of osseous surgery in periodontal therapy were outlined by Schluger (1949) and Goldman (1950). They pointed out that alveolar bone loss caused by inflammatory periodontal disease often results in an uneven outline of the bone crest. Since, according to these authors, the gingival contour is closely dependent on the contour of the underlying bone as well as the proximity and anatomy of adjacent tooth surfaces, the elimination of soft tissue pockets often has to be combined with osseous reshaping and the elimination of osseous craters and angular bony defects to establish and maintain shallow pockets and optimal gingival contour after surgery.

Osteoplasty

The term *osteoplasty* was introduced by Friedman in 1955. The purpose of osteoplasty is to reshape the alveolar bone *without* removing any "supporting" bone. Examples of osteoplasty are the thinning of thick osseous ledges and the establishment of a scalloped contour of the buccal (lingual and palatal) bone crest (Fig. 39-39). In flap surgery without bone recontouring, interdental morphology may sometimes

preclude optimal mucosal coverage of the bone postsurgically, even if pronounced scalloping of soft tissue flaps is performed. In such a situation, removal of non-supporting bone by vertical grooving to reduce the faciolingual dimension of the bone in the interdental areas may facilitate flap adaptation, thereby reducing the risk of bone denudation as well of ischemic necrosis of unsupported mucosal flaps due to flap margin deficiencies.

Removal of non-supporting bone may sometimes also be required to gain access for intrabony root surface debridement. The leveling of interproximal craters and the elimination (or reduction) of bony walls of circumferential osseous defects are often referred to as "osteoplasty" since usually no resection of supporting bone is required (Fig. 39-40).

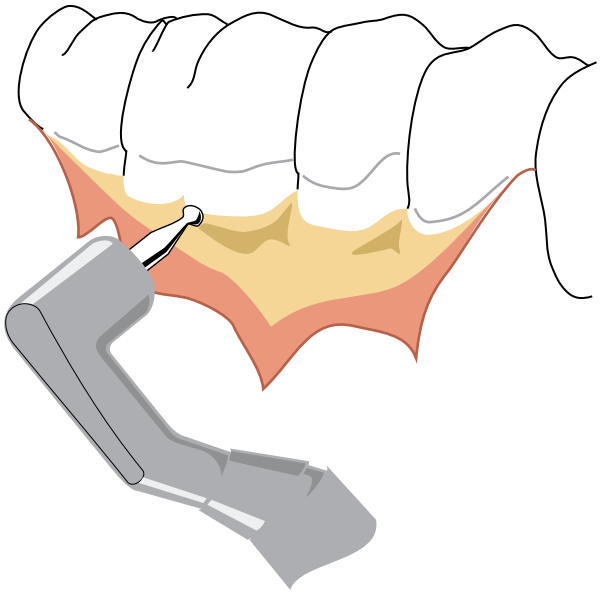

Fig. 39-39 Osteoplasty. Thick osseous ledges in a mandibular molar region area are eliminated with the use of a round bur to facilitate optimal flap adaptation.

Ostectomy

In *ostectomy*, supporting bone, that is bone directly involved in the attachment of the tooth, is removed to reshape hard tissue deformities caused by periodontitis. Ostectomy is considered to be an important part of surgical techniques aimed at pocket elimination. As a general rule, however, care must be exercised when supporting bone is to be removed.

After exposing the alveolar bone by elevation of a flap, buccal and/or lingual crater walls are reduced to the base of the osseous defect using bone chisels and bone rongeurs (Fig. 39-41a). A round bur or a diamond stone under continuous saline irrigation can also be used. If bone resection has been carried out in the interdental area, the buccal and lingual/palatal bone margins may subsequently be recontoured to compensate for discrepancies in bone height resulting from the interdental bone resection (Fig. 39-41b). It is considered important to remove the small ledges of bone, which often remain in the area of the line angles. The objective of bone surgery is thus to establish a "physiologic" anatomy of the alveolar bone, but at a more apical level.

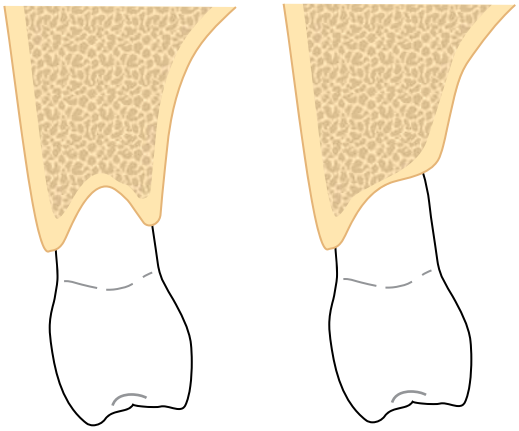

Fig. 39-40 Osteoplasty. Leveling of an interproximal bone crater through the removal of the palatal bone wall. For esthetic reasons, the buccal bone wall is maintained to support the height of the soft tissue.

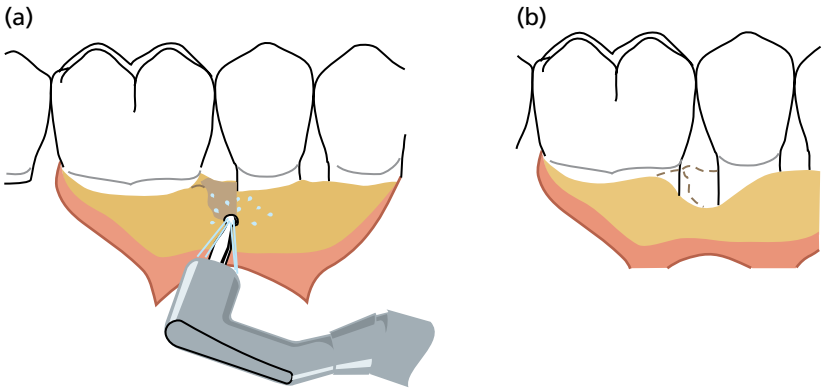

Fig. 39-41 Ostectomy. (a) Combined one- and two-wall osseous defect on the distal aspect of a mandibular bicuspid has been exposed following reflection of mucoperiosteal flaps. Since esthetics is not a critical factor to consider in the posterior tooth region of the mandible, the bone walls are reduced to a level close to the base of the defect using rotating round burs under continuous saline irrigation. (b) Osseous recontouring completed. Note that some supporting bone has to be removed from the buccal and lingual aspect of both the second bicuspid and the first molar in order to provide a hard tissue topography which allows a close adaptation of the covering soft tissue flap.

General guidelines for periodontal surgery

Objectives of surgical treatment

Traditionally, *pocket elimination* has been a main objective of periodontal therapy. The removal of the pocket by surgical means served two purposes: (1) the pocket, which established an environment conducive to progression of periodontal disease, was eliminated and (2) the root surface was made accessible for professional debridement and for self-performed tooth cleaning after healing.

While these objectives cannot be entirely discarded today, the necessity for pocket elimination in periodontal therapy has been challenged. During recent years our understanding of the biology of the periodontium, the pathogenesis of periodontal disease, and the healing capacity of the periodontium has markedly increased. This new information has thus formed the basis for a more differentiated understanding of the role played by periodontal surgery in the preservation of teeth.

In the past, *increased pocket depth* was the main indication for periodontal surgery. However, pocket depth is no longer as unequivocal a concept as it used to be. The *probeable depth*, that is the distance from the gingival margin to the point where tissue resistance stops further periodontal probe penetration, may only rarely correspond to the "true" depth of the pocket (see Chapter 29). Furthermore, regardless of the accuracy with which pockets can be measured, there is no established correlation between probeable pocket depth and the presence or absence of active disease. This means that signs other than increased probing depth should be present to justify surgical therapy. These include clinical signs of inflammation, especially exudation and bleeding on probing (to the bottom of the pockets), as well as aberrations of gingival morphology.

In conclusion, the main objective of periodontal surgery is to contribute to the long-term preservation of the periodontium by facilitating plaque removal and infection control, and periodontal surgery can serve this purpose by:

- Creating accessibility for proper professional scaling and root planing
- Establishing a gingival morphology which facilitates self-performed infection control.

In addition, periodontal surgery may aim to regenerate the periodontal attachment lost due to destructive disease. (New attachment procedures in periodontal therapy are discussed in Chapter 45)

Indications for surgical treatment

Impaired access for scaling and root planing

The difficulties in accomplishing proper root debridement with a non-surgical approach increase with (1) increasing depth of the periodontal pockets, (2) increasing width of the tooth surfaces, and (3) the presence of root fissures, root concavities, furcations, and defective margins of dental restorations in the subgingival area.

Provided a correct technique and suitable instruments are used, it is usually possible properly to debride pockets that are up to 5 mm deep (Waerhaug 1978; Caffesse *et al*. 1986). However, this 5 mm limit cannot be used as a universal rule of thumb. Reduced accessibility and the presence of one or several of the above-mentioned impeding conditions may prevent proper debridement of shallow pockets, whereas at sites with good accessibility and favorable root morphology, proper debridement can be accomplished even in deeper pockets (Badersten *et al*. 1981; Lindhe *et al*. 1982a).

It is often difficult to ascertain by clinical means whether subgingival instrumentation has been properly performed. Following scaling, the root surface should be smooth – roughness will often indicate the presence of remaining subgingival calculus. It is also important to monitor carefully the gingival reaction to subgingival debridement. If inflammation persists and if bleeding is elicited by gentle probing in the subgingival area, the presence of subgingival deposits should be suspected (Fig. 39-42). If such symptoms are not resolved by repeated subgingival instrumentation, surgical treatment should be performed to expose the root surfaces for proper cleaning.

Impaired access for self-performed plaque control

The level of infection control that can be maintained by the patient is determined not only by his/her interest and dexterity, but also, to some extent, by the morphology of the dentogingival area. The patient's responsibilities in an infection-control program must include the cleansing of the supragingival tooth surfaces and the marginal part of the gingival sulcus.

Pronounced gingival hyperplasia and presence of gingival craters (Fig. 39-43) are examples of

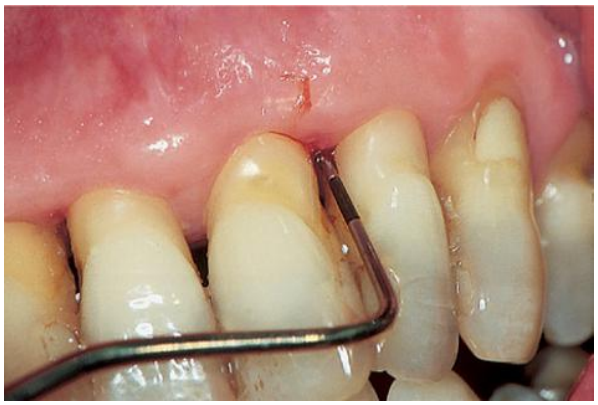

Fig. 39-42 Evaluation following non-surgical instrumentation reveals persistent signs of inflammation, bleeding following pocket probing, and probing depth of ≥6 mm. Flap elevation to expose the root surface for proper cleaning should be considered.

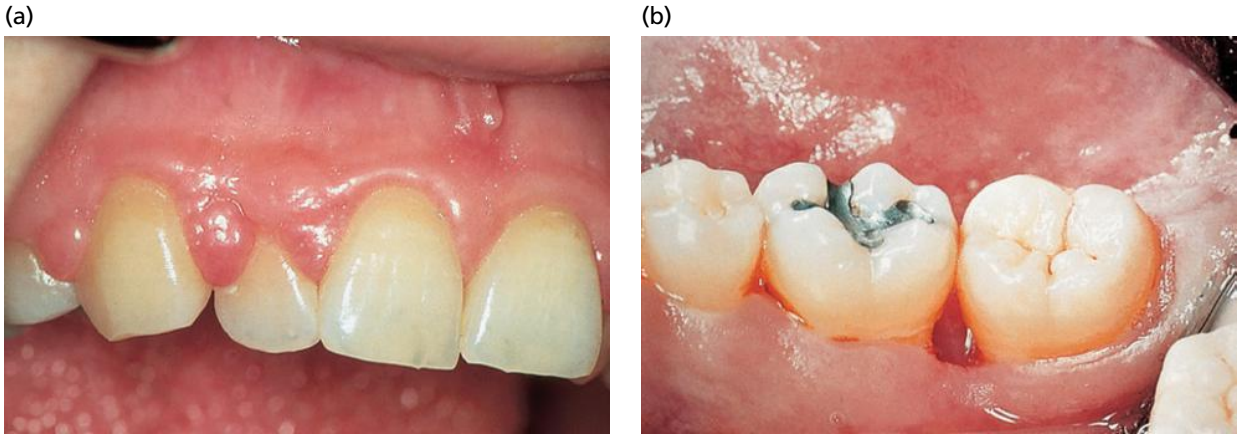

Fig. 39-43 Examples of gingival aberrations, (a) gingival enlargement and (b) proximal soft tissue crater, which favor plaque retention and thereby impede the patient's plaque control.

morphologic aberrations that may impede proper home care. Likewise, the presence of restorations with defective marginal fit or adverse contour and surface characteristics at the gingival margin may seriously compromise plaque removal.

In the professional treatment of periodontal disease, the dentist prepares the dentition in such a way that home care can be effectively managed. At the completion of treatment, the following objectives should have been met:

- No sub- or supra-gingival dental deposits
- No pathologic pockets (no bleeding on probing to the bottom of the pockets)
- No plaque-retaining aberrations of gingival morphology
- No plaque-retaining parts of restorations in relation to the gingival margin.

These requirements lead to the following indications for periodontal surgery:

- Accessibility for proper root debridement
- Establishment of a morphology of the dentogingival area conducive to infection control
- Pocket depth reduction
- Correction of gross gingival aberrations
- Shift of the gingival margin to a position apical to plaque-retaining restorations
- Facilitation of proper restorative therapy.

Contraindications for periodontal surgery

Patient cooperation

Since optimal postoperative infection control is decisive for the success of periodontal treatment (Rosling *et al*. 1976a; Nyman *et al*. 1977; Axelsson & Lindhe 1981), a patient who fails to cooperate during the cause-related phase of therapy should not be exposed to surgical treatment. Even though short-term postoperative infection control entails frequent professional treatments, the long-term responsibility for maintaining good oral hygiene must rest with the patient. Theoretically, even the poorest oral hygiene performance by a patient may be compensated for by frequent recall visits for supportive therapy (e.g. once a week), but it is unrealistic to consider larger groups of patients being maintained in this manner. A typical recall schedule for periodontal patients involves professional consultations for supportive periodontal therapy once every 3–6 months. Patients who cannot maintain satisfactory oral hygiene standards over such a period should normally not be considered to be candidates for periodontal surgery.

Smoking

Although smoking negatively affects wound healing (Siana *et al*. 1989), it may not be considered a contraindication for surgical periodontal treatment. The clinician should be aware, however, that less resolution of probing pocket depth, smaller improvement in clinical attachment, and less bone regeneration might occur in smokers than in non-smokers (Labriola *et al*. 2005; Javed *et al*. 2012; Patel *et al*. 2012).

General health conditions

It is important to re-evaluate the patient's medical history before any surgical intervention to identify whether there is any medical condition that may preclude periodontal surgery or whether certain precautions should be taken, for example prescription of prophylactic antibiotics or the use of local anesthetics without epinephrine. Consultation with the patient's physician should also be considered.

Local anesthesia in periodontal surgery

Pain management is an ethical obligation and will improve patient satisfaction in general (e.g. increased confidence and improved cooperation) as well as recovery and short-term functioning after periodontal surgical procedures. In order to prevent pain during the performance of a periodontal surgical procedure,

the entire area of the dentition scheduled for surgery, the teeth as well as the periodontal tissues, requires proper local anesthesia.

Dental local anesthetics

Anesthetics from the chemical group amino amides, for example lidocaine, mepivacaine, prilocaine, and articaine, are more potent and significantly less allergenic than amino esters (e.g. procaine and tetracaine), and have therefore replaced esters as the "gold standard" for dental local anesthetics.

Due to the specific need for bone penetration, dental local anesthetics contain high concentrations of the active agent. Although most amide local anesthetics may cause local vasoconstriction in low concentrations, the clinically used concentrations in dental solutions will cause an increase in the local blood flow. A significant clinical effect of this induced vasodilatation is an increased rate of absorption, thus decreasing the duration of anesthesia. Major benefits can therefore be obtained by adding relatively high concentrations of vasoconstrictors (e.g. epinephrine >1 : 200 000 or >5 mg/mL) to dental local anesthetic solutions; the duration is considerably prolonged, the depth of anesthesia may be enhanced, and the peak concentrations of the local anesthetic in blood can be reduced. Furthermore, in periodontal surgery, incorporation of adrenergic vasoconstrictors into the local anesthetic is of considerable value to allow for only minimal bleeding during surgery (to better visualize the surgical site and to shorten the procedural time spent maintaining surgical quality). In fact, the use of a dental local anesthetic without a vasoconstrictor during a periodontal surgical procedure is counterproductive because the vasodilating properties of such a local anesthetic will increase bleeding in the area of surgery.

Vasoconstrictors and local hemostasis

Epinephrine is the vasoconstrictor of choice for local hemostasis and is most commonly used in a concentration of 1 : 80 000 (12.5 mg/mL). However, 1 : 100 000 epinephrine also provides excellent hemostasis and most periodontists are unable to detect a clinical difference between the two concentrations. It therefore seems prudent to use the least concentrated form of epinephrine that provides clinically effective hemostasis (i.e. the 1 : 100 000 concentration).

Although the cardiovascular effects of the usually small amounts of epinephrine used during a periodontal surgical procedure are of little practical concern in most individuals, accidental intravascular injections, unusual patient sensitivity, and unanticipated drug interactions (or excessive doses), can result in potentially serious outcomes. It must also be understood that the use of epinephrine for hemostasis during periodontal surgery has some potential drawbacks. Epinephrine will produce a rebound vasodilatation after the vasoconstriction has worn off, leading to increased risk for bleeding in the immediate postoperative period. There is a greater potential for such undesirable delayed hemorrhage following the use of 1 : 80 000 epinephrine than after the use of 1 : 100 000 epinephrine.

Postoperative pain may increase and wound healing may be delayed when adrenergic vasoconstrictors are used because of local ischemia with subsequent tissue acidosis and accumulation of inflammatory mediators. Furthermore, the possibility of an ischemic necrosis of surgical flaps infiltrated with an adrenergic vasoconstrictor (especially if norepinephrine is used instead of epinephrine) cannot be discounted. For these reasons, as well as the possibility of the systemic reactions eluded to above, dental local anesthetics containing adrenergic vasoconstrictors for hemostasis should be infiltrated *only* as needed and *not* according to habit.

Felypressin, another commonly used vasoconstrictor, appears to act preferentially on the venous side of the microcirculation and is not very active in constricting the arteriolar circulation. Felypressin is therefore not nearly as effective as adrenergic vasoconstrictors in limiting hemorrhage during a surgical procedure.

Techniques

Injections of dental local anesthetics prior to a periodontal surgical procedure may be routine for the dentist, but is often a most unpleasant experience for the patient. Reassurance and psychological support are essential and will increase the patient's confidence in his/her dentist. The creation of a relaxed atmosphere to decrease the patient's fear in an unusual situation is of course also a useful way of increasing the patient's own defense mechanisms against pain perception (e.g. release of endogenous endorphins).

Anesthesia for periodontal surgery is obtained by nerve block and/or by local infiltration. In cases of flap surgery, complete anesthesia must be attained before commencing the operation, as it may be difficult to supplement the anesthesia after the bone surface has been exposed. In addition, the pain elicited by needle insertion can be significantly reduced if the mucosa at the puncture site is anesthetized in advance by the use of a suitable topical ointment or spray.

Local infiltration may have a greatly decreased rate of success in areas where inflammation remains in the periodontal tissues, in spite of optimal conservative periodontal therapy and good oral hygiene. The suggested reason for this is that tissue pH tends to be low in inflamed areas and anesthetic solutions are less potent at low pH because there is a greater proportion of charged cation molecules than of the uncharged base molecules. Because of this, diffusion of the local anesthetic into the axoplasm is slower, with subsequent delayed onset and decreased efficacy. Another more recent hypothesis suggests that

nerve growth factor (NGF) released during tissue inflammation will induce sprouting or proliferation of sensory nerve endings expressing a different (sub) type of sodium channel than is expressed in normal tissues. Currently used dental local anesthetics may not be selective enough for proper interaction with these sodium channel subtypes to induce anticipated anesthesia.

Local anesthesia in the mandible

As a rule, analgesia of the teeth and the soft and hard tissues of the mandible should be obtained by a mandibular block and/or a mental block. In the anterior region of the mandible, canines and incisors can often be anesthetized by infiltration, but there are often anastomoses over the midline. These anastomoses must be anesthetized by bilateral infiltration or by bilateral mental blocks. The buccal soft tissues of the mandible are anesthetized by local infiltration or by blocking the buccal nerve. Local infiltration, performed as a series of injections in the buccal fold of the treatment area, has of course the added advantage of providing a local ischemic effect if a suitable anesthetic is used.

The lingual periodontal tissues must also be anesthetized. This is accomplished by blocking the lingual nerve and/or by infiltration into the floor of the mouth close to the site of operation. If necessary to obtain proper ischemia, and only then, supplementary injections may be made in the interdental papillae (intraseptal injections).

Local anesthesia in the maxilla

Local anesthesia of the teeth and buccal periodontal tissues of the maxilla can easily be obtained by injections into the mucogingival fold of the treatment area. If larger areas of the maxillary dentition are scheduled for surgery, repeated injections (into the mucogingival fold) have to be performed, for example at the central incisor, canine, second premolar, and second molar. In the posterior maxillary region, a tuberosity injection can be used to block the superior alveolar branches of the maxillary nerve. However, because of the vicinity to the pterygoid venous plexus, this type of block anesthesia is not recommended due to the risk of intravenous injection and/or hematoma formation.

The palatal nerves are most easily anesthetized by injections made at right angles to the mucosa and placed about 10 mm apical to the gingival margin adjacent to teeth included in the operation. In cases of advanced bone loss, the pain produced by injecting into the non-resilient palatal mucosa can be minimized if the injections are performed from the buccal aspect, that is through the interdental gingiva. Sometimes blocks of the nasopalatine nerves and/or the greater palatine nerves can be applied. Supplementary blocking of the greater palatine nerve should be considered, especially for periodontal surgery involving molars.

Instruments used in periodontal surgery

General considerations

Surgical procedures used in periodontal therapy often involve the following measures (instruments):

- Incision and excision (periodontal knives)
- Deflection and re-adaptation of mucosal flaps (periosteal elevators)
- Removal of adherent fibrous and granulomatous tissue (soft tissue rongeurs and tissue scissors)
- Scaling and root planing (scalers and curettes)
- Removal of bone tissue (bone rongeurs, chisels, and files)
- Root sectioning (burs)
- Suturing (sutures and needle holders, suture scissors)
- Application of wound dressing (plastic instruments).

The set of instruments used for the various periodontal surgical procedures should have a comparatively simple design. As a general rule, the number and varieties of instruments should be kept to a minimum. In addition to particular instruments used for periodontal treatment modalities, equipment and instruments used generally in oral surgery are often needed. Within each category of surgical instruments used for periodontal therapy there are usually several brands available, varying in form and quality, leaving ample room for individual preferences.

The instruments should be stored in sterile "ready-to-use" packs or trays. Handling, storing, and labeling of surgical instruments and equipment must be managed in such a way that interchange of sterile and non-sterile items is prevented.

It is also important that the instruments are kept in good working condition. The maintenance routine should ensure that scalers, curettes, knives with fixed blades, etc., are sharp and the hinges of scissors, rongeurs, and needle holders are properly lubricated. Spare instruments (sterile) should always be available to replace instruments found to be defective or accidentally contaminated.

Instrument tray

Different trays can be used for different procedures or a standard tray can be used for all procedures supplemented with the particular instruments that are needed for a specific procedure.

A commonly used standard tray combines the basic set of instruments used in oral surgery and a few periodontal instruments. The instruments listed below are often found on such a standard tray (Fig. 39-44):

- Mouth mirrors
- Graduated periodontal probe/explorer
- Handles for disposable surgical blades (e.g. Bard–Parker® handle)

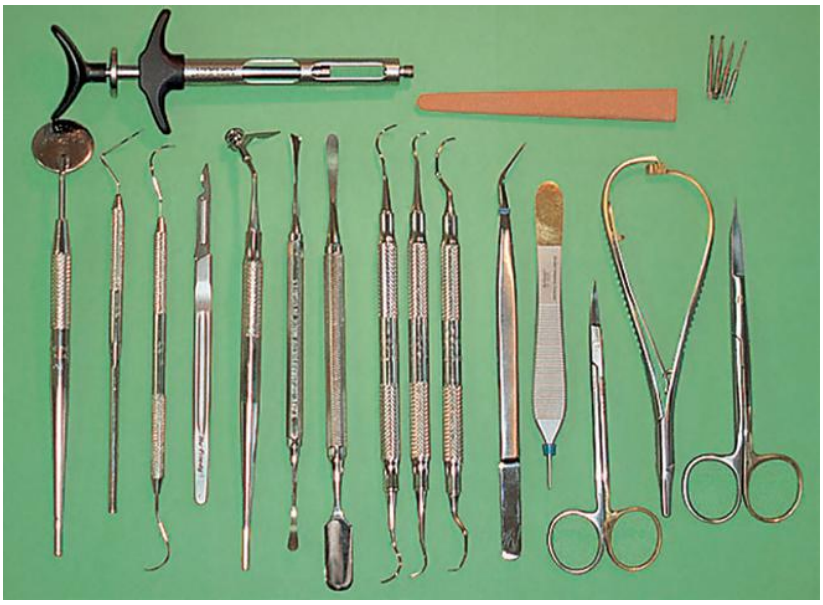

Fig. 39-44 Set of instruments used for periodontal surgery and included in a standard tray.

- Mucoperiosteal elevator and tissue retractor
- Scalers and curettes
- Cotton pliers
- Tissue pliers (*ad modum* Ewald)
- Tissue scissors
- Needle holder
- Suture scissors
- Plastic instrument
- Hemostat
- Burs.

Additional equipment may include:

- Syringe for local anesthesia
- Syringe for irrigation
- Aspirator tip
- Physiologic saline
- Drapings for the patient
- Surgical gloves, surgical mask, surgeon's hood.

Surgical instruments

Knives

Knives are available with fixed or replaceable blades. The advantage of the fixed blade versions is that the blade can be given any desired shape and orientation in relation to the handle. A disadvantage is that such instruments need frequent resharpening. Figure 39-45 shows examples of knives with fixed blades.

New disposable blades are always sharp. They can be rapidly replaced if found to be defective. The cutting edge of the blades normally follows the long axis of the handle, which limits their use. However, knives with disposable blades fitted at an angle to the handle are also available. Disposable blades are manufactured in different shapes (Fig. 39-46). When mounted in ordinary handles (Bard–Parker®), they are used to release incisions in flap operations and mucogingival surgery, and for reverse bevel incisions where access can be obtained. Special handles (Fig. 39-47) make it possible to mount blades in angulated positions, which facilitate the use of such knives for both gingivectomy excisions and reverse bevel incisions.

Fig. 39-45 Examples of gingivectomy knives with fixed blades. From left to right: Kirkland 15/16, Orban 1/2, and Waerhaug 1/2.

Scalers and curettes

Scaling and root planing in conjunction with periodontal surgery take place on exposed root surfaces. Access to the root surfaces for debridement may therefore be obtained with the use of comparatively sturdy

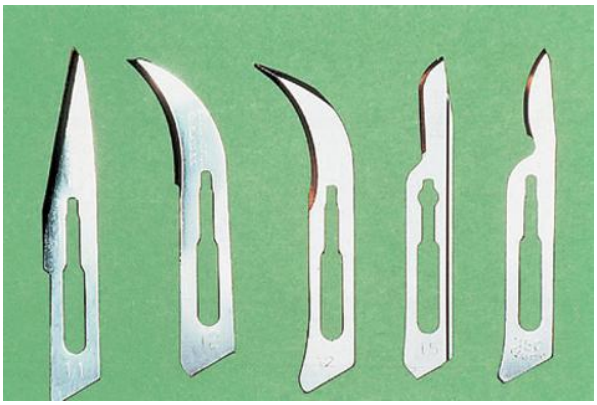

Fig. 39-46 Disposable blades which can be mounted in various types of handles. From left to right, blade shapes are: No. 11, No. 12, No. 12D, No. 15, and No. 15C.

Fig. 39-47 Universal 360° handle for disposable blades, which allows the mounting of the blade in any angulated position of choice.

instruments (Fig. 39-48). Rotating fine-grained diamond stones (Fig. 39-49) may be used within infrabony pockets, root concavities, and entrances to furcations. An ultrasonic device with sterile saline solution as coolant may also be used for root debridement during surgery. With the continuous irrigation of saline during the instrumentation of the roots, blood is rinsed away, offering improved visibility in the surgical field.

Instruments for bone removal

Sharp bone chisels or bone rongeurs (Fig. 39-50) cause the least tissue damage and should be employed whenever access permits. With reduced access,

Fig. 39-48 Examples of double-ended sickle scalers and curettes useful for root debridement in conjunction with periodontal surgery. From left to right: Curette SG 215/16C Syntette, Sickle 215-216 Syntette, and mini-curette SG 215/16MC.

Fig. 39-49 Set of burs useful in periodontal surgery. The rotating fine-grained diamond stones may be used for debridement of infrabony defects. The round burs are used for bone recontouring.

surgical burs or files may be used. The burs should operate at low speed and ample rinsing with sterile physiologic saline should ensure cooling and removal of tissue remnants.

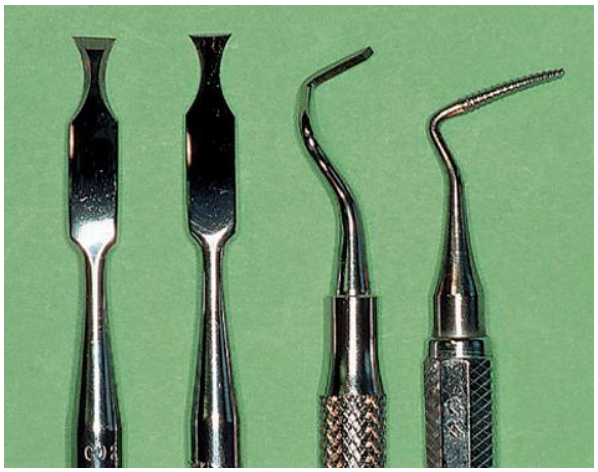

Fig. 39-50 Examples of instruments used for bone recontouring. From left to right: Bone chisels Ochsenbein No. 1 and 2 (Kirkland 13K/13KL), Bone chisel Ochsenbein No. 3, and Schluger curved file No. 9/10.

Instruments for handling flaps

The proper healing of the periodontal wound is critical for the success of the operation. It is therefore important that the manipulations of soft tissue flaps are performed with the minimum of tissue damage. Care should be exercised in the use of periosteal elevators when flaps are deflected and retracted for optimal visibility. Surgical pliers and tissue retractors that pierce the tissues should not be used in the marginal area of the flaps. Needle holders with small beaks and atraumatic sutures should be used.

Additional equipment

Hemorrhage is rarely a problem in periodontal surgery. The characteristic oozing type of bleeding can normally be controlled with a pressure pack (sterile gauze moistened with saline). Bleeding from small vessels can be stopped by clamping and tying using a hemostat and resorbable sutures. If the vessel is surrounded by bone, bleeding may be stopped by crushing the nutrient canal in which the vessel runs with a blunt instrument.

Sterile physiologic saline is used for rinsing and moistening the field of operation and for cooling when burs are employed. The saline solution may be kept in a sterile metal cup on the instrument tray and may be applied to the wound by means of a sterile disposable plastic syringe and a needle with a blunt tip.

Visibility in the field of operation is secured by using effective suction. The lumen of the aspirator tip should have a smaller diameter than the rest of the tube, in order to prevent clogging.

The patient's head may be covered by autoclaved cotton drapings or sterile disposable plastic/paper drapings. The surgeon and all assistants should wear sterile surgical gloves, a surgical mask, and a surgeon's hood.

Selection of surgical technique

Many of the technical problems experienced in periodontal surgery stem from the difficulties in accurately assessing the degree and type of breakdown that has occurred prior to surgery. Furthermore, at the time of surgery, previously undiagnosed defects may be recognized or some defects may have a more complex outline than initially anticipated. Since each of the surgical procedures described above is designed to deal with a specific situation or to meet a certain objective, it must be understood that in most patients no single standardized technique alone can be applied when periodontal surgery is undertaken. Therefore, in each surgical field, different techniques are often used and combined in such a way that the overall objectives of the surgical part of the periodontal therapy are met. As a general rule, surgical modalities of therapy that preserve or induce the formation of periodontal tissue should be preferred over those that resect or eliminate tissue.

General indications for various surgical techniques

Gingivectomy

The obvious indication for gingivectomy is the presence of deep supra-alveolar pockets. In addition, the gingivectomy technique can be used to reshape abnormal gingival contours such as gingival craters and gingival hyperplasias (see Fig. 39-43). In such cases, the technique is often termed *gingivoplasty*.

Gingivectomy is usually not considered suitable in situations where the incision will lead to the removal of the entire zone of gingiva. This is the case when the bottom of the probeable pocket to be excised is located at or below the mucogingival junction. As an alternative in such a situation, an *internal beveled gingivectomy* may be performed (Fig. 39-51). Furthermore, since the gingivectomy procedure is aimed at the complete elimination of the periodontal pocket, the procedure cannot be used in periodontal sites where bony craters are present.

These limitations, combined with the development in recent years of surgical methods which have a broader field of application, have led to less frequent use of gingivectomy.

Flap operation with or without osseous surgery

Flap operations can be used in all cases where surgical treatment of periodontal disease is indicated. Flap procedures are particularly useful at sites where pockets extend beyond the mucogingival border and/or where treatment of bony defects and furcation involvements is required.

The advantages of flap operations include:

- Existing gingiva is preserved
- Marginal alveolar bone is exposed such that the morphology of bony defects can be identified and the proper treatment rendered

- Furcation areas are exposed, and the degree of involvement and the "tooth–bone" relationship can be identified
- Flap can be repositioned at its original level or shifted apically, thereby making it possible to adjust the gingival margin to the local conditions
- Flap procedure preserves the oral epithelium and often makes the use of a surgical dressing superfluous
- Postoperative period is usually less unpleasant to the patient when compared to gingivectomy.

Treatment decisions for soft and hard tissue pockets in flap surgery

Classifications of different flap modalities used in the treatment of periodontal disease often make distinctions between methods involving the marginal tissues and those involving the mucogingival area and, further, between tissue-eliminating/resective and tissue-preserving/reconstructive types (access flaps for debridement). Such classifications appear to be less than precise since several techniques are often combined in the treatment of individual cases, and since there is no clear-cut relationship between disease characteristics and selection of surgical methods. From a didactic point of view, it seems more appropriate to consider surgical therapy with regard to how to deal with (1) the soft tissue component and (2) the hard tissue component of the periodontal pocket at a specific tooth site (Fig. 39-52).

Soft tissue pockets

The description of the various flap procedures reveals that, depending on the surgical technique used, the soft tissue flap should either be apically positioned at the level of the bone crest (original Widman flap, Neumann flap, and apically repositioned flap) or maintained in a coronal position (Kirkland flap, modified Widman flap, and papilla preservation flap) at the completion of the surgical intervention. The maintenance of the presurgical soft tissue height is of importance from an esthetic point of view, particularly in the anterior tooth region. However, long-term results from clinical trials have shown that major differences in the final position of the soft tissue margin are not evident between surgical procedures involving coronal and apical positioning of the flap margin. The reported difference in final positioning of the gingival margin between surgical techniques is attributed to osseous recontouring (Townsend-Olsen *et al*. 1985; Lindhe *et al*. 1987; Kaldahl *et al*. 1996; Becker *et al*. 2001). In many patients it may be of significance to position the flap coronally in the anterior tooth region in order to give the patient a prolonged

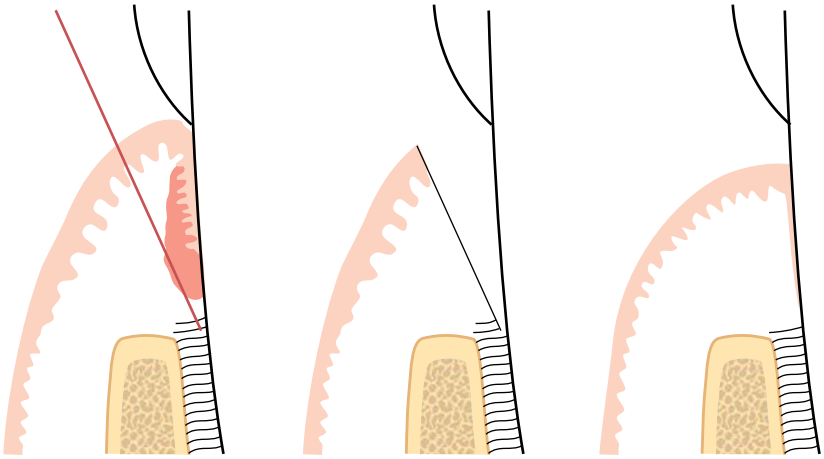

Fig. 39-51 Internal beveled gingivectomy. Schematic illustration of the incision technique in case of the presence of only a minimal zone of gingiva.

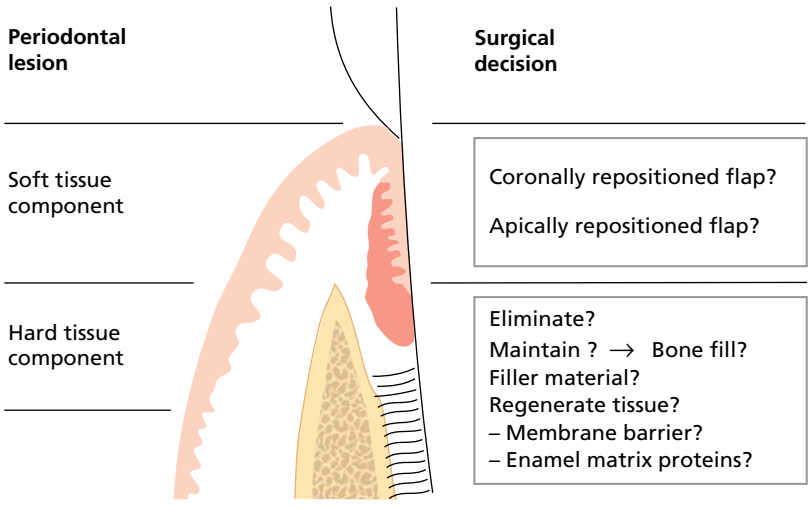

Fig. 39-52 Surgical decisions. Treatment decisions with respect to the soft and the hard tissue component of a periodontal pocket.

time of adaptation to the inevitable soft tissue recession. In the posterior tooth region, however, an apical position should be the standard.

Independent of flap position, the goal should be to achieve complete soft tissue coverage of the alveolar bone, not only at buccal/lingual sites but also at proximal sites. It is therefore of utmost importance to carefully plan the incisions in such a way that this goal is achieved at the termination of the surgical intervention.

Hard tissue pockets

During conventional periodontal surgery, one would usually opt for the conversion of an intrabony defect into a suprabony defect, which then is eliminated by apical repositioning of the soft tissue flap(s). Osseous recontouring of angular bony defects and craters is an excisional technique, which should be used with caution and discrimination. However, the therapist is often faced with the dilemma of deciding whether or not to eliminate an angular bony defect. There are a number of factors that should be considered in the treatment decision, such as:

- Esthetics
- Tooth/tooth site involved
- Defect morphology
- Amount of remaining periodontium.

Since alveolar bone supports the soft tissue, an altered bone level through recontouring will result in recession of the soft tissue margin. For esthetic reasons, one may therefore be restrictive in eliminating proximal bony defects in the anterior tooth region. For example, in the case of an approximal crater, it may often be sufficient to reduce/eliminate the bone wall on the lingual side of the crater, thereby maintaining the bone support for the soft tissue on the facial aspect (see Fig. 39-40). In favor of esthetics, one may even have to compromise the amount of bone removal and accept that a certain pocket depth will remain in certain situations. In addition to esthetics, the presence of furcations may limit the extent to which bone recontouring can be performed.

Defect morphology is a variable of significance for repair/regeneration during healing (Rosling *et al*. 1976a; Cortellini *et al*. 1993, 1995a). While two- and, especially, three-wall defects may show great potential for repair/regeneration, one-wall defects and interproximal craters will rarely result in such resolution. Further, the removal of intrabony connective tissue/granulation tissue during a surgical procedure will always lead to crestal resorption of bone, especially in sites with thin bony walls. This results in reduction of the vertical dimensions of the bone tissue at the site (Fig. 39-53).

The various treatment options available for the hard tissue defect may include:

- Eliminating the osseous defect by resection of bone (osteoplasty and/or ostectomy)
- Maintaining the area without osseous resection (hoping for some type of periodontal repair, e.g. bone fill leading to gain of clinical attachment)

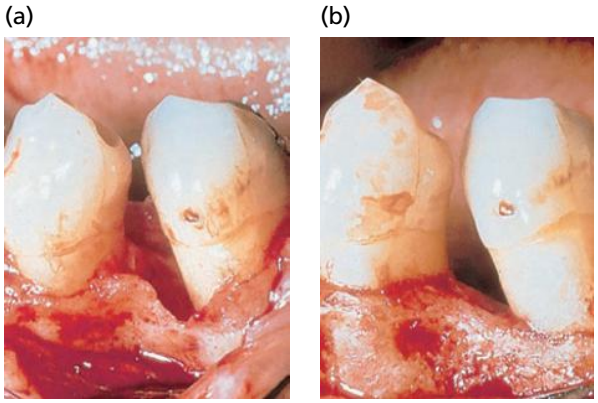

Fig. 39-53 Crestal bone resorption following a modified Widman flap procedure without bone recontouring. (a) View of the area at time of initial surgical treatment. (b) At the re-entry operation performed after 6 months of healing.

- Compromising the amount of bone removal and accepting that a certain pocket depth will remain
- Attempting to improve healing through the use of a regenerative procedure
- Extracting the involved tooth if the bony defect is considered too advanced.

After careful consideration, indications for osseous surgery in conjunction with apical repositioning of flaps may also include subgingival caries, perforations or root fractures in the coronal third of the root, as well as inadequate retention for fixed prosthetic restorations due to a short clinical crown (crown lengthening procedures). The "crown lengthening" needed in such cases is performed by removing often significant amounts of supporting bone and by recontouring. A dimension of approximately 3 mm between the alveolar bone crest and the anticipated restoration margin must be ensured (Brägger *et al*. 1992; Herrero *et al*. 1995; Pontoriero & Carnevale 2001).

Root surface instrumentation

Before incisions are made to excise or elevate the soft tissue, a careful examination should be carried out to identify at which tooth sites periodontal lesions remain. Only tooth sites with signs of pathology (bleeding following pocket probing) should be subjected to root instrumentation following surgical exposure. Before root instrumentation is executed, remaining granulation tissue must be removed and indicated bone recontouring carried out.

The root instrumentation can be performed with hand or ultrasonic instruments according to the operator's preferences. Ultrasonic (sonic) instrumentation offers the additional benefits of improved visibility due to the irrigating effect of the cooling solution (sterile saline). For root instrumentation within intrabony defects, root concavities, and entrances to furcations, the use of rotating fine-grained diamond stones may be used.

Root surface conditioning/biomodification

An important consideration in periodontal surgery is to make the exposed root surface biologically compatible with a healthy periodontium. In addition to mechanical debridement, agents such as citric acid/orthophosphoric acid, tetracycline, and EDTA have been used for root surface conditioning. Root surface conditioning/biomodification by means of an etching procedure may serve several purposes:

- Removal of the smear layer following mechanical debridement
- Demineralization of the root surface (citric acid)
- Selective removal of hydroxyapatite and exposure of the collagenous matrix of the root surface (EDTA)
- Local delivery of antimicrobial compound (tetracycline HCl)
- Inhibition of collagenolytic activity (tetracycline HCl)
- Enhancing cellular responses
- Prevention of epithelial down-growth
- Improving retention of different biomolecules to exposed collagen
- Expression of a cementoblast phenotype for colonizing cells.

It should be noted that etching of a root surface with an agent operating at a low pH (e.g. citric acid or orthophosphoric acid) might exert immediate necrotizing effects on the surrounding periodontal ligament and other periodontal tissues, whereas agents operating at a neutral pH (e.g. EDTA) do not seem to have this negative effect (Blomlöf & Lindskog 1995a, b).

Although *in vitro* results have indicated possible benefits of the use of root surface conditioning/biomodification agents through enhanced cellular responses during wound healing, the usefulness of acids as well as other chemical agents for conditioning of root surfaces in conjunction with conventional periodontal surgery has been questioned (Blomlöf *et al*. 2000). Histologic evidence indicates that healing following root surface conditioning with acids or other chemical agents occurs predominately by a long junctional epithelium or connective tissue attachment without new cementum formation.

Suturing

When a flap procedure has been employed it is important to ensure that, at the end of surgery, the flaps are placed in the intended position and that they are properly adapted to each other and to the tooth surfaces. Preferably, full coverage of the buccal/lingual (palatal) and interdental alveolar bone should be obtained by full (primary) closure of the soft tissue flaps. If this can be achieved, healing is by first intention and postoperative bone resorption is minimal. Therefore, prior to suturing, the flap margins should be trimmed to properly fit the buccal and lingual (palatal) bone margin as well as the interproximal areas; excessive soft tissue must be removed. If the amount of flap tissue present is insufficient to cover the interproximal bone, the flaps at the buccal or lingual aspects of the teeth must be recontoured and, in some cases, even displaced coronally.

Following proper trimming, the flaps are secured in the correct position by sutures. Sutures should not interfere with incision lines and must not pass through the tissues near the flap margins or too close to a papilla, because this may result in tearing of the tissues. The use of non-irritating, mono-filamentous materials is recommended. These materials are non-resorbable and extremely inert, do not adhere to tissues, and are therefore easy to remove. "Wicking", the phenomenon of bacteria moving along or within multistranded suture materials, particularly silk, is also avoided. The dimensions usually preferred are 4/0 or 5/0, but even finer suture material (6/0 or 7/0) may be used. Sutures are removed after 7–14 days.

Since the flap tissue following the final preparation is thin, either curved or straight non-traumatic needles (eyeless), with a small diameter, should be used. Such needles are available as rounded (non-cutting) or with different cutting edges. In the latter case, a reverse-cutting needle should be selected.

Technique

The three most frequently used sutures in periodontal flap surgery are:

- Interrupted interdental sutures
- Suspensory sutures
- Continuous sutures.

The *interrupted interdental suture* (Fig. 39-54) provides a close interdental adaptation between the buccal and lingual flaps with equal tension on both units. This type of suture is therefore not recommended when the buccal and lingual flaps are repositioned at different levels. When this technique of suturing is employed, the needle is passed through the buccal flap from the external surface, across the interdental area, and through the lingual flap from the internal surface, or vice versa. When closing the suture, care must be taken to avoid tearing the flap tissues.

In order to avoid having the suture material between the mucosa and the alveolar bone in the interdental area, an alternative technique with the interrupted interdental suture can be used if the flaps have not been elevated beyond the mucogingival line (Fig. 39-55). With the use of a curved needle, the suture is anchored in the attached tissue on the buccal aspect of the proximal site, brought to the lingual side through the proximal sites, and anchored in the attached tissue on the lingual side. The suture is then brought back to the starting point and tied (Fig. 39-55b). Hence, the suture will lie on the surface of the interdental tissue, keeping the soft tissue flaps in close contact with the underlying bone.

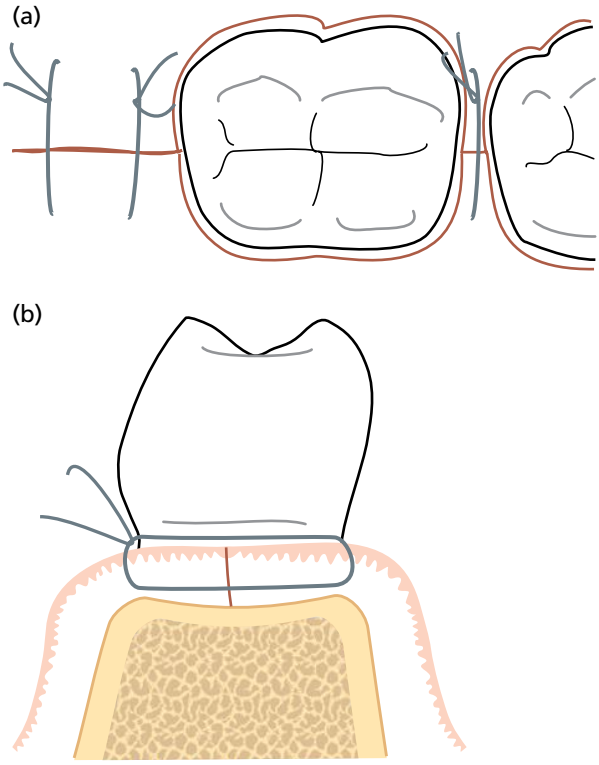

Fig. 39-54 Suturing. (a, b) Interrupted interdental suture.

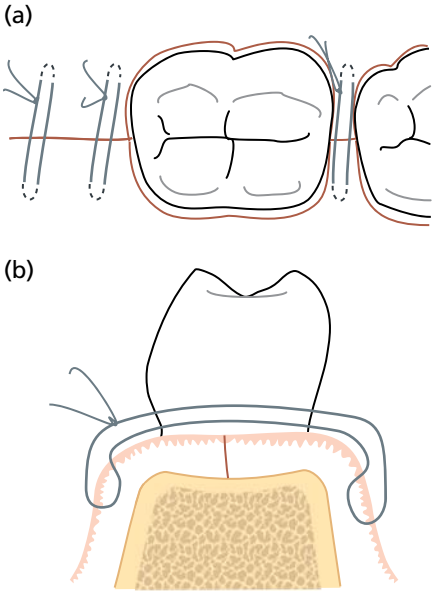

Fig. 39-55 Suturing. (a, b) Modified interrupted interdental suture. Note that with this suturing technique the suture lies on the surface of the interdental tissue keeping the soft tissue flaps in close contact with the underlying bone.

In regenerative procedures, which usually require a coronal advancement of the flap, a *modified mattress suture* may be used as an interdental suture to secure close flap adaptation (Fig. 39-56). As for the interupted suture, the needle is passed through the buccal flap from the external surface, across the interdental area, and through the lingual flap from the internal surface. The suture is then run back to the buccal side by passing the needle through the lingual and buccal flaps. Thereafter, the suture is brought through the approximal site coronally to the tissue, passed through the loop of the suture on the lingual aspect, and then brought back to the starting point on the buccal side and tied.

The *suspensory suture* (Fig. 39-57) is used primarily when the surgical procedure is of limited extent and involves only the tissue of the buccal or lingual aspect of the teeth. It is also the suture of choice when the buccal and lingual flaps are repositioned at different levels. The needle is passed through the buccal flap from its external surface at the mesial side of the tooth, the suture is placed around the lingual surface of the tooth, and the needle is passed through the buccal flap on the distal side of the tooth (Fig. 39-57a). The suture is brought back to the starting point via the lingual surface of the tooth and tied (Fig. 39-57b, c). If a lingual flap has been elevated as well, this is secured in the intended position using the same technique.

The *continuous suture* (Fig. 39-58) is commonly used when flaps involving several teeth are to be repositioned apically. When flaps have been elevated on both sides of the teeth, one flap at a time is secured in its correct position. The suturing procedure is started at the mesial/distal aspect of the buccal flap by passing the needle through the flap and across the interdental area. The suture is laid around the lingual surface of the tooth and returned to the buccal side through the next interdental space. The procedure is repeated tooth by tooth until the distal/mesial end of the flap is reached. Thereafter, the needle is passed through the lingual flap (Fig. 39-58a), with the suture laid around the buccal aspect of each tooth and through each interproximal space. When the suturing of the lingual flap is completed and the needle has been brought back to the first interdental area, the positions of the flaps are adjusted and secured in their proper positions by closing the suture (Fig. 39-58b). Thus, only one knot is needed.

Periodontal dressings

Periodontal dressings are mainly used:

- To protect the wound post-surgically
- To obtain and maintain a close adaptation of the mucosal flaps to the underlying bone (especially when a flap has been repositioned apically)
- For the comfort of the patient.

In addition, periodontal dressings can prevent postoperative bleeding during the initial phase of healing and, if properly placed in the operated segment (especially interproximally), prevent the formation of excessive granulation tissue.

Periodontal dressings should have the following properties:

- Soft, but with enough plasticity and flexibility to facilitate placement in the operated area and to allow proper adaptation

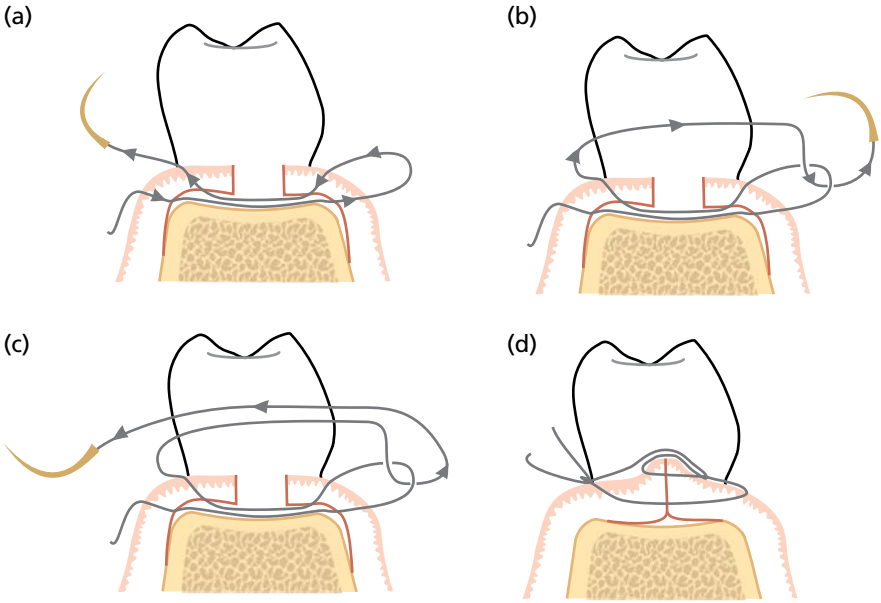

Fig. 39-56 Suturing. (a–d) Modified mattress suture.

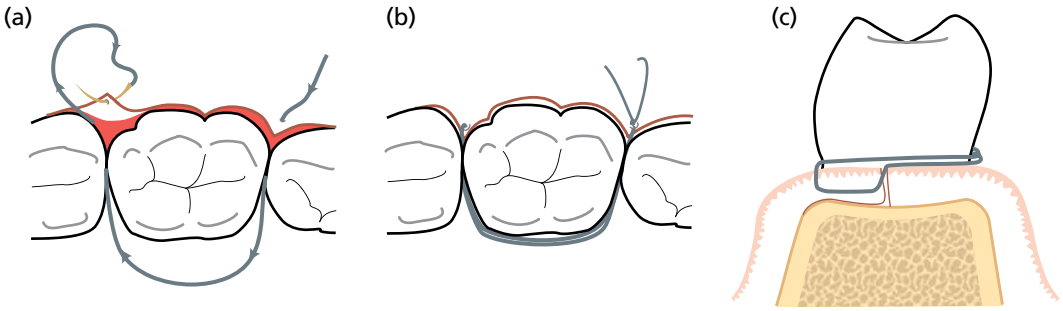

Fig. 39-57 Suturing. (a–c) Suspensory suture.

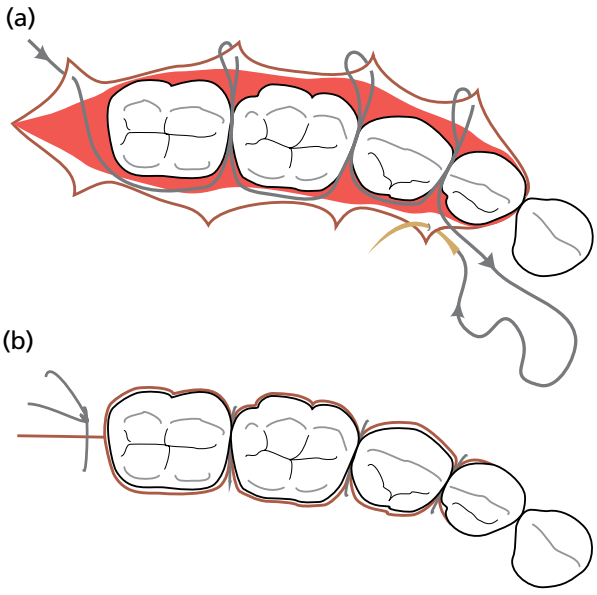

Fig. 39-58 Suturing. (a, b) Continuous suture.

- Hardens within a reasonable time
- After setting, sufficiently rigid to prevent fracture and dislocation
- Smooth surface after setting to prevent irritation of the cheeks and lips
- Preferably, bacteriocidal properties to prevent excessive plaque formation
- Must not detrimentally interfere with healing.

It has been suggested that antibacterial agents should be incorporated into periodontal dressings to prevent bacterial growth in the wound area during healing. Results from clinical studies and *in vitro* evaluation of the antibacterial properties of various periodontal dressings, however, suggest that the antibacterial activity of most commercial dressings probably is exhausted long before the end of the 7–14-day period during which the dressing is frequently maintained in the operated segment (O'Neil 1975; Haugen *et al*. 1977).

Mouth rinsing with antibacterial agents such as chlorhexidine does not prevent the formation of plaque *under* the dressing (Plüss *et al*. 1975) and should therefore not be regarded as a means to improve or shorten the period of wound healing. On the other hand, results from clinical studies as well as clinical experience suggest that a periodontal dressing may often be unnecessary or even undesirable after periodontal flap procedures and may be usefully replaced by rinsing with chlorhexidine only (Sanz *et al*. 1989; Vaughan & Garnick 1989).

A commonly used periodontal dressing is Coe-Pak™ (GC America Inc., Alsip, IL, USA), which is

supplied in two tubes. One tube contains oxides of various metals (mainly zinc oxide) and lorothidol (a fungicide). The second tube contains non-ionizing carboxylic acids and chlorothymol (a bacteriostatic agent). Equal parts from both tubes are mixed together immediately prior to insertion. Adding a retarder can prolong the setting time of the dressing.

A light-cured dressing, for example Barricaid™ (Dentsply Caulk., Milford, DE, USA), is useful in the anterior tooth region and particularly following mucogingival surgery, because it has a favorable esthetic appearance and it can be applied without dislocating the soft tissue. However, the light-cured dressing is not the dressing of choice for situations where the flap has to be retained apically, due to its soft state before curing.

Cyanoacrylates have also been used as periodontal dressings with varying success. These dressings are applied in a liquid directly on to the wound, or sprayed over the wound surface. Although the application of this kind of dressing is simple, its properties often do not meet clinical demands.

Application technique

1. Ensure that bleeding from the operated tissues has ceased before the dressing material is inserted.
2. Carefully dry the teeth and soft tissue before application for optimal adherence of the dressing.
3. Moisten the surgical gloves to avoid the material sticking to the fingertips.
4. When using the Coe-Pak™ dressing material, the interproximal areas are filled first. Thin rolls of the dressing, adjusted in length to cover the entire field of operation, are then placed against the buccal and lingual surfaces of the teeth. The rolls are pressed against the tooth surfaces and the dressing material is forced into the interproximal areas. Coe-Pak™ may also be applied to the wound surfaces by means of a plastic syringe. It is important to ensure that dressing material is never introduced between the flap and the underlying bone or root surface.

   The light-cured dressing (Barricaid™) is preferably applied with the supplied syringe, adjusted, and then cured by light.
5. The surface of the dressing is subsequently smoothened and excess material is removed with a suitable instrument (a knife or finishing burs in a low-speed handpiece). The dressing should not cover more than the apical third of the tooth surfaces. Furthermore, interference of the dressing with mucogingival structures (e.g. vestibular fold, frenula) should be carefully checked to avoid displacement of the dressing during normal function.

Postoperative pain control

In order to minimize postoperative pain and discomfort for the patient, surgical handling of the tissues should be as atraumatic as possible. Care should be taken during surgery to avoid unnecessary tearing of the flaps, to keep the bone moistened, and to secure complete soft tissue coverage of the alveolar bone at suturing. With a carefully performed surgical procedure, most patients will normally experience only minimal postoperative problems. The pain experience is usually limited to the first days following surgery and of a level that in most patients can be adequately controlled with normally used drugs for pain control. However, it is important to recognize that the pain threshold level is subjective and may vary between individuals. It is also important to give the patient information about the post-surgical sequence and that uncomplicated healing is the common event. Further, during the early phase of healing, the patient should be instructed to avoid chewing in the area subjected to surgical treatment.

Post-surgical care

Postoperative plaque control is the most important variable in determining the long-term result of periodontal surgery. Provided proper postoperative infection control levels are established, most surgical treatment techniques will result in conditions that favor the maintenance of a healthy periodontium. Although there are other factors of a more general nature affecting surgical outcome (e.g. the systemic status of the patient at the time of surgery and during healing), disease recurrence is an inevitable complication, regardless of surgical technique used, in patients not given proper post-surgical and maintenance care.

Since self-performed oral hygiene is often associated with pain and discomfort during the immediate post-surgical phase, regularly performed professional tooth cleaning is a more effective means of mechanical infection control following periodontal surgery. In the immediate post-surgical period, self-performed rinsing with a suitable antiplaque agent, for example twice daily rinsing with 0.1–0.2% chlorhexidine solution, is recommended. Although an obvious disadvantage with the use of chlorhexidine is the staining of the teeth and tongue, this is usually not a deterrent for compliance. Nevertheless, it is important to return to and maintain good mechanical oral hygiene measures as soon as possible, particularly since rinsing with chlorhexidine, in contrast to properly performed mechanical oral hygiene, is unlikely to have any influence on subgingival recolonization of plaque.

Maintaining good post-surgical wound stability is another important factor affecting the outcome of some types of periodontal flap surgery. If wound stability is judged an important part of a specific procedure, the procedure itself as well as the post-surgical care must include measures to stabilize the healing wound (e.g. adequate suturing technique, protection from mechanical trauma to the marginal tissues during the initial healing phase). If a mucoperiosteal flap is replaced rather than repositioned apically, early apical migration of gingival epithelial cells will occur as a consequence of a break between root surface and healing connective tissue. Hence, maintenance of a tight adaptation of the flap to the root surface is essential and one may therefore consider keeping the

sutures in place for longer than the 7–10 days usually prescribed following standard flap surgery.

Following suture removal, the surgically treated area is thoroughly irrigated with a dental spray and the teeth are carefully cleaned with a rubber cup and polishing paste. If the healing is satisfactory for starting mechanical tooth cleaning, the patient is instructed in gentle brushing of the operated area using a toothbrush that has been softened in hot water. Toothpicks are prescribed for cleaning the interdental area. In this early phase following surgical treatment, the use of interdental brushes is abandoned due to the risk of traumatizing the interdental tissues. Visits are scheduled for supportive care at 2-week intervals to monitor the patient's plaque control closely. During this postoperative maintenance phase, adjustments to the methods for optimal self-performed mechanical cleaning are made depending on the healing status of the tissues. The time interval between visits for supportive care may gradually be increased, depending on the patient's plaque control standard.

Outcome of surgical periodontal therapy

Healing following surgical pocket therapy

Gingivectomy

Within a few days following excision of the inflamed gingival soft tissues coronal to the base of the periodontal pocket, epithelial cells start to migrate over the wound surface. The epithelialization of the gingivectomy wound is usually complete within 7–14 days following surgery (Engler *et al*. 1966; Stahl *et al*. 1968). During the following weeks, a new dentogingival unit is formed (Fig. 39-59). The fibroblasts in the supraalveolar tissue adjacent to the tooth surface proliferate (Waerhaug 1955) and new connective tissue is laid down. If the wound healing occurs in the vicinity of a plaque-free tooth surface, a free gingival unit will form which has all the characteristics of a normal free gingiva (Hamp *et al*. 1975). The height of the newly formed free gingival unit may vary not only between different parts of the dentition, but also from one tooth surface to another due primarily to anatomic factors.

The re-establishment of a new, free gingival unit by coronal regrowth of tissue from the line of the "gingivectomy" incision implies that sites with so-called "zero pockets" only occasionally occur following gingivectomy. Complete healing of the gingivectomy wound takes 4–5 weeks, although from clinical inspection of the surface of the gingiva, it may appear to be healed after approximately 14 days (Ramfjord *et al*. 1966). Minor remodeling of the alveolar bone crest may also occur postoperatively.

Apically repositioned flap

Following osseous surgery for elimination of bony defects and the establishment of "physiologic contours" and repositioning of the soft tissue flaps to the level of the alveolar bone, healing will occur primarily by first intention, especially in areas where proper soft tissue coverage of the alveolar bone has been obtained. During the initial phase of healing, bone resorption of varying degrees almost always occurs in the crestal area of the alveolar bone (Fig. 39-60) (Ramfjord & Costich 1968). The extent of the reduction of the alveolar bone height resulting from this resorption is related to the thickness of the bone in each specific site (Wood *et al*. 1972; Karring *et al*. 1975).

During the phase of tissue regeneration and maturation, a new dentogingival unit will form by coronal growth of the connective tissue. This regrowth occurs in a manner similar to that which characterizes healing following gingivectomy.

Modified Widman flap

If a "modified Widman flap" procedure is carried out in an area with a deep infrabony lesion, bone repair may occur within the boundaries of the lesion (Rosling *et al*. 1976a; Polson & Heijl 1978). However, crestal bone resorption is also seen. The amount of bone fill

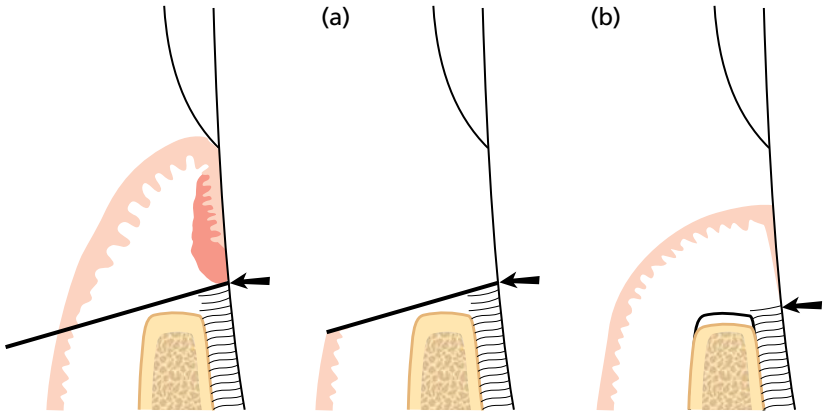

Fig. 39-59 Gingivectomy. Dimensional changes as a result of therapy. (a) Preoperative dimensions and position of the incision line. Black line indicates the location of the primary incision, that is the suprabony pocket is eliminated with the gingivectomy technique; before and after excision of the soft tissue corresponding to the depth of the periodontal pocket. (b) Dimensions following proper healing. Minor resorption of the alveolar bone crest as well as some loss of connective tissue attachment may occur during the healing. The arrows indicate the coronal position of the connective tissue attachment to the root.

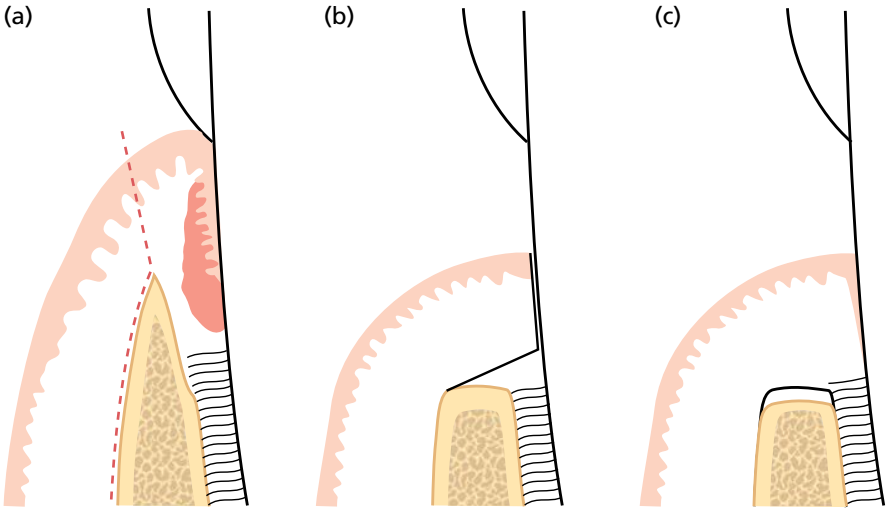

Fig. 39-60 Apically repositioned flap. Dimensional changes. (a) Preoperative dimensions. The dashed line indicates the border of the elevated mucoperiosteal flap. (b) Bone recontouring has been completed and the flap repositioned to cover the alveolar bone. (c) Dimensions following healing. Minor resorption of the marginal alveolar bone has occurred as well as some loss of connective tissue attachment.

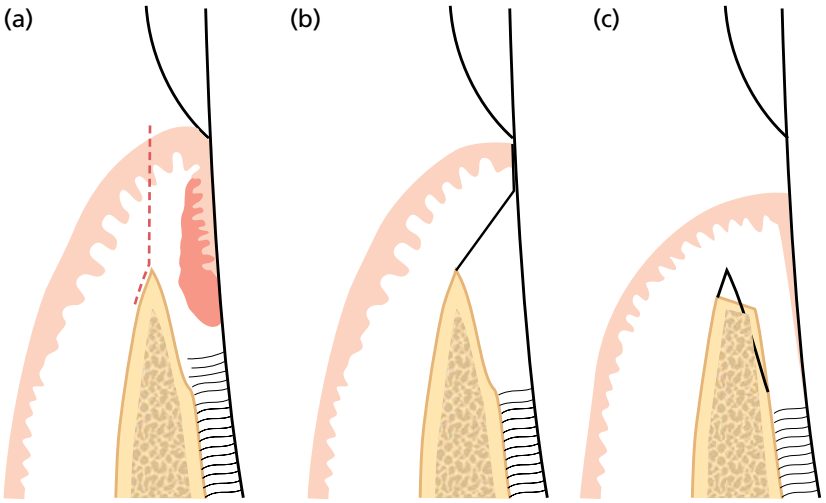

Fig. 39-61 Modified Widman flap. Dimensional changes. (a) Preoperative dimensions. The dashed line indicates the border of the elevated mucoperiosteal flap. (b) Surgery (including curettage of the angular bone defect) is completed with the mucoperiosteal flap repositioned as close as possible to its presurgical position. (c) Dimensions following healing. Osseous repair as well as some crestal bone resorption can be expected during healing with the establishment of a "long" junctional epithelium interposed between the regenerated bone tissue and the root surface. Apical displacement of the soft tissue margin has occurred.

obtained is dependent upon (1) the anatomy of the osseous defect (e.g. a three-walled infrabony defect often provides a better mold for bone repair than two- or one-walled defects), (2) the amount of crestal bone resorption, and (3) the extent of chronic inflammation, which may occupy the area of healing. Interposed between the regenerated bone tissue and the root surface, a long junctional epithelium is always found (Fig. 39-61) (Caton & Zander 1976; Caton *et al*. 1980). The apical cells of the newly formed junctional epithelium are found at a level on the root that closely coincides with the presurgical attachment level.

Soft tissue recession will take place during the healing phase following a modified Widman flap procedure. Although the major apical shift in the position of the soft tissue margin will occur during the first 6 months following the surgical treatment (Lindhe *et al*. 1987), the soft tissue recession may often continue for >1 year. Factors influencing the degree of soft tissue recession as well as the time period for soft tissue remodeling include the initial height and thickness of the supracrestal flap tissue and the amount of crestal bone resorption.

Clinical outcome of surgical access therapy in comparison to non-surgical therapy

Surgical treatment of periodontal lesions mainly serves the purpose of (1) creating accessibility for proper professional debridement of the infected root surfaces and (2) establishing a gingival morphology that facilitates the patient's self-performed infection control, in order to enhance the long-term preservation of the dentition. Hence, the amount of tooth loss is the most relevant

criterion in an evaluation of the relative importance of surgical access therapy in the overall treatment of periodontal disease. However, this requires studies with extremely long follow-up periods and, therefore, other criteria are commonly used to evaluate the efficacy of periodontal therapy, even if these may only be considered as surrogate end points. The most commonly used outcome criteria in clinical research have been resolution of gingivitis (bleeding on probing), probing pocket depth reduction, and clinical attachment level change. An additional variable often of concern is gingival recession, since this outcome variable may affect the patient's overall appreciation of the treatment result. With regard to changes in probing attachment levels, it should be recalled that healing following conventional surgical access therapy consistently results in the formation of a junctional epithelium to a level on the root that closely coincides with the presurgical attachment level. Hence, when evaluating the outcome of various therapeutic approaches, the magnitude of *gain* of clinical attachment may be of less importance since it mainly is a measure of "pocket closure". Instead, maintained probing attachment levels or further loss should be focused on as the pertinent outcome variable.

Pioneering contributions to the understanding of the relative importance of the surgical component of periodontal therapy were generated by the classical longitudinal studies of the Michigan group (Ramfjord and co-workers) and the Gothenburg group (Lindhe and co-workers). Subsequently, several other clinical research centers contributed important data regarding the efficacy of surgical access therapy in comparison to non-surgical periodontal therapy. The topic has been extensively reviewed (e.g. Kaldahl *et al*. 1993; Palcanis 1996; Heitz-Mayfield *et al*. 2002) and some of the general conclusions from these reviews will be highlighted below.

Plaque accumulation

An important factor to consider in the evaluation of the relative effect of the surgical component of periodontal therapy is the standard of postoperative infection control. Nyman *et al*. (1977) reported on a clinical study in which the patients received only a single episode of oral hygiene instruction before the surgical treatment and no specific postoperative supportive care. As a consequence, both plaque and gingival indices remained relatively high during the 2 years of postoperative follow-up. Independent of the surgical technique used, the patients showed a rebound of pocket depths to more or less pretreatment levels and further deterioration of clinical attachment levels at both proximal and lingual tooth sites (Fig. 39-62). In contrast, in a parallel study in which the patients received repeated oral hygiene instructions and professional tooth cleaning once every 2 weeks during the postoperative period (Rosling *et al*. 1976b), the patients maintained the surgically reduced pocket depth throughout the 2-year follow-up period and clinical attachment level gains were observed for most of the surgical procedures evaluated (Fig. 39-63). The fact that the standard of postoperative oral hygiene is decisive for the outcome of surgical pocket therapy is further underlined by data from a 5-year

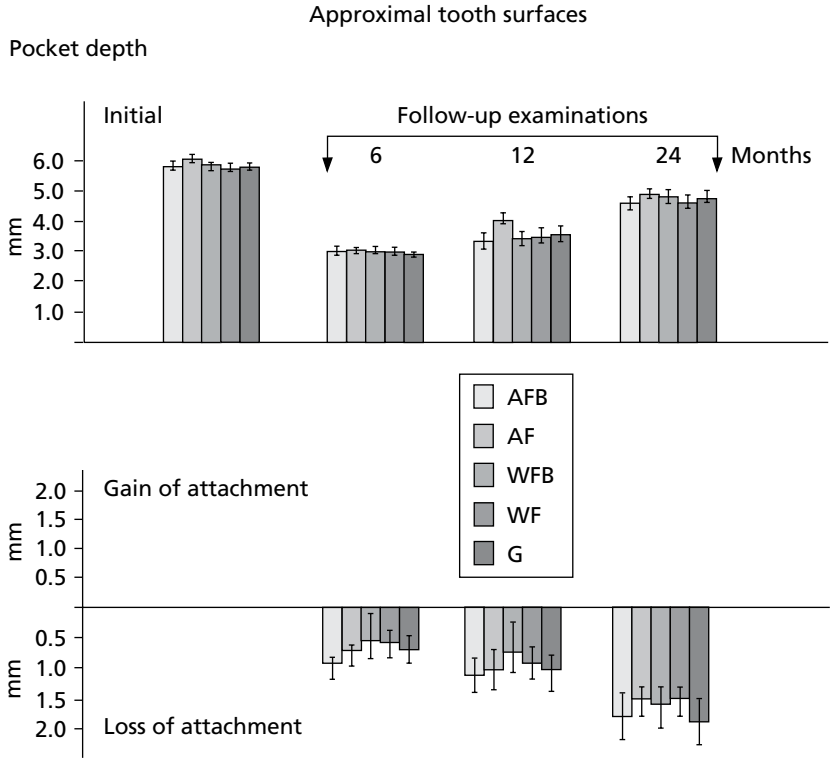

Fig. 39-62 Average approximal pocket depth at the initial examination and 6, 12, and 24 months after surgery (top), and alterations in approximal attachment levels from the initial examination immediately prior to surgery to the re-examinations 6, 12, and 24 months postoperatively (bottom). Note that only areas with pockets that at the initial examination had a depth of 3 mm or more are included in the analysis. (AFB, apically repositioned flap with bone recontouring; AF, apically repositioned flap; WFB, modified Widman flap with bone recontouring; WF, modified Widman flap; G, gingivectomy including curettage of bone defects. Bars show standard error.) (Data from Nyman *et al*. 1977.)

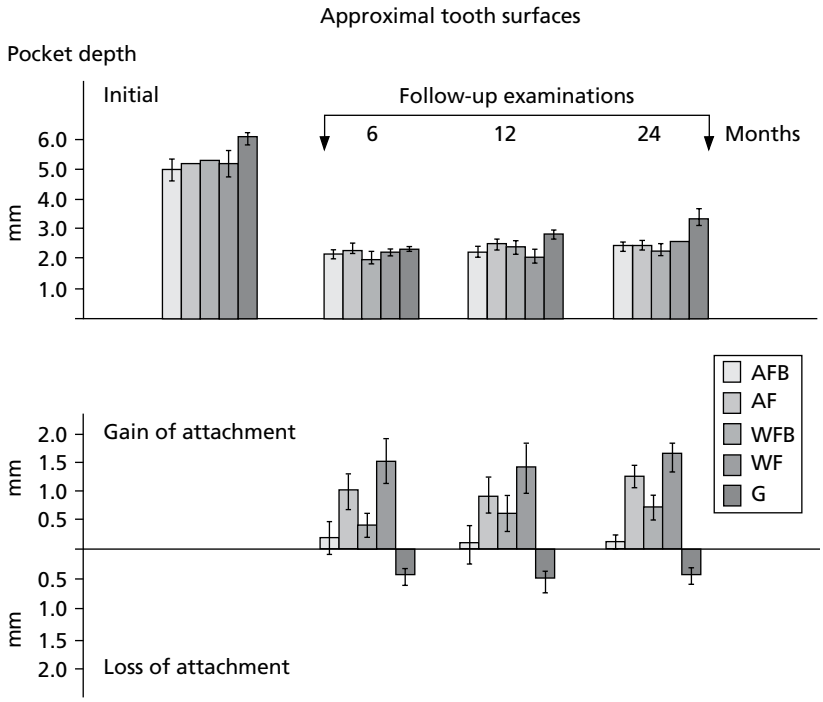

Fig. 39-63 Average approximal pocket depth at the initial examination and 6, 12, and 24 months after surgery (top), and alterations in approximal attachment levels from the initial examination immediately prior to surgery to the re-examinations 6, 12, and 24 months postoperatively (bottom). Note that only areas with pockets that at the initial examination had a depth of 3 mm or more are included in the analysis. (AFB, apically repositioned flap with bone recontouring; AF, apically repositioned flap; WFB, modified Widman flap with bone recontouring; WF, modified Widman flap; G, gingivectomy including curettage of bone defects. Bars show standard error.) (Data from Rosling *et al*. 1976b.)

longitudinal study by Lindhe *et al*. (1984), which showed that patients with a high standard of infection control maintained clinical attachment levels and probing depth reductions following treatment more consistently than patients with poor plaque control. On the other hand, professional tooth cleaning, including subgingival scaling every 3 months, may partly compensate for the negative effects of variations in self-performed plaque control (Ramfjord *et al*. 1982; Isidor & Karring 1986).

With regard to post-treatment plaque accumulation, there is no evidence to suggest that differences exist between non-surgical or surgical treatment or between various surgical procedures. In addition, most studies have shown that the magnitude of gingivitis resolution is not influenced by the treatment modality.

Probing pocket depth reduction

All surgical procedures result in a decrease in probing pocket depths with greater reduction occurring at the initially deeper sites (Knowles *et al*. 1979; Lindhe *et al*. 1984; Ramfjord *et al*. 1987; Kaldahl *et al*. 1996; Becker *et al*. 2001). Furthermore, surgical therapy generally creates greater short-term reduction of probing depth than non-surgically performed scaling and root planing. Flap surgery with bone recontouring (pocket elimination surgery) usually results in the most pronounced short-term pocket reduction. Long-term (5–8 years) results show various outcomes. Some studies reported greater probing depth reduction following surgery while others reported no differences in relation to non-surgical therapy. Also, the magnitude of the initial probing depth reduction shows a tendency to decrease with time, independent of treatment modality.

Clinical attachment level change

In sites with shallow initial probing depth, both short- and long-term data demonstrate that surgery creates a greater loss of clinical attachment than non-surgical treatment, whereas in sites with initially deep pockets (≥7 mm), a greater gain of clinical attachment is generally obtained (Knowles *et al*. 1979; Lindhe *et al*. 1984; Ramfjord *et al*. 1987; Kaldahl *et al*. 1996; Becker *et al*. 2001) (Fig. 39-64). When clinical attachment levels following surgery with and without osseous resection were compared, either no difference was found between therapies, or flap surgery without osseous resection produced a greater gain. In addition, there was no difference in the longitudinal maintenance of clinical attachment levels between sites treated non-surgically and those treated surgically, with or without osseous resection.

Based on data generated from a clinical trial comparing non-surgical and surgical (modified Widman flap) approaches to root debridement, Lindhe *et al*. (1982b) developed the concept of *critical probing depth* (CPD) in relation to clinical attachment level change. For each treatment approach, the clinical attachment change was plotted against the initial pocket depth and regression lines were calculated (Fig. 39-65). The point where the regression line crossed the horizontal axis (initial probing depth) was defined as the CPD, that is the level of pocket depth below which clinical attachment loss would occur as the result of the treatment procedure performed. The CPD was consistently found to be greater for the surgical approach than for the non-surgical treatment. Furthermore, at incisors and premolars, the surgical therapy showed superior outcome only when the initial probing depth was >6–7 mm, while at molars the corresponding cut-off point was 4.5 mm. The interpretation of the latter

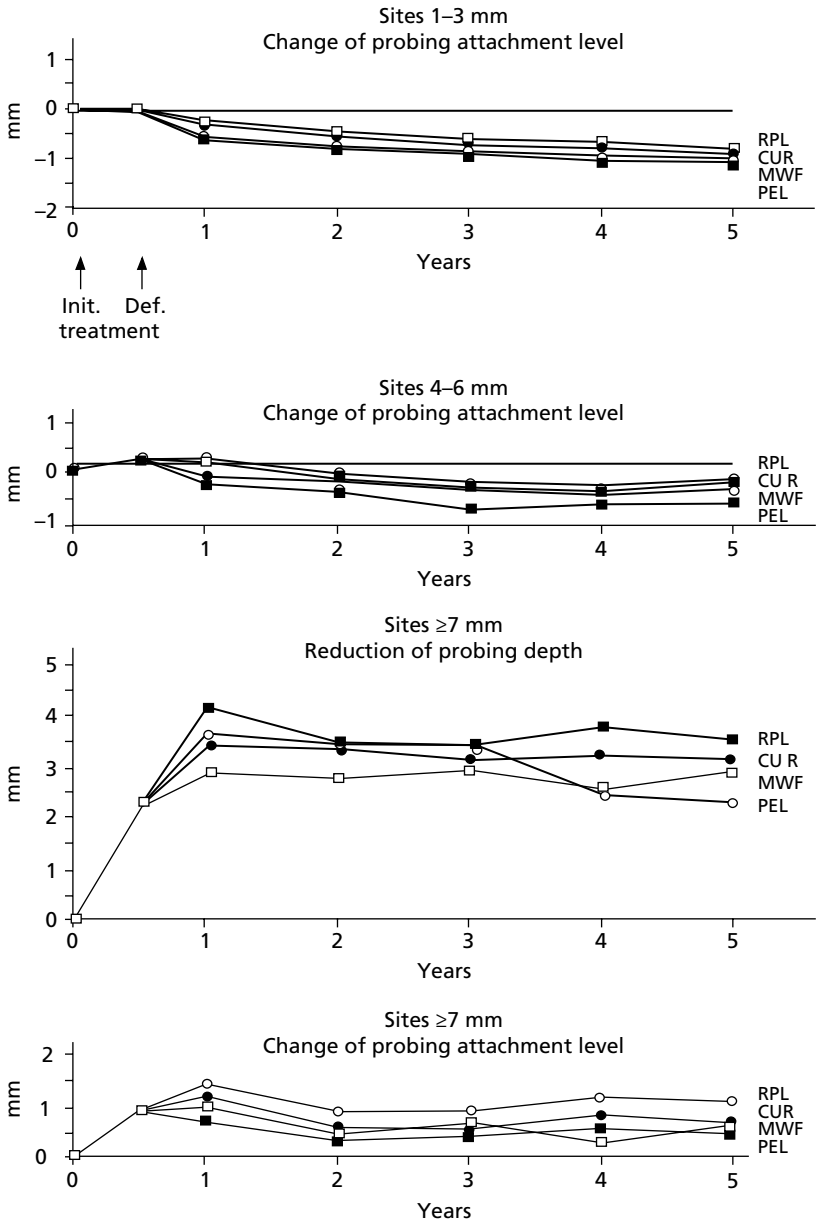

Fig. 39-64 Longitudinal evaluation of four treatment modalities in the three categories of initial probing depth; 1–3 mm, 4–6 mm and ≥7 mm. (RPL, scaling and root planning; CUR, subgingival curettage; MWF, modified Widman flap; PEL, pocket elimination surgery.) (Source: Egelberg 1995. Reproduced from Odonto Science. Data from Ramfjord *et al*. 1987.))

finding is that, in the molar tooth regions, the surgical approach to root debridement offers advantages over the non-surgical approach. This interpretation is supported by the observation that inferior results are obtained by non-surgical therapy in molars compared to single-rooted teeth (Nordland *et al*. 1987; Loos *et al*. 1988). Also, data generated from studies comparing closed and open root debridement in furcation sites favor surgical access therapy in the treatment of molar tooth regions (Matia *et al*. 1986).

The removal of the pocket epithelium and the soft tissue lesion by curettage (Echeverria & Caffesse 1983; Ramfjord *et al*. 1987) or surgical excision (Lindhe & Nyman 1985) is not a prerequisite for proper healing of the treated periodontal site. In the study by Lindhe and Nyman (1985), three treatment modalities were used: excision of the soft tissue lesion during flap surgery (modified Widman flap procedure), surgery without removal of the soft tissue lesion (Kirkland flap), and non-surgical scaling and root planing. The 1-year follow-up examination revealed about 1 mm of gain in clinical attachment level for all three procedures. Thus, deliberate excision of the soft tissue lesion did not improve the healing result.

Gingival recession

Gingival recession is an inevitable consequence of periodontal therapy. Since it occurs primarily as a result of resolution of the inflammation in the periodontal tissues, it is seen both following non-surgical and surgical therapy. Irrespective of treatment modality used, initially deeper pocket sites will experience more pronounced signs of recession of the gingival margin than sites with shallow initial probing depths (Badersten *et al*. 1984; Lindhe *et al*. 1987; Becker *et al*. 2001).

A general finding in short-term follow-up studies of periodontal therapy is that non-surgically performed scaling and root planing causes less gingival

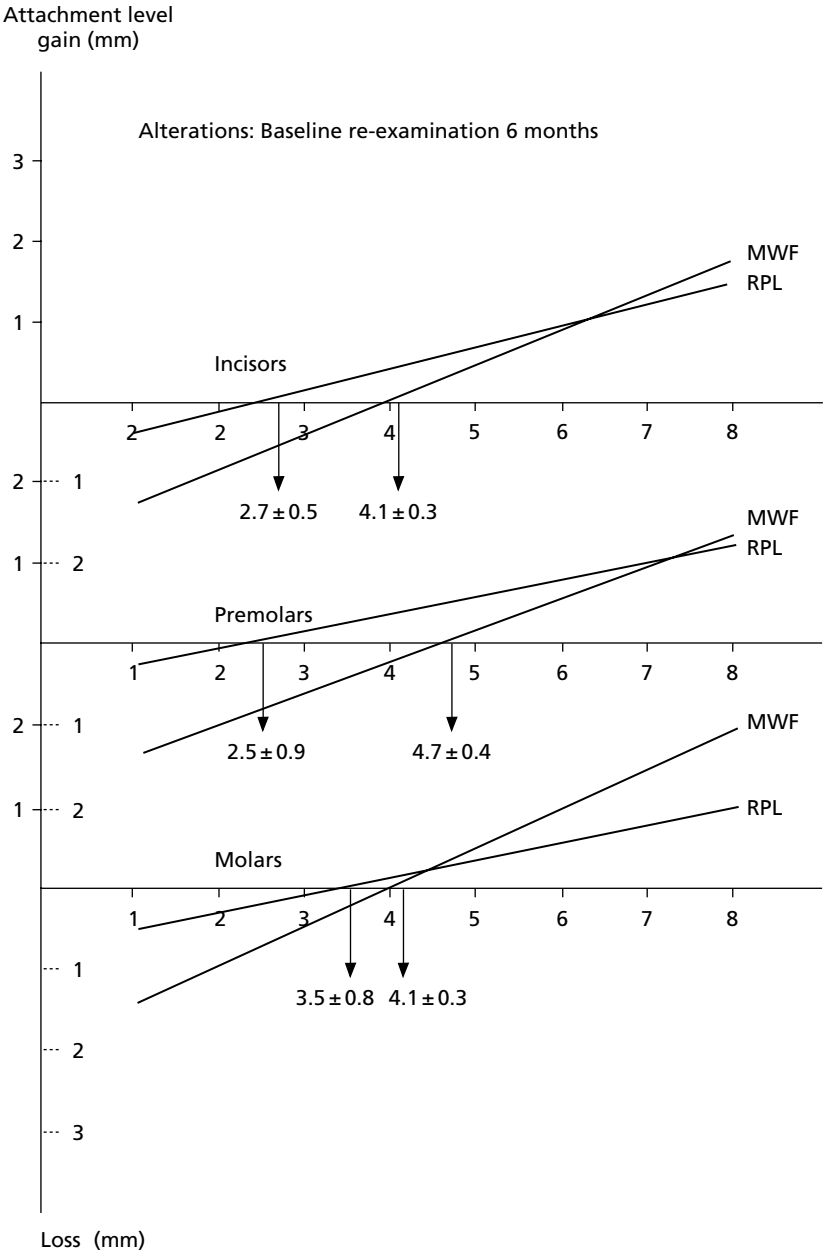

Fig. 39-65 Gain and loss of clinical attachment (y axis) at incisors, premolars, and molars, calculated from measurements taken prior to and 6 months after treatment. The non-surgical approach (RPL) consistently yielded lower critical probing depth (CPD) values than the surgical approach. (RPL, scaling and root planning; MWF, modified Widman flap surgery.) (Data from Lindhe *et al*. 1982b.)

recession than surgical therapy, and that surgical treatment involving osseous resection results in the most pronounced recession. However, data obtained from long-term studies reveal that the initial differences seen in amount of recession between various treatment modalities diminish over time due to a coronal rebound of the soft tissue margin following surgical treatment (Kaldahl *et al*. 1996; Becker *et al*. 2001) (Fig. 39-66). Lindhe and Nyman (1980) found that after an apically repositioned flap procedure, the buccal gingival margin shifted to a more coronal position (by about 1 mm) during 10–11 years of maintenance. In interdental areas denuded following surgery, van der Velden (1982) found an up-growth of around 4 mm of gingival tissue 3 years after surgery, while no significant change in attachment levels was observed. A similar finding was reported by Pontoriero and Carnevale (2001) 1 year after an apically positioned flap procedure for crown lengthening.

Bone fill in angular bone defects

The potential for bone formation in angular defects following surgical access therapy has been demonstrated in a number of studies. Rosling *et al*. (1976a) studied the healing of two- and three-wall angular bone defects following a modified Widman flap procedure, including careful curettage of the bone defect and proper root debridement, in 24 patients with multiple osseous defects. Following active treatment, patients assigned to the test group received supportive periodontal care once every 2 weeks for a 2-year period, while the patients in the control group were only recalled once a year for prophylaxis. Re-examination carried out 2 years after therapy demonstrated that the patients who had been subjected to the intensive professional tooth-cleaning regimen had experienced a mean gain of clinical attachment in the angular bone defects amounting to 3.5 mm.

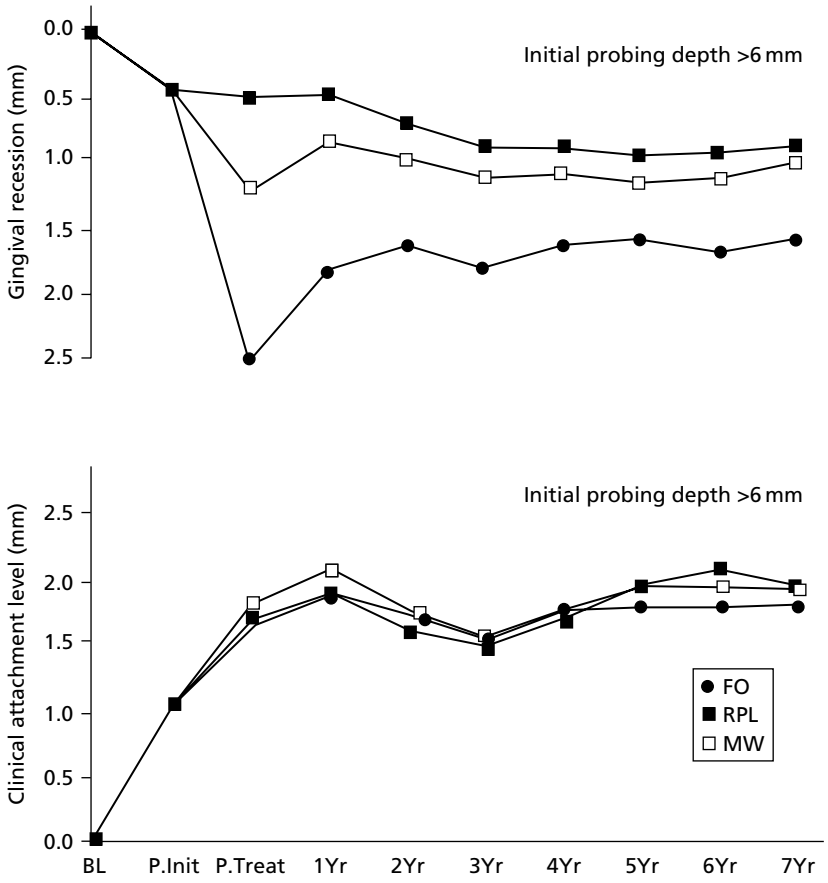

Fig. 39-66 Longitudinal changes over 7 years in recession (top) and clinical attachment levels (bottom) at sites with initial probing pocket depth of >6 mm following three different periodontal treatment modalities. (RPL, scaling and root planning; MWF, modified Widman flap procedure; FO, flap and osseous surgery.) (Data from Kaldahl *et al*. 1996.)

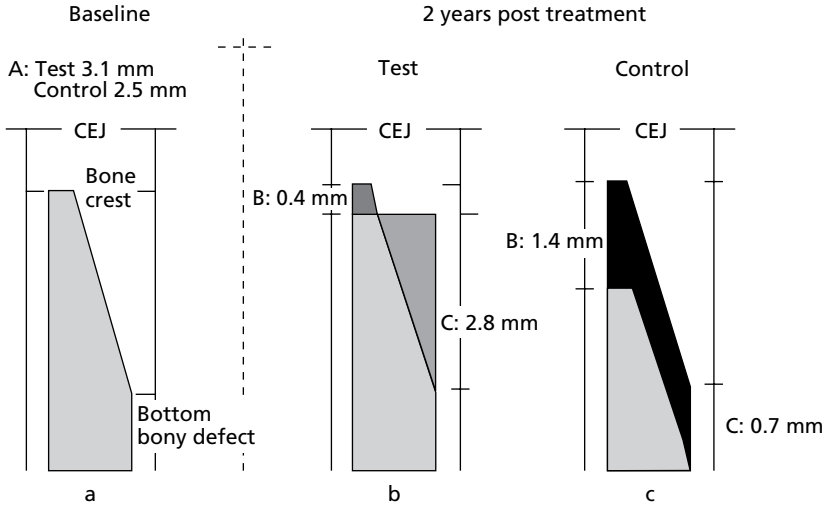

Fig. 39-67 Alterations in the level of the marginal bone crest and the level of the bottom of the bone defects in the test and control groups of the study by Rosling *et al*. (1976a). (a) Distance A denotes the depth of the bone defects at the initial examination; test group 3.1 mm, control 2.5 mm. (b, c) Distance B denotes resorption of the alveolar crest, which amounted to 0.4 mm in the test patients (b) and 1.4 mm in the controls (c). Distance C denotes gain or loss of bone in the apical portion of the defect. There was a refill of bone in the test patients (b) amounting to 2.8 mm, whereas a further 0.7 mm loss of bone occurred in the control patients (c). (CEJ, cementoenamel junction.) (Data from Rosling *et al*. 1976a.)

Measurements performed on radiographs revealed a marginal bone loss of 0.4 mm, but the remaining portion of the original bone defect (2.8 mm) was refilled with bone (Fig. 39-67). All the 124 bone defects treated were completely resolved. In the control group, most of the sites treated showed signs of recurrent periodontitis, including further loss of clinical attachment and alveolar bone. Similar healing results were reported by Polson and Heijl (1978). They treated 15 defects (two- and three-wall) in nine patients using a modified Widman flap procedure. Following curettage of the bone defect and root planing, the flaps were closed to achieve complete soft tissue coverage of the defect area. All patients were enrolled in a professional tooth-cleaning program. The healing was evaluated at a re-entry operation 6–8 months after the initial surgery. Eleven of the 15 defects had resolved completely. The healing was characterized by a combination of coronal bone regeneration (77% of the initial depth of the defects) and marginal bone resorption (18%). The authors concluded that intrabony defects might predictably remodel after surgical debridement and establishment of optimal plaque control.

The results from the studies referred to demonstrate that a significant bone fill may be obtained in two- and three-wall intrabony defects at single-rooted teeth, provided the postoperative supportive

care is of very high quality. Two reviews (Laurell *et al*. 1998; Lang 2000), focusing on the outcome of surgical access therapy in angular bone defects, gave additional information regarding expected bone regeneration in angular defects following open-flap debridement (modified Widman flap). In the review by Laurell *et al*. (1998), 13 studies were included, representing a total of 278 treated defects with a mean depth of 4.1 mm. The weighted mean bone fill in the angular defects amounted to 1.1 mm. Lang (2000) reported an analysis of 15 studies providing data generated from radiographic assessments of the healing of 523 angular bone defects. The analysis yielded a weighted mean of 1.5 mm of bone gain. Since the studies included in these reviews showed great variability in bone fill, one may assume that the standard of post-surgical plaque control varied between the studies. As shown in the study by Rosling *et al*. (1976a), meticulous post-surgical plaque control and close professional supervision of the patients are critical for optimal healing conditions. One also has to consider that the potential for bone fill may differ depending on the morphology of the angular bone defect. Most angular defects appear as combinations of one-, two- and three-wall defects and whereas the two- and three-wall component of an angular bone defect may show great potential for bone fill during healing, the one-wall component will rarely demonstrate this type of healing.

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Chapter 40

Treatment of Furcation-Involved Teeth

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Detailed knowledge of the morphology of the multi-rooted teeth and their position in the dental arch is a fundamental prerequisite for a proper understanding of the problems which may occur when such teeth become involved in destructive periodontal disease. The first part of this chapter therefore includes a brief description of some important anatomic features of the root complexes and related structures of premolars and molars.

Terminology

The root complex is the portion of a tooth that is located apical to the cementoenamel junction (CEJ), that is the portion that normally is covered with a root cementum. The root complex may be divided into two parts: the *root trunk* and the *root cone(s)* (Fig. 40-1).

The *root trunk* represents the *undivided region* of the root. The height of the root trunk is defined as the distance between the CEJ and the separation line (furcation) between two root cones (roots). Depending on the position of the separation line, the height of the root trunk may vary from one surface to the next in one given molar or premolar.

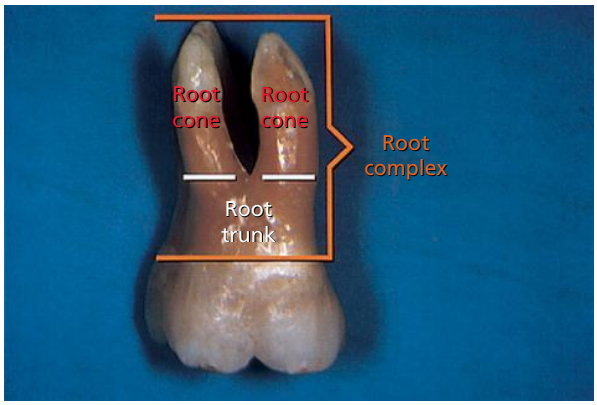

Fig. 40-1 Root complex of a maxillary molar. The root complex is separated into one undivided region – the root trunk, and one divided region – the (three) root cones.

The *root cone* is included in the *divided region* of the root complex. The root cone (root) may vary in size and position, and may at certain levels be connected to or separated from other root cones. Two or more

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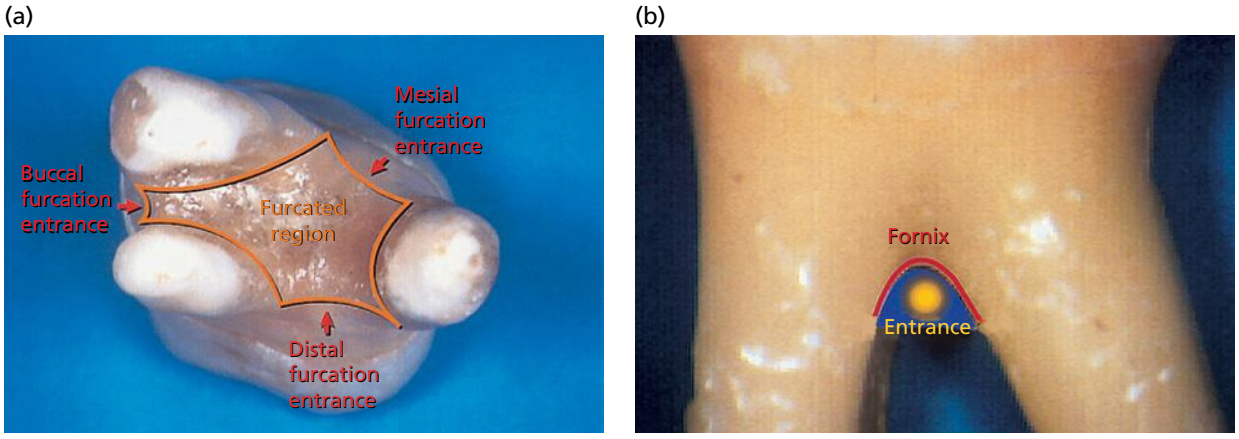


Fig. 40-2 (a) Apical–occlusal view of a maxillary molar where the three root cones make up the furcated region and the three furcation entrances. (b) Buccal view of the furcation entrance and of its roof.

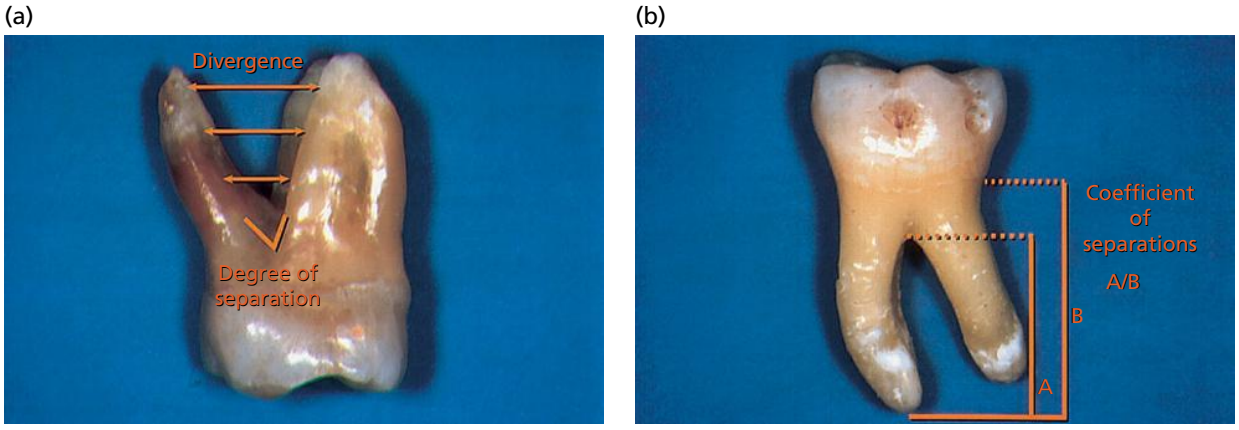


Fig. 40-3 (a) Angle (degree) of separation and the divergence between the mesiobuccal and the palatal roots of a maxillary molar. (b) Coefficient of separation (A/B) of the illustrated mandibular molar is 0.8 (A = 8 mm; B = 10 mm).

root cones make up the *furcated region* of the root complex (Fig. 40-2a). The *furcation* is the area located between individual root cones.

The *furcation entrance* is the transitional area between the undivided and the divided part of the root (Fig. 40-2a, b). The *furcation fornix* is the roof of the furcation (Fig. 40-2b).

The *degree of separation* is the angle of separation between two roots (cones) (Fig. 40-3a). *Divergence* is the distance between two roots; this distance normally increases in the apical direction (Fig. 40-3a). The *coefficient of separation* is the length of the root cones in relation to the length of the root complex (Fig. 40-3b).

Fusion between divergent root cones may occur. The fusion may be complete or incomplete. In the case of an incomplete fusion, the root cones may be fused in the area close to the CEJ, but separated in a more apical region of the root complex.

Anatomy

Maxillary molars

As a general rule, the maxillary first molar in all respects – crown and individual roots – is larger than the second molar, which in turn is larger than the third molar. The first and second molars most often have three roots; one mesiobuccal, one distobuccal, and one palatal. The mesiobuccal root is normally vertically positioned, while the distobuccal and the palatal roots are inclined. The distobuccal root projects distally and the palatal root projects in the palatal direction (Fig. 40-4). The cross-sections of the distobuccal and the palatal roots are generally circular. The palatal root is generally wider in the mesiodistal than in the buccopalatal direction. The distal surface of the mesiobuccal root has a concavity which is about 0.3 mm deep (Bower 1979a, b). This concavity gives the cross section of the mesiobuccal root an "hourglass" configuration (Fig. 40-5).

The three furcation entrances of the maxillary first and second molars vary in width and are positioned at varying distances apical to the CEJ. As a rule, the first molar has a shorter root trunk than the second molar. In the first molar the mesial furcation entrance is located about 3 mm from the CEJ, while the buccal entrance is 3.5 mm and the distal entrance about 5 mm apical to the CEJ (Abrams & Trachtenberg 1974; Rosenberg 1988). This implies that the furcation fornix is inclined; in the mesiodistal plane, the fornix is comparatively

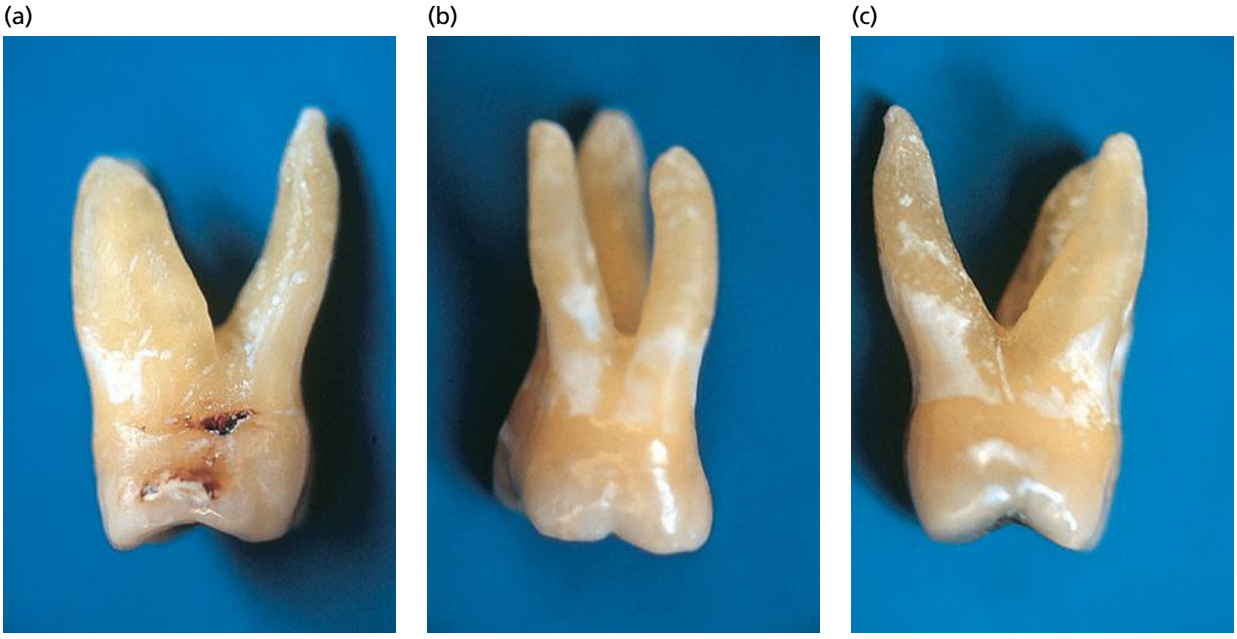


Fig. 40-4 Furcation entrances (a) mesial; (b) buccal; (c) distal), and position of the roots of a maxillary first molar.

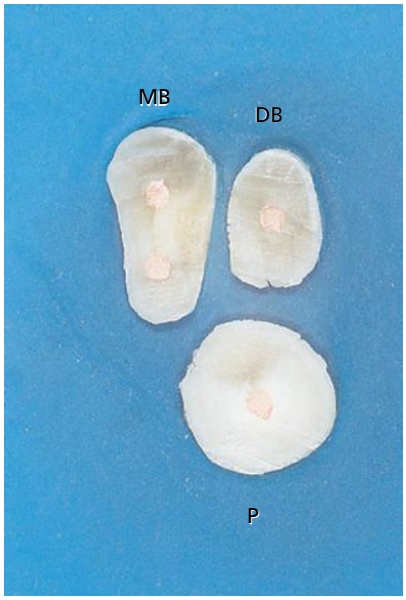


Fig. 40-5 Root shape of a maxillary first molar in a horizontal cut at the level of the coronal third of the cones. Note the circular shape of the palatal root (P) in comparison with the mesiodistally compressed shape of the mesiobuccal root (MB), which also exhibits a concavity in the distal aspect (DB).

close to the CEJ at the mesial surface but closer to the apex at the distal surface. The buccal furcation entrance is narrower than its distal and mesial counterparts.

The degree of separation between the roots and their divergence decreases from the first to the second, and from the second to the third maxillary molar. The mesiobuccal root of the first molar is frequently located more buccally in the arch than the distobuccal root. If the buccal bone plate is thin, the mesiobuccal root frequently projects through the outer surface of the alveolar bone and bone fenestrations and/or dehiscences may occur.

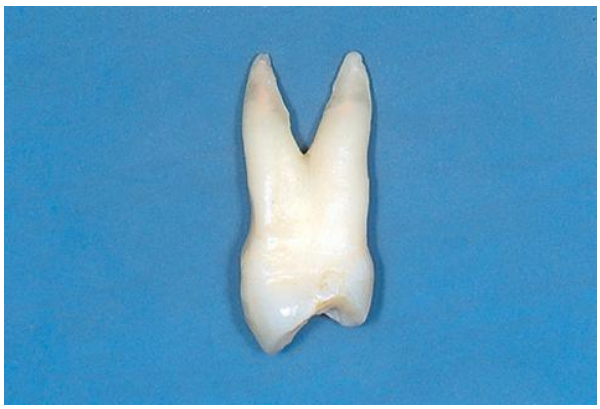


Fig. 40-6 Maxillary first premolar with the furcation located in the apical third of the root complex.

Maxillary premolars

In about 40% of cases, the maxillary first premolars have two root cones, one buccal and one palatal, and hence have a mesiodistal furcation. A concavity (about 0.5 mm deep) is often present in the furcation aspect of the buccal root. In many cases, the furcation is located in the middle or in the apical third of the root complex (Fig. 40-6). The mean distance between CEJ and the furcation entrance is about 8 mm. The width of the furcation entrance is about 0.7 mm.

Mandibular molars

The mandibular first molar is larger than the second molar, which in turn is larger than the third molar. In the first and second molars, the root complex almost always includes two root cones, one mesial and one distal. The mesial root is larger than the distal root. The mesial root has a mainly vertical position, while the distal root projects distally. The mesial root is wider in the buccolingual direction

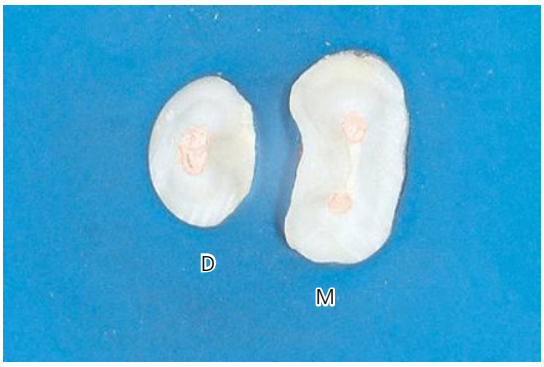


Fig. 40-7 "Hour-glass" shape of the mesial root (M) – with a concavity in the distal aspect, and the circular shape of the distal root (D) (horizontal section at the level of the coronal third of the cones).

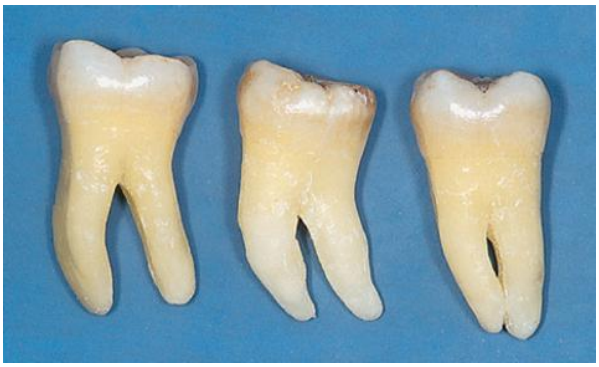


Fig. 40-8 From left to right, differences in degree of separation and in divergence between the root cones from the first to the mandibular third molar.

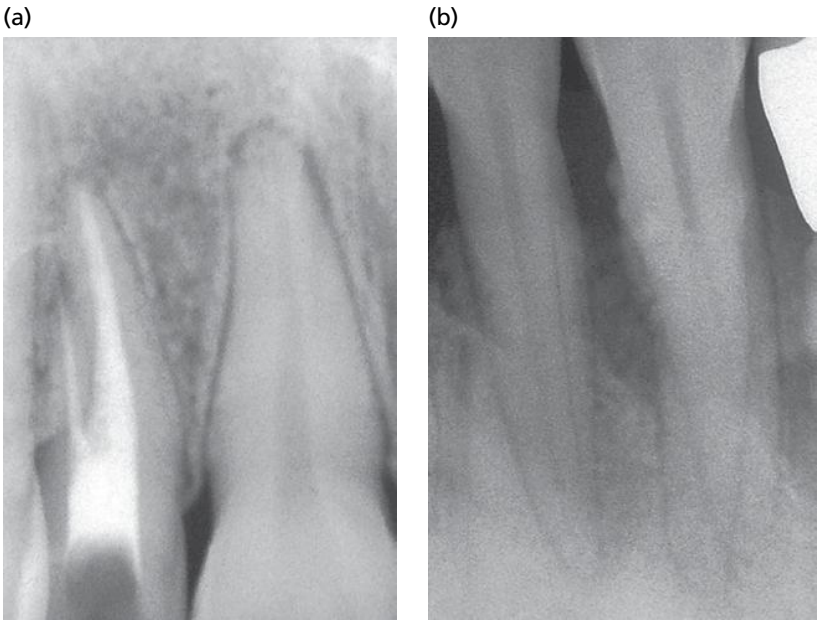


Fig. 40-9 Radiographs showing morphologic variations represented by a two-rooted (a) maxillary lateral incisor and (b) mandibular canine.

and has a larger cross-sectional area than the distal root. The cross-section of the distal root is circular, while the mesial root has an "hour-glass" shape. In addition, furrows and concavities often occur on the distal surface of the mesial root (Fig. 40-7). The distal concavity of the mesial root is more pronounced than that of the distal root (Bower 1979a, b; Svärdström & Wennström 1988).

The root trunk of the first molar is often shorter than the trunk of the second molar. The furcation entrances of the mandibular first molar, similar to those of the maxillary first molar, are located at different distances from the CEJ. Thus, the lingual entrance is frequently found more apical to the CEJ (>4 mm) than the buccal entrance (>3 mm). Thus, the furcation fornix is inclined in the buccolingual direction. The buccal furcation entrance is often <0.75 mm wide, while the lingual entrance is >0.75 mm in most cases (Bower 1979a, b). The degree of separation and divergence between the roots decreases from the first to the third molar (Fig. 40-8).

It should also be observed that the buccal bone plate is thinner outside the roots of the first than of the second molar. Bone fenestrations and dehiscences are, as a consequence, more frequent in the first than in the second molar region.

Other teeth

Furcations may be present also in teeth which normally have only one root. In fact, two-rooted incisors (Fig. 40-9a), canines (Fig. 40-9b), and mandibular premolars may exist. Occasionally three-rooted maxillary premolars (Fig. 40-10a) and three-rooted mandibular molars can be found (Fig. 40-10b).

Diagnosis

The presence of furcation-involved teeth in a periodontal patient will influence the treatment plan (see Chapter 32). The selection of procedures to be used in the treatment of periodontal disease at

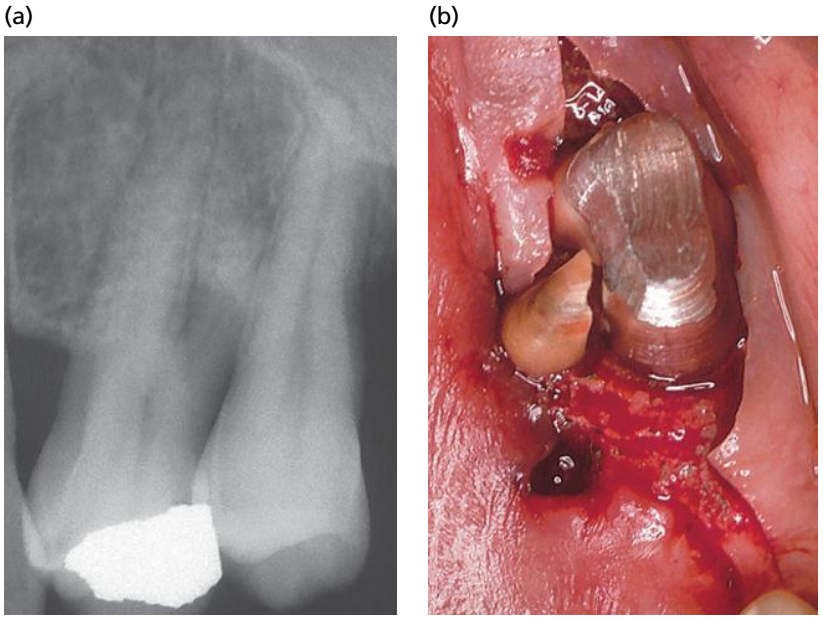


Fig. 40-10 (a) Anatomic variation shown in a radiograph of a three-rooted mandibular first premolar. (b) Clinical surgical photograph showing the separation – before extraction – of an "abnormal" second mesial root of a mandibular molar.

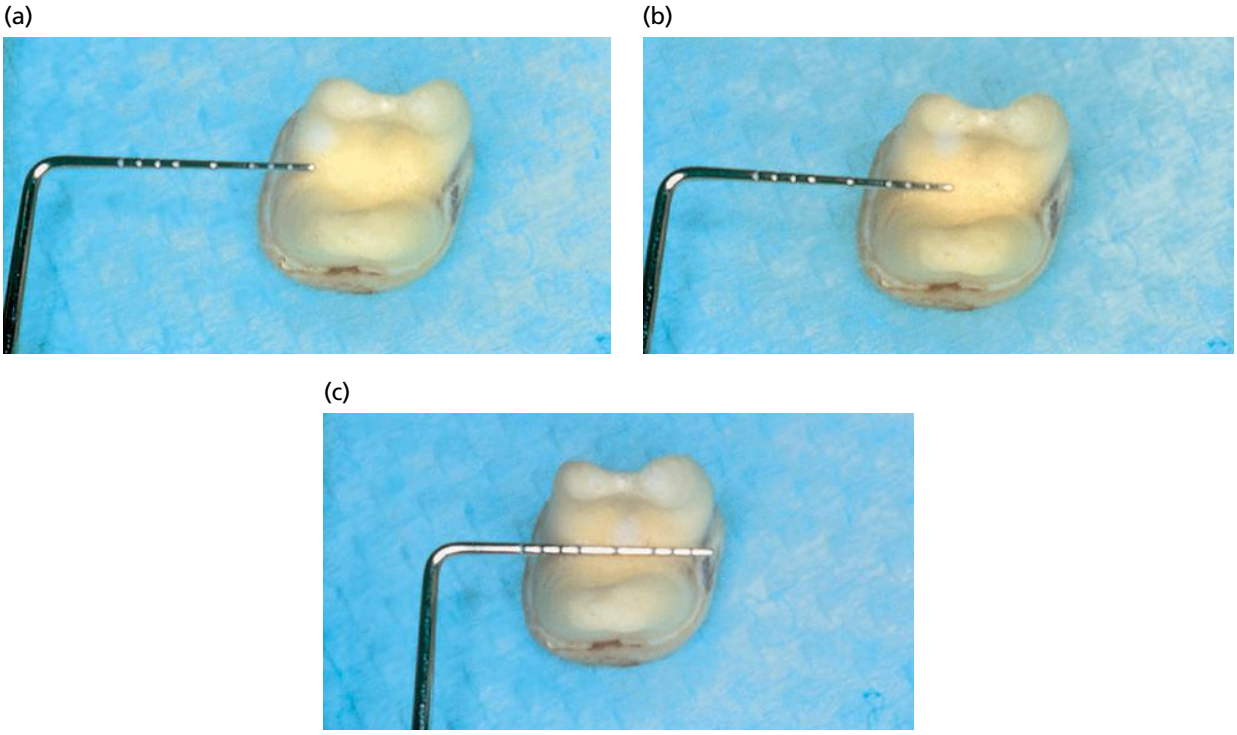


Fig. 40-11 Different degrees of furcation involvement in relation to the probe (penetration/superimposition) in the inter-radicular space of a mandibular molar. (a) Class I; (b) class II; (c) class III.

multirooted teeth can first be made when the presence and depth of furcation lesions have been assessed. In this examination, traditional measures of periodontal disease are used (see Chapter 29), but special attention is paid to findings from clinical probing and analysis of radiographs from the premolar–molar regions.

The classification description of the involved furcation is based on the amount of periodontal tissue destruction that has occurred in the inter-radicular area, that is the degree of "horizontal root exposure" or attachment loss that exists within the root complex. Hamp *et al*. (1975) has suggested the following classification of the involved furcation:

- *Class I:* horizontal loss of periodontal support not exceeding one-third of the width of the tooth (Fig. 40-11a)
- *Class II*: horizontal loss of periodontal support exceeding one-third of the width of the tooth, but not encompassing the total width of the furcation area (Fig. 40-11b)
- *Class III*: horizontal "through-and-through" destruction of the periodontal tissues in the furcation area (Fig. 40-11c).

(a) (b)

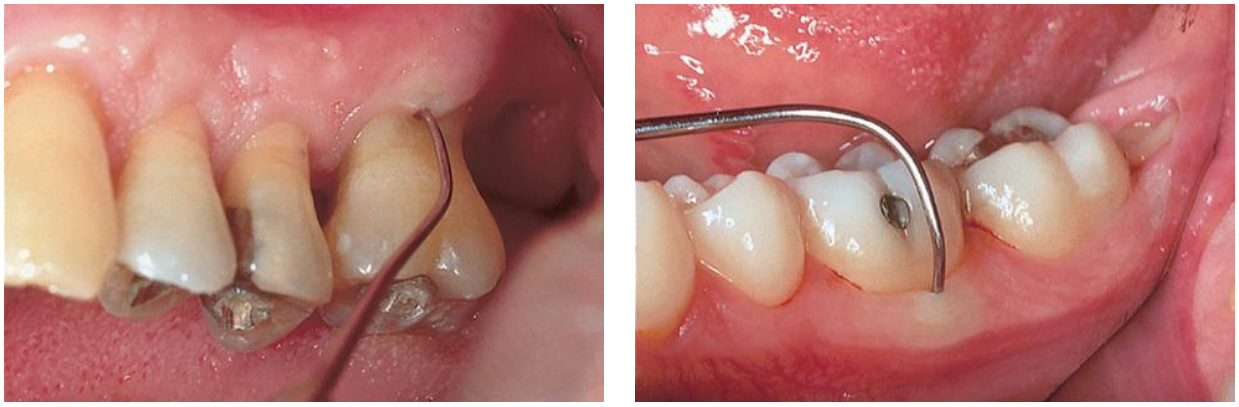


Fig. 40-12 Easily accessible vestibular furcation entrances for probing of a (a) maxillary molar and (b) mandibular molar.

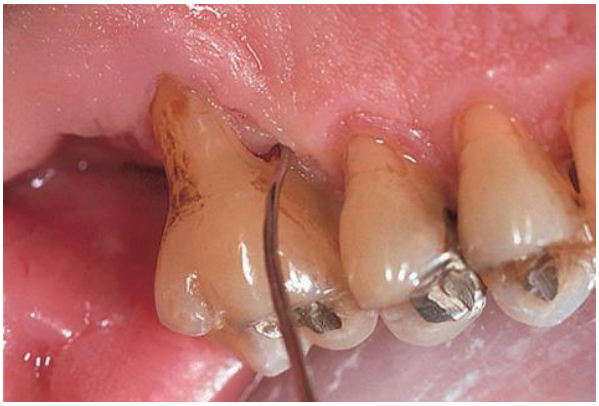


Fig. 40-13 Common access for probing of a mesial furcation entrance of a maxillary molar. The mesial furcation entrance is generally located at the palatal aspect of the tooth, while the distal entrance is located midway between the buccal and the palatal surface.

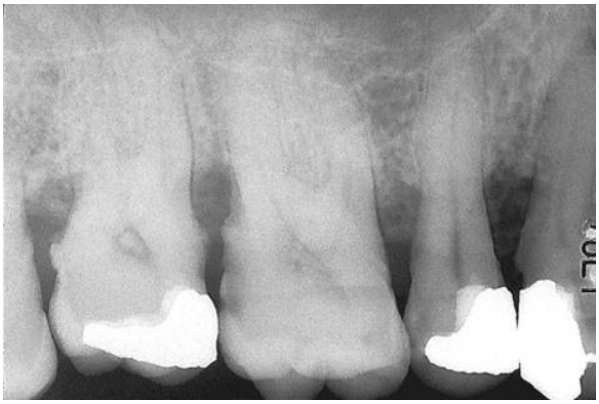


Fig. 40-14 Radiograph showing the location of the interdental bone level in relation to the furcation entrances of the maxillary first and second molars.

It is important to appreciate that each furcation entrance must be examined and each entrance must be classified according to the above criteria.

Probing

The buccal furcation entrance of the *maxillary molars* and the buccal and lingual furcation entrances of the *mandibular molars* are normally accessible for examination using a curved graduated periodontal probe (Fig. 40-12), an explorer or a small curette. The examination of approximal furcations is more difficult, in particular when neighboring teeth are present. Large contact areas between the teeth further impair access to approximal furcation entrances.

In maxillary molars, the mesial furcation entrance is located much closer to the palatal than to the buccal tooth surface. Thus, the mesial furcation should be probed from the palatal aspect of the tooth (Fig. 40-13). The distal furcation entrance of a maxillary molar is generally located midway between the buccal and palatal surfaces and, as a consequence, this furcation could be probed from either the buccal or the palatal aspect of the tooth.

In *maxillary premolars*, the root anatomy often varies considerably. The roots may also harbor irregularities such as longitudinal furrows, invaginations or true furcations, which may open at varying distances from the CEJ. Due to the above variations and limited access, the clinical assessment of a furcation involvement in maxillary premolars is often difficult. In some patients, a furcation involvement may, in such teeth, first be identified after the elevation of a soft tissue flap.

Radiographs

Radiographs must always be obtained to confirm findings made during probing of a furcation-involved tooth. The radiographic examination should include both paralleling "periapical" and vertical "bitewing" radiographs. In the radiographs, the location of the interdental bone as well as the bone level within the root complex should be examined (Fig. 40-14). Situations may occur when findings from clinical probing and from the radiographs are inconsistent. Thus, the localized but extensive attachment loss which may be detected within the root complex of a maxillary molar with the use of a probe, will not always appear in the radiograph. This may be due to the superimposition in the radiograph of the palatal root and remaining

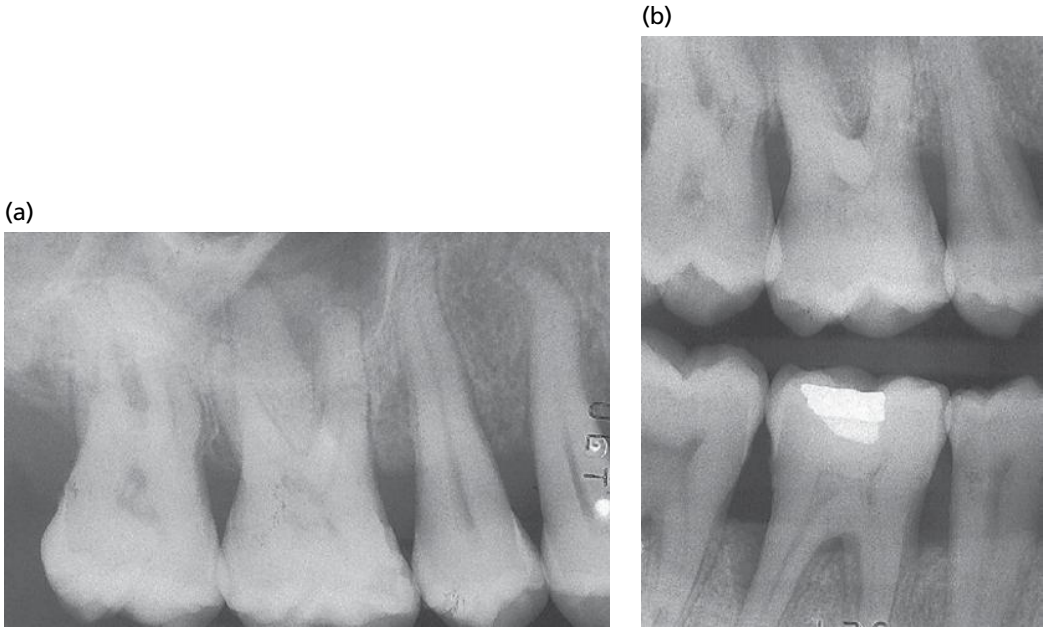


Fig. 40-15 Radiographs of the right maxillary molar region.(a) In a normal bisecting projection, the furcation defect of the first molar is not evident. (b) It is, however, easily identified in a bitewing radiograph.

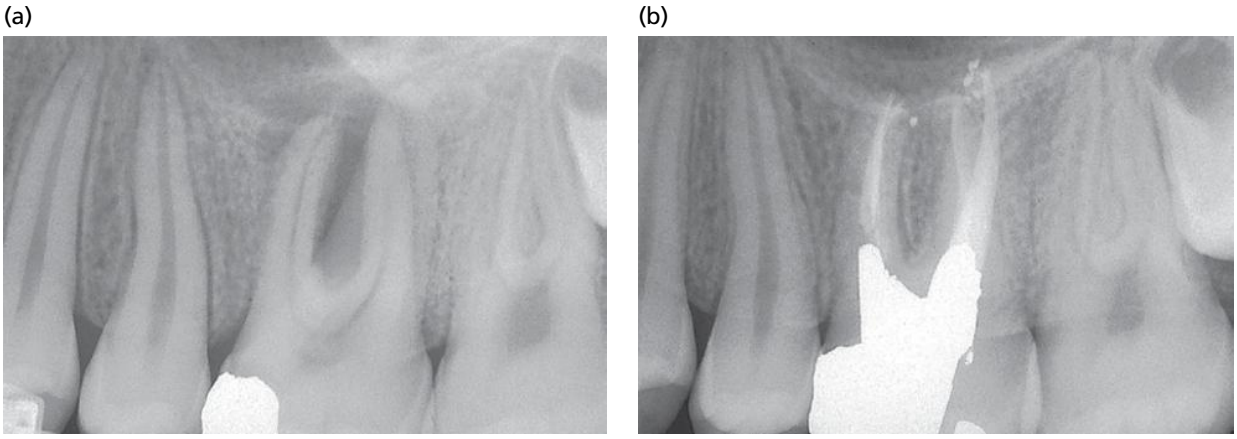


Fig. 40-16 (a) Radiograph demonstrating destruction of inter-radicular bone and the presence of periapical defects at the mesial and distal roots of a maxillary first molar. (b) Radiographic appearance of complete healing of the inter-radicular and periapical lesions after endodontic treatment.

bone structures (Fig. 40-15a). In such a case, additional radiographs with different angles of orientation of the central beam should be used to identify bone loss within the root complex (Fig. 40-15b).

Differential diagnosis

A lesion in the inter-radicular space of a multirooted tooth may be associated with problems originating from the root canal or be the result of occlusal overload. The treatment of a furcation-involved tooth, therefore, should not be initiated until a proper differential diagnosis of the lesion has been made.

Pulpal pathosis may sometimes cause a lesion in the periodontal tissues of the furcation (see Chapter 25). The radiographic appearance of such a defect may have some features in common with a plaque-associated furcation lesion. In order to differentiate between the two lesions, the vitality of the affected tooth must always be tested. If the tooth is vital, a plaque-associated lesion should be suspected. If the tooth is non-vital, the furcation involvement may have an endodontic origin. In such a case, proper endodontic treatment must always precede periodontal therapy. In fact, endodontic therapy may resolve the inflammatory lesion, soft and hard tissue healing may occur, and the furcation defect will disappear (Fig. 40-16). If signs of healing of a furcation defect fail to appear within 2 months of endodontic treatment, the furcation involvement is probably associated with marginal periodontitis.

Trauma from occlusion

Forces elicited by occlusal interferences, for example bruxers and clenchers (see Chapters 16 and 52), may cause inflammation and tissue destruction or

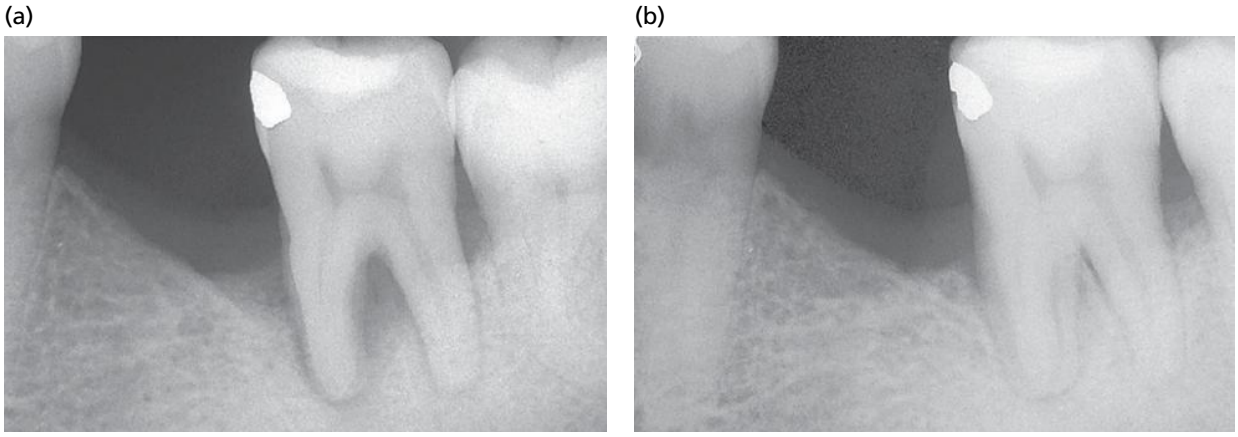


Fig. 40-17 (a) Radiographic appearance of a defect in the furcation area caused by occlusal overload. After occlusal adjustment the inter-radicular defect spontaneously healed, as documented 6 months after therapy in a radiograph (b). (Courtesy of M. Cattabriga.)

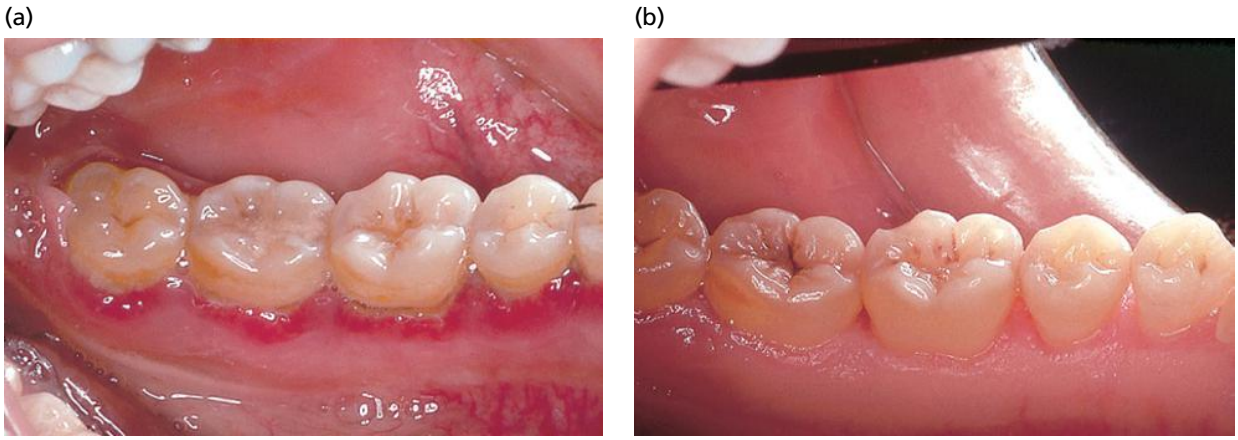


Fig. 40-18 Resolution of inflammatory lesions in the gingiva achieved by scaling and root planing, and the re-establishment of a correct tissue morphology in the inter-radicular area of class I furcation-involved mandibular molars. (a) Before therapy; (b) 6 months after therapy.

adaptation within the inter-radicular area of a multirooted tooth. In such a tooth, a radiolucency may be seen in the radiograph of the root complex. The tooth may exhibit increased mobility. Probing, however, fails to detect an involvement of the furcation. In this particular situation, occlusal adjustment must always precede periodontal therapy. If the defects seen within the root complex are of "occlusal" origin, the tooth will become stabilized and the defects disappear within weeks following correction of the occlusal overload (Fig. 40-17).

Therapy

Treatment of a defect in the furcation region of a multirooted tooth is intended to meet two objectives:

1. Elimination of the microbial plaque from the exposed surfaces of the root complex
2. Establishment of an anatomy of the affected surfaces that facilitates proper self-performed plaque control.

Different methods of therapy are recommended:

- *Class I furcation involvement*: scaling and root planing (SRP); furcation plasty
- *Class II furcation involvement*: furcation plasty; tunnel preparation; root resection; tooth extraction; guided tissue regeneration at mandibular molars
- *Class III furcation involvement*: tunnel preparation; root resection; tooth extraction.

Scaling and root planing

Scaling and planing of the root surfaces in the furcation entrance of a class I involvement in most situations result in the resolution of the inflammatory lesion in the gingiva. Healing will re-establish a normal gingival anatomy with the soft tissue properly adapted to the hard tissue walls of the furcation entrance (Fig. 40-18).

Furcation plasty

Furcation plasty (Fig. 40-19) is a resective treatment modality which should lead to the elimination of the inter-radicular defect. Tooth substance is removed (odontoplasty) and the alveolar bone crest is remodeled (osteoplasty) at the level of the furcation entrance. Furcation plasty is used mainly at buccal and lingual furcations. At approximal surfaces, access is often too limited for this

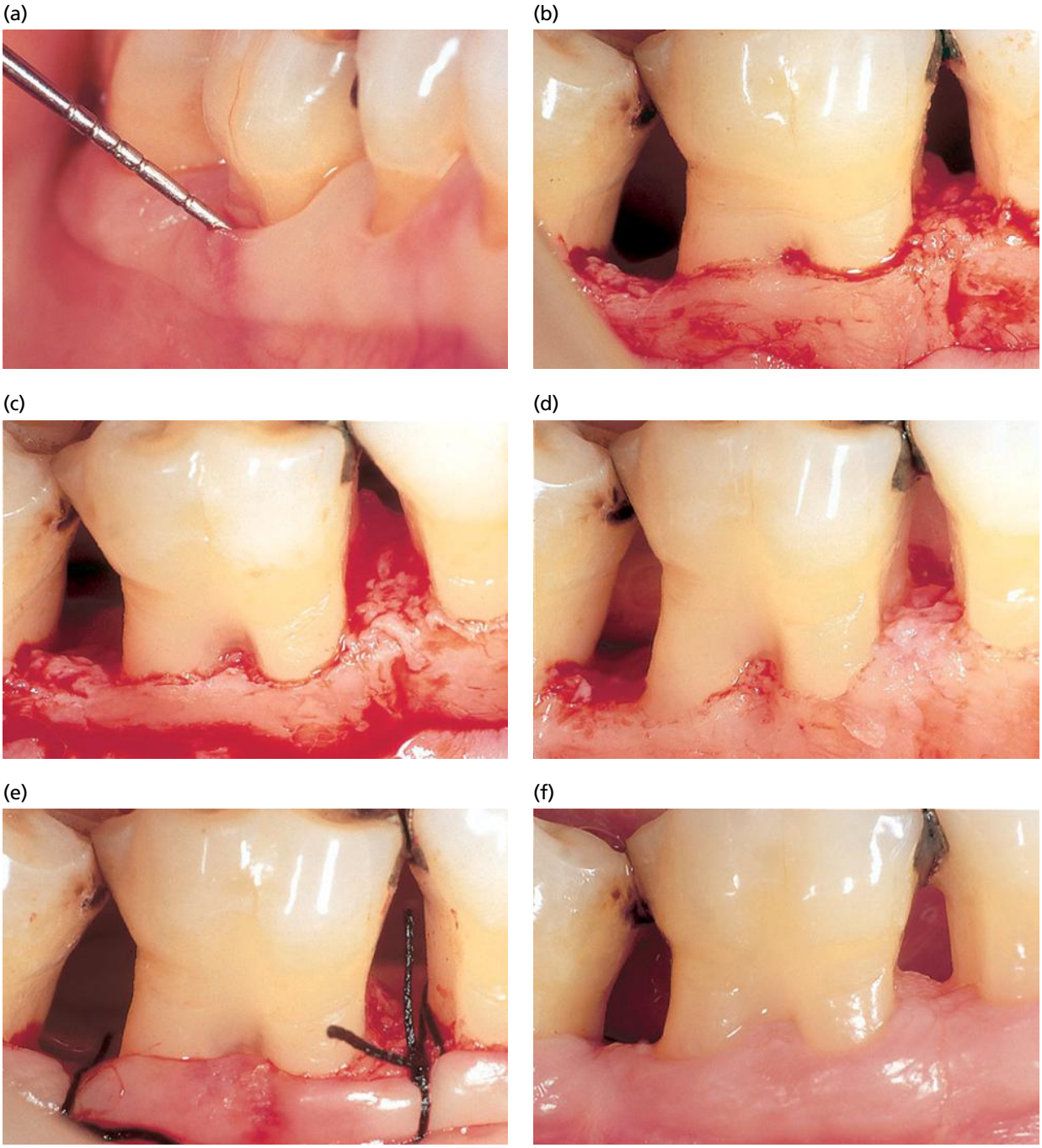


Fig. 40-19 Furcation plasty performed at the buccal aspect of a mandibular molar. (a) Initial class II furcation involvement; (b) after flap elevation, removal of the granulation tissue and scaling of the exposed root surfaces; (c) after odontoplasty; (d) after osteoplasty; (e) apical position of the flap managed by periosteal sutures; (f) healing resulting in the elimination of the furcation defect and in the establishment of a proper soft tissue morphology.

treatment. Furcation plasty involves the following procedures:

- Dissection and reflection of a soft tissue flap to obtain access to the inter-radicular area and the surrounding bone structures
- Removal of the inflammatory soft tissue from the furcation area followed by careful SRP of the exposed root surfaces
- Removal of crown and root substance in the furcation area (odontoplasty) to eliminate or reduce the horizontal component of the defect and to widen the furcation entrance
- Recontouring of the alveolar bone crest in order to reduce the buccal–lingual dimension of a bone defect in the furcation area
- Positioning and suturing of the mucosal flaps at the level of the alveolar crest in order to cover the furcation entrance with soft tissue; following healing a "papilla-like" tissue should close the entrance of the furcation.

Care must be exercised when odontoplasty is performed on vital teeth. Excessive removal of tooth structure will enhance the risk for increased root sensitivity.

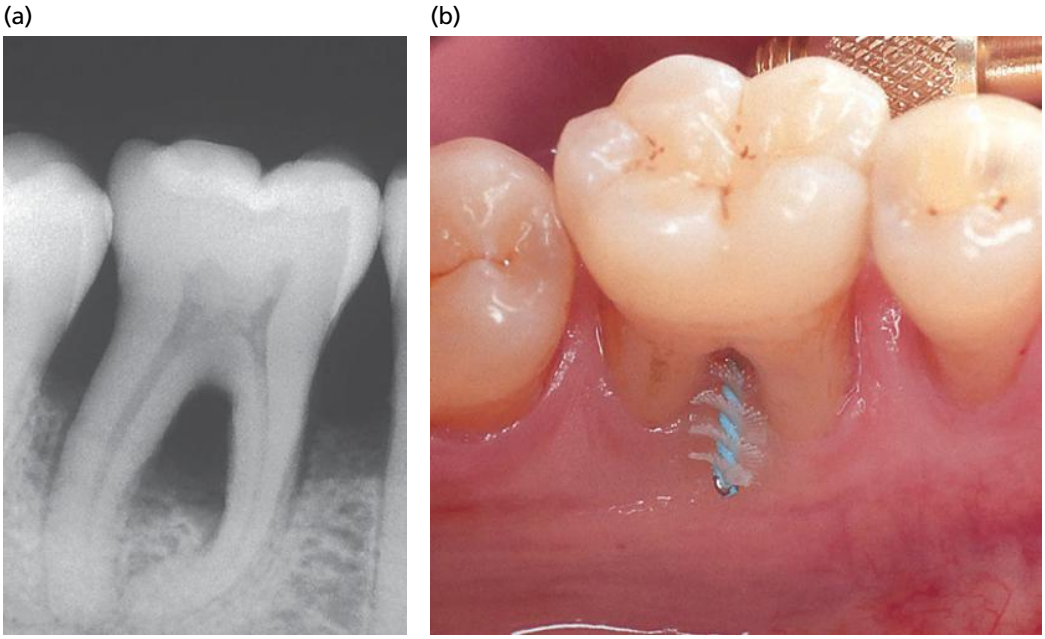


Fig. 40-20 Tunnel preparation of a class III-involved mandibular molar. (a) Radiograph and (b) photograph showing a wide inter-radicular space where self-performed plaque control can be achieved with the use of an interproximal brush.

Tunnel preparation

Tunnel preparation is a technique used to treat deep class II and class III furcation defects in mandibular molars. This type of resective therapy can be offered at mandibular molars which have a short root trunk, a wide separation angle, and long divergence between the mesial and distal root. The procedure includes the surgical exposure and management of the entire furcation area of the affected molar.

Following the reflection of buccal and lingual mucosal flaps, the granulation tissue in the defect is removed and the root surfaces are scaled and planed. The furcation area is widened by the removal of some of the inter-radicular bone. The alveolar bone crest is recontoured; some of the interdental bone, mesial and distal to the tooth in the region, is also removed to obtain a flat outline of the bone. Following hard tissue resection, enough space will have been established in the furcation region to allow access for cleaning devices to be used during self-performed plaque control measures (Fig. 40-20). The flaps are apically positioned to the surgically established inter-radicular and interproximal bone level.

During maintenance the exposed root surfaces should be treated with topical application of chlorhexidine digluconate and fluoride varnish. This surgical procedure should be used with caution, because there is a pronounced risk for root sensitivity and for carious lesions developing on the denuded root surfaces within artificially prepared tunnels (Hamp *et al.* 1975).

Root separation and resection

Root separation involves the sectioning of the root complex and the maintenance of all roots. *Root resection* involves the sectioning and the removal of one or two roots of a multirooted tooth. Root separation and resection (RSR) is frequently used in cases of deep class II and class III furcation-involved molars.

Before RSR is performed, the following factors must be considered:

- *Length of the root trunk*. In a patient with progressive periodontal disease, a tooth with a short root trunk may have an early involvement of the furcation (Larato 1975; Gher & Vernino 1980). A tooth with a short root trunk is a good candidate for RSR; the amount of remaining periodontal tissue support following RSR is often sufficient to ensure the stability of the remaining root cone. If the root trunk is long, the furcation involvement occurs later in the disease process, but, once established, the amount of periodontal tissue support left apical to the furcation may be insufficient to allow RSR.
- *Divergence between the root cones*. The distance between the root cones must be considered. Roots with a short divergence are technically more difficult to separate than roots which are wide apart. In addition, the smaller the divergence is, the smaller also is the inter-radicular (furcation) space. In cases where the divergence between two roots is small, the possibility of increasing the inter-radicular distance with an orthodontic root movement may be considered (Fig. 40-21). The furcation space may also be increased by odontoplasty performed during surgery. Figure 40-22 shows that *odontoplasty* was performed on (1) the distal part of the mesial root and (2) the mesial part of the distal root, with deep finishing lines prepared for the subsequent restoration (Di Febo *et al.* 1985).
- *Length and the shape of the root cones*. Following separation, short and small root cones (Fig. 40-23) tend

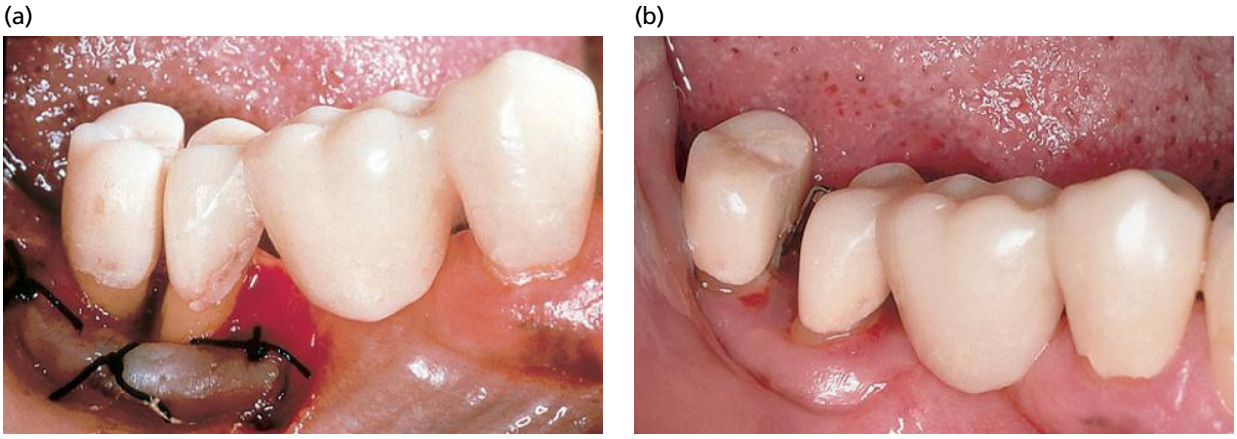


Fig. 40-21 Effect of orthodontic treatment of a separated mandibular molar with a small root divergence. (a) After root separation; (b) 3 months after completion of orthodontic therapy.

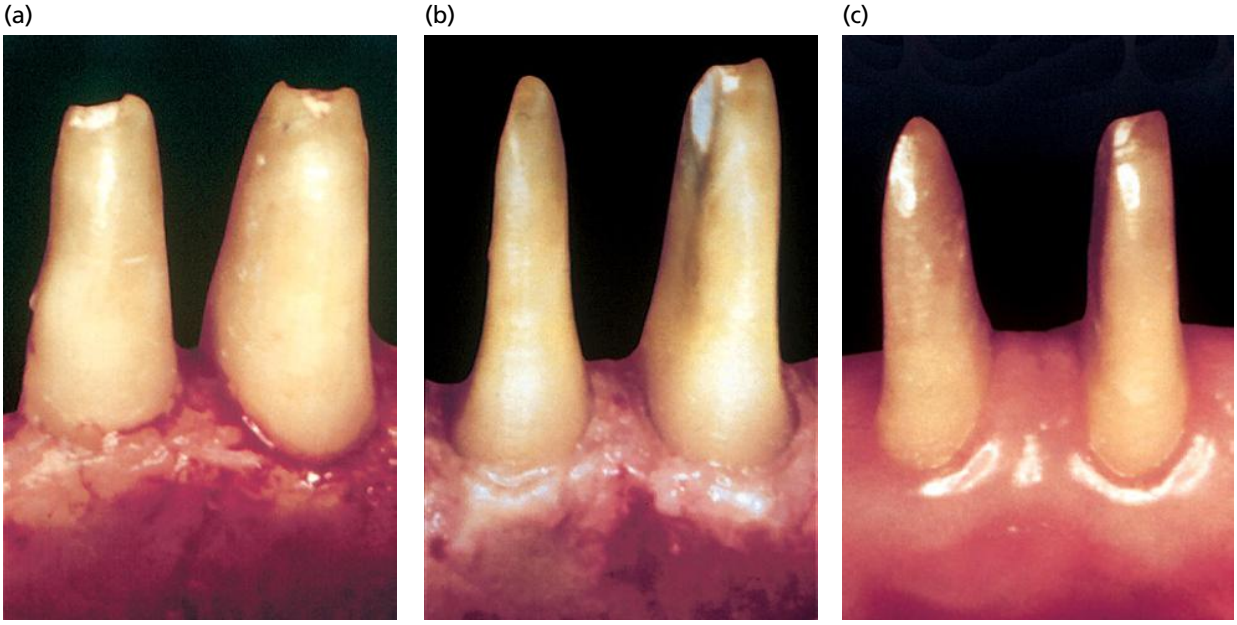


Fig. 40-22 Odontoplasty of a separated mandibular molar performed during surgery to increase the furcation space. (a) After flap elevation and exposure of the alveolar bone, it is evident that the distance between the two roots is small. (b) By preparing the inter-radicular surfaces during surgery, the furcation space is increased and is sufficient for self-performed plaque control measures (c).

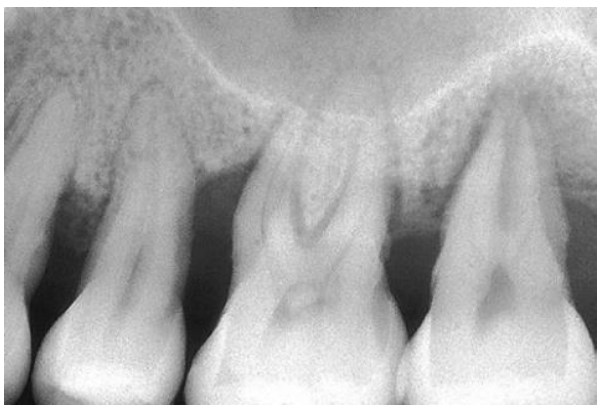


Fig. 40-23 Radiograph showing maxillary molars with thin, short, and conical roots.

to exhibit an increased mobility. Such roots, in addition, have narrow root canals which are difficult to ream. Short and small roots consequently should be regarded as poor abutments for prosthetic restorations.

- *Fusion between root cones*. When a decision has been made to perform RSR, it is important that the clinician first determines that the cones within the root complex are not fused. This is generally an uncomplicated diagnostic problem for mandibular molars or for the buccal furcation of maxillary molars (Fig. 40-24). At such teeth, the separation area between the roots can easily be identified both with the probe and on a radiograph. It is more difficult to identify a

separation line between mesiobuccal (or distobuccal) and palatal roots of a maxillary molar or maxillary first premolar with a narrow root complex. In such situations, a soft tissue flap must often be raised to allow the operator to obtain proper access to the approximal tooth surfaces. The mesial (or distal) entrance of the furcation must be probed to a depth of 3–5 mm to ascertain that a fusion does not exist between the roots scheduled for RSR.

- *Amount of remaining support around individual roots*. This should be determined by probing the entire circumference of the separated roots. It should be observed that a localized deep attachment loss at one surface of one particular root (e.g. on the buccal surface of the palatal root or the distal surface of the mesiobuccal root of a maxillary molar) may compromise the long-term prognosis for an otherwise ideal root.
- *Stability of individual roots*. This must be examined following root separation. A rule of thumb is that the more mobile the root cone is, the less periodontal tissue support remains.
- *Access for oral hygiene devices*. After completion of therapy, the site must have an anatomy which facilitates proper self-performed tooth cleaning.

Maxillary molars

Several decisions must be made when RSR is planned for a furcation-involved maxillary molar. Since such teeth have three root cones, one or two cones may be retained after separation. Different treatment alternatives exist (Table 40-1).

Prior to RSR, the morphology of the individual roots as well as the surface area of each root must be carefully analyzed. The *distobuccal root* of a maxillary molar is the shortest of the three roots, but its root trunk is comparatively long. Thus, the distal root has a small quantity of bone support and once separated, the cone may exhibit increased mobility. The distobuccal root is, therefore, often removed as part of RSR (Rosenberg 1978; Ross & Thompson 1980).

The *mesiobuccal root* has a wide buccopalatal dimension and an hour-glass cross-section, and therefore a large root surface area. In fact, the mesiobuccal cone often has a total root surface area that is equal to or greater than that of the palatal root cone. The mesiobuccal root is located centrally in the alveolar process, is properly aligned with the maxillary premolars, and is in an ideal position to function as a separate unit (Fig. 40-25). For these reasons, the mesiobuccal root may be preferred for retention when the clinician is selecting between the mesiobuccal or

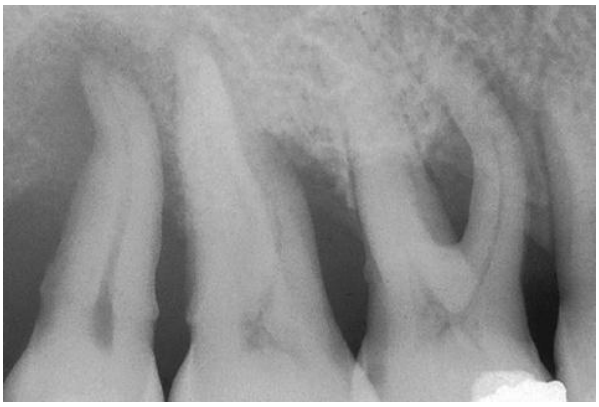


Fig. 40-24 Radiograph indicating the presence of a class III involvement of the buccal furcation of the maxillary first molar. This tooth is a candidate for root resection.

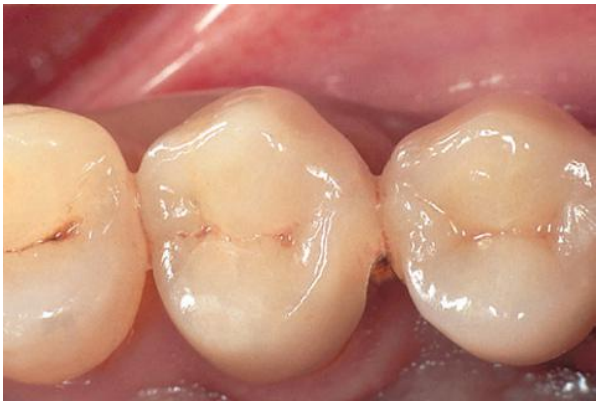


Fig. 40-25 Occlusal view of a restoration using the mesial root of a maxillary first molar as abutment. Note the alignment of the mesial root and the adjacent premolars.

Table 40-1 Root resective treatment possibilities in molars with furcation involvement.

Furcation involvement	Root resection	Root resection plus separation of the remaining roots
Buccal	Mesiobuccal, distobuccal	
Mesial	Mesiobuccal, palatal	
Distal	Distobuccal, palatal	
Buccal and distal	Distobuccal, mesiobuccal, and palatal	Palatal
Buccal and mesial	Mesiobuccal, distobuccal, and palatal	Palatal, distobuccal
Mesial and distal	Palatal, mesial, and distobuccal	Distobuccal
Buccal, distal, and mesial	Distobuccal and palatal, mesiobuccal and palatal, mesiobuccal and distobuccal	Palatal, distobuccal

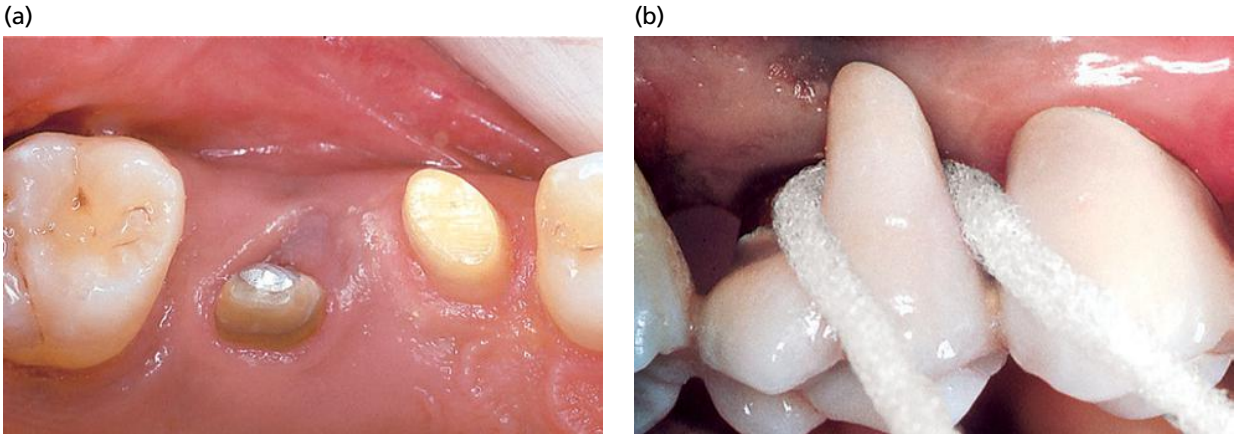


Fig. 40-26 (a) Palatal root of a root-resected maxillary molar serving as a single abutment for a crown restoration. (b) Mesiobuccal root included in the restoration for esthetic reasons.

palatal root. It should be remembered, however, that the root canals of the mesiobuccal root are narrow and more difficult to treat than the single and wide canal of the palatal root.

The tissue destruction in the furcation area often causes deep attachment and bone loss at the distal palatal surface of the mesiobuccal root. In such situations the palatal root remains as the only candidate for retention (Fig. 40-26).

The series of images presented in Fig. 40-27 demonstrates two left maxillary molars (teeth 26 and 27) with class III involvement of all six furcation entrances. Both teeth were, following a detailed examination and diagnosis, scheduled for treatment with RSR. Note that in this case the second premolar was missing. In cases of advanced periodontal disease at maxillary molars, it is often necessary to separate all three roots of the individual tooth to obtain access to the inter-radicular area for assessment of the height of the remaining bone at (1) the buccal surface of the palatal root and (2) the palatal surfaces of the buccal roots. Figure 40-27b shows the two maxillary molars with all six roots separated. Because of anatomic considerations and increased mobility, the distobuccal roots of teeth 26 and 27 were extracted (Fig. 40-27c). The palatal root of the first molar had a deep area of localized attachment loss on its buccal surface, was considered to be a poor candidate for a bridge abutment, and was extracted. The mesiobuccal root of the first molar as well as the mesiobuccal and palatal roots of the second molar (tooth 27) were stable and exhibited moderate probing depth. It was anticipated that at all three roots the anatomy would allow proper plaque control following healing after treatment. The three roots were maintained (Fig. 40-27d). Figure 40-27e shows the area after 3 months of healing and Fig. 40-27f illustrates the segment properly restored. Since in this segment one premolar was missing, the mesiobuccal root of the first molar was used as second premolar in the prosthetic reconstruction and the two roots of the second molar served as abutments for a crown restoration in the position of a molar.

Maxillary premolars

Root resection of maxillary first premolars is possible only in rare instances due to the anatomy of the root complex (Joseph *et al*. 1996) (Fig. 40-28). The furcation of this premolar is often located at such an apical level that the maintenance of one root serves no meaningful purpose. In most cases, therefore, the presence of a deep furcation involvement of class II or class III in a maxillary first premolar calls for tooth extraction.

Mandibular molars

If RSR must be applied in a furcation-involved mandibular molar, three treatment alternatives exist:

1. Separate the two roots, but maintain both roots (premolarization)
2. Separate and extract the mesial root
3. Separate and extract the distal root.

In some situations, both roots may be maintained following separation. If one root is to be removed, the following facts must be considered:

- The *mesial root* has a significantly greater root surface area than the distal root. The mesial root, however, has an hour-glass–shaped cross-section which may be difficult to manage in self-performed plaque control and in the restorative procedure. In addition, the mesial root frequently has two narrow root canals. The root canals are often close to the external root surface. This may complicate root preparation during the subsequent restorative treatment.
- The *distal root* has an oval cross-section and, as a rule, only one, wide root canal. The distal root is comparatively large, providing a greater mass of dentin to resist root fracture (Langer *et al*. 1981); and a good candidate for pin or post placement. Further, when the resected mandibular molar is a terminal abutment for a bridge, the retention of the distal root will result in a longer dental arch than would be the case had the mesial root been retained (Fig. 40-29).

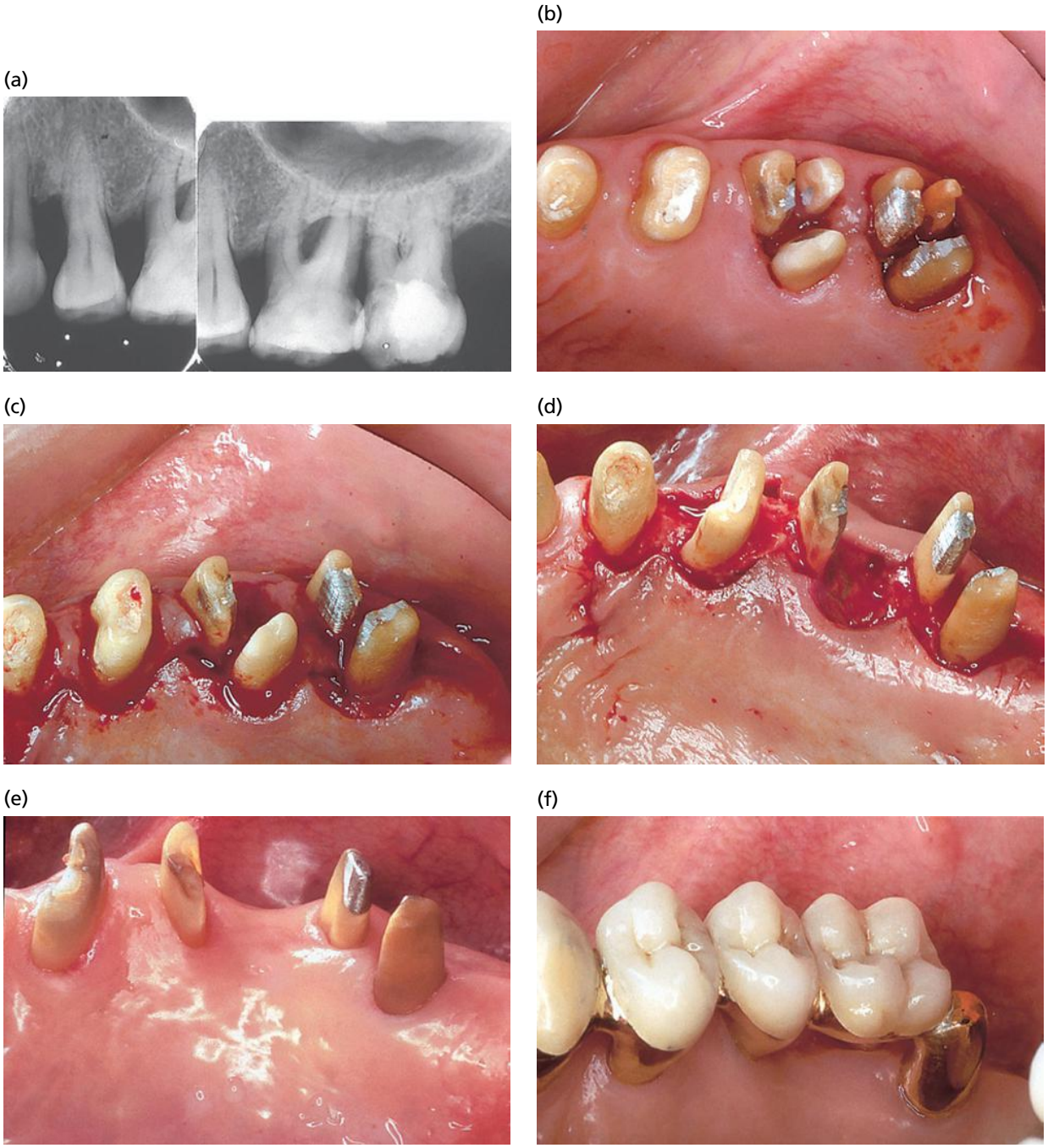


Fig. 40-27 Sequential stages of root separation and resection (RSR) of two maxillary molars with class III involvement. (a) Radiograph showing the pre-RSR situation; (b) roots were separated before flap elevation (c, d) distal roots of both molars and the palatal root of the first molar were extracted and the teeth prepared; (e) after 3 months of healing; (f) final prosthetic restoration of the site.

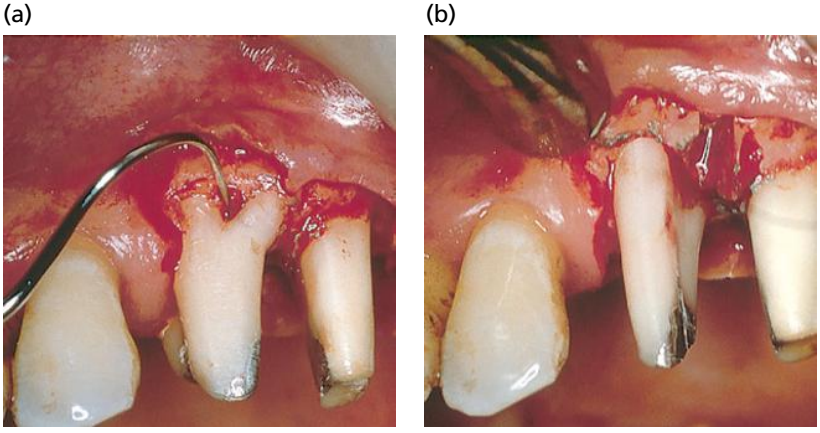


Fig. 40-28 (a, b) Resection of the distobuccal root of a three-rooted maxillary first premolar.

Sequence of treatment

Once anatomic and pathologic characteristics of the root complex(es) of multirooted teeth have been documented, treatment should follow a logical plan (see also Chapter 32).

Endodontic treatment

If the tooth to be resected is vital or if an improper root canal filling was placed in a non-vital tooth, RSR starts with endodontic therapy. A rubber dam can be placed, and optimal conditions thus be established for the important management (cleaning and shaping) of the root canal. The structural integrity of the root must be maintained and minimal amounts of root dentin should be removed (Fig. 40-30a, b). Direct filling with amalgam or chemically-cured composite of the endodontically treated tooth should be performed before RSR (Fig. 40-30c). Each root should have individual retention for a restoration which should not break or detach during RSR, removal and relining of the provisional restorations, impressions, and prosthetic try-in. Endocanal posts or endodontic screws are used only if natural retention needs improvement.

Occasionally, a furcation involvement may first be identified during periodontal surgery. In this emergency situation, RSR may be completed but the root canal entrance(s) of the remaining root(s) must be properly sealed. Definitive root canal therapy must be completed within 2 weeks (Smukler & Tagger 1976).

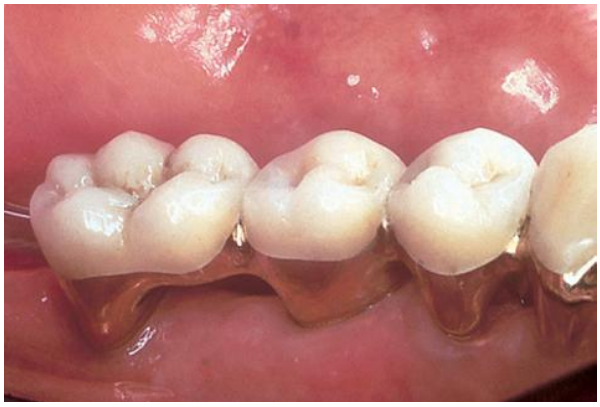


Fig. 40-29 Results of the root resection of a mandibular first molar of which the distal root was retained.

Provisional restoration

Alginate impressions of the area to be treated are taken and sent to the laboratory together with a wax record of the intercuspal position. A provisional restoration is prepared.

Root separation and resection

RSR may be performed as part of the preparation of the segment for prosthetic rehabilitation ("prosthetic preparation"), that is prior to periodontal surgery (Carnevale *et al*. 1981). During the prosthetic preparation it is important to avoid:

- Exposing the inter-radicular bone to undue mechanical trauma (Fig. 40-31)
- Leaving behind parts of the furcation fornix (Fig. 40-32)
- Perforating the root canals
- Preparing the vertical surfaces of the remaining roots with sharp angles (Fig. 40-33).

Situation 1: Mandibular molar. Following separation, both roots are maintained. The distal surface of the distal root and the mesial surface of the mesial root must be prepared parallel to each other to increase the retention for a subsequent restoration. The mesial surface of the distal root and the distal surface of the mesial root should be prepared with diverging angles to increase the space available between the separated roots (Fig. 40-34).

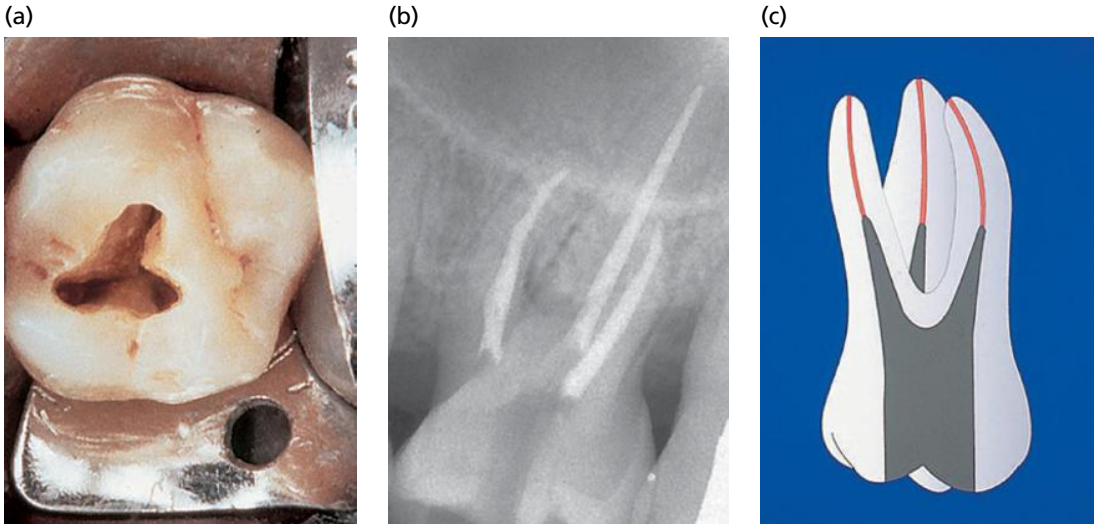


Fig. 40-30 (a) Photograph and (b) radiograph showing the "conservative" approach both regarding the access to the pulp chamber (a) and the shaping and filling of the root canal system (b). (c) Schematic illustration showing the temporary restoration of the endodontically treated tooth.

Situation 2: Maxillary molar. Following separation, the distobuccal root is extracted. The distal surface of the crown is prepared with a bevel cut and in such a way that the concave curvature (in the apicocoronal direction) is eliminated (Fig. 40-35). If the mesiobuccal and the palatal roots of this molar must be separated but maintained, it is important that the buccal surface of the mesiobuccal root and the palatal surface of the palatal root are prepared parallel to each other. This will enhance the retention of the subsequent restoration. The palatal surface of the mesiobuccal root and the buccal surface of the palatal root must be prepared at diverging angles to increase the space available between the separated roots (Fig. 40-36). At this stage the provisional restoration is relined with cold-cured acrylic and cemented after RSR.

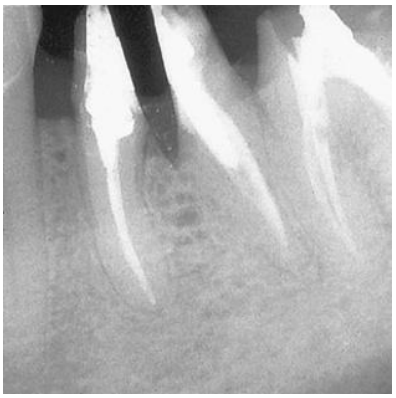


Fig. 40-31 Radiograph showing the damage which occurred to the inter-radicular septum during root separation.

Periodontal surgery

Following flap elevation, osseous resective techniques are used to eliminate angular bone defects that may exist around the maintained roots. Bone resection may also be performed to reduce the buccolingual dimension of the alveolar process of the extraction site. The remaining root(s) may be prepared with a bevel cut to the level of the supporting bone (Levine 1972; Ramfjord & Nissle 1974; Carnevale *et al*. 1983). This additional preparation may serve the purposes of eliminating residual soft and hard deposits, and eliminating existing undercuts to facilitate the final impression (Fig. 40-37). The provisional restoration is relined. The margins of the provisional restoration must end ≥3 mm coronal of the bone crest. The soft tissue flaps are secured with sutures at the level of the bone crest. The relined provisional restoration is cemented and a periodontal dressing is applied to cover the surgical area. The dressing and the sutures are removed 1 week later. The roots are debrided and a new dressing applied. After another

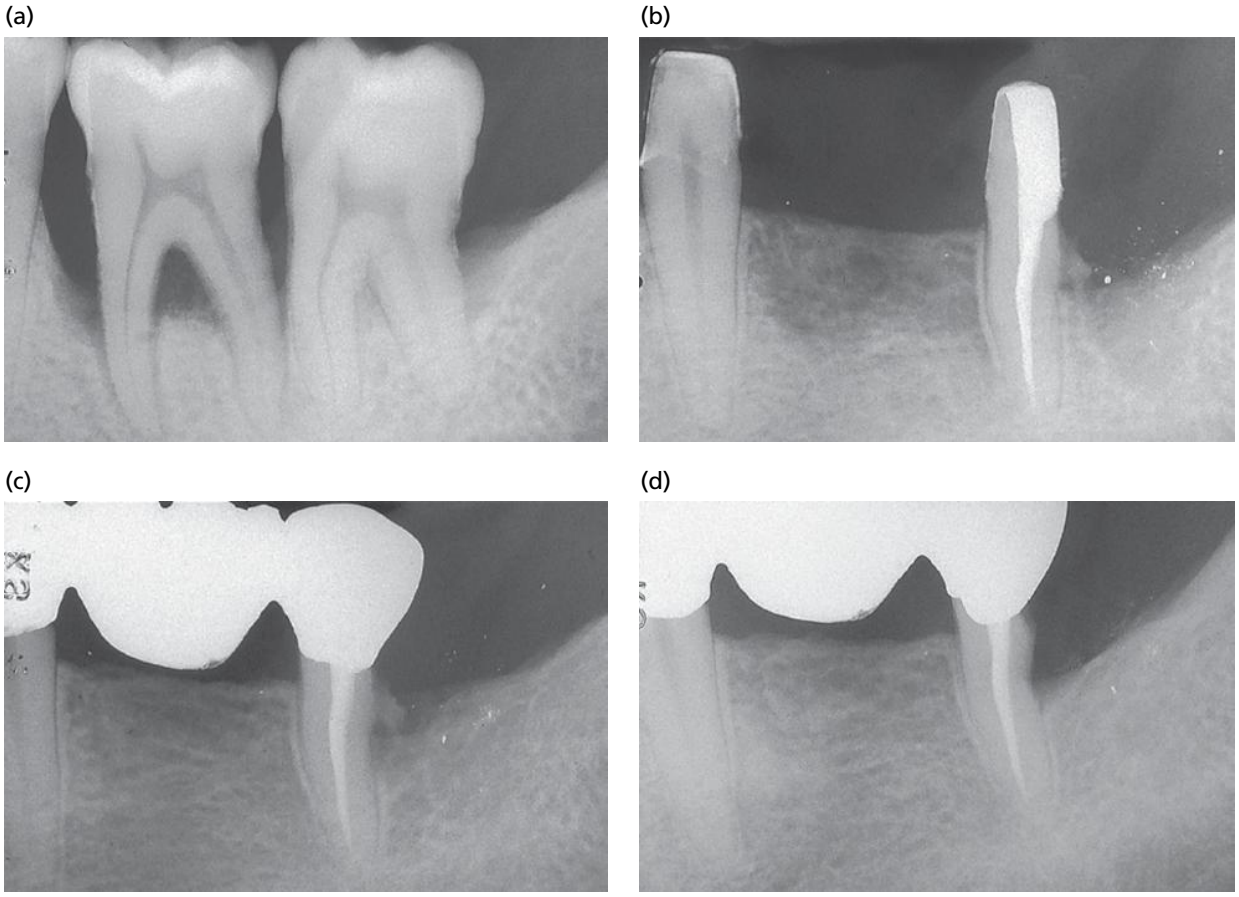


Fig. 40-32 (a) Radiograph of a mandibular first molar to be extracted and of a second molar to be root resected. (b) During hemisection, an overhang is left behind as a result of an oblique sectioning of the tooth distal to the furcation. (c) In a radiograph obtained 2 years later, the presence of an angular bony defect can be seen adjacent to the "overhang". The lesion was resolved and the angular defect disappeared following removal of the "overhang". (d) Radiograph after 2 years.

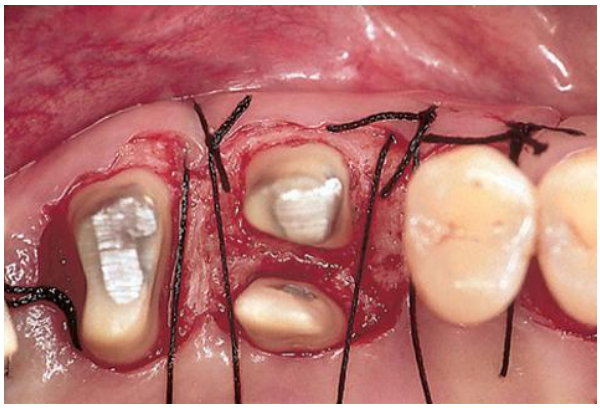


Fig. 40-33 Maintenance of the two fused buccal roots of a maxillary first molar. The buccal roots were separated from the palatal root. Note the rounded line angles and the wide space created between the separated roots.

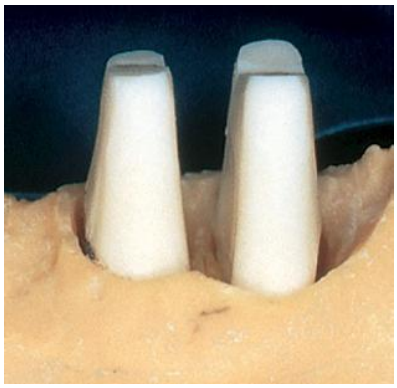


Fig. 40-34 Mandibular molar after root separation. Note the diverging angle of preparation performed to increase the inter-radicular space between the mesial and distal roots and the parallel approximal surfaces.

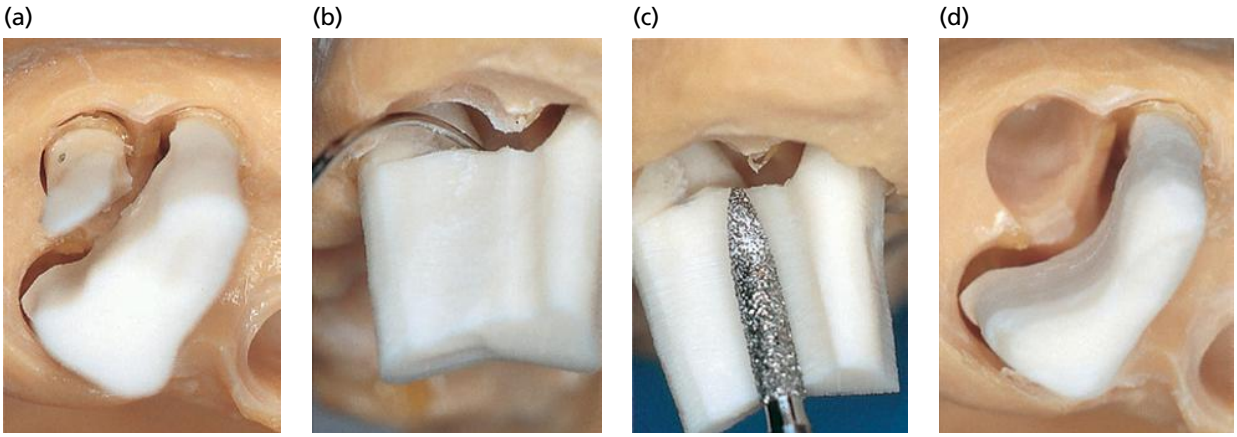


Fig. 40-35 (a, b) Sequential stages of root resection and extraction of the distal root of a maxillary molar. In order to minimize the concave outline of the cut surfaces, the sectioning should be performed with a straight line cut. (c, d) After extraction of the distal root, the furcation area of the remaining roots must be reprepared to eliminate undercuts.

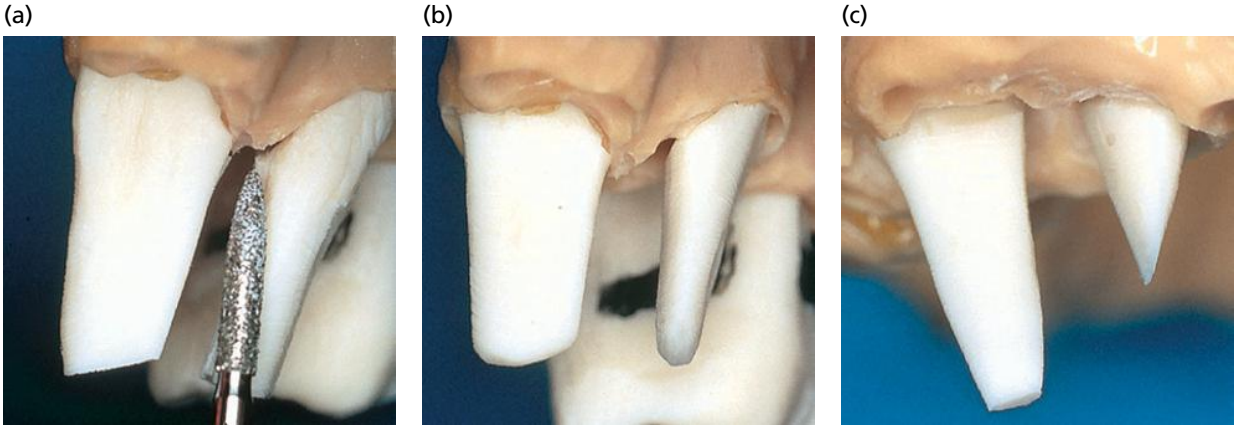


Fig. 40-36 (a, b) Preparation during separation of the mesiobuccal and palatal roots after the distobuccal root of a maxillary molar had been extracted. The internal (furcation) surfaces of the two roots should be prepared with diverging angles to increase the inter-radicular space, while the external surfaces of the two roots should be prepared parallel to each other to increase the subsequent retention of the restoration. (c) When the palatal surface of the palatal root is not prepared parallel to the buccal surface, the palatal abutment will shorten and not be self-retentive.

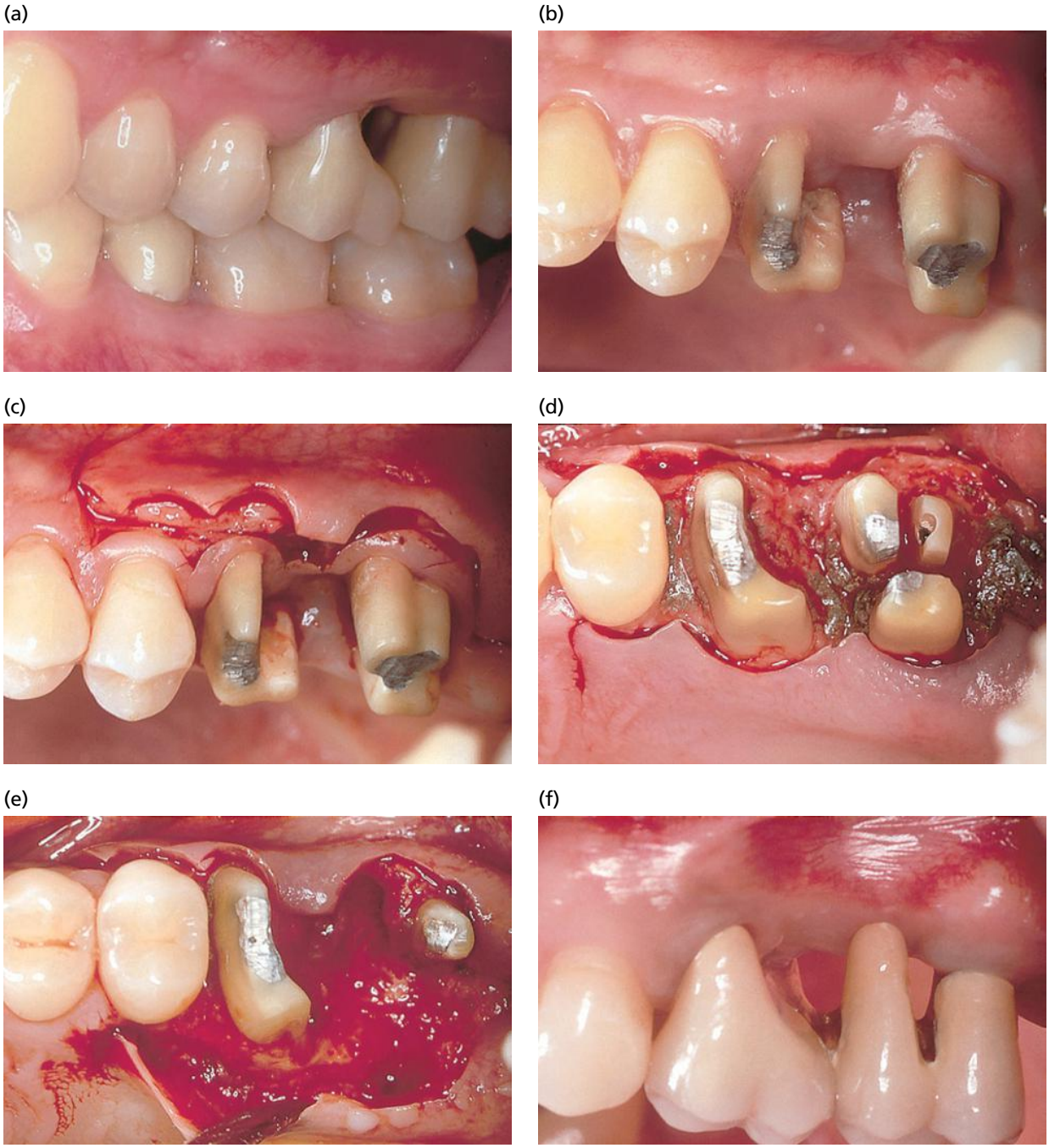


Fig. 40-37 (a, b) Sequential stages of root resection at maxillary first and second molars. The extraction of the distal root of the first molar was performed during tooth preparation and prior to the insertion of the provisional restoration. (c–e) During the surgical procedure, after flap elevation, the furcation-involved second molar was separated, the mesial and palatal roots were extracted, and the osseous defects were eliminated. (f) Healing with the definitive prosthetic restoration in place.

week, the dressing is finally removed and the patient instructed in proper plaque-control techniques.

Final prosthetic restoration

Since the prosthetic preparation of the roots is completed during surgery, the clinician concerns him/herself only with minor adjustments. The preparation margins are located supragingivally, which improves the precision of the definitive crown restoration. The framework of the restoration must be rigid to compensate for the compromised abutments (roots) with a compromised periodontal tissue support. The occlusion should be designed to minimize lateral deflective forces (see Chapter 52) (Fig. 40-38).

Regeneration of furcation defects

The possibility of regenerating and closing a furcation defect has been investigated (see Chapter 45). Following an early case report publication (Gottlow *et al*. 1986), where histologic documentation of new attachment formation in human furcation defects (Fig. 40-39) treated by "guided tissue regeneration" (GTR) therapy was provided, the results of several investigations on this form of

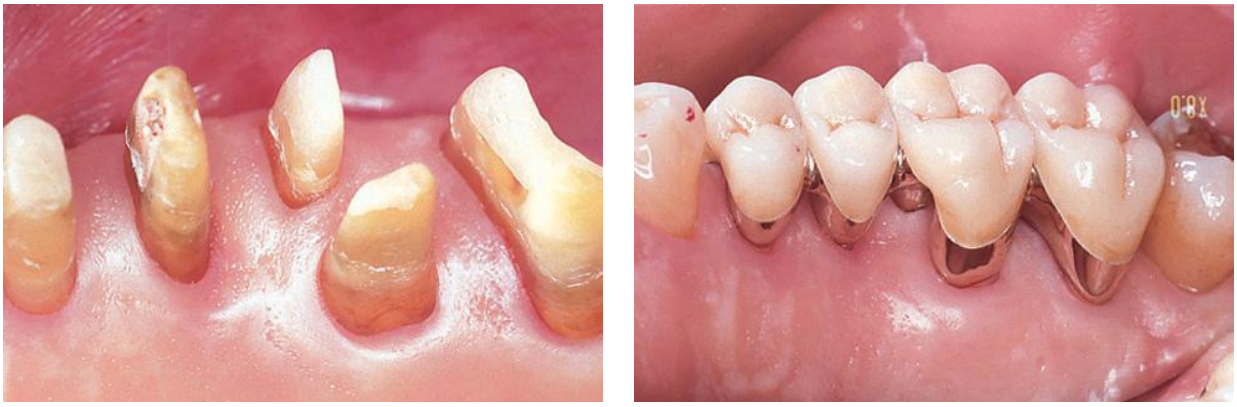


Fig. 40-38 (a) Soft tissue healing at a separated maxillary first molar and at a root-resected second molar. (b) Final prosthetic restoration in place with the occlusion designed to minimize the lateral stresses on the roots left as abutments.

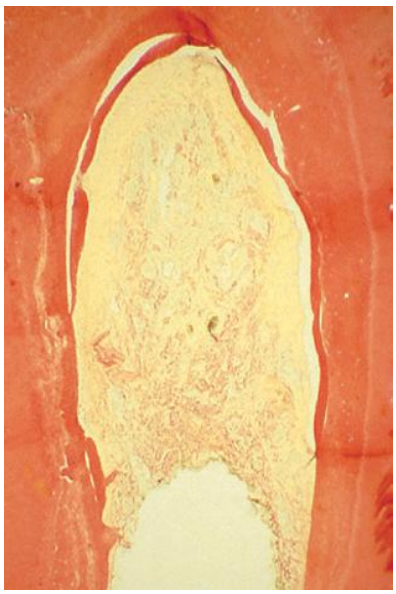


Fig. 40-39 Histologic mesiodistal section of a previous class II furcation involvement of a human mandibular molar, treated with guided tissue regeneration. The section demonstrates that the newly formed cementum covers the entire circumference of the furcation defect.

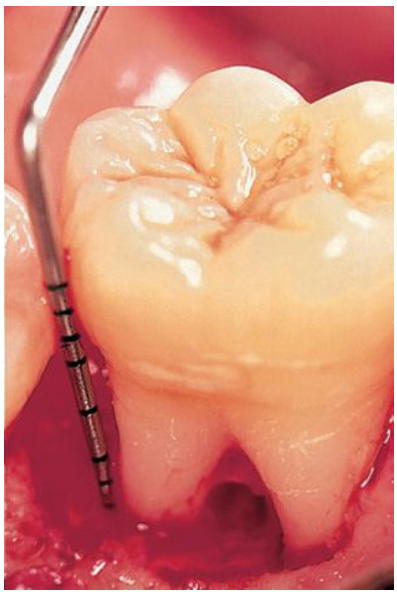


Fig. 40-40 Position of the furcation fornix in relation to the level of the supporting bone and attachment apparatus in a lingual class II furcation-involved mandibular molar.

treatment in furcation-involved teeth have been presented. In these reports, a reasonably predictable outcome of GTR therapy was demonstrated only in class II furcation-involved mandibular molars, where a clinical soft tissue closure or a decreased probing depth of the furcation defect was recorded (Pontoriero *et al.* 1988; Lekovic *et al.* 1989; Caffesse *et al.* 1990). Less favorable results have been reported when GTR therapy was used in other types of furcation defects such as class III furcation-involved mandibular and maxillary molars (Pontoriero *et al.* 1989; Pontoriero & Lindhe 1995a) and class II furcations in maxillary molars (Metzeler *et al.* 1991; Pontoriero & Lindhe 1995b). The reason for the limited predictability of GTR therapy in furcation-involved teeth may be related to several factors:

- Morphology of the periodontal defect, which in the root complex often has the character of a "horizontal lesion". New attachment formation is hence dependent on coronal up-growth of periodontal ligament tissue (Fig. 40-40).
- Anatomy of the furcation, with its complex internal morphology, may prevent proper instrumentation and debridement of the exposed root surface (Fig. 40-41).
- Varying and changing location of the soft tissue margins during the early phase of healing with a possible recession of the flap margin and early exposure of both the membrane material and the fornix of the furcation (Fig. 40-42).

GTR treatment could be considered in dentitions with isolated class II furcation defects in mandibular molars. The predictability of this treatment outcome improves following GTR therapy if:

- The interproximal bone is located at a level which is close to the CEJ of the approximal surface. This "keyhole" type of class II involvement allows for an effective retention of the membrane material and retention also of the position of the coronally placed flap margins (Fig. 40-43).
- The debridement of the exposed root surfaces in the furcation area is comprehensive. Since the width of the furcation entrance and the internal morphology of the inter-radicular area may limit the access of curettes for proper debridement, the removal of hard and soft bacterial deposits from the root surfaces must frequently be done with ultrasonic instruments, rotating, flame-shaped fine diamond burs, and endodontic files (Fig. 40-44).
- The membrane material is properly placed and a "space" between the tooth and the material established. A "primary" wound closure is thereby

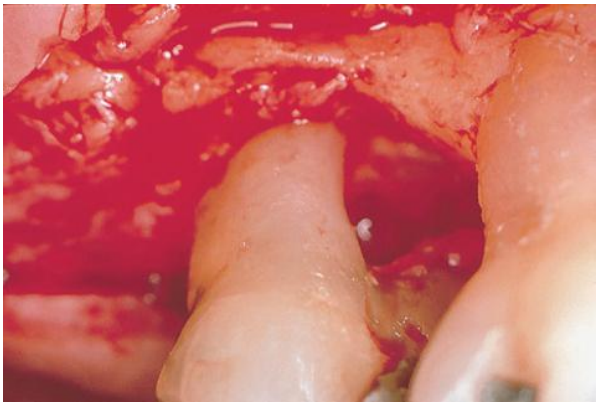


Fig. 40-41 Internal morphology of the furcation of a maxillary molar. Note the invagination of the palatal root.

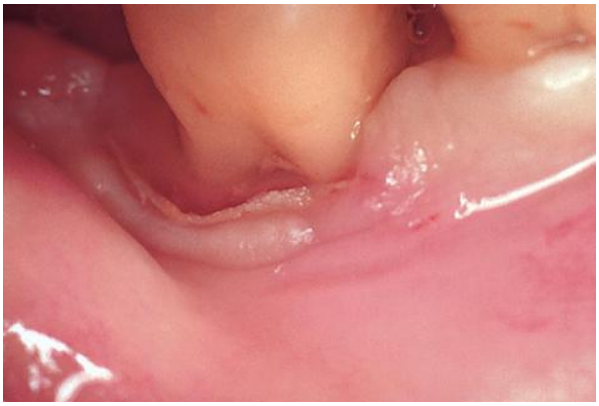
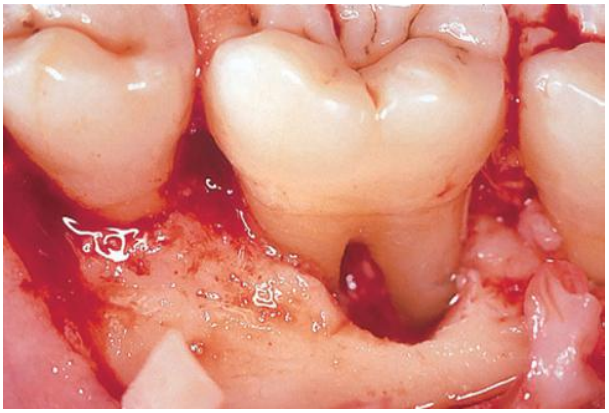
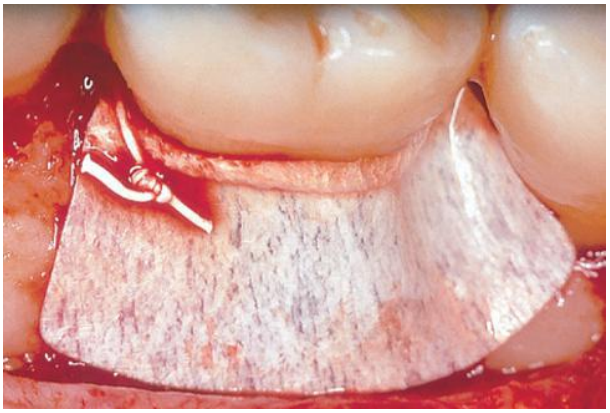


Fig. 40-42 Exposure of the membrane and of the furcation entrance as a consequence of recession of the flap margin. The photograph is taken at 3 weeks of healing after guided tissue regeneration treatment of a class II buccal furcation of a mandibular molar.

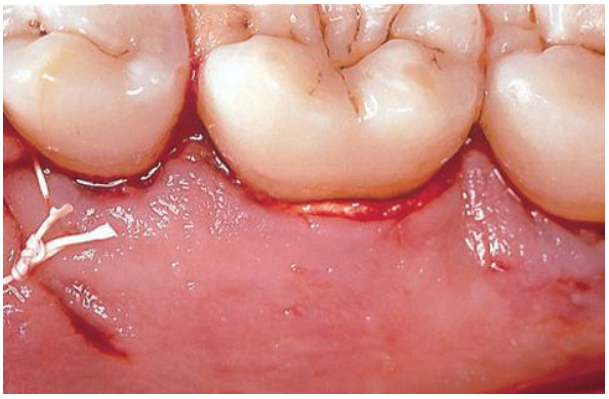
(a)



(b)



(c)



(d)

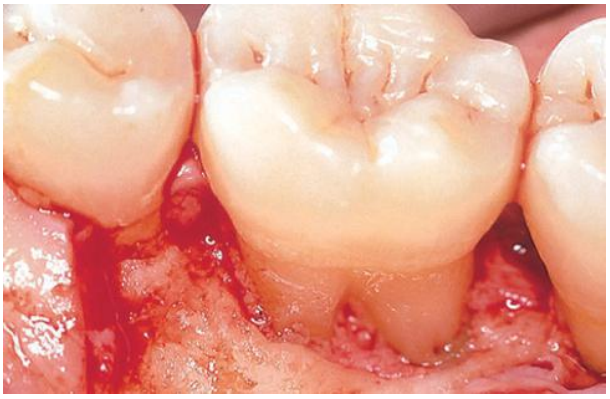


Fig. 40-43 Aspect of a lingual class II furcation involvement in a mandibular first molar. (a) Note the infrabony component of the defect and the level of the approximal supporting bone in relation to the furcation fornix. (b) Teflon membrane sutured in position and supported by the interproximal alveolar bone. (c) Flap positioned and sutured over the membrane. (d) At re-entry, after 6 months of healing, the previously exposed furcation defect was closed and filled with bone tissue.

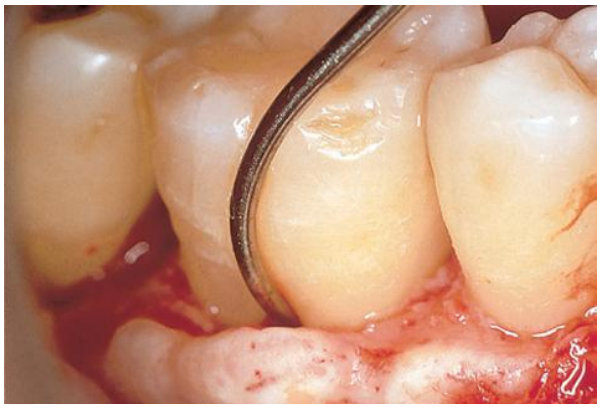


Fig. 40-44 Phase of debridement of a buccal degree II furcation defect using an "extra-fine" ultrasonic tip.

obtained, blood clot protection will occur, and recession of the soft tissue margin during the early phase of healing will be minimized (Fig. 40-45).

- A plaque-control program is put in place. This should include daily rinsing with a chlorhexidine solution and professional tooth cleaning once a week for the first month, and once every 2–3 weeks for at least another 6 months of healing following the surgical procedure.

Enamel matrix proteins included in a commercially available product (Emdogain®; Straumann, Basel, Switzerland) were used in the treatment of furcation defects in experimental studies in animals (Araùjo & Lindhe 1998) and in clinical trials in humans (Jepsen *et al*. 2004; Meyle *et al.* 2004). The ability of Emdogain® (EMD), applied to the root surfaces in the furcation area, to stimulate periodontal regeneration in surgically created class III furcation defects in dogs was documented histologically by Araùjo and Lindhe (1998). In a multicenter randomized controlled clinical trial, including 45 subjects with 45 paired mandibular molars with buccal class II furcation involvements, Jepsen *et al*. (2004) compared EMD with GTR therapy. After 14 months of healing, the subjects were re-examined. The authors reported a mean reduction in the open horizontal furcation depth of 2.8 mm for EMD-treated sites and of 1.8 mm for GTR-treated defects. In addition, the frequency of complete closed furcation defects was higher for EMD sites (8 of 45) than for GTR sites (3 of 45). It was concluded that both treatment modalities resulted in significant clinical improvements although the EMD method provided (1) greater reduction of the furcation depths, (2) a smaller incidence of postoperative pain/swelling, and (3) less gingival recession (Meyle *et al*. 2004) as compared to GTR therapy. The outcome of the regenerative procedures at furcation-involved molars should result in the complete elimination of the defect within the inter-radicular space in order to establish anatomic conditions which facilitate optimal self-performed plaque-control measures. In fact, partial gain of clinical attachment levels within the furcation defect, although statistically significant, will not necessarily improve the site's accessibility for plaque-control measures.

Extraction

The extraction of a furcation-involved tooth must be considered when the attachment loss is so extensive that no root can be maintained or when the treatment will not result in a tooth/gingival anatomy that allows proper self-performed plaque-control measures. Moreover, extraction can be considered as an alternative form of therapy when the maintenance of the affected tooth will not improve the overall treatment plan or when, due to endodontic or caries-related lesions, the preservation of the tooth will represent a risk factor for the long-term prognosis of the overall treatment. The possibility of substituting a furcation-involved tooth with an osseointegrated implant should be considered with extreme caution and only if implant therapy will improve the prognosis of the overall treatment (see Chapter 33). In fact, the implant alternative has obvious anatomic limitations in the maxillary and mandibular molar regions.

Prognosis

Several studies have evaluated the long-term prognosis of multirooted teeth with furcation involvement that were treated in accordance with the principles described in this chapter (Table 40-2). In a 5-year study, Hamp *et al*. (1975) observed the outcome of treatment of 175 teeth with various degrees of furcation involvement in 100 patients. Of the 175 teeth, 32 (18%) were treated by SRP alone, 49 (28%) were subjected, in addition to SRP, to furcation plasty which included odonto- and/or osteo-plasty. In 87 teeth (50%), root resection had been carried out and in seven teeth (4%) a tunnel had been prepared. At the completion of the active phase of therapy, the patients were enrolled in a maintenance program which included a recall visit every 3–6 months. The plaque and gingivitis scores assessed immediately after treatment and once a year during maintenance indicated that the patients' oral hygiene was of high quality. None of the teeth treated was lost during the 5 years of study. Only 16 furcation sites exhibited probing depths exceeding 3 mm. During the observation period, carious lesions were detected in 12 surfaces of the 32 teeth which had been treated by SRP, in three surfaces of the 49 teeth subjected to furcation plasty, in five surfaces of the 78 root-resected teeth, and in four surfaces of the seven teeth where a tunnel was prepared.

The results of this study were basically confirmed in another investigation (Hamp *et al.* 1992). In this 7-year study, the authors followed 100 patients with 182 furcation-involved teeth. Of the 182 furcation-involved teeth, 57 had been treated by SRP alone, 101 were treated by furcation plasty, and 24 were subjected to root resection or hemisection. No tunnel preparation was performed.

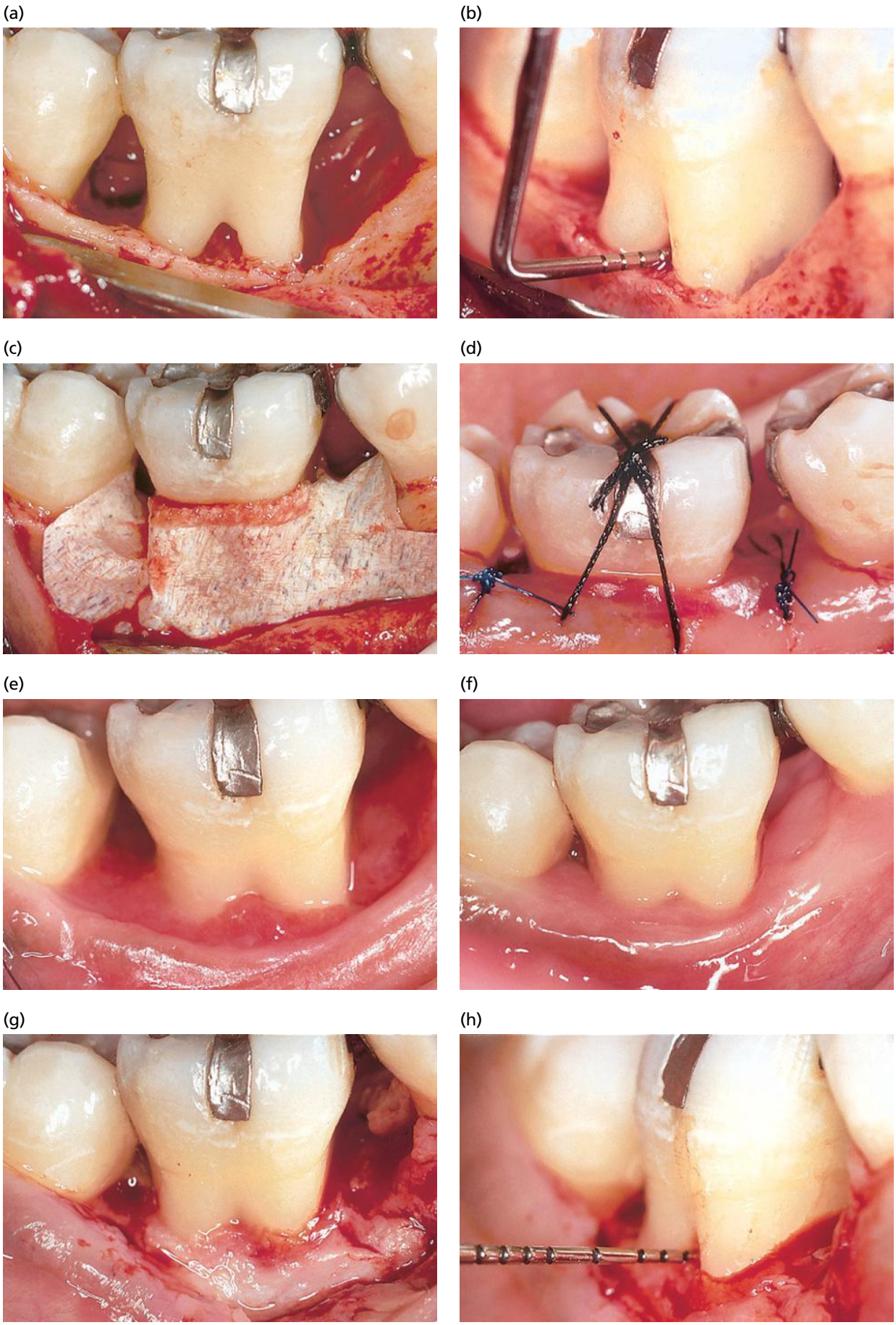


Fig. 40-45 Sequential stages of guided tissue regeneration treatment of a buccal class II furcation-involved mandibular first molar. (a, b) Clinical appearance and horizontal probing of the defect. (c, d) Membrane placement and retention. (e) Clinical aspect of the soft tissue at 4 weeks after membrane removal and (f) after 6 months of healing. During the re-entry procedure the furcation defect appeared completely closed (g) and was not probeable (h).

Table 40-2 Long-term clinical studies on root resection therapy in molars with furcation involvement.

Study	Observation period	No. of teeth examined	Causes of tooth loss					
			% Teeth lost	% Root/ tooth fracture	% Periodontal	% Endodontic	% Caries or decementation	% Strategic
Bergenholtz (1972)	21 teeth/2–5 years 17 teeth/5–10 years	45	6		4	2		
Klavan (1975)	3 years	34	3		3			
Hamp *et al.* (1975)	5 years	87	0					
Langer *et al.* (1981)	10 years	100	38	18	10	7	3	
Erpenstein (1983)	4–7 years	34	9		3	6		
Bühler (1988)	10 years	28	32	3.6	7.1	17.7	3.6	
Carnevale *et al.* (1991)	303 teeth/3–6 years 185 teeth/7–11 years	488	4	1.8	0.4	0.9	0.9	
Basten *et al.* (1996)	2–23 years	49	8			2	4	2
Carnevale *et al.* (1998)	10 years	175	7	1.1	1.8	2.3	1.8	

After the active phase of therapy, the patients were enrolled in a meticulous maintenance care program including recall appointments once every 3–6 months. During the course of the study, >85% of the furcations treated with SRP alone, or in conjunction with furcation plasty, maintained stable conditions or showed signs of improvement. Only one tooth and one mesial root of a mandibular molar were extracted among the root-resected or hemisected teeth.

Carnevale *et al.* (1998), in a 10-year prospective controlled clinical trial, demonstrated a 93% survival rate of root resected furcation-involved teeth and a 99% survival rate of non-furcation-involved teeth.

More recently, Svärdström (2001) presented the results of a retrospective analysis on factors influencing the decision-making process regarding the treatment for 1313 molars with furcation involvement in 222 patients, and the outcome of the treatment decisions after 8–12 years (mean 9.5 years) of regular maintenance care. The treatment options included were: tooth extraction, root separation/resection, and maintenance of the tooth with non-surgically/surgically performed SRP with or without furcation plasty. Of the 1313 furcation-involved molars, 366 (28%) were extracted during the active phase of therapy. The decision for tooth extraction was primarily influenced by factors such as tooth mobility, tooth position, absence of occlusal antagonism, degree of furcation involvement, probing depth, and amount of remaining periodontal support. Of the 685 molars with furcation involvement and the 160 patients who were available for the follow-up examination 8–12 years after treatment, 47 teeth were root separated/resected and 638 teeth were considered to be maintainable after a non-surgical or conservative surgical therapy.

The factor found to have the strongest influence on the decision to perform root separation/resection was the degree of furcation involvement (classes II and III). Tooth position, probing depth, and tooth mobility were also factors of statistical significance. The author indicated that other factors such as endodontic conditions, root anatomy, and overall treatment strategy may also have influenced the choice of treatment. The long-term outcome of the treatment decisions made for furcation-involved molars showed a favorable survival rate for both root resective (89%) and non-resective (96%) therapy options in patients included in a proper maintenance care program. Of the 47 root-separated/resected teeth, only five (11%) were lost during the 9.5 years of follow-up. Of the 638 molars initially considered to be maintainable by a non-resective treatment, 21 (3.5%) were extracted and three were root resected.

Recently, Huynh-Ba *et al.* (2009) published a systematic review of articles reporting the results of different periodontal treatment modalities in multirooted teeth with furcation involvement of various degrees. The authors selected 22 publications where it was possible to determine both the survival rate and the incidence of complications in furcation-involved teeth after a

mean period of at least 5 years of observation following active periodontal therapy. The reported treatment modalities ranged from non-surgical and surgical debridement, furcation tunnel preparation, hemisection, root resection, and regenerative procedures. Reported tooth survival rates by procedure were:

- *Non-surgical furcation therapy*: 90.7–100% at the end of the observation period of 5–12 years. Tooth survival in molars with class I furcation defects (74% of the analyzed teeth at the beginning of the study) was 99– 100%; in molars with class II furcation defects it was 95% and in class III furcation defects it was 25%.
- *Surgical furcation therapy* (i.e. flap with or without osseous resection, gingivectomy/gingivoplasty, but not including furcation odontoplasty): 43.1–96% at the end of an observation period of 5–53 years.
- *Tunnel preparation* of the furcation: 42.9–92.9% after 5–8 years of observation. Carious lesions were a reported complication.
- *Surgical resective therapy* (i.e. root resection or root separation): 62–100% after an observation period of 5–13 years. Reported complications were mainly root fractures and endodontic failures.
- *Surgical regenerative therapy* (i.e. GTR, bone grafts): 62–100% after a period of 5–12 years. However, despite a horizontal furcation depth reduction in most of the cases following treatment, a complete furcation closure was not a consistent finding, especially in severely involved mandibular and maxillary molars.

Table 40-3 Factors to consider in treatment of furcation-involved molars.

Tooth-related factors	Patient-related factors
Degree of furcation involvement	Strategic value of the tooth in relation to the overall plan
Amount of remaining periodontal support	Patient's functional and esthetic demands
Probing depth	Patient's age and health conditions
Tooth mobility	Oral hygiene capacity
Endodontic conditions and root/root–canal anatomy	
Available sound tooth substance	
Tooth position and occlusal antagonisms	

The authors concluded that since no form of treatment performed in the various studies clearly demonstrated superiority over any of the others in terms of tooth survival, guidelines and therapeutic decisions could not be recommended based on this review.

Conclusion

In treatment decisions for furcation-involved molars (Table 40-3), it must be realized that there is no scientific evidence that any given treatment modality is superior to the others.

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Chapter 41

Endodontics and Periodontics

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Introduction

Inflammatory lesions of the attachment apparatus of teeth involve a variety of etiologies other than plaque accumulations in the dentogingival region; these require attention in diagnosis and treatment planning processes. In fact, signs and symptoms seen as typical of periodontitis, such as pocket probing depths, loss of attachment, increased tooth mobility, pain, swellings, and suppurations, may reflect several tooth-associated infections, including infections of endodontic origin (here termed endodontic lesions), infections initiated and maintained by iatrogenic root perforations, vertical root fractures, or root surface resorptions. It should be recognized that microorganisms located in niches other than the gingival sulcus trigger the host reaction in these conditions.

The differential diagnosis of inflammatory conditions of the periodontium is not normally a thorny exercise. This is because symptoms of periodontitis usually affect several teeth in the dentition and are confined to the marginal periodontium. Other tooth-associated infections, by contrast, are usually isolated to a single tooth and display rather typical clinical symptoms and radiographic signs. These conditions can nevertheless produce confusing clinical expressions and lead to misinterpretation of their cause, especially when affecting teeth in dentitions diseased by periodontitis. Diagnostic difficulties arise particularly when lesions appear deep in the lateral aspects of roots in what can be a marginal–apical communication. These lesions present the clinician with exceptional challenges in that the origin and thus the proper course of treatment are not readily revealed. Often the term "endo–perio lesion" is used in this context, as both the pulp and the periodontium may be diseased simultaneously but form what appears to be a single periodontal lesion. Yet, the process may be

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of periodontal origin in its entirety or the lesion may just be a representation of a root canal infection alone. Hence, determination of causality is crucial in these cases not only to avoid unnecessary and possibly detrimental treatment, but also to assess whether the disease condition stands a reasonable chance of being successfully treated.

To guide clinical decision-making on diagnosis and treatment of inflammatory lesions in the periodontium, the focus of this chapter is on various tooth-associated disorders that display similar signs and symptoms to periodontitis. Specifically addressed are the clinical presentations and the means by which endodontic infections and infections associated with root perforations, root fractures, cemental tears, tooth malformations, and cervical invasive root resorptions can be identified and distinguished from manifestations of periodontitis. Management principles will be addressed where appropriate. Non-infectious processes *viz.* developmental cysts and tumors, which also can interfere with the supporting tissues, will not be discussed in this chapter.

Infectious processes of endodontic origin in the periodontium

General features

Disease conditions of the dental pulp are for the most part infectious in nature and involve inflammatory processes. Caries, restorative procedures, and traumatic injuries are common etiologies (see Chapter 25). In fact, any loss of hard tissue integrity of teeth, exposing dentin or the pulp directly to the oral environment, may allow bacteria and bacterial elements to adversely affect the normally healthy condition of the pulp. The resulting inflammatory lesion will then be directed towards the source of irritation and be confined for as long as the inflammatory defense does not collapse and convert into a major destructive breakdown of the pulpal tissue. Consequently, inflammatory alterations in the vital pulp will not normally produce lesions in the adjoining periodontium that can be detected by clinical means. Yet, disruption of the apical lamina dura or widening of the periodontal ligament space can occasionally be observed radiographically (Fig. 41-1a). Teeth, particularly in young individuals with large pulp chambers, may also display minor radiolucent areas either apically or laterally along the root surface at exits of accessory canals and apical foramina or both, in spite of the fact that vital pulp functions prevail (Langeland 1987; Gesi *et al*. 2006). In such cases, typical clinical signs of pulpitis, including spontaneous pain, thermal sensitivity or tenderness to percussion, may or may not be present.

Overt lesions in the periodontium, on the other hand, are common in teeth where the pulp has lost its vitality. In these cases the process is associated either with a non-treated necrotic pulp or a tooth that has been subjected to endodontic treatment. In both cases, the cause of the lesion is to be found in an existing, in the latter case not successfully managed, root canal infection (Fig. 41-1b). Extrusion of toxic medicaments and root-filling materials into the periodontium in conjunction with endodontic treatments may also cause periodontal lesions. While severe damage to the periodontal tissue support formerly was a rather common complication following the use of arsenic- or formaldehyde-based preparations to devitalize pulps, medicate, and fill root canals (Fig. 41-2), modern day medicaments for canal irrigation and disinfection, as well as materials for root canal filling, are comparatively well tolerated (Geurtsen & Leyhausen 1997). However, severe acute toxic and allergic reactions may be, albeit rarely, encountered from the use of highly

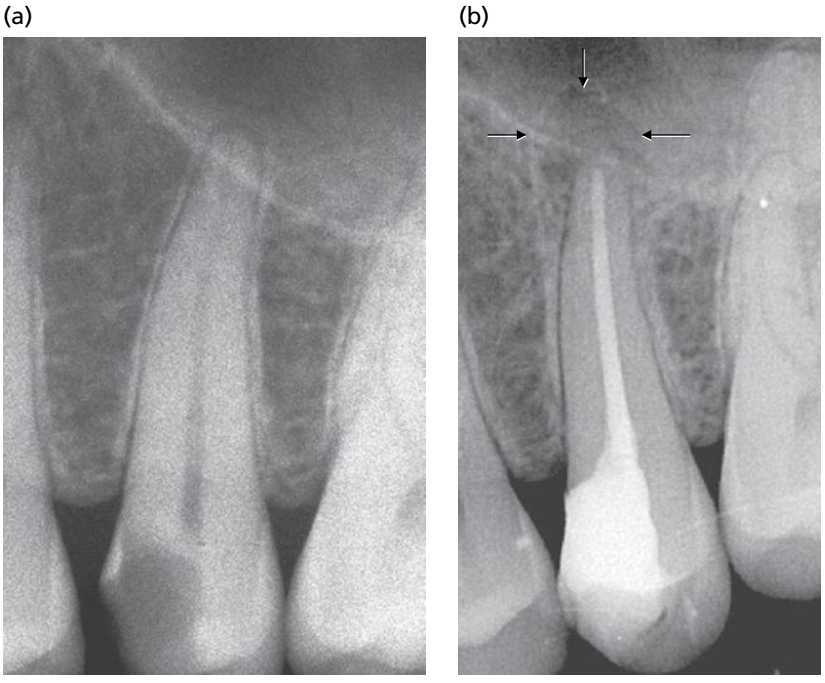

Fig. 41-1 (a) Radiograph of a maxillary second premolar with caries extending to the vicinity of the pulp. There is loss of lamina dura at the root tip. (b) 3-year recall radiograph after pulpectomy of the vital pulp and root filling shows a periapical radiolucency suggesting existence of a persistent root canal infection.

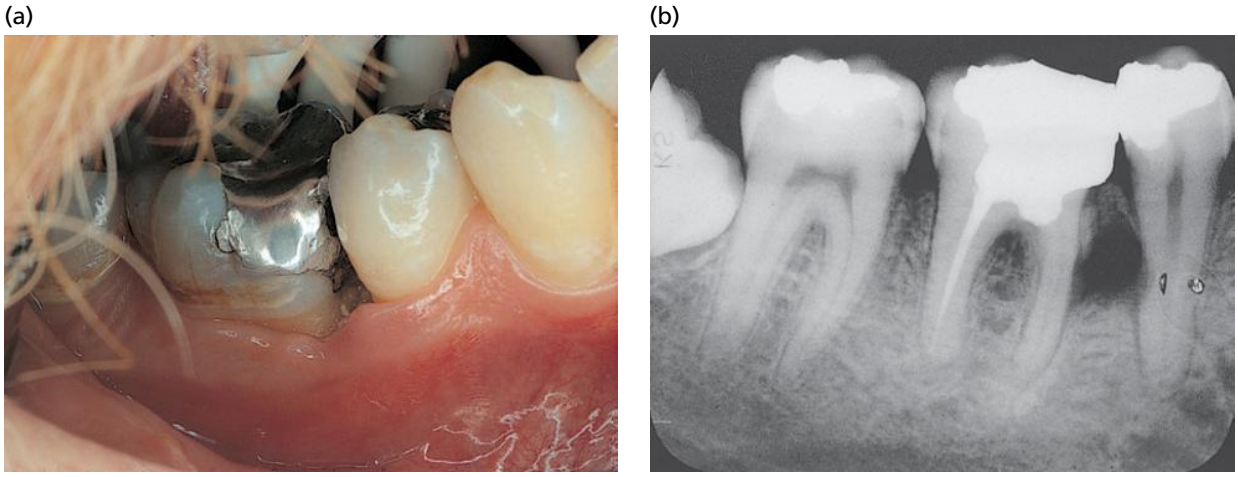

Fig. 41-2 (a) Clinical photograph showing a periodontal defect at the mesial aspect of tooth 46. The pulp had been subjected to devitalization by the use of a paraformaldehyde-containing paste. (b) There is loss of proximal bone and emergence of a bone sequestrum. Leakage of the agent most likely occurred along the margins of the prior temporary filling used between treatment sessions.

concentrated sodium hypochlorite (NaOCl) and adverse components of root-filling material (Swedish Council on Health Technology Assessment 2010).

Conclusion: It is important to realize that as long as the pulp maintains vital functions, even if inflamed or scarred, it is unlikely to produce irritants that cause overt periodontal tissue lesions. For clinically significant periodontal lesions to occur, the pulp must have lost its vitality. Consequently, no benefit will normally be gained from extirpation of vital pulps (pulpectomy) as an adjunct or alternative to the treatment of teeth for periodontal disease.

Clinical presentations

Inflammatory lesions in the periodontal tissues, induced and maintained by root canal infection, typically expand around the apex of teeth, where the root canal space interconnects with the periodontium along apical foramina. Lesions develop more rarely in juxtaposition with the lateral aspects of roots (Fig. 41-3a) and in furcations of multirooted teeth (Fig. 41-4a). An important reason for this is that accessory canals that can mediate the release of bacterial elements from the pulpal chamber to cause discernable lesions clinically are relatively uncommon in cervical and mid-root portions in adult teeth. Many accessory canals are also of a thin diameter (see Chapter 25). Another important factor is that an intact layer of root cementum blocks potential dissemination of bacteria and their products along the dentinal tubules.

The clinical presentation varies. Lesions can either be in a silent, non-symptomatic state or appear with more or less salient signs of acute infection. In the former case, a balanced host–parasite interrelationship has usually been established. The only means to diagnose the condition is then by radiography (see Fig. 41-1b). Unless transformed to a cyst, the extension of such non-symptomatic lesions may remain limited and stable over many years. This applies in particular to lesions associated with root-filled teeth, where the persisting root canal infection has assumed a relatively low grade of metabolic activity (see Chapter 25).

Lesions associated with untreated infections of a necrotic pulp or with inadequately treated root canals by endodontics may, either soon after pulp tissue breakdown or after a period of silence, turn into an exacerbating, acute inflammatory process. Exacerbating lesions may also be induced in conjunction with endodontic treatment from over-instrumentation along with extrusion of bacteria and tissue-irritating medicaments. Exudation and pus production dictate the clinical course. Typical symptoms include throbbing pain, pain on percussion, tenderness to palpation, increased tooth mobility, and apical as well as marginal swellings. The severity of these symptoms may have escalated over a period of time, although a single sign may be the only presenting symptom. It should be noted that the very same symptoms may occasionally occur with some forms of aggressive periodontitis, iatrogenic root perforation, root fracture, malformed teeth, and external root resorption (see below).

The pressure the exudative process exerts results in tissue destruction as a path for drainage is sought. This expansion of the lesion may take a variety of directions. Significant in the context of the differential diagnosis from periodontitis are those lesions that drain off at or near to the gingival margin. The character of the accompanying bone lesion may add to the risk of misdiagnosis, as it may look similar to that of aggressive periodontitis (Figs. 41-5, 41-6).

The following two routes of drainage from a suppurating endodontic lesion should be recognized (Fig. 41-7):

1. Drainage may occur along the periodontal ligament space and exit at the bottom of the sulcus (Fig. 41-7a). This usually results in only a narrow opening of the fistula into the gingival sulcus/pocket and may not be detected unless careful

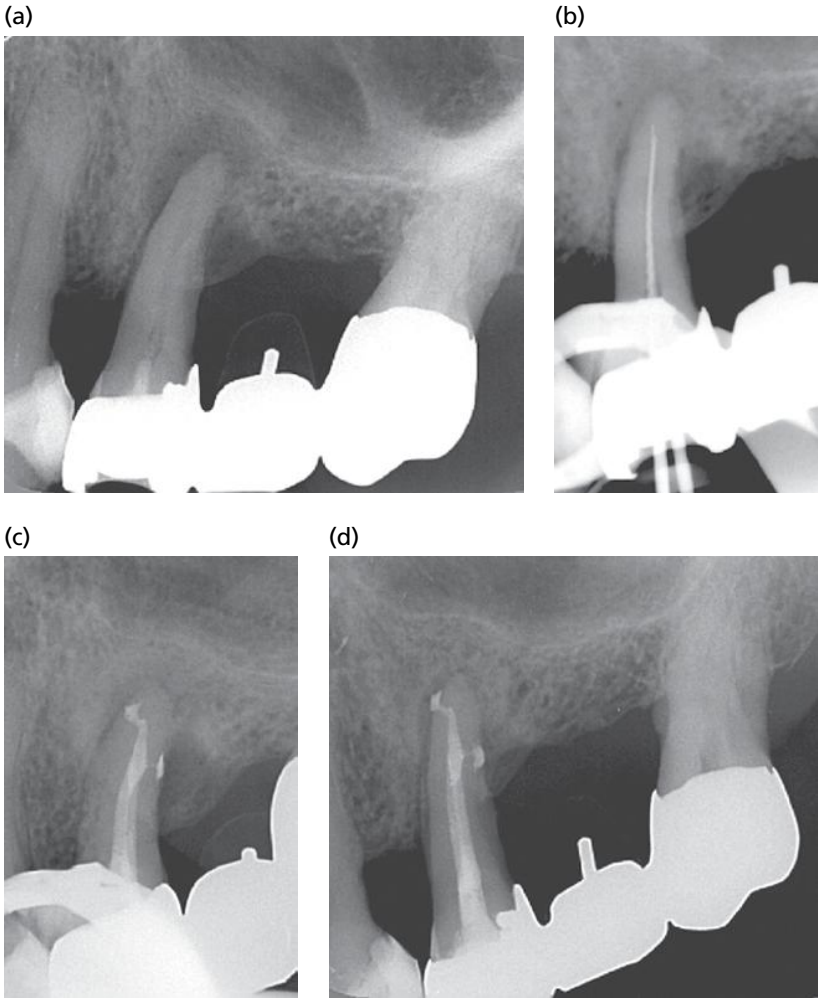

Fig. 41-3 Series of radiographs showing endodontic treatment of a maxillary premolar included as an abutment in a three-unit bridge. The patient, a 78-year-old male, had been treated and maintained for periodontal disease. (a) Bone lesions both at the apical and at the distal aspect of the tooth. Following endodontic treatment of the necrotic pulp (b) and root filling (c), an accessory canal communicating with the lateral lesion became evident. (d) Six-month recall radiograph shows substantial reduction of both bone lesions. (Courtesy of P. Jonasson.)

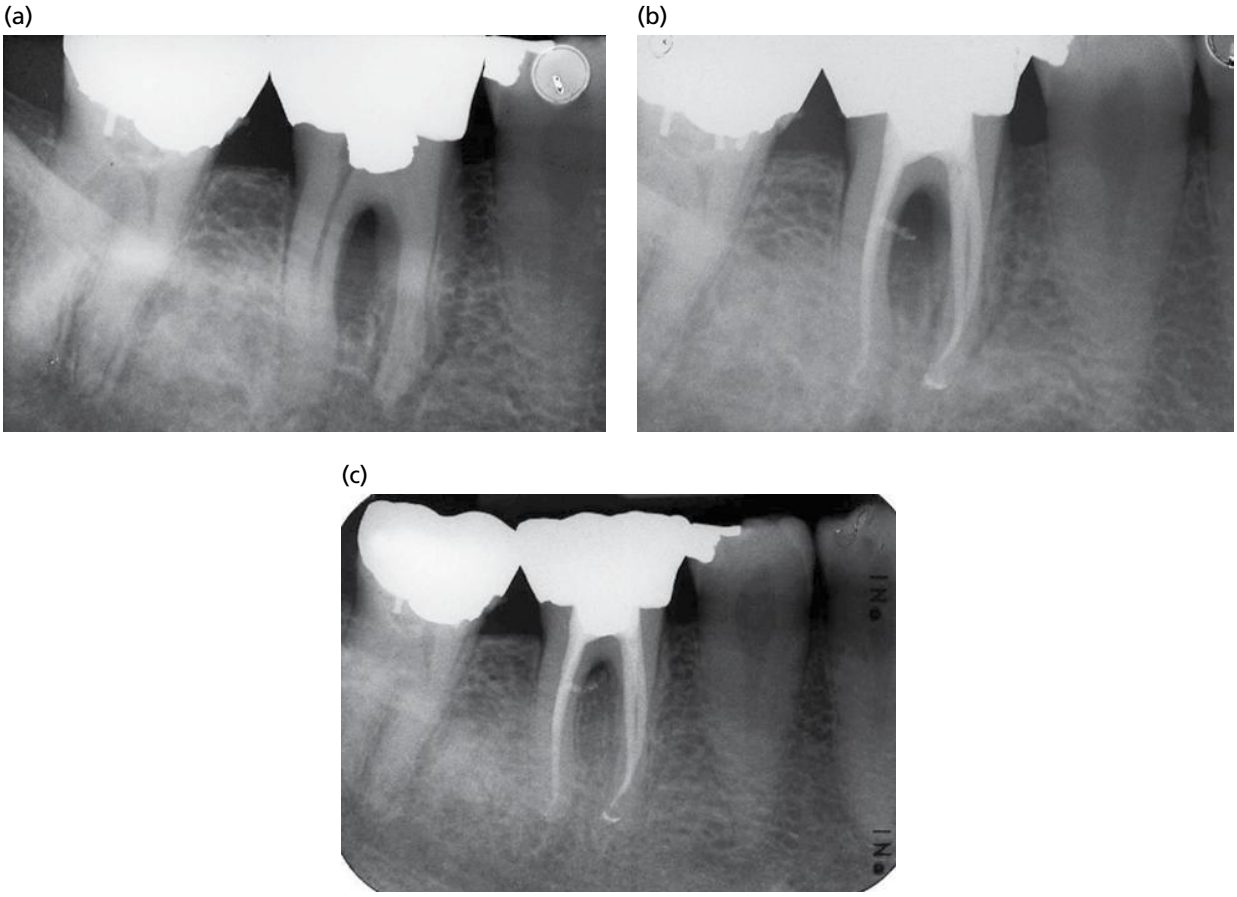

Fig. 41-4 (a) Overt bone loss in the furcal region of a first mandibular left molar with a necrotic pulp. An apical bone lesion can also be seen at the mesial root. (b) Upon root canal filling after endodontic treatment, an accessory canal communicating with the furcal lesion became evident. (c) Eight-month recall radiograph shows a substantially reduced furcal lesion. (Courtesy of A. Gesi.)

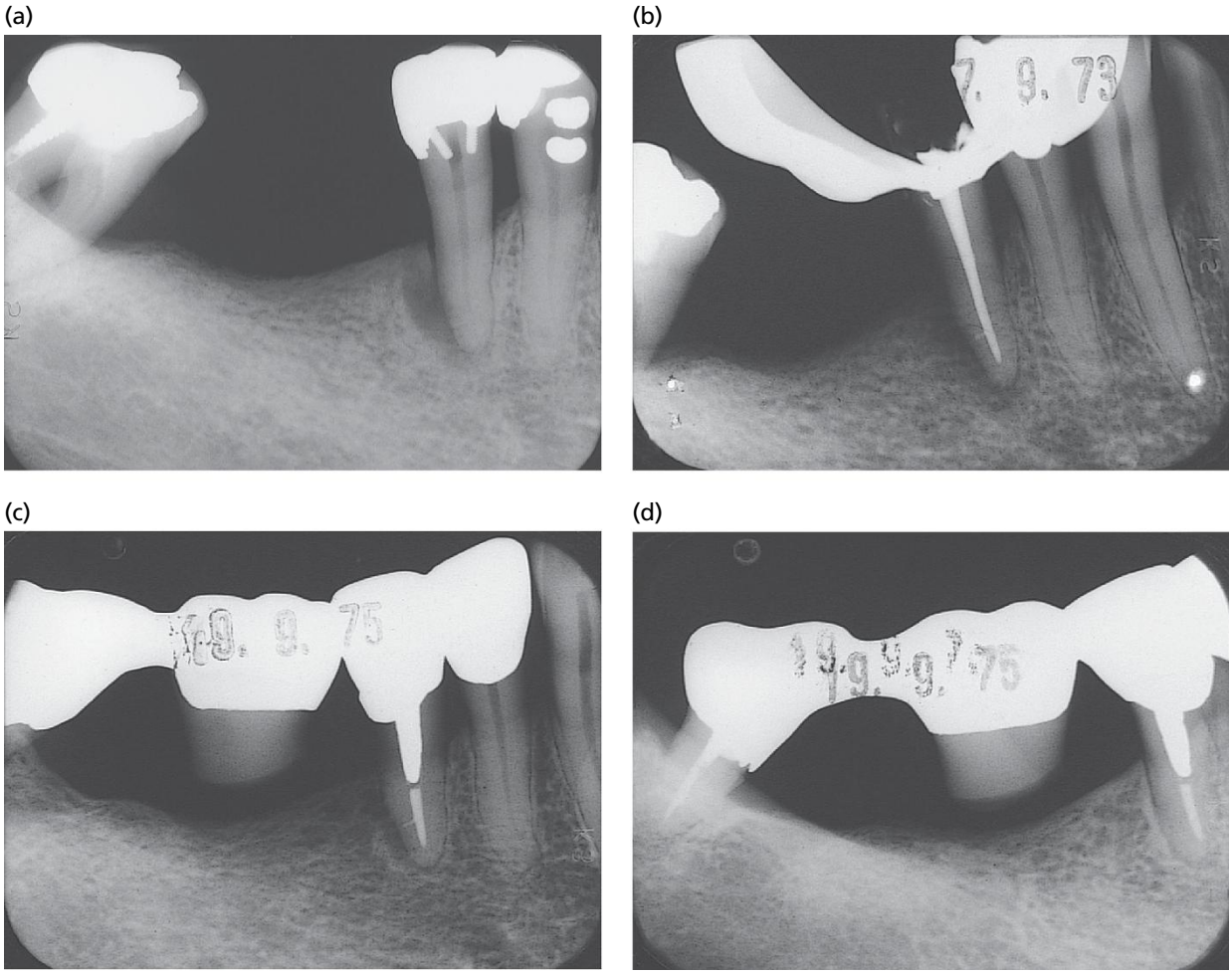

Fig. 41-5 (a) Radiolucent area along the distal root surface of tooth 45 is combined with horizontal loss of marginal bone. (b) Pulp was non-vital and subjected to endodontic treatment. After prosthodontic treatment (c), the 2-year recall radiograph (d) shows bone fill in the previous angular defect. Careful examination of the radiographs in (b) and (c) reveals a filled accessory canal communicating with the lateral bone defect.

probing of the sulcus is carried out at multiple sites. Such a sinus tract may readily be probed down to the apex of the tooth, where no increased probing depth otherwise may exist around the tooth (Fig. 41-8). In multirooted teeth, a sinus tract along the periodontal ligament can drain into the furcation area as it exits along the root surface. The resulting bone lesion may then resemble a "through-and-through" furcation defect from periodontal disease.

2. A periapical abscess can also perforate the cortical bone close to the apex. In this acute stage, the soft tissue, including the periosteum, may be elevated from the bone surface to the extent that a wide opening for drainage of pus is created in the gingival sulcus/pocket area (extraosseous drainage; Fig. 41-7b). Later this route of drainage may develop into a chronic sinus tract that may remain in or near the sulcus, often at the buccal aspect of the involved tooth. Such a fistula may also emerge following a less aggressive process. It is important to note that this type of drainage is not associated with loss of bone tissue at the inner walls of the alveolus, and that a periodontal probe cannot penetrate into the periodontal ligament space.

Conclusion: Endodontic lesions for the most part run without overt clinical signs, but may occasionally present with acute symptoms of root canal infection. The asymptomatic lesions usually assume a limited extension around the apex, while rapid and extensive destruction that may extend marginally along the attachment apparatus may accompany acute exacerbations. Exudation and pus formed in the process may drain off in different directions; pathways along the periodontal ligament space or following penetration of the alveolar bone at the apical region with drainage in or near the gingival sulcus/pocket warrant particular attention from a differential diagnostic point of view. In addition to deep pocket probing depths, the associated bone lesion may mimic that of periodontitis.

Distinguishing lesions of endodontic origin from periodontitis

Pulp vitality testing

Differential diagnosis is important because at times endodontic lesions may produce clinical signs and symptoms similar to those of periodontitis. Tools to

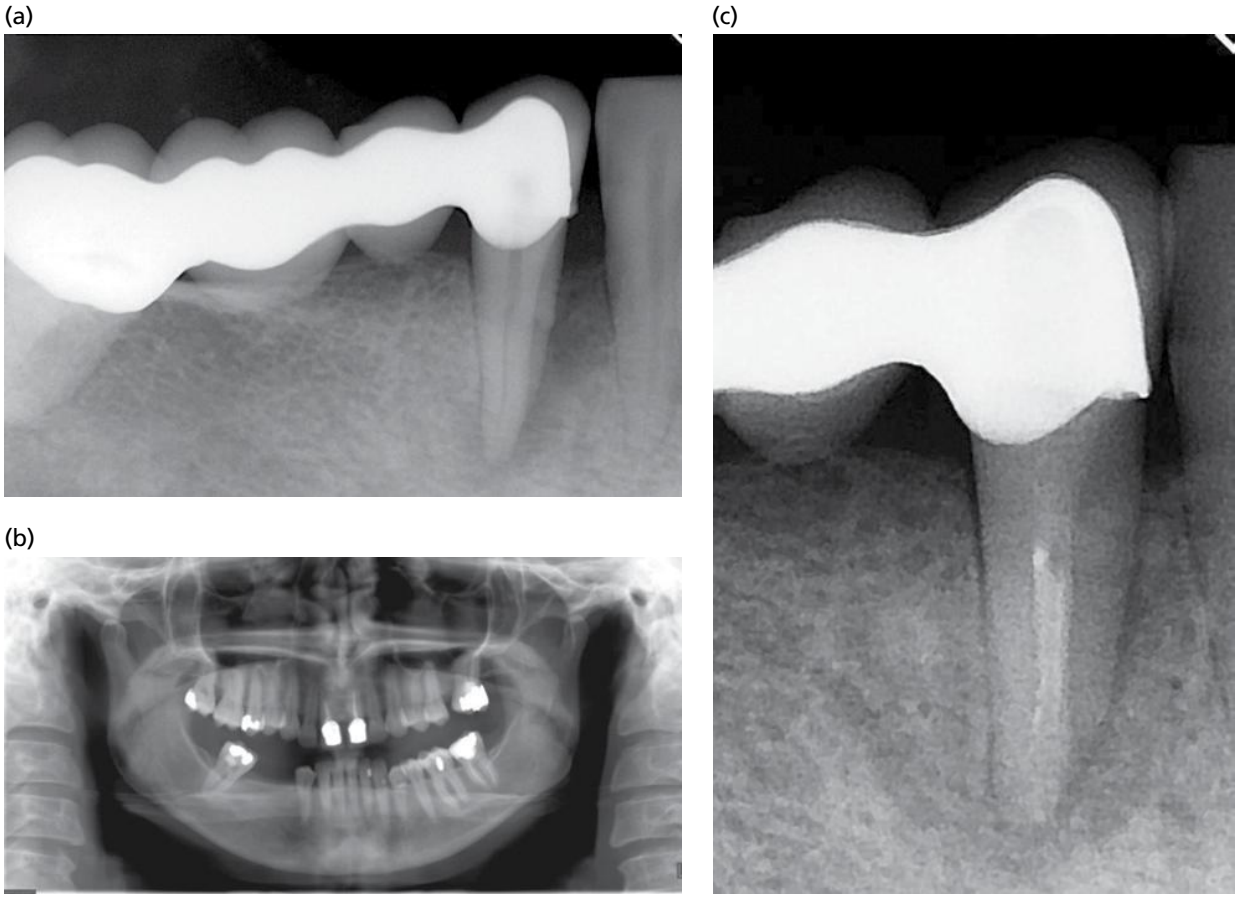

Fig. 41-6 (a) Radiolucency along the mesial aspect of the first mandibular right premolar included in a bridgework 47–44 mimicking an angular bone defect often seen with periodontitis. Prosthetic reconstruction associated with the tooth was severely mobile. (b) Panorex showing normal bone height in the area 8 months prior to prosthodontics. (c) Tooth turned out to have a non-vital pulp. (c) Endodontic treatment followed by calcium hydroxide medication over 5 months resulted in almost complete resolution of the bone defect and substantially reduced tooth mobility.

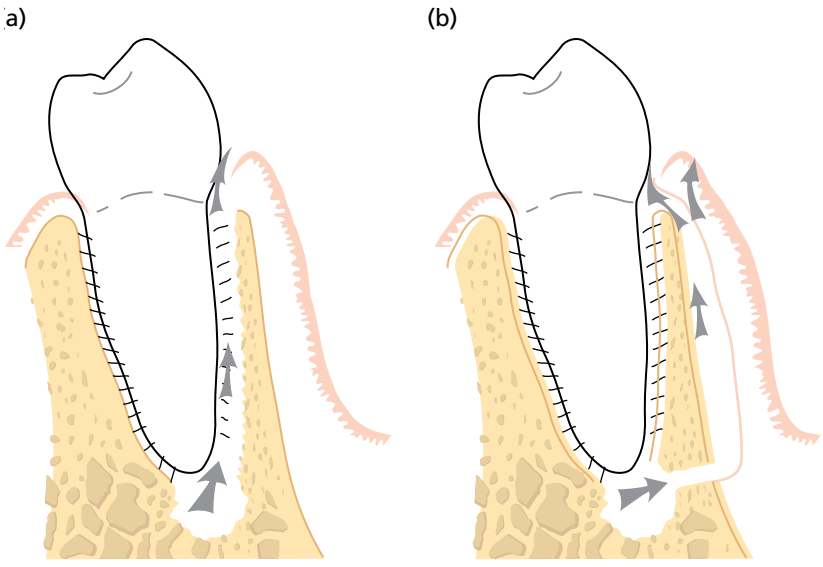

Fig. 41-7 Schematic illustrations demonstrating possible pathways for drainage of a periapical abscess. (a) Drainage along the periodontal ligament with an exit in the sulcus. (b) Extraosseous drainage with exits either in or near the sulcus.

distinguish the two disease conditions from each other, however, are limited as invariably neither the patient's disease history, nor the clinical presentation, nor the radiographic signs are clear-cut. As an endodontic lesion of clinical significance in this context cannot emerge unless the pulpal tissue has turned necrotic and become infected, determination of pulp vitality is a most important measure in cases where an endodontic etiology is suspected. Endodontic lesions associated with root-filled teeth are discussed separately below.

Pulp vitality implies that the tissue has an intact neurovascular supply to support cell and tissue functions. Although a vital pulp may be inflamed

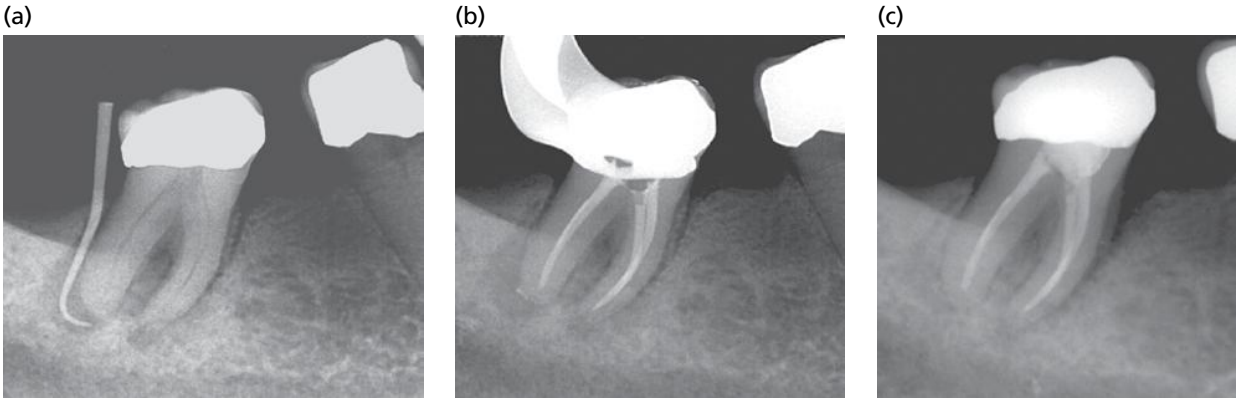

Fig. 41-8 (a) Second mandibular right molar displaying an apical–marginal communication along the distal root surface. The communication was made visible by a gutta-percha point brought into the sulcus. Endodontic treatment (b) resulted in complete resolution of the bone lesions associated with the distal root (c). At an emergency visit 2 years later, the patient complained of pain and tenderness that turned out to be caused by a longitudinal root fracture involving the mesial root. (Courtesy of P. Jonasson.)

or display a variety of degenerative changes, the vasculature is still functioning in a vital pulp. Most methods of determining pulp vitality act by stimulating the pulp's sensory nerve function and presume that the provocation of a sharp pain sensation indicates a vital pulp. This means that in reality the *sensitivity* of the pulp is tested rather than its *vitality*. However, there is ample documentation to support the concept that a tooth that responds to sensory stimuli has vital pulp functions. Conversely, if a tooth does not respond, the pulp may be nonvital (for reviews see Gopikrishna *et al.* 2008; Jafarzadeh & Abbott 2010a, b). Yet, caution should be exercised in interpreting sensitivity tests as findings can reflect both false-positive and false-negative readings (Mumford 1964; Petersson *et al.* 1989; Peters *et al.* 1994; Pitt Ford & Patel 2004; Jafarzadeh & Abbott 2010a, b). A combination of different test methods should therefore be employed to ensure the correct diagnosis, especially in doubtful cases. Also, the equipment and the results should be tested for accuracy by comparing results from tests of neighboring and contralateral teeth. No test that can identify the disease status of the pulp in other terms than vital or nonvital has so far been advanced (Mejàre *et al.* 2012).

Testing non-restored or minimally restored teeth in dentitions affected by periodontitis can usually be successfully conducted by mechanical, thermal, and electric stimulation. Common methods utilize tests to stimulate nociceptive mechanoreceptors at the pulp–dentin border, primarily the fast conducting A-delta fibers. Useful techniques include direction of a jet of compressed air against an exposed root surface, scratching such surfaces, use of a rubber wheel to generate frictional heat, and various cold tests; all are intended to elicit movement of dentinal fluid. Carbon dioxide snow (Fulling & Andreasen 1976) and dichlorodifluoro-methane sprayed on a cotton pellet are highly effective and reliable. The boiling points of these two agents are –72 °C and –50 °C, respectively. For this reason patients should be cautioned prior to application

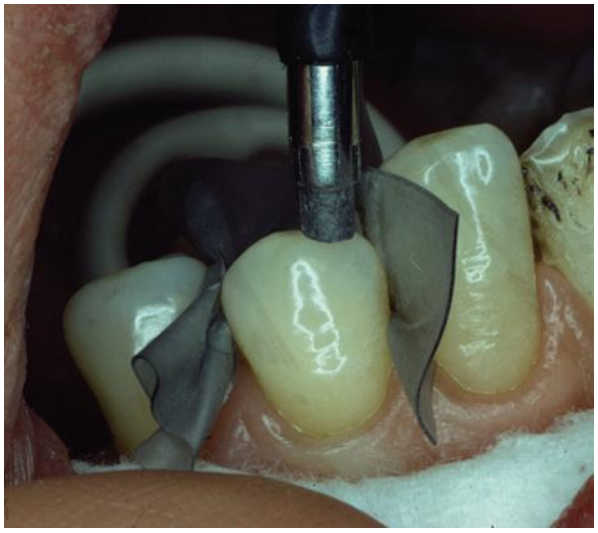

Fig. 41-9 Demonstration of proper tooth isolation to avoid leakage of current during pulp sensitivity testing with an electric pulp tester.

that an intense pain response might be elicited. Clues can also be obtained with less potent means such as ice sticks and ethyl chloride, as well as heated gutta-percha sticks (for review see Pitt-Ford & Patel 2004).

In dubious cases, mechanical and thermal provocation should be supplemented with electric pulp testing. Units are available which provide a read-out value of the voltage or microcurrent being applied to generate the pain response. This function is important so that the test result can be repeated and compared for assessment of patient reliability. Electric pulp testing is technique sensitive and therefore warrants extra precaution to avoid leakage of current to the gingiva and neighboring teeth. To avoid this risk, the test should only be carried out on cleaned and dry teeth isolated from saliva and adjacent teeth with pieces of rubber dam placed in the tooth contacts (Fig. 41-9). The test further requires that the tooth electrode is provided with a good conducting medium and applied directly to the enamel or dentin and not to restoratives.

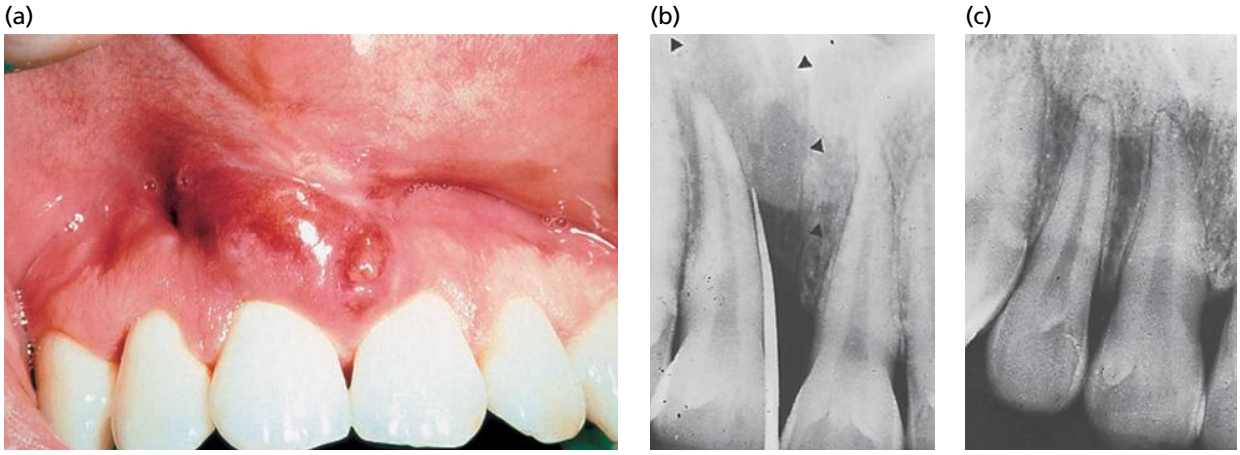

Fig. 41-10 (a) Gingival swelling at the buccal aspect of tooth 11. (b) There is advanced destruction of alveolar bone along the mesial aspect of the root (arrowheads). (c) Following periodontal treatment the bone lesion resolved. (Courtesy of H. Rylander.)

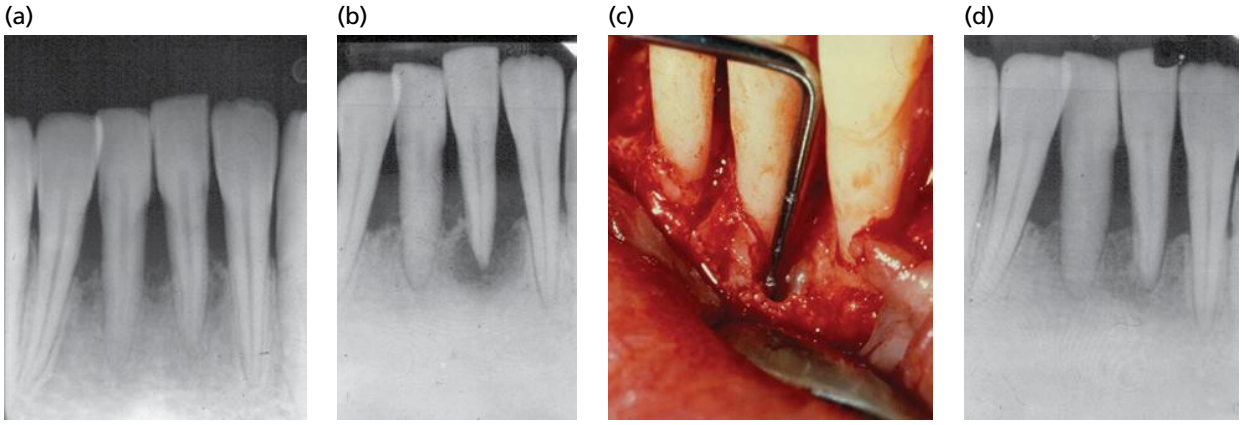

Fig. 41-11 (a) Advanced horizontal loss of alveolar bone in a patient subjected to periodontal therapy. (b, c) In the course of follow-up, a bone defect simulating an endodontic lesion appeared around the root tip of tooth 31. The pulp responded sensitive on testing and the tooth was therefore not subjected to endodontic therapy but to periodontal treatment only (d). For further case history see the text. (Courtesy of I. Magnusson.)

Means to detect blood flow within the pulp by non-invasive methods have been developed and tested. Examples are laser light scattering and pulse oximetry. So far, such methods have gained only limited clinical application.

Cases with extensive restorations and crowned teeth present particular challenges, as none of the normal test procedures is useful. Unless tooth substance can be reached beneath the restoration with a good margin to the gingiva, a test cavity should be prepared to make pulp testing possible. Even then, a false-negative response can be obtained as extensive hard tissue repair may have developed in the pulp from previous disease and cutting traumas, thus attenuating the stimulus.

Three cases are described to illustrate the significance of pulp vitality testing in the process of distinguishing endodontic lesion from periodontitis. The cases demonstrate, in addition, that diagnostic entities such as location, form, and extension of radiolucencies, clinical symptoms of pain or swelling, and increased probing depths may not serve as accurate diagnostic signs.

The clinical photograph in Fig. 41-10a shows swelling of the marginal gingiva on the buccal aspect of tooth 11. Severe throbbing pain had preceded the swelling for a few days. Radiographic examination (Fig. 41-10b) disclosed the presence of an angular bone defect that involved the apical portions of the tooth. In this case the pulp clearly responded on testing, indicating that the pathologic condition was not of endodontic origin. Pocket debridement was combined with irrigation with 0.2% chlorhexidine digluconate solution and systemic administration of an antibiotic. The lesion healed rapidly. Seven months following treatment new bone had formed around the apex and in the defect along the mesial root surface (Fig. 41-10c). Thus, in this case the periodontal lesion was a manifestation of periodontal disease.

In Fig. 41-11a the radiograph of the lower front teeth demonstrates advanced horizontal loss of alveolar bone in a 25-year-old male subjected to periodontal therapy. In the course of the recall program, tooth 31 developed an apical radiolucency (Fig. 41-11b). The form and extension of the lesion suggested an endodontic cause. Clinically, a deep periodontal pocket could be probed along the distobuccal aspect of the root. The gingival conditions after periodontal treatment had been excellent. Sensitivity tests by cold

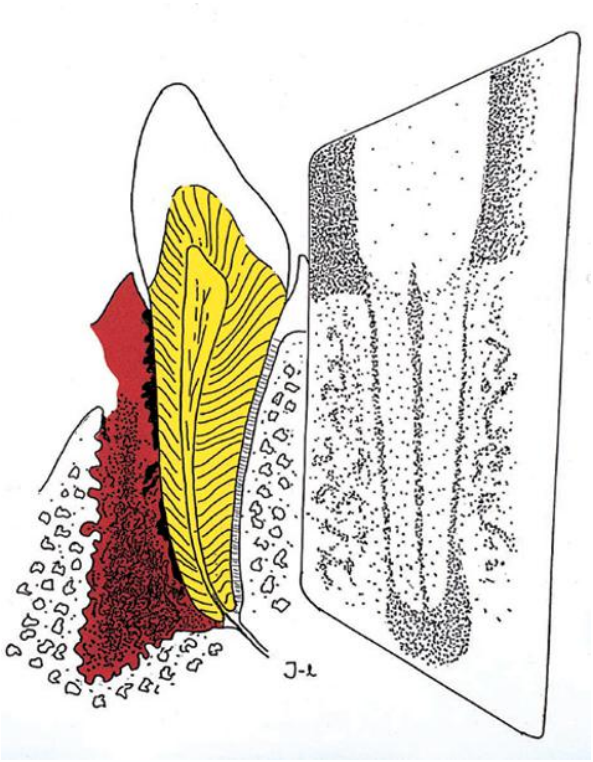

Fig. 41-12 Schematic illustration depicting a potential mechanism for the radiographic lesion in tooth 31 shown in Fig. 41-11. While there was substantial breakdown of alveolar bone, there was no interference of the inflammatory lesion with the neurovascular supply of the pulp. The fact that the bone lesion appeared as an apical radiolucency is explained by the superimposition of the bone loss on the root tip. (Courtesy of M. Jontell.)

and electricity, however, indicated a vital pulp. Therefore, endodontic treatment was not performed. On elevating a mucoperiosteal flap (Fig. 41-11c), an angular bone defect was found at the buccal aspect of the root without involvement of the root tip. The wound area was debrided along with scaling of the root surface. Rapid bone fill followed surgery without undertaking any adjunctive measures to support tissue regeneration (Fig. 41-11d). The pulp maintained its vitality, although later the root canal became obliterated by hard tissue, most likely as a result of ischemic injury in conjunction with the surgical procedure. The apically positioned radiolucency in Fig. 41-11b is explained by superimposition of the loss of alveolar bone buccally to the root tip of tooth 31, which went beyond its most apical level (Fig. 41-12) without interfering with the neurovascular supply of the pulp.

Figure 41-13 shows a clinical case where pulp vitality was difficult to ascertain. A swelling had appeared at the buccal aspect of tooth 46 (Fig. 41-13a) after the patient had experienced pain and tenderness in the area for approximately 1 week. Periodontal probing disclosed a deep facial pocket along the mesial root (Fig. 41-13b). Radiographic examination indicated a lesion that seemed to circumscribe the mesial root with a marginal extension into the furcation (Fig. 41-13c). Frictional heat by drilling, as well as cold and electric tests, failed to give a positive response even in a test cavity preparation. After finding a sensitive and bleeding pulp in the distal root, a necrotic pulp with pus drainage was detected once the mesial root canal orifices were approached, confirming an endodontic cause of the lesion. Endodontic treatment with a temporary intracanal dressing with calcium hydroxide over 3 months resulted in an obvious reduction of the bone lesion (Fig. 41-13d). The gingival lesion resolved with no abnormal pocket probing depth (Fig. 41-13e), although a small bone defect remained in the furcation area (Fig. 41-13d). Treatment was then completed with root canal fillings. The 12-month recall radiograph demonstrates complete resolution of the bone defect (Fig. 41-13f).

Other signs of endodontic lesions

Except for a negative pulp test response, single-tooth lesions in a dentition otherwise free from periodontal disease strongly suggest an endodontic cause, provided other tooth-associated disorders such as external root resorption and root fracture can be excluded. An endodontic etiology should be explored particularly in cases with extensive restoration or a crowned tooth (Figs. 41-4, 41-8, 41-13), bridge abutment (Fig. 41-3, 41-6), caries, a root-filled tooth, and in patients with a history of a previous dental trauma. The character of the pocket probing depth should also be taken into consideration. Endodontic lesions, when extending marginally, usually do not follow more than one root surface and then exit in a rather narrow area of the sulcus. Deep pocket probing depth may also be in an area uncharacteristic of periodontitis, for example at the buccal aspect, when all other sites display normal probing depths.

Conclusion: The clinical presentation and the character of radiographic findings may lead to erroneous diagnosis where an endodontic lesion emerges in a patient with periodontal disease. The recognition of pulp vitality is crucial because clinically significant lesions of endodontic origin rarely develop in teeth with vital but inflamed pulps. The clinician should always be watchful for false leads and consider features normally associated with diseased pulps, such as extensive restoration, previous pulp capping, history of dental trauma, and endodontic treatment.

Endo–perio lesions: Diagnosis and treatment aspects

The potential for an infected, necrotic pulp to cause breakdown of the attachment apparatus with extension into the marginal periodontium has been addressed above, along with the measures to arrive at the diagnosis. Once confirmed, the mode of treatment in this type of case is simple and should involve only conservative root canal therapy.

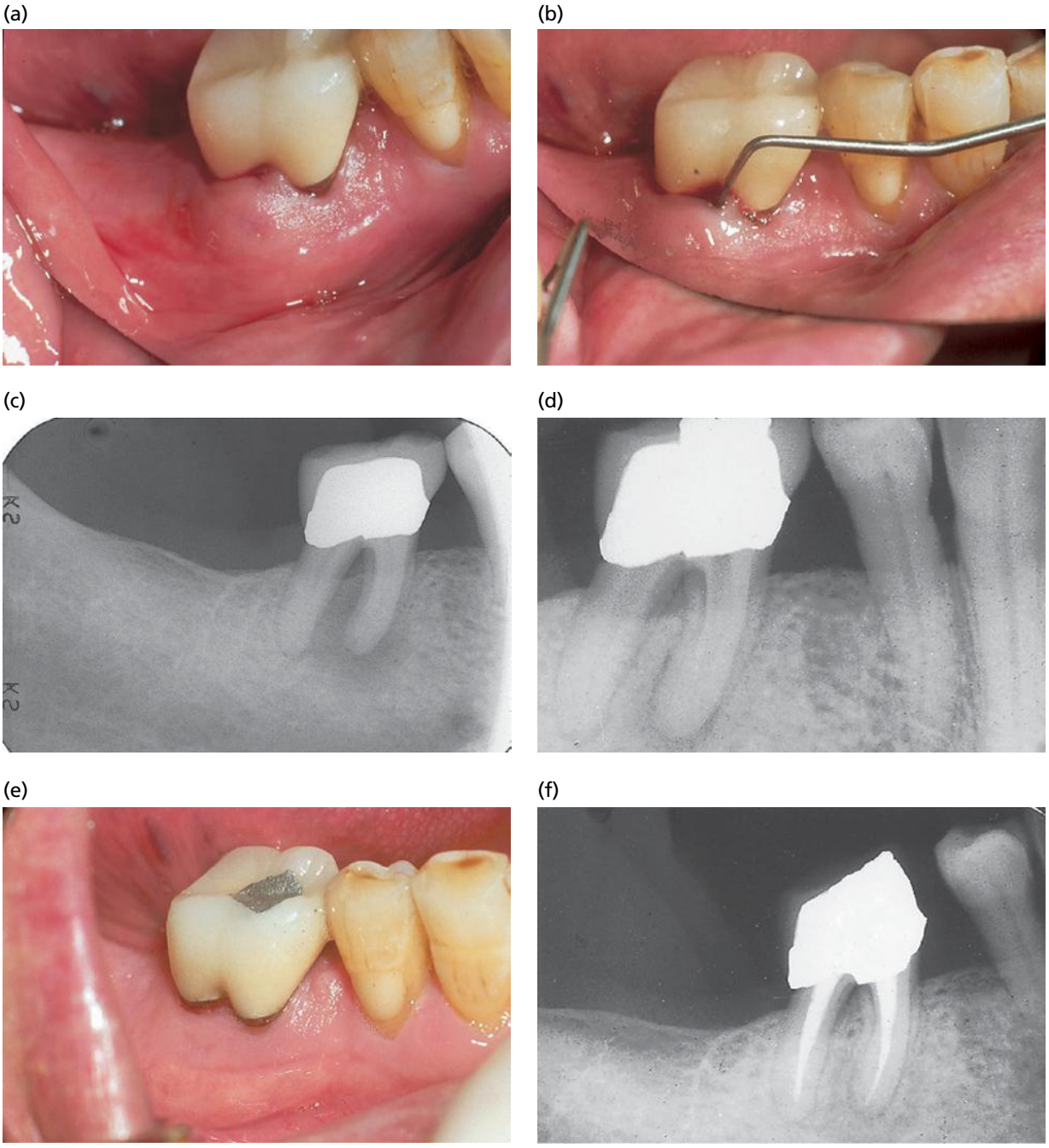

Fig. 41-13 Case with an initially unclear etiology of a facial swelling and deep pocket probing depth that turned out to have an endodontic etiology. The case history is given in the text. Diagnosis and treatment of this case was carried out by one of the authors (G.B.) in collaboration with Dr David Simpson.

Following adequate treatment, directed at elimination of the root canal infection, the lesion should be expected to heal without a persistent periodontal defect (Figs. 41-3, 41-4, 41-5, 41-6, 41-8, 41-13). Adjunctive periodontal therapy will have no treatment effect and would be inappropriate.

A more complex situation arises when a periodontal lesion is sustained by concurrent plaque infection and root canal infection. This kind of lesion is associated with a deep pocket probing depth and a lateral bone defect that extends to the apex (see Fig. 41-8). The problem here is that it is not normally possible to determine how much of the lesion is sustained by which infection. In fact, there are three scenarios: (1) the entire lesion may be a manifestation of a root canal infection alone; (2) the entire lesion may be the result of plaque infection; (3) there are, in fact, two disease processes, one marginal associated with a plaque infection and one apical associated with a root canal infection, but the two soft tissue lesions have merged and there is no longer a clear demarcation zone between the two as a probe easily may penetrate both soft tissue lesions.

Pulp vitality testing only partly settles the diagnostic quandary in this kind of case. Yet, if distinctly positive, one can exclude the contribution of an

Table 41-1 Outline of treatment strategies.

Cause	Condition of the pulp	Treatment
Endodontic	Non-vital	Endodontic
Periodontal	Vital	Periodontal
EndodonticPeriodontal	Non-vital	Endodontic: first observe the result of this therapy and institute periodontal therapy later if necessary

endodontic infection and the process should be subjected to periodontal therapy alone. Taking the pulp out and replacing it with a root filling is then a meaningless and unnecessary treatment effort. In the case of a negative pulp test, death of the pulp may have occurred as a direct result of the periodontal disease process or it may have developed independently as a separate condition. In the former case, prognosis for any other treatment than extraction must be regarded as bleak. A major reason for this is that not only may a substantial portion of the attachment apparatus be lost, but the root surface may be bacterially infected close to the root tip as well. In addition, the infection may have entered the root canal space after the development of pulp necrosis due to severance of the neurovascular supply of the pulp (see Fig. 25-20). Accessing this kind of infection for treatment is therefore a very challenging task with a most questionable outcome.

If a portion of the lesion is sustained by a root canal infection independent of periodontal disease, the potential for periodontal tissue regeneration is much increased. Because it is not possible to know beforehand how far the endodontic lesion has extended along the root, root canal treatment should be attempted first and periodontal treatment postponed until the result of the endodontic treatment can be evaluated. The part of the lesion sustained by root canal infection can usually be expected to heal rapidly (see Fig. 41-3). Periodontal attachment along with bone healing can then be expected within a few months. The part of the lesion caused by plaque infection may also heal following adequate periodontal therapy. Yet, little or no regeneration of the attachment apparatus should be anticipated for this portion of the lesion. Table 41-1 outlines the strategy to be taken for treatment of these so called endo–perio lesions.

Conclusion: Deep pocket probing depths associated with angular bone defects may reflect a combined endodontic and periodontal lesion. Yet, the extent to which an endodontic infection has contributed to the attachment loss cannot normally be determined from a negative sensitivity test, as the entire loss might be caused by plaque infection. Therefore, a treatment strategy should be applied which includes endodontic treatment in the first place, but only in cases where an endodontic etiology is reasonably plausible, that is in teeth with large restorations, full-coverage crowns or history of dental trauma. If the tooth is completely intact without major restoration, caries or history of trauma, the potential of an endodontic etiology of the process is remote (Figs. 41-10, 41-11).

Endodontic treatment and periodontal lesions

Periodontal lesions, as already stated, may be maintained by infectious elements released from endodontically treated teeth. The lesion may have never resolved or may have developed after the completion of treatment. Several routes for dissemination of bacterial elements to the periodontium in such teeth are possible. Except for apical foramina and accessory canals, another possible pathway is inadvertently produced communication by root perforation (see below). The clinical presentation is no different from the one described above and consequently may involve acute exacerbations with extensive breakdown of the attachment apparatus as well as localized, non-symptomatic lesions, only apparent on radiographs.

A persistent infection in root-filled teeth may also impact on the periodontium along the dentinal tubules in areas where cementum has been damaged or lost (Blomlöf *et al*. 1988). The potential significance of such an avenue has been highlighted in clinical studies. Compared with teeth with healthy pulps, endodontically treated teeth with periapical pathology, indicating presence of persistent root canal infection, showed increased pocket probing depths (Jansson *et al*. 1993a), more marginal bone loss (Jansson *et al*. 1993b), and retarded or impaired periodontal tissue healing subsequent to periodontal therapy (Ehnevid *et al*. 1993a, b). Although the differences in probing depths and attachment losses in these studies were rather small, the observations suggest that endodontic retreatment should be considered as an adjunct to periodontal therapy when a root canal filling is defective and/or displays signs of periapical inflammation. Observations in a retrospective analysis of patients affected by periodontitis indicated that the periodontal condition may also affect the periapical status in root-filled teeth (Stassen *et al.* 2006). Significantly fewer teeth with apical periodontitis were seen in patients treated for periodontitis compared with untreated patients. In individuals with no or minor evidence of periodontal disease, the root canal condition, whether root filled or not or infected or not, did not seem to affect the periodontal status in a controlled study (Miyashita *et al*. 1998).

Conclusion: Unfilled spaces in endodontically treated root canals can sustain bacterial growth, and infectious products from these areas may reach the periodontium along the very same pathways as in an untreated tooth

with infected pulp. Endodontic retreatment may be considered as an adjunct to periodontal therapy when a root canal filling is of poor quality and/or the tooth displays signs of periapical inflammation, because of the potential that bacterial elements may become disseminated to the periodontium along dentinal tubules exposed by periodontal instrumentation.

Iatrogenic root perforations

Loss of attachment including pocket formation in a narrow area of a restored, root-filled tooth may be related to an iatrogenic root perforation. The injury may have been induced during the endodontic treatment procedure *per se* or subsequently in conjunction with preparation for a root canal retained post (Sinai 1977; Kvinnsland *et al*. 1989; Eleftheriadis & Lambrianidis 2005; see also review by Tsesis & Fuss 2006). The clinical significance of such a complication depends largely on whether the wound site becomes infected or not (Beavers *et al*. 1986; Holland *et al.* 2007). If promptly and properly treated, a bacterially-induced periodontal lesion can be prevented. Otherwise, and especially if carried out in the crestal bone area, epithelial proliferation and periodontal pocket formation (Lantz & Persson 1967; Petersson *et al*. 1985) will ensue. In more apical areas, a lateral bone lesion may develop, which may or may not be accompanied by clinical symptoms, including acute pain, drainage of pus, loss of fibrous attachment, and deep pocket probing depths (Fig. 41-14).

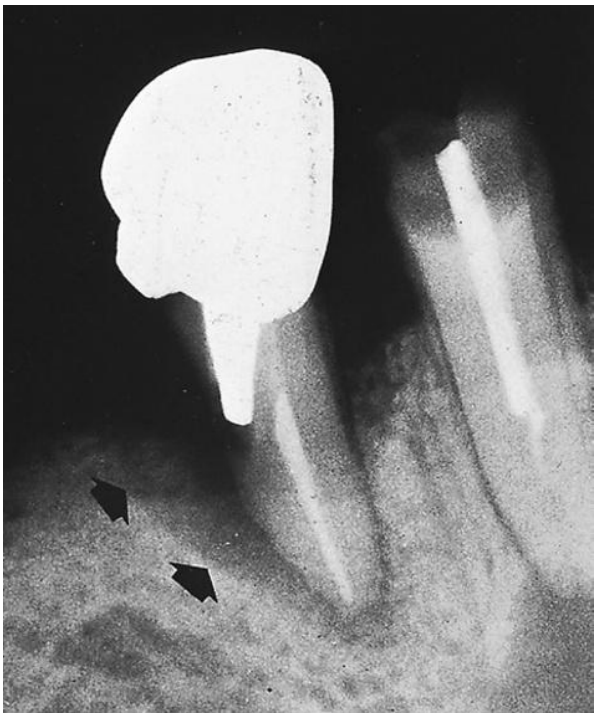

Fig. 41-14 Angular bone defect at the distal root surface of a mandibular molar (arrows). The root is perforated as indicated by the misaligned post. Clinical symptoms included drainage of pus from the pocket and increased tooth mobility. The tooth was extracted.

Occurrence

The occurrence of iatrogenic root perforation in conjunction with endodontic and prosthodontic therapies has been estimated to vary between 2% and 12% (Tsesis & Fuss 2006). In a retrospective analysis of a sample of 2000 patients accepted for treatment in a university clinic, 2.3% of all root-filled teeth (n=5505) showed signs of root perforation on radiography. Pathologic changes in the adjacent periodontal tissues were seen in nearly 70% of these cases (Tsesis *et al.* 2010).

Diagnosis

Diagnosis is based on the occurrence of sudden pain and bleeding during preparation of root canals coronally of the working length. Such signs are likely to be less distinct if the perforation occurs during a procedure conducted under local anesthesia. A perforation may also go undetected as bleeding may not invariably be provoked. For example, when post preparations are carried out by means of a machine-driven instrument, a smear layer is formed that may clog the blood vessels. Thus, in many instances no bleeding will be noticed until the following visit, when granulation tissue will have proliferated into the root canal space along the perforation defect. On attempts to remove the granulation tissue, bleeding is usually profuse, making sealing precarious. Electronic apex locators are helpful to confirm a root perforation, which should be suspected when readings are substantially shorter than the length of the root canal (Fuss *et al*. 1996). New imaging technologies such as cone-beam computed tomography (CBCT) have been reported to aid diagnosis (de Paula Silva *et al.* 2009; Venskutonis *et al*. 2014). Scattering artifacts caused by high density neighboring structures such as metal posts and root-filling material may, however, limit the diagnostic accuracy of CBCT. Further limitations are higher radiation dose and costs than examination by intraoral periapical radiographs (Patel 2009; Shemesh *et al.* 2011).

Treatment approaches

Early detection is critical for a successful outcome of a treatment attempt as the potential for repair of a long-standing perforation with a manifest infection is poor (Holland *et al.* 2007). Successful treatments have, nevertheless, been achieved even in such cases (Tsesis & Fuss 2006; Mente *et al.* 2010).

Over the years many therapeutic agents and methods have been proposed for the management of root perforations (reviewed by Tsesis & Fuss 2006). Materials proposed for sealing from the inside of the root canal space include amalgam, zinc oxide and eugenol cements, both chemically cured and light-cured calcium hydroxide-containing pastes, and plaster of Paris. Alkaline calcium silicate cements such as mineral trioxide aggregate (MTA) based on

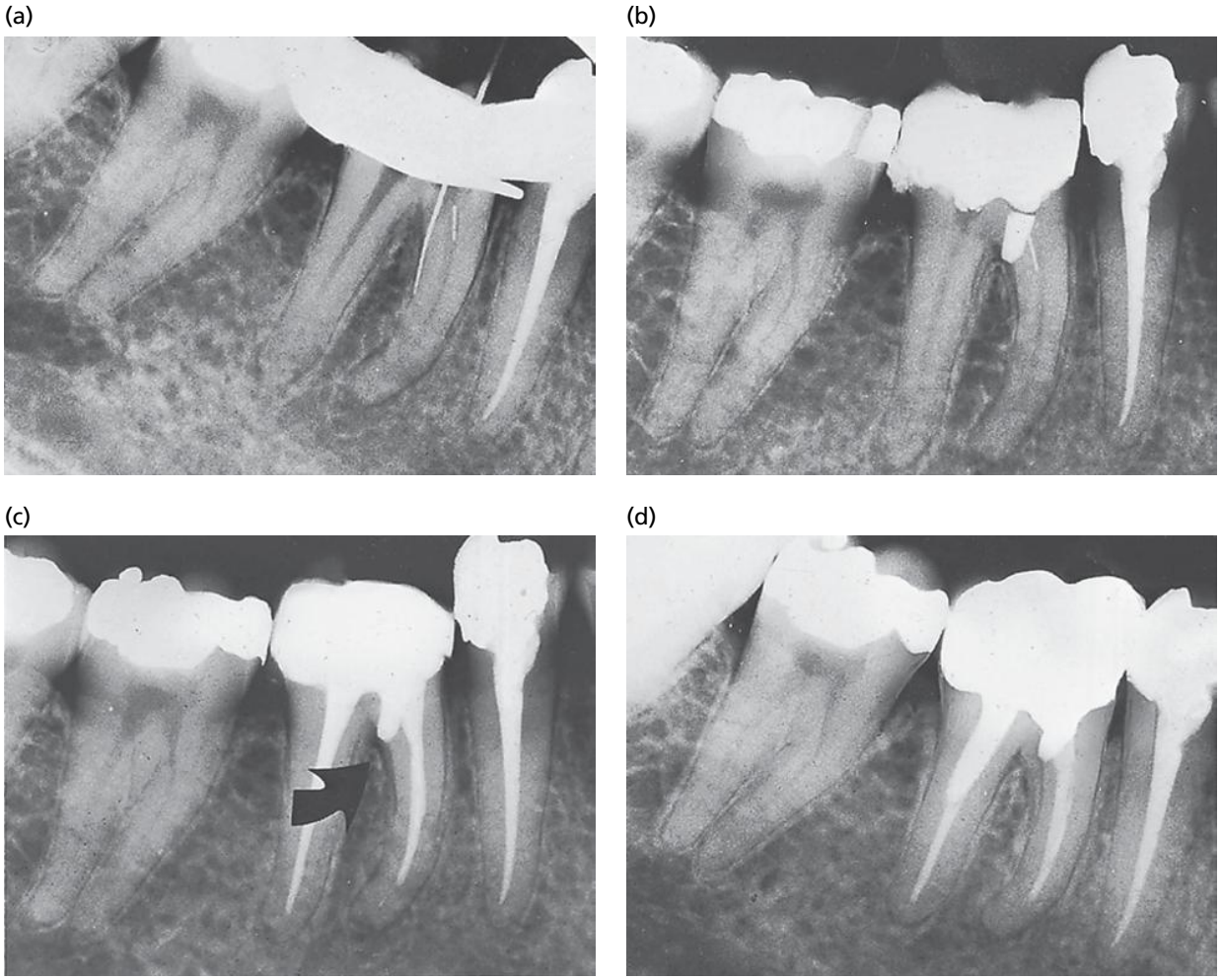

Fig. 41-15 (a) Perforation of the pulpal floor of the mandibular first molar occurred in conjunction with a search for root canal openings. There is also a file fragment in one of the mesial canals. (b) The perforation was immediately sealed with gutta-percha. (c) On a radiograph taken 1 month after treatment, a slight radiolucency is seen at the site of the perforation (arrow). (d) Follow-up after 2 years showed normal periodontal conditions both clinically and radiographically. (Courtesy of G. Heden.)

Portland cement are now considered to be the state-of-the art material to fill root canal perforations. This is because of their antimicrobial properties, superior sealing effect, and biocompatibility in the set stage (for reviews see Parirokh & Torabinejad 2010a, b; Torabinejad & Parirokh 2010). MTA furthermore permits cementum repair (Arens & Torabinejad 1996; Schwartz *et al*. 1999).

The location of the perforation dictates the choice of material to seal the perforation. In supracrestal areas, the dentin can be conditioned, and a dual-curing composite material be applied directly over the perforation. In infracrestal locations, MTA or another biocompatible cement should be applied. Regardless of the material used, healing of the lesion in the periodontium depends on whether bacterial infection can be excluded from the wound site by a tight seal of the perforation (Beavers *et al*. 1986; Holland *et al.* 2007) (Fig. 41-15). This may be difficult to achieve, particularly if the perforation runs deep into the root canal at an oblique angle, giving it an oval-shaped orifice into the periodontium. Nevertheless, for mid-root and cervical perforations, non-surgical approaches, including placement of an internal seal, are preferable to a surgical approach, as the latter often results in persistent pocket formation and furcation involvement. Furthermore, surgical treatment is not always feasible because of the inherent difficulty of accessing many perforation sites. If controlled disinfection and sealing of the perforation site are not possible because of its location or extent, extraction may be the only reasonable therapy. In multirooted teeth, hemisection and extraction of the perforated root may be a treatment of choice.

Conclusion: Inflammatory lesions in the marginal periodontium, as manifested by increased probing depth, suppuration, increased tooth mobility, and loss of fibrous attachment, may result from an undetected or unsuccessfully treated root perforation. If an iatrogenic root perforation occurs during instrumentation of root canals, filling of the artificial canal to the periodontium should be carried out without delay to prevent granulation tissue formation and wound site infection. Outcome of treatment depends on how well the wound site can be disinfected and sealed. The closer the perforation is to the bone margin, the greater the likelihood of proliferation of epithelium at the perforation site with bacterial contamination and a resulting deep, potentially suppurating pocket.

Vertical root fractures

Clinical symptoms that are typical of tooth-associated infections such as endodontic lesions and plaque-induced periodontitis may also appear at teeth with cracks and vertical root fractures. It is important to distinguish between different forms of these complications. The American Association of Endodontists has identified five specific variations of cracked teeth: craze line, fractured cusp, cracked tooth, split tooth, and vertical root fracture. This differentiation appears to be clinically relevant, because cracks are rarely associated with major periodontal breakdown and can be prevented from developing into split teeth by placing a crown (Krell & Rivera 2007). Cracks typically occur in a mesiodistal direction and initiate from the crown (Roh & Lee, 2006) (Fig. 41-16); they may engage the root canal space. Vertical root fractures, on the other hand, usually initiate from somewhere on the root and are typically located in a faciolingual direction. Eventually vertical root fractures extend along the entire length of a root to involve the gingival sulcus/pocket area and will then be associated with periodontal tissue breakdown (Fig. 41-17). It should be noted that vertical root fractures, although often expanding in opposite directions from the root canal space, may extend to one root surface only. Teeth with vertical root fractures have a hopeless prognosis and are reason for extraction or resection of the affected root.

Mechanisms

Endodontically treated teeth appear over-represented among teeth with vertical root fracture in comparison to teeth with vital pulps (Meister *et al*. 1980; Gher *et al*. 1987; Patel & Burke 1995). Generally, the increased fracture propensity of root-filled teeth has been attributed to loss of tooth structure as a result of endodontic instrumentation and subsequent restorative procedures (Reeh *et al*. 1989; Sedgley & Messer 1992). Loss of fracture resistance increases especially after overzealous root canal preparation, leaving thin dentin walls to the periodontium (Tjan & Whang 1985). Notches, ledges, and cracks induced by root canal preparation, root canal filling procedures, and seating of threaded pins and posts also contribute to sites of stress concentration during mastication that eventually may lead to fracture (Kishen 2006). Recently, it has been shown *in vitro* that any type of file inserted into the root canal may cause apical craze lines or cracks, which over time may propagate coronally (Adorno *et al.* 2010). Decrease of moisture content following root canal treatment is another alleged cause of increased fracture susceptibility of root-filled teeth; insignificant moisture differences were found, however, when dentin of teeth with vital pulps and dentin of root-filled teeth were compared (Papa *et al*. 1994). More recent observations have nevertheless demonstrated that effects occur in dehydrated dentin that may render endodontically treated teeth prone to fracture (Kishen 2006). Dehydrated dentin *in vitro* was observed to assume increased stiffness as well as a decrease in toughness (e.g. the total energy a material can absorb before fracturing) in comparison to hydrated dentin (Jameson *et al*. 1994; Kahler *et al*. 2003; Kishen & Asundi 2005). Hence, fluid-filled dentinal tubules as well as a water-rich pulp tissue may give normal teeth better resistance to occlusal loading forces than root-filled teeth. There is evidence that NaOCl as irrigating solution alters the mechanical properties of root canal dentin and may lower its fracture resistance (Pascon *et al.* 2009). Calcium hydroxide, a commonly used medicament for inter-appointment dressing in root canal therapy, may also decrease fracture resistance of root-filled teeth (Andreasen *et al.* 2002). It has also been speculated that, along with loss of vital pulp tissue there is concomitant loss of mechanoreceptive functions, allowing larger loads to be placed during mastication than the patient could normally tolerate (Löwenstein & Rathkamp 1955; Randow & Glantz 1986).

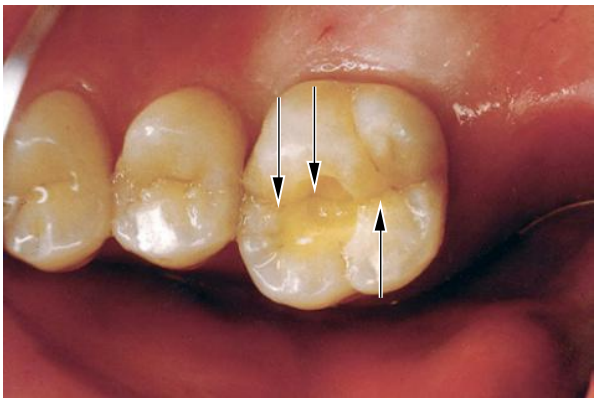

Fig. 41-16 Crack in an unrestored maxillary molar causing symptoms of pulpitis. The patient, a 47-year-old male, had thought the pain problem originated from the temporomandibular joint. Following the preparation of a test cavity, a clear split line was observed at the bottom of the cavity (arrows), confirming the cause of the pain condition. (Courtesy of H. Suda.)

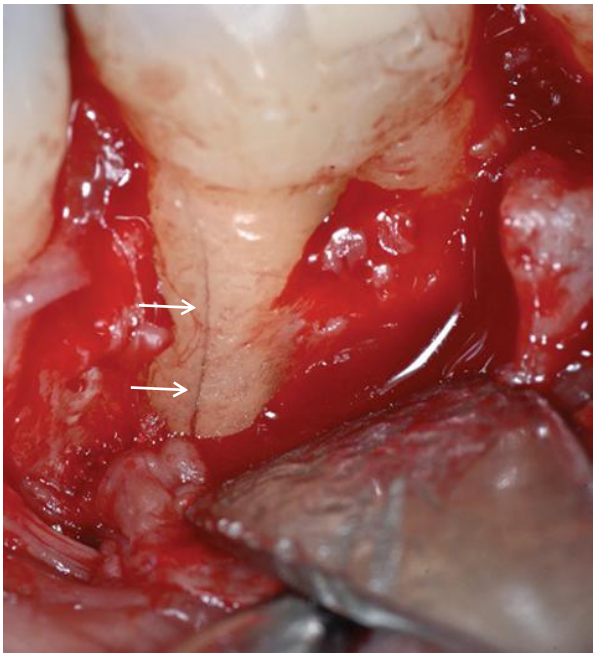

Fig. 41-17 Vertical root fracture of the mesial root of a lower molar (arrows). Note the typical bone dehiscence.

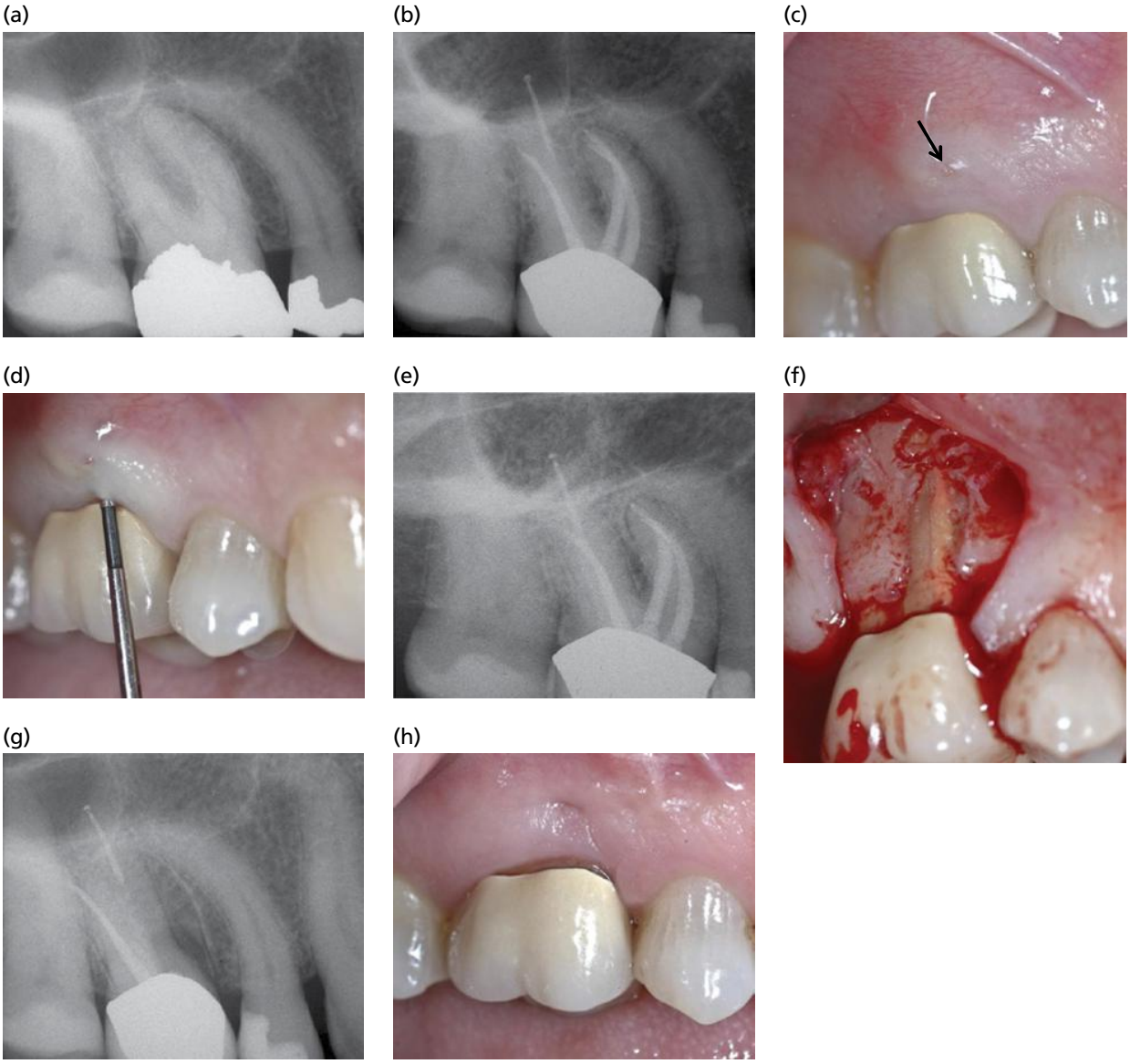

Fig. 41-18 Vertical root fracture in a maxillary right first molar treated endodontically 4 years prior to diagnosis. (a) Root canal treatment initiated because of need for post-retained crown. (b) Cemented crown in place with a composite post in the palatal root canal. (c) At a regular recall appointment 4 years later, the patient complained of a "funny sensation" in the upper right jaw, but reported no other discomfort such as pain or tenderness to biting pressure. Gingiva was slightly inflamed in the area. A closer look revealed a small sinus tract. (d) A pocket probing depth of 8 mm was found over the mesiobuccal root. Remaining probing sites were within normal limits. (e) Radiographic examination was inconclusive. (f) Exploratory surgery revealed a bone dehiscence and a vertical root fracture associated with the mesiobuccal root. (g) Root was extracted. (h) 4 months post surgery, the patient was able to clean the area properly. There was no bleeding on probing or abnormal probing depths.

Vertical root fracture may also occur in clinically intact teeth with no or minor restoration. As posterior teeth are exposed to heavier occlusal forces, mandibular molars appear to be especially at risk for fracture (Yang *et al*. 1995; Chan *et al*. 1999). Subsequent to fracture of teeth with vital pulps, typical pulpitis symptoms may be initiated, together with pain on percussion and mastication.

Occurrence

The rate at which vertical root fractures occur is not well established. While it appears to be a rare condition, the complication is probably more common than clinicians are able to diagnose (Testori *et al*. 1993; Tamse *et al*. 1999b). Endodontically treated teeth appear more prone to vertical root fracture than non–root-filled teeth, with molars and premolars more commonly affected than incisors and canines (Meister *et al*. 1980; Testori *et al*. 1993; Cohen & Louis 2006). In longitudinal clinical follow-up studies of patients treated with fixed prostheses, vertical root fractures were frequent in root-filled teeth with posts and especially so in teeth serving as terminal abutments in cantilever bridges (Randow *et al*. 1986).

It is important to recognize that root fractures of endodontically treated teeth may occur several years after the completion of endodontic therapy and restoration of the tooth (Figs. 41-18, 41-19). In a study comprising 32 vertical root fractures, the average time between the completion of endodontics and

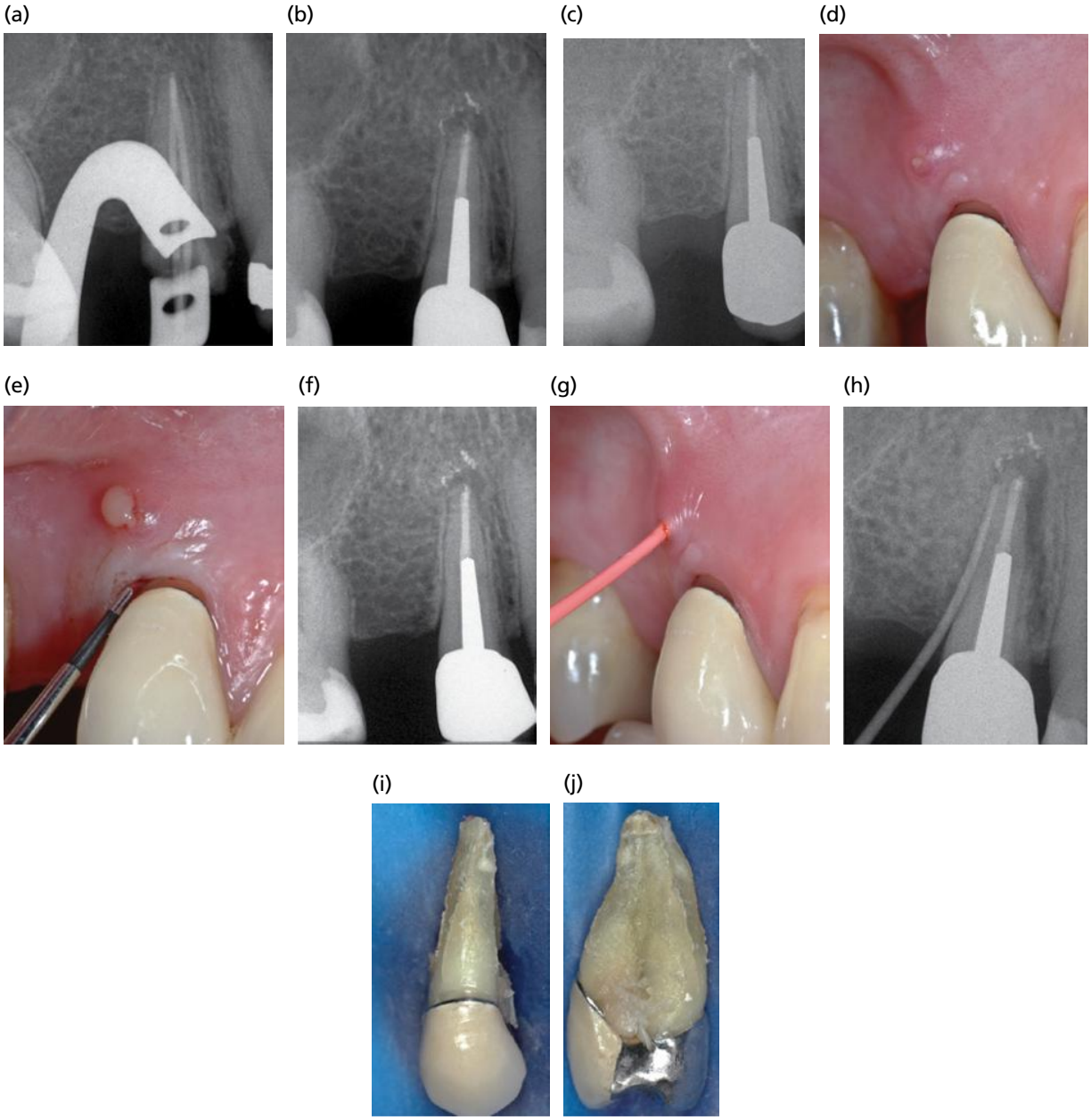

Fig. 41-19 (a) Maxillary right, severely broken down first premolar subjected to root canal therapy. (b) Tooth restored with cast post and core and crown to be included as an abutment in a removable partial denture. Radiograph taken at a recall visit 4 years after initial treatment shows a periapical lesion. Patient had no clinical symptoms and denied further treatment. (c) Over the subsequent 5 years, the size of the lesion did not change. (d) Fourteen years after initial treatment, the patient returned and complained about occasional inflammation at the buccal aspect of the tooth. A slight swelling could be discerned. (e) Periodontal probing to a depth of approximately 6 mm released suppuration of pus of a sinus tract. (f) Ortoradial first radiograph shows the periapical lesion of a similar size as in earlier radiographs. (g) Tracing the fistulous tract with a gutta-percha point with an angulated radiograph (h) shows a periodontal bone lesion extending along the mesial aspect of the root, suggestive of a vertical root fracture. (i, j) Fracture lines can be seen on the buccal as well as on the palatal root surface.

diagnosis of fracture was 3.25 years, with a range of 3 days to 14 years (Meister *et al*. 1980). In another study comprising 36 teeth, symptoms of root fracture developed on average >10 years after completion of treatment (Testori *et al*. 1993). In a further study of 325 endodontically treated and restored teeth, 19 developed a vertical root fracture within a mean observation time of 5.3 years (Salvi *et al*. 2007). In that study, 11 of 13 fractured mandibular molars, restored with a prefabricated titanium post in the distal root, presented with a fracture of the mesial root, which had no post.

Clinical signs and symptoms

Clinical signs and symptoms associated with vertical root fractures vary hugely. Occasionally, there may be pronounced pain and abscess formation because of active bacterial growth in the fracture space (Fig. 41-20). In other instances, clinical symptoms may be limited to tenderness on mastication, mild pain, and dull discomfort. Sinus tracts may emerge near the gingival margin (Figs. 41-18, 41-19). A strong indication of a vertical root fracture is sinus tracts occurring at both buccal and lingual/palatal sites

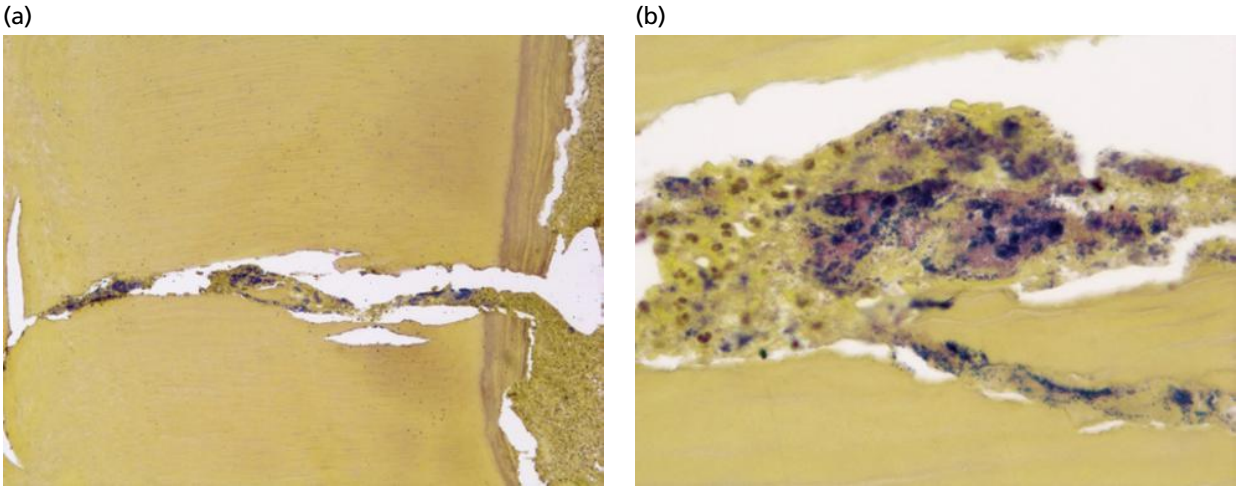

Fig. 41-20 (a) Bacterial masses and polymorphonuclear leukocytes in the fracture space of a maxillary premolar. (b) Magnification of area in the center.

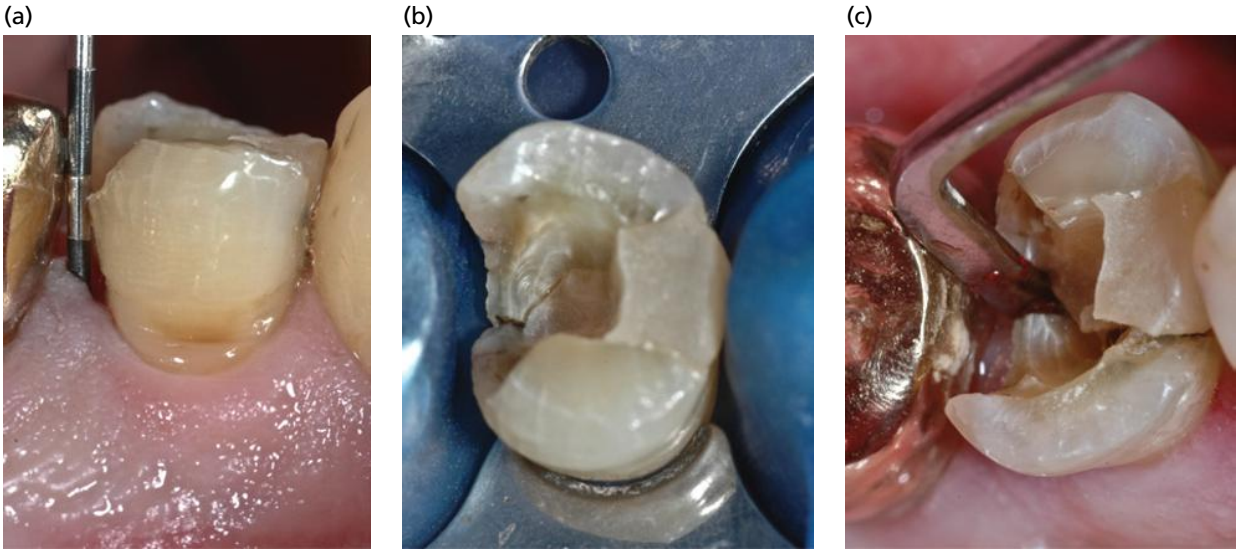

Fig. 41-21 (a) Mandibular second premolar in a periodontally healthy patient with a 5-mm deep pocket probing depth along the distal root surface. Patient had a history of recurring tenderness and abscesses associated with the tooth. Six months earlier it had been subjected to root canal therapy but clinical symptoms prevailed. Radiographs were inconclusive and showed only a minor periapical lesion and slight widening of the periodontal ligament space along the mesial root surface. Except for the pocket probing depth, there were no other clinical signs of acute infection at the time of examination. Mobility was within normal limits. (b) On removing the composite restoration in conjunction with an access opening preparation for endodontic retreatment, a dark line suspicious of a fracture was revealed. (c) Following removal of the clamp and rubber dam, two root fragments could be dislodged with a plastic instrument.

(Tamse 2006). In other instances, a narrow, local deepening of a periodontal pocket may be the only clinical finding (Fig. 41-21).

The osseous defect emanating from the periodontal tissue lesion may take different shapes depending on how the fracture extends. If there is a buccal extension, the thin alveolar bone plate readily resorbs and a typical bone cleft can be seen upon raising a mucoperiosteal flap (Fig. 41-17). At palatal or lingual extensions, the lesion may not resorb the entire bone wall. Therefore, the osseous defect may take a U shape with the height of the bone margin preserved. In fractures that are limited to the apical portion of the root, the bone defect may center on the root apex, similar to that of a periapical lesion associated with an infected root canal.

On conventional intraoral periapical radiographs these bone lesions may not be readily visible, depending on the location, character, and shape of the bone destruction (Fig. 41-22). Absence of a lesion, even when radiographs are taken at different angles, can also be explained by superimposition of roots and bone structures over the bone dehiscence. In yet other cases, radiographic signs may be limited to widening of the periodontal ligament space. Lateral radiolucency along one or both of the lateral root surfaces may be discerned with more pronounced bone lesions. A thin halo-like apical radiolucency is another example of a radiographic lesion suggestive of a vertical root fracture (Pitts & Natkin 1983; Testori *et al*. 1993; Tamse *et al*. 1999a). Developments of tomographic

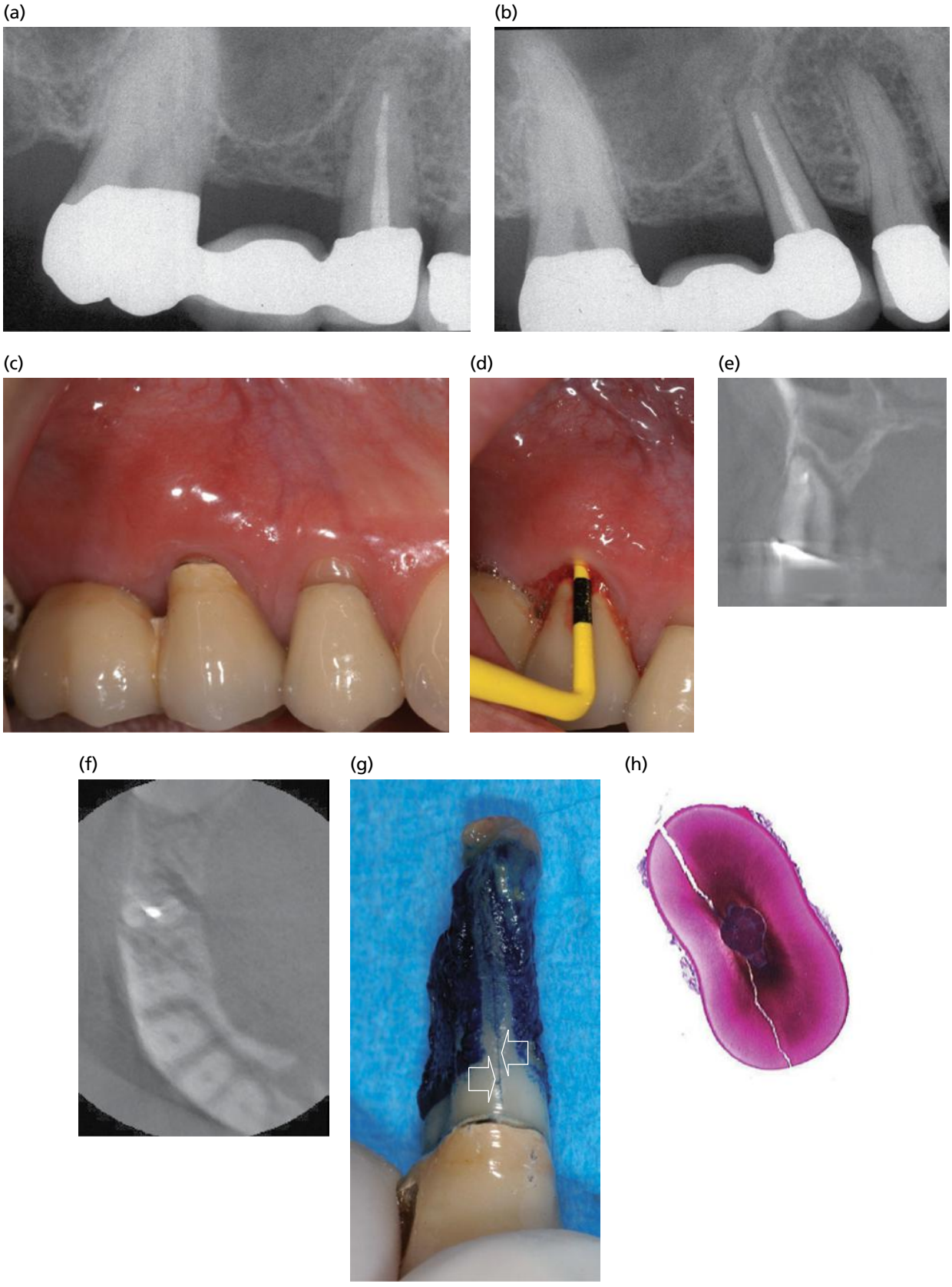

Fig. 41-22 Case of vertical root fracture, where ordinary intraoral radiographs failed to provide evidence of the associated bone lesion. (a) Radiograph shows normal periodontal contours. (b) Second radiograph indicates a widened periodontal ligament space. (c) Patient had complained of recurrent pain on occlusal load for several weeks and presented at the clinic with a slight swelling on the buccal aspect that had appeared several weeks before. (d) Clinically there was an isolated 9-mm pocket probing depth mid-buccally, suggesting root fracture. (e, f) Limited cone beam computed tomography was helpful in revealing a bone lesion along the palatal aspect of the tooth. (g) After extraction, methylene blue staining visualized the fracture line (arrows) that turned out to extend to both the lingual and the buccal root surfaces (h). (Courtesy of T. von Arx.)

techniques have brought valuable new diagnostic tools as they can remove interference from anatomic structures and thereby help to visualize the presence, location, and extension of bone lesions (Gröndahl & Hummonen 2004) (Fig. 41-22e, f).

Diagnosis

The diagnosis of a vertical root fracture is often difficult to ascertain because the fracture is usually not readily detectable by clinical inspection unless there is a clear separation of the root fragments (Testori *et al.* 1993). In fact, diagnosis is often precarious in that the clinical signs often overlap with those of apical and marginal periodontitis. Moreover intraoral radiographs are seldom of diagnostic value unless the central X-ray beam is parallel to the fracture plane, which rarely is achieved (Fig. 41-23). In a sample of 29 patients presenting with clinical signs and symptoms of suspected vertical root fracture in endodontically treated teeth, CBCT provided accurate diagnostic leads (Edlund *et al.* 2011). With surgical exploration as the reference test, sensitivity and specificity were calculated to be 88% and 75%, respectively. To visualize fractures in teeth, it is essential to use CBCT with sufficiently small voxel size. The accuracy of detecting vertical root fracture, however, seems to depend on the CBCT system used (Metska *et al*. 2012).

The suspicion of a vertical root fracture is often inferred from a pocket probing depth in an aberrant position, for example at a buccal or lingual aspect of a tooth, in a dentition otherwise minimally affected by periodontitis (Fig. 41-22d). The sudden appearance of multiple fistulas in a tooth free from restorations may also be indicative. Another strong indicator is the sudden appearance of clinical symptoms and/or a radiographic lesion on a root-filled tooth that has remained asymptomatic and without lesion for many years (Fig. 41-24).

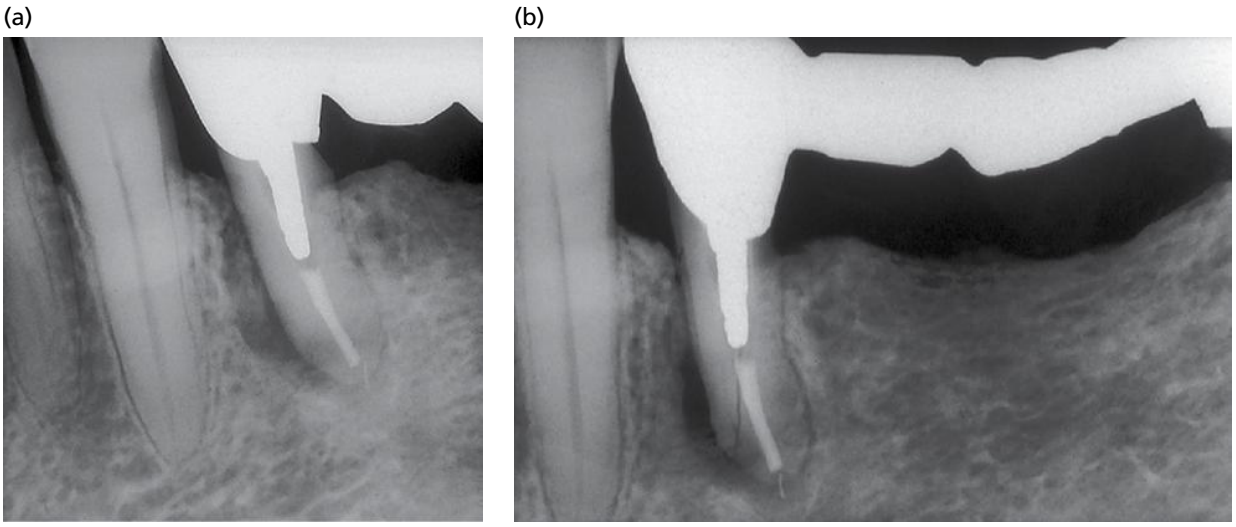

Fig. 41-23 (a) Mandibular premolar included in a four-unit bridge showing a bone lesion at the mesial aspect of the root. In this projection there is no sign of fracture, while in a radiograph (b) taken with a slight shift of angle, a fracture line is clearly visible. (Courtesy of K.-G. Olsson.)

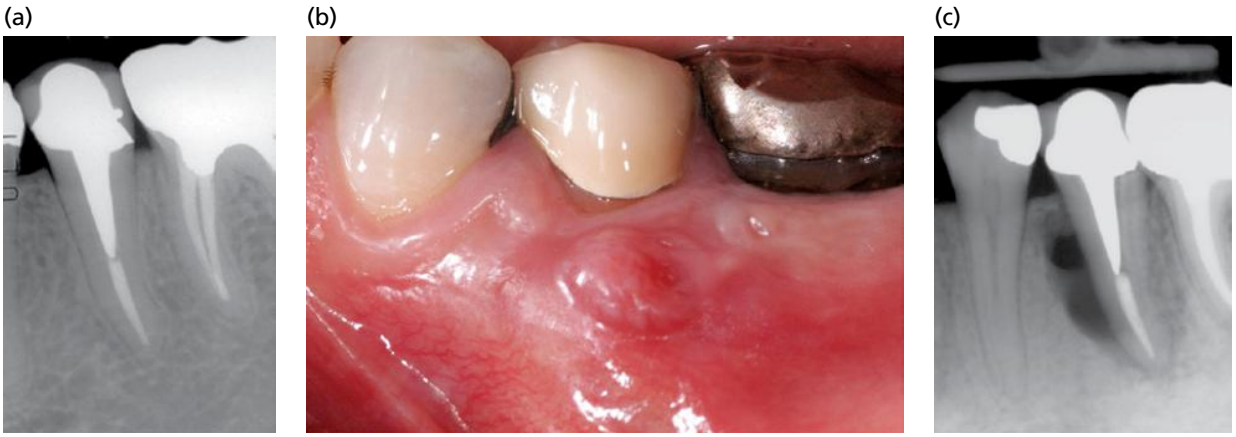

Fig. 41-24 (a) Twelve-year follow-up radiograph of crown-restored, endodontically treated premolar showing excellent periodontal bone tissue structures. (b) Two years later, 14 years after completion of treatment, the tooth became painful and a buccal swelling appeared. (c) Radiograph taken at this time showed severe periodontal tissue breakdown at the mesial aspect of the root. Findings in (b) and (c) are highly suggestive of a vertical root fracture.

Fig. 41-25 Vertical root fracture made visible by a micro-spatulum.

A number of diagnostic procedures can be undertaken to confirm the diagnosis. Application of various dye solutions, e.g. methylene blue or iodine tincture, to the crown and the root surface can sometimes be indicative. As the dye enters the fracture space, it will show up as a distinct line against the surrounding tooth substance. Indirect illumination of the root, using fiber-optic light, can also be of value. The fiber-optic probe should be placed at various positions on the crown or the root to disclose the fracture line. It is often necessary to remove restorations to allow light access to the crown of the tooth. A surgical microscope or an endoscope, providing both enlargement and directed light, are other valuable tools to disclose vertical root fractures. It is also usually helpful to expose the facial or lingual root surface by inserting a micro-spatulum into the sulcus, thus gaining direct sight (Fig. 41-25). This can also be achieved by gently blowing air from a micro-tip into the sulcus. In premolars and molars the diagnosis may be supported from observation of varying pain sensations elicited by loading facial and lingual cusps. The procedure includes asking the patient to bite down on a small object or a specially designed plastic stick (FracFinder). A piece of tooth pick wrapped in tape in such a manner that one can place/steer the piece to different parts of the occlusal surface may also be useful. Separate loading of either buccal or lingual cusps eliciting pain sensation from one, but not the other, loaded cusp suggests the presence of a crack or fracture. Often the diagnosis of a vertical root fracture has to be confirmed by surgical exposure of the root for direct visual examination (Walton *et al*. 1984) at which one may also discover a typical bone dehiscence (see Fig. 41-17).

Treatment considerations

Vertical root fractures that involve the gingival sulcus/pocket area usually have a hopeless prognosis due to continuous microbial invasion of the fracture space from the oral environment. While there are reports of successful management of fractured teeth by reattaching the fragments with bonding resin or laser fusing after extraction followed by re-implantation, fractured teeth are normally candidates for extraction. In multirooted teeth, a treatment alternative is hemisection and extraction of the fractured root.

Conclusion: Symptoms and signs associated with vertical root fractures vary and may be difficult to distinguish from those prevalent with other tooth-associated infections. A variety of diagnostic procedures should therefore be considered. Except for the leads obtained from anamnestic findings and pocket probing depths in buccal or lingual positions or both, clinical examination should include measures to disclose fracture lines *viz.* application of disclosing solutions, use of fiber-optic light, inspection by a surgical microscope or endoscope, or by raising a surgical flap. Pain on selective loading of cusps may indicate root fracture. A vertical root fracture should be anticipated in root-filled teeth, which, after a long history of being asymptomatic and without signs of infection, suddenly present with tenderness, pain, and a radiographic bone lesion. Roots with vertical root fracture usually have a hopeless prognosis and are clear candidates for extraction or, if possible, amputation/hemisection of the fractured root.

Cemental tears

A cemental tear is a special form of root fracture. It is defined as a fracture within the cementum layer or between the cementum layer and the dentin (Leknes *et al.* 1996). These dental hard tissue lesions occur more frequently in men than in women, and in individuals older than 60 years (Lin *et al.* 2011). They seem to be associated with heavy biting and/or grinding. Incisors are the most frequently affected tooth group. In contrast to vertical root fractures, cemental tears do not run perpendicular to the root surface. Consequently, they do not destroy the collagen network of the dentin. This implies that through a cemental tear microbial transgression is not possible between the periodontium and the pulpal space. However, microorganisms can gain access to the marginal periodontium from the oral cavity and thus cause inflammatory lesions. These lesions can be associated with the development of a periodontal pocket adjacent to the torn cementum (Fig. 41-26).

Diagnosis and treatment

Lesions associated with a cemental tear can be hard to differentiate from counterparts induced by vertical root fractures, as it is not always possible to spot the separation in the apparent cementum layer on two-dimensional radiographs (Lin *et al.* 2011). As with suspected vertical root fractures, explorative surgery remains the best option to reach a diagnosis. In contrast to vertical root fractures, however, cemental tears can, depending on their location and extent, be treated conservatively by removing the torn fragment (Fig. 41-26).

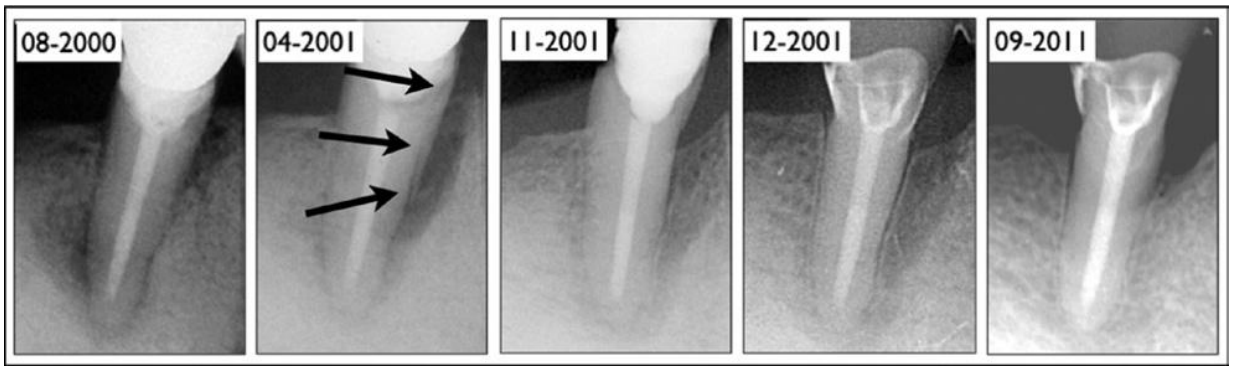

Fig. 41-26 Mandibular right premolar, which had received a root canal treatment through a pre-existing bridge. At the first endodontic recall visit (04-2001), the apical lesion had almost healed. However, a periodontal breakdown mesial to the root of this tooth was noted. Radiographically, the lesion was associated with an apparent abfraction of dental hard tissue in the root opposing the bone defect (arrows). Periodontal surgery was performed, and the diagnosis of cemental tear was verified clinically. The torn fragment was removed and Emdogain® was placed. Seven months later (11-2001), periodontal healing was noted both clinically and radiologically. The tooth was included as an abutment for a new full-ceramic bridge (12-2001). Ten years later (09-2011), the tooth and its surrounding structures were within normal limits. (Courtesy of P. Schmidlin and B. Lehnert.)

Root malformations

Root malformations, which can mediate the development of both localized periodontal tissue breakdown and pulpal infections, are palatoradicular grooves (also known as palatogingival grooves) and invaginations. Both malformations most often affect the lateral maxillary incisor (Lee *et al.* 1968; Alani & Bishop 2008). Their etiology is largely unknown, but genetic predisposition and local factors interfering with normal tooth development have been discussed (Alani & Bishop 2008). Palatoradicular grooves start at the junction of the cingulum with one of the lateral marginal ridges and continue apically, sometimes all the way to the apex (Lara *et al.* 2000). Invaginations can extend into the pulp chamber and/or communicate with the periodontal ligament apically or laterally on the tooth root through a pseudo-foramen (Alani & Bishop 2008). Palatoradicular grooves and invaginations may or may not communicate with the pulpal space (Lara *et al.* 2000; Alani & Bishop 2008).

Diagnosis

Prior to the advent of CBCT, diagnosis of root malformations was hampered by the limitations of intraoral radiographs to depict their anatomic configuration in all dimensions (Patel 2010). Yet, the issue is still complicated, as teeth affected by these malformations often have a vital pulp and thus respond within normal limits to routine sensitivity tests. Consequently, a palatoradicular groove or invagination is often diagnosed only when clinical manifestations are apparent. In the case of a palatoradicular groove, increased probing depth on the palatal aspect of a maxillary front tooth is suggestive. An invagination with a relationship to the pulpal space also reveals itself by symptoms of pulpitis in an otherwise healthy tooth without deep caries or restoration. In other invaginations with an opening to the periodontium, but without a direct communication with the pulpal space, periodontal manifestations of an acute nature mimicking symptomatic apical periodontitis may develop in a tooth with vital pulp (Fig. 41-27). If any of these lesions is suspected, limited-volume CBCT at maximum resolution helps the clinician to render minimally invasive treatment.

Treatment considerations

The type of malformation and the associated clinical features decide the treatment approach. Verifying pulpal vitality of the affected tooth is a first critical step. If clearly vital with no obvious periodontal involvement, treatment aims to prevent oral microorganisms from colonizing these niches to trigger inflammatory periodontal tissue breakdown. The prevention of this colonization by oral hygiene measures is usually not possible (Everett & Kramer 1972). Surgery with removal of granulation tissue combined with scaling and root planing and placement of a polytetrafluoroethylene membrane over the palatogingival groove has been reported to be successful in a limited series of cases with loss of clinical attachment (Anderegg & Metzler 1993). For invaginations with periodontal lesions, cleaning and sealing the defect may be sufficient to attain periodontal healing (Fig. 41-26) (Pitt Ford 1998). Where a groove or invagination corresponds with the pulpal space and has caused a pulpal condition, root canal treatment is necessary. Yet, the outcome is not always predictable and treatment may need to include surgery (Nallapati 2004).

Root surface resorptions

Root surface resorptions usually progress without producing clinical symptoms and may therefore go undetected unless observed radiographically. However, in advanced stages, the surface defect may interfere with the gingival sulcus and thereby initiate an infectious process (Fig. 41-28). Different forms of root surface resorption as sequelae to traumatic incidents have

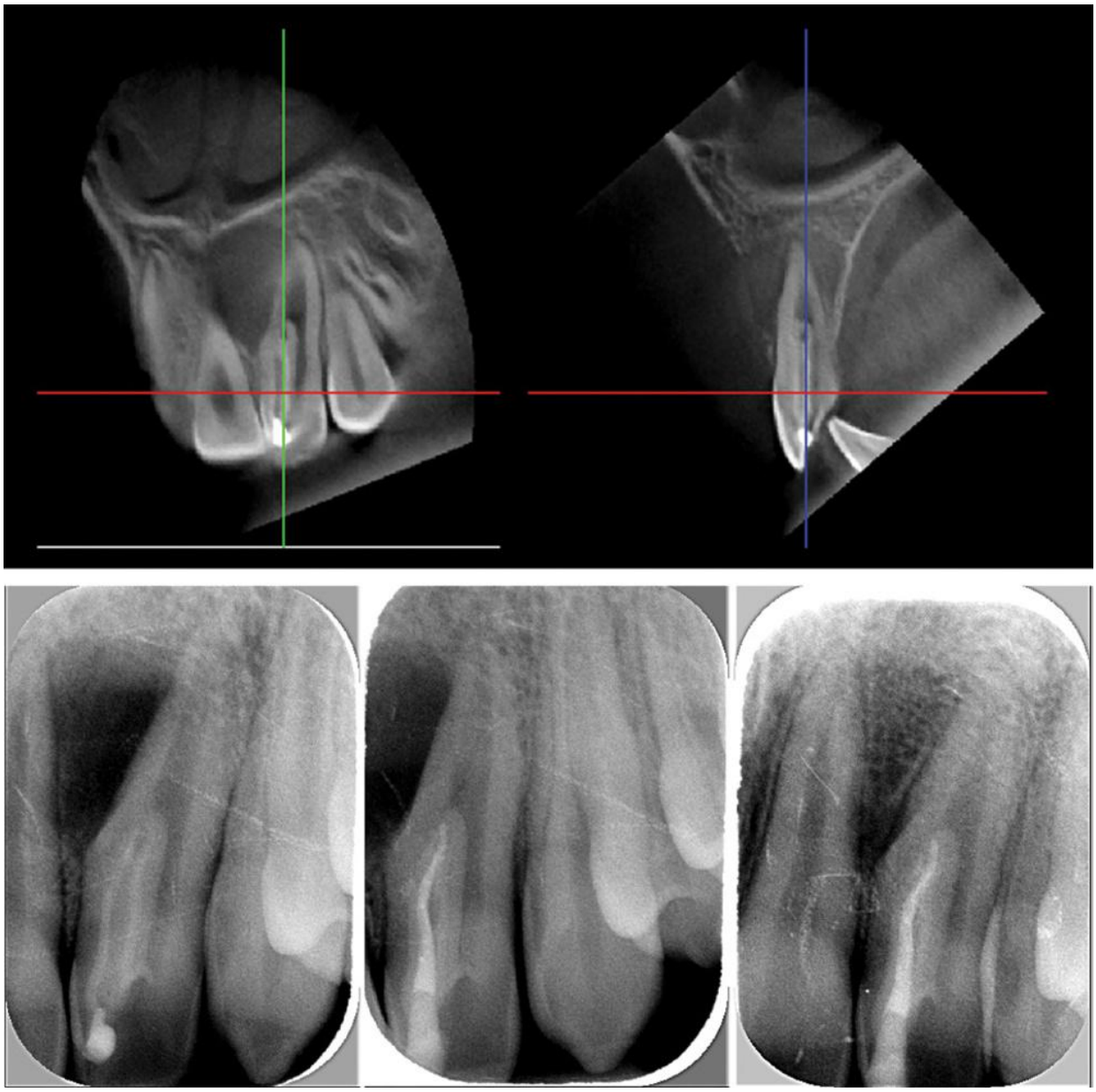

Fig. 41-27 Lateral maxillary incisor of a then 11-year-old boy. The patient presented with an acute abscess related to tooth 22. The tooth had an invagination, which communicated with the marginal periodontium. Note the apparent complete absence of bone on the buccal root aspect as depicted in the cone-beam computed tomogram. There was no communication of the invagination with the pulpal space. Hence, the root canal was not treated. The invagination space was chemomechanically cleaned, filled with gutta-percha and a sealer, and coronally sealed using a bonded composite material. The lesion resolved clinically and radiographically within 1 year (lower right panel). The tooth remained within normal limits to sensitivity tests.

been described (Andreasen & Andreasen 1992). In the discussion of potential interrelationships between endodontics and periodontics, one type is of particular clinical importance. This form of root surface resorption, here termed cervical invasive root resorption, is not, or at least not exclusively, related to injury from trauma (Heithersay 1999b).

Cervical invasive root resorptions

Often misdiagnosed, cervical invasive root resorption has been given various names, including odontoclastoma, asymmetric internal resorption, progressive intradental resorption, idiopathic external resorption, peripheral cervical resorption, cervical external resorption, extracanal invasive resorption, supraosseous extracanal invasive resorption, peripheral inflammatory root resorption, or simply cervical resorption (Frank & Bakland 1987; Gold & Hasselgren 1992; Heithersay 1999a). Geoffrey S. Heithersay, who arguably has studied the disease condition most extensively, coined the term cervical invasive root resorption (CIRR) (Heithersay 1999b). Yet, some dispute regarding the correct nomenclature remains, as these lesions are not always located cervically (Gold & Hasselgren 1992). CIRR can be associated with pulpal breakdown, increased pocket probing depths, as well as drainage of pus upon probing (Fig. 41-28).

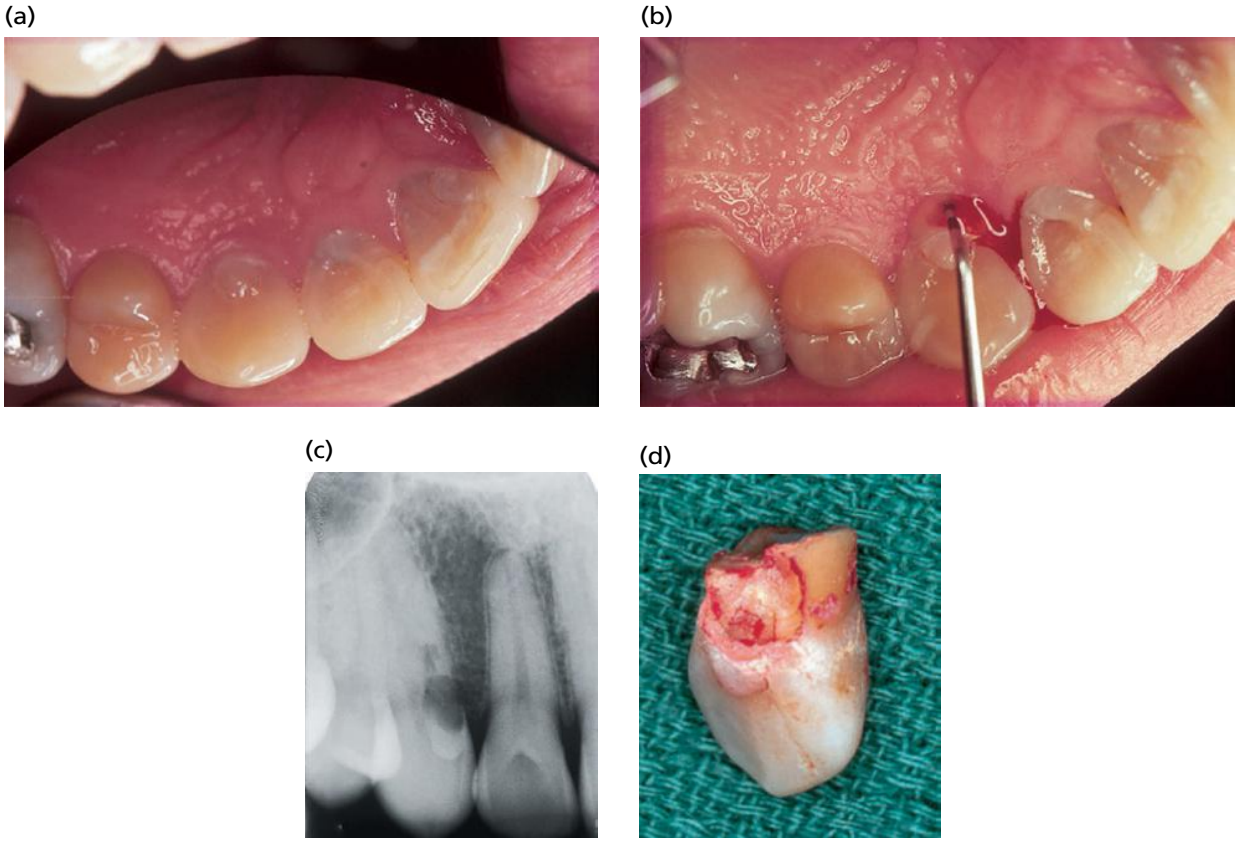

Fig. 41-28 Case of cervical invasive root resorption (CIRR). Pain and tenderness of the right maxilla for several weeks prompted the 30-year-old male patient to seek treatment. (a) Clinical inspection revealed no obvious pathosis. (b) Periodontal probing, however, released pus drainage from the lingual aspect of tooth 13. Pulp sensitivity test of the tooth and its neighboring teeth gave clear positive responses. (c) Angulated radiograph disclosed the presence of a resorptive defect. (d) Tooth was extracted as successful treatment was deemed unlikely. An extensive resorptive defect had undermined the clinical crown.

There are different forms of CIRR. In most cases, small openings penetrate the cementum layer along which the resorptive process continues inside the tooth structure without causing major peripheral breakdown (Fig. 41-29). Other forms of CIRR may be associated with a broad opening to the periodontium (Fig. 41-30).

Etiology

Under normal, physiologic conditions, hard tissues are protected from resorption by their respective surface layers of blast cells; in the case of the cementum, by cementoblasts. As long as these blast cell layers remain intact with the unmineralized layer of osteoid or cementoid at the surface of the mineralized tissue, resorption will not occur (Gottlieb 1942).

While known for several other forms of root surface resorptions, the triggering mechanism for CIRR is far from completely understood. Predisposing factors, which may all interfere with the integrity of the cementoid layer, seem to be orthodontic treatment, trauma, and chemical injury in conjunction with intracoronal bleaching, while few of 222 retrospectively analyzed cases had a history of periodontitis or periodontal treatment (Heithersay 1999b). The reason for the low incidence following periodontal treatment could be that, even upon excessive scaling and root planing, the damaged area of the root surface usually becomes covered by junctional epithelium. A further potential cause of CIRR, especially when it affects multiple teeth in the same dentition, may be viral (von Arx *et al*. 2009). A similar, presumed virus-related, disease known as feline odontoclastic resorptive lesions is common in cats. It has been speculated that virus transmission from cats to humans can occur and is a possible cause of the condition (von Arx *et al*. 2009). Firm evidence of a viral causation of CIRR in multiple teeth is lacking, however.

In the case of CIRR, the predentin is not resorbed unless the lesion becomes infected. Obviously clastic cells avoid non- or less mineralized tissues (Stenvik & Mjör 1970) (Fig. 41-31). This explains why CIRR expands laterally without directly invading the pulp. Yet, this peripheral extension can markedly undermine the tooth structure (Figs. 41-29, 41-32, 41-33). If there is a non-vital pulp and thus no resorption inhibition mechanism in place in the form of odontoblast-supported predentin, CIRR may extend to the pulpal space.

A special form of resorptive process in the cervical region of teeth may develop subsequent to intracoronal bleaching of root-filled teeth (Harrington & Natkin 1979; Montgomery 1984). The use of concentrated, tissue-toxic hydrogen peroxide has been especially implicated as the agent is capable of penetrating dentin and cementum (Fuss *et al*. 1989).

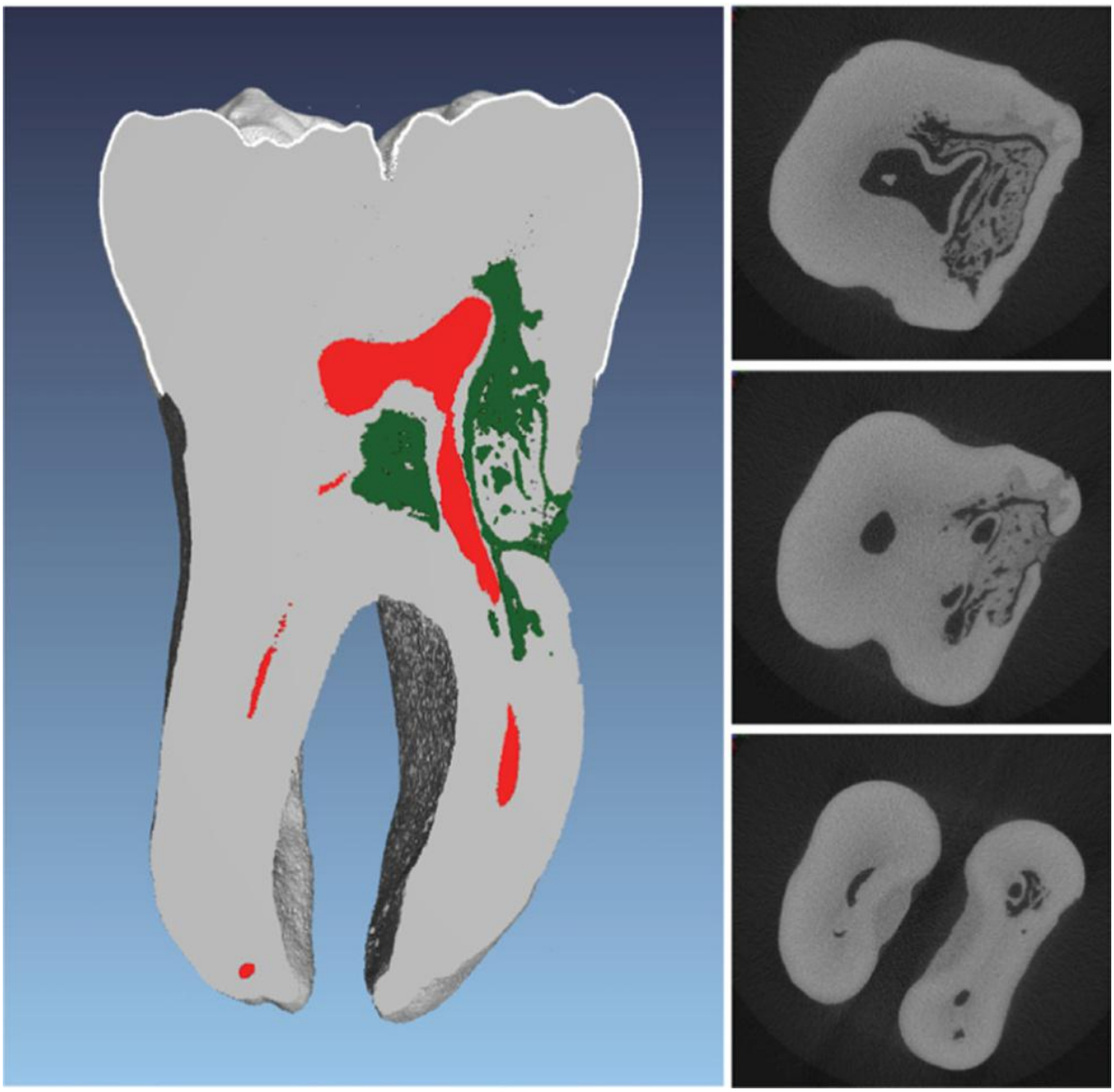

Fig. 41-29 Micro-computed tomography scan depicting a mandibular molar, which was extracted due to advanced cervical invasive root resorption (CIRR). Longitudinal section on left panel: false colors indicate the pulpal space (red) and the invagination (green). Original trans-sections on right panels. Note how the lesion circumvents the pulpal space. The apparent bone structure of the invading tissue is also to be noted. (Courtesy of F. Paqué.)

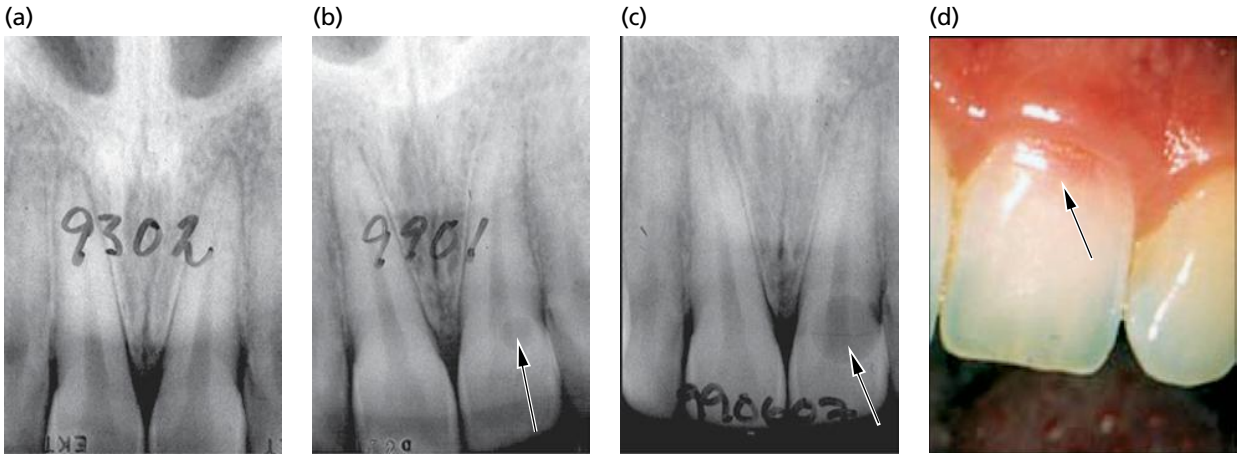

Fig. 41-30 Series of radiographs taken at different time intervals showing the appearance of a cervical invasive root resorption (CIRR) in a young adult patient. (a) At the age of 15 years there was no sign of resorption. (b) Six years later a small radiolucency emerged (arrow). (c) In just 6 months the lesion expanded considerably (arrow). (d) Lesion appeared clinically as a pink spot in the cervical area of the tooth (arrow). (Courtesy of A. Molander.)

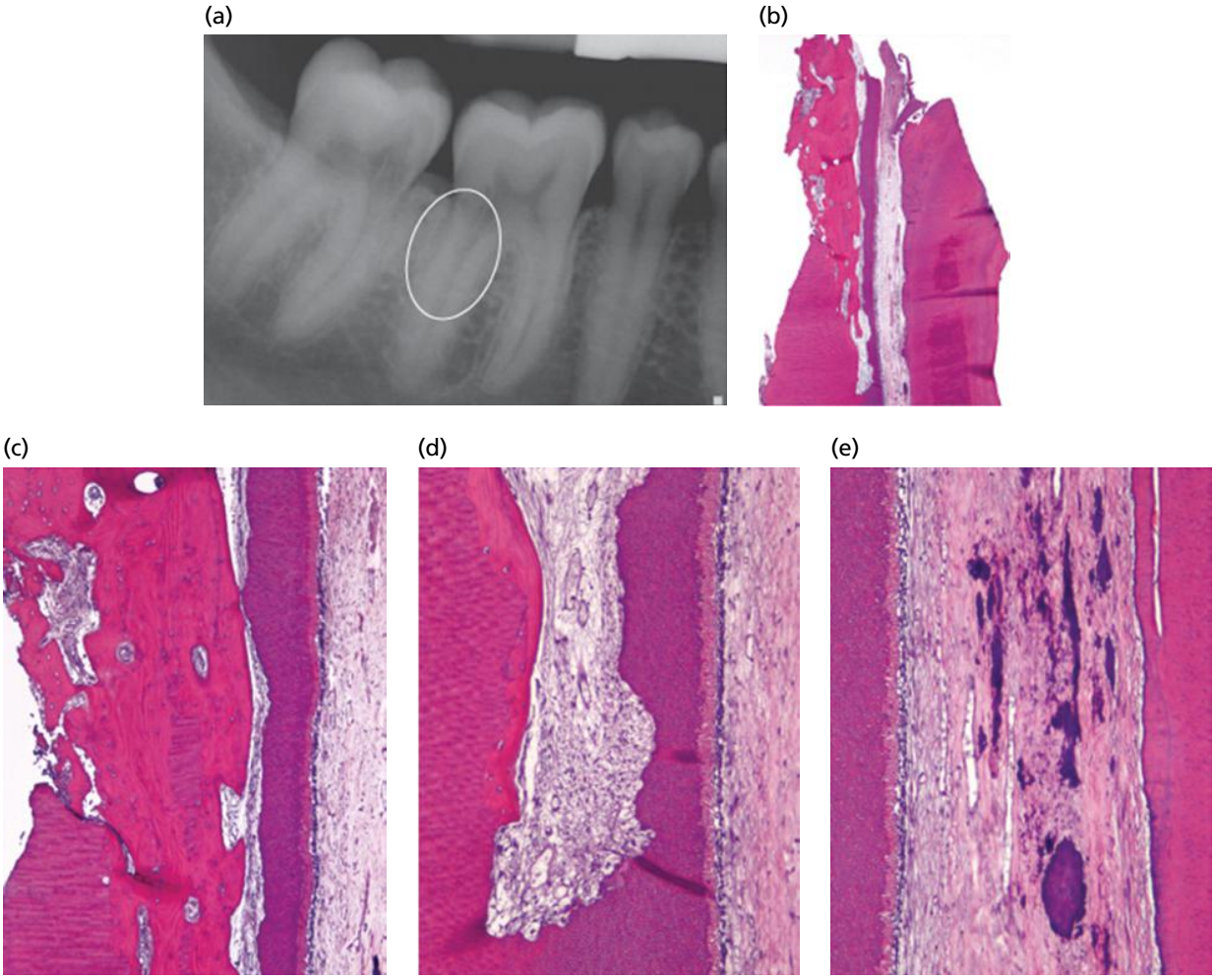

Fig. 41-31 (a) Mandibular first and second molar with the diagnosis of cervical invasive root resorption (CIRR). The teeth were deemed non-treatable and extracted. (b) Histologic section from the distal cervical area of the first molar encircled in (a). Overview shows that distally a large amount of dentin has been resorbed followed by invasion of bone tissue in the defect. The pulp space and the inner dentin layer are unaffected. (c) Detail from (b). The newly formed tissue shows the characteristic of lamellar bone with marrow spaces. (d) Magnification of the most apical portion of the resorptive defect in (b). Resorption of dentin and bone apposition can be observed on the opposite walls of the defect. Note the apparently normal predentin and odontoblast layer. (e) Pulp space immediately apical to the resorption. The pulp is uninflamed with prevalence of fibers and diffuse dystrophic calcifications.

It appears that the resorption is caused by bone remodeling units: clastic cells with hard-tissue forming counterparts in their trail. These cell units gain access to the root dentin by local loss of the cementoid layer. A histologic study by Southam (1967) revealed that CIRR lesions are filled with granulation tissue and bone. Consequently, these types of lesions are not inflammatory in nature, at least not initially. CIRR with a localized entrance to the bone tissue into the tooth are rather *a form of replacement resorption*. Initially, the point of entry of the bone remodeling units is small (Fig. 41-29). However, once the undermining process of the root surface becomes more severe, parts of the root surface layer may be lost, resulting in larger openings. Larger openings in the cervical area may also be related to diffusion of bleaching agents through the dentinal tubules. Oral microorganisms, rendering the case symptomatic, can invade these portals of entry for the resorbing tissue. The portal of entry of the CIRR is usually close to the crest of the alveolar bone. It may also be supraosseous or infraosseous (Frank & Torabinejad 1998).

Diagnosis

Root resorptions *per se* do not cause painful symptoms and may remain clinically quiet for years. While radiography is the only means of detection, a pinkish spot at the facial aspect of a tooth in the cervical region is a warning signal (Fig. 41-30). In very late stages, as the resorptive process engages the gingival sulcus, an infectious process may emerge with typical features of a periodontal abscess (Fig. 41-28).

A single radiograph is usually not sufficient to define a radiolucent area within the confines of a root as an external resorption. In fact, a radiolucency may portray a variety of conditions including a resorptive process inside the root canal (internal root resorption), or a resorptive defect located buccally or lingually as the image of the root is superimposed. It may also be an artifact and reflect a radiolucent bone area superimposed on the root. Therefore, more than one radiograph at different angulations should be

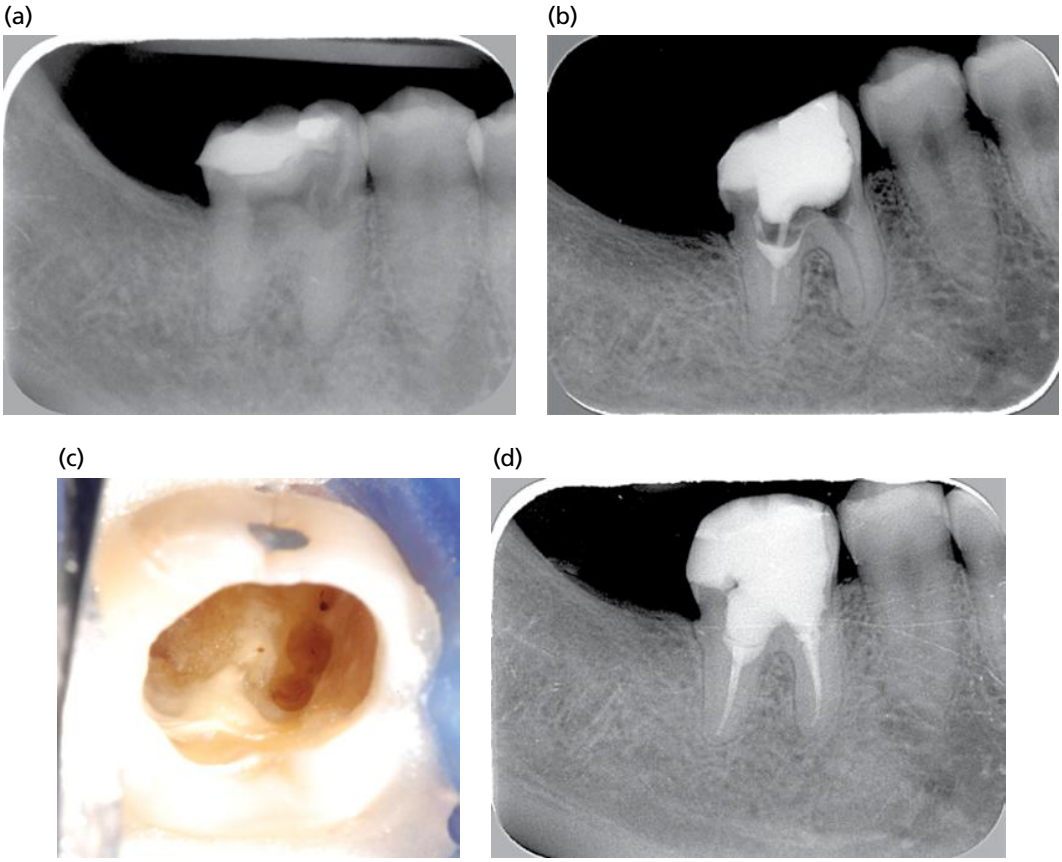

Fig. 41-32 (a) Radiograph of a 40-year-old female patient suffering from multiple cervical invasive root resorptions (CIRR) on her first molars. She had a history of high orthodontic forces applied to these teeth. When she first presented, she complained of severe spontaneous pain in the mandibular right molar region. Tooth 46 was diagnosed with symptomatic pulpitis related to CIRR. (b) Pulp space was accessed, and the resorptive tissue was mechanically removed using a long-shank bur under direct vision with the aid of a dental microscope. Subsequently, the resorption space and the root canal system were dressed with a suspension of calcium hydroxide powder in a 2.5% sodium hypochlorite solution. (c) On the second visit, the patient presented symptom-free. Because the bleeding could now be controlled, the points of entry of the resorptive tissues could be visualized, and the bone-like tissue removed. Mineral trioxide aggregate (MTA) was placed on the communications between the canal space and the periodontium. On the third visit, the root canal system was filled, and the tooth was restored with a bonded composite material. (d) At recall after 2 years, the tooth was free of symptoms and without radiologic signs of rarefaction.

taken to observe whether the radiolucent area affects the external root surface or not. New tomographic techniques can be of great benefit in distinguishing external from internal root resorptions (Patel *et al.* 2009). High-resolution, limited-volume CBCT is now the standard method for diagnosis of these cases. As these lesions are rare (Heithersay 1999a) and CBCT requires relatively high radiation dosages, the method should only be applied when CIRR is suspected.

The location of the lesion is important. A facial or lingual root resorption defect is more difficult to visualize radiographically than a proximal cavity, unless tomography is used. One should be aware that in the cervical region it may be difficult to differentiate radiographically between those cavities caused by caries and those caused by root resorption. To distinguish caries from resorption it is useful to recognize that bacterial acids that demineralize dentin leave a soft cavity surface. By contrast, clastic resorption removes both the mineral and the organic phases of the hard tissues, resulting in a cavity floor that is *hard to probing*.

The clinical features of CIRR include a granulation tissue that bleeds freely on probing. Occasionally, a periodontal abscess may develop due to marginal infection, which may mimic a periodontal or endodontic condition (Fig. 41-29). When the lesion is located more apically or proximally, probing is usually difficult. Radiographically, the lesion may only be seen after it reaches a certain size (Andreasen *et al*. 1987) (Figs. 41-29, 41-31). Sometimes the appearance is mottled due to the proliferation of bone tissue into the resorptive defect (Seward 1963) (Fig. 41-34). The outline of the root canal can often be seen within the radiolucent area (Figs. 41-31, 41-35), which is a diagnostic feature of root surface resorption. The presence of profuse bleeding upon probing and granulation tissue formation, in combination with a hard cavity bottom, confirms the diagnosis of CIRR. Electric pulp test and cold tests are usually positive, but will not distinguish this condition from caries or internal resorption, the two major differential diagnostic options (Frank & Bakland 1987).

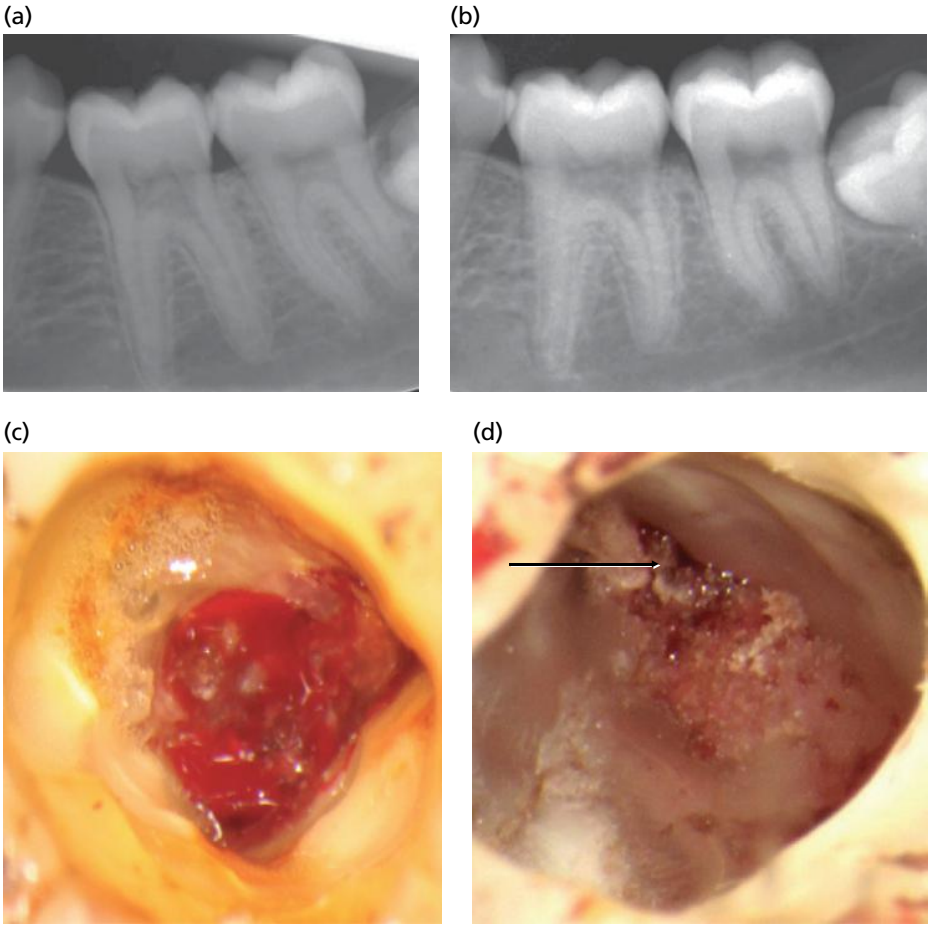

Fig. 41-33 (a, b) CIRR in a first mandibular molar showing a mottled appearance. There are pulp stones within the pulp tissue and bone tissue formation within the resorptive defect superimposed on the pulpal space. Following accessing both the pulp and the resorptive process (c) and removing the bleeding tissue, bone tissue appeared at the lingual wall of the cavity, where the resorptive process had entered the tooth (d). Arrow in (d) indicates the orifice of the root canal in the distal root. (Courtesy of M. Fridjon Ragnarsson.)

Clinical management aspects

The location and size of the portal of entry dictate the choice of treatment attempt. Surgical exposure of the area to allow removal of the granulation tissue is the only reasonable option in cases with accessible, wide openings (Heithersay 1999c). A dental filling, for example a resin composite, is subsequently placed in the defect followed by resuturing of the flap. The mechanical removal of the granulation tissue can be aided by chemically pretreating it with trichloracetic acid (Heithersay 1999c). Other treatment options from the periodontal side include repositioning the flap apical to the resorption or orthodontic extrusion of the tooth (Gold & Hasselgren 1992). Guided tissue regeneration has also been advocated after surgical removal of the granulation tissue, to promote ingrowth of periodontal ligament cells into the resorbed area (Rankow & Krasner 1996). In teeth with root anatomy that allows atraumatic extraction, intentional re-implantation can be performed (Frank & Torabinejad 1998). This approach will require root canal treatment. The costs of root canal treatment and potential resorptive sequelae of intentional re-implantation are reasons why this combined approach is usually not the first treatment choice.

Treating CIRR from the periodontal side has the advantage that the pulp may be kept vital. However, in most cases, the portal of entry is located in areas that are hard to access (Frank & Torabinejad 1998). Maintaining pulpal vitality in these cases is therefore near impossible, and it is often less invasive to sacrifice the pulp and treat the lesion from the pulpal side. This approach has become much easier with the advent of dental microscopes and MTA. To rid the tooth of the resorbing tissue, a two-visit approach is advocated: at the first visit, the defect inside the tooth is located and the bulk of the ossifying granulation tissue is removed using long-shank round burs (Fig. 41-32). A slurry of calcium hydroxide powder in a NaOCl solution can then be placed as an interim medication. This will dissolve soft tissue remnants inside the lesion (Zehnder *et al.* 2003). At the second visit, bleeding can be controlled more easily. The portal of entry of the CIRR can then be identified and closed with a cement such as MTA (Fig. 41-32). As with perforation defects, supracrestal lesions are best sealed directly with a dual-curing composite resin bonded to dentin.

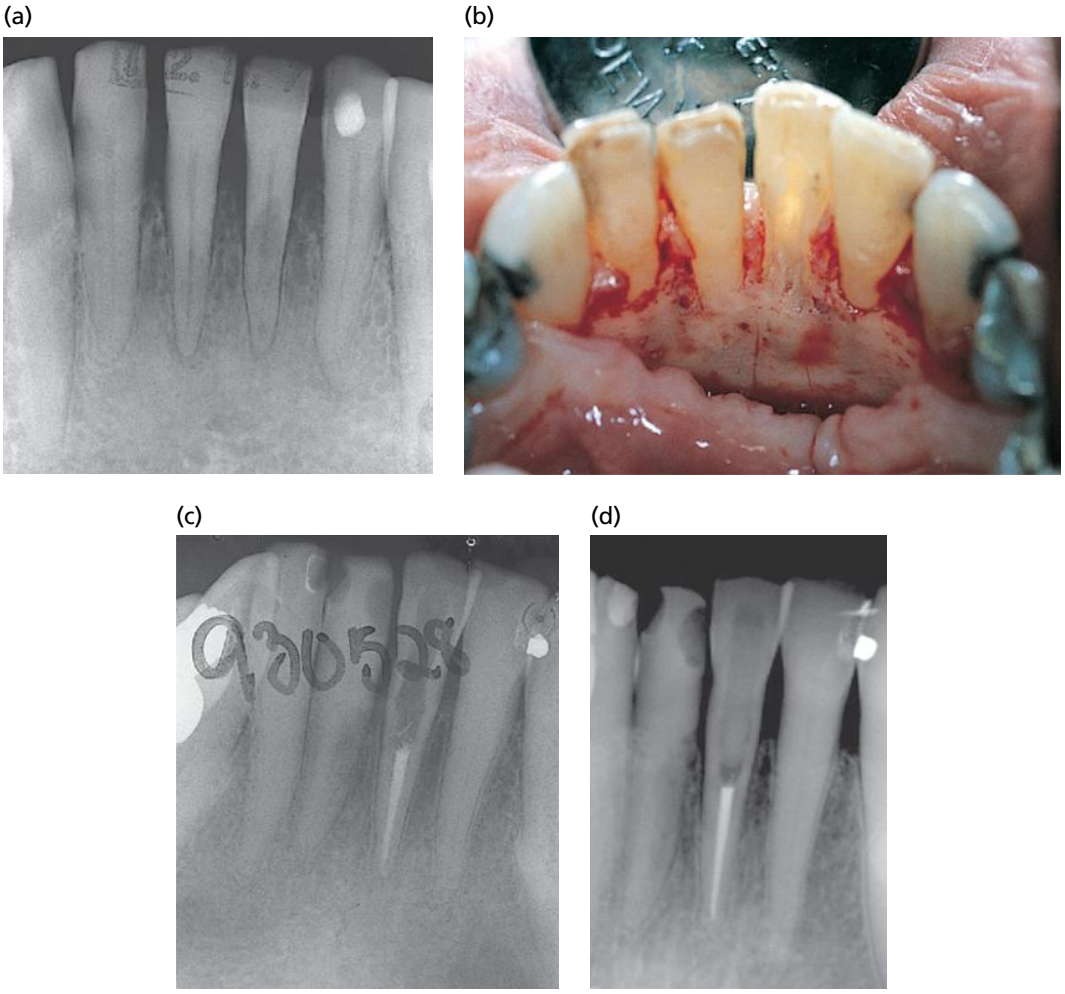

Fig. 41-34 Case with root surface resorption on the lingual aspect of both central incisors. (a) The patient, a 78-year-old woman, presented to the clinic after an episode of severe pain and development of a lingual periodontal abscess. The medical history was unremarkable. The patient was initially managed with antibiotic treatment. (b) Later, upon flap elevation and accessing the resorbing area and removal of the granulation tissue, a necrotic pulp of tooth 31 was noted. (c) Endodontic treatment was carried out during the surgical procedure. Tooth 41 was left without any further treatment and the case was followed clinically and radiographically. No recurrence of resorption occurred on either tooth and the patient remained comfortable. (d) Radiograph of the last follow-up is 8 years after treatment. Note that there is no progression of the resorptive process associated with tooth 41.

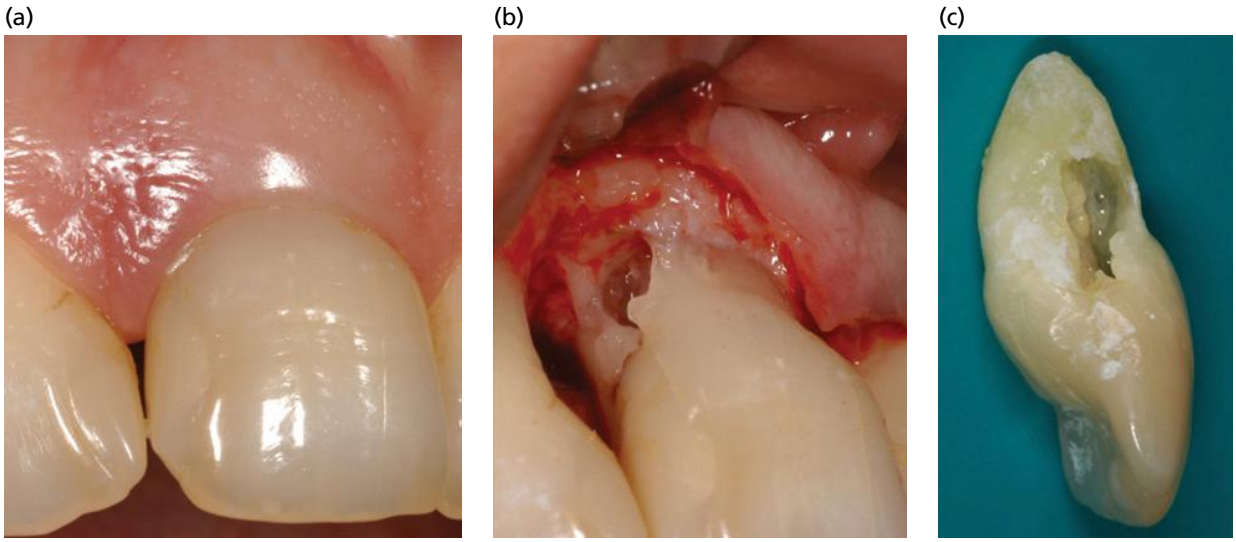

Fig. 41-35 (a) Maxillary left front tooth with a massive CIRR. (b) Periodontal surgery revealed that the lesion was too extensive for the tooth to be saved. (c) In this case, extraction was the only reasonable treatment option. Note the undermining nature of the lesion on the extracted tooth. The predentin is not resorbed, and thus the shell of the pulp space appears like a column in the hollowed space. (Courtesy of C. Schädle.)

Another treatment option is extraction of the affected tooth. This becomes necessary in advanced cases, when it is impossible to restore the structural integrity of the affected tooth (Fig. 41-35). Yet another alternative is to inform the patient about the tooth's lack of viability but to leave it alone for the time being, while recommending regular follow-up checks. Experience has shown that the resorptive process occasionally may slow down and such teeth can therefore last for several years (Fig. 41-34). This option is especially advocated if the CIRR lesion is located in apical portions of the root. Apically positioned subcrestal lesions are hard to reach surgically or endodontically, but have a lower likelihood of becoming infected compared to supracrestal counterparts.

Conclusion: CIRR in advanced stages can be associated with persistent inflammation in the periodontal tissues and pulpal breakdown. The cause for the occurrence of this type of root surface resorption is not well understood. To remedy the condition, it is necessary to remove the resorbing granulation tissue surgically and to fill the resorption cavity. Modern endodontic techniques allow the treatment to be carried out from the pulpal side (Figs. 41-33, 42-34). However, regardless of approach, periodontal tissue complications may ensue, including deep pockets and suppuration from such pockets. Treated cases should therefore be monitored by regular clinical/radiographic follow-ups to observe any signs of recurrence and how the periodontal tissue copes. In advanced cases, extraction is the only reasonable treatment option (Figs. 41-29).

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Chapter 42

Treatment of Peri-implant Mucositis and Peri-implantitis

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Introduction

Inflammatory lesions occurring in peri-implant tissues were described in Chapter 26. Such processes are the result of opportunistic infections and may, if left untreated, progress deep into the supporting bone and lead to implant loss. It is, therefore, imperative that the tissues around implants be monitored at regular intervals to identify biologic complications and to treat the disease process at an early stage. The appropriate therapy following diagnosis must aim to reduce the submucosal biofilm and alter the ecology of the bacterial habitat.

Treatment strategies

The choice of treatment strategy is based on the diagnosis and the severity of the peri-implant lesion. Peri-implant mucositis and incipient forms of peri-implantitis require less extensive measures than advanced peri-implantitis lesions with severe bone loss. In all situations of peri-implant disease, however, the treatment strategy must include mechanical cleaning (infection control) procedures. Thus, information and instruction on the use of oral hygiene measures must be provided to the patient in combination with professional mechanical cleaning, including removal of plaque and calculus from implant surfaces. In this context it is important that the design of the implant-supported prosthesis allows access for oral hygiene. In cases where access is obstructed, the prosthesis must be modified to promote self-performed and professional mechanical infection control.

Two cases that illustrate the outcome of self-performed and professional mechanical cleaning are shown in Figs. 42-1 and 42-2. While plaque, calculus, and signs of inflammation are evident at implants in the initial examination, the follow-up visit after 3 months of infection control demonstrates improved oral hygiene and soft tissue conditions.

Non-surgical therapy

There are obvious similarities between treatment strategies for periodontal and peri-implant infections. One important difference, however, relates to difficulties with instrumentation of the implant surface below the margin of the mucosa. Thus, subgingival scaling and root planing are well-known procedures in the treatment of periodontitis, while in peri-implantitis the geometry of the implant with threads of different designs may impede the ability of the clinician to detect and remove calculus located below the mucosal margin. During such "blind" instrumentation at implants there is also a risk that deposits may be dislodged and be displaced into the mucosa. It is thus recommended

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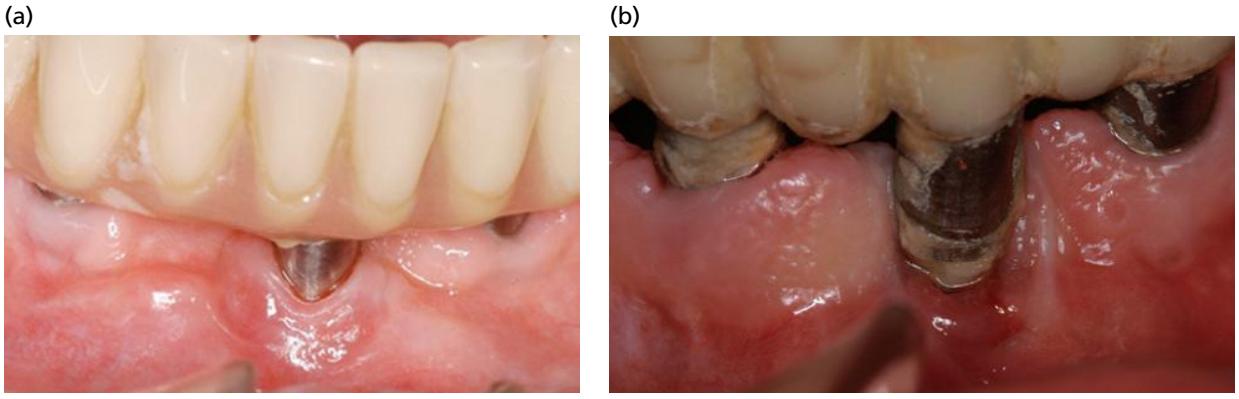

Fig. 42-1 Clinical photographs of implant sites in the mandible of (a) a 70-year-old and (b) a 62-year-old woman. Note the overt signs of inflammation in the peri-implant mucosa (a, b) and the large amounts of plaque and calculus (b).

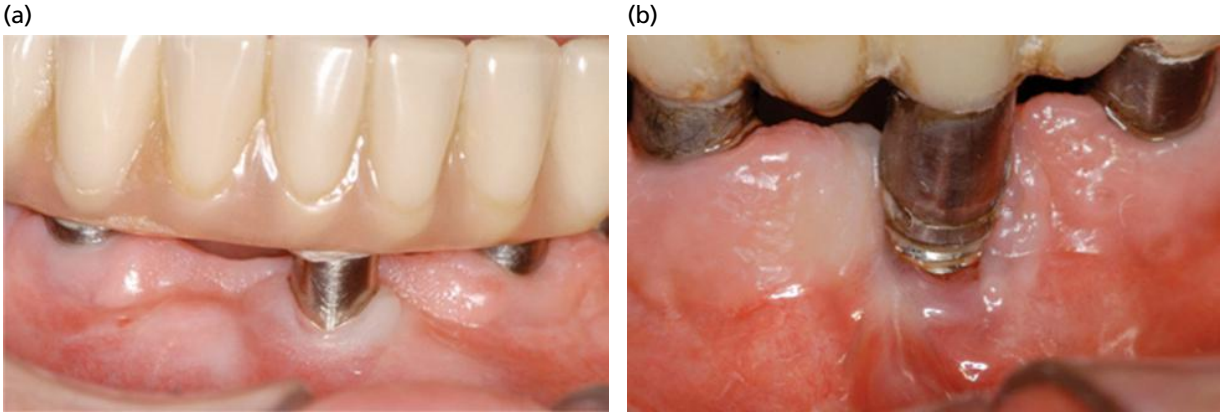

Fig. 42-2 (a, b) Implant sites shown in Fig. 42-1 after 3 months of self-performed mechanical infection control combined with professional cleaning. Improved oral hygiene and soft tissue conditions are seen.

that non-surgical debridement of implant surfaces, that is procedures that aim to remove calculus and plaque, should be restricted to the portion of the implant located coronal to or at the level of the mucosal margin. While calculus may be chipped off using titanium-coated or carbon-fiber curettes, plaque is removed by polishing the implant surface with rubber cups and a polishing paste. Carbon-fiber curettes do not damage the implant surface. They may be sharpened and are strong enough to remove most accumulations of calculus. Ultrasonic instruments with non-metallic tips may also be used for calculus removal.

Peri-implant mucositis and incipient peri-implantitis lesions may be resolved using the cause-related measures described above. Heitz-Mayfield *et al.* (2011) in a study of treatment of peri-implant mucositis in 29 patients reported that non-surgical debridement and oral hygiene were effective and that the adjunctive use of a chlorhexidine gel did not enhance treatment outcome.

Non-surgical therapy of moderate and severe forms of peri-implantitis, however, is ineffective in resolving inflammation, including the combined use of non-surgical mechanical debridement and topical application of antibiotics and/or the use of lasers.

Surgical therapy

A re-examination of peri-implant tissues following initial therapy that reveals absence of bleeding on probing (BoP) and pocket closure indicates resolution of peri-implant lesions. On the other hand, if signs of pathology, that is BoP and/or suppuration in combination with deep pockets, remain at the re-examination, additional therapy is required. Surgical procedures are one treatment option, which provide access to the implant surfaces harboring biofilms. A prerequisite for surgical therapy in treatment of peri-implantitis is appropriate standards of self-performed infection control.

The goal of surgical treatment of peri-implantitis is to acquire access to the implant surface for debridement and decontamination in order to achieve resolution of the inflammatory lesion (Lindhe & Meyle 2008). Surgical therapy of peri-implantitis lesions is shown in Figs. 42-3, 42-4, and 42-5. Clinical signs of inflammation, probing pocket depth (PPD) of about 10 mm in combination with BoP and suppuration were detected at the initial examination (Fig. 42-3). The radiograph revealed the presence of angular bone defects around the two implants. Flap elevation allowed access to the area and inflamed tissue in the defects was removed

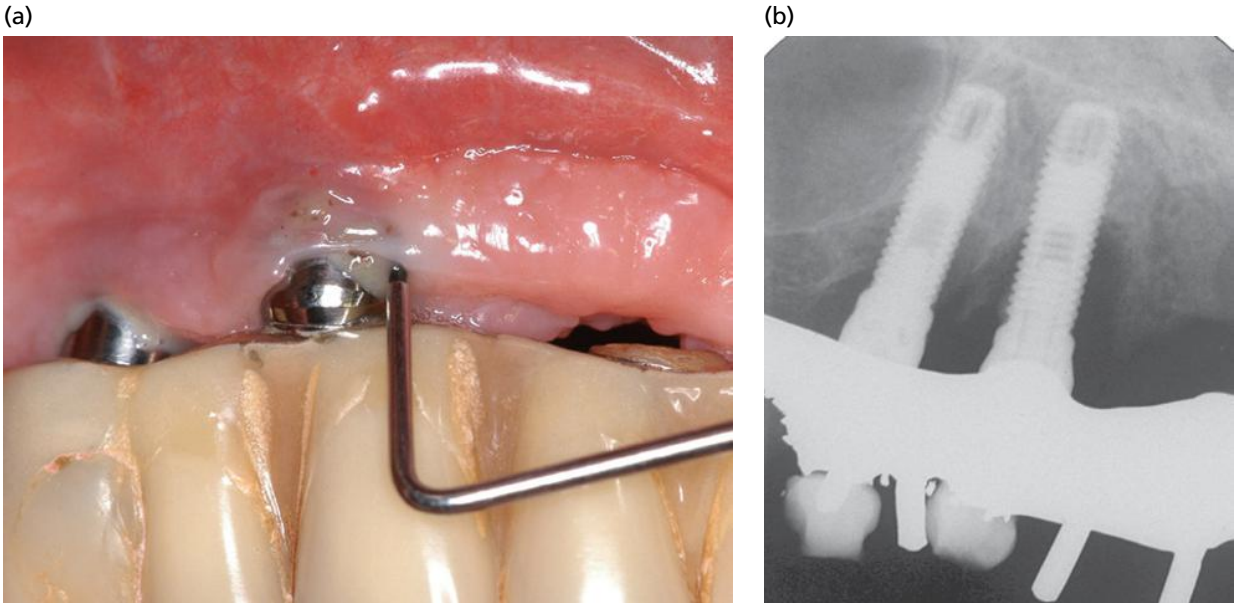

Fig. 42-3 (a) Clinical photograph and (b) radiograph from implant sites with peri-implantitis. Note the probing pocket depth of 10 mm and suppuration (a) and the angular bone defects (b).

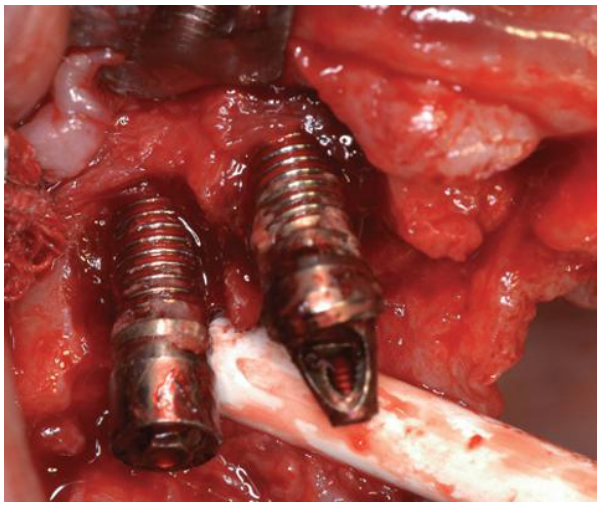

Fig. 42-4 Implant sites shown in Fig. 41-3 after flap elevation and removal of granulation tissue. Note the absence of buccal bone walls of the osseous defects. The implant surfaces are now accessible for mechanical debridement.

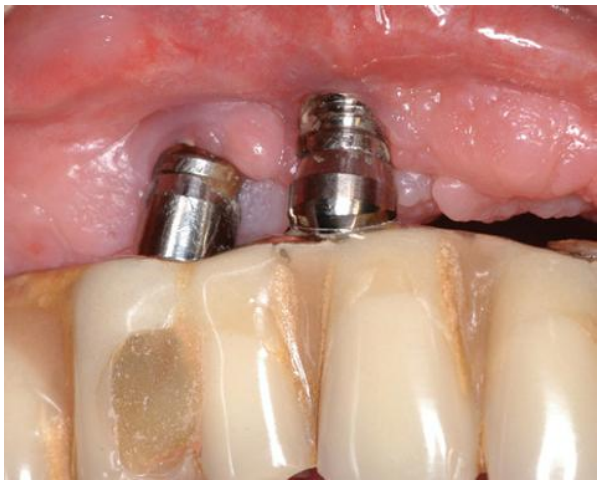

Fig. 42-5 Implant sites shown in Fig. 41-3 at 6 months after surgical therapy. Maintenance therapy with supervised infection control is provided. Note the soft tissue recession following the pocket elimination procedure.

using curettes (Fig. 42-4). Mechanical debridement of the implant surface was performed using carbon-fiber curettes and small pieces of gauze or pellets soaked in saline. The peri-implantitis–associated bone defect may be treated using either resective or reconstructive procedures. In this case, the morphology of the osseous defect was unsuitable for reconstructive techniques and, hence, bone resection was performed to adjust the morphology of the interproximal bone walls. At the 6-month follow-up after surgery, it was observed that PPD was reduced and clinical signs of inflammation were absent (Fig. 42-5).

Most studies on the treatment of peri-implantitis have been carried out using small patient groups and with a considerable variation in case definitions of disease (see Chapter 26). In addition to mechanical debridement, a vast number of different procedures have been proposed, including antiseptic agents and/or systemic antibiotics. Serino and Turri (2011) evaluated results at 2 years after surgical therapy of sites with peri-implantitis in 31 patients. It was reported that pocket elimination combined with bone recontouring was an effective therapy for the majority of patients and implants. The results also indicated that resolution of the disease depended on the amount of bone loss around the implants prior to treatment. In addition, implant sites that resolved following surgical therapy remained healthy during the 2-year period of follow-up, while disease progression occurred at implants that showed lack of disease resolution in the initial phase after treatment. At a 12-month examination following surgical therapy of

peri-implantitis in 24 patients, Heitz-Mayfield *et al.* (2012) reported that a significant reduction of PPD, BoP, and suppuration had occurred. While 47% of the implant sites exhibited complete resolution of disease, 92% of the sites showed stable crestal bone levels or bone gain.

The treatment procedures that were applied in the studies by Serino and Turri (2011) and Heitz-Mayfield *et al.* (2012) included the adjunctive use of systemic antibiotics. Although this approach has been applied in most clinical reports, it is not known if the adjunctive use of systemic antibiotics improves treatment outcome.

Implant surface decontamination

One of the largest challenges in the treatment of peri-implantitis is implant surface decontamination. Figure 42-6 illustrates the complexity of a biofilm residing on implants presenting with peri-implantitis: the high magnification of the micrographs reveals microorganisms of various morphotypes occupying micro-sized compartments of the implant surface. Although complete biofilm removal using a mechanical approach appears to be difficult, results from preclinical and clinical studies demonstrate that resolution of peri-implantitis lesions can indeed occur following implant surface decontamination. In the study by Heitz-Mayfield *et al.* (2012) referred to above, all implants were cleaned during surgery using gauze soaked in saline. Evidence for complete resolution of peri-implantitis lesions following mechanical debridement combined with saline was presented in a preclinical study by Albouy *et al.* (2011). They produced experimental peri-implantitis around different types of implants in dogs according to techniques previously described (Lindhe *et al.* 1992) (see Chapter 26). The surgical therapy was

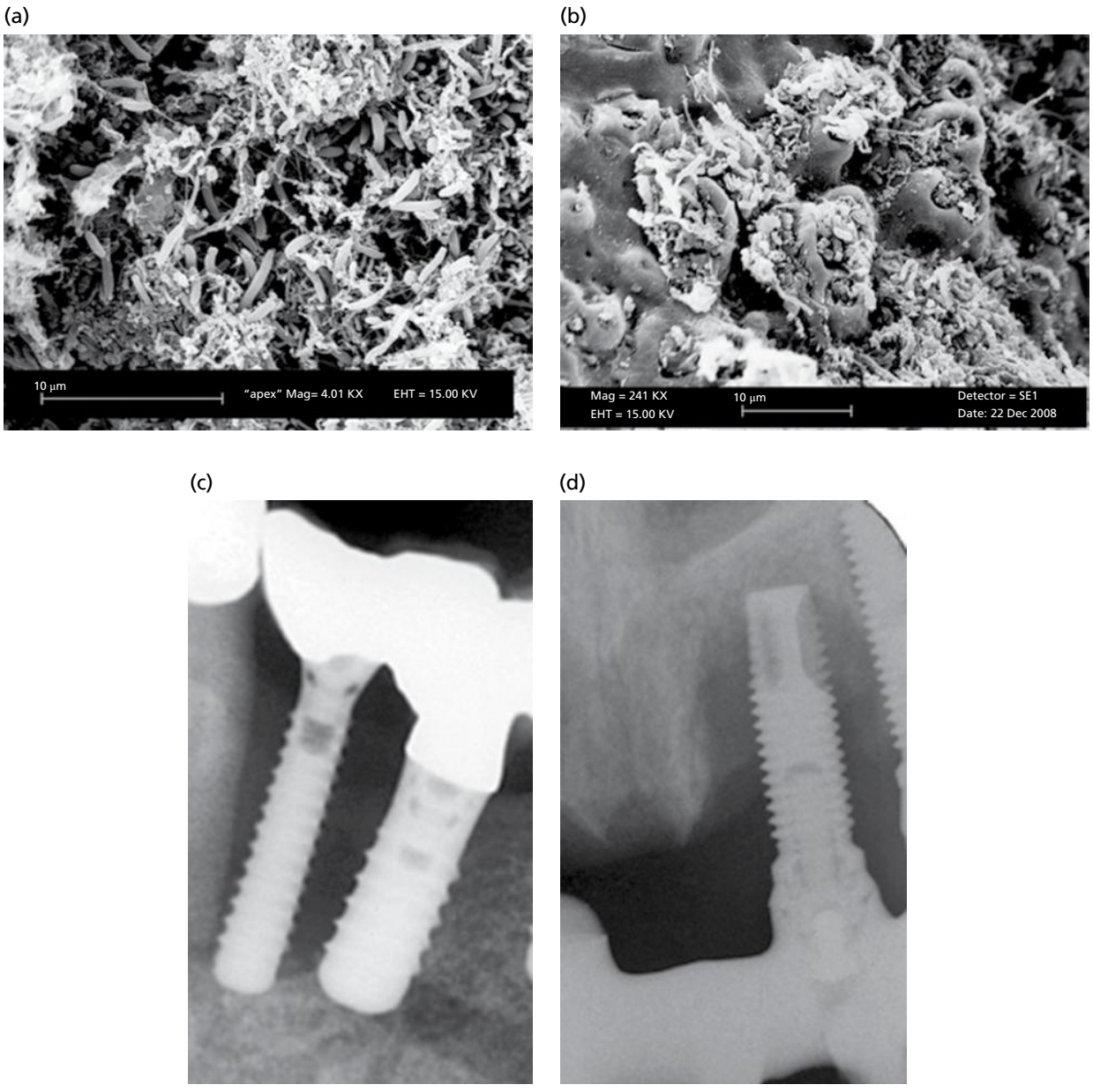

Fig. 42-6 Scanning electron micrographs (a, b) from implants that were surgically removed from sites with severe peri-implantitis (c, d). Note the microorganisms of various morphotypes occupying compartments of the modified implant surfaces (a, b).

carried out without the adjunctive use of systemic antibiotics or local antimicrobial agents. The histologic examination of biopsies obtained at 6 months after surgery revealed complete resolution of the lesions at most implant sites.

Taken together, data from preclinical and clinical research on the treatment of peri-implantitis reveal that the local use of antiseptic agents, air abrasives or lasers for surface decontamination during surgical treatment of peri-implantitis does not enhance treatment outcomes in relation to mechanical debridement combined with topical application of saline.

In the preclinical study by Albouy *et al*. (2011), it was also concluded that the resolution of peri-implantitis lesions was influenced by implant surface characteristics. Thus, the results from the radiologic examination of the experimental sites revealed that, of implants with different types of implant surface modification, those with a turned surface exhibited the largest amount of bone gain following surgery. In addition, the evaluation of the histologic sections disclosed that the peri-implant tissues around the turned implants showed a higher degree of resolution of inflammation than the implants with modified surfaces. Similar observations were made by Roccuzzo *et al*. (2011) in a study of 26 patients with peri-implantitis around implants with either a rough [titanium plasma-sprayed (TPS)] or moderately rough surface [sandblasted large-grit acid-etched (SLA)]. It was reported that reduction of PPD and BoP was more pronounced at the implants with the SLA surface than those with the TPS surface.

Procedures that include more aggressive techniques have also been suggested to achieve implant surface decontamination. Such procedures have included grinding of the implant surface and removing threads from the titanium cylinder together with polishing of rough implant surfaces. Results from one study with a 3-year follow up following surgical therapy indicated some benefit when using such "implant-resective techniques" on TPS surface implants (Romeo *et al*. 2007). In this context, however, the risks involved in implant grinding procedures – potential damage to the peri-implant bone caused by overheating as well as spreading of metal particles – must be considered.

Reconstructive procedures

The bone loss that occurs during progression of peri-implantitis results in osseous defects with varying morphology. As described in Chapter 26, at sites where the width of the ridge exceeds that of the peri-implantitis lesion, a buccal and lingual bone wall may remain and a crater form. Conversely, in sites with a narrow ridge, the buccal and lingual bone walls will be resorbed and lost during progression of peri-implantitis. Thus, sites with peri-implantitis often present with an angular ("one-wall") bone defect on the mesial and distal aspects of the implant only. The potential for a reconstructive approach in such cases is questionable and, hence, hard tissue resection is recommended. On the other hand, at sites with peri-implantitis presenting with circumferential bone craters, a reconstructive approach may be considered. A vast number of procedures have been proposed to promote bone fill of such defects. It is currently not known, however, if the use of bone grafts/substitutes or barrier membranes improves treatment outcome in surgical therapy of peri-implantitis.

Re-osseointegration

Bone fill of osseous defects detected on radiographs following treatment of peri-implantitis indicates that new bone has formed, but this should not be taken to indicate that re-osseointegration has occurred. The term re-osseointegration can be defined as the establishment of *de novo* bone formation and *de novo* osseointegration to a portion of an implant that during the development of peri-implantitis suffered loss of bone–implant contact and became exposed to microbial colonization.

Assessment of bone–implant contact requires histologic examination, which calls for the use of preclinical research models. As described in Chapter 26, experimental peri-implantitis can predictably be produced using well-established techniques and different treatment protocols can be applied accordingly. Persson *et al*. (1999) induced experimental peri-implantitis in dogs according to the model described by Lindhe *et al*. (1992). The subsequent treatment included (1) systemic administration of antibiotics; (2) elevation of full thickness flaps at the experimental sites and curettage of the hard tissue defect; (3) mechanical debridement of the exposed portion of the implants; and (4) flap management and closure of the soft tissue wound. Radiographs and biopsies were obtained after 7 months of submerged healing. The analysis of the radiographs indicated a complete bone fill in the hard tissue defects (Fig. 42-7). Histologic analysis of the biopsy sections revealed that treatment had resulted in a complete resolution of the soft tissue inflammation and the formation of substantial amounts of new bone in the previous hard tissue defects (Fig. 42-8). However, only small amounts of re-osseointegration to the once decontaminated titanium surface could be observed and consistently only at the apical base of the defects. At most sites a thin connective tissue capsule separated the "exposed" implant surface from the newly formed bone (Fig. 42-9). Similar findings were reported by Wetzel *et al*. (1999) from another study in dogs and the use of implants with various surface characteristics (turned, TPS, and SLA surfaces).

Based on the outcome of the above studies, it was concluded that the problem inherent in re-osseointegration appears to be the implant surface rather than the host tissues at the site. The problem regarding the implant surface was addressed in a study in dogs by Persson *et al*. (2001). They evaluated the potential for re-osseointegration to implants designed with either

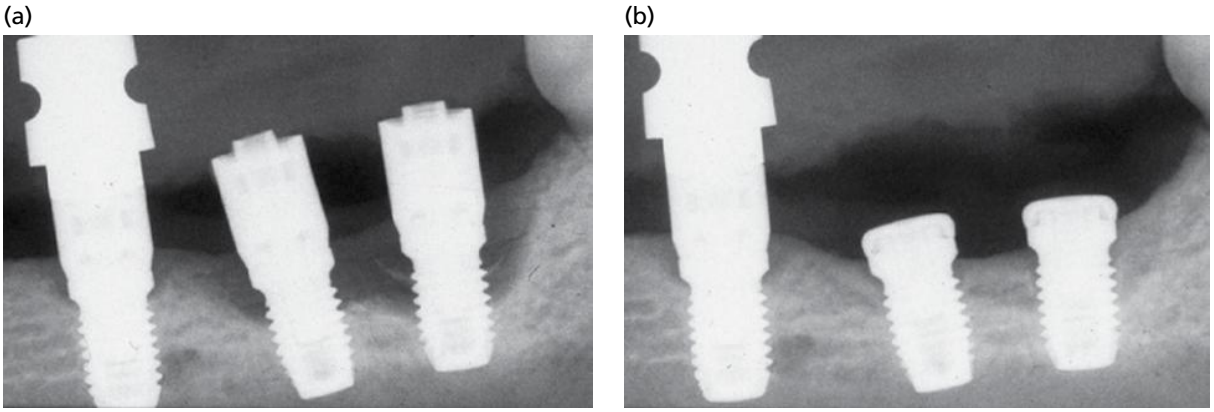

Fig. 42-7 (a) Radiographs obtained from two sites exposed to experimental peri-implantitis. (b) Sites at 7 months of submerged healing after treatment of peri-implantitis. Note the bone fill in the previous osseous defects.

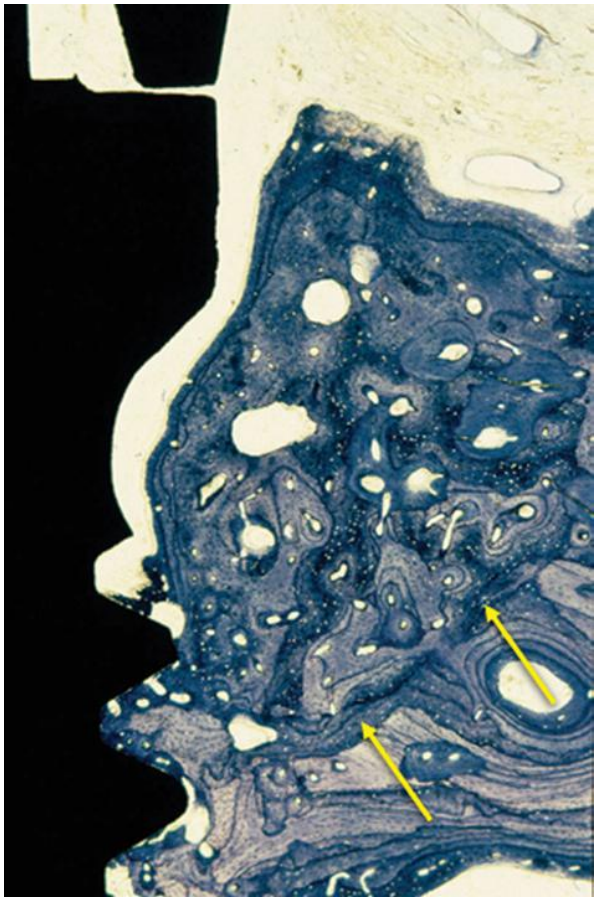

Fig. 42-8 Ground section following 7 months of submerged healing after treatment of peri-implantitis. Note the newly formed bone in the hard tissue defects (arrows).

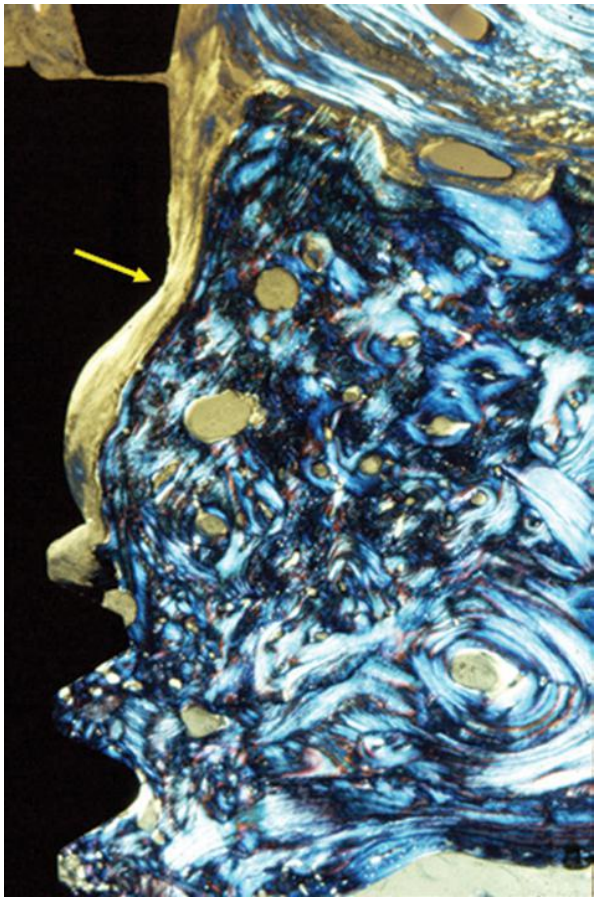

Fig. 42-9 Ground section shown in Fig. 43.8 under polarized light. Note the connective tissue capsule located between the newly formed bone and the implant surface (arrow).

smooth (polished) or roughened (SLA) surfaces. Experimental peri-implantitis was induced and bone loss of about 50% of the peri-implant bone support was produced (Fig. 42-10). Treatment included (1) systemic antibiotics; (2) flap elevation and curettage of the bone defect; and (3) mechanical debridement of the implant surface (gauze soaked in saline). The implants were submerged and biopsies were obtained after 6 months of healing. At all implant sites, most of the crater-like defects had been filled with newly formed bone (Fig. 42-11). However, at sites with smooth surface implants, only small amounts of re-osseointegration had occurred (Fig. 42-12). The examination of the histologic sections from sites with moderately rough surface implants, however, revealed that >80% of the previously exposed rough surface exhibited re-osseointegration (Fig. 42-13).

It may be hypothesized that the surface characteristics (smooth versus rough) of the implant may influence the process of bone healing that eventually may result in re-osseointegration. In this context, it is important to point out that these surface

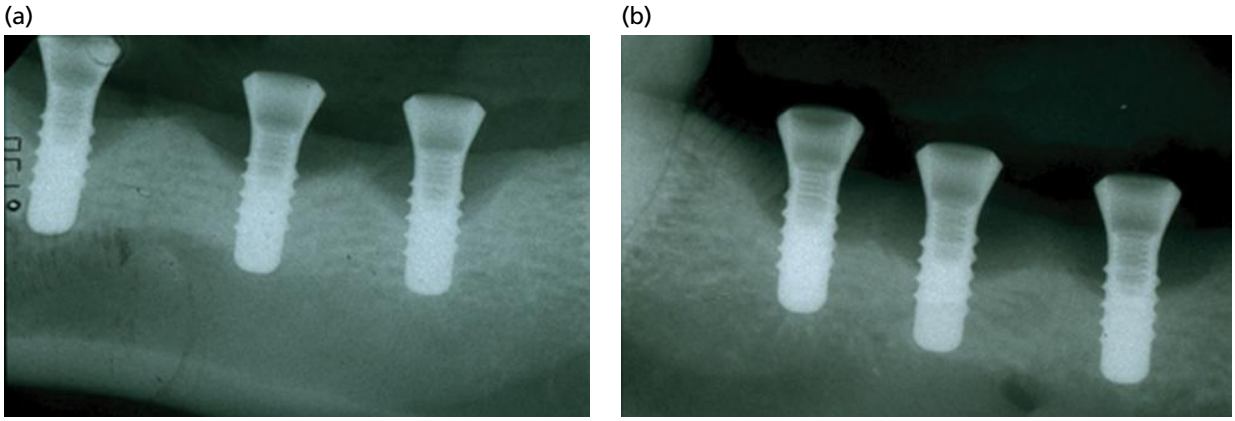

Fig. 42-10 Radiographs showing crater-like bone defects following experimental peri-implantitis at implants with (a) a smooth and (b) a rough surface.

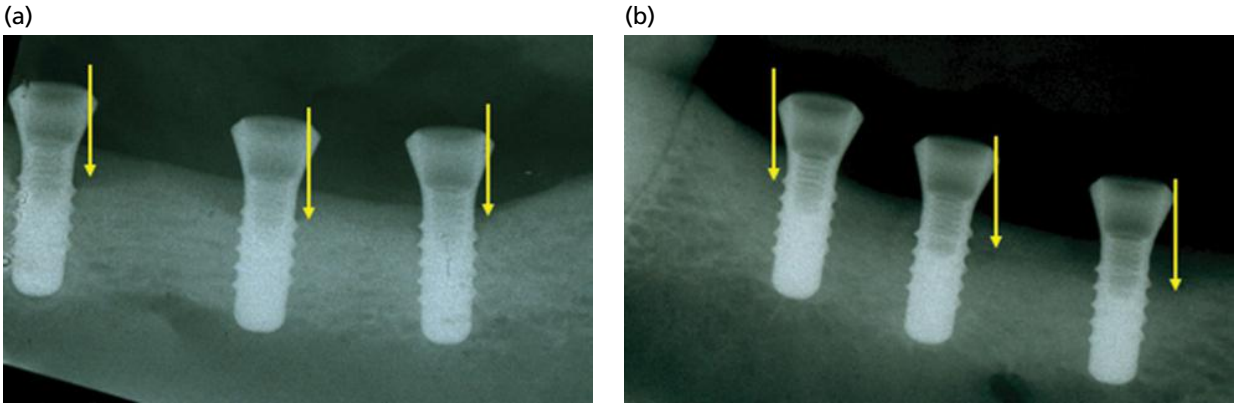

Fig. 42-11 Radiographs showing substantial bone fill (arrows) in bone defects at 6 months of healing after treatment of experimental peri-implantitis at implants with (a) a smooth and (b) a rough surface.

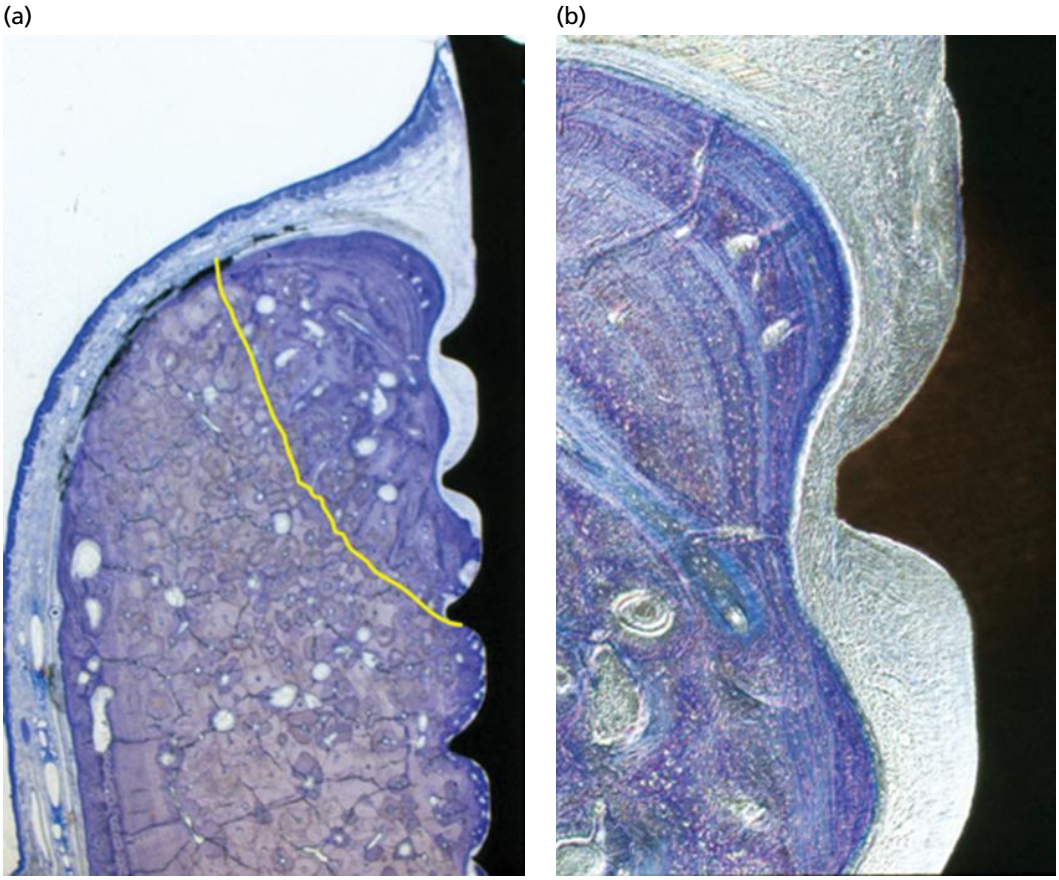

Fig. 42-12 (a) Ground section following 6 months of healing after treatment of peri-implantitis at sites with smooth surface implants. The yellow line indicates the outline of the previous hard tissue defect. (b) Note the connective tissue capsule between the newly formed bone and the implant surface. (Source: Persson et al. 2001, with permission from John Wiley & Sons.)

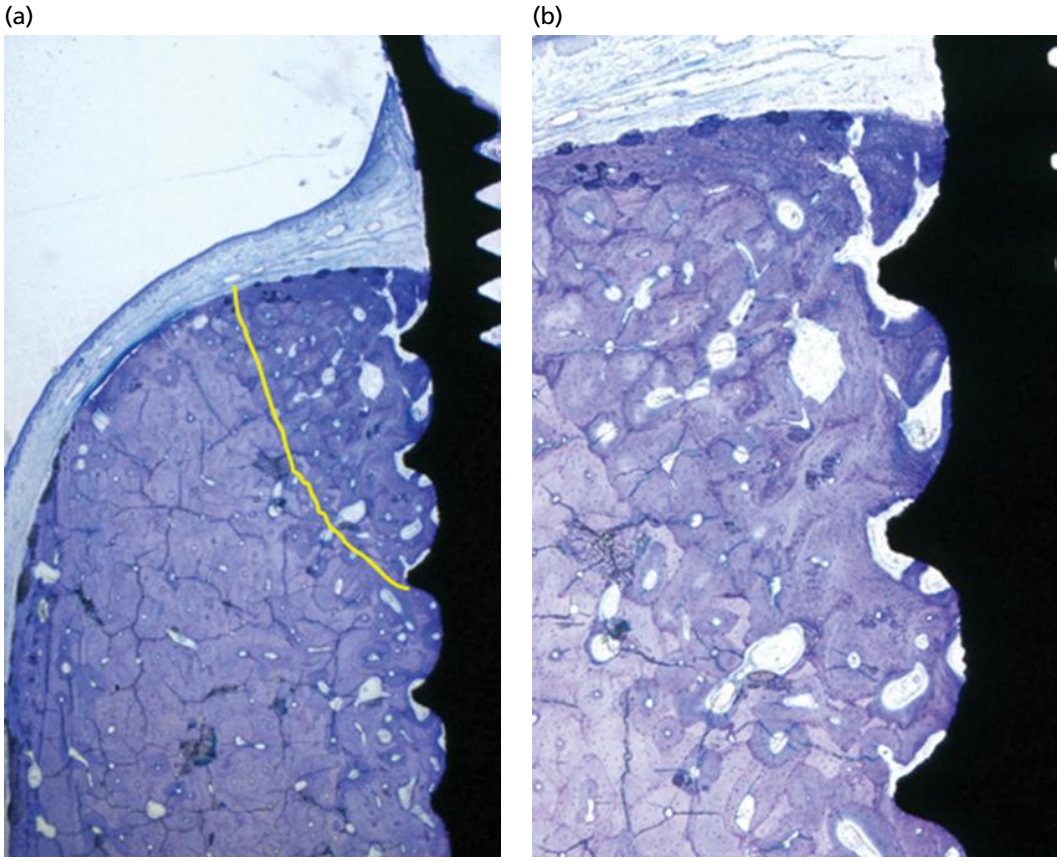

Fig. 42-13 (a) Ground section following 6 months of healing after treatment of peri-implantitis at sites with rough surface implants. The yellow line indicates the outline of the previous hard tissue defect. (b) Note the high degree of re-osseointegration to the previously exposed rough implant surface (b). (Source: Persson *et al.* 2001, with permission from John Wiley & Sons.).

characteristics do influence the risk for progression of peri-implantitis (see Chapter 26). In addition, from the preclinical study by Albouy *et al*. (2011) it was concluded that resolution of the disease was influenced by implant surface characteristics.

Conclusion

Treatment of peri-implant mucositis and peri-implantitis should include anti-infective measures and the evaluation of treatment outcome must include parameters that describe resolution of inflammation and preservation of the supporting bone. Non-surgical therapy with mechanical infection control procedures is effective in resolving peri-implant mucositis and incipient forms of peri-implantitis. In moderate and severe forms of peri-implantitis, however, non-surgical procedures may be insufficient to resolve disease but should always precede surgical therapy to establish appropriate standards of self-performed infection control. Treatment of peri-implantitis is influenced by the surface characteristics of the implant.

There is no evidence that adjunctive systemic antibiotics or local antiseptics, or reconstructive procedures (bone grafts/substitutes, membranes) have additional beneficial effects on treatment outcome of peri-implantitis.

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Chapter 43

Antibiotics in Periodontal Therapy

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Introduction

Antibiotics are drugs that kill or stop the multiplication of bacterial cells at concentrations that are relatively harmless to host tissues, and therefore can be used to treat infections caused by bacteria. The term was originally applied to natural substances produced by certain groups of microorganisms, distinguishing them from other antimicrobial agents that are chemically synthesized. However, some antimicrobial compounds, originally discovered as products of microorganisms, can be synthesized entirely by chemical means. Therefore, in medicine and pharmaceutics, antimicrobial agents used in the treatment of bacterial infections are now generally referred to as antibiotics, interpreting the word literally. Antibiotics are just one group of antimicrobial agents, which also comprise antiviral, antifungal, and antiparasitic chemicals. The capacity of the drug to reach the infected site and the ability of targeted bacteria to resist or deactivate the agent determine the effectiveness of therapy. Based on their effect at concentrations tolerated by the host, antibiotics can be categorized as "bactericidal" or "bacteriostatic", and, depending on the range of susceptible bacteria, "narrow-spectrum" or "wide-spectrum".

In the late 1930s and early 1940s the appearance of powerful agents selectively active against bacteria – sulfonamides, penicillin, and streptomycin – revolutionized the treatment of bacterial infections. The outstanding success of these agents in the treatment of formerly life-threatening diseases led many to believe that bacterial infections would never again be a major medical concern. Seven decades of experience with these and hundreds of additionally developed antimicrobial drugs have shown that, despite their success, this view was too optimistic. Emerging problems resulting from the widespread use of antibiotics have modified the general perception of the capabilities of antimicrobial agents. Many bacteria have developed a significant capacity to resist or repel antibiotic agents. It has been noted that antibiotics may disturb the delicate ecologic equilibrium of

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the body, allowing the proliferation of non-bacterial microorganisms and resistant strains. Sometimes this may initiate new infections that are worse than the ones originally treated. Antimicrobial agents may have other unwanted properties, such as toxicity, that need to be considered as well.

The purpose of this chapter is to discuss the utility of systemic and locally applied antimicrobials in periodontal therapy. Given the limitations of mechanical treatment, the use antibacterial agents may enhance the effect of therapy. Potential benefits must be balanced against the risks of unwanted effects.

Principles of antibiotic use in periodontics

Is periodontitis an infection and should it be treated as one?

The recognition of periodontitis as an infection caused or sustained by living bacteria that are present at diseased sites is fundamental for any antimicrobial treatment concept. Antibiotics can kill or suppress living bacteria but they cannot remove calculus and bacterial residues, which is traditionally perceived to be an essential part of periodontal therapy.

The continued presence of large masses of bacteria on hard oral surfaces induces inflammation in adjacent soft tissues such as gingiva or mucosa. The importance of removing bacterial deposits for resolution of gingivitis or peri-implant mucositis is therefore undisputed. The propensity of sites to undergo further periodontal destruction is felt to be more specific in nature, since not all sites with gingivitis invariably progress to periodontitis and since increased proportions and detection frequencies of suspected oral pathogens are found in periodontitis lesions. Still, thorough mechanical cleaning of the root surfaces to remove bacterial deposits has proven to be beneficial for all cases of periodontitis, irrespective of type or clinical circumstances. Furthermore, it has been shown that efficient self-performed mechanical oral hygiene to prevent the re-establishment of bacterial deposits is essential for long-term stability (for review see Chapter 60). Nevertheless, this way of treating periodontal disease is time consuming, requires high levels of motivation and manual skills – of both the clinician and the patient – and can induce tissue damage. It would be irrational to believe that mechanical instruments alone are able to completely remove periodontal pathogens from all infected sites (Mombelli *et al*. 2000). Bacteria may be inaccessible to mechanical instruments in concavities, lacunae, and dentin tubules, not to mention invaded soft tissues. Substantial hard tissue trauma can arise from repeated instrumentation attempts in locally unresponsive sites, or sites with recurrent disease. In addition, successfully treated sites may be recolonized by pathogens persisting in non-dental areas.

Specific characteristics of the periodontal infection

Two specific features of periodontal infection are of uppermost importance in relation to the use of antimicrobials.

First, the term infection usually refers to tissue invasion and multiplication of pathogenic microorganisms in tissues. The uniqueness of biofilm-associated dental diseases as infections however relates to the lack of massive bacterial tissues invasion. Although there is confirmation of bacterial penetration in highly active conditions such as periodontal abscesses and necrotizing periodontal diseases (Listgarten 1965; Saglie *et al*. 1982a, b; Allenspach-Petrzilka & Guggenheim 1983; Carranza *et al*. 1983), invasion and multiplication of bacteria within periodontal tissues is not considered to be indispensable for developing disease. Evidently, microorganisms present in subgingival deposits can harm these tissues also without penetrating them. It follows that in order to be effective, antimicrobial agents used in the context of periodontal therapy need to be available at a sufficiently high concentration not only inside but also outside of the affected tissues (Fig. 43-1). In the periodontal pocket environment these agents may be inhibited, inactivated or degraded by the large masses of microorganisms present. Therapeutic concentrations may be difficult to achieve everywhere, and antibiotic resistance is bound to occur first where the penetration of the agent is restricted.

Second, the subgingival microbiota accumulate on the root surface to form an adherent layer of plaque called "biofilm". Comprehensive review papers highlight the importance of biofilm formation in the etiology of many infections and point to the consequences of this for therapy in a broader perspective (Socransky & Haffajee 2002; Costerton 2005; Costerton *et al*. 2005; Marsh 2005; Davey & Costerton 2006,). Dental biofilms have most of the features of other currently known biofilms, with antimicrobial resistance being of special relevance (Marsh 2004; Marsh *et al*. 2011). Periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* (formerly known as *Actinobacillus actinomycetemcomitans*) (Norskov-Lauritsen & Kilian 2006) and *Porphyromonas gingivalis* show higher levels of tolerance to several antimicrobial agents when embedded in biofilms than as planktonic cells (Larsen 2002; Noiri *et al*. 2003; Eick *et al*. 2004; Takahashi *et al*. 2007). Furthermore, within biofilms resistant microorganisms of low intrinsic virulence can protect antibiotic-sensitive pathogens (O'Connell *et al*. 2006).

The mechanisms increasing the antimicrobial resistance of microorganisms in biofilms differ between bacterial species and depend on the composition and the ecologic conditions within a biofilm. These include the protection by extracellular polymeric substances, leading to failure of the antimicrobial agent to penetrate the biofilm, and the adoption

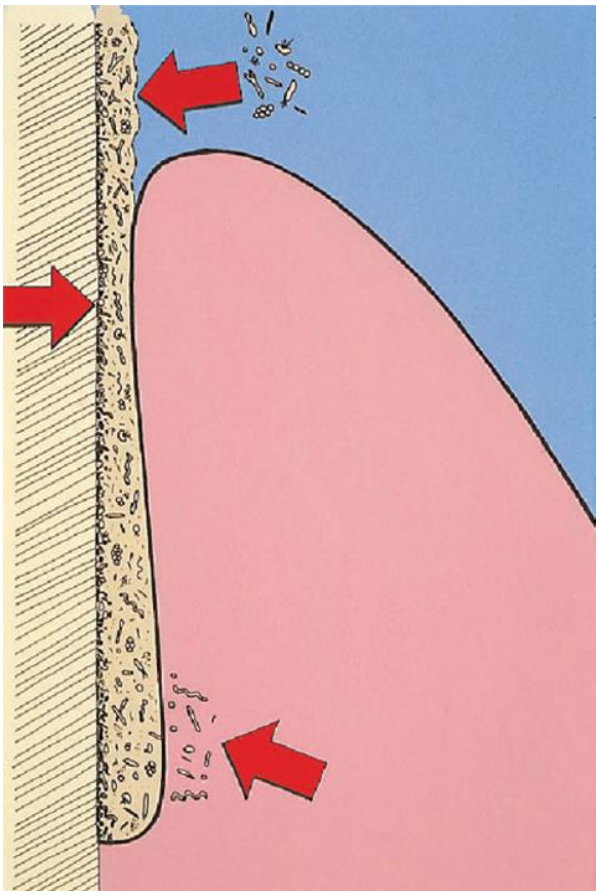

Fig. 43-1 Specific conditions for the use of antimicrobial agents in periodontal therapy: periodontal pocket as an open site is subject to recolonization after therapy (top arrow); subgingival bacteria are protected from antimicrobial agents in a biofilm (middle arrow); agent must be available at a sufficiently high concentration not only within the periodontal tissues, but also in the subgingival environment outside the periodontal tissues (bottom arrow).

of a resistant physiologic state or phenotype related to the multicellular nature of the biofilm community. Biofilms play an important role in the spread of antibiotic resistance. Within the dense bacterial population, efficient horizontal transfer of resistance and virulence genes takes place.

In recognition of these phenomena, there is general consensus that periodontal diseases should not be treated with antimicrobial agents alone (Herrera *et al*. 2008; Sanz & Teughels 2008). Thorough mechanical debridement must always be performed to disrupt the structured aggregates protecting embedded bacteria and to markedly reduce the microbial mass that may inhibit or degrade the antimicrobial agent.

Should antimicrobial therapy be aimed at specific pathogens?

A closer look at the composition of the subgingival microbiota reveals that periodontal treatment is targeted at a variable mixture of different bacteria (Kroes *et al*. 1999; Paster et al. 2001). The number of different species and subspecies occasionally identified in samples from human dental biofilms far exceeds 100, but only relatively few show a distinctive pattern of association with disease. While most of these organisms are thought to significantly harm tissues only if present in high numbers over prolonged periods, certain species may have a negative effect when present in relatively low numbers in susceptible individuals. On the basis of their pathogenicity, demonstrated in animal experiments, and the identification of virulence factors, a limited number of organisms have been suggested as specific periodontal pathogens (for review see Chapter 8). *A. actinomycetemcomitans* and *P. gingivalis* have attracted particular attention because longitudinal and retrospective studies indicated an increased risk for periodontal breakdown in positive sites and because results of treatment were better if these organisms could no longer be detected at follow-up (Haffajee et al. 1991; Grossi *et al*. 1994; Haffajee & Socransky 1994; Dahlén *et al*. 1996; Rams *et al*. 1996; Bragd *et al*. 1987; Wennström *et al*. 1987; Carlos *et al*. 1988; Chaves *et al*. 2000). *A. actinomycetemcomitans* displays a broad genetic and phenotypic diversity and is heterogeneously distributed in various populations and cohorts worldwide (Kilian *et al*. 2006). In one large prospective study (Haubek *et al*. 2008), only one subpopulation of *A. actinomycetemcomitans*, the "JP2 clone" (Tsai *et al*. 1984), showed the properties of a true pathogen. There is an ongoing debate on the utility of microbiologic tests to identify such organisms in order to optimize periodontal therapy. As will be discussed further in the section on Systemic antibiotics, recent studies show clinical benefits of therapies supposedly targeting such organisms even in their absence.

Narrow-spectrum antibiotics, such as metronidazole, have been proposed for periodontal therapy in *A. actinomycetemcomitans*-negative patients based on the hypothesis that beneficial bacteria, which are intrinsically resistant to metronidazole, could suppress the re-emergence of anaerobic pathogens such as *P. gingivalis*. This theory has not been proven by clinical trials. Given the large diversity of the microbiota associated with all forms of periodontitis, and the complex synergistic and antagonistic interactions between the members of this flora, the concept of specifically identifying and eradicating a particular pathogen may be illusionary (Cionca *et al*. 2010), although the results of previous trials may suggest the opposite (Pavicic *et al*. 1994). In most trials showing beneficial effects of antimicrobials, neither the agents nor the subjects have in fact been selected based on microbiologic testing. This does not exclude the possibility that in some cases virulent organisms may be present that are resistant to a tested drug.

Drug delivery routes

By mouth (*per os*, p.o.) is the most common route for delivering antibiotics in the treatment of bacterial infections. Administration by means other than through the alimentary tract (by intramuscular or

Table 43-1 Comparison of local and systemic antimicrobial therapy.

Issue	Systemic administration	Local administration
Drug distribution	Wide	Narrow effective range
Drug concentration	Variable levels in different body compartments	High dose at treated site, low levels elsewhere
Therapeutic potential	May reach widely distributed microorganisms better	May act better locally on biofilm-associated bacteria
Problems	Systemic side effects	Re-infection from non-treated sites
Clinical limitations	Requires good patient compliance	Requires infection to be limited to the treated site
Diagnostic problems	Identification of pathogens, choice of drug	Distribution pattern of lesions and pathogens, identification of sites to be treated

intravenous injection) is usually reserved for serious medical conditions where the oral route has proven ineffective. Some local infections can be treated with topically administered antimicrobials, such as with eye drops or ointments. In the therapy of periodontal diseases, antimicrobials may be delivered via the systemic route or by direct placement into the periodontal pocket. Each method of delivery has specific advantages and disadvantages (Table 43-1).

Local therapy may allow the application of antimicrobial agents at levels that cannot be reached by the systemic route and may be suitable for agents, for example antiseptics, that are too toxic to be delivered by the systemic route. This form of application seems to be particularly promising if the target organisms are confined to the clinically visible lesions.

Systemic administration of antibiotics may be better if the target bacteria are distributed more widely. Studies have shown that periodontal bacteria may in fact be distributed throughout the whole mouth in some patients (Mombelli *et al*. 1991a, 1994), including in non-dental sites such as the dorsum of the tongue or tonsillary crypts (Zambon *et al*. 1981; Müller *et al*. 1993; Pavicic *et al*. 1994; Müller *et al*. 1995; van Winkelhoff *et al*. 1988). Disadvantages of systemic antibiotic therapy relate to the fact that the drug is diluted by dispersal through the whole body, and only a small portion of the total dose actually reaches the subgingival microbiota in the periodontal pocket.

Adverse drug reactions are a greater concern and more likely to occur if drugs are distributed via the systemic route. Even mild forms of unwanted effects may severely decrease patient compliance (Loesche *et al*. 1993). Local delivery is independent of patient compliance.

Methods suggested for local drug application in periodontal pockets range from simple irrigation, or placement of drug-containing ointments and gels, to sophisticated techniques involving devices for sustained release of antibacterial agents. In order to be effective, the drug should reach the entire area affected by the disease, especially the base of the pocket, and should remain there at a sufficiently high concentration for a specific period of time. With mouth rinse or supragingival irrigation, it is not possible to predictably deliver an agent to the deeper parts of a periodontal defect (Pitcher *et al*. 1980; Eakle *et al*. 1986). The gingival crevicular fluid (GCF) rapidly washes out agents brought into periodontal pockets by subgingival irrigation. Based on an assumed pocket volume of 0.5 mL and a GCF flow rate of 20 µL/h, Goodson (1989) estimated that the half-time of a non-binding drug placed into a pocket is about 1 minute. Even a highly concentrated, highly potent agent would thus be diluted below a minimum inhibitory concentration (MIC) for oral microorganisms within minutes. If an agent can bind to surfaces and be released in an active form, a prolonged time of antibacterial activity could be expected. Such an effect has in fact been noted for salivary concentrations of chlorhexidine after use of a chlorhexidine mouth rinse (Bonesvoll & Gjermo 1978). Although there are indications that this may also occur to a certain extent within the periodontal pocket, for instance after prolonged subgingival irrigation with tetracycline (Tonetti *et al*. 1990), the potential to create a drug reservoir of significant size on the small surface area available in a periodontal pocket is limited. To maintain a high concentration over a prolonged period, the flushing action of the GCF flow has to be counteracted by a steady release of the drug from a larger reservoir. Considering the small volume of a periodontal pocket and the pressure exerted by the tonus of the periodontal tissues on anything that is inserted, it appears unlikely that this can be achieved by a carrier that does not maintain its physical stability for some time and that cannot be secured against premature loss. Gels, for instance, rapidly disappear after instillation into periodontal pockets (Fig. 43-2), unless their viscosity changes immediately after placement (Oostervaal *et al*. 1990; Stoltze 1995). Viscous and/or biodegradable devices show an exponential decrease in concentration in gingival fluid. In order to have sustained control over drug release, it is necessary to have a matrix that is stable for longer than the drug load. Controlled delivery of an antimicrobial agent over several days has been shown for tetracycline released from non-degradable monolithic ethylene vinyl acetate fibers (Fig. 43-3).

Systemic antibiotics

Only a limited number of the large range of antimicrobial agents has been tested thoroughly for use in periodontal therapy. The drugs most extensively investigated for systemic use include tetracycline, minocycline and doxycycline, clindamycin, ampicillin, amoxicillin (with or without clavulanic acid), macrolides such as

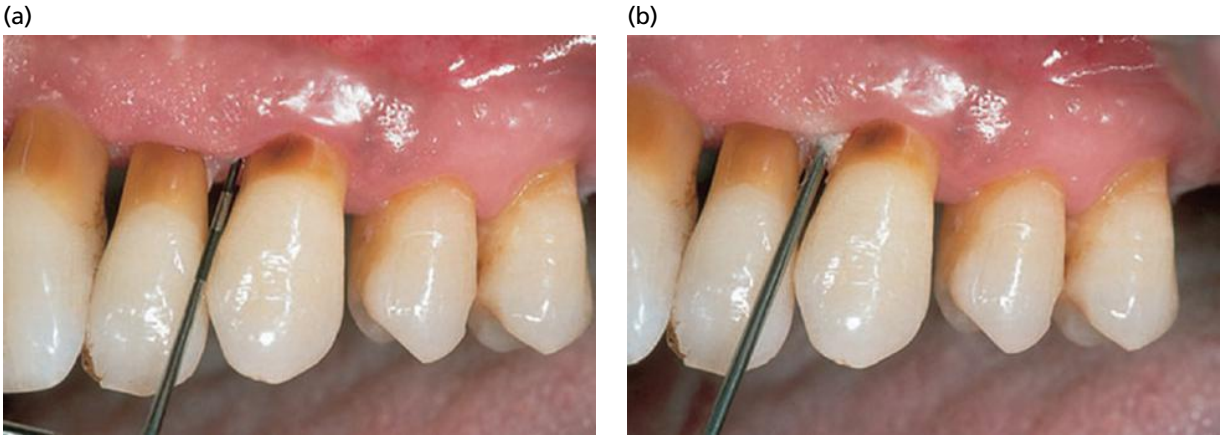

Fig. 43-2 (a) Antimicrobial gel is applied with a syringe inserted into a residual pocket (a). For retention of the agent in the site, the viscosity of the carrier should change immediately. A large portion of the product may otherwise be expelled from the pocket quickly (b).

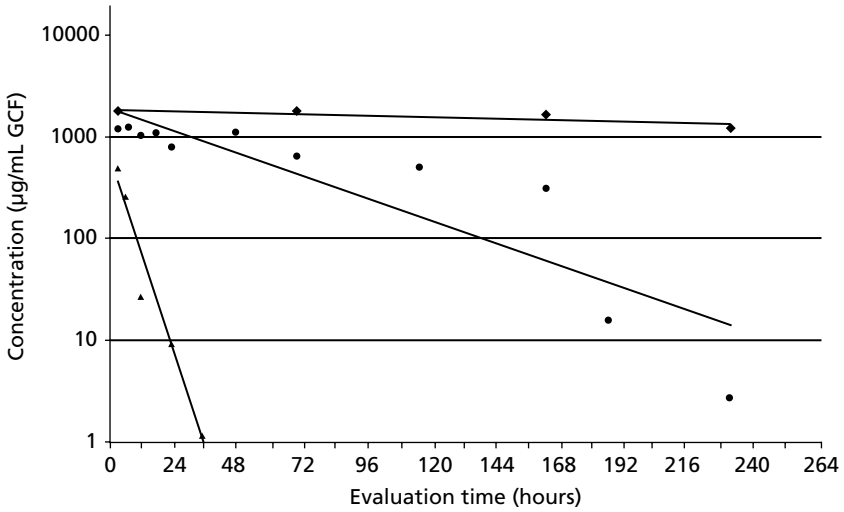

Fig. 43-3 Mean concentration of tetracycline (♦) in gingival crevicular fluid (GCF) during tetracycline fiber treatment (Tonetti *et al*. 1990), of doxycycline hyclate (●) after application in a biodegradable polymer (Stoller *et al*. 1998), and of metronidazole (▲) after application of 25% metronidazole dental gel (Stoltze 1992).

erythromycin, spiramycin, azithromycin and clarithromycin, and the nitro-imidazole compounds metronidazole and ornidazole, and certain combinations thereof.

The first antibiotics used in periodontal therapy were mainly systemically administered *penicillins*. The choice was initially exclusively based on empirical evidence. Penicillins and cephalosporins act by inhibition of cell wall synthesis. They have a narrow spectrum of activity and are bactericidal. Among the penicillins, amoxicillin has been favored for treatment of periodontal disease because of its considerable activity against several periodontal pathogens at levels achievable in gingival fluid. The molecular structure of penicillins includes a β-lactam ring that may be cleaved by bacterial enzymes. Some bacterial β-lactamases have a high affinity for clavulanic acid, a β-lactam molecule without antimicrobial activity. To inhibit bacterial β-lactamase activity, clavulanic acid has been added successfully to amoxicillin. This combination (Augmentin®) has been tested for periodontal therapy in clinical studies.

Tetracycline–HCl became popular in the 1970s due to its broad-spectrum antimicrobial activity and low toxicity. The tetracyclines, clindamycin, and macrolides are inhibitors of protein synthesis. They have a broad spectrum of activity and are bacteriostatic. In addition to their antimicrobial effect, tetracyclines are capable of inhibiting collagenase (Golub *et al*. 1985). This inhibition may interfere with tissue breakdown in periodontal disease. Furthermore, they bind to tooth surfaces, from where they may be released slowly over time (Stabholz *et al*. 1993).

The *nitro-imidazoles* were introduced into the periodontal field in 1962 when *The Lancet* published the report of a female patient, who after a week of treatment for trichomonal vaginitis with metronidazole declared she had undergone "a double cure". The vaginitis was cured and the "acute marginal gingivitis" she was also suffering from was relieved (Shinn 1962). The nitro-imidazoles (metronidazole and ornidazole) and the quinolone antibiotics (e.g. ciprofloxacin) act by inhibiting DNA synthesis. Metronidazole is known to convert into several short-lived intermediates after diffusion into an anaerobic organism. These products react with the DNA and other bacterial macromolecules, resulting in cell

Table 43-2 Characteristics of antimicrobial agents used in the treatment of periodontal disease.

Antibiotic	Dose (mg)	Serum concentration (μg/mL)	Crevicular fluid concentration (μg/mL)	t_{max} serum (h)	Half-life (h)
Penicillin	500	3	ND	1	0.5
Amoxicillin	500	8	3–4	1.5–2	0.8–2
Doxycycline	200	2–3	2–8	2	12–22
Tetracycline	500	3–4	5–12	2–3	2–3
Clindamycin	150	2–3	1–2	1	2–4
Metronidazole	500	6–12	8–10	1–2	6–12
Ciprofloxacin	500	1.9–2.9	ND	1–2	3–6

t_{max}, hours to reach peak serum concentration; ND, not determined.
Data from Lorian (1986) and Slots & Rams (1990).

death. The process involves reductive pathways characteristic of strictly anaerobic bacteria and protozoa, but not aerobic or microaerophilic organisms. Thus, metronidazole is active specifically against the obligately anaerobic part of the oral flora, including *P. gingivalis* and other black-pigmenting Gram-negative organisms, but not *A. actinomycetemcomitans*, the latter being a facultative anaerobe.

The concentrations following systemic administration of the most common antimicrobial agents used in the treatment of periodontal disease are listed in Table 43-2. The *in vitro* susceptibility of *A. actinomycetemcomitans* to selected antimicrobial agents is given in Table 43-3 and of *P. gingivalis* in Table 43-4. The data given in these tables may serve as a base for the choice of an appropriate agent. However, it is important to remember that *in vitro* tests do not reflect the true conditions found in periodontal pockets. In particular, they do not account for the biofilm effect. In addition, MIC values depend on technical details that may vary between laboratories. As a consequence, demonstration of *in vitro* susceptibility is no proof that an agent will be effective in the treatment of periodontal disease.

Combination antimicrobial drug therapy

Since the subgingival microbiota in periodontitis often harbors several putative periodontopathic species with different antimicrobial susceptibility, combination antimicrobial drug therapy with a wider spectrum of activity than a single agent may be useful. Overlaps in the antimicrobial spectrums of different agents may reduce the possible development of bacterial resistance. Some combinations of drugs have a synergistic action against target organisms, allowing lower doses of the single agents to be used. A synergistic effect against *A. actinomycetemcomitans* has been noted *in vitro* between metronidazole and its hydroxy metabolite (Jousimies-Somer *et al*. 1988; Pavicic *et al*. 1991) and between these two compounds and amoxicillin (Pavicic *et al*. 1992). Some drugs, however, may interact antagonistically. For instance, bacteriostatic agents such as

Table 43-3 Susceptibility of *Aggregatibacter actinomycetemcomitans* to selected antimicrobial agents.

Antibiotic	MIC90 (μg/mL)	Reference
Penicillin	4.0	Pajukanta *et al*. (1993b)
	1.0	Walker *et al*. (1985)
	6.25	Höffler *et al*.(1980)
Amoxicillin	1.0	Pajukanta *et al*. (1993b)
	2.0	Walker *et al*. (1985)
	1.6	Höffler *et al*. (1980)
Tetracycline	0.5	Pajukanta *et al*. (1993b)
	8.0	Walker (1992), Walker *et al*. (1985)
Doxycycline	1.0	Pajukanta *et al*. (1993b)
	3.1	Höffler *et al*. (1980)
Metronidazole	32	Pajukanta *et al*. (1993b)
	32	Jousimies-Somer *et al*. (1988)
	12.5	Höffler (1980)

MIC90, minimal inhibitory concentration for 90% of the strains.
Adapted from Mombelli & van Winkelhoff (1997) from Quintessence Pub. Co.

Table 43-4 Susceptibility of *P. gingivalis* to selected antimicrobial agents.

Antibiotic	MIC90 (μg/mL)	Reference
Penicillin	0.016	Pajukanta *et al*. (1993a)
	0.29	Baker *et al*. (1983)
Amoxicillin	0.023	Pajukanta *et al*. (1993a)
	<1.0	Walker (1992)
Doxycycline	0.047	Pajukanta *et al*. (1993a)
Metronidazole	0.023	Pajukanta *et al*. (1993a)
	2.1	Baker *et al*. (1983)
	2.0	Walker (1992)
Clindamycin	0.016	Pajukanta *et al*. (1993a)
	<1.0	Walker (1992)

MIC90, minimal inhibitory concentration for 90% of the strains.
Adapted from Mombelli & van Winkelhoff (1997) from Quintessence Pub. Co.

tetracyclines, which suppress cell division, may decrease the antimicrobial effect of bactericidal antibiotics such as β-lactam drugs or metronidazole, which act during bacterial cell division. Combination drug therapy may also lead to increased adverse reactions.

Adverse reactions

Table 43-5 lists common adverse reactions to systemic antibiotic therapy (for a detailed overview, see Hersh & Moore 2008). The *penicillins* are among the least toxic antibiotics. Hypersensitivity reactions are by far the most important and most common adverse effects of these drugs. Most reactions are mild and limited to a rash or skin lesion in the head or neck region. More severe reactions may induce swelling and tenderness of joints. In highly sensitized patients, a life-threatening anaphylactic reaction may develop. The systemic use of *tetracyclines* may lead to epigastric pain, vomiting or diarrhea. Tetracyclines can induce changes in the intestinal flora, and superinfections with non-bacterial microorganisms (e.g. *Candida albicans*) may emerge. Tetracyclines are deposited in calcifying areas of teeth and bones where they cause yellow discoloration. Systemic administration of *clindamycin* may be accompanied by gastrointestinal disturbances, leading to diarrhea or cramps, and may cause mild skin rashes. The suppression of the normal intestinal flora increases the risk for colonization of *Clostridium difficile*, which may cause a severe colon infection (antibiotic-associated colitis). Although not related to *C. difficile*, gastrointestinal problems are also the most frequent adverse event of systemic *metronidazole* therapy. Nausea, headache, anorexia, and vomiting may be experienced. Symptoms may be more pronounced with alcohol consumption (disulfiram or antabuse-like effect), because imidazoles inhibit the enzyme acetaldehyde dehydrogenase in the ethanol degradation pathway, resulting in an accumulation of acetaldehyde. Alcohol consumption should therefore be avoided during and immediately after therapy. As cases of permanent peripheral neuropathies (numbness or paresthesia) have been reported, patients should be advised to stop therapy immediately if such symptoms occur. Metronidazole has shown evidence of carcinogenic activity in studies involving chronic oral administration in mice and rats, but not in other tested species. Due to inadequate evidence, metronidazole is not considered a risk factor for cancer in humans (Bendesky *et al*. 2002). Previously unrecognized candidiasis may show more prominent symptoms during antibiotic therapy.

Table 43-5 Adverse effects of antibiotics used in the treatment of periodontal diseases.

Antibiotic	Frequent effects	Infrequent effects
Penicillins	Hypersensitivity (mainly rashes), nausea, diarrhea	Hematologic toxicity, encephalopathy, pseudomembranous colitis (ampicillin)
Tetracyclines	Gastrointestinal intolerance, candidiasis, dental staining and hypoplasia in childhood, nausea, diarrhea, interaction with oral contraceptives	Photosensitivity, nephrotoxicity, intracranial hypertension
Metronidazole	Gastrointestinal intolerance, nausea, antabuse effect, diarrhea, unpleasant metallic taste	Peripheral neuropathy, furred tongue
Clindamycin	Rashes, nausea, diarrhea	Pseudomembranous colitis, hepatitis

Systemic antimicrobial therapy in clinical trials

Although clinical efficacy is not an absolute proof for bacteriologic efficacy (Marchant *et al*. 1992), evidence advocating the use of systemic antibiotics must come from clinical trials in humans with periodontitis. A large number of reports suggesting beneficial effects in various clinical situations have been published. However, many of these have a high risk of bias due to low scores in quality criteria. Studies may be difficult to interpret and compare due to an unclear patient status at baseline (treatment history, disease activity, composition of subgingival microbiota), insufficient or non-standardized maintenance after therapy, short observation periods, or lack of randomization and controls. Studies not only vary with regard to the treatment provided, but also in the selection of subjects, sample size, range of study parameters, outcome variables, duration, and the controls to which the test procedure is compared. In most trials, systemic antibiotics have been used as an adjunct to scaling and root planing (SRP). Typically, the effect of mechanical therapy plus the antimicrobial agent has been compared to mechanical treatment alone or placebo. In studies evaluating the effect of antimicrobial therapy in patients with refractory periodontitis or with recurrent abscess formation, a placebo control is often lacking for ethical reasons.

A decade ago, in the context of consensus conferences issuing recommendations for periodontal care, the benefit of adjunctive systemically administered antibiotics was assessed for the first time in two systematic reviews. Herrera *et al*. (2002) included 25 controlled clinical trials of at least 6 months' duration in which systemically healthy subjects with chronic or aggressive forms of periodontitis were treated with or without adjunctive systemic antibiotics. On the whole, patients treated with antibiotics showed better results than patients not receiving antibiotics. In deep pockets, a specific benefit in terms of change of periodontal clinical attachment level (CAL) was found for the combination of amoxicillin plus metronidazole, as was true for spiramycin with regards to

changes in probing pocket depth (PPD). Results with metronidazole alone showed a tendency to statistical significance. Haffajee *et al*. (2003) included 27 controlled clinical trials with a follow-up of >1 month and using mean CAL change as the primary outcome. Within a broad range of therapeutic protocols, metronidazole, alone or in combination with amoxicillin, was the most frequently used drug. In all studies, the antibiotic groups showed significantly better mean CAL changes than the control groups. Trials allowing a more detailed analysis indicated antibiotics to have the greatest effect in sites with deep pockets (Lindhe *et al*. 1983a, b; Palmer *et al*. 1996, 1998; Winkel *et al*. 1999; Ramberg *et al*. 2001; Winkel *et al*. 2001; Rooney *et al*. 2002). Specifically, useful antibiotic regimens for distinct clinical or microbiologic conditions could, however, not be identified based on the evidence available at that time. Definite conclusions could also not be made concerning the optimal dosage and duration of antibiotic therapy.

Further well-designed trials have been conducted since that substantiate the benefit of adjunctive antibiotics and provide further information. Twenty-three more recent articles, concerning 18 randomized clinical trials, consistently corroborate the specific benefit of supplementing SRP with amoxicillin plus metronidazole (Ehmke *et al*. 2003, 2005; Guerrero *et al*. 2005; Mombelli *et al*. 2005; Giannopoulou *et al*. 2006; Xajigeorgiou *et al*. 2006; Guerrero *et al*. 2007; Kaner *et al*. 2007b; Moeintaghavi *et al*. 2007; Moreira & Feres-Filho 2007; Akincibay *et al*. 2008; Johnson *et al*. 2008; Machtei & Younis 2008; Cionca *et al*. 2009; Ribeiro Edel *et al*. 2009; Valenza *et al*. 2009; Cionca *et al*. 2010; Mestnik *et al*. 2010; Yek *et al*. 2010; Baltacioglu *et al*. 2011; Heller *et al*. 2011; Silva *et al*. 2011; Varela *et al*. 2011). Results of a few studies comparing different antimicrobial regimens are available (Rooney *et al*. 2002; Haffajee *et al*. 2007; Akincibay *et al*. 2008; Machtei & Younis 2008; Baltacioglu *et al*. 2011; Silva *et al*. 2011). No study has demonstrated better results than for systemic amoxicillin plus metronidazole with other protocols in any clinically or microbiologically defined variant of periodontal disease, but the comparison between metronidazole plus amoxicillin and metronidazole alone has not consistently shown significant benefits for the combination (Silva *et al*. 2011).

Timing of systemic antibiotic therapy

The optimal timing of antimicrobial drug administration is a subject of controversy (Table 43-6). In clinical practice, periodontal therapy is usually performed in two stages. An attempt to remove bacterial deposits is made first without flap elevation. After 3–6 months the case is re-evaluated, and, if deemed necessary, further root surface instrumentation follows, this time in the context of a local surgical intervention (Fig. 43-4).

Table 43-6 Potential benefits and risks from early or late adjunctive antimicrobial therapy.

Administration		Effects
Early (initial, non-surgical treatment phase)	Benefits	Shorter anti-infective treatment Reduced need for periodontal surgery
	Risks	Incomplete removal of subgingival biofilm and calculus at time of administration
Late (secondary treatment phase)	Benefits	Constrains prescription of antibiotics to cases that cannot be resolved by scaling and root planing alone
	Risks	No evidence for advantage from specifically designed clinical trials Benefits of antibiotics used as adjunct to surgical procedures unclear

Source: Mombelli (2012). Reproduced with permission from S Karger AG.

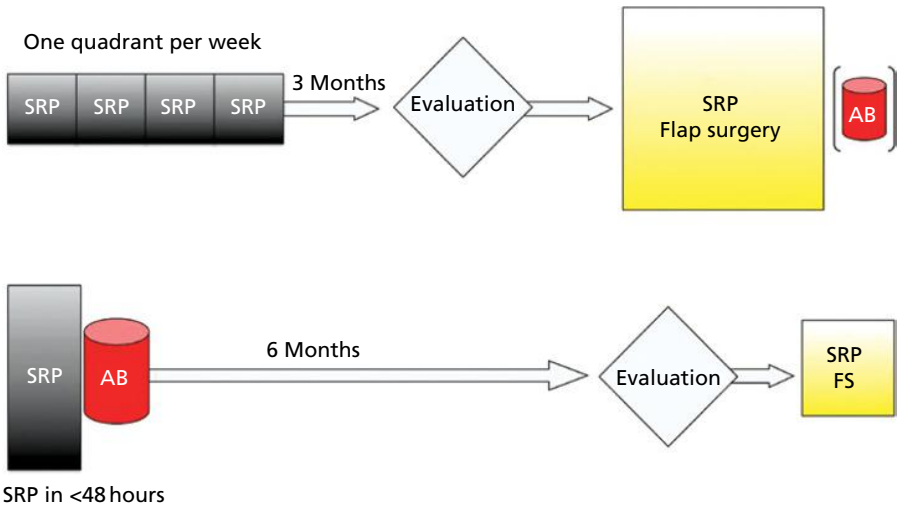

Fig. 43-4 Traditional (top) and alternative approach (bottom) to periodontal therapy. (AB, adjunctive antibiotics; FS, flap surgery, SRP, scaling and root planning.) (Adapted from Mombelli *et al*. 2011, with permission from John Wiley & Sons.)

The first study demonstrating a reduced need for surgical therapy in patients who were treated early with systemic metronidazole as an adjunct to SRP (Loesche *et al*. 1992), as well as a later publication claiming sustained benefits 5 years after initial antimicrobial therapy (Loesche *et al*. 2002), met with disapproval from prominent members of the periodontal community. Postponing antibiotic therapy to the second surgical treatment phase may be defended by two arguments: (1) as it is known that SRP alone is able to resolve a considerable amount of periodontal pathology on its own (Heitz-Mayfield *et al*. 2002; van der Weijden & Timmerman 2002), this strategy may help to restrict the prescription of antibiotics to a minimum; (2) given the restricted effects of antibiotics on intact biofilm (Sedlacek & Walker 2007) and the known limitations of non-surgical mechanical debridement (Rabbani *et al*. 1981; Buchanan & Robertson 1987), surgical intervention may be needed for access to assure complete removal of subgingival biofilm and calculus. As much as this reasoning seems logical, data from specifically designed controlled trials are unavailable to support this recommendation. Contrary to this view, the vast majority of trials have tested antibiotics as adjuncts to non-surgical debridement. A systematic review to assess the relative benefit of prescribing antibiotics either during the non-surgical or the surgical phase of therapy was inconclusive (Herrera *et al*. 2008). However, two studies, not included in this review, showed that for subjects with generalized aggressive periodontitis, better clinical outcomes were achieved if patients were given amoxicillin plus metronidazole immediately after initial SRP rather than after retreatment of persisting pathology (Kaner *et al*. 2007b; Griffiths *et al*. 2011).

Since in most cases mechanical periodontal therapy cannot be accomplished in one session for practical reasons, it is necessary to decide if the adjunctive systemic antimicrobial therapy should start before, during or after debridement. A comparison of outcomes from two studies, one prescribing metronidazole or placebo after the first session of debridement, and the other after the last session of debridement, yielded a significant protocol-effect favoring medication after debridement (Loesche & Giordano 1994). Based on these findings, and on the fact that undisturbed biofilm protects bacteria from the antibiotics, it is recommended that antimicrobial therapy commences immediately after mechanical therapy (i.e. in the evening after the last session of non-surgical treatment). Antibiotics have been administered that way in several studies with good outcomes.

In some cases, mechanical therapy is initially carried out without antimicrobials and evaluated after an appropriate period of time. If it is judged necessary to administer antibiotics at re-evaluation, the subgingival area should be re-instrumented immediately before starting the antimicrobial regimen to reduce the bacterial mass as much as possible and to disrupt newly formed biofilm, even if there is no sign of subgingival persistence of hard deposits. This may be accomplished during a surgical intervention, but is indicated also if no further mechanical therapy seems necessary from a clinical point of view.

Selection of patients who may benefit most from systemic antibiotics

To limit the development of microbial antibiotic resistance in general, and to avoid the risk of unwanted systemic effects of antibiotics for the treated individual, a precautionary, restrictive attitude towards using antibiotics is appropriate. It has been recommended that systemic antibiotics should be considered as adjuncts to SRP for patients with deep pockets, aggressive forms of disease, "active" sites or specific microbiologic profiles (Lindhe & Palmer 2002). However, strictly based on evidence from well-performed randomized clinical trials, and with the exception of patients with known medical contraindications (e.g. confirmed hypersensitivity), it is difficult to define clear-cut exclusion criteria for antibiotic therapy. The following criteria will be addressed in more detail: disease severity, patient compliance, diagnosis as aggressive or chronic periodontitis, microbiologic profile, and risk of adverse events.

Disease severity

It has been pointed out in several of the studies that were cited above that deep pockets benefitted more from antibiotics than shallow ones. Although in some trials treatment with antibiotics reduced PPD in moderately deep pockets by more than if no antibiotics were given, SRP alone is able to predictably resolve a considerable amount of pathology (Heitz-Mayfield *et al*. 2002; van der Weijden & Timmerman 2002). Therefore, it is recommended that in the first place mild and moderate periodontitis are treated non-surgically and without antibiotics. Some studies have shown a certain benefit of antibiotics even when administered without meticulous subgingival debridement (Berglundh *et al*. 1998; Lopez & Gamonal 1998; Lopez *et al*. 2000, 2006). Nevertheless, systemic antibiotics should not be prescribed to counteract incomplete mechanical debridement. Furthermore, for a favorable clinical response and long-term stability, optimal plaque control by the patient is of paramount importance, independent of whether short-term treatment results were obtained with or without antibiotics (Kornman *et al*. 1994).

With regards to diagnosis, it can be stated that not all therapies work equally well in all forms of periodontal disease. It has been noted that after treatment with amoxicillin plus metronidazole patients have an extremely low incidence of suppuration (Rooney *et al*. 2002; Cionca *et al*. 2009), pointing to a potential indication for this regimen particularly in cases with active, suppurating lesions. The problem with recommendations for particular diagnoses is the lack of

Table 43-7 Adjunctive systemic antibiotic regimens currently recommended for the therapy of periodontal diseases.

Antibiotic	Usual dosage	Microbiology
Metronidazole	250–500 mg t.i.d. 7–10 days	*P. gingivalis, T. forsythia, Treponema* spp.
Clindamycin	300 mg q.i.d. 7–8 days	Gram-negative anaerobes Absence of *A. actinomycetemcomitans*
Doxycycline	100–200 mg once a day 7–14 days	Non-specific infection
Metronidazole + amoxicillin	250–500 mg t.i.d. 375–500 mg t.i.d. 7 days	*A. actinomycetemcomitans* or *P. gingivalis* with high numbers of Gram-positive pathogens
Metronidazole + cefuroximaxetil	250–500 mg t.i.d. 250–500 mg b.i.d. 7 days	*A. actinomycetemcomitans*, hypersensitivity towards amoxicillin
Metronidazole + Ciprofloxacin	250–500 mg t.i.d. 500 mg b.i.d. 7 days	*A. actinomycetemcomitans*, hypersensitivity towards β-lactams or presence of susceptible enteric microorganisms

Adapted from van Winkelhoff & Winkel (2005), with permission from John Wiley & Sons.

evidence from specifically designed studies evaluating outcomes of a particular therapy in subjects with different diagnoses. It is however clear from studies with very similar designs (e.g. Guerrero *et al*. 2005; Cionca *et al*. 2009) that the most extensively tested regimen, amoxicillin plus metronidazole, has a beneficial effect in subjects with chronic and aggressive periodontitis.

Table 43-7 lists adjunctive systemic antibiotic regimens currently recommended for the therapy of periodontal diseases. Metronidazole alone has proven to be effective against *P. gingivalis, Tannerella forsythia,* spirochetes, and other strictly anaerobic Gram-negative bacteria. Clindamycin and tetracyclines have also been shown to act on a broad range of periodontal bacteria. Therapy with a single antibiotic as an adjunct to mechanical instrumentation can change the composition of the subgingival microbiota significantly, but certain periodontal organisms cannot be eliminated predictably. The combination of amoxicillin plus metronidazole has a proven capacity to suppress *A. actinomycetemcomitans* from periodontitis lesions and other oral sites (van Winkelhoff *et al*. 1989; Goené *et al*. 1990; Pavicic *et al*. 1992; van Winkelhoff *et al*. 1992; Pavicic *et al*. 1994; Berglundh *et al*. 1998; Flemmig *et al*. 1998b; Mombelli *et al*. 2002; Dannewitz *et al*. 2007) and is therefore the first choice of many clinicians, especially for the treatment of advanced *A. actinomycetemcomitans*-associated periodontitis. For patients intolerant of amoxicillin, metronidazole combined with cefuroximaxetil or ciprofloxacin has been suggested (Rams *et al*. 1992; van Winkelhoff & Winkel 2005).

The problem with issuing a strong recommendation that microbiologic testing should be performed prior to prescribing systemic antibiotics is the lack of unequivocal evidence that patients testing negative for certain bacteria do not benefit from treatment. In four randomized clinical trials (Flemmig *et al*. 1998a; Winkel *et al*. 2001; Rooney *et al*. 2002; Cionca *et al*. 2010), a specific clinical benefit of amoxicillin plus metronidazole in *A. actinomycetemcomitans*-positive subjects only could not be demonstrated. On the contrary, the majority of the participants in these trials were *A. actinomycetemcomitans* negative; hence, the benefit of amoxicillin plus metronidazole resulted to a large part from treatment of *A. actinomycetemcomitans*-negative patients. A recent study determined if microbiologic testing for the presence or absence of *A. actinomycetemcomitans* before therapy identified patients with moderate-to-advanced periodontitis who would specifically benefit from adjunctive amoxicillin plus metronidazole, when given in the context of full-mouth debridement within 48 hours. With respect to the persistence of pockets that are considered to be in need of further therapy according to common practice, that is still deeper than 4 mm and bleeding upon probing at re-evaluation, the answer was no (Mombelli *et al*. 2013). This observation cannot be generalized to all antimicrobial protocols, particularly if agents with a narrow spectrum of activity are used. Findings may have been different if metronidazole alone had been prescribed.

It has been argued that the administration of antibiotics to *P. gingivalis*-negative patients may be overtreatment (van Winkelhoff & Winkel 2009). The authors who raised this issue cited their own study of 49 subjects with chronic periodontitis who were treated with full-mouth SRP and amoxicillin plus metronidazole or placebo (Winkel *et al*. 2001). In this study, *P. gingivalis*-positive patients showed significantly better results when treated with antibiotics than when treated with placebo. However, a closer look at their data shows that the percentage of

pockets of >4 mm decreased to a very similar extent also in *P. gingivalis*-negative subjects treated with antibiotics. At least three other studies (Flemmig *et al*. 1998a; Rooney *et al*. 2002; Cionca *et al*. 2010) clearly demonstrated a benefit of supplementing mechanical therapy with amoxicillin plus metronidazole in *P. gingivalis*-negative cases.

The risk of adverse effects should be considered especially when prescribing more than one antibiotic. Although reported adverse effects tend to be minor, serious problems cannot be discounted. To put things into perspective, the frequency and consequences of adverse effects of antibiotics have to be balanced against the potential health consequences of not rapidly suppressing a periodontal infection, and the inconvenience, discomfort, and financial consequences of further therapy. The traditional approach sometimes expands treatment over several months, while SRP and amoxicillin plus metronidazole may be able to resolve the infection within a few days (Mombelli *et al*. 2011). SRP and amoxicillin plus metronidazole have been shown to decrease clinical signs of inflammation and inflammatory biomarkers in GCF more profoundly than SRP alone (Giannopoulou *et al*. 2006). Although not directly confirmed by a clinical trial, it seems preferable, from a general health point of view, that patients benefit early from the positive systemic effects of successful periodontal therapy (Noack *et al*. 2001; D'Aiuto *et al*. 2004, 2005). If the number of subjects complaining of gastrointestinal problems, notably diarrhea, were indeed higher in the test than the placebo groups of one clinical trial (Cionca *et al*. 2009), it is also worth considering that tooth loss and suppuration despite therapy were exclusively noted in the control group.

Minimizing the risk of the development of antimicrobial antibiotic resistance

Antibiotic therapy carries the risk of promoting the development of bacterial antibiotic resistance. Since periodontal diseases are not life threatening and can be managed largely without antibiotics, this concern needs to be taken seriously. However, the impact of various treatment protocols on the development of bacterial antibiotic resistance has unfortunately not been evaluated thus far in adequately designed clinical trials. Microbiologic evaluations will need to focus not only on their action against microorganisms directly involved in periodontal diseases, that is the predominantly Gram-negative complex of the subgingival microbiota, but also on organisms that are relevant for other reasons, such as staphylococci or enterococci. The resistance developments of greatest concern today are MRSA (*Staphylococcus aureus* strains resistant to methicillin and usually also to multiple other antibiotics), VRE (*Enterococcus* species resistant to vancomycin), PRSP (*Streptococcus pneumoniae* strains highly resistant to penicillin), and ESBL (*Escherichia coli* and other Gram-negative bacteria resistant to antibiotics such as penicillins, cephalosporins, and monobactams).

Table 43-8 Strategies to reduce the risk of bacterial antimicrobial resistance.

Issues	Recommendations
Agents	Consider prescription of a combination therapy (i.e. amoxicillin + metronidazole)
Dosage and timing	Administer a high dose for a short period
Clinical protocol	Use antimicrobials as adjuncts to thorough mechanical debridement
Indication	Use antibiotics for therapy where scaling and root planing alone is insufficient Limit prophylactic use to high-risk patients and to the prevention of severe complications

Source: Mombelli (2012). Reproduced with permission from S Karger AG.

Proposed strategies to reduce the risk of bacterial antimicrobial resistance are listed in Table 43-8. In the mixed subgingival microbiota, some microorganisms can always be expected to be resistant to any single antimicrobial agents (Ardila *et al*. 2010). To overcome single antibiotic resistance, combination therapies may therefore be advantageous. It has been recognized that the dose and duration of antimicrobial therapy are crucial parameters for resistance development. Suboptimal dosage of antibiotics, caused by either inadequate prescribing or poor patient compliance, favors the emergence of antibiotic-resistant bacterial clones. Clinical studies in other fields indicate that it is preferable to deliver antibiotics at a high dose over a short time. As an example, a randomized trial conducted in an outpatient clinic involving 795 children receiving antibiotic prescriptions for upper respiratory tract infections demonstrated the advantage of short-course, high-dose outpatient antibiotic therapy to minimize the impact of antibiotic use on the spread of drug-resistant pneumococci (Schrag *et al*. 2001). The classical oral dosage for metronidazole in many older studies was 250 mg t.i.d. for 10–14 days. This dosage might not be sufficient in subjects with a high body mass. Today, for a person weighing 75–80 kg, 500 mg metronidazole t.i.d for 7 days is recommended. As discussed above, biofilm-associated infections are notoriously resistant to antimicrobial therapy unless the biofilm is disrupted mechanically. It is therefore reiterated here that all antimicrobial therapy should be preceded by mechanical debridement. To limit their overuse, it is furthermore recommended to avoid antibiotics whenever there is ample evidence that thorough non-surgical mechanical debridement alone can resolve the problem, as is the case for mild-to-moderate periodontitis (van der Weijden & Timmerman 2002). Last but not least, the prophylactic use of antibiotics should be limited to high-risk patients and to the prevention of severe complications (Duval *et al*. 2006; Esposito *et al*. 2008; Nishimura *et al*. 2008; Berbari *et al*. 2010).

Local antimicrobial therapy (see also Chapter 44)

Local antimicrobial therapy in clinical trials

Various methods to deliver antimicrobial agents into periodontal pockets have been devised and subjected to numerous types of study. The shortcomings of rinsing, irrigating, and similar forms of drug placement – rapid clearance resulting in inadequate exposure of subgingival bacteria to the drug and lack of significant clinical effects – have already been discussed. This section will deal with clinically tested drug delivery systems that fulfil at least the basic pharmacokinetic requirements of sustained drug release. Much of what has been stated about difficulties in the interpretation of studies dealing with the systemic use of antibiotics applies to the studies conducted with local delivery devices. Again, comparisons are complicated because studies vary with regard to sample size, selection of subjects, range of parameters, controls, duration, and the inclusion of only one form of local drug delivery. Most of the evidence for a therapeutic effect of local delivery devices comes from trials involving patients with previously untreated chronic ("adult") periodontitis. The best available evidence comes from randomized clinical trials where local antimicrobials were administered as an adjunct to SRP, and where the control group was treated with SRP alone or with a placebo. Only a few studies have addressed the use of local drug delivery in recurrent or persistent periodontal lesions, the potentially most valuable area for their application. Some protocols compare local drug delivery to a negative control, such as the application of only the carrier without the drug. These studies may be able to show a net effect of the drug, but they are not able to demonstrate a benefit over the most obvious alternative – SRP – and the question remains as to how much value the procedure has in addition to mechanical treatment. If a study is unable to demonstrate a significant difference between local drug delivery and SRP, this is not automatically proof of equivalence of the two treatments (equivalence testing requires statistical testing of the power of the data, taking into account the size of the study sample).

The drugs investigated for local application include tetracycline, minocycline, doxycycline, metronidazole, azithromycin, and chlorhexidine. The agents were administered using the following devices: varnishes (chlorhexidine), gels (doxycycline, metronidazole, minocycline, azithromycin), nonresorbable polymer fibers (tetracycline), gelatin chips (chlorhexidine; Fig. 43-5), ointments (tetracycline), and resorbable polymer microspheres (minocycline). Unfortunately, several of the commercial formulations that have been adequately tested in clinical trials are currently unavailable in certain regions of the world, or have disappeared completely, while other products without proven clinical efficacy continue to be introduced and are utilized on an empirical basis. Since most studies have been performed in chronic periodontitis patients, the evidence described below will not include studies of early-onset periodontitis (Yilmaz *et al*. 1996) or aggressive periodontitis (Duarte *et al*. 2009).

Minocycline ointment and microspheres

The subgingival delivery of minocycline has been investigated as a 2% ointment (Dentomycin; Cyanamid, Lederle Division, Wayne, NJ, USA) or as a powder consisting of resorbable polymer microspheres (Arestin; OraPharma, Warminster, PA, USA) in at least 13 randomized clinical trials (Nakagawa *et al*. 1991; van Steenberghe *et al*. 1993; Jones *et al*. 1994; Graca *et al*. 1997; Jarrold *et al*. 1997; Kinane & Radvar 1999; Williams *et al*. 2001; Henderson *et al*. 2002; Meinberg *et al*. 2002; Van Dyke *et al*. 2002; Goodson *et al*. 2007; Bland *et al*. 2010).

Differences of changes in mean PPD were statistically significant between test and control groups in five trials. Control groups demonstrated a mean change ranging from 0.4 to 1.9 mm, and the test groups from 0.9 to 2.6 mm. Four trials reported a statistically significant intergroup difference for CAL changes. The magnitude of the differences between groups ranged from 0 to 1.6 mm in the control and

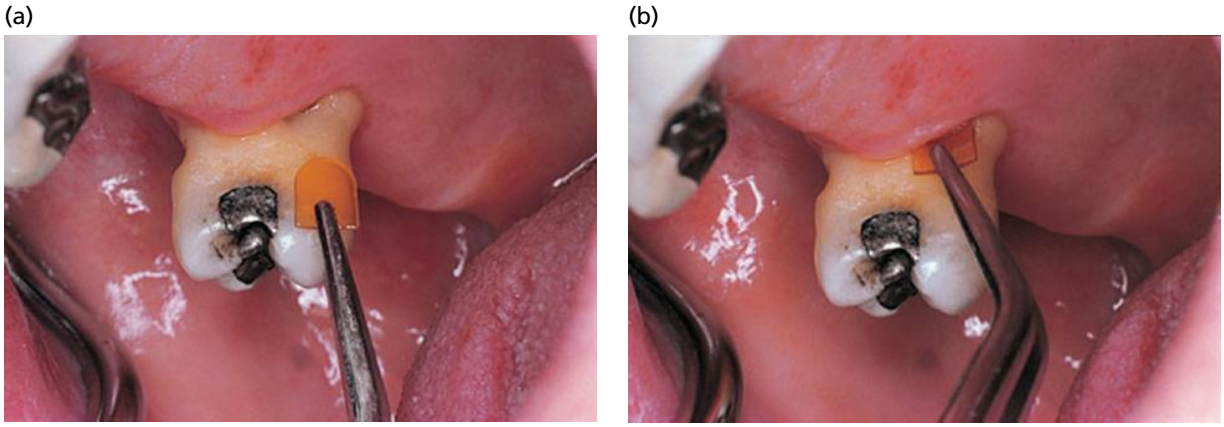

Fig. 43-5 (a, b) Insertion of a chlorhexidine chip into a residual pocket mesial of an upper molar with a furcation involvement.

from 0.8 to 1.9 mm in the test groups. Three trials reported significant differences between groups with regards to bleeding on probing (BoP), with reductions ranging from 5% to 46% in the control and from 4% to 87% in the test groups. Compared to SRP alone, the results from the different studies were consistently in favor of SRP with minocycline with regards to PPD, but not to CAL and BoP.

Doxycycline hyclate in a biodegradable polymer

A two-syringe mixing system for the controlled release of doxycycline (Atridox; Block Drug, Jersey City, NJ, USA) has been available commercially for some years. One syringe contains the delivery vehicle, flowable bioabsorbable poly(DL-lactide) dissolved in *N*-methyl-2-pyrrolidone, and the other a doxycycline hyclate powder. At least seven randomized clinical trials have tested this formulation (Wennström *et al*. 2001; Eickholz *et al*. 2002; Akalin *et al*. 2004; Agan *et al*. 2006; Machion *et al*. 2006; Bogren *et al*. 2008; Gupta *et al*. 2008).

Differences in changes of PPD were statistically significant between test and control groups in three of these seven trials. Control groups demonstrated a mean change ranging from 1.1 to 3.1 mm, and the test groups from 1.2 to 4.0 mm. Three trials reported statistically significant intergroup differences for CAL changes. The magnitude of the differences between groups ranged from 0.5 to 1.6 mm in the control and from 0.7 to 3.2 mm in the test groups. Five papers reported BoP changes, with reductions ranging from 8% to 56% in the control and from 13% to 64% in the test groups, but no significant differences between groups. Short-term data for PPD and CAL consistently favored SRP with doxycycline over SRP alone across the different studies. No clear trends were observed for BoP and plaque levels.

In one study involving 105 patients at three centers (Wennström *et al*. 2001), the effect of Atridox, applied after no more than 45 minutes of debridement without analgesia, was compared to 4 hours of thorough SRP in subjects with moderately advanced chronic periodontitis. Interestingly, clinical parameters indicated a better result for the pharmacomechanical treatment approach after 3 months, although considerably less time had been invested than for conventional mechanical therapy.

Metronidazole gel

Dialysis tubing, acrylic strips, and poly-OH-butyric acid strips have been tested as solid devices for delivery of metronidazole. The most extensively used device for metronidazole application is a gel consisting of a semi-solid suspension of 25% metronidazole benzoate in a mixture of glyceryl mono-oleate and sesame oil (Elyzol Dental Gel; Dumex, Copenhagen, Denmark). The gel is applied with a syringe into the pocket, and its viscosity should increase after placement. Seven randomized clinical trials have evaluated the effects of this formulation as an adjunct to non-surgical mechanical therapy (Noyan *et al*. 1997; Lie *et al*. 1998; Kinane & Radvar 1999; Palmer *et al*. 1999; Riep *et al*. 1999; Griffiths *et al*. 2000; Stelzel & Flores-de-Jacoby 2000).

PPD changes were reported in all seven studies, with the mean differences between groups ranging from 0.7 to 1.7 mm in the control groups and from 0.9 to 2.1 mm in the test groups. However, differences between groups reached significance at the end of the follow-up period in only two trials. For CAL changes, the differences between groups ranged from 0.4 to 0.9 mm in the control and from <0.1 to 0.8 mm in the test groups, and the differences between groups were statistically significant in three studies. BoP was registered in six studies, with changes ranging from 6% to 48% and from 11% to 59% in the control and test groups, respectively, with statistically significant differences between groups in only one trial. The results of the different studies were consistent, favoring SRP with metronidazole over SRP alone in terms of PPD and BoP, but not of CAL.

Tetracycline in a non-resorbable plastic co-polymer

Devices such as dialysis tubing, acrylic strips, collagen, or poly-OH-butyric acid strips have been tested for tetracycline delivery in several studies. Semi-solid viscous media include white petrolatum and poloxamer or carbopol gels. The most extensively tested tetracycline-releasing device is the Actisite periodontal fiber (ALZA, Palo Alto, CA, USA). This currently unavailable product consists of a monolithic thread of a biologically inert, non-resorbable plastic co-polymer (ethylene and vinyl-acetate) containing 25% tetracycline–HCl powder. The fiber is packed into the periodontal pocket, secured with a thin layer of cyanoacrylate adhesive, and left in place for 7–12 days (Goodson *et al*. 1983, 1991). The continuous delivery of tetracycline maintains a local concentration of the active drug in excess of 1000 mg/L throughout that period (see Fig. 43-3). At least nine randomized clinical trials have assessed the effect of tetracycline in this vehicle (Minabe *et al*. 1991; Jeong *et al*. 1994; Newman *et al*. 1994; Drisko *et al*. 1995; Tonetti *et al*. 1998; Wong *et al*. 1998; Kinane & Radvar 1999; Yalcin *et al*. 1999; Aimetti *et al*. 2004).

PPD changes were calculated in all the studies, with reductions amounting to 0.4–1.2 mm and 1.3–2.6 mm in the control and test groups, respectively; three studies found statistically significant differences between the groups. Changes in CAL were also reported in all studies, with differences between groups ranging from 0.1 to 0.7 mm and 0.3 to 2.3 mm in the control and test groups, respectively. The differences between groups were statistically significant in one of these investigations. Changes in BoP ranged

from 5% to 42% in the control groups and from 4% to 79% in the test groups, with significant differences found in five studies. The results of the different studies were quite consistent, favoring SRP with tetracycline fibers over SRP alone in terms of PPD, CAL, and BoP.

Azithromycin gel

Only one study has reported data on the adjunctive effect of local azithromycin on SRP (Pradeep *et al*. 2008). Differences in PPD reduction were statistically significant and CAL gains were significantly greater in the test than in the control group after 3 months. BoP was not assessed.

Chlorhexidine products

Several attempts have been made to develop local delivery devices for the subgingival application of antiseptics, rather than antibiotic agents. Different products containing chlorhexidine have been evaluated, including gelatin chips, varnishes, and a xanthan gel.

PerioChip (Perio Products, Jerusalem, Israel), a degradable gelatin chip containing 2.5 mg of chlorhexidine, has been extensively tested in at least 11 trials (Soskolne *et al*. 1997; Jeffcoat *et al*. 1998, 2000; Heasman *et al*. 2001; Azmak *et al*. 2002; Grisi *et al*. 2002; Mizrak *et al*. 2006; Carvalho *et al*. 2007; Kasaj *et al*. 2007; Paolantonio *et al*. 2008; Sakellari *et al*. 2010). All of them assessed PPD. The improvements ranged from 0.3 to 2.3 mm in the control and from 0.8 to 3.8 mm in the test groups. The differences between groups were statistically significant in only six of the trials. All 11 studies assessed CAL. The changes ranged from −0.4 to 1.6 mm in the control and from −0.9 to +2.8 mm in the test groups and were significantly different between groups in six studies. Changes in BoP ranged from 33% to 64% in the control and from 22% to 63% in the test groups, with differences between groups reaching a level of statistical significance in two trials. The results of the different studies were heterogeneous in terms of PPD and CAL, and only longer-term studies and split-mouth designs provided clear differences between test and control groups.

A chlorhexidine varnish was tested by one research group in four different investigations (Cosyn *et al*. 2005, 2006a, b, 2007). PPD changes ranged from 0.7 to 1.2 mm in the control groups and from 1.1 to 2.0 mm in the test groups, and the differences between groups were statistically significant in two of the trials. For CAL, minor changes were registered, without significant differences between groups. BoP decreased by 27–50% in the control and by 34–47% in the test groups, with no significant differences between groups. The results of these studies performed by the same group consistently favored the test group in terms of PPD, CAL, and BOP.

A xanthan-based gel containing a combination 0.5% chlorhexidine digluconate and 1% chlorhexidine dihydrochloride (ChloSite®; Casalecchio di Reno, BO, Italy) has been proposed for local antimicrobial application. This product has been tested in at least two trials (Gupta *et al*. 2008; Paolantonio *et al*. 2009). PPD changes seen in the test group (range 1.4–2.0 mm) were significantly better than in the control group (range 0.5–0.9 mm). CAL changes ranging from 2.4 to 2.8 mm in the test groups were also significantly better than those in the control groups (range 1.5–1.7 mm). BoP was recorded in one trial and did not show significant differences between the groups.

Comparative evaluation of treatment methods

The results described above indicate that several local antimicrobial treatment protocols have the potential to improve the results of non-surgical periodontal therapy, although primarily relating to PPD changes, but statistically significant benefits were generally ascertained in less than half of the available trials. In addition, most studies tested a single form of local drug delivery instead of comparing various forms of therapy. Understandably, the primary interest of developers and distributors is to register and promote their own product for the broadest possible usage, and not to differentiate specific benefits or shortcomings of various applications. The efficacy of commercially available local delivery systems as adjuncts to SRP was only tested in two trials including patients with persistent periodontal lesions: Actisite, Dentomycin, and Elyzol Dental Gel (Radvar *et al*. 1996; Kinane & Radvar 1999); Atridox, Elyzol Dental Gel, and PerioChip (Salvi *et al*. 2002).

One systematic review has evaluated the combined literature-based evidence to determine the relative effect of local controlled-release anti-infective drug therapy in patients with chronic periodontitis (Hanes & Purvis 2003). A meta-analysis including 19 studies, comparing SRP plus local sustained-release agents with SRP alone, confirmed the clinical advantages of minocycline gel, micro-encapsulated minocycline, doxycycline gel, and chlorhexidine chips over SRP alone. Due to the heterogeneity of the studies, the authors could not make any firm statements regarding the superiority of one system over any other. A further systematic review looked at the relative adjunctive benefits of various locally applied agents (Bonito *et al*. 2005). Unfortunately, data were combined from studies exploring various modes of local treatment, including irrigation, impregnated strips, and pastes. Nonetheless, a statistically significant mean advantage was seen for four agents in terms of additional CAL gain – best for minocycline, followed by tetracycline, chlorhexidine, and metronidazole. One cannot exclude, however, that the differences noted between the drugs primarily reflect

differences in modes of application and study populations, not the potency of the agent.

Few studies have addressed the problem of incorporating local or systemic antimicrobial therapy into an overall treatment strategy. As there has been as yet little direct comparison of the various methods of treatment, well-founded decision algorithms to direct the choice of specific methods of intervention for distinct clinical situations are not yet available. A key issue requiring clarification concerns the selection of a local or a systemic delivery approach whenever the use of an antibiotic seems to be indicated. For patients with chronic periodontitis, two studies reported better results for SRP supplemented with locally applied metronidazole than adjunctive systemic metronidazole (Paquette *et al*. 1994; Noyan *et al*. 1997). Two investigations addressed this question in patients with aggressive periodontitis. No significant differences were noted between systemic administration of either amoxicillin plus clavulanic acid or tetracycline fibers as an adjunct to mechanical therapy (Bernimoulin *et al*. 1995). More recently, the same group reported that SRP plus amoxicillin and metronidazole provided better clinical results after 6 months than chlorhexidine-loaded gelatin chips (Kaner *et al*. 2007a).

As different oral distribution patterns can be recognized in periodontitis patients for microorganisms such as *P. gingivalis* (Mombelli *et al*. 1991a, b), local therapy may be less successful in patients where pathogens are widespread than in patients where their presence is confined to isolated areas. However, no diagnostic tool is available presently that can give the clinician a detailed distribution map of periodontal pathogens at a reasonable cost. However, even if such information were available, a study evaluating the effect of local antibiotic therapy given to every tooth with cultural evidence of *P. gingivalis* or *A. actinomycetemcomitans* demonstrated the limits of this approach (Mombelli *et al*. 2002).

Local antibiotics in clinical practice

To treat periodontal disease successfully, local delivery devices must provide therapeutic levels of antimicrobial agents in the subgingival area over several days. Clinical trials show the efficacy of local antibiotic therapy under these conditions. The current evidence suggests that local delivery may be most beneficial in the control of localized ongoing disease in otherwise stable patients. Maintenance patients with a few non-responding sites may therefore benefit most from local antimicrobial therapy. Potential uses for locally delivered antimicrobials furthermore include the treatment of peri-implant infections (Mombelli *et al*. 2001; Renvert *et al*. 2006). Local antimicrobial therapy adds flexibility and improves the efficacy of periodontal care by providing a non-surgical local treatment alternative with more powerful antibacterial effects than SRP. However, a cost-effectiveness analysis concluded that systemic antimicrobials are more cost-effective than locally delivered antimicrobials (Heasman *et al*. 2011). In recent years, the perceived value of local antibiotic therapy has decreased, as a majority of adequately tested formulations have been withdrawn from the market. So far, no local antimicrobial treatment has proven to be equally efficient or better than systemic amoxicillin plus metronidazole.

Conclusion

Antibiotics delivered either systemically or locally, can enhance the effect of periodontal therapy. To limit the development of microbial antibiotic resistance in general, and to avoid the risk of unwanted systemic effects of antibiotics for the treated individual, a precautionary, restrictive attitude towards using antibiotics is indicated. To limit their overuse, it is recommended not to prescribe antibiotics whenever there is ample evidence that thorough non-surgical mechanical debridement alone can resolve the problem, and this is the case for mild-to-moderate periodontitis. By providing an additional treatment benefit for SRP in deep pockets, systemic antibiotics can reduce the need for further surgical therapy. Systemic antibiotics may be useful also as an adjunct in the retreatment of cases with unsatisfactory response to mechanical therapy. Localized non-responding sites and localized recurrent disease may be treated with locally delivered antibiotics. All antimicrobial therapy should be preceded by thorough mechanical debridement (SRP). After resolution of the periodontal infection, the patient should be placed on an individually tailored maintenance care program to prevent re-infection.

At present, the most thoroughly documented way of using antibiotics in periodontal therapy is SRP with adjunctive oral amoxicillin and metronidazole. Other protocols, including SRP with metronidazole or SRP with azithromycin may be considered, especially in chronic periodontitis patients.

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Chapter 44

Local Drug Delivery for the Treatment of Periodontitis

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Introduction

Treatment of periodontitis is routinely based on oral hygiene, root debridement, and risk factor modification. Given the bacterial etiology and the inflammatory pathogenesis of periodontitis, the adjunctive use of locally applied or systemic administration of antimicrobials and/or host response-modulating medications has been proposed. Localized therapy has received significant attention because of the site-specific pattern of destruction of periodontal infections and the potential side effects of systemic antimicrobials and anti-inflammatory agents. Another important rationale for the development of effective ways to locally apply medications into the periodontal pockets comes from the realization that systemic administration of many medications (and antibiotics in particular) results in marginally effective local concentrations of free, active drug in the periodontal pocket and surrounding tissues.

There are three basic routes to localized adjunctive pharmacologic periodontal therapy: mouth rinses (toothpaste or varnishes), subgingival irrigation, and periodontal application of local delivery systems.

Rinses are useful for supragingival biofilm control, modulation of gingival inflammation, and potentially for recolonization of the subgingival environment following periodontal treatment. Their major limitation, in the context of pharmacologic therapy of periodontitis, is that they do not gain access to the subgingival environment and therefore do not reach the desired site of action (Pitcher *et al*. 1980).

Irrigation solutions placed directly into periodontal pockets initially reach effective concentrations in the area, but the flow of the gingival crevicular fluid (GCF) – which is replaced about 40 times per hour – leads to rapid clearance of subgingivally placed drugs. Clearance of a medication locally placed in a periodontal pocket follows exponential kinetics and it has been calculated that the concentration of a highly concentrated irrigating solution of a non-substantive (non-binding) drug becomes ineffective about 15 minutes following application. This time can be prolonged by the application of substantive drugs such as tetracyclines or chlorhexidine that bind to the root surface and/or the soft tissue wall of the periodontal pocket and thus establish a drug reservoir that can be slowly released to counteract the clearance by the GCF flow. Limitations on reservoir volume, however, limit the duration of the possible pharmacologic effect. Thus, efficient delivery of pharmacologic agents into the periodontal microenvironment is difficult to achieve using rinses and irrigating solutions.

Goodson – a pharmacologist who in the early 1970s pioneered the field of local delivery to treat

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periodontitis – pointed out that successful pharmacologic control of the periodontal microflora requires (1) delivery of an intrinsically efficacious drug to the site of action (periodontal pocket and surrounding tissues); (2) a concentration of the drug higher than the minimum efficacious concentration; and (3) maintenance of this concentration long enough for the effect to occur. These three principles – site, concentration, and time – are the key parameters in the optimization of local pharmacologic treatment (Goodson 1989, 1996).

Periodontal pharmacokinetics

The action of an intrinsically efficacious drug in a body site is dependent upon the bioavailability of free active medication at the desired location; here specifically the periodontal pocket and the neighboring soft and hard tissues. From a pharmacologic standpoint, the periodontal pocket is a challenging microenvironment: it is characterized by the rapid flow of GCF, has a small resting volume, and has an uneven topography. Periodontal pockets are uneven in terms of depth, width, presence of furcation involvements, composition and amounts of subgingival biofilm, and calculus deposits. These characteristics translate into specific difficulties for the design of periodontal local delivery devices.

Pocket volume and clearance

Clearance of a drug placed into a periodontal pocket follows the exponential function:

$$C_{(t)} = C_{(0)} e^{-t\frac{F}{V}}$$

where $C_{(t)}$ is the concentration of the drug as a function of time (t), $C_{(0)}$ is the initial concentration obtained in the GCF, F is the GCF flow rate, and V is the resting fluid volume of the pocket.

Using an estimated periodontal pocket volume of 0.5 µL (Binder *et al*. 1987) and a GCF flow rate of 20 µL/h (Goodson 1989), the half-time (the time that it takes to reach half of the initial concentration) for a non-substantive medication placed in the periodontal pocket will be 0.017 hours (or about 1 minute). From these calculations Goodson (1989) concluded that the subgingival irrigation route is theoretically feasible only for very potent (i.e. antimicrobials that can act at very low concentrations) substantive drugs.

In the case of a substantive compound, the exponential function can be rewritten by introducing a multiplicative constant K into the denominator of the exponential term to account for binding of the drug to the root surface (and/or periodontal pocket wall):

$$C_{(t)} = C_{(0)} e^{-t\frac{F}{KV}}$$

where K is the affinity constant, which is experimentally estimated from the determined clearance half-time.

This equation can be conveniently rearranged to estimate the effect of the various parameters on the duration of the desired therapeutic effect:

$$t_{(MIC)} = \frac{KV}{F} \ln \frac{C_{(0)}}{C_{(MIC)}}$$

where $C_{(MIC)}$ is the minimum inhibitory concentration (MIC) and $t_{(MIC)}$ is the time taken to reach the MIC or the expected time of antibacterial action.

From this relation, it is apparent that the time over which a therapeutic effect is observed ($t_{(MIC)}$) will be longer when the:

- Volume of the pocket is large
- GCF flow rate is low
- Affinity constant for the drug is higher, that is a highly substantive drugs is used
- Initial concentration is very high, that is the drug has good solubility in the applied vehicle
- MIC is low, that is a very potent agent is used.

While the first two parameters relate to the specific disease state of each tooth and thus cannot be easily modified without intervention, the remaining three parameters relate to the choice of drug. Preclinical data related to the *in vitro* antimicrobial susceptibility profile and pharmacokinetic data are at the base of the rationale choice of the active agent.

Development of periodontal local delivery devices

To overcome the challenges represented by the pharmacokinetic parameters of the local microenvironment, Goodson designed a first generation of local drug delivery devices for application into periodontal pockets. The concept was to constantly replenish the free drug in the periodontal pocket that is cleared by the GCF flow with the release of drug from a drug reservoir placed into the periodontal pocket (Goodson *et al*. 1979). These devices consisted of permeable hollow cellulose acetate fibers (with an internal thickness of 200 µm) filled with a 20% tetracycline–HCl solution. The fiber was tied around the crevice of the pocket, pressed into the subgingival environment, and removed after 24 hours. In spite of the short duration of application, an important effect on the composition of the subgingival microflora was observed. A subsequent clinical study compared hollow fibers left in place for 2 days with scaling and root planning (SRP). Microbial and clinical parameters improved, but less than in the SRP group (Lindhe *et al.* 1979). These early attempts produced limited clinical outcomes and this was explained by the insufficient duration of drug delivery. Subsequent efforts focused on leaving the delivery device longer

in the periodontal pocket, but it became apparent that these devices were exhausted relatively quickly (Addy *et al*. 1982; Coventry & Newman 1982).

Better release profiles were obtained with a second generation of devices characterized by a monolithic design (drug crystals interspersed within an inert matrix) such as acrylic strips or extruded ethylene vinyl acetate fibers (Addy *et al*. 1982; Goodson *et al*. 1983). In particular, following placement of 0.5-mm diameter 25% tetracycline fibers, GCF concentrations in the order of 500–1500 μg/mL were reported (Tonetti *et al*. 1989). Parallel efforts with bioresorbable matrices focused on chlorhexidine in cellulose acetate (Soskolne *et al*. 1983) and on release platforms made of hydroxypropylcellulose (Noguchi *et al*. 1984) or collagen matrices (Minabe *et al*. 1989a, b).

Studies have estimated that the resting fluid volume of a 5-mm pocket is about 0.5 μL (or 0.5 mm^3). While deeper pockets and pockets at dental implants (that also include a sizeable mucosal tunnel) may have a significantly larger volume, these data indicate that any periodontal local delivery device needs to be able to expand the pocket volume in order to establish a large enough drug reservoir that will be able to release free drug over time to counteract the GCF clearance. Early attempts using dimensionally stable acrylic strips or tetracycline fibers achieved pocket expansion.

Phase I and II studies with these devices reported improvements in the microbial flora and clinical parameters (Addy & Langeroudi 1984; Goodson *et al*. 1985a, b). The pivotal trial required for regulatory clearance by the US Food and Drug Administration (FDA) of 25% tetracycline–HCl ethylene vinyl acetate fibers was the first multicenter trial in the field of periodontology to be conducted under stringent quality control and was a stepping stone towards modern clinical trial design and execution in dentistry (Goodson *et al*. 1991a, b).

Over the following two decades, several local antimicrobial delivery devices have been developed and have undergone clinical testing for safety and effectiveness to satisfy clearance by the local regulatory agencies (Goodson *et al*. 1991a–c; van Steenberghe *et al*. 1993; Soskolne *et al*. 1997, 1998; Stoller et al 1998, Garrett *et al*. 1999; van Steenberghe *et al*. 1999; Garrett *et al*. 2000; Williams *et al*. 2001; Soskolne *et al*. 2003).

Antimicrobial effects of local delivery devices

Early studies mandated by regulatory agencies to provide proof of efficacy of the locally delivered antimicrobial alone showed consistent suppression of total bacterial loads and frequency of detection of target pathogens. A host of later studies, however, showed that better clinical and microbiologic outcomes were obtained by combining mechanical debridement with local delivery of the antimicrobial. This established the key role of mechanical debridement in successful clinical strategies for application of local delivery devices (Johnson *et al*. 1998).

Clinical studies evaluating microbiologic outcomes of local delivery devices – used in combination with mechanical debridement – have shown drastic reductions in both total bacterial load and periodontal pathogens. With the most effective devices (those delivering high concentrations of intrinsically efficacious antimicrobials for >1 week), suppression of 99–99.9% of total microbial load was reported, leading to effective disinfection of the treated periodontal pocket. After exhaustion of the drug reservoir, however, rapid recolonization was observed. Three possible sources for this recolonization were hypothesized: (1) regrowth from the residual microbiota from within the periodontal pocket; (2) recolonization from other intraoral areas of infection; and/or (3) re-infection of the patient from other subjects.

A pilot study conducted at the Forsyth Institute in 1988 by the Goodson group started to address the question of the source of recolonization (Holborow *et al*. 1990; Niederman *et al*. 1990). The study employed tetracycline fibers and SRP with or without chlorhexidine mouth rinsing to complete the treatment of the subjects who had participated in the pivotal study leading to FDA approval of tetracycline fibers (Goodson *et al*. 1991a, b). The hypothesis was that the intraoral antibacterial effect of chlorhexidine would modulate bacterial recolonization of tetracycline fiber-treated pockets. Results showed that chlorhexidine mouth rinsing over a 28-day period led to significant depression of the bacterial recolonization profiles for three target pathogens. The data were interpreted as an indication that the overall oral ecology of the patient was a critical determinant of success with this therapeutic modality. This concept was further assessed by a study conducted at the University of Berne. Subjects with generalized periodontitis who were *Porphyromonas gingivalis* positive were enrolled into a randomized controlled trial testing two extreme forms of therapy: localized treatment of two isolated pockets (with the rest of the dentition being monitored over the study period) and full-mouth disinfection of the whole dentition by tetracycline fiber application, SRP, and chlorhexidine mouth rinsing for 4 weeks. Clinical and radiographic outcomes showed greater improvement in the index teeth of the full-mouth disinfection group compared to the index teeth of the localized treatment group (Mombelli *et al*. 1996, 1997; Fourmousis *et al*. 1998). Most importantly, while similar levels of pocket disinfection were achieved for total bacterial counts at the time of tetracycline fiber removal, the recolonization kinetics showed rapid return towards baseline bacterial levels in the localized treatment group (Fig. 44-1) (Tonetti *et al*. 1995). Persistent, stable suppression of bacterial levels was observed in the full-mouth disinfection group. Interestingly, early recolonization kinetics predicted clinical (reduction of pocket depth and bleeding on probing) and

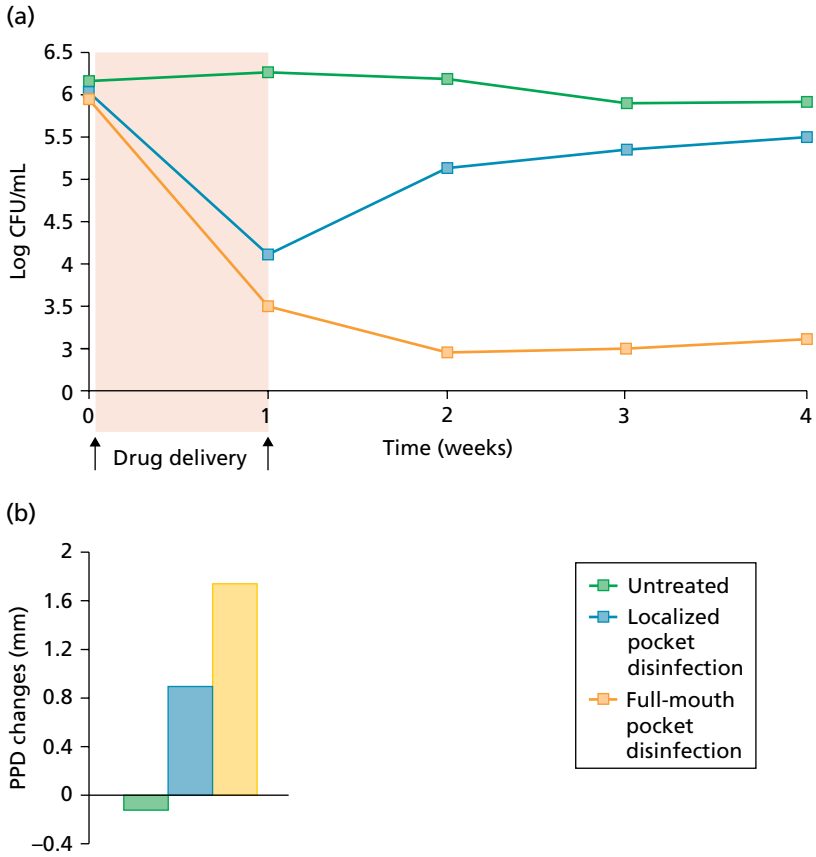

Fig. 44-1 (a) Kinetics of change following local drug delivery with tetracycline fibers in untreated sites; localized treated areas (only two teeth treated in subjects with widespread periodontitis and *P. gingivalis* infection); and full-mouth pocket disinfection (all pockets treated plus chlorhexidine mouth rinse in subjects with widespread periodontitis and *P. gingivalis* infection). Note the different patterns of recolonization. The vertical axis displays total colony forming units (CFU) (Log10)/mL. (b) Changes in probing depths at 6 months for the three groups displayed in (a). Note the greater pocket depth reductions observed in the full-mouth pocket disinfection group.

radiographic (hard and soft tissue subtraction analysis) outcomes 3 and 6 months later (Tonetti *et al*. 1995). Several important conclusions were drawn from these studies and these represent important strategic elements for the rationale use of local delivery devices:

1. Effective local delivery devices have the potential to dramatically change the microbial profile of treated periodontal pockets. Recolonization, however, is a critical phenomenon that may undermine clinical benefit.
2. Bacteria present in other areas of the mouth are the major source of recolonization and need to be addressed by improved oral hygiene measures, treatment of the whole dentition, and – perhaps – antimicrobial mouth rinsing.
3. Local delivery devices are not a promising treatment for subjects who are unable or unwilling to achieve improved (optimal) oral hygiene levels.

Efficacy of local delivery devices

A systematic review and meta-analysis by Hanes and Purvis (2003) along with a more recent one by Matesanz-Pérez *et al*. (2013) represent the major evidence base for the use of local delivery devices.

The 2003 review, conducted for the American Academy of Periodontology workshop, examined the clinical outcomes of 32 studies incorporating 3705 subjects and established that adjunctive local drug delivery resulted in significant reductions in gingival inflammation and probing depths, and improvements in clinical attachment level. Nineteen randomized controlled clinical trials were subjected to meta-analysis and the additional benefit was estimated to be an average 0.34 mm reduction in probing depth (Fig. 44-2). While the estimate seems modest in absolute value, it must be underlined that a systematic review conducted by Haffajee *et al*. (2003) for the same consensus conference and assessing the adjunctive benefit of systemic antibiotics reported exactly the same estimate for systemic antibiotics (see Chapter 43). While the systematic review (Hanes & Purvis 2003) addressed the concept of local delivery as a whole, it also analyzed the single technology platforms and molecules. It observed clinical improvements for the adjunctive application of minocycline gel, microencapsulated minocycline, doxycycline gel, and chlorhexidine chips. Indeed, the efficacy of each of the available local delivery devices needs to be assessed individually, as if any product does not satisfy the pharmacokinetic principles, it cannot be expected to provide significant clinical benefit.

	Adjunct	Reference	n1	n2	Effect	n total	*P* value
	CHX	Azmak *et al*. (2002)	20	20	0.350	40	0.266
	CHX	Grinsi *et al*. (2002)	9	10	–0.089	19	0 .841
	CHX	Jeffcoat *et al*. (1998)	208	211	0.405	419	0 .000
	CHX	Soskolne *et al*. (1997)	94	94	1.264	188	0 .000
Random	CHX (4)		331	335	0.553	886	0.058
	DOXY	Eickholz *et al*. (2002)	108	108	0.528	216	0 .000
	DOXY	Wennströ *et al*. (2001)	50	50	0.138	100	0.489
Random	DOXY (2)		158	158	0.360	318	0 .084
	MET	Riep *et al*. (2000)	29	29	–0.218	58	0 .404
	MET	Steilzel *et al*. (1999)	59	59	0.166	118	0 .367
Random	MET (2)		88	88	0.020	176	0 .915
	MINO	Graça *et al*. (1997)	13	13	0.131	26	0.733
	MINO	Jarrold *et al*. (1997)	22	22	0.297	44	0.322
	MINO	Timmerman *et al*. (1996)	10	10	0.026	20	0.953
	MINO	Van Steenberghe *et al*. (1993)	39	42	0.440	81	0.049
Random	MINO (4)		84	87	0.306	171	0.049
	MINO micro	Jones *et al*. (1994)	6	11	0.366	17	0.459
	MINO micro	Meinberg *et al*. (2002)	24	24	0.975	48	0.001
	MINO micro	Williams *et al*. (2001)	229	237	0.391	466	0.000
Random	MINO micro (3)		259	272	0.538	531	0.006
	TET	Drisko *et al*. (1995) <7 mm	116	116	0.139	232	0.289
	TET	Drisko *et al*. (1995) >7 mm	116	116	–0.097	232	0.458
	TET	Newman *et al*. (1994)	105	105	0.584	210	0.000
	TET	Wong *et al*. (1998)	30	30	0.068	60	0.790
Random	TET (4)		367	367	0.180	734	0.264
Random combined (19)			1287	1307	0.338	2594	0.000

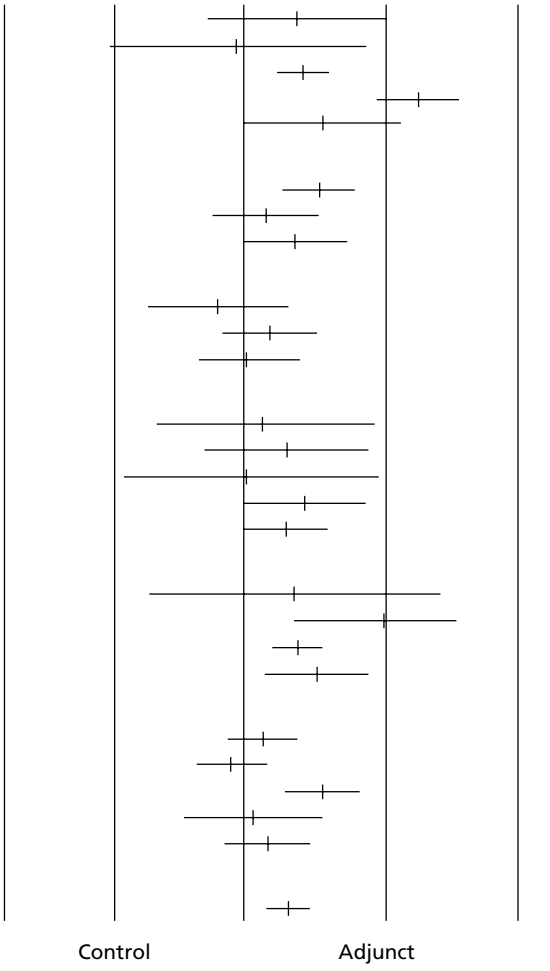

Fig. 44-2 Meta-analysis displaying reductions in probing pocket depths with adjunctive use of local delivery devices. (CHX, chlorhexidine; DOXY, doxycycline; MET, metronidazole; MINO, minocycline; TET, tetracycline.) (Source: Hanes & Purvis 2003. Reproduced with permission from the American Academy of Periodontology.)

Interestingly, this systematic review found no evidence of an adjunctive benefit from the application of local irrigants during or immediately after mechanical debridement. This finding is consistent with what can be expected based on local pharmacokinetic parameters: irrigating solutions are probably rapidly cleared by GCF flow.

The evidence base for this adjunctive treatment has considered essentially two types of populations: untreated patients and treated patients with recurrent/persistent disease participating in supportive periodontal care programs. Benefits have been established for both populations, although the size of the benefit in treated patients is expected to be smaller.

Few studies have addressed the management of furcation defects with local delivery devices. Short-term (3–6 months) adjunctive benefits in controlling gingival inflammation as well as improvements in probing depths and clinical attachment levels have been reported (Tonetti *et al*. 1995; Dannewitz *et al*. 2009). Interestingly, but perhaps not unexpectedly, the benefits did not persist medium to long term in these difficult anatomic areas.

Another interesting and rapidly emerging area of application of local delivery devices relates to the control of peri-implant infections, particularly peri-implantitis. Two independent systematic reviews on effective interventions for peri-implantitis (Esposito *et al*. 2012; Muthukuru *et al*. 2012) identified some initial evidence that local delivery combined with subgingival debridement may be of greater benefit than subgingival debridement alone. Further studies are necessary in this area.

Clinical indications for treatment of periodontitis with adjunctive local delivery devices

The majority of studies assessing the adjunctive benefit of local delivery devices to mechanical debridement have identified a range of clinical conditions where the addition of these devices leads to improved outcomes (Tonetti *et al*. 1994; Tonetti 1998; Greenstein & Tonetti 2000). These include special local conditions and special patient groups.

Local conditions

As the majority of untreated shallow (4–5 mm) pockets are expected to heal with mechanical debridement alone, local delivery devices are of potential benefit for deeper pockets (6–8 mm range) or furcation involvements (Tonetti *et al*. 1998; Dannewitz *et al*. 2009). Furthermore, incorporation of local delivery devices into the treatment armamentarium requires reconciliation of the localized nature of the treatment target (the periodontal pocket) with the overall ecologic determinants of clinical outcomes in light of available treatment alternatives [adjunctive systemic antimicrobials (see Chapter 43) or adjunctive access flap surgery (see Chapter 39)]. In general, adjunctive treatment with local delivery devices is favored when there are relatively few residual pockets and systemic delivery of the antimicrobial may not be warranted. In this respect, local delivery may be advantageous in the management of local non-responding sites or disease recurrence during supportive periodontal care. This latter application has received considerable attention (Garrett *et al*. 2000; McColl *et al*. 2006; Bogren *et al*. 2009; Tonetti *et al*. 2012).

Another potentially important application is when residual pockets are present in the so-called esthetic zone where a surgical intervention may compromise esthetics or phonetics. Lastly, application of local delivery devices seems to be a rationale choice at sites with deep pockets and persistent bleeding on probing that are associated with intrabony defects after completion of the cause-related phase of therapy. As these sites are likely to be treated with periodontal regeneration (see Chapter 45) and the outcome of periodontal regeneration is negatively affected by the degree of bacterial contamination and spectrum of pathogens persisting into the lesion (Heitz-Mayfield *et al*. 2006), local drug delivery may be an important means of pocket disinfection before regenerative periodontal surgery.

Special patient groups

From a clinical standpoint, important attenuations of the expected benefits of non-surgical and surgical treatment have been observed in high-risk groups. These include smokers and subjects with diabetes, significant co-morbidities or erratic compliance with oral hygiene and/or long-term adherence to the necessary supportive periodontal care program. The effect of adjunctive local drug delivery has been assessed in such subjects.

Studies have reported that the adjunctive effect of local drug delivery may not be adversely affected by cigarette smoking (Ryder *et al.* 1999). In a planned secondary analysis of a multicenter trial assessing the adjunctive benefits of minocycline microspheres, the enhanced response to local delivery device application was greatest among smokers (Paquette *et al*. 2003, 2004).

Older patients as well as those with concomitant self-reported cardiovascular disease have also been reported to respond better to adjunctive local delivery than to mechanical debridement alone. Local drug delivery may contribute to better control of periodontitis in subjects with relative or absolute contraindications to surgical intervention.

Lastly, in patients with diabetes and periodontitis, recent randomized controlled clinical trials have shown benefits in the control of gingival inflammation and better clinical outcomes from the application of adjunctive local drug delivery with respect to subgingival debridement alone (Agarwal *et al*. 2012).

Conclusion

Local drug delivery into the periodontal pocket is an effective treatment adjunct to mechanical debridement. Clinical application requires the use of a well-designed technology platform that is able to counteract GCF clearance of the locally applied antibiotic and maintain effective concentrations for long enough for the desired pharmacologic effect to occur. Pocket disinfection is feasible, but recolonization is a critical phenomenon that needs to be prevented with a specific clinical strategy: optimal supragingival hygiene, full-mouth approach, and/or use of an antiseptic mouth rinse. Clinical applications range from the management of few residual pockets in otherwise healthy subjects to the management of residual lesions in groups at high risk because of age, smoking, frailty, or the presence of important co-morbidities.

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Part 13: Reconstructive Therapy

Chapter 45

Regenerative Periodontal Therapy

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Introduction

The advances in the understanding of the biology of wound healing and periodontal regenerative technologies are applied to improve long-term clinical outcomes of teeth that are periodontally compromised by intrabony or inter-radicular defects. The treatment objective is to obtain shallow, maintainable pockets by reconstruction of the destroyed attachment apparatus and thereby also limit recession of the gingival margin. In general, periodontal regeneration is selected to obtain: (1) an increase in the periodontal attachment of a severely compromised tooth; (2) a decrease in deep pockets to a more maintainable range; and (3) a reduction of the vertical and horizontal component of furcation defects. Current approaches, however, remain technique sensitive and clinical success requires application of meticulous diagnostic and treatment strategies.

Classification and diagnosis of periodontal osseous defects

Site-specific periodontal breakdown compromises the long-term prognosis of teeth by producing three types of defects: suprabony (or horizontal) defects, infrabony (or vertical) defects, and inter-radicular (or furcation) defects.

According to the classification by Goldman and Cohen (1958), suprabony defects are those where the base of the pocket is located coronal to the alveolar crest. This chapter does not deal with suprabony defects.

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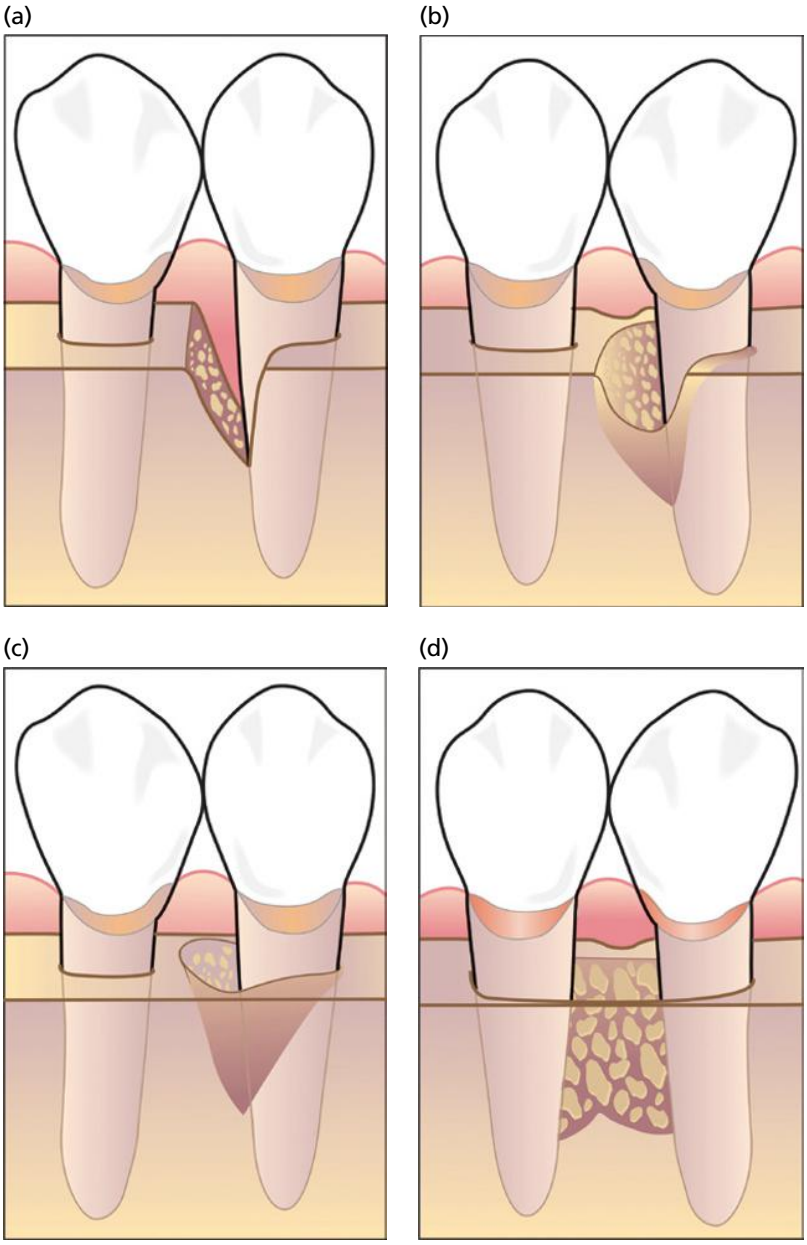


Fig. 45-1 Infrabony defects. (a) One-wall intrabony defect; (b) two-wall intrabony defect; (c) three-wall intrabony defect; (d) interproximal crater. (Source: Papapanou & Tonetti 2000. Reproduced with permission from John Wiley & Sons.)

Infrabony defects, on the other hand, are defined by the apical location of the base of the pocket with respect to the residual alveolar crest. With regard to infrabony defects, two types can be recognized: intrabony defects and craters. Intrabony defects are bony defects whose infrabony component affects primarily one tooth, while in craters the defect affects two adjacent root surfaces to a similar extent. Intrabony defects (Fig. 45-1) have been classified according to their morphology in terms of residual bony walls, width of the defect (or radiographic angle), and topographic extension around the tooth. Three-wall, two-wall, and one-wall defects have been defined on the basis of the number of residual alveolar bone walls. This represents the primary classification system. Frequently, intrabony defects present a complex anatomy consisting of a three-wall component in the most apical portion of the defect, and two- and/or one-wall components in the more superficial portions. Hemiseptal defects, that is vertical defects in the presence of adjacent roots and where half of a septum remains on one tooth, represent a special case of one-wall defects. Several authors have also used descriptive terms to define special morphologic characteristics: funnel-shaped defects, moat-like defects, trenches, etc.

Of particular interest is a special morphology: the crater (Fig. 45-1). It is defined as a cup- or bowl-shaped defect in the interdental alveolar bone with bone loss nearly equal from the roots of two contiguous teeth and a more coronal position of the buccal and lingual alveolar crest; the facial and lingual/palatal walls may be of unequal height. This defect can be considered to be the result of the apical spread of periodontitis along two adjacent roots in a relatively narrow (mesiodistally) interproximal area.

Notably, all the definitions above are not based on radiographic assessments, but on the actual

morphology of the defects after flap elevation. Conditions entailing pathologic resorption of bone within the furcation of a multirooted tooth, defined as furcation invasions, are also classed as periodontal bony defects; the reader is referred to Chapter 40 for a discussion of the anatomy and classification of furcations.

The diagnosis of the presence and the morphology of periodontal osseous lesions represents a major clinical challenge. It is primarily performed by combining clinical information derived from the evaluation of the attachment level with information derived from diagnostic-quality parallel-technique intraoral radiographs. A precise knowledge of root anatomy and its variations is also important for the diagnosis of periodontal osseous defects, and inter-radicular defects in particular. Diagnostic-quality radiographs provide additional information on the morphology of the alveolar bone resorption. In this context, interpretation of the radiographic image of the interdental septum is complicated, since the radiograph provides a two-dimensional image of a three-dimensional anatomy consisting of superimposed structures, including alveolar bone, hard tooth substances, and soft tissue. This complexity of the visualized structures means that a certain amount of tissue destruction must occur before it can be radiographically detected, often rendering incipient bone lesions obscure. Furthermore, even advanced lesions may be masked by the presence of superimposed structures. It is therefore generally stated that radiographic diagnosis has a high positive predictability (i.e. the visualized lesions are indeed there) but a low negative predictability (i.e. the absence of radiographically detectable bone loss does not exclude the presence of an osseous lesion).

Clinical attachment level (CAL), on the other hand, is a highly sensitive diagnostic tool; its combination with radiographs, therefore, confers a higher degree of accuracy to the diagnostic approach (Tonetti *et al.* 1993b). In particular, the site-specific comparison of radiographic bone loss with clinical attachment loss allows the clinician to make a qualified guess of the true osseous architecture, whose exact morphology, however, can only be established after flap elevation. Detection of the defect, its location and extension, along with its major morphologic features, should be performed before flap elevation. A further aid to this end is the use of transgingival probing or bone sounding.

Clinical indications

Periodontal treatment, either surgical or non-surgical, results in recession of the gingival margin after healing (Isidor *et al*. 1984). In advanced cases of periodontitis, this may lead to poor esthetics in the front areas of the dentition, in particular when applying surgical procedures with osseous recountouring for the eradication of bone defects. Treatment of such cases without bone contouring, on the other hand, may result in residual pockets inaccessible to proper cleaning during post-treatment maintenance. These problems can be avoided or reduced by applying regenerative surgical procedures to restore the lost periodontal attachment in the bone defects. Thus, the indication for applying regenerative periodontal therapy is often based on esthetic considerations, besides the fact that the function or long-term prognosis of the treated teeth may be improved.

Other indications for regenerative periodontal therapy include furcation-involved teeth. The furcation area is often inaccessible to adequate instrumentation and frequently the roots present concavities and furrows that make proper cleaning of the area impossible after access or resective surgery. Considering the long-term results and complications reported following treatment of furcation involvements by traditional surgical therapy (Hamp *et al*. 1975; Bühler 1988), the long-term prognosis of furcation-involved teeth can be improved considerably by successful regenerative periodontal therapy.

Case reports also exist demonstrating that "hopeless" teeth with deep vertical defects, increased tooth mobility or through-and-through furcations can be successfully treated with regenerative periodontal therapy (Gottlow *et al*. 1986). Teeth with deep pockets associated with deep intrabony defects are considered a clinical challenge. Most authors have classified such teeth as having either a questionable or a hopeless prognosis. Key elements supporting these opinions are the complex interplay of reduced residual periodontal attachment, deep pocketing, functional demands, and frequently the resulting tooth hypermobility (Lang & Tonetti 1996; McGuire & Nunn 1996a, b; Kwok & Caton 2007). It is therefore clear that the possibility of changing the prognosis of a tooth from "questionable" or "hopeless" to "fair" or "favorable" would greatly help clinicians and patients in the difficult job of maintaining teeth over time, and the possibility of gaining periodontal support would help improve patient comfort and function.

Long-term effects and benefits of regeneration

A pertinent question with respect to regenerative treatment is whether or not the achieved attachment level gains can be maintained over an extended period of time. In a long-term follow-up study, Gottlow *et al*. (1992) assessed the stability of new attachment gained through guided tissue regeneration (GTR) procedures. Eighty sites in 39 patients, which 6 months after surgery exhibited a gain of clinical attachment of ≥2 mm (2–7 mm), were monitored over an additional period of 1–5 years. Of the 80 sites, 65 were monitored for 2 years, 40 for 3 years, 17 for 4 years, and nine for 5 years. The results of this study and those of other trials indicate that attachment gain obtained following GTR treatment can be maintained on a long-term basis (Becker & Becker 1993; McClain & Schallhorn 1993).

An investigation of intrabony defects demonstrated that the stability of sites treated with GTR

was dependent on patient participation in a recall program, and on the absence of bacterial plaque, bleeding on probing (BoP), and re-infection of the treated sites with periodontal pathogens (Cortellini *et al*. 1994). The susceptibility to disease recurrence at sites treated with non-bioresorbable barrier membranes was assessed in a study comparing long-term changes in attachment levels at regenerated and non-regenerated sites in the same patient (Cortellini *et al*. 1996a). Results indicated that there was a high degree of concordance in the clinical outcomes (stability versus recurrence of attachment loss) within the same patient, suggesting that patient factors, rather than site factors, including the specifics of the histologic type of expected wound healing, are associated with disease recurrence. Among patient factors, compliance with oral hygiene, smoking habits, and susceptibility to disease progression were the major determinants of stability of the treated sites, rather than the employed treatment modality.

Support for a limited impact of the histologic type of healing comes from an experimental study. In a study in monkeys (Kostopoulos & Karring 1994), periodontal breakdown was produced by the placement and retention of orthodontic elastics on experimental teeth until 50% bone loss was recorded. The experimental teeth were endodontically treated and subjected to a flap operation, and all granulation tissue was removed. The crowns of the teeth were resected at the level of the cementoenamel junction and a barrier membrane was placed to cover the roots before they were submerged. Following 4 weeks of healing, the membranes were removed. At the same time, the contralateral teeth that served as controls were endodontically treated and subjected to a sham operation during which the crowns were resected at the level of the cementoenamel junction. Artificial composite crowns were then placed on both the experimental and the control roots. The sites were allowed to heal for 3 months during which period careful plaque control was performed. At the end of this period, cotton-floss ligatures were placed on both experimental and control teeth to induce periodontal tissue breakdown. After another 6 months, the animals were sacrificed. With respect to attachment level, bone level, probing pocket depth (PPD), and gingival recession, similar results were recorded in the histologic specimens of experimental (Fig. 45-2) and control (Fig. 45-3) teeth. This indicates that the new connective tissue attachment formed with GTR is no

Fig. 45-2 Microphotograph of test specimen with a reformed connective tissue attachment. After 6 months of ligature-induced periodontitis, loss of attachment has occurred from the coronal cut root surface to the level indicated by the arrow.

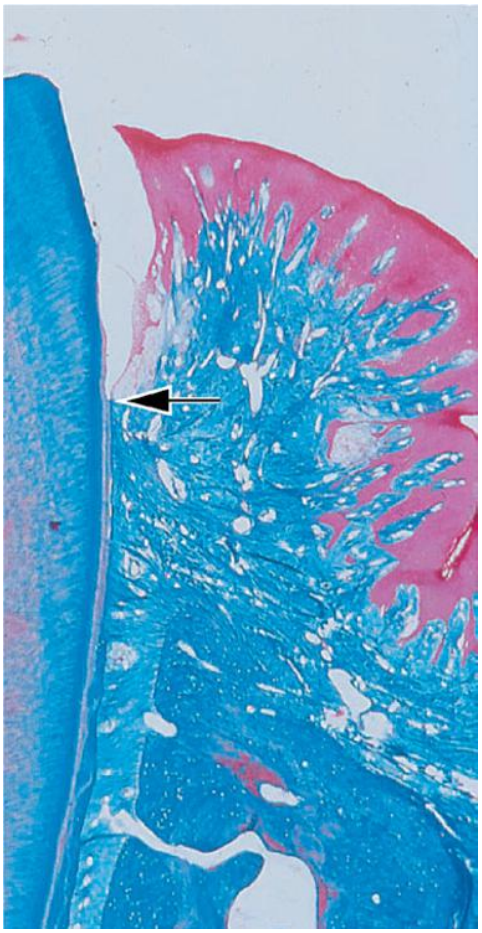


Fig. 45-3 Microphotograph of control specimen with a naturally existing periodontium. After 6 months of ligature-induced periodontitis, loss of attachment has occurred from the coronal cut tooth surface to the level indicated by the arrow.

Table 45-1 Survival analysis of regenerated periodontal attachment over a 16-year follow-up period in 175 subjects treated with periodontal regeneration. In this survival analysis, the event is represented by clinical attachment level (CAL) loss of ≥2 mm from the level of attachment obtained at completion of healing 1 year after regeneration. No substantial recurrence of periodontitis (CAL loss) was observed in 92% of treated cases who participated in a secondary prevention program.

Time at risk (years)	Number of CAL loss ≥2 mm	Censored	Effective sample size	Conditional probability of CAL loss (%)	Survival (%)
0–2	2	0	175	1.1	100
2–4	3	0	166	1.7	98.9
4–6	2	0	155	1.2	97.1
6–8	1	55	119	0.7	96
8–10	0	47	70.5	0	95.3
10–12	2	16	41	3.5	95.3
12–14	0	25	24.5	0	92
14–16	0	21	8	0	92
16	0	1	0.5	0	92

Source: Cortellini & Tonetti (2004). Reproduced with permission from the American Academy of Periodontology.

more susceptible to periodontitis than the naturally existing periodontium.

Other long-term studies show that, if the patient participates in a professionally delivered supportive periodontal care program and maintains good oral hygiene, the regenerated attachment can be maintained long term (Sculean *et al*. 2006; Christgau *et al*. 1997; Eickholz *et al*. 2007; Slotte *et al*. 2007; Sculean *et al*. 2008; Nickles *et al*. 2009; Pretzl *et al*. 2009; Nygaard-Østby *et al*. 2010).

Few investigations have looked at the long-term effects of periodontal regeneration on tooth survival. Cortellini and Tonetti (2004) performed a Kaplan–Mayer analysis of tooth survival following periodontal regenerative treatment in a sample of 175 patients followed up for 2–16 years (average 8 ± 3.4 years) in a specialist environment. In this study, 96% of teeth treated with periodontal regeneration survived. Of interest was the observation that tooth loss was observed among only the 32% of the population who smoked (tooth survival was 89% among smokers and 100% among non-smokers). CALs were located at the same level or coronal to the pretreatment levels in 92% of cases up to 15 years after treatment (Table 45-1, Fig. 45-4).

The potential clinical benefits of periodontal regeneration are best illustrated in a consecutive case series of strategic abutments severely compromised by the presence of deep intrabony defects with associated deep pockets, which were followed up for up to 8 years following regenerative treatment (Tonetti *et al*. 1996b; Cortellini *et al*. 1999b). At baseline, the periodontal defect rendered these teeth unsuitable as abutments to be included in a reconstruction. In all cases, periodontal regeneration with barrier membranes was able to change the clinical prognosis by providing both a 30% increase in radiographic bone support and shallow, maintainable PPD. These outcomes remained stable during the follow-up period (Fig. 45-5).

A few studies have evaluated the long-term prognosis for furcation defects treated with regenerative therapy. Sixteen mandibular class II furcation defects, following coronal flap positioning and citric acid root biomodification with and without implantation of demineralized freeze-dried bone allografts (DFDBAs), were determined to be completely resolved with bone fill assessed by re-entry surgery. They were re-evaluated after 4–5 years (Haney *et al*. 1997), when 12 of the 16 sites exhibited recurrent class II furcations and all 16 sites demonstrated probable buccal furcation defects. The investigators concluded that these findings question the long-term stability of bone regeneration in furcations following coronally advanced flap procedures. A similar benefit has been reported following use of combination therapy (barrier membranes and DFDBA) in teeth compromised by class II furcation defects (Bowers *et al*. 2003): 92% of the class II defects were either closed or transformed into class I and thus at lower risk of tooth loss 1 year after therapy (McGuire & Nunn 1996a, b).

The long-term stability of mandibular furcation defects regenerated following GTR alone or in combination with root surface biomodification with citric acid and bone grafting, was also evaluated by McClain and Schallhorn (1993). Of the 57% of the furcation defects that were assessed as completely filled at 6 and 12 months, only 29% were completely filled after 4–6 years. However, 74% of the furcations treated with GTR in combination with the placement of DFDBA were completely filled at both the short- and long-term evaluation, suggesting that the results obtained with the combined procedure were more stable over time. Long-term results of GTR treatment of mandibular class II furcations with expanded polytetrafluoroethylene (ePTFE) membranes were also reported by Machtei *et al*. (1996). The teeth were followed up for 4 years and compared with non-furcated molars. Improvements assessed in vertical (V-CAL) and horizontal CAL (H-CAL) after treatment were also maintained after 4 years, suggesting that changes obtained in class II furcation defects by GTR are stable. Only 9% of the treated defects were unstable, which was similar to the

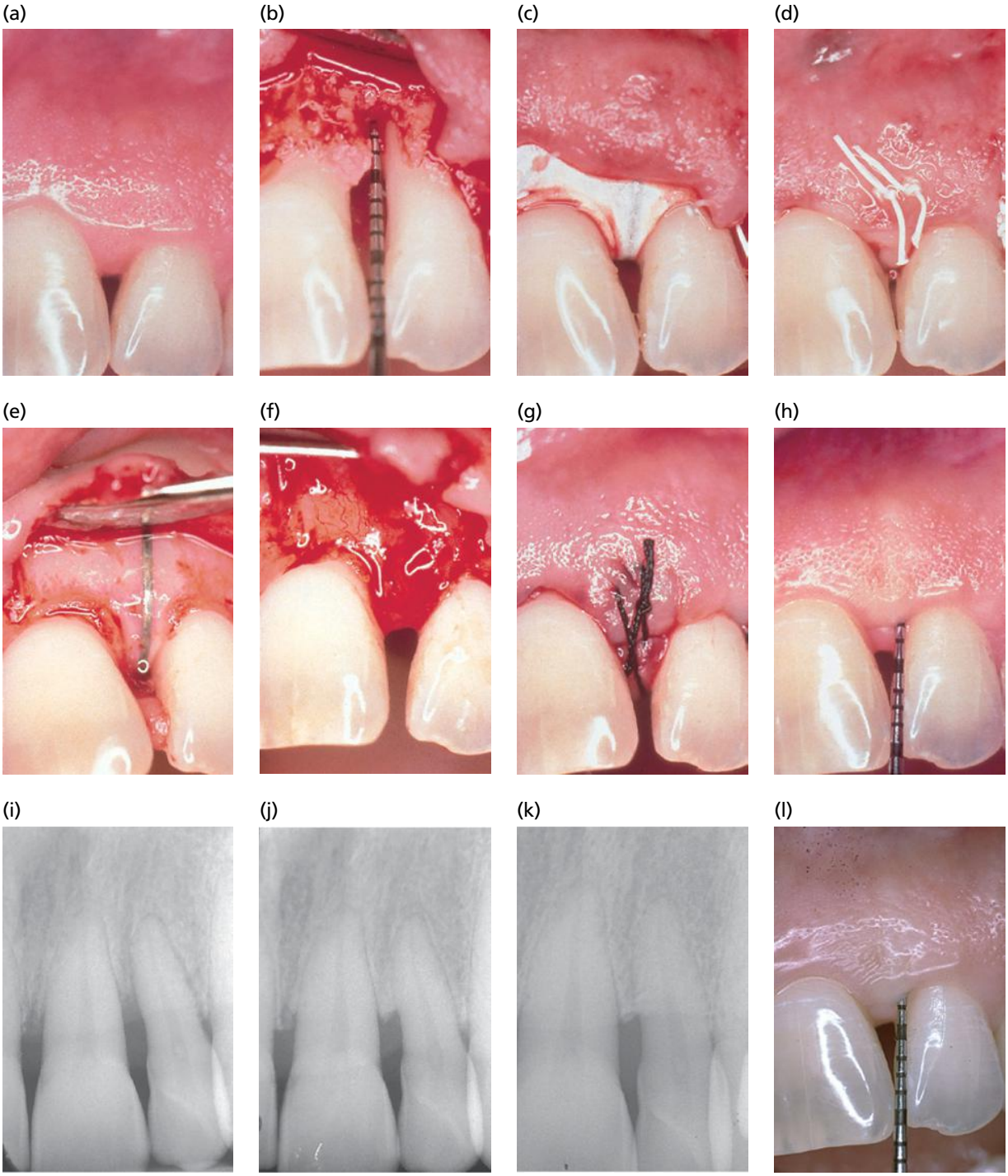


Fig. 45-4 (a, b) Left maxillary lateral incisor with a deep interproximal intrabony defect on the mesial surface. (c) Flaps are raised according to the modified papilla preservation technique, and a titanium-reinforced barrier membrane is placed over the defect. (d) By coronal displacement of the flap and preservation of the interdental papilla, the membrane is completely covered. (e, f) After 6 weeks of uneventful postoperative healing, the membrane was removed and (g) the newly formed tissue was completely covered. (h) At 1 year, residual probing pocket depth was 2 mm and no buccal or interdental recession had occurred. (i) Baseline radiograph showed radiolucency approaching the apex of the tooth, but after 1 year the intrabony defect is resolved and some supracrestal bone apposition seems to have occurred (j). Radiograph taken at 6 years confirms the supracrestal bone regeneration (k) and the clinical image showed the integrity of the interdental papilla with optimal preservation of the esthetic appearance (l).

percentage observed for non-furcated molars. Good oral hygiene, as reflected in low plaque scores and elimination of periodontal pathogens, was closely related to the long-term stability. On the basis of these results, it was concluded that furcation defects treated with membrane barriers can be maintained in health for at least 4 years, provided good oral hygiene and frequent recall visits are established.

The survival rate of furcated teeth treated with regenerative therapy has been investigated in a few studies. Yukna and Yukna (1997) reported a 100% survival rate after an average observation period of

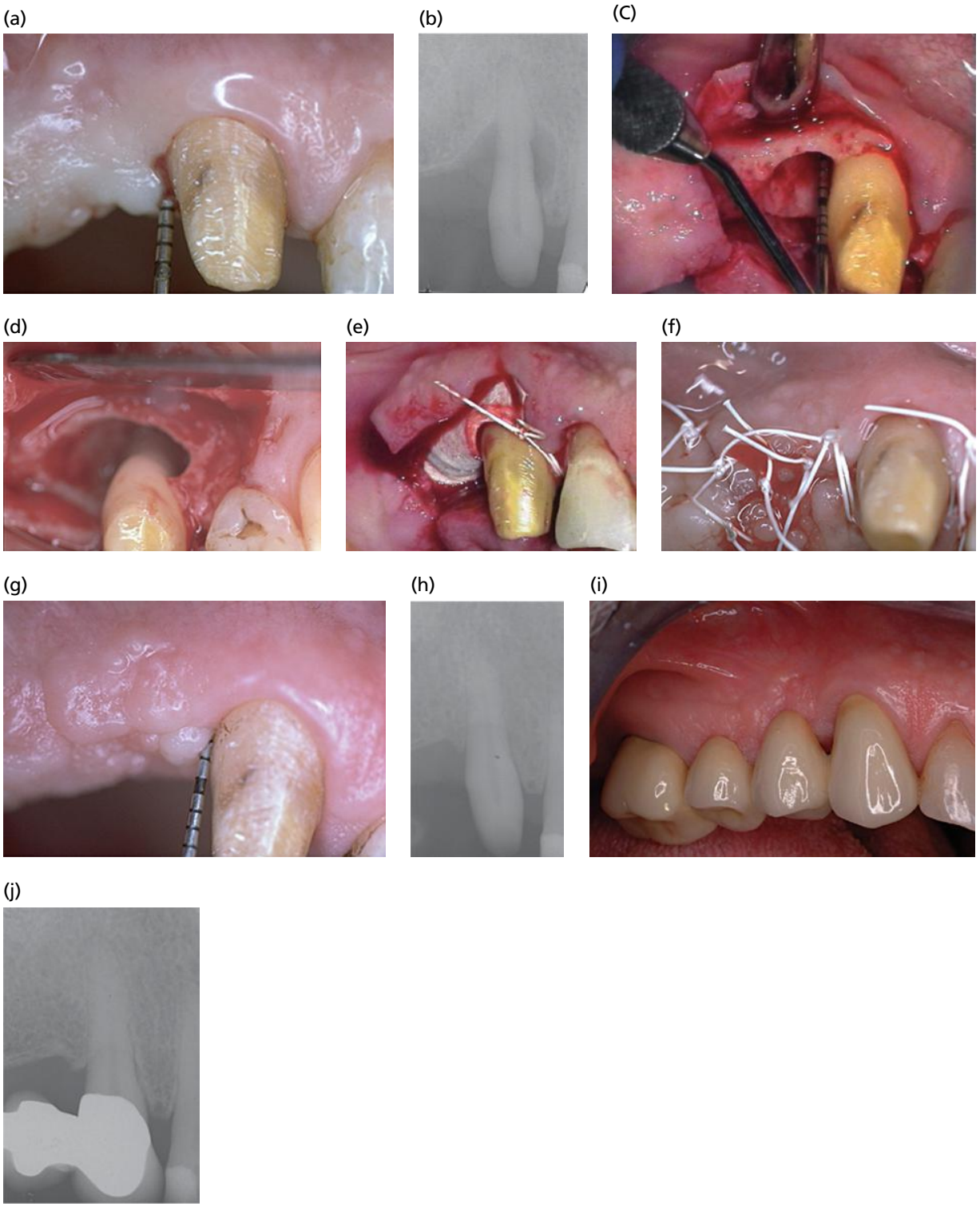


Fig. 45-5 Clinical benefits of periodontal regeneration. Patient presented with periodontally compromised mesial abutment of the bridge: a 10-mm pocket was associated with a 10-mm intrabony defect extending on three of the four surfaces of the tooth (a–d). A barrier membrane was positioned and secured around the root of the tooth (e). Primary closure with internal mattress sutures was achieved (f) and maintained during the healing period. At 1 year, periodontal probing showed a shallow maintainable pocket (3 mm) (g) and the complete resolution of the defect (h). Clinical and radiographic stability of the outcome is shown 10 years following regenerative therapy (i, j): stability of the gingival margin, shallow pockets, good esthetics, and good periodontal support for the abutment are evident.

6.6 years in 26 mandibular and maxillary furcated molars treated with synthetic bone graft and coronally advanced flap. Eickholz and Hausmann (2002) reported a 100% survival rate after 60 months in 10 mandibular and 10 maxillary furcated molars treated with barriers. A survival rate of 98.1% was reported by Dannewitz *et al*. (2006) after a 107-month observation period of 29 maxillary and 24 mandibular furcated molars treated with GTR. Eickholz *et al*. (2006) reported an 83.3% survival rate after 10 years

in 18 mandibular and maxillary molars treated with barriers.

Summary: Several clinical studies addressing the long-term effects of periodontal regeneration show that, if the patient participates in a professionally delivered supportive periodontal care program and maintains good oral hygiene, the regenerated attachment can be maintained long term. Risk factors for attachment loss are those associated with disease recurrence: poor compliance with supportive periodontal care, poor oral hygiene, and cigarette smoking. In addition, most treated teeth affected by intrabony defects or furcation involvement can be maintained over long periods of time provided proper supportive periodontal and home care is undertaken.

Evidence for clinical efficacy and effectiveness

Questions of efficacy relate to the added benefit of a treatment modality under ideal experimental conditions (such as those of a highly controlled research center environment). Effectiveness, on the other hand, relates to the benefit that can be achieved in a regular clinical setting where the procedure is likely to be performed in relation to morbidity and adverse events. Besides efficiency considerations, both evidence for efficacy and effectiveness need to be available in order to provide support for the adoption of a novel approach in clinical practice.

The clinical efficacy of periodontal regenerative procedures has been extensively evaluated in randomized controlled clinical trials that have compared the regenerative procedure with a standard approach. To limit sample size and study duration, these trials have utilized surrogate outcomes – CAL changes, decrease in PPD, furcation closure or radiographic measurements–rather than changes in tooth survival. These surrogate outcomes, however, are considered to be adequate proxies of the true outcome represented by tooth survival: persistence of deep pockets or furcation involvement are associated with a higher risk of periodontal breakdown and tooth extraction.

The majority of clinical trials have been small single-center studies. The evidence from these studies has been summarized in meta-analyses performed on data retrieved by systematic reviews of the published literature. In 2002, 2003, and 2008, the European Workshop on Periodontology and the Workshop on Emerging Technologies in Periodontics provided much of the systematic assessment of the evidence for currently available technologies. These include the use of barrier membranes (GTR), bone replacement grafts (BRGs), and biologically active regenerative materials, as well as the application of combination therapy. The clinical evidence must be interpreted in the context of the biologic mechanisms and evidence for regeneration discussed in Chapter 28.

The evidence for clinical efficacy of barrier membranes has been assessed in the systematic reviews and meta-analyses performed by Needleman *et al*. (2002, 2006), Jepsen *et al*. (2002), Murphy and Gunsolley (2003), and Kinaia (2011).

For intrabony defects, 26 controlled trials with 867 intrabony defects were included (Murphy & Gunsolley 2003). The application of barrier membranes resulted in an additional CAL gain of >1 mm compared to that with an access flap approach control (Fig. 45-6). A more recent meta-analysis (Needleman *et al*. 2006) was performed on 17 randomized controlled trials (16 studies testing GTR alone and two testing GTR + bone substitutes). For CAL change, the mean difference between GTR and open flap debridement (OFD) was 1.22 mm (95% CI random

	Barrier	Reference	SD/SE date provided	Test barrier	n1	n2	Effect	n total	*P* value
	Collagen	Quteish 1992	N	Hum coll	16	16	0.703	32	0.050
	Collagen	Blumethal 1990	Y	Bov coll	10	10	0.706	20	0.117
	Collagen	Al-Arrayed 1995	N	Hum coll	11	11	0.743	22	0.085
Random	**Collagen (3)**				**37**	**37**	**0.716**	**74**	**0.004**
	e-PTFE	Nygaard-Østby 1996	Y	e-PTFE	15	13	0.121	28	0.744
	e-PTFE	Zybutz 2000	Y	e-PTFE	14	14	0.388	28	0.300
	e-PTFE	Pontoriero 1999	N	e-PTFE	10	10	0.691	20	0.124
	e-PTFE	Kilic 1997	Y	e-PTFE	18	18	0.796	36	0.020
	e-PTFE	Kim 1996	Y	e-PTFE	19	18	1.030	37	0.003
	e-PTFE	Cortellini 1995	Y	e-PTFE	15	15	1.153	30	0.003
	e-PTFE	Tonetti 1996	Y	e-PTFE	15	15	1.153	30	0.003
	e-PTFE	Cortellini 1995	Y	e-PTFE-TR	15	15	1.816	30	0.000
	e-PTFE	Cortellini 1996	Y	e-PTFE	12	12	2.545	24	0.000
Random	**e-PTFE (9)**				**133**	**130**	**1.014**	**263**	**0.000**
	Polymeric	Ratka-Kruger 2000	Y	PLA	16	16	–0.077	32	0.824
	Polymeric	Mayfield 1998	Y	PLA	22	22	0.109	44	0.714
	Polymeric	Cortellini 2001	Y	PGA	55	55	0.458	110	0.017
	Polymeric	Brathall 1998	Y	PLA/PGA	9	9	0.476	18	0.305
	Polymeric	Tonetti 1998	Y	PLA/PGA	69	69	0.552	138	0.001
	Polymeric	Zybutz 2000	Y	PLA	15	15	0.563	30	0.124
	Polymeric	Cortellini 1998	Y	PLA	23	23	0.786	46	0.009
	Polymeric	Pontoriero 1999	Y	PLA	10	10	0.879	20	0.055
	Polymeric	Pontoriero 1999	N	PLA/PGA	10	10	1.005	20	0.031
	Polymeric	Sculean 2001	N	PLA/PGA	14	14	1.046	28	0.008
	Polymeric	Joly 2002	Y	PLA/PGA	10	10	1.915	20	0.000
	Polymeric	Cortellini 1996	Y		12	12	2.221	24	0.000
Random	**Polymeric (12)**				**265**	**265**	**0.700**	**530**	**0.000**
	Random combined (24)				435	432	0.811	867	**0.000**

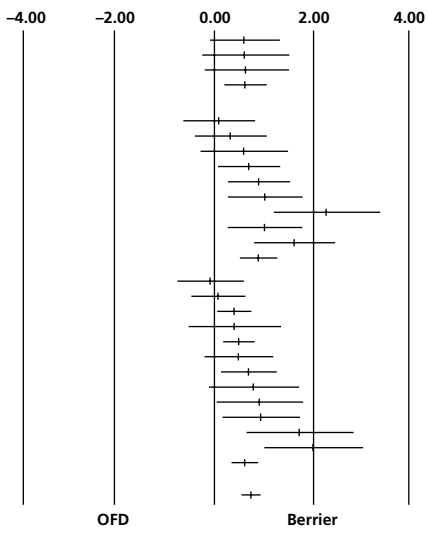


Fig. 45-6 Meta-analysis of intrabony defect studies examining open flap debridement versus guided tissue regeneration (GTR) with barrier, using clinical attachment level (CAL) gain as an outcome variable. (Bov coll, bovine collagen; e-PTFE, expanded polytetrafluoroethylene; Hum coll, human collagen; PLA, polylactic acid; PLA/PGA, polylactic/polyglycolic acid; TR, titanium-reinforced; OFD, open flap debridement.) (Source: Murphy & Gunsolley, 2003. Reproduced from the American Academy of Periodontology.)

effects 0.80–1.64) and for GTR + bone substitutes was 1.25 mm (95% CI 0.89–1.61). The authors highlighted that GTR showed a significant benefit when comparing the numbers of sites failing to gain 2 mm of attachment, with a risk ratio of 0.54 (95% CI random effects 0.31–0.96). The number needed to treat (NNT) for GTR to achieve one extra site gaining 2 mm or more of attachment over OPD was therefore eight (95% CI 5–33), based on an incidence of 28% of sites in the control group failing to gain 2 mm or more of attachment. For baseline incidences in the range of the control groups of 3% and 55%, the NNT would be 71 and four, respectively. The authors concluded that GTR has a greater effect on probing measures of periodontal treatment than OPD, including improved attachment gain, reduced PPD, less increase in gingival recession, and more gain in hard tissue probing at re-entry surgery. However, there was marked variability between the studies and the clinical relevance of these changes is unknown.

For class II furcation defects, 15 controlled trials with 376 involved teeth were included (Murphy & Gunsolley 2003). Membrane application resulted in additional vertical and horizontal (depth of the furcation involvement) CAL gains (Fig. 45-7). A meta-analysis of re-entry studies on the treatment of class II molar furcation involvement (Kinaia *et al*. 2011) was performed on 13 controlled clinical trials. There was a significant improvement for bioresorbable versus non-bioresorbable membranes mainly in vertical bone fill (0.77–0.33 mm; 95% CI 0.13, 1.41). Non-bioresorbable membranes showed significant improvement in vertical probing reduction (0.75–0.31 mm; 95% CI 0.14, 1.35), attachment gain (1.41–0.46 mm; 95% CI 0.50, 2.31), horizontal bone fill (1.16–0.29 mm; 95% CI 0.59, 1.73), and vertical bone fill (0.58–0.11 mm; 95% CI 0.35, 0.80) over OFD. Bioresorbable membranes showed significant reduction in vertical probing depth (0.73–0.16 mm; 95% CI 0.42, 1.05), attachment gain (0.88–0.16 mm; 95% CI 0.55, 1.20), horizontal bone fill (0.98–0.12 mm; 95% CI 0.74, 1.21), and vertical bone fill (0.78–0.19 mm; 95% CI 0.42, 1.15) over OFD.

These data alone, however, did not present conclusive evidence of efficacy as the possibility of bias arising from a possible tendency to report studies with positive results could not be ruled out. Multicenter studies were designed to assess efficacy conclusively. These were performed in a private practice environment in order to assess also the generalizability of the benefit to this specific setting (effectiveness). The results of large prospective multicenter studies in private practice settings (Tonetti *et al*. 1998, 2004b; Cortellini *et al*. 2001) conclusively support the additional benefit of membranes in improving CAL in intrabony defects, and thus their efficacy and effectiveness. More limited evidence is also available for combination therapy (BRG + barrier membranes) in furcation defects (Bowers *et al*. 2003).

The efficacy of BRG materials has been assessed in two systematic reviews (Trombelli *et al*. 2002; Reynolds *et al*. 2003). As these two systematic reviews used significantly different criteria for study inclusion, their results do not fully overlap. Trombelli *et al*. (2002), who included only controlled studies that reported changes in CAL as the primary outcome, concluded that there was insufficient evidence to support the clinical use of BRG materials in intrabony defects, since: (1) there was significant heterogeneity among the included studies; (2) the size of the adjunctive effect was small; and (3) there were differences that did not allow pooling of results obtained with different materials. In the other meta-analysis for intrabony defects, 27 controlled trials with 797 intrabony defects were included (Reynolds *et al*. 2003). The application of BRG resulted in an additional CAL gain of 0.5 mm compared to an access flap approach control (Fig. 45-8). Greater additional benefits from the application of BRG were observed whenever hard tissue measurements (bone fill or defect resolution) were utilized as outcome measures.

For furcation defects, the lack of consistent comparisons did not allow a meaningful assessment of the potential benefits of the use of BRGs alone (Reynolds *et al*. 2003). No large multicenter trials

	Barrier	Reference	Location	SD/SE data provided	n1	n2	Effect	n total	*P* value
	Collagen	Wang 1994	Mand	Y	12	12	0.516	24	0.204
Random	**Collagen (1)**				**12**	**12**	**0.516**	**24**	**0.228**
	e-PTFE	Pontoriero 1995	Max	N	8	8	0.000	16	1.000
	e-PTFE	Lekovic 1989	Mand	Y	12	12	0.026	24	0.949
	e-PTFE	Pontoriero 1995	Max	N	10	10	0.190	20	0.663
	e-PTFE	Pontoriero 1995	Max	N	10	10	0.759	20	0.093
	e-PTFE	Metzler 1991	Max	Y	17	17	1.172	34	0.001
	e-PTFE	Pontoriero 1988	Mand	Y	21	21	1.450	42	0.000
	e-PTFE	Avera 1998	Max	Y	8	8	9.115	16	0.000
Random	**e-PTFE (7)**				**86**	**86**	**0.930**	**172**	**0.025**
	Por coll	Flanary 1991	Mixed	Y	19	19	0.857	38	0.011
	Peristeum	Lekovic 1991	Mand	Y	15	15	2.943	30	0.000
Random	**Other (2)**				**34**	**34**	**1.856**	**68**	**0.080**
Random	**Combined (10)**				**132**	**132**	**1.063**	**264**	**0.001**

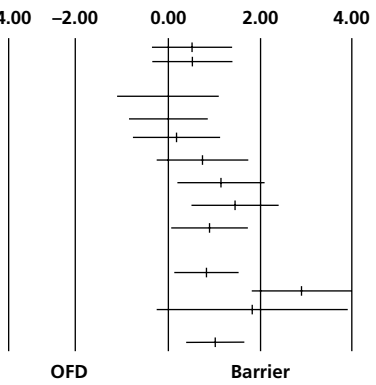


Fig. 45-7 Forest plot of furcation defect studies examining open flap debridement (OFD) versus guided tissue regeneration (GTR) with barrier, using horizontal open probing attachment gain as an outcome variable. (e-PTFE, expanded polytetrafluoroethylene; Mand, mandibula; Max, maxilla.) (Source: Murphy & Gunsolley 2003. Reproduced from the American Academy of Periodontology.)

	Graft	Reference	n1	n2	Effect	n total	*P* value
	ALL	Masters 1996	15	15	–0.316	30	0.382
	ALL	Brown 1998	8	8	–0.279	16	0.565
	ALL	Yukna 1998	31	31	0184	62	0.465
	ALL	Borgetti 1993	10	10	0.272	20	0.533
	ALL	Masters 1996	15	15	0.293	30	0.417
	ALL	Mabry 1995	8	8	0.292	16	0.546
	ALL	Schrad 1986	6	6	0.347	12	0.530
	ALL	Altiere 1979	9	9	0.362	18	0.432
	ALL	Mellonig 1984	11	11	0.813	22	0.061
	ALL	Movin 1982	22	6	1.023	28	0.031
	ALL	Blumenthal 1990	10	10	1.056	20	0.024
	ALL	Pearson 1981	7	7	1.479	14	0.012
Random	**ALL (12)**		**152**	**136**	**0.376**	**288**	**0.008**
	AUT	Renvert 1985	19	19	0.277	38	0.390
	AUT	Carraro 1976	39	26	0.562	65	0.028
	AUT	Movin 1982	6	6	1.644	12	0.012
Random	**AUT (3)**		**64**	**51**	**0.584**	**115**	**0.030**
	CER	Yukna 1985	13	13	0.205	26	0.595
	CER	Galgut 1992	10	10	0.584	20	0.190
	CER	Mora 1995	10	10	0.917	20	0.046
	CER	Kenney 1985	25	25	1.279	50	0.000
Random	**CER (4)**		**58**	**58**	**0.783**	**116**	**0.003**
	COR	Yukna 1994	20	20	0.299	40	0.342
	COR	Kim 1996	13	18	0.464	31	0.201
	COR	Schulz 2000	11	12	1.233	23	0.006
	COR	Mora 1995	10	10	1.226	20	0.010
Random	**COR (4)**		**54**	**60**	**0.705**	**114**	**0.004**
	GLA	Zamet 1997	20	20	0.111	40	0.722
	GLA	Ong 1998	13	14	0.254	27	0.503
	GLA	Park 2001	38	38	0.902	76	0.000
	GLA	Rosenberg 2000	12	6	1.264	18	0.017
Random	**GLA (4)**		**83**	**78**	**0.585**	**161**	**0.022**
Random	**Combined (27)**		**411**	**383**	**0.553**	**794**	**0.000**

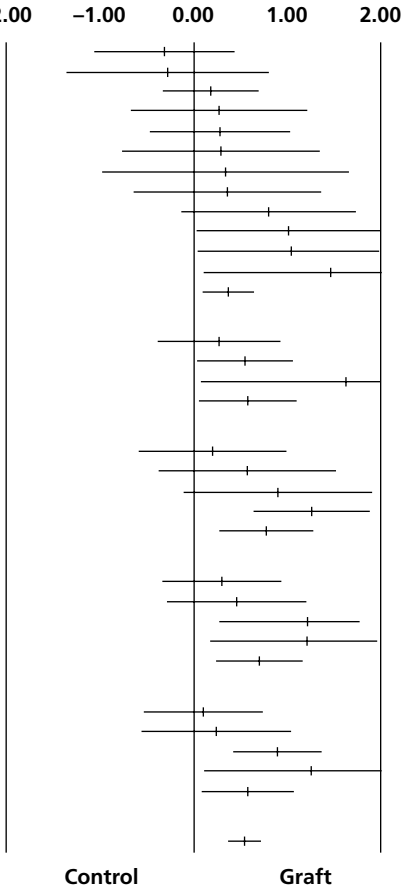


Fig. 45-8 Final meta-analysis of clinical attachment level in randomized controlled clinical studies comparing bone replacement graft (BRG) to open flap debridement (OFD) in the treatment of intrabony defects. (ALL, allograft; AUT, autograft; CER, calcium phosphate (hydroxyapatite) ceramic; COR, coralline calcium carbonate; GLA, bioactive glass.) (Source: Reynolds *et al.* 2003. Reproduced from the American Academy of Periodontology.)

have provided definitive support for efficacy and/or effectiveness of the use of BRGs.

The evidence for clinical efficacy of biologically active regenerative materials has been summarized in meta-analyses for enamel matrix derivatives (EMDs) (Trombelli *et al*. 2002; Giannobile & Somerman 2003; Esposito *et al*. 2009; Koop *et al*. 2012), for growth factors (Darby & Morris 2013), and for platelet concentrate (*et al*. 2011) in the treatment of intrabony defects only.

The outcomes of eight studies including 444 defects have indicated that EMD application provides additional benefits of a magnitude of 0.75 mm in terms of CAL gain (Giannobile & Somerman 2003). These data are in accordance with those of a large practice-based multicenter trial that demonstrated both efficacy and effectiveness of EMDs in intrabony defects (Tonetti *et al*. 2002). The meta-analysis by Esposito *et al*. (2009) included 13 trials. A meta-analysis including nine trials showed that EMD-treated sites displayed statistically significant CAL improvements (mean difference 1.1 mm; 95% CI 0.61–1.55) and PPD reduction (0.9 mm; 95% CI 0.44–1.31) when compared to placebo- or control-treated sites, though a high degree of heterogeneity was found. Approximately nine patients needed to be treated (NNT) for one to gain 2 mm or more probing attachment level (PAL) over the control group, based on a prevalence in the control group of 25%. No differences in tooth loss or esthetic appearance as judged by the patients were observed. When evaluating only trials at a low risk of bias in a sensitivity analysis (four trials), the effect size for PAL was 0.62 mm (95% CI 0.28–0.96), which was <1.1 mm for the overall result.

A more recent meta-analysis (Koop *et al*. 2012) on 20 randomized controlled trials showed a significant additional gain in CAL of 1.30 mm of EMD-treated sites compared with OFD, ethylenediaminetetra-acetic acid (EDTA), or placebo (Fig. 45-9).

The systematic review by Darby and Morris (2013) reported a meta-analysis on two studies on the use of recombinant human platelet-derived growth factor-BB (rhPDGF-BB). Sites treated with rhPDGF-BB had greater CAL gain of around 1 mm, a greater percentage bone fill of around 40%, and an increased rate of bone growth of around 2 mm compared to sites treated with an osseoconductive control, beta-tricalcium phosphate (β-TCP).

Del Fabbro *et al*. (2011) in a meta-analysis on 10 studies reported a significantly greater CAL gain in cases treated with platelet-rich plasma (PRP) compared to control sites (mean adjusted percentage difference 5.50%; 95% CI 1.32–9.67%; $P = 0.01$). The mean weighted CAL gain difference was 0.50 mm (95% CI 0.12–0.88 mm).

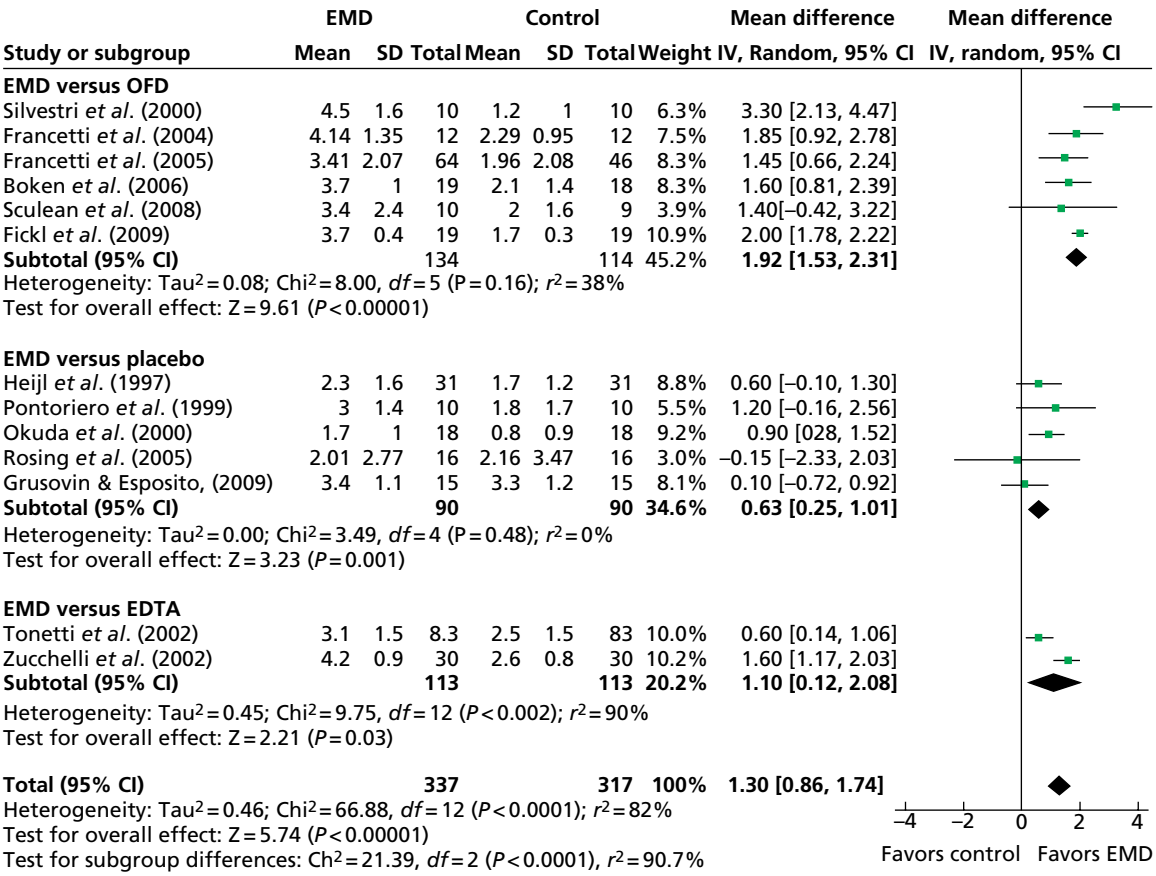


Fig. 45-9 Meta-analysis of intrabony defect studies. Comparison of enamel matrix derivatives (EMDs) versus control: change in clinical attachment level (CAL) after 1 year. (Total, number of patients; IV, inverse variance; CI, confidence interval.) (Source: Koop *et al*. 2012. Reproduced with permission from the American Academy of Periodontology.)

Combination therapy has been explored in two recent meta-analyses. Trombelli *et al*. (2008) evaluated the clinical effects of bioactive agents when used in addition to OFD either alone or in association with grafts and/or barrier membranes. The authors concluded that there was evidence to support the use of EMDs either alone or in combination with grafts to effectively treat intraosseous defects and the additional use of a graft seems to enhance the clinical outcome of EMDs; the combined use of rhPDGF-BB and P-15 with a graft biomaterial has shown beneficial effects in intraosseous defects; contrasting results were reported for PRP and graft combinations. Tu *et al.* (2010) explored the additional treatment effect of barriers or bone grafts to EMDs in 28 studies. EMD plus bone grafts and EMD plus membranes attained 0.24 mm and 0.07 mm more PPD reduction than EMD alone, respectively. EMD plus bone grafts and EMD plus membranes attained 0.46 mm and 0.15 mm more CAL gain, respectively. When different types of bone grafts and barrier membranes were treated separately, EMD with bovine bone grafts showed greater treatment effects. The authors concluded that there was little evidence to support the additional benefits of EMDs in conjunction with other regenerative materials.

Comparative studies between different regenerative approaches have been analyzed in a systematic review by Esposito *et al*. (2009) including six studies. The authors did not find any difference between EMDs and barriers in terms of CAL gain and PPD reduction. These data are supported by two large practice-based multicenter trials (Silvestri *et al*. 2003; Sanz *et al*. 2004). The Sanz *et al*. (2004) study, however, reported a significantly higher prevalence of complications in the barrier-treated group compared to the EMD-treated one. More recently, Tu *et al*. (2012) compared GTR, EMDs, and their use in conjunction with other regenerative materials with a Bayesian network meta-analysis of 53 randomized controlled trials. The authors found small differences between regenerative therapies which were non-significant statistically and clinically. GTR and GTR-related combination therapies achieved greater PPD reduction than EMDs and EMD-related combination therapies. Combination therapies achieved slightly greater CAL gain than the use of EMDs or GTR alone. The authors concluded that combination therapies performed better than single therapies, but the additional benefits were small. The same conclusions were reached by Koop *et al.* (2012).

Patient, defect, and tooth prognostic factors

The results reported in the above-cited meta-analyses indicate that clinical improvements beyond those from flap surgery can be obtained by treating periodontal

Table 45-2 Outcomes of regression analyses performed to explain variability in terms of clinical attachment gain at 1 year.

	Tonetti *et al.* (1998)	Cortellini *et al.* (2001)	Tonetti *et al.* (2002)	Sanz *et al.* (2004)	Tonetti *et al.* (2004b)
No. of patients	143	113	166	67	120
Treatment	Bioresorbable barriers vs flap	Bioresorbable barriers vs flap	EMD vs flap	EMD vs bioresorbable barriers	Bioresorbable barriers + filler vs flap
Treatment effect[a]	0.6 mm	1.0 mm	0.5 mm	0.8	0.8
Center effect[b]	2.4 mm	2.1 mm	2.6 mm	2.6	2.8

[a] Treatment effect = added clinical benefit on top of control treatment.
[b] Center effect = clinical outcomes of the best center versus the worst center.
EMD, enamel matrix derivative.

defects with regenerative therapies, but they also suggest a great variability in clinical outcomes among the different studies. In addition, it is apparent from the results that the complete resolution of the intrabony component of the defect and of the horizontal component of a furcation is observed in only a minority of sites. Regeneration, in fact, is an advanced healing event that occurs when the systemic and local conditions are favorable and when therapy is properly applied. A significant "center effect" was consistently observed in five randomized multicenter studies (Tonetti *et al*. 1998; Cortellini *et al.* 2001; Tonetti *et al.* 2002; Sanz *et al*. 2004; Tonetti *et al.* 2004a). The center variability, defined as the difference in CAL between the best and the worst center, had a highly significant impact on the outcomes, greater than the impact of the tested regenerative materials (Table 45-2).

The observed variability among centers may depend on differences in the enrolled patients in terms of socioeconomic background, form of periodontal disease, response to therapy, and persistence of specific pathogens; or differences in clinical experience, surgical skills, and clinical organization of the clinicians. In addition, a series of prognostic factors associated with the clinical outcomes has been identified using multivariate approaches (Tonetti *et al*. 1993a, Cortellini *et al*. 1994; Machtei *et al*. 1994; Tonetti *et al.* 1995, 1996a; Falk *et al*. 1997; Cortellini & Tonetti 2000b). The main sources of clinical variability are patient-, defect-, and surgery-associated factors (Cortellini & Tonetti 2000a). Attention has focused on some important patient, defect, and tooth factors.

Patient factors

Periodontal infection

Periodontal regeneration does not treat periodontitis, but rather is an approach for regenerating defects that have developed as a result of periodontitis. Therefore, appropriate periodontal treatment should always be completed before periodontal regeneration is initiated. In this context, that is in patients who have undergone a cycle of cause-related periodontal therapy to the satisfaction of the treating clinician, evidence suggests that the level of control of periodontitis achieved before a periodontal regenerative procedure is initiated is associated with outcomes: the persistence of poor plaque control, high levels of bleeding upon probing, as well as the persistence of high loads of total bacteria or of specific microbial pathogens (or complexes of pathogens) have all been associated in a dose-dependent manner with poor clinical outcomes (Tonetti *et al*. 1993a; Cortellini *et al*. 1994; Machtei *et al*. 1994, Cortellini *et al*. 1995a, b; Tonetti *et al.* 1995; Machtei *et al*. 2003; Silvestri *et al.* 2003; Heitz-Mayfield *et al.* 2006).

The level of self-performed plaque control has a great and dose-dependent effect on the outcome of periodontal regeneration. Better CAL gains were observed in patients with optimal levels of plaque control as compared with those in patients with less ideal oral hygiene (Cortellini *et al*. 1994, 1995a, b; Tonetti *et al*. 1995, 1996a). Patients with plaque on <10% of the tooth surfaces [full-mouth plaque score (FMPS)] had a gain of CAL which was 1.89 mm greater than that observed in patients with a FMPS of >20% (Tonetti *et al*. 1995).

Although not formally tested for efficacy in randomized trials, achieving high levels of plaque control and suppression of the pathogenic microflora through behavioral intervention and intensive anti-infective periodontal therapy are generally advocated before proceeding with periodontal regeneration. Furthermore, some proof of principle investigations have assessed the adjunctive effect of using an antibiotic locally delivered within the wound area or in the regenerative material (Yukna & Sepe 1982; Sanders *et al*. 1983; Machtei *et al*. 2003; Stavropoulos *et al*. 2003). Results showed consistently better outcomes in the groups that received the systemic/local antibiotic. At present, however, no regenerative device with enhanced antimicrobial activity is commercially available. Local contamination of the defect-associated pocket should be as low as possible (Heitz-Mayfield *et al*. 2006). Presence of BoP (i.e. bacteria) should be controlled with additional gentle root planing and eventually with the additional use of local antimicrobials (Tunkel *et al*. 2002; Hanes & Purvis 2003).

Smoking

A retrospective study found that cigarette smokers displayed significantly impaired regenerative outcomes compared to non-smokers (Tonetti *et al*. 1995). Data showed that cigarette smoking was associated with reduced CAL gains. The CAL gain in subjects smoking more than ten cigarettes/day was 2.1 ± 1.2 mm versus 5.2 ± 1.9 mm in non-smokers (Tonetti *et al*. 1995). Thereafter a series of investigations has confirmed that cigarette smoking displays a dose-dependent detrimental effect on CAL gains in intrabony defects (Cortellini *et al*. 1995b; Falk *et al*. 1997; Trombelli *et al*. 1997; Tonetti *et al*. 1998; Cortellini *et al*. 2001; Ehmke *et al*. 2003; Stavropoulos *et al*. 2004) and furcations (Luepke *et al*. 1997; Bowers *et al*. 2003; Machtei *et al*. 2003).

Although no formal evidence is available, it is generally suggested that smoking cessation counseling should be initiated in the context of cause-related periodontal therapy, and that patients who are unable to quit the habit should be informed of the possibility of reduced outcomes and of the need to abstain from smoking during the perioperative and early healing period.

Other patient factors

It has been suggested that other patient factors, such as age, genetics, systemic conditions or stress levels, may be associated with suboptimal regenerative outcomes. In the light of lack of evidence, however, no action is required with the exception of considering the patient characteristics that represent a contraindication to surgery (e.g. uncontrolled diabetes or unstable, severe diseases).

Clinical relevance of patient factors

The data discussed above indicate that patient factors play an important role in regenerative periodontal therapy (Fig. 45-10). Some of these factors can be modified by appropriate interventions in some patients. These interventions should be performed before periodontal regenerative therapy. Whenever modification is not possible, reduced outcomes in terms of extent and predictability should be considered.

Defect factors

Type of defect

With the currently available periodontal regenerative technologies, there is no evidence that suprabony (horizontal) defects, supracrestal components of intrabony defects or class III furcation involvements can be predictably treated with regenerative approaches. This limitation is also true for interdental craters, thus limiting the type of defects that can be treated to intrabony defects and class II furcation defects.

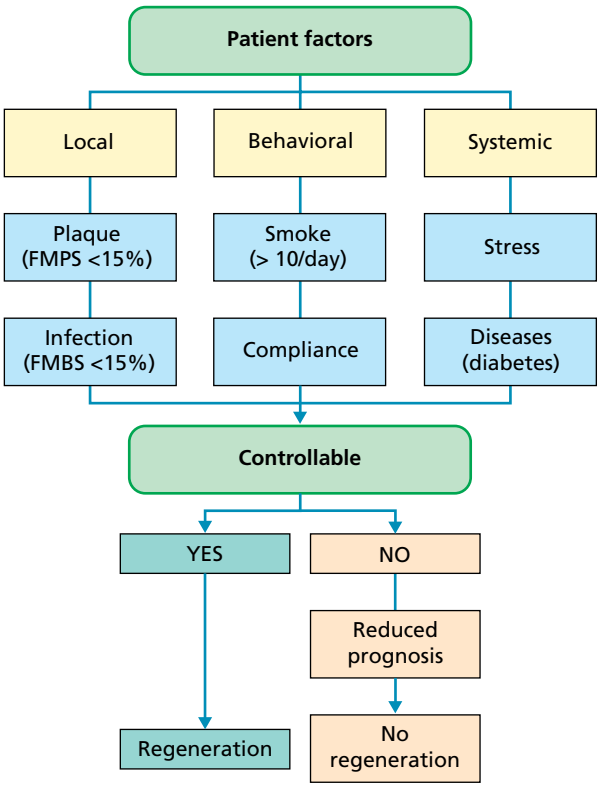


Fig. 45-10 Patient selection criteria. It can be seen that control of local, behavioral, and systemic patient characteristics may improve the treatment outcomes. (FMPS, full mouth plaque score; FMBS, full mouth bleeding score.) (Adapted from Cortellini & Bowers 1995 from Quintessence Pub. Co.)

Morphology of the defect

Defect morphology plays a major role in healing following periodontal regenerative treatment of intrabony defects. This was demonstrated in studies showing that the depth and width of the intrabony component of the defect influenced the amount of CAL and bone gained at 1 year. The deeper the defect, the greater was the amount of clinical improvements (Tonetti *et al*. 1993a, 1996a; Garrett *et al*, 1988; Ehmke *et al*. 2003; Silvestri *et al*. 2003).

In a controlled study, however, it was demonstrated that deep and shallow defects have the "same potential" for regeneration (Cortellini *et al*. 1998). Deep defects (>3 mm) resulted in larger linear CAL gain than shallow defects (3.7 ± 1.7 mm versus 2.2 ± 1.3 mm), but the percentage of CAL gain as related to the baseline defect depth was similar in deep (76.7 ± 27.7%) and in shallow (75.8 ± 45%) defects.

Another important morphologic characteristic of the defect is the *width* of the intrabony component, measured as the angle that the bony wall of the defect forms with the long axis of the tooth (Steffensen & Weber 1989). Wider defects have been associated with reduced CAL and bone gain at 1 year (Tonetti *et al*. 1993, 1996; Garrett *et al*. 1988). In a study on 242 intrabony defects treated with membranes, Cortellini & Tonetti (1999) demonstrated that defects with a radiographic angle of ≤25° gained consistently more attachment (1.6 mm on average) than defects

with an angle of ≥37°. Two follow-up studies addressed the significance of the baseline radiographic angle of the intrabony defect following the use of either EMDs (Tsitoura *et al*. 2004) or a combination of BRG with a barrier membrane (Linares *et al*. 2006). The impact of the width of the baseline radiographic angle was confirmed for the non–space-making biologic mediator, but not for the more stable combination therapy. These data are consistent with the notion that the choice of the regenerative technology may partially overcome negative morphologic characteristics of intrabony defects. An earlier secondary analysis of a controlled clinical trial using titanium-reinforced membranes (Tonetti *et al*. 1996a) indicated that the relevance of defect morphology parameters may be diminished with the use of supported membranes.

It was also shown that the number of residual bony walls was related to the outcomes of various regenerative approaches (Goldman & Cohen 1958; Schallhorn *et al*. 1970). This issue as related to GTR therapy was addressed in three investigations (Selvig *et al*. 1993; Tonetti *et al*. 1993a, 1996a). In one study, the reported 1-year mean CAL gain was 0.8 ± 0.3 mm. This gain corresponded to the depth of the three-wall intrabony component of the defect (Selvig *et al*. 1993). In contrast, in the other two investigations, CAL gain was not related to the defect configuration in terms of one-wall, two-wall, and three-wall subcomponents (Tonetti *et al*. 1993a, 1996a). A total of 70 defects were examined in these two latter studies, utilizing a multivariate approach. The treatment resulted in mean attachment gains of 4.1 ± 2.5 mm and 5.3 ± 2.2 mm, and it was observed that the most coronal portion of the defects, which is the most susceptible to negative influences from the oral environment, was often incompletely filled with bone, irrespective of whether these were one-wall, two-wall or three-wall defects.

Thus, these studies questioned the impact of the number of residual bony walls of the defect on the clinical outcomes of periodontal regeneration with membranes and suggested that location of the one-wall subcomponent (the one most likely to be the most superficial) may have acted as a confounder in other studies and be an important predictor of the outcomes. The number of walls was not significant when titanium barriers (Tonetti *et al*. 1996a) or combination therapy (Tonetti *et al.* 2004a, b) were used, but were significant when bioresorbable barriers (Falk *et al*. 1997; Silvestri *et al*. 2003) and EMDs were used (Tonetti *et al*. 2002; Silvestri *et al*. 2003). In particular, a secondary analysis of a multicenter trial showed that, in intrabony defects, the added benefit of EMDs was greater in three-wall defects compared to one-wall defects (Tonetti *et al*. 2002, 2004a).

These data also questioned the suitability of the gel formulation of EMDs for the treatment of defects with a non-supporting anatomy (wide defects with missing bony walls). More recently, however, two studies demonstrated a reduced impact of the number of residual bony walls and of defect width on the outcomes obtained with EMDs when a minimally invasive surgical technique (MIST) was used (Cortellini *et al.* 2008; Cortellini & Tonetti 2009a). This finding clearly differs from the evidence discussed above of a strong impact of the defect anatomy in terms of residual bony walls and defect width on the clinical outcomes observed in previous studies in which EMDs were used under conventional large and intrinsically less stable papilla preservation flaps (Tonetti *et al.* 2002, 2004a).

Tooth factors

The endodontic status of the tooth has been suggested as a potential relevant factor in periodontal therapy. Emerging evidence (see Chapter 41) indicates that root canal-treated teeth may respond differently to periodontal therapy. A clinical study of 208 consecutive patients with one intrabony defect each demonstrated that properly performed root canal treatment does not negatively affect the healing response and the long-term stability of deep intrabony defects treated with membranes (Cortellini & Tonetti 2000b).

Tooth mobility has long been considered an important factor for periodontal regeneration (Sanders *et al*. 1983). A multivariate analysis of a multicenter controlled clinical trial demonstrated that tooth hypermobility was negatively and dose-dependently associated with the clinical outcomes of regeneration (Cortellini *et al*. 2001). Though significant, the size of the effect was small, within the range of physiologic mobility. Another secondary analysis of three previously reported trials assessed the regenerative outcomes for hypermobile teeth (Trejo & Weltman 2004). This report indicated that teeth with baseline mobility amounting to <1 mm horizontally could be successfully treated with periodontal regeneration. Although no intervention trial has been performed to date, these results are generally considered supportive of an approach that does not base the prognosis of the tooth or the regenerative procedure on tooth mobility, but rather considers splinting hypermobile teeth before periodontal regenerative surgery.

Conclusion: Based on these results, it can be concluded that deep and narrow intrabony defects at either vital or endodontically-treated teeth are the ones in which the most significant and predictable outcomes can be achieved with GTR treatment. Number of walls and width of the defect are influential when non-supportive biomaterials are used. The influence of defect anatomy appears to be reduced to some extent when a more stable flap design is applied. Severe, uncontrolled dental hypermobility (Miller class II or higher; Miller 1943) may impair the regenerative outcomes. Significant clinical improvements can be expected only in patients with optimal plaque control, with reduced levels of periodontal contamination, and who are non-smokers.

Factors affecting the clinical outcomes in furcations

Significant evidence has demonstrated that treatment of maxillary class II furcations and maxillary and mandibular class III furcation involvements with regeneration is unpredictable, while clinical improvements can be expected for mandibular class II furcations. The great variability in clinical outcomes following treatment of mandibular class II furcations with regeneration is probably related to the factors discussed relative to intrabony defects.

Regarding tooth/defect factors, it was shown that first and second mandibular molars and buccal and lingual furcations respond equally well to GTR treatment (Pontoriero *et al*. 1988; Machtei *et al*. 1994). It was also demonstrated that the preoperative horizontal pocket depth directly correlates with the magnitude of attachment gain and bone formation in the furcation area (Machtei *et al*. 1993, 1994; Horwitz *et al*. 2004). The deeper the baseline horizontal pocket, the greater the H-CAL and bone gain. The anatomy of the furcations in terms of height, width, depth, and volume, however, did not correlate with the clinical outcome (Machtei *et al*. 1994). Horwitz *et al*. (2004) demonstrated that a long root trunk, a wide furcation entrance, and a furcation fornix coronal to the alveolar crest have negative influences on the success of therapy. Anderegg *et al*. (1995) demonstrated that sites with a gingival thickness of >1 mm exhibited less gingival recession post surgery than sites with a gingival thickness of <1 mm. Bowers *et al*. (2003) reported that increases in presurgical PAL-H were associated with monotonic decreases in the percentage of sites demonstrating complete clinical closure, with only 53% of lesions of ≥5 mm responding with complete closure. Similarly, significant reductions in the frequency of clinical closure were associated with increases in the distance between the roof of the furcation and the crest of the bone, roof of the furcation and base of the defect, and depth of the horizontal defect and the divergence of the roots. The authors concluded that the highest frequency of clinical furcation closure was observed in early class II defects. Tsao *et al*. (2006a) treated class II furcations in lower molars with either OFD alone or with additional use of bone graft or bone graft plus a collagen barrier. Among the anatomic factors, only the baseline vertical depth was found to affect the clinical outcomes in terms of vertical CAL gain. The most influential factor was the type of surgical treatment: the regenerative procedures performed better than the flap alone.

Relevance of the surgical approach

At the beginning of the 1980s, the need to modify standard periodontal surgical procedures to favor periodontal regeneration became apparent. In particular, the need to preserve soft tissues in order to attempt primary closure of the interdental space to contain grafts or coronally advanced flaps to cover furcation entrances led to the development of specific flap designs for periodontal regeneration (Takei *et al*. 1985; Gantes & Garret 1991).

In fact, graft exfoliation and membrane exposure with consequent bacterial contamination during healing represented the major complications of periodontal regenerative procedures at the time. Membrane exposure was reported to be a major complication with a prevalence of 50–100% (Becker *et al*. 1988; Cortellini *et al*. 1990; Selvig *et al*. 1992; Cortellini *et al*. 1993a; Selvig *et al*.1993; Murphy 1995a; De Sanctis *et al*. 1996a, b; Falk *et al*. 1997; Trombelli *et al*. 1997; Mayfield *et al*. 1998). Cortellini *et al*. (1995c, d) reported that the prevalence of membrane exposure could be greatly reduced with the use of access flaps specifically designed to preserve the interdental tissues (modified papilla preservation technique) (Fig. 45-11).

Many studies have shown that the exposed membranes are contaminated with bacteria (Selvig *et al*. 1990; Grevstad & Leknes 1992; Selvig *et al*. 1992; Machtei *et al*. 1993; Mombelli *et al*. 1993; Tempro & Nalbandian 1993; Nowzari & Slots 1994; Novaes *et al*. 1995; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). Contamination of exposed non-bioresorbable as well as bioresorbable membranes was associated with lower PAL gains in intrabony defects (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). The impaired clinical results in some studies were associated with high counts of bacteria and with the presence of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* (Machtei *et al*. 1994; Nowzari & Slots 1994; Nowzari *et al*. 1995).

Bacterial contamination of the regenerative biomaterials may occur during surgery, but also during the postoperative healing phase. Bacteria from the oral cavity may colonize the implanted biomaterials. Frequently, this results in recession of the gingival tissues, which allows colonization of the material further apically. The significance of bacterial contamination was addressed in an investigation in monkeys (Sander & Karring 1995). The findings of this study showed that new attachment and bone formation occurred consistently when bacteria were prevented from invading the membrane and the wound during healing.

In order to prevent wound infection, some investigators have administered systemic antibiotics to patients before and during the first weeks after membrane application (Demolon *et al*. 1993; Nowzari & Slots 1994). However, despite the application of systemic antibiotics, postoperative wound infection related to implanted barrier membranes was noted. This indicates that either the drug administered is not directed against the microorganisms responsible for the wound infection, or that the drug does not reach the infected site at a concentration sufficiently high enough to inhibit the target microorganisms. An

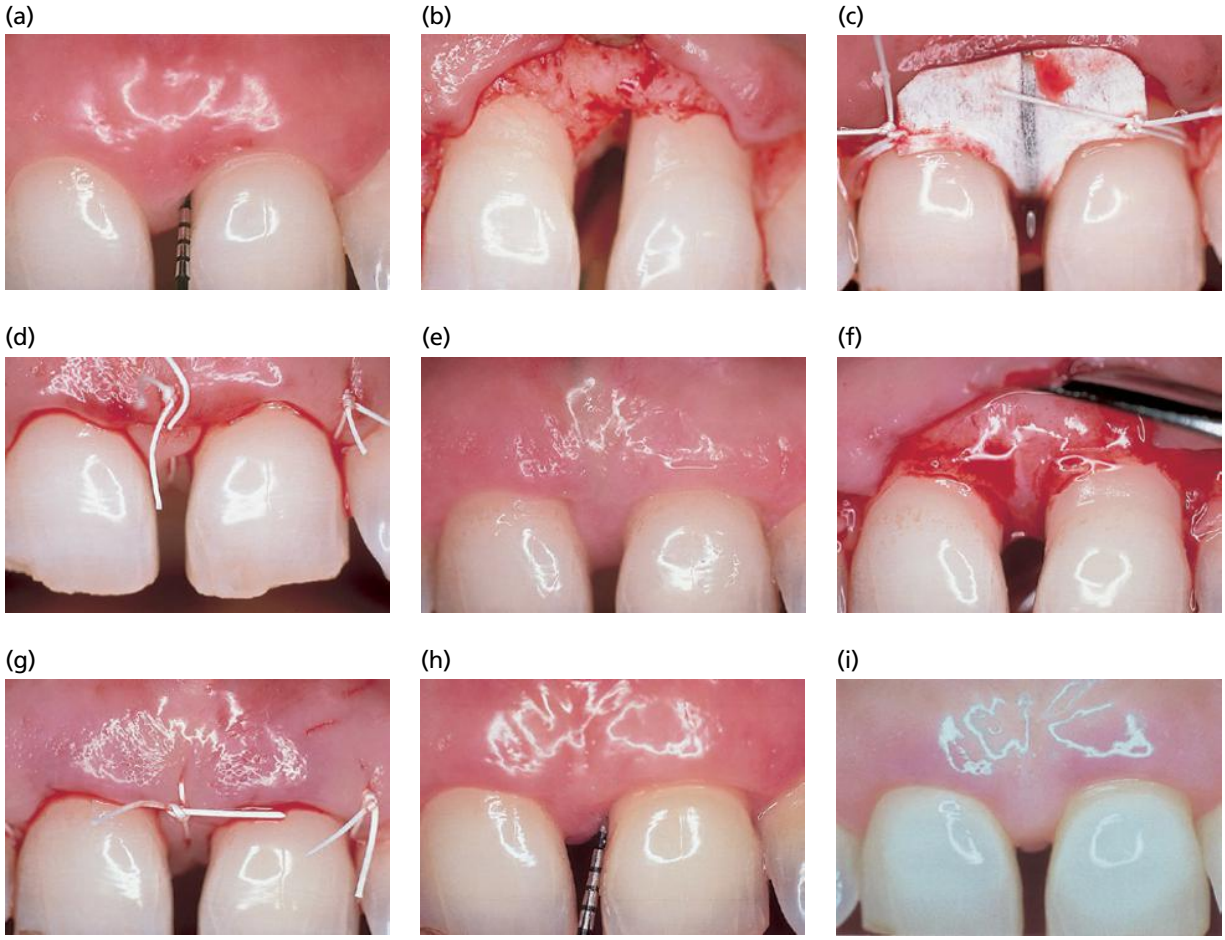


Fig. 45-11 (a) Left maxillary central incisor with a 10-mm pocket depth and 11 mm of clinical attachment loss on the mesial surface. A diastema is present between the two central incisors. (b) Full thickness buccal and palatal flaps have been raised and an intrabony defect can be seen. The interdental papilla has been incised on the buccal aspect and elevated with the palatal flap (modified papilla preservation technique). (c) Titanium-reinforced e-PTFE barrier membrane has been placed and fixed close to the level of the cemento-enamel junction. (d) Membrane is completely covered. This primary closure has been obtained by preserving the interdental papilla and by coronal displacement of the buccal tissue flap. (e) At 6 weeks, the membrane is completely covered with healthy tissue. (f) After membrane removal at 6 weeks, dense newly formed tissue is evident in the defect and in the supracrestal space maintained by the titanium-reinforced membrane. (g) Newly formed tissue is completely covered by the raised and well-preserved tissue flaps. (h) Clinical photograph after 1 year showed a 4-mm residual pocket depth. A gain of clinical attachment of 6 mm was recorded, and no recession had occurred compared to baseline. (i) Ten-year clinical photograph showing the optimal preservation of the interdental tissues.

improved effect on periodontal healing after GTR in association with local application of metronidazole was reported by Sander *et al*. (1994). Twelve patients each with two similar intrabony defects participated in this intraindividual study. Metronidazole in a gel form was placed in the test defects and on the membrane prior to wound closure, while the control defects were treated with a membrane alone. Six months following membrane removal the medium gain in PAL, presented as a percentage of the initial defect depth, was 92% for the test defects versus 50% for the control defects. Other clinical parameters, like plaque index, BoP, PPD reduction, and recession of the gingival margin, were similar in the test and control sites. Although local or systemic antibiotics may reduce the bacterial load on exposed membranes, they seem ineffective in preventing the formation of a microbial biofilm (Frandsen *et al*. 1994; Nowzari *et al*. 1995). In addition to the erythema and swelling related to such infection of the wound, more severe postoperative complications such as suppuration, sloughing or perforation of the flap, membrane exfoliation, and postoperative pain have been reported (Murphy 1995a, b).

Another important issue associated with the clinical results is the coverage of the regenerated tissue after removal of a non-bioresorbable membrane. Many authors have reported that the frequent occurrence of a gingival dehiscence over the membrane is likely to result in insufficient protection of the interdental regenerated tissue (Becker *et al*. 1988; Selvig *et al*. 1992; Cortellini *et al*. 1993a; Tonetti *et al*. 1993a). Exposure of the regenerated tissue to the oral environment introduces the risk of mechanical and infectious insults that in turn may prevent complete maturation of the regenerated tissue into a new connective tissue attachment. In fact, incomplete coverage of the regenerated tissue was associated

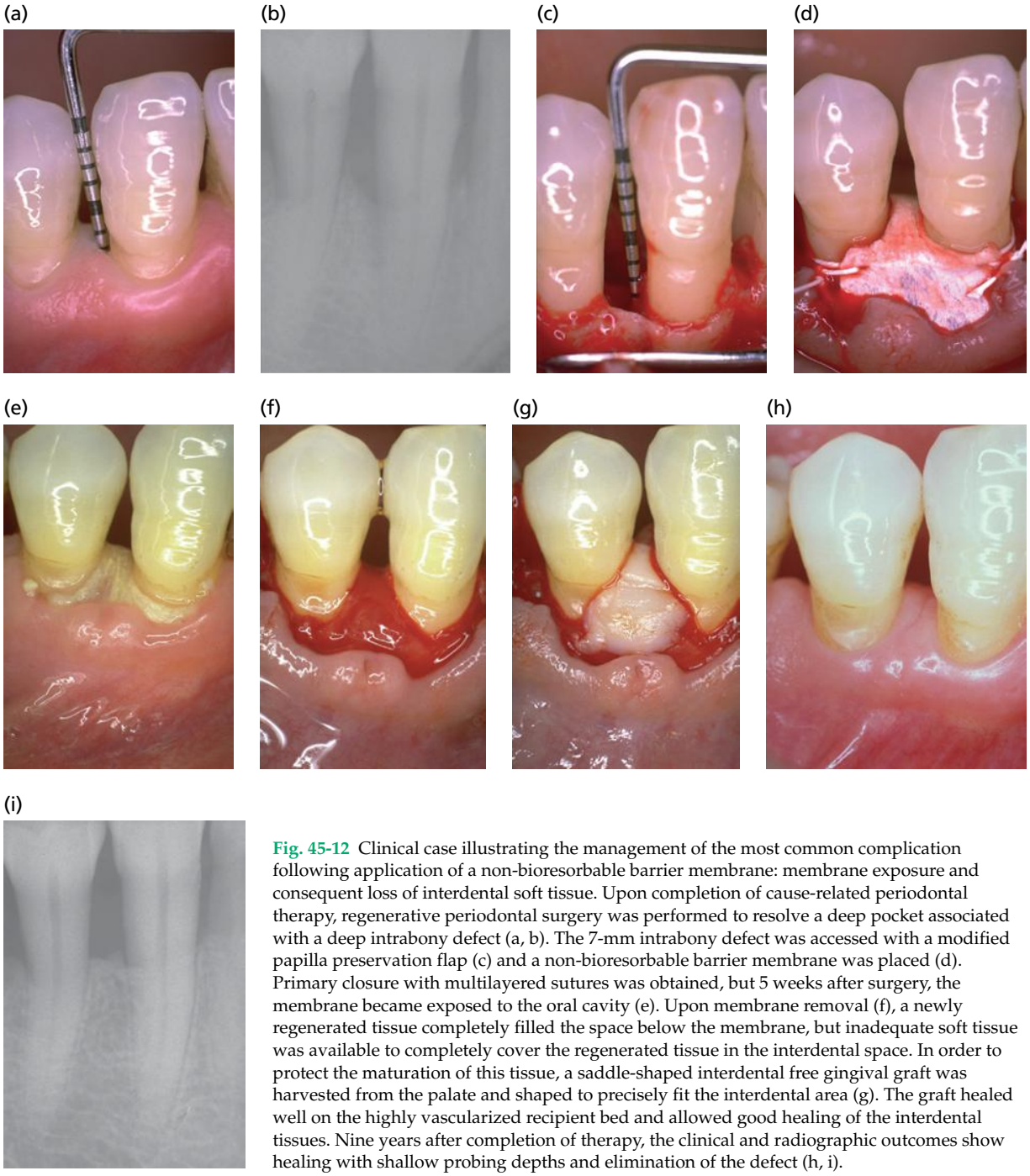


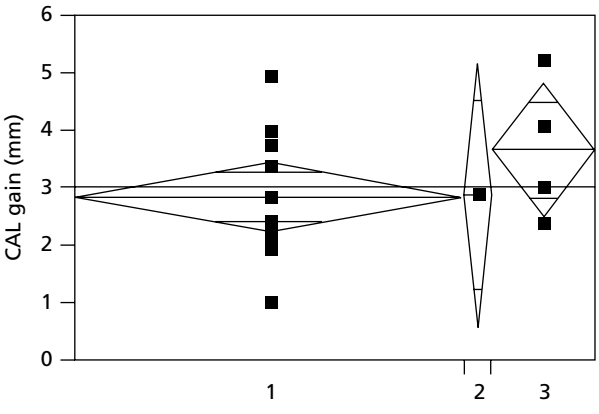
Fig. 45-12 Clinical case illustrating the management of the most common complication following application of a non-bioresorbable barrier membrane: membrane exposure and consequent loss of interdental soft tissue. Upon completion of cause-related periodontal therapy, regenerative periodontal surgery was performed to resolve a deep pocket associated with a deep intrabony defect (a, b). The 7-mm intrabony defect was accessed with a modified papilla preservation flap (c) and a non-bioresorbable barrier membrane was placed (d). Primary closure with multilayered sutures was obtained, but 5 weeks after surgery, the membrane became exposed to the oral cavity (e). Upon membrane removal (f), a newly regenerated tissue completely filled the space below the membrane, but inadequate soft tissue was available to completely cover the regenerated tissue in the interdental space. In order to protect the maturation of this tissue, a saddle-shaped interdental free gingival graft was harvested from the palate and shaped to precisely fit the interdental area (g). The graft healed well on the highly vascularized recipient bed and allowed good healing of the interdental tissues. Nine years after completion of therapy, the clinical and radiographic outcomes show healing with shallow probing depths and elimination of the defect (h, i).

with reduced attachment and bone gain at 1 year (Tonetti *et al*. 1993a). The positioning of a saddle-shaped free gingival graft over the regenerated interdental tissue (Fig. 45-12) was suggested to offer better coverage and protection than a dehiscent gingival flap (Cortellini *et al*. 1995a). In this randomized controlled study (Cortellini *et al*. 1995a) more gain of attachment was observed in the 14 sites where a free gingival graft was positioned after membrane removal (5.0 ± 2.1 mm), than in the 14 sites where conventional protection of the regenerated tissue was accomplished (3.7 ± 2.1 mm).

The systematic assessment of the relevant factors associated with variability of periodontal regenerative outcomes performed at the beginning of the 1990s (Tonetti *et al*. 1993a; Machtei *et al*. 1994; Tonetti *et al*. 1995, 1996a; Falk *et al*. 1997) provided further evidence that surgical factors had a great impact on regeneration and led the way to the development of procedures specifically designed for periodontal regeneration. In general, the development of new procedures was aimed at complete tissue preservation in order to achieve and maintain primary closure on top of the applied regenerative material during the critical stages of healing and to save space for blood clot formation and maturation. Specifically, flap designs attempted to achieve passive primary closure of the flap combined with optimal wound stability. In fact, basic and clinical research indicate that, among many, absolute requirements for

regeneration include the presence of space for the formation of the blood clot at the interface between the flap and root surface (Haney *et al*. 1993; Sigurdsson *et al*. 1994, Cortellini *et al*. 1995b, c; Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al*. 2004), the stability of the blood clot to maintain a continuity with the root surface and thereby prevent the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993), and protection of the soft tissue of the treated area to avoid bacterial contamination (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b; Sanz *et al*. 2004).

Development of periodontal regenerative medicine in the last 25 years has followed two distinct, though totally interlaced, paths. The interest of researchers has so far focused on regenerative materials and products on the one hand and on novel surgical approaches on the other hand.



Ranks	Number of studies	Mean (mm)
1	15	2.84
2	1	2.90
3	4	3.68

Fig. 45-13 Means of intrabony defect studies examining the relationship between flap closure technique ranking and gain in clinical attachment level (CAL) (in mm) considering only e-PTFE barrier types. Groupings were not statistically different from one another. (Source: Murphy & Gunsolley 2003. Reproduced from the American Academy of Periodontology.)

Surgical approach to intrabony defects

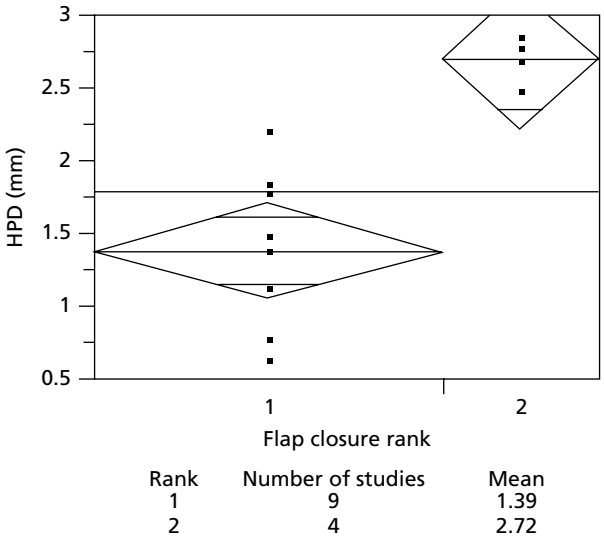
Papilla preservation flaps

The modified papilla preservation technique (MPPT) was developed in order to increase the space for regeneration and to achieve and maintain primary closure of the flap in the interdental area (Cortellini *et al*. 1995c, d). This approach combines special soft tissue management with the use of a self-supporting titanium-reinforced membrane capable of maintaining a supra-alveolar space for regeneration. The MPPT allows primary closure of the interdental space, resulting in better protection of the membrane from the oral environment (Cortellini *et al*. 1995d). The technique involves the elevation of a full-thickness palatal flap which includes the entire interdental papilla. The buccal flap is mobilized with vertical and periosteal incisions, coronally positioned to cover the membrane, and sutured to the palatal flap through a horizontal internal crossed mattress suture over the membrane. Primary closure between the flap and the interdental papilla is obtained with a second internal mattress suture. Representative cases are shown in Figs. 45-4 and 45-11.

In a randomized controlled clinical study of 45 patients (Cortellini *et al*. 1995c), significantly greater attachment gain were obtained with the MPPT (5.3 ± 2.2 mm) in comparison with either conventional GTR (4.1 ± 1.9 mm) or flap surgery (2.5 ± 0.8 mm), demonstrating that a modified surgical approach can result in improved clinical outcomes. In this study, 100% of the sites were closed on top of a titanium-reinforced membrane and 73% remained closed for up to 6 weeks, when the barrier membrane was removed. This study provided proof of principle of the benefit of specific flap designs for periodontal regeneration. The MPPT has been successfully applied in multicenter randomized clinical trials designed to test the generalizability of the added benefits of regenerative approaches in deep intrabony defects (Tonetti *et al*. 1998; Cortellini *et al*. 2001; Tonetti *et al*. 2002, 2004b).

A meta-analysis (Murphy & Gunsolley 2003) showed the existence of a trend associating better clinical outcomes with flap designs and closing techniques considered conducive to the achievement and maintenance of primary closure of the flap (Figs. 45-13, 45-14). A similar trend was observed by Graziani *et al*. (2011) in their meta-analysis of flap surgery studies, where papilla preservation flaps performed better than conventional flap surgery.

The reported MPPT can be successfully applied in sites where the interdental space width is at least 2 mm at the most coronal portion of the papilla. When interdental sites are narrower, the reported technique is difficult to apply. In order to overcome this problem, a different papilla preservation procedure [the simplified papilla preservation flap (SPPF)] has been proposed for narrow interdental spaces (Cortellini *et al*. 1999a). This approach includes an oblique incision across the defect-associated papilla, starting from the buccal angle of the defect-associated tooth and continuing to the mid-interdental part of the papilla at the adjacent tooth under the contact point. In this way, the papilla is cut into two equal parts of which the buccal part is elevated with the buccal flap and the lingual part with the lingual flap. In the cited study, 100% of the narrow interdental papillae could be closed on top of bioresorbable barriers, and 67% maintained primary closure over time, resulting in 4.9 ± 1.8 mm of CAL gain. This approach has been successfully applied in different multicenter randomized clinical trials designed to test the generalizability of the added benefits of using barrier



	Difference	t test	DF	Prob > ltl
Estimate	–1.3319	–7.014	10.538	<0.0001
Standard error	0.1899			
Lower 95%	–1.9277			
Upper 95%	–0.7361			

Fig. 45-14 Regression analysis of furcation defect studies examining the relationship between flap closure technique ranking and the reduction (in mm) in horizontal probing depth (HPD). Groups 1 and 2 are statistically different from one another. (Source: Murphy & Gunsolley, 2003. Reproduced from the American Academy of Periodontology.)

membranes on deep intrabony defects (Tonetti *et al*. 1998, 2002, 2004b; Cortellini *et al*. 2001).

In the cited studies, GTR therapy of deep intrabony defects performed by different clinicians on various patient populations resulted in both greater amounts and improved predictability of CAL gain than access flap alone. The issue of soft tissue manipulation to obtain stable protection of the regeneration site has been further explored by applying a microsurgical approach in the regenerative therapy of deep intrabony defects (Fig. 45-15). In a patient cohort study of 26 patients with 26 intrabony defects treated with papilla preservation techniques, primary closure on the barrier was obtained in 100% of the cases and maintained over time in 92.3% of the sites (Cortellini & Tonetti 2001). Treatment resulted in large CAL gain (5.4 ± 1.2 mm) and minimal gingival recession (0.4 ± 0.7 mm). Thus, the improved vision and better soft tissue handling improved the predictability of periodontal regeneration.

Today, the use of papilla preservation flap designs and closure techniques has become the standard approach for regenerative periodontal surgery.

Modified papilla preservation technique

The rationale for developing this technique was to achieve and maintain primary closure of the flap in the interdental space over the membrane (Cortellini *et al*. 1995d) (Figs. 45-16, 45-17, 45-18). Access to the interdental defect is achieved with a horizontal incision traced in the buccal keratinized gingiva at the base of the papilla and connected to mesiodistal buccal intrasulcular incisions. After elevation of a full-thickness buccal flap, the residual interdental tissues are dissected from the neighboring teeth and the underlying bone, and elevated towards the palatal aspect. A full-thickness palatal flap, including the interdental papilla, is elevated and the interdental defect exposed. Following debridement of the defect, the buccal flap is mobilized with vertical and periosteal incisions, when needed.

This technique was originally designed for use in combination with self-supporting barrier membranes. In fact, the suturing technique requires a supportive (or supported) membrane to be effective (Figs. 45-16, 45-17). To obtain primary closure of the interdental space over the membrane, a first suture (horizontal internal crossed mattress suture) is placed beneath the mucoperiosteal flaps between the base of the palatal papilla and the buccal flap. The interdental portion of this suture hangs on top of the membrane, allowing the coronal displacement of the buccal flap. This suture relieves all the tension in the flaps. To ensure primary passive closure of the interdental tissues over the membrane, a second suture (vertical internal mattress suture) is placed between the buccal aspect of the interdental papilla (i.e. the most coronal portion of the palatal flap, which includes the interdental papilla) and the most coronal portion of the buccal flap. This suture is free of tension.

An alternative type of suture to close the interdental tissues has been proposed by Dr Lars Laurell. This modified internal mattress suture starts from the external surface of the buccal flap, crosses the interdental area, and runs through the lingual flap at the base of the papilla. The suture runs back through the external surface of the lingual flap and the internal surface of the buccal flap, about 3 mm distant from the first two bites. Finally, the suture is passed through the interdental area above the papillary tissues, passed through the loop of the suture on the lingual side, and brought back to the buccal side, where it is tied. This suture is very effective in ensuring stability and primary closure of the interdental tissues.

In a randomized controlled clinical study of 45 patients (Cortellini *et al*. 1995c), significantly greater

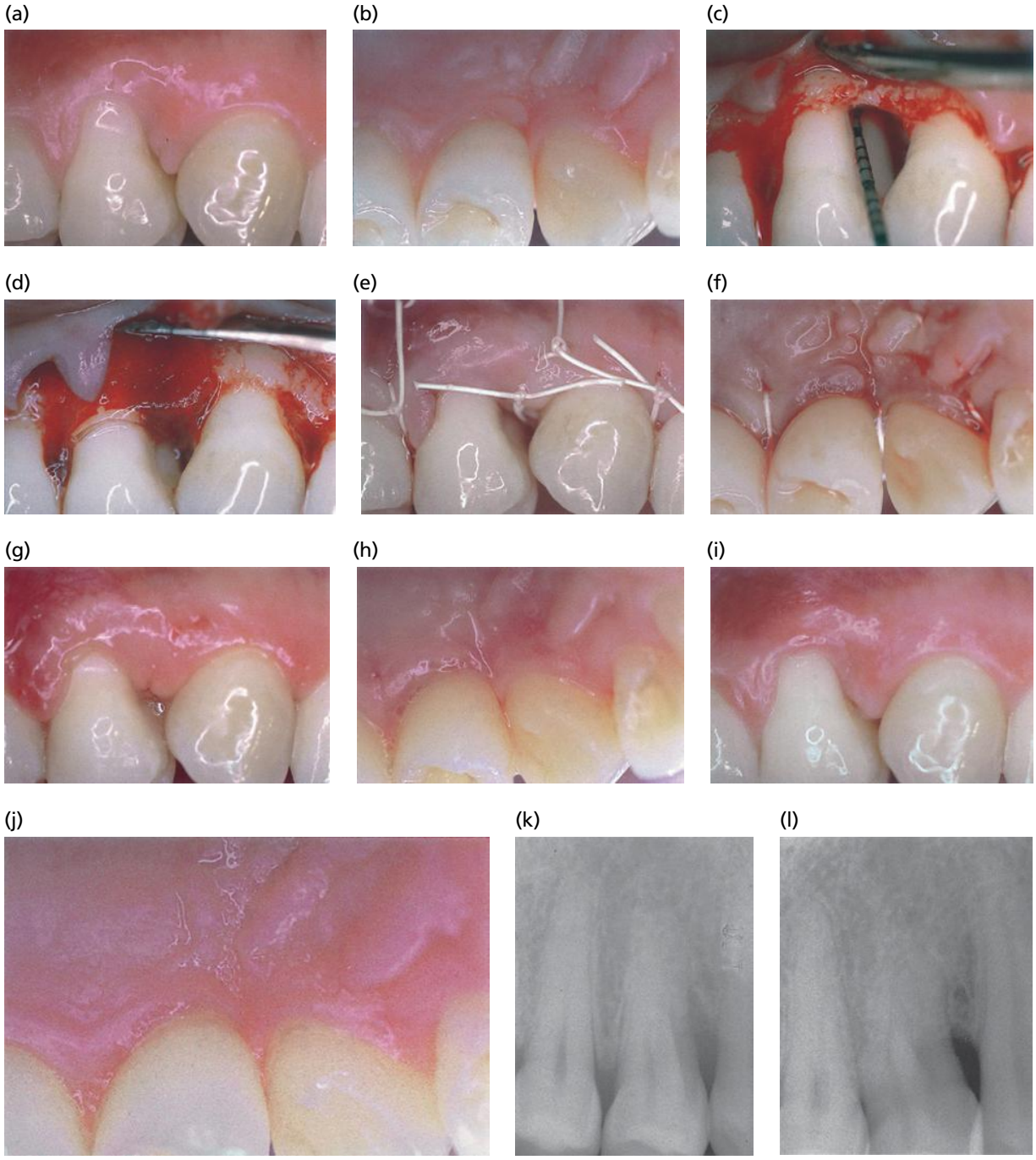


Fig. 45-15 (a) Right first maxillary premolar with a 7-mm pocket on the mesial surface. The interdental space (b) is very narrow (>2 mm), and is accessed with a simplified papilla preservation flap using a microsurgical approach (operative microscope and microsurgical instruments). The 5-mm deep intrabony defect (c) is covered with a bioresorbable barrier membrane (d). Primary closure of the flap over the membrane (e, f) is maintained over time (g, h). After 1 year, the interdental papilla is completely preserved and the residual pocket depth is 3 mm (i, j). The radiograph taken at baseline (k) compared with that taken 1 year after treatment (l) shows that the intrabony defect has healed completely.

PAL was gained with the MPPT (5.3 ± 2.2 mm) in comparison with either conventional GTR (4.1 ± 1.9 mm) or access flap surgery (2.5 ± 0.8 mm), demonstrating that a modified surgical approach can result in improved clinical outcomes. The sites accessed with the MPPT showed primary closure of the flap in all but one case, and no gingival dehiscence until membrane removal in 73% of the cases.

This surgical approach has also been used in combination with non-supported bioresorbable barrier membranes (Cortellini *et al*. 1996c), with positive results. Clinical attachment level gains at 1 year were 4.5 ± 1.2 mm. In all the cases, primary closure of the flap was achieved and about 80% of the sites maintained primary closure over time (Fig. 45-19). It should be underlined, however, that the horizontal internal crossed mattress suture most probably caused an apical displacement of the interdental portion of the membrane, thereby reducing the space for regeneration.

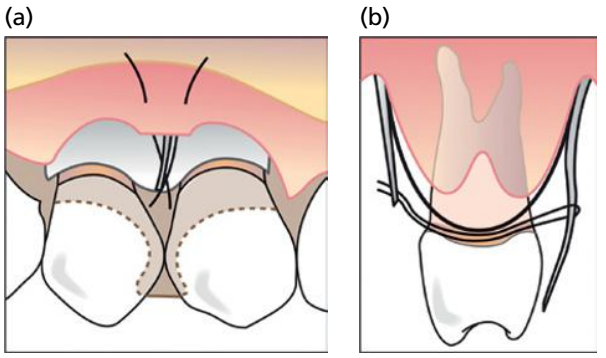


Fig. 45-16 Suture to obtain coronal positioning of the buccal flap: schematic illustration of the crossed horizontal internal mattress suture between the base of the palatal papilla and the buccal flap immediately coronal to the mucogingival junction. Note that the suture crosses above the titanium reinforcement of the membrane. (a) Buccal view; (b) mesiodistal view. (Source: Cortellini *et al*. 1995d. Reproduced with permission from the American Academy of Periodontology.)

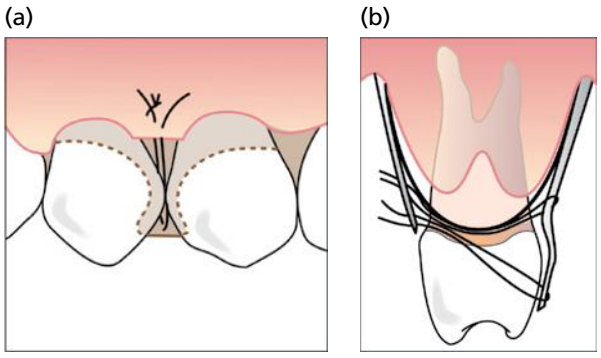


Fig. 45-17 Suture to obtain tension-free primary closure of the interdental space: schematic illustration of the vertical internal mattress suture between the most coronal portion of the palatal flap (which includes the interdental papilla) and the most coronal portion of the buccal flap. (a) Buccal view; (b) mesiodistal view. (Source: Cortellini *et al*. 1995d. Reproduced with permission from the American Academy of Periodontology.)

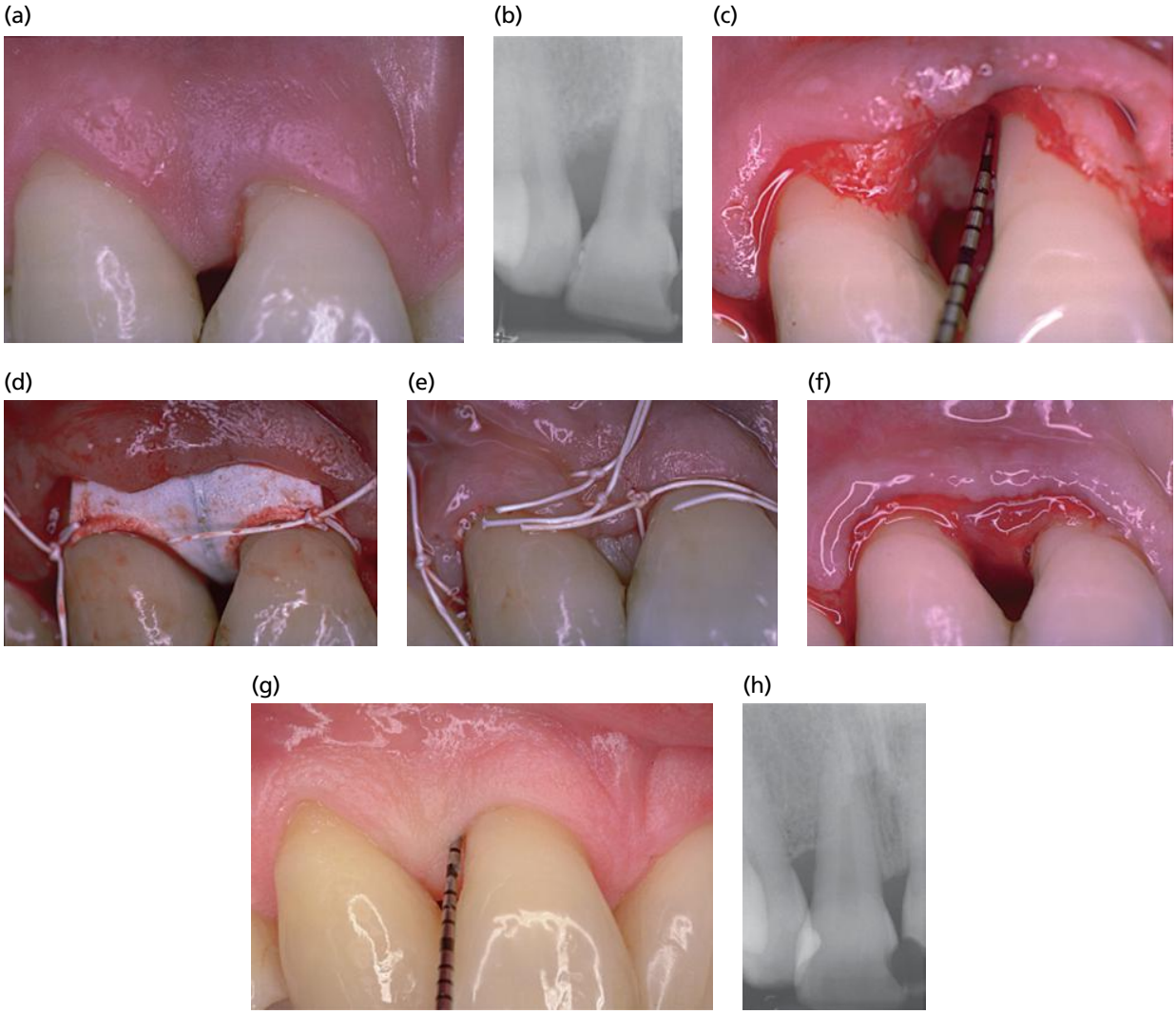


Fig. 45-18 Clinical case illustrating the modified papilla preservation technique (MPPT) used to completely close the interdental space above a barrier membrane. Following completion of initial cause-related therapy, an 8-mm pocket associated with 2 mm of recession of the gingival margin was present on the distal aspect of the central incisor (a). A wide intrabony defect was detectable on the radiograph (b). Defect was accessed with the MPPT, keeping the whole interdental tissue connected with the palatal flap. A 7-mm intrabony defect was uncovered (c). Following root debridement, a titanium-reinforced barrier membrane was positioned (d). Primary closure of the interdental space was obtained by suturing back the papilla preservation flap using a multilayered suturing technique aimed at coronal advancement of the flap, complete relief of wound tension, and good flap stability (e). Six weeks thereafter, the same flap was elevated in order to remove the membrane that had remained completely submerged for the whole time. New tissue filled the space maintained beneath the membrane (f). Following completion of healing (1 year), a 3-mm probing depth and fill of the intrabony defect were observed. The results were maintained over time as indicated by the clinical and radiographic appearance 6 years after regeneration (g, h).

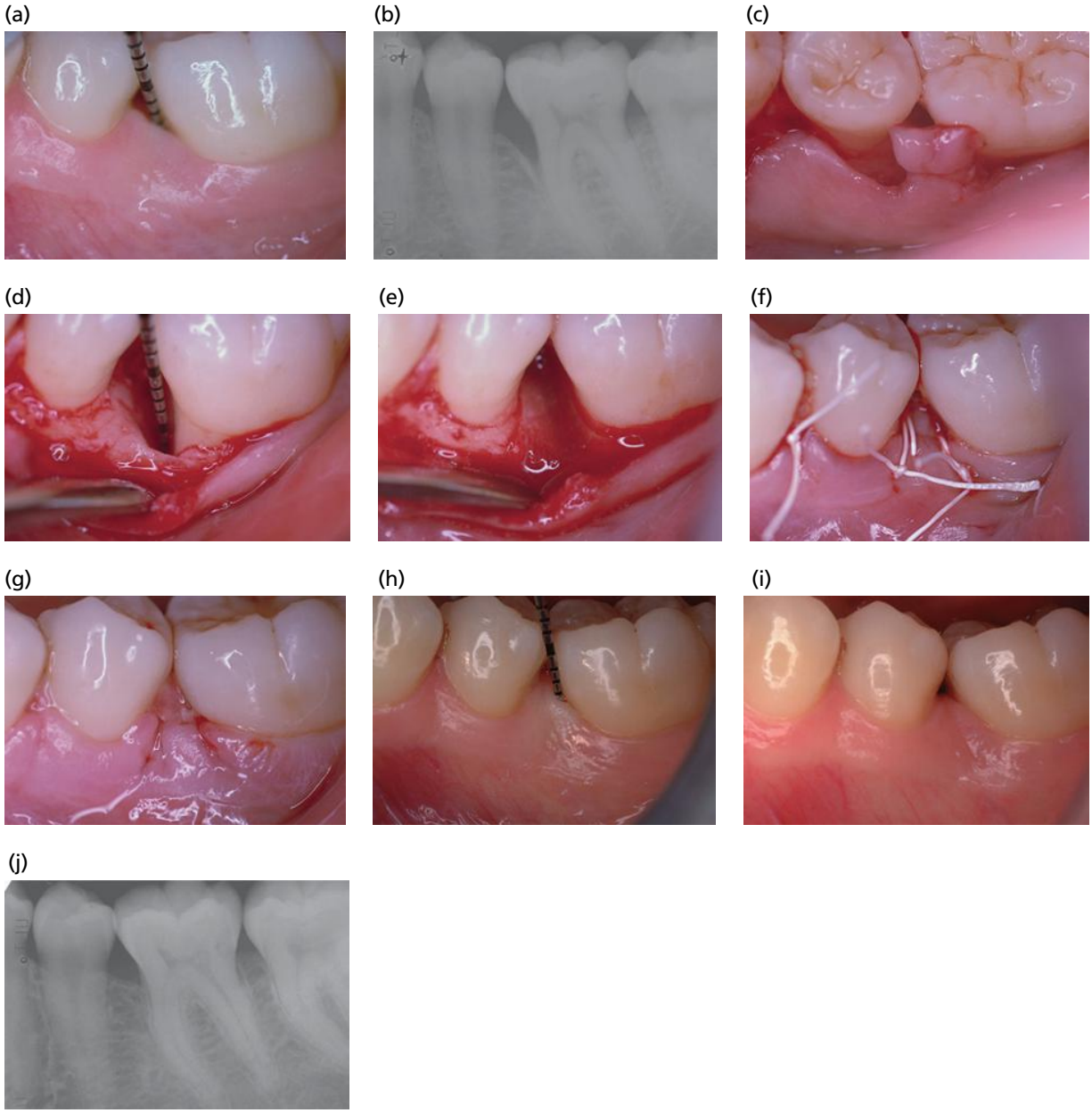


Fig. 45-19 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) to a case treated with a bioresorbable barrier membrane. An 8-mm pocket associated with an intrabony defect persisted on the mesial aspect of the lower first molar following completion of initial cause-related therapy (a, b). The defect was accessed with the MMPT. Note the papilla preserved attached to the lingual flap (c) as well as the presence of a 7-mm intrabony defect (d). Following root debridement, a bioresorbable barrier membrane was positioned and secured around the root of the tooth with bioresorbable sutures (e). Primary closure of the interdental space was obtained with multilayered sutures (f) and was fully maintained at the 1-week suture removal appointment (g). At 6 years, probing depths were 2–3 mm, the soft tissue profile was conducive to optimal self-performed oral hygiene measures, and the radiograph showed elimination of the defect (h–j).

The MPPT can be successfully applied in conjunction with a variety of regenerative materials, including biologically active materials such as EMDs (Tonetti *et al*. 2002) (Fig. 45-20) or growth factors and BRGs (Fig. 45-21) (Tonetti *et al*. 2004b; Cortellini & Tonetti 2005).

The surgical access of the interdental space with the MPPT is technically very demanding, but it has been reported to be very effective and applicable to wide interdental spaces (>2 mm at the interdental tissue level), especially in the anterior dentition. In properly selected cases, large attachment gain and consistent reduction of PPD associated with no or minimal recession of the interdental papilla can be consistently expected. It is, therefore, indicated in cases in whom esthetics are particularly important.

Simplified papilla preservation flap

To overcome some of the technical problems encountered with the MPPT (difficult application in narrow interdental spaces and in posterior areas, suturing technique not appropriate for use with

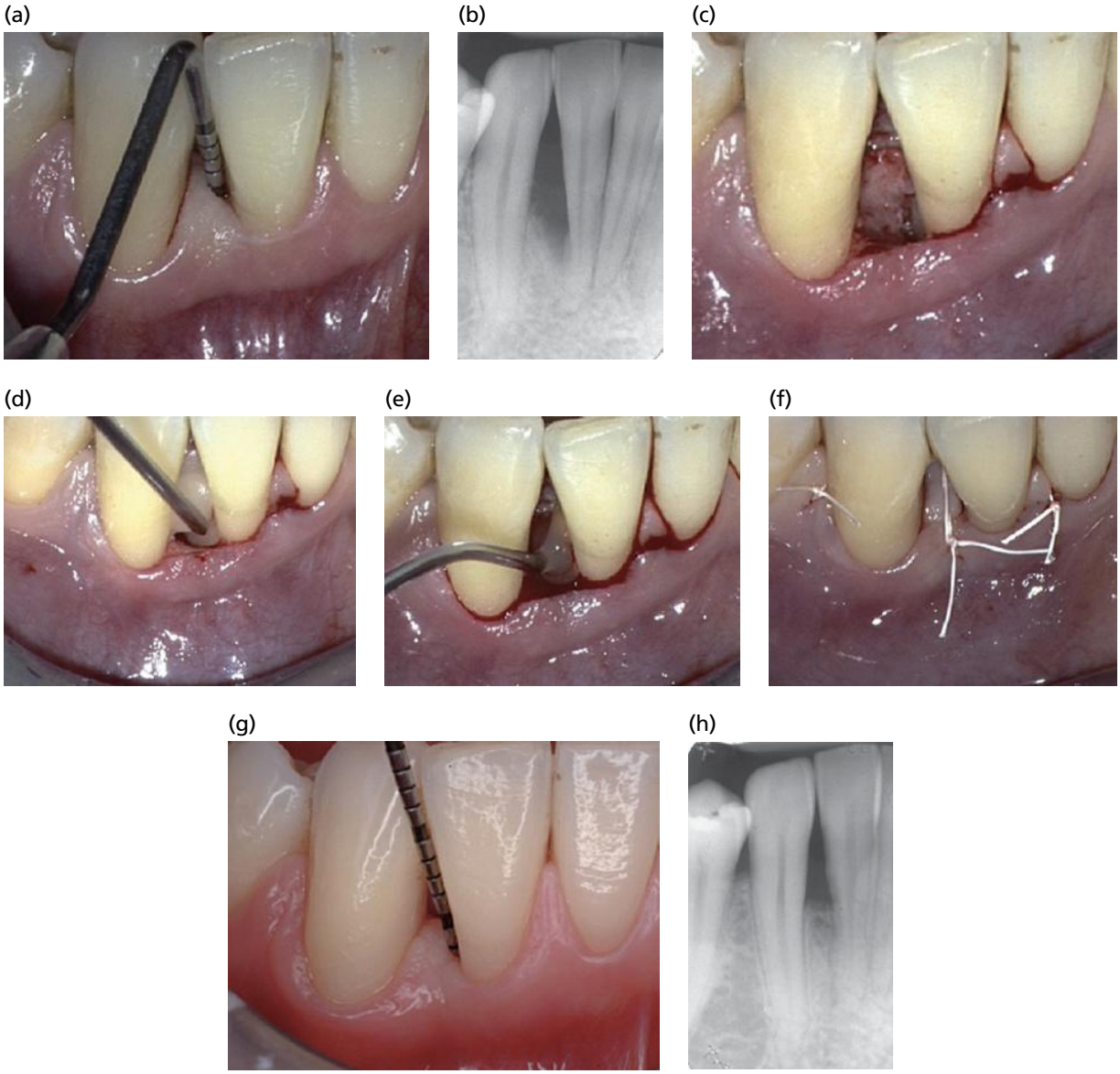


Fig. 45-20 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) in conjunction with the application of enamel matrix derivatives (EMDs). A 10-mm pocket was detectable on the distal aspect of the lower lateral incisor following successful completion of initial cause-related therapy (a). The radiograph showed the presence of a deep intrabony defect extending to the apical third of the root (b). The defect was accessed with the MPPT (c) with limited mesial and distal extension of the flap. Following careful debridement, the root was conditioned with an EDTA gel according to the manufacturer's instructions for the application of EMDs (d). After rinsing and drying of the defect and root surface, the EMD gel was applied to the root surface and to fill the defect (e), and flaps were sutured with a multilayer technique to achieve primary closure in the absence of tension (f). One year following regenerative surgery, shallow pockets and radiographic resolution of the defect were apparent (g, h).

non-supportive barriers), a different approach, the simplified papilla preservation flap (SPPF) (Figs. 45-15, 45-22) was subsequently developed (Cortellini *et al*. 1999a).

This simplified approach to the interdental papilla includes a first incision across the defect-associated papilla, starting from the gingival margin at the buccal-line angle of the involved tooth and extending to the mid-interdental portion of the papilla under the contact point of the adjacent tooth. This oblique incision is carried out by keeping the blade parallel to the long axis of the teeth in order to avoid excessive thinning of the remaining interdental tissues. The first oblique interdental incision is continued intrasulcularly in the buccal aspect of the teeth neighboring the defect. After elevation of a full-thickness buccal flap, the remaining tissues of the papilla are carefully dissected from the neighboring teeth and the underlying bone crest. The interdental papillary tissues at the defect site are gently elevated along with the lingual/palatal flap to fully expose the interdental defect. Following defect debridement and root planing, vertical releasing incisions and/or periosteal incisions are performed, when needed, to improve the mobility of the buccal flap. After application of a barrier membrane, primary closure of the interdental

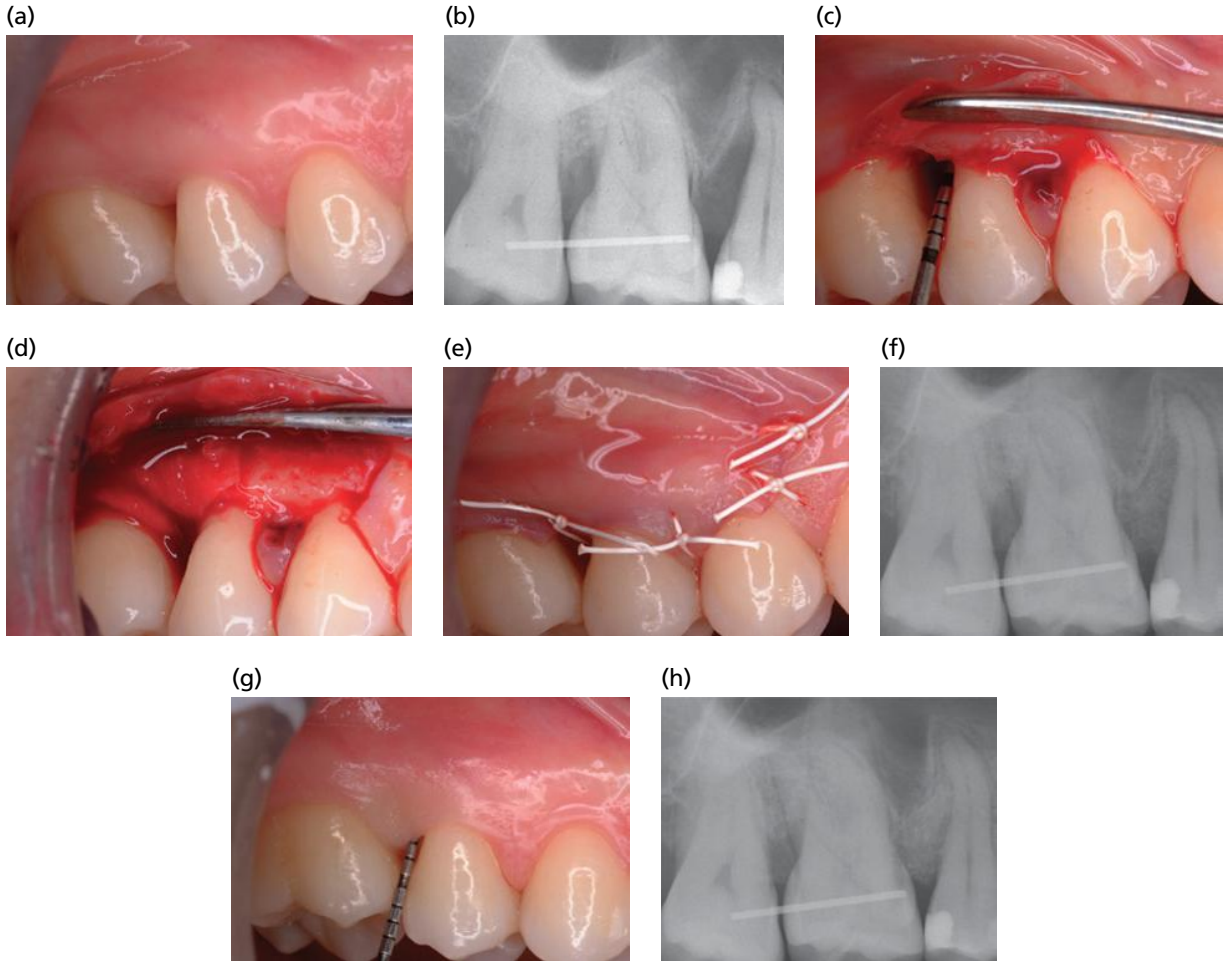


Fig. 45-21 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) in conjunction with a bone replacement graft (BRG) in combination with a bioresorbable membrane. After completion of initial cause-related therapy, a 9-mm pocket associated with an intrabony defect was present on the distal aspect of the upper second premolar (a, b). The defect reached the apical portion of the root and had a 9-mm intrabony component (c). Following careful root debridement, a bioresorbable membrane was adapted to the local anatomy and was positioned to contain the defect. A BRG was subsequently inserted under the membrane to provide additional support for the membrane and for the soft tissues (d). Primary closure was achieved with a single internal mattress suture (e). The control radiograph taken upon completion of the surgery showed the presence of the radio-opaque BRG in the defect (f). At 1-year follow-up, a 3-mm probing depth associated with resolution of the intrabony component of the defect was apparent (g, h). Note that the radio-opaque BRG particles are still detectable but appear embedded in newly formed mineralized tissue.

tissues above the membrane is attempted in the absence of tension, with the following sutures:

1. A first horizontal internal mattress suture (offset mattress suture) is positioned in the defect-associated interdental space running from the base (near to the mucogingival junction) of the keratinized tissue at the mid-buccal aspect of the tooth not involved with the defect to a symmetrical location at the base of the lingual/palatal flap. This suture rubs against the interdental root surface, hangs on the residual interdental bone crest, and is anchored to the lingual/palatal flap. When tied, it allows the coronal positioning of the buccal flap. Importantly, this suture, lying on the interdental bone crest, does not cause any compression at the mid-portion of the membrane, therefore preventing its collapse into the defect.
2. The interdental tissues above the membrane are then sutured to obtain primary closure with one of the following approaches: one interrupted suture whenever the interdental space is narrow and the interdental tissues thin; two interrupted sutures when the interdental space is wider and the interdental tissues thicker; an internal vertical/oblique mattress suture when the interdental space is wide and the interdental tissues are thick.

Special care has to be paid to ensure that the first horizontal mattress suture relieves all the tension in the flaps, and to obtain primary passive closure of the interdental tissues over the membrane with the second suture. When tension is observed, the sutures should be removed and the primary passive closure attempted again.

This approach has been preliminarily tested in combination with bioresorbable barrier membranes in a case series of 18 deep intrabony defects (Cortellini *et al*. 1999a). The average CAL gain observed at 1 year was 4.9 ± 1.8 mm. In all the cases it was possible to

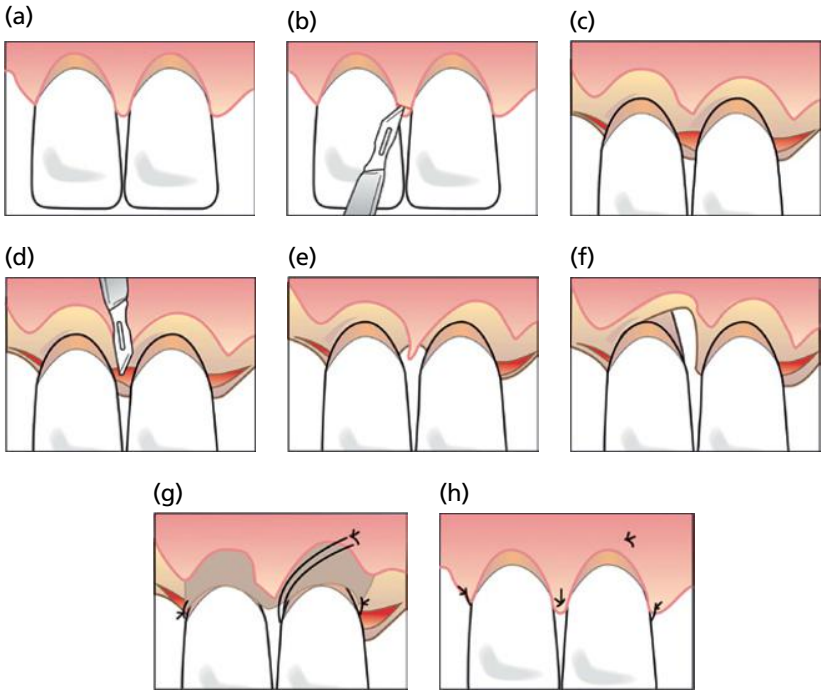


Fig. 45-22 (a) Presurgical appearance of the area to be accessed with a simplified papilla preservation flap (SPPF). The defect is located on the mesial aspect of the maxillary right lateral incisor. (b) First oblique incision in the defect-associated papilla begins at the gingival margin of the mesiobuccal line angle of the lateral incisor. The blade is kept parallel to the long axis of the tooth and reaches the mid-point of the distal surface of the central incisor just below the contact point. (c) First oblique incision continues intrasulcularly in the buccal aspect of the lateral and central incisors, extending to the adjacent papillae, and a buccal full-thickness flap is elevated to expose 2–3 mm of bone. Note the defect-associated papilla is still in place. (d) Buccolingual horizontal incision at the base of the papilla is as close as possible to the interproximal bone crest. Care is taken to avoid a lingual/palatal perforation. (e) Intrasulcular interdental incisions continue in the palatal aspect of the incisors to the adjacent partially dissected papillae. A full-thickness palatal flap including the interdental papilla is elevated. (f) Intrabony defect following debridement. Note the position of the bone crest on the distal aspect of the central incisor. (g) Membrane is positioned to cover the defect and 2–3 mm of remaining bone and secured to neighboring teeth. A horizontal internal mattress suture runs from the base of the keratinized tissue at the mid-buccal side of the central incisor to a symmetric location at the base of the palatal flap. This suture causes no direct compression of the mid-portion of the membrane, preventing its collapse into the defect. (h) Primary closure and complete coverage of the membrane are obtained. (Source: Cortellini *et al*. 1999a. Reproduced with permission from Quintessence Pub. Co.)

obtain primary closure of the flap over the membrane, and 67% of the sites maintained primary closure over time. This approach was tested in a multicenter controlled randomized clinical trial involving 11 clinicians from seven different countries and a total of 136 defects (Tonetti *et al*. 1998). The average CAL gain observed at 1 year in the 69 defects treated with the SPPF and a bioresorbable barrier membrane was 3 ± 1.6 mm. More than 60% of the treated sites maintained primary closure over time. It is important to underline that these results were obtained by different clinicians treating different populations of patients and defects, including those with narrow spaces and involving the posterior areas of the mouth. The SPPF was successfully applied in conjunction with a variety of regenerative materials, including biologically active materials such as EMDs (Tonetti *et al*. 2002) (Fig. 45-23) and BRG (Fig. 45-24) (Cortellini & Tonetti 2004; Tonetti *et al*. 2004b).

Minimally invasive surgical technique

More recently there has been a growing interest in a friendlier, patient-oriented surgery and clinical investigators have focused their interest on the development of less invasive approaches. Harrel and Rees (1995) proposed the minimally invasive surgery (MIS) approach with the aim of producing minimal wounds, minimal flap reflection, and gentle handling of the soft and hard tissues (Harrel & Nunn 2001; Harrel *et al*. 2005). In order to provide even greater wound stability and to further limit patient morbidity, a papilla preservation flap can be used in the context of a minimally invasive, high-power magnification-assisted surgical technique (Cortellini & Tonetti 2007a). Such a minimally invasive approach is particularly suited for treatment in conjunction with biologically active agents such as EMDs or growth factors and/or grafting materials.

The defect-associated interdental papilla is accessed either with the SPPF (Cortellini *et al*. 1999a) or the MPPT (Cortellini *et al*. 1995d). The SPPF is performed whenever the width of the interdental space is 2 mm or narrower, while the MPPT is applied at interdental sites wider than 2 mm. The interdental incision (SPPF or MPPT) is extended to the buccal and lingual aspects of the two teeth adjacent to the defect. These incisions are strictly intrasulcular to preserve all the height and width of the gingiva, and their mesiodistal extension is kept to a

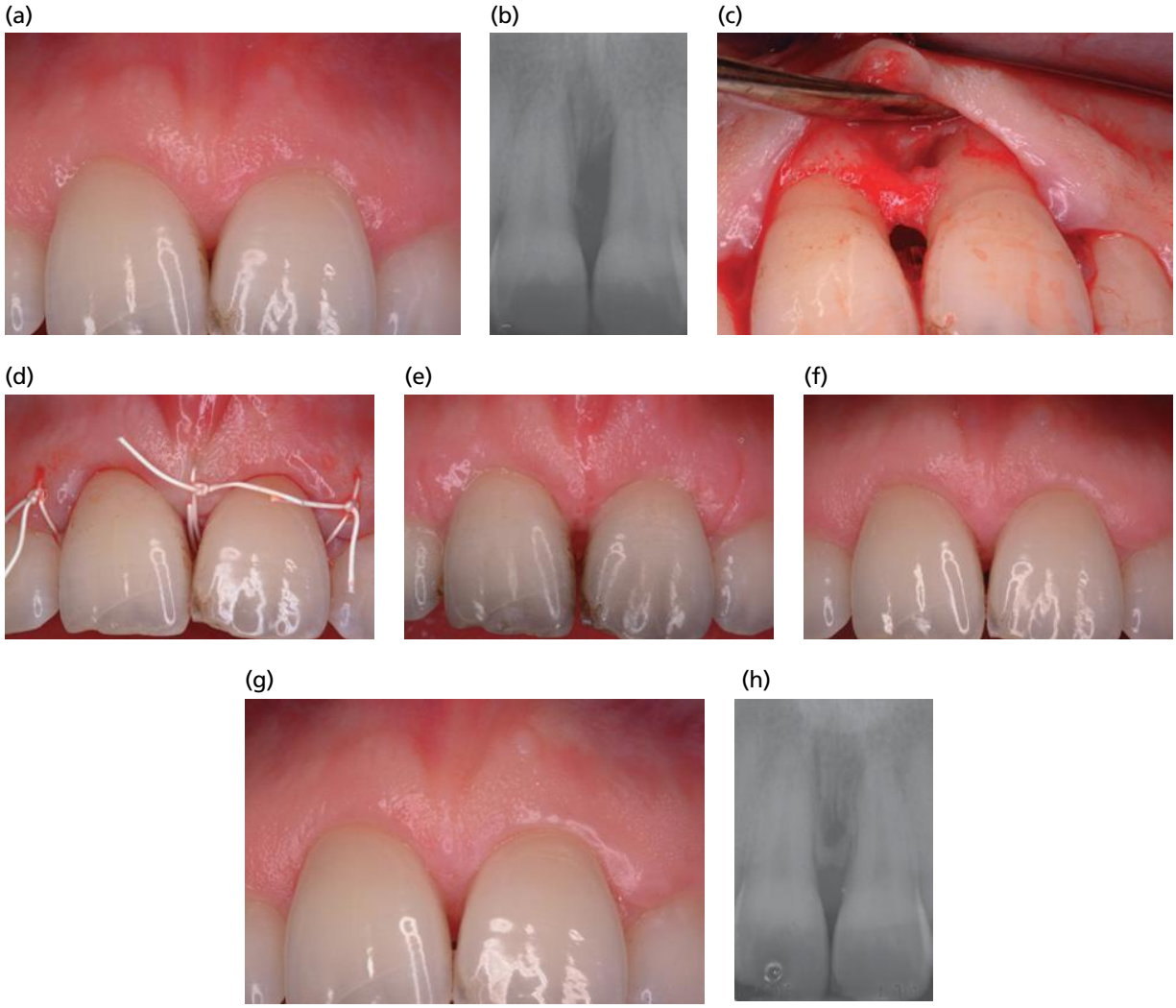


Fig. 45-23 Clinical case illustrating the clinical application of the simplified papilla preservation flap (SFFP) in conjunction with the application of a biologically active regenerative material [enamel matrix derivatives (EMDs) in gel form]. At re-evaluation following completion of successful initial cause-related therapy, an 8-mm pocket was detected on the mesial palatal aspect of the left central incisor (a). An angular defect was evidenced on a periapical radiograph (b). The complex anatomy of the defect was apparent following access to the defect with the modified papilla preservation technique (MPPT): a buccal fenestration was apparent with the majority of the defect extending palatally to the apical third of the root (c). Following application of the EMDs, primary closure of the flap was achieved with a multilayered suture (d). At the 1-week suture removal appointment, excellent maturation of the soft tissue healing was apparent (e). At 6 months, a well-represented interdental papilla was present thanks to both the papilla preservation approach and the presence of a bony bridge that assisted in soft tissue support, in spite of the gel formulation of the EMDs (f). Clinical and radiographic outcomes at 1 year showed preservation of excellent esthetics and elimination of the defect (g, h). Probing depths were in the 2–3-mm range.

minimum to allow the coronoapical elevation of a very small full-thickness flap with the objective of exposing just 1–2 mm of the defect-associated residual bone crest. When possible, only the defect-associated papilla is accessed and vertical releasing incisions are avoided. With these general rules in mind, different clinical pictures can be encountered in different defects.

The shortest mesiodistal extension of the incision and the minimal flap reflection occurs when the intrabony defect is a pure three-wall, or has shallow two- and/or one-wall subcomponents allocated entirely in the interdental area. In these instances, the mesiodistal incision involves only the defect-associated papilla and part of the buccal and lingual aspects of the two teeth neighboring the defect. The full-thickness flap is elevated minimally, just enough to expose the buccal and lingual bone crest delineating the defect in the interdental area (Fig. 45-25).

A larger coronoapical elevation of the full-thickness flap is necessary when the coronal portion of the intrabony defect has a deep two-wall component. The coronoapical extension of the flap is kept to a minimum at the aspect where the bony wall is preserved (either buccally or lingually), and extends more apically at the site where the bony wall is missing (lingually or buccally), the objective being to reach and expose 1–2 mm of the residual bone crest (Fig. 45-26).

When a deep one-wall defect is approached, the full-thickness flap is elevated to the same extent on both the buccal and the lingual aspects.

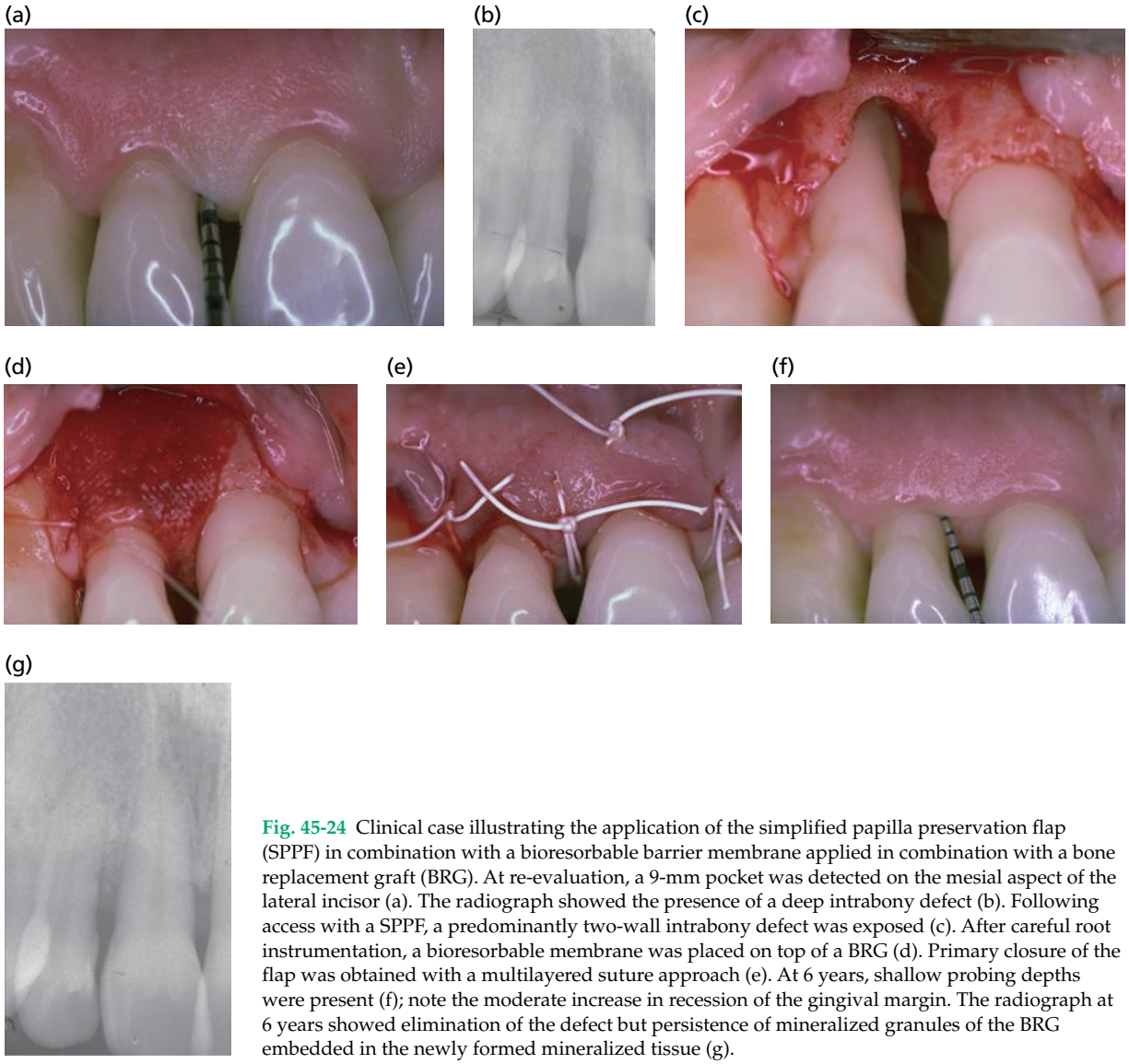


Fig. 45-24 Clinical case illustrating the application of the simplified papilla preservation flap (SPPF) in combination with a bioresorbable barrier membrane applied in combination with a bone replacement graft (BRG). At re-evaluation, a 9-mm pocket was detected on the mesial aspect of the lateral incisor (a). The radiograph showed the presence of a deep intrabony defect (b). Following access with a SPPF, a predominantly two-wall intrabony defect was exposed (c). After careful root instrumentation, a bioresorbable membrane was placed on top of a BRG (d). Primary closure of the flap was obtained with a multilayered suture approach (e). At 6 years, shallow probing depths were present (f); note the moderate increase in recession of the gingival margin. The radiograph at 6 years showed elimination of the defect but persistence of mineralized granules of the BRG embedded in the newly formed mineralized tissue (g).

When the position of the residual buccal/lingual bony wall(s) is very deep and difficult or impossible to reach with the above-described minimal incision of the defect-associated interdental space, the flap(s) is(are) further extended mesially or distally and one extra interdental space is involved to obtain a larger flap reflection. The same approach is used when the bony defect also extends to the buccal or the palatal side of the involved tooth, or when it involves the two interdental spaces of the same tooth (Fig. 45-27) or two approximal teeth (Fig. 45-28). In the latter instance, a second interdental papilla is accessed, either with an SPPF or an MPPT, according to the indication. Vertical releasing incisions are performed when flap reflection causes tension at the extremities of the flap(s). The vertical releasing incisions are always kept very short and within the attached gingiva (never involving the mucogingival junction). The overall aim of this approach is to avoid using vertical incisions whenever possible or to reduce their number and extent to a minimum when there is a clear indication for them. Periosteal incisions are never performed.

The defects are debrided with the combined use of mini-curettes and power-driven instruments, and the roots carefully planed. During the instrumentation, the flaps are slightly reflected and carefully protected with periosteal elevators and frequent saline irrigations. At the end of instrumentation, the biologically active agent is applied. Then the flaps are repositioned.

The suturing approach in most instances consists of a single modified internal mattress suture at the defect-associated interdental area to achieve primary closure of the papilla in the absence of any tension (Cortellini & Tonetti 2001, 2005). When a second interdental space has been accessed, the same suturing technique is used to obtain primary closure in this area. Vertical releasing incisions are sutured with simple passing sutures. The buccal and lingual flaps are repositioned at their original level, without any coronal displacement to avoid any additional tension in the healing area.

All the surgical procedures can be performed with the aid of an operating microscope or magnifying loupes at a magnification of ×4 to ×16 (Cortellini &

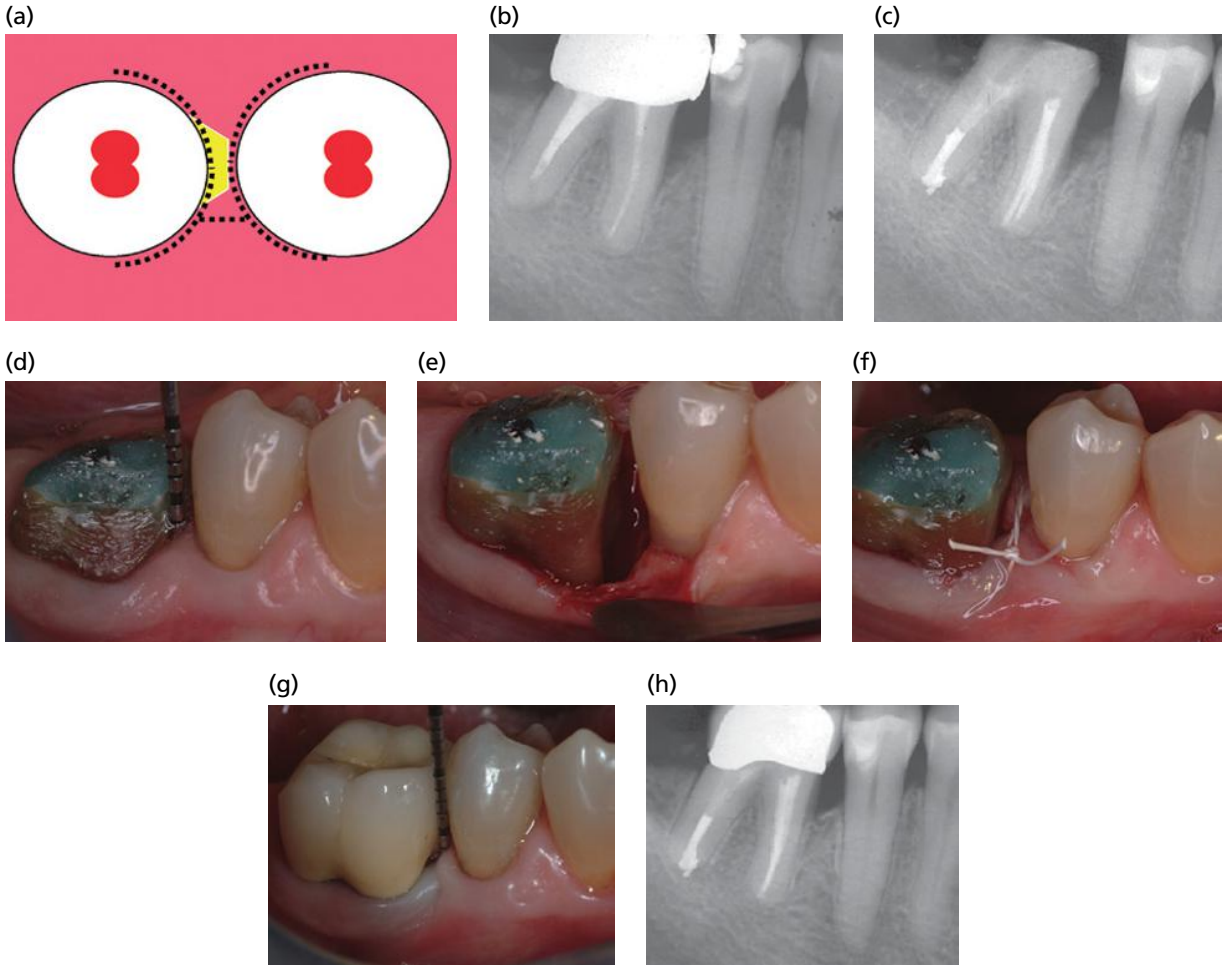


Fig. 45-25 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in an isolated interdental three-wall defect. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the interdental space associated with the defect. Mesiodistal extension of the flap was limited to the buccal aspect of the teeth adjacent to the defect in order to optimize wound stability (a). The baseline radiograph showed the presence of dental diseases (periapical infection and caries) that needed to be controlled during the initial cause-related phase of therapy (b). At re-evaluation, an 8-mm pocket associated with the presence of a deep intrabony defect was detected on the mesial aspect of the first molar (c, d). The defect was accessed in a minimally invasive fashion using the MPPT. The three-wall intrabony defect was exposed and carefully debrided (e). After application of enamel matrix derivatives, primary closure was obtained with a single modified internal mattress suture (f). One-year outcomes showed shallow probing depths and almost complete resolution of the defect (g, h).

Tonetti 2001, 2005). Microsurgical instruments are utilized, whenever needed as a complement to the normal set of periodontal instruments.

This approach has been preliminary tested in two case series with a total of 53 deep intrabony defects (Cortellini & Tonetti 2007a, b). One-year results showed clinically significant improvements (CAL gain of 4.8 ± 1.9 mm with 88.7 ± 20.7% clinical resolution of the defect) and greatly reduced patient morbidity. The same approach was successfully applied to multiple intrabony defects in 20 patients (Cortellini *et al.* 2008). The 44 treated defects gained on average 4.4 ± 1.4 mm of clinical attachment and 73% of defects showed CAL improvements of ≥4 mm. This corresponded to an 83 ± 20% resolution of the defect (15 defects were completely filled). Residual PPDs were 2.5 ± 0.6 mm. A minimal increase of 0.2 ± 0.6 mm in gingival recession between baseline and 1 year was recorded.

A recent controlled clinical study of 30 patients compared MIST plus EMD to MIST alone (Ribeiro *et al.* 2011a). The authors reported significant PPD reduction, CAL gain, and radiographic bone gain at 3 and 6 months in both groups. No differences were detected between therapies at any time point. It was concluded that the use of EMDs did not improve the outcome of the MIST for the treatment of intrabony defects.

An enhancement of this technique, the modified minimally invasive surgical technique (M-MIST) (Cortellini & Tonetti 2009b) has been tested (Fig. 45-29). The M-MIST was designed especially to improve flap stability and to provide self-ability to maintain space for regeneration. The surgical approach consists of a tiny interdental access through which only a buccal triangular flap is elevated, while the papilla is left in place, connected to the root of the crest-associated tooth with its supracrestal fibers

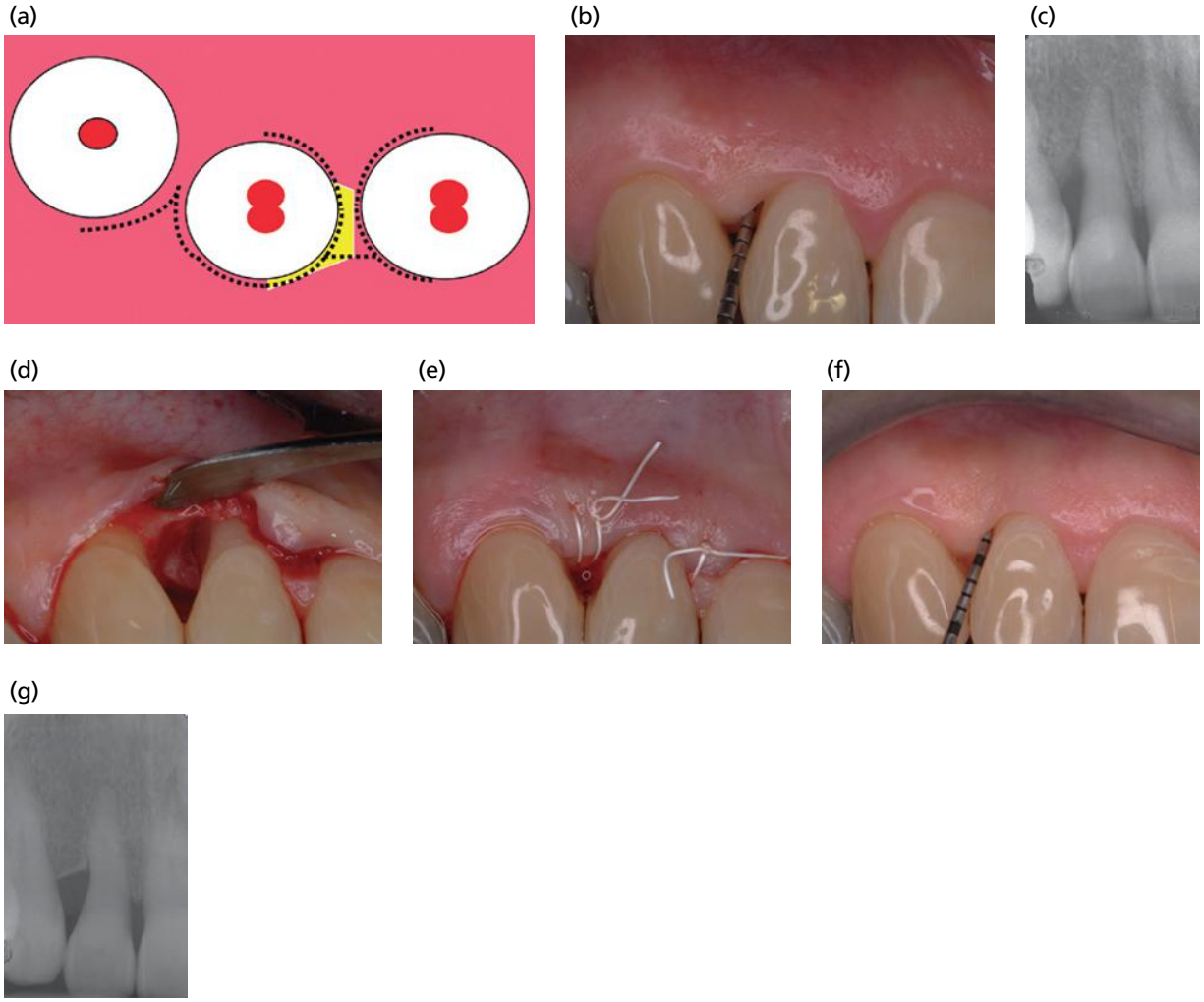


Fig. 45-26 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in an isolated interdental defect extending towards the buccal aspect of the tooth. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the interdental space associated with the defect. Mesiodistal extension of the flap was limited to the buccal aspect of the teeth adjacent to the defect and to the interdental aspect adjacent to the buccal extension of the defect in order to optimize wound stability (a). Following completion of successful initial cause-related therapy, a 6-mm pocket associated with an intrabony defect was detected on the distal aspect of the lateral incisor (b, c). The attachment loss extended to the buccal aspect of the lateral incisor, suggesting the need to obtain access to the buccal aspect of this tooth. The defect was therefore accessed with a minimally invasive approach using the MPPT to access the interdental area and extending the incision to the papilla between the lateral and central incisors to ensure adequate access to the defect (d). Primary closure was obtained with a modified internal mattress suture and a simple passing suture (e). One-year outcomes showed shallow probing depths, good preservation of the soft tissue heights, and resolution of the defect (f, g).

(see Fig. 45-5). Access to the defect is gained through the tiny buccal triangular flap: from the buccal "window", the soft tissue filling the defect (i.e. the so-called granulation tissues) is sharply dissected from the papillary supracrestal connective tissue and from the bony walls with a microblade, and removed with a mini-curette. Then, the root surface is carefully debrided with hand and mechanical instruments. The supracrestal fibers of the defect-associated papilla and the palatal tissues are left untouched. The minimal wound and the minimal flap elevation allows for preservation of most of the vessels providing the blood supply to the interdental tissues, with obvious advantages for the healing process of the interdental wound. This surgical approach with its novel design ensures self-support to the interdentally soft tissues through the "hanging" papilla, thereby enhancing space provision. The flap is extremely stable since most of the soft tissue around the bony defect is not incised or elevated, thereby enhancing blood clot stability. Minimal flap trauma, integrity of the blood supply, and absolute passivity in the suturing technique ensures primary closure of the interdental wound in the majority of the cases, thereby preventing bacterial contamination. The suturing approach is based on the use of a single internal modified mattress suture. Additional sutures can be applied to further increase primary closure, when needed. The reduced buccal access, however, means this approach is not applicable to very deep defects that involve the lingual side of a tooth for which the diseased root surface is not easily accessible for instrumentation from the small buccal window (Cortellini & Tonetti 2009b).

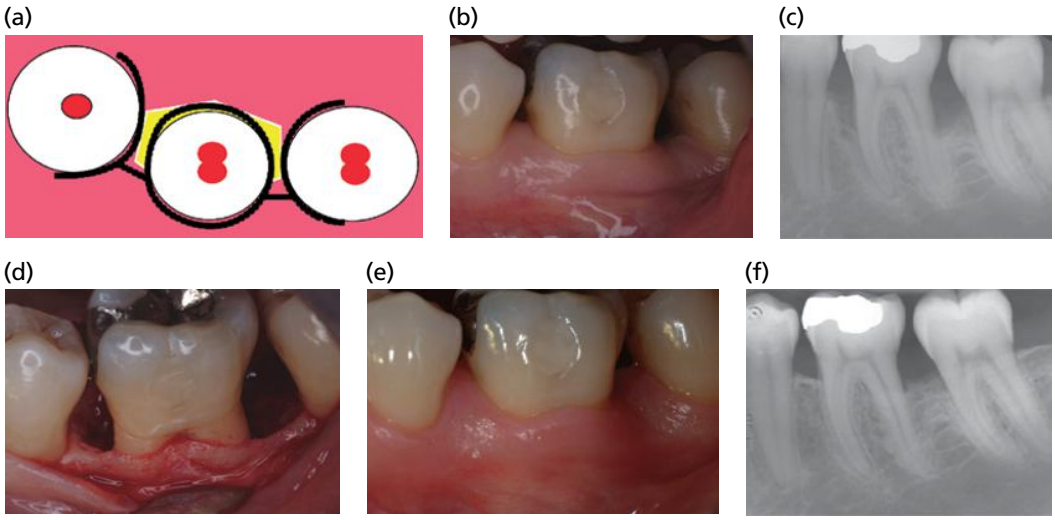


Fig. 45-27 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in intrabony defects involving both interdental spaces of the same tooth. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the two interdental spaces associated with the defects. Mesiodistal extension of the flap was limited to the two interdental papillae associated with the defects (a) and reached the line angle of the two adjacent teeth in order to limit the loss of wound stability, while allowing adequate access to the defects. The clinical and radiographic appearance at baseline highlighted the good control of inflammation obtained following completion of initial cause-related therapy and the presence of deep mesial and distal pockets with associated intrabony defects (b, c). Both the mesial and distal defects were accessed with papilla preservation flaps, the defects were debrided, and the root surfaces were carefully instrumented (d). Following application of enamel matrix derivatives in the well-contained defects, primary closure of the flap was achieved by modified internal mattress sutures. At 1-year follow-up, shallow pockets, preservation of soft tissues, and elimination of the defects were apparent (e, f).

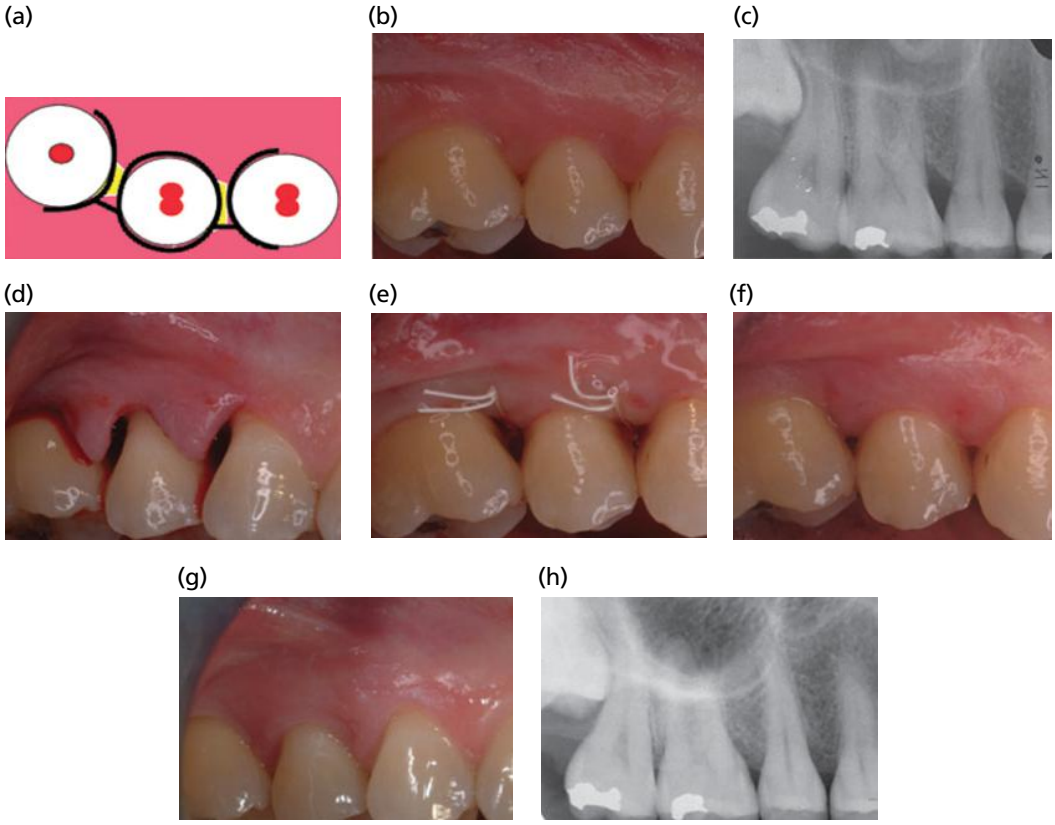


Fig. 45-28 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in intrabony defects involving two adjacent teeth. The schematic diagram shows the extent of the incision performed according to the principles of the papilla preservation flaps in the two interdental spaces associated with the defects. Mesiodistal extension of the flap was limited to the two interdental papillae associated with the defects (a) and reached the line angle of the two adjacent teeth in order to limit the loss of wound stability and to limit flap extension. After successful initial cause-related therapy, two defects were present on the mesial aspect of the first molar and second premolar (b, c). Simplified papilla preservation flaps (SPPF) were used to access the defects (d). Incisions were stopped at the distal line angle of the first premolar and on the buccal aspect of the first molar. Root debridement and application of enamel matrix proteins in gel form were performed before primary closure of the flap with two modified internal vertical mattress sutures (e). Excellent early healing in the absence of pain or discomfort was evident at the 1-week suture removal (f). At 1-year follow-up, absence of inflammation, shallow probing depths, and resolution of the defects were evident (g, h).

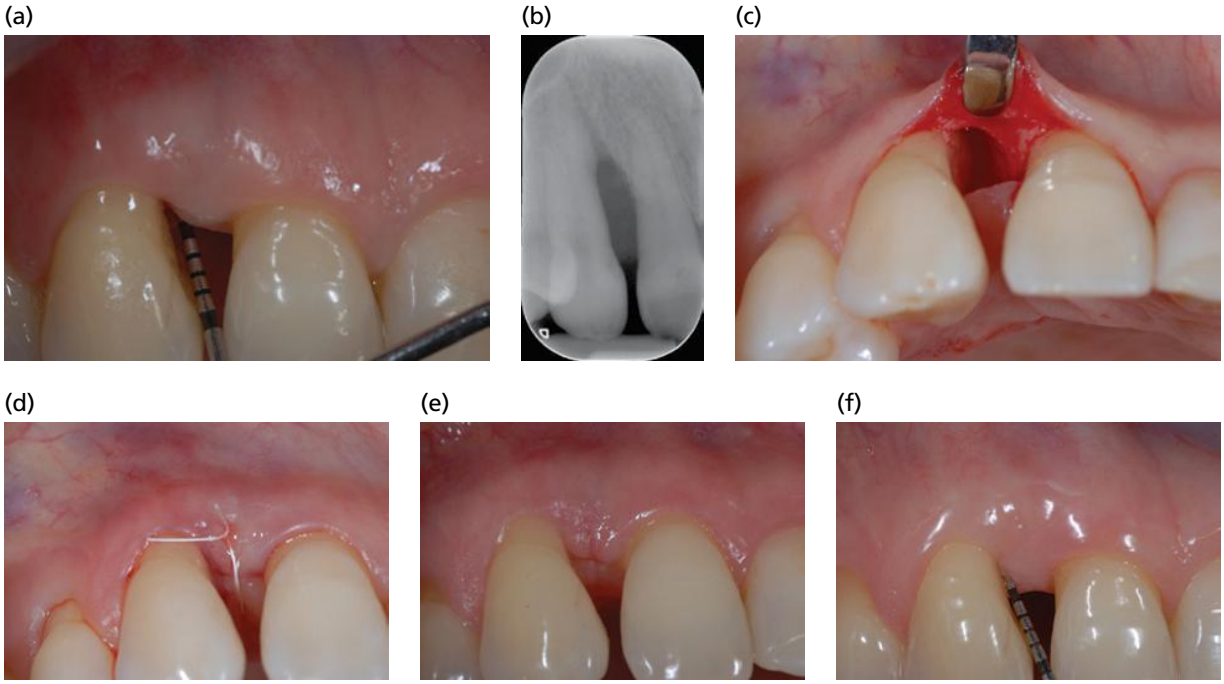


Fig. 45-29 Clinical case treated with the modified minimally invasive procedure (M-MIST). A 10-mm pocket mesial to the upper right cuspid (a) was associated with a deep intrabony defect reaching the mid third of the root (b). Area was accessed with the M-MIST procedure (c). Buccal flap was minimally elevated to the mid-buccal contour of the cuspid and the lateral incisor. The defect-associated interdental papilla was left untouched and the lingual flap was not elevated. The intrabony defect and the exposed root surface were instrumented through the small buccal surgical "window". A single modified internal mattress suture was positioned to close the area (d). No regenerative material was placed into the defect, leaving the natural blood clot alone to fill the intrabony component. Integrity of the primary closure of the wound was maintained after 1 week (e). One-year clinical photograph showed a 3-mm normal sulcus, associated with a 7-mm clinical attachment gain and no increase in gingival recession (f). One-year radiograph showed the complete resolution of the intrabony component of the defect (g).

Recently, a three-arm randomized controlled clinical trial was designed to compare the clinical efficacy of the M-MIST alone versus M-MIST combined with EMD and EMD plus bone mineral derived xenograph (BMDX), in the treatment of isolated, interdental intrabony defects (Cortellini & Tonetti 2011). The study was performed on 45 deep isolated intrabony defects accessed with the M-MIST and randomly assigned to three experimental groups: 15 to M-MIST alone, 15 to M-MIST + EMD, and 15 to M-MIST + EMD–BMDX (Fig. 45-30). The differences between baseline and 1 year were statistically significant in the three groups for PPD reduction (P >0.0001, student t-test) as well as CAL gain (P >0.0001). Comparisons between the three groups showed no statistically significant difference in any of the measured clinical outcomes. In particular, CAL gain of 4.1 ± 1.4 mm was observed in the M-MIST control group, 4.1 ± 1.2 mm in the EMD group, and 3.7 ± 1.3 mm in the EMD + BMDX one. The percentage radiographic bone fills of the intrabony component were 77 ± 19%, 71 ± 18%, and 78 ± 27%, respectively. This initial controlled study could detect a true difference in CAL of 0.96 mm between the treatment groups. However, the fact that the outcomes among the three groups could not be discriminated raises a series of hypotheses that focus on the intrinsic healing potential of a wound when ideal conditions are provided with the surgical approach. In other words, the outcomes of this study lay down the challenge to clinicians of possibly achieving substantial clinical improvements without the use of products or materials. An independent study (Trombelli *et al*. 2010) reported similar outcomes with no difference between a single flap approach (SLA) alone and SLA plus a bioresorbable barrier and hydroxyapatite.

Technical implications

The above cited studies propose two different minimally invasive approaches to intrabony defects. The MIS (Harrel 1995) and the MIST (Cortellini & Tonetti 2007a, b) include the elevation of the interdental papillary tissues to uncover the interdental space, gaining complete access to the intrabony defect, while in the M-MIST (Cortellini & Tonetti 2009a) access to the defect is gained through the reflection of a small buccal flap, without elevation of the interdental papilla (Figs. 45-27, 45-28, 45-29, 45-30). The major problem to be overcome when applying minimally invasive surgery is the visibility and manipulation of

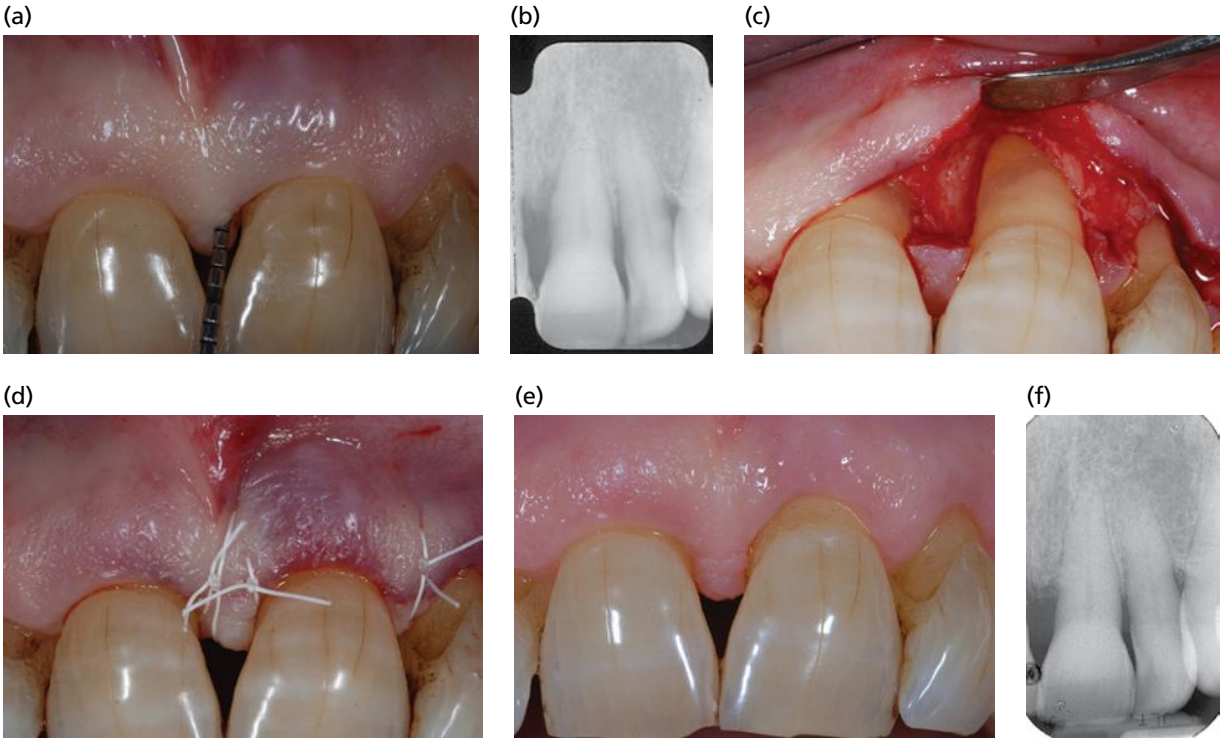


Fig. 45-30 Clinical case treated with the modified minimally invasive procedure (M-MIST) + enamel matrix derivatives (EMDs) + Bio-Oss. A 7-mm attachment loss was associated with a 6-mm pocket depth at the mesial side of the left upper central incisor (a). The intrabony defect was evident on the baseline radiograph (b). Area was accessed with the M-MIST approach. The flap was extended to the distal interdental space to uncover the buccal bone dehiscence (c). Flap was sutured after positioning of EMDs and grafting material (d). Clinical photograph (e) and radiograph (f) at 1 year showed the resolution of the periodontal lesion.

the surgical field. This issue is clearly enhanced in the M-MIST approach with its high magnification and direct optimal illumination. Traditionally, dental surgeons are taught to raise large flaps to completely expose the area of interest. In reality, visibility of the defect is restricted by the residual bony walls that surround the defect. The elevation of a flap to the edge of the residual bony walls should therefore be sufficient to visualize the defect: over-reflection of the flaps does not increase defect visibility. However, the minimal flap reflection narrows the angle of vision and especially the light penetration into the surgical field. In addition, the soft tissue manipulation during instrumentation requires more care since the flaps, which are not fully reflected, lie very close to the working field. Use of small instruments, like small periosteal elevators and tiny tissue players, is mandatory for soft and hard tissue manipulation. Microblades, mini-curettes, and mini-scissors allow for full control over the incision, debridement, and refinement of the surgical area, and sutures from 6-0 to 8-0 are mandatory for wound closure.

Flap design for furcation involvement

Flap design for buccal and lingual mandibular and buccal maxillary class II furcations were described >20 years ago and have not been substantially modified since (Pontoriero *et al*. 1988; Andersson *et al*. 1994; Jepsen *et al*. 2004). Following intrasulcular incisions, a mucoperiosteal flap is raised at the buccal or lingual aspect of the alveolar process (Fig. 45-31). The root surfaces are carefully scaled and planed using hand and power-driven instruments and rotating, flame-shaped diamond burs. Remaining granulation tissue in the furcation area is carefully removed to expose the surface of the alveolar bone.

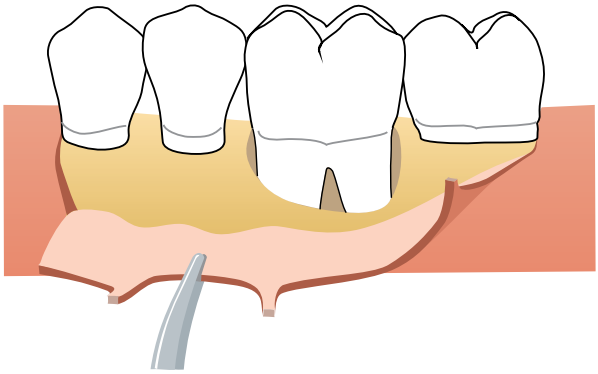


Fig. 45-31 Furcation involvement: step-by-step approach. Following marginal incisions and vertical releasing incisions on the buccal aspect of the jaw, buccal and lingual full-thickness flaps are elevated.

The regenerative material of choice (a non-bioresorbable or a bioresorbable barrier, a bone graft, a biologically active agent, or a combination approach) is positioned at the furcation area (Fig. 45-32). When a barrier is used, it is adjusted to cover the entrance (buccal or lingual) of the furcation area, the adjacent root surfaces (from the distobuccal/lingual line angle of the distal root to the mesiobuccal/lingual line angle

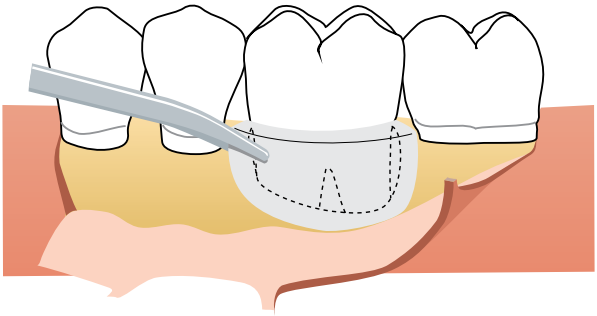


Fig. 45-32 Furcation involvement: step-by-step approach. The barrier material is placed in such a way that it completely covers the defect and extends over at least 3 mm of bone beyond the defect margin.

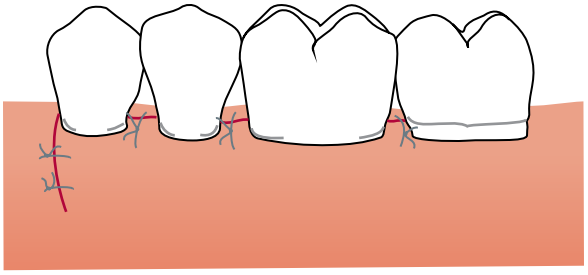


Fig. 45-33 Furcation involvement: step-by-step approach. The elevated tissue flaps are coronally displaced and sutured in such a way that the border of the barrier material is at least 2 mm below the flap margin.

of the mesial root), and a 4–5-mm wide surface of the alveolar bone apical to the bone crest. The membrane can be retained in position by sutures placed around the crown of the molar using a sling technique. When a graft is preferred, it is positioned to completely fill the furcation area and slightly overfill the entrance. Biologically active agents are delivered into the furcation area. A combination approach requires the positioning of different biomaterials according to the properties of each material.

Following placement of the regenerative material, the mucoperiosteal flap is repositioned to completely cover the furcation and the biomaterials (Fig. 45-33). A periosteal incision can be made, when needed, to coronally advance the flap. The flap is secured with interdental or sling sutures. The sutures are removed 7–15 days after surgery. When a non-bioresorbable barrier is positioned, a second surgical procedure to remove the barrier is performed after a healing period of about 6 weeks (Fig. 45-34).

The surgical technique has been carefully refined and revised by McClain and Schallhorn (2000). Their surgical technique is especially designed for combination therapy (barrier plus grafting material) and is based on a common core, modified as necessary for specific situations. This common core employs a sulcular incision full-thickness envelope flap with maximum retention of gingival and papillary tissues and sufficient exposure of the defect for adequate visualization and access for debridement. If recession

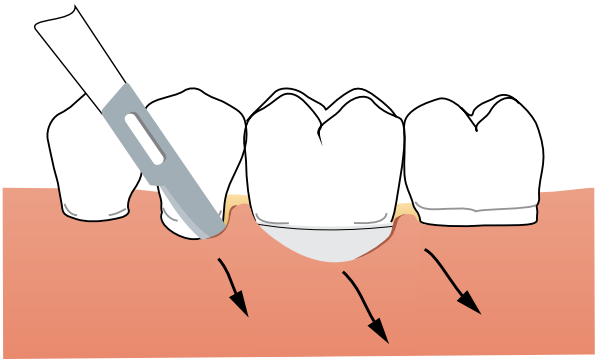


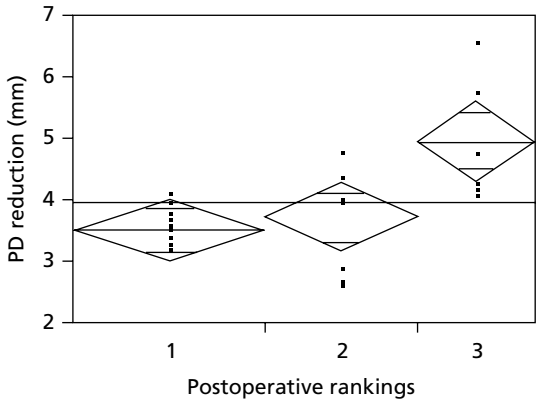
Fig. 45-34 Furcation involvement: step-by-step approach. In order to remove the barrier material, an incision is made extending one tooth mesially and distally to the border of the barrier. After reflecting the covering tissue flaps, the barrier can be removed without compromising the newly regenerated tissue.

has occurred and/or coronal flap positioning is required for membrane coverage, periosteal separation is also performed.

The defect is debrided and the root surface planed to remove plaque, accretions, enamel projections, and other root surface alterations (grooves, notches, caries, etc.) employing ultrasonic or sonic, hand and rotary (fine diamond and/or finishing burs) instrumentation. Odontoplasty and/or osteoplasty are performed if required for adequate access to the defect, including intraradicular or furcation fundus concavities, and/or for reduction of enamel projections. Adequate root preparation is considered critical to a successful outcome.

The bone graft is prepared (typically by DFDBA) in a dappen dish with hydration with sterile saline or local anesthetic solution and, if there is no contraindication, combined with tetracycline (125 mg/0.25 g of DFDBA). After mixing, the dappen dish is covered with a sterile, moistened gauze to prevent drying of the graft. The appropriate membrane is selected and trimmed to fit into the desired position, and then placed on sterile gauze. Care is taken to prevent membrane contamination via contact with the lips, tongue, mucosa or saliva.

The area is thoroughly cleansed and isolated, and the root surface at the regenerative site is treated with citric acid (pH1) for 3 minutes using cotton pellets, with care taken to contain the solution to the root and bone surface. The pellets are removed and the site inspected for any residual cotton fibers prior to flushing it with sterile water or saline. Intramarrow penetration is then performed with a 1/4 round bur if a sclerotic bone surface exists in the graft site. The ligament surface is "scraped" with a periodontal probe to remove any eschar and to stimulate bleeding, and the DFDBA is packed firmly into the defect using an overfill approach, along with covering the root trunk and combination or confluent intrabony, dehiscence or horizontal/crestal osseous defects. The custom-made membrane is placed over the graft and secured as appropriate. After rechecking



Rank	Number of studies	Mean
1	10	3.52
2	8	3.73
3	6	4.97

Source	DF	Sum of squares	Mean square	F ratio	Prob F
Post-op rank	2	8.45	4.22	7.21	0.004
Error	21	12.29	0.58		
C. Total	23	20.75			

Fig. 45-35 Regression analysis of intrabony defect studies examining the relationship between postoperative care protocol ranking and the reduction (in mm) in probing depth (PD). Group 3 is statistically different from groups 1 and 2. (Source: Murphy & Gunsolley 2003. Reproduced from the American Academy of Periodontology.)

to be sure adequate graft material remains in the desired area, the flap is positioned to cover the membrane and secured with non-bioresorbable sutures (typically Gore sutures). Throughout the root conditioning and subsequent treatment to closure, the site remains isolated to avoid saliva contamination.

If a non-bioresorbable membrane is used, it is removed at 6–8 weeks postoperatively by employing minor flap reflection, de-epithelialization of the internal aspect of the flap adjacent to the membrane, gentle removal (peeling) of the membrane outward from the site, and flap positioning to cover the regenerated tissues as feasible. Closure with sutures is then accomplished with non-bioresorbable sutures.

Postoperative regimen

The postoperative regimen prescribed to the patients is aimed at controlling wound infection or contamination as well as mechanical trauma to the treated sites. A meta-analysis indicated that differences in regenerative outcomes can be expected based on the postoperative care protocol: more frequent, intensive regimens were associated with better CAL gain in intrabony defects (Murphy & Gunsolley 2003) (Fig. 45-35). It generally includes the prescription of systemic antibiotics (doxycycline or amoxicillin) in the immediate postoperative period (1 week), 0.2 or 0.12% chlorhexidine mouth rinsing b.i.d. or t.i.d., and weekly professional tooth cleaning until the membrane is in place. Professional tooth cleaning consists of supragingival prophylaxis with a rubber cup and chlorhexidine gel. Patients are generally advised not to perform mechanical oral hygiene and not to chew in the treated area.

Non-bioresorbable membranes are removed 4–6 weeks after placement, following elevation of partial-thickness flaps. Patients are re-instructed to rinse b.i.d. or t.i.d. with chlorhexidine, not to perform mechanical oral hygiene, and not to chew in the treated area for 3–4 weeks. In this period, weekly professional control and prophylaxis are recommended. When bioresorbable membrane, BRG or biologically active regenerative materials are used, the period of tight infection control is extended for 6–8 weeks. After this period, patients are re-instructed to resume mechanical oral hygiene gradually, including interdental cleaning, and to discontinue chlorhexidine. Patients are then enrolled in a monthly periodontal care program for 1 year. Probing or deep scaling in the treated area is generally avoided before the 1-year follow-up visit.

Postoperative period and local side effects

From the very beginning of the "guided tissue regeneration era", the frequent occurrence of complications, in particular barrier exposure, was apparent. Complications occurred in almost 100% of the cases in the prepapilla preservation techniques period (Becker *et al*. 1988; Cortellini *et al*. 1990; Selvig *et al*. 1992; Cortellini *et al*. 1993a, b; Falk *et al*. 1997; Trombelli *et al*. 1997; Murphy 1995a, b; Mayfield *et al*. 1998) but negative occurrences reportedly reduced to amounts ranging from 50% to 6% when papilla preservation flaps were adopted (Cortellini *et al*. 1995a, 1996; Tonetti *et al*. 1998; Cortellini *et al*. 1999a; Cortellini & Tonetti 2000; Cortellini *et al*. 2001; Machtei 2001; Tonetti *et al*. 2002; Murphy & Gunsolley 2003; Tonetti *et al*. 2004a; Cortellini & Tonetti 2005). A consistent decrease of complications was observed when barriers were not incorporated into the surgical procedure. In particular, the adoption of EMDs largely reduced the prevalence of complications (Tonetti *et al*. 2002; Esposito *et al*. 2009; Sanz *et al*. 2004). Sanz

et al. (2004) showed that all sites treated with membranes showed at least one surgical complication during healing, while a complication was observed in only 6% of sites treated with EMDs. This study indicates that some regenerative materials/procedures may be less technique sensitive than others.

The development of minimally invasive surgery has greatly reduced the amount of complications and side effects in the postoperative period. Primary closure of the flap was reported in 100% of cases treated with MIST and was maintained in single sites in 95% of cases at 1 week (Cortellini & Tonetti 2007a, b) and in multiple sites in 100% of cases (Cortellini *et al.* 2008). Edema was noted in few cases (Cortellini and Tonetti 2007a, b; Cortellini *et al*. 2008). No postsurgical hematoma, suppuration, flap dehiscence, presence of granulation tissue, or other complications were reported in any of the treated sites (Cortellini & Tonetti 2007a, b; Cortellini *et al*. 2008). Root sensitivity was not a frequent occurrence: reported at 1 week by about 20% of the patients but this percentage rapidly decreased in the following weeks, with only one patient still reporting some root sensitivity a 6 weeks (Cortellini & Tonetti 2007b). Ribeiro *et al*. (2011a) reported that the extent of root hypersensitivity and edema was very discreet and no patients developed hematoma.

When applying the M-MIST, Cortellini and Tonetti (2009b) reported primary closure obtained and maintained in 100% of the cases. In a second controlled study (Cortellini & Tonetti 2011), one M-MIST/EMD/BMDX-treated site presented at suture removal (week 1) with a slight discontinuity of the interdental wound. At week 2, the gap appeared to have closed. No edema, hematoma or suppuration was noted in any of the treated sites in these studies (Cortellini & Tonetti 2009a, 2011).

Surgical and post-surgical morbidity

To date, little consideration has been given to critical elements that could contribute to the patient's assessment of the cost–benefit ratio of GTR procedures. These include postoperative pain, discomfort, complications, and the perceived benefits from the treatment. A parallel group, randomized, multicenter and controlled clinical trial designed to test the efficacy of GTR versus flap surgery alone assessed these patient issues (Cortellini *et al*. 2001). During the procedure, 30.4% of the test group and 28.6% of the controls reported moderate pain, and subjects in the test group estimated the hardship of the procedure as 24 ± 25 units on a visual analog scale (VAS from 0 to 100, with 0 = no hardship and 100 = unbearable hardship) and subjects in the control group 22 ± 23 VAS. Surgery with membranes required longer chair time than flap surgery alone (on average 20 minutes longer). Among the postoperative complications, edema was most prevalent at week 1 and most frequently associated with the GTR treatment, while postoperative pain was reported by fewer than 50% of both the test and control patients. Pain intensity was described as mild and lasted on average 14.1 ± 15.6 hours in the test patients and 24.7 ± 39.1 hours in the controls. Postoperative morbidity was limited to a minority of subjects: 35.7% of the test patients and 32.1% of the controls reported that the procedures interfered with daily activities for an average of 2.7 ± 2.3 days in the test group and 2.4 ± 1.3 days in the control group. These data indicate that GTR adds almost 30 minutes to a flap procedure and is followed by a greater prevalence of post-surgical edema, while no difference was observed between GTR and flap surgery alone in terms of postoperative pain, discomfort, and interference with daily activities.

No comparative study has reported the morbidity associated with the various regenerative approaches. Reports of multicenter trials on the application of EMDs or barrier membranes using the same methodology, however, show similar results for the two regenerative materials (Tonetti *et al*. 1998, 2004a; Cortellini *et al*. 2001).

Morbidity of the regenerative procedure was tested on a population treated with MIST and EMDs. Patients were questioned at the end of surgery and at week 1 about the intraoperative and postoperative period, respectively, and reported no pain (Cortellini & Tonetti 2007a). Three of the 13 patients reported very limited discomfort in the first 2 days of the first postoperative week. Seventy-seven percent of the patients described the first postoperative week as uneventful, reporting no feeling of having been surgically treated after the second postoperative day.

In a large case cohort of 40 patients treated with MIST and EMDs (Cortellini & Tonetti 2007b), none of the patients reported intraoperative pain or discomfort and 70% did not experience any postoperative pain. The subjects reporting pain described it as being very moderate (VAS 19 ± 10, with 0 = no pain and 100 = unbearable pain). In these patients, pain lasted for 26 ± 17 hours on average. Home consumption of analgesic tablets was 1 ± 2 on average. Twenty-three patients did not use any pain killer in addition to the first two compulsory tablets that were administered in the practice immediately after the surgery and 6 hours later. Seven of the 12 patients (17.5%) reporting pain also experienced some discomfort (VAS 28 ± 11, with 0 = no discomfort and 100 = unbearable discomfort) that lasted for 36 ± 17 hours on average. Only three patients reported some interference with daily activities (work and sport) for 1–3 days.

In a second case cohort study of MIST and EMDs on multiple adjacent intrabony defects (Cortellini *et al*. 2008), 14 of the 20 patients did not experience any postoperative pain. The six subjects reporting pain described it as being very mild (VAS 19 ± 9) and lasting for 21 ± 5 hours on average. Home consumption of painkillers was 0.9 ± 1.0. Nine patients did not use any analgesic in addition to the first two

Table 45-3 Comparison between clinical studies of conventional versus those of minimally invasive surgery.

	Cortellini *et al.* (2001)	Tonetti *et al.* (2004b)	Cortellini *et al.* (2007b)	Cortellini & Tonetti (2011)
Regenerative approach	SPPF/MPPT + bioresorbable barrier	SPPF/MPPT+ EMD	MIST + EMD	M-MIST + EMD
Number of patients	56	83	40	15
Chair time (minutes)[a]	99 ± 46	80 ± 34	58 ± 11	54.2 ± 7.4
Interference with daily activity[b]	35.7%	29.5%	7.5%	0
Subjects with postoperative discomfort[b]	53.6%	47.5%	17.5%	13.3%
Subjects with postoperative pain[b]	46%	50%	30%	0
Pain intensity[c]	28.1 ± 2.5	28 ± 20	19 ± 10	–
Number of pain killers[d]	4.1 ± 2.5	4.3 ± 4.5	1.1 ± 2	0.3 ± 0.6

[a] Chair time measured from delivery of anesthesia to completion of the regenerative surgical procedures.
[b] Percentage of subjects reporting postoperative interference with daily activities, discomfort, and pain, as questioned at 1-week recall visit.
[c] Intensity of pain measured with a visual analog scale (VAS).
[d] Number of pain killers taken in addition to the two compulsory ones delivered at the end of surgery.
SPPF, simplified papilla preservation flap; MPPT, modified papilla preservation technique; MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique; EMD, enamel matrix derivative; bioresorbable barrier, polylactic and polyglycolic acid barrier.

compulsory tablets. Ten patients experienced mild discomfort (VAS 21 ± 10) that lasted for 20 ± 9 hours on average. Only four patients reported some interference with daily activities (work and sport) for 1–3 days.

Ribeiro *et al*. (2011b) reported that the extent of discomfort/pain experienced during therapy with MIST and EMDs was very limited. In addition, the extent of discomfort during the first postoperative week was very discreet, and no patients developed high fever or reported any interference with daily activities. The quantity of analgesic medication taken by patients was minimal (fewer than one analgesic medication per patient).

In a case cohort study where 15 patients were treated with M-MIST and EMDs (Cortellini & Tonetti 2009b), none of the patients reported intraoperative or significant postoperative pain. Three of the patients reported very limited discomfort in the first 2 days after surgery. Fourteen described the first postoperative week as uneventful, reporting no feeling of having been surgically treated after the second postoperative day.

In a controlled study of the additional benefit from EMDs or EMD/BMDX with M-MIST compared to M-MIST alone (Cortellini & Tonetti 2011), none of the 45 patients reported having experienced intra- and post-operative pain. Slight discomfort was reported by three patients in the M-MIST group (average VAS 10.7 ± 2.1), by two patients in the M-MIST/EMD group (VAS 11.5 ± 0.7), and by four patients in the M-MIST/EMD/BMDX group (VAS 12.3 ± 3.1). Few patients needed pain control medications: three patients from the M-MIST group (average number of tablets 0.4 ± 0.7; maximum 2), four patients from the M-MIST/EMD group (average 0.3 ± 0.6; maximum 2), and four patients from the M-MIST/EMD/BMDX group (average 0.5 ± 1; maximum 3).

Table 45-3 gives some of surgical and postsurgical parameters used in four studies. Two studies concerned the application of traditional large papilla preservation flaps (MPPT and SPPF) with bioresorbable barriers (Cortellini *et al*. 2001) or EMDs (Tonetti *et al*. 2004b). The other two studies concerned the MIST in combination with EMDs (Cortellini *et al*. 2007; Cortellini & Tonetti 2011). This historical comparison clearly shows differences in most of the parameters between the four studies. Surgical chair time was the longest when large papilla preservation flaps and barriers were applied, shorter when large papilla preservation flaps were combined with EMDs, and by far the shortest when M-MIST and EMDs were used. The number of subjects reporting postoperative interference with daily activities, discomfort, and pain was similar in the two papilla preservation flap studies, much reduced in the MIST study, and very limited or none in the M-MIST study; similarly pain intensity and consumption of pain killers was very low in both studies. The reported outcomes indicate that postoperative discomfort and pain apparently are not influenced by the type of regenerative material, but are by the type of surgical approach: a more friendly, shorter chair time, minimally invasive surgery is associated with fewer postoperative problems. These considerations may prompt clinicians to adopt more patient-friendly approaches whenever possible.

Barrier materials for regenerative surgery

In the first GTR attempts, a bacterial filter produced from cellulose acetate (Millipore®) was used as an occlusive membrane (Nyman *et al*. 1982; Gottlow *et al*. 1984; Magnusson *et al*. 1985). Although this type of membrane served its purpose, it was not ideal for clinical application.

Non-bioresorbable materials

Later studies have utilized membranes of e-PTFE specially designed for periodontal regeneration (Gore Tex Periodontal Material®). The basic molecule of this material consists of a carbon–carbon bond with four attached fluorine atoms to form a polymer. It is inert and does not result in any tissue reaction when implanted in the body. This type of membrane persists after healing and must be removed in a second operation. Membranes of e-PTFE have been used successfully in animal experiments and in several clinical studies. From such studies it was found that for a barrier material to function optimally, it has to meet certain essential design criteria:

- Biocompatibility to assure good tissue acceptance. The material should not elicit an immune response, sensitization or chronic inflammation that may interfere with healing and present a hazard to the patient. Biocompatibility, however, is a relative term since practically no materials are completely inert.
- Acts as a barrier to exclude undesirable cell types from entering the secluded space adjacent to the root surface. It is also considered to be an advantage that the material allows the passage of nutrients and gases.
- Tissue integration that allows the tissue to grow into the material without completely penetrating it. The goal of tissue integration is to prevent rapid epithelial down-growth on the outer surface of the material or encapsulation of the material, and to provide stability to the overlying flap. The importance of tissue integration was demonstrated in a study in monkeys (Warrer *et al*. 1992) in which bioresorbable membranes of polylactic acid, a synthetic polymer, were used to treat circumferential periodontal defects. Due to the lack of tissue integration, the membranes in this study became surrounded by an epithelial layer and were often encapsulated and exfoliated.
- Capable of creating and maintaining a space adjacent to the root surface. This allows the blood clot to form at the interface between the flap and root surface (Haney *et al*. 1993; Sigurdsson *et al*. 1994; Cortellini *et al*. 1995c, d; Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al*. 2004). Some materials may be so soft and flexible that they collapse into the defect. Other materials are too stiff and may perforate the overlying tissue.
- Provide stability to the blood clot to maintain continuity with the root surface, thereby preventing the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993).

Bioresorbable materials

In recent years, natural or synthetic bioresorbable barrier materials for GTR have been introduced in order to avoid the second surgery necessary for removal of non-bioresorbable materials. Barrier materials of collagen from different species and from different anatomic sites have been tested in animals and in humans (Blumenthal 1988; Pitaru *et al*. 1988; Tanner *et al*. 1988; Paul *et al*. 1992; Blumenthal 1993; Wang *et al*. 1994; Camelo *et al*. 1998; Mellonig 2000). Often the collagen used is a cross-linked variety of porcine or bovine origin. When a collagen membrane is implanted in the human body, it is resorbed by the enzymatic activity of macrophages and polymorphonuclear leukocytes (Tatakis *et al*. 1999). Successful treatment with these barrier materials has been demonstrated, but the results of studies vary. Several complications, such as early degradation, epithelial down-growth along the material, and premature loss of the material, have been reported. The varying results are probably due to differences in the properties of the material and the handling of the material at the time of implantation. Although probably very minimal, there is a risk that infectious agents from animal products can be transmitted to humans, and autoimmunization has also been mentioned as a risk.

Barrier materials of polylactic acid or co-polymers of polylactic acid and polyglycolic acid were evaluated in animal and human studies and are now commonly used (Magnusson *et al*. 1988; Caffesse *et al*. 1994; Caton *et al*. 1994; Gottlow *et al*. 1994; Laurell *et al*. 1994; Hugoson *et al*. 1995; Polson *et al*. 1995a; Cortellini *et al*. 1996c; Hürzeler *et al*. 1997; Sculean *et al*. 1999a; Tonetti et al 1998; Cortellini *et al*. 2001). These materials are biocompatible, but by definition they are not inert since some tissue reaction may be expected during degradation. The materials are degraded by hydrolysis and eliminated from the organism through the Krebs cycle as carbon dioxide and water (Tatakis *et al*. 1999).

The types of barrier materials that have been tested differ both in configuration and design. It appears that a number of bioresorbable materials meet to a varying extent the requirements of a good barrier listed above. Indeed, there are several studies (Hugoson *et al*. 1995; Cortellini *et al*. 1996b; Smith MacDonald *et al*. 1998; Tonetti *et al*. 1998; Cortellini & Tonetti 2000a, 2005) indicating that similar satisfactory results can be obtained with bioresorbable barrier materials of polylactic and polyglycolic acid as with non-bioresorbable materials.

Membranes for intrabony defects

Early evidence that GTR treatment of deep intrabony defects may produce clinical improvements in terms of CAL was presented in several case reports (Nyman *et al*. 1982; Gottlow *et al*. 1986; Becker *et al*. 1988; Schallhorn & McClain 1988; Cortellini *et al*. 1990). In recent years, a considerable number of clinical investigations have reported on intrabony defects treated with GTR (see Table 43-2). In these studies, the issue of evaluating the predictability of the clinical outcomes following application of GTR procedures was addressed. Table 43-4 gives the results for a total of 1283 intrabony defects treated with GTR. The weighted mean of the reported results indicates a mean CAL gain of 3.8 ± 1.7 mm, with a 95% CI of 3.7–4.0 mm (Cortellini & Tonetti 2000a). The reported CAL gains following GTR treatment were significantly larger than those obtained with conventional flap surgery. A review 40 studies on flap surgery with a weighted mean of 1172 defects reported CAL gains of 1.8 ± 1.4 mm (95% CI of 1.6–1.9 mm) (Lang 2000). A more recent review and meta-analysis of 27 trials on access flap surgery included 647 subjects and 734 defects (Graziani *et al*. 2011). Twelve months after flap surgery, tooth survival was 98% (IQ 96.77–100%), CAL gain was 1.65 mm (95% CI 1.37–1.94; P <0.0001), PPD reduction was 2.80 mm (CI 2.43–3.18; P <0.0001), and recession (REC) increase 1.26 mm (CI 0.94–1.49; P <0.0001).

Different types of non-bioresorbable (Fig. 45-36) and bioresorbable (Fig. 45-37) barrier materials were used in the clinical studies summarized in Table 45-4. Analysis of the results reported in some of the published studies (Proestakis *et al*. 1992; Cortellini *et al*. 1993a; Cortellini & Pini-Prato 1994; Laurell *et al*. 1994; Cortellini *et al*. 1995b, c; Mattson *et al*. 1995; Mellado *et al*. 1995; Cortellini *et al*. 1996b; Tonetti *et al*. 1996b) provides important information regarding the predictability of GTR in intrabony defects. CAL gains of 2–3 mm were observed in 29.2% of the defects, of 4–5 mm in 35.4% of the defects, and of ≥6 mm in 24.9% of the defects. Only in 10.5% of the treated defects was the gain <2 mm, while no change or attachment loss was observed in two cases.

In some of the investigations, changes in bone levels were also reported (Becker *et al*. 1988; Handelsman *et al*. 1991; Kersten *et al*. 1992; Cortellini *et al*. 1993a, b; Selvig *et al*. 1993). Bone gains ranged between 1.1 and 4.3 mm and correlated with the reported CAL gains. In a study by Tonetti *et al*. (1993b), 1 year after GTR the bone was found to be located 1.5 mm apically to the position of the attained CAL.

Another important parameter related to the outcome of regenerative procedures is the residual pocket depth. In the studies in Table 45-4, shallow pockets were consistently found at 1 year. The weighted mean residual pocket depth was 3.4 ± 1.2 mm (95% CI 2.3–3.5 mm).

The reported outcomes indicate that GTR procedures predictably result in clinical improvements in intrabony defects beyond those of flap surgery (see Fig. 45-6). This was further confirmed in 11 controlled randomized clinical trials in which GTR was compared with conventional flap surgery (Table 45-5). A total of 267 defects were treated with flap surgery and 317 with GTR. In nine of the 11 investigations, GTR resulted in a statistically significantly greater PAL gain when compared to flap surgery. Similar results were also observed for residual pocket depth.

Membranes for furcation involvement

The invasion of the furcation area of multirooted teeth by periodontitis represents a serious complication in periodontal therapy. The furcation area is often inaccessible to adequate instrumentation, and the roots frequently present concavities and furrows which make proper cleaning of the area impossible (see Chapter 40). As long as the pathologic process only extends a small distance (<5 mm; class I and II involvements) into the furcation area, further progress of the disease can usually be prevented by scaling and root planing, provided a proper oral hygiene program is established after treatment. In more advanced cases (5–6 mm; class II involvements), the initial cause-related treatment is frequently supplemented with surgery involving contouring of the inter-radicular bone (osteoplasty) or reduction of the tooth prominence at the furcation entrance by grinding (odontoplasty), in order to reduce the horizontal extension of the furcation involvement. In cases where the involvement extends even deeper into the furcation area (>5mm; class II involvements), or a through-and-through defect (class III involvements) has developed, tunnel preparation or root resection has been advocated as the treatment of choice. However, both of these treatments run a risk of complications on a long-term basis. Following tunnel preparation, caries frequently develops in the furcation area and root-resected teeth often present complications of a non-periodontal nature, although controversial reports exist regarding the long-term results of these treatment modalities (Hamp *et al*. 1975; Langer *et al*. 1981; Erpenstein 1983; Bühler 1988; Little *et al*. 1995; Carnevale *et al*. 1998).

Considering the complexity of current techniques for the treatment of furcation problems, and in view of the long-term results and complications reported following treatment of advanced furcation involvements by traditional resective therapy, predictable regeneration of the periodontium at furcation-involved sites would represent considerable progress in periodontics.

Mandibular class II furcations

Pontoriero *et al*. (1988) reported a controlled randomized clinical trial in which significantly greater H-CAL gain (3.8 ± 1.2 mm) were obtained in 21 mandibular class II furcations treated with e-PTFE

Table 45-4 Clinical outcomes of guided tissue regeneration (GTR) treatment of deep intrabony defects.

Study	Membranes	Number	Gains in CAL ± SD (mm)	Residual PPD ± SD (mm)
Becker *et al*. (1988)	e-PTFE	9	4.5 ± 1.7	3.2 ± 1.0
Chung *et al*. (1990)	Collagen	10	0.6 ± 0.6	
Handelsman *et al*. (1991)	e-PTFE	9	4.0 ± 1.4	3.9 ± 1.4
Kersten *et al*. (1992)	e-PTFE	13	1.0 ± 1.1	5.1 ± 0.9
Proestakis *et al*. (1992)	e-PTFE	9	1.2 ± 1.3	3.5 ± 0.9
Quteish & Dolby (1992)	Collagen	26	3.0 ± 1.5	2.2 ± 0.4
Selvig *et al*. (1992)	e-PTFE	26	0.8 ± 1.3	5.4
Becker & Becker (1993)	e-PTFE	32	4.5	3.9 ± 0.3
Cortellini *et al*. (1993a)	e-PTFE	40	4.1 ± 2.5	2.0 ± 0.6
Falk *et al*. (1993)	Polylactic acid	25	4.5 ± 1.6	3.0 ± 1.1
Cortellini & Pini-Prato (1994)	Rubber dam	5	4.0 ± 0.7	2.4 ± 0.5
Laurell *et al*. (1994)	Polylactic acid	47	4.9 ± 2.4	3.0 ± 1.5
Al-Arrayed *et al*. (1995)	Collagen	19	3.9	2.5
Chen *et al*. (1995)	Collagen	10	2.0 ± 0.4	4.2 ± 0.4
Cortellini *et al*. (1995c)	e-PTFE	15	4.1 ± 1.9	2.7 ± 1.0
Cortellini *et al*. (1995c)	e-PTFE + titanium	15	5.3 ± 2.2	2.1 ± 0.5
Cortellini *et al*. (1995a)	e-PTFE + FFG	14	5.0 ± 2.1	2.6 ± 0.9
Cortellini *et al*. (1995a)	e-PTFE	14	3.7 ± 2.1	3.2 ± 1.8
Cortellini *et al*. (1995b)	e-PTFE + fibrin	11	4.5 ± 3.3	1.7
Cortellini *et al*. (1995b)	e-PTFE	11	3.3 ± 1.9	1.9
Mattson *et al*. (1995)	Collagen	13	2.5 ± 1.5	3.6 ± 0.6
Mattson *et al*. (1995)	Collagen	9	2.4 ± 2.1	4.0 ± 1.1
Mellado *et al*. (1995)	e-PTFE	11	2.0 ± 0.9	
Becker *et al*. (1996)	Polylactic acid	30	2.9 ± 2.0	3.6 ± 1.3
Cortellini *et al*. (1996c)	Polylactic acid	10	4.5 ± 0.9	3.1 ± 0.7
Cortellini *et al*. (1996b)	e-PTFE	12	5.2 ± 1.4	2.9 ± 0.9
Cortellini *et al*. (1996b)	Polylactic acid	12	4.6 ± 1.2	3.3 ± 0.9
Gouldin *et al*. (1996)	e-PTFE	25	2.2 ± 1.4	3.5 ± 1.3
Kim *et al*. (1996)	e-PTFE	19	4.0 ± 2.1	3.2 ± 1.1
Murphy (1996)	e-PTFE + ITM	12	4.7 ± 1.4	2.9 ± 0.8
Tonetti *et al*. (1996b)	e-PTFE	23	5.3 ± 1.7	2.7
Benqué *et al*. (1997)	Collagen	52	3.6 ± 2.2	3.9 ± 1.7
Caffesse *et al*. (1997)	Polylactic acid	6	2.3 ± 2.0	3.8 ± 1.2
Caffesse *et al*. (1997)	e-PTFE	6	3.0 ± 1.2	3.7 ± 1.2
Christgau *et al*. (1997)	e-PTFE	10	4.3 ± 1.2	3.6 ± 1.1
Christgau *et al*. (1997)	Polyglactin	10	4.9 ± 1.0	3.9 ± 1.1
Falk *et al*. (1997)	Polylactic acid	203	4.8 ± 1.5	3.4 ± 1.6
Kilic *et al*. (1997)	e-PTFE	10	3.7 ± 2.0	3.1 ± 1.4
Cortellini *et al*. (1998)	Polylactic acid	23	3.0 ± 1.7	3.0 ± 0.9
Eickholz *et al*. (1998)	Polylactic acid	14	3.4 ± 1.6	3.2 ± 0.7

(*Continued*)

Table 45-4 *Continued.*

Study	Membranes	Number	Gains in CAL ± SD (mm)	Residual PPD ± SD (mm)
Smith MacDonald *et al*. (1998)	e-PTFE	10	4.3 ± 2.1	3.7 ± 0.9
Smith MacDonald *et al*. (1998)	Polylactic acid	10	4.6 ± 1.7	3.4 ± 1.2
Parashis *et al*. (1998)	Polylactic acid	12	3.8 ± 1.8	3.5 ± 1.4
Tonetti *et al*. (1998)	Polylactic acid	69	3.0 ± 1.6	4.3 ± 1.3
Cortellini *et al*. (1999a)	Polylactic acid	18	4.9 ± 1.8	3.6 ± 1.2
Pontoriero *et al*. (1999)	Diff. barriers	30	3.1 ± 1.8	3.3 ± 1.3
Sculean *et al*. (1999a)	Polylactic acid	52	3.4 ± 1.4	3.6 ± 1.3
Dorfer *et al*. (2000)	Polylactic acid	15	4.0 ± 1.2	2.7 ± 0.7
Dorfer *et al*. (2000)	Polidiossanon	15	3.4 ± 1.9	3.1 ± 1.1
Eickholz *et al*. (2000)	Polylactic acid	30	3.9 ± 1.2	2.6 ± 1.0
Karapataki *et al*. (2000)	Polylactic acid	10	4.7 ± 0.7	4.2 ± 1.4
Karapataki *et al*. (2000)	e-PTFE	9	3.6 ± 1.7	4.6 ± 1.4
Ratka-Kruger *et al*. (2000)	Polylactic acid	23	3.1 ± 2.3	4.7 ± 1.3
Zybutz *et al*. (2000)	Polylactic acid	15	2.4 ± 1.9	
Zybutz *et al*. (2000)	e-PTFE	14	2.4 ± 0.8	
Cortellini & Tonetti (2001)	Diff. barriers	26	5.4 ± 1.2	3.3 ± 0.6
Cortellini *et al*. 2001	Polylactic acid	55	3.5 ± 2.1	3.8 ± 1.5
Weighted mean		**1283**	**3.8 ± 1.7**	**3.4 ± 1.2**

CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; FGG, free gingival graft; ITM, interproximal tissue maintenance; PPD, probing pocket depth; SD, standard deviation.

membranes compared to those in a control group treated with OFD alone (H-CAL gain of 2.0 ± 1.2 mm). Complete closure of the furcation was observed at 67% of the test sites and at only 10% of the control sites. Results from later studies, however, have not been as promising (Becker *et al*. 1988; Lekovic *et al*. 1989; Caffesse *et al*. 1990). Analysis of a series of studies published between 1988 and 1996 demonstrates a great variability in the clinical outcomes (Figs. 45-38, 45-39). Table 45-6 summarizes the outcomes of 21 clinical trials in which a total of 423 mandibular class II furcations were treated with different types of non-bioresorbable and bioresorbable barrier membranes. The weighted mean of the reported results showed an H-CAL gain of 2.3 ± 1.4 mm (95% CI 2.0–2.5 mm) in defects with a baseline horizontal PPD of 5.4 ± 1.3 mm. The reported number of complete furcation closures after GTR ranged from 0% to 67%. In three studies none of the treated furcations was closed (Becker *et al*. 1988; Yukna 1992; Polson *et al*. 1995b), in seven studies <50% were closed (Schallhorn & McClain 1988; Blumenthal 1993; Bouchard *et al*. 1993; Parashis & Mitsis 1993; Laurell *et al*. 1994; Mellonig *et al*. 1994; Hugoson *et al*. 1995), and in only one study were >50% of the treated furcations completely resolved (Pontoriero *et al*. 1988).

A subset analysis of the studies reported in Table 45-6 indicated that furcations treated with non-bioresorbable barrier membranes (287) showed a gain in H-CAL of 1.8 ± 1.4 mm (95% CI 1.5–2.1 mm) as compared with 2.3 ± 1.2 mm (95% CI 2–2.6 mm) in 174 defects treated with bioresorbable barrier membranes. Five controlled clinical trials compared treatment with non-bioresorbable e-PTFE membranes and treatment with different types of bioresorbable membranes (Table 45-7). In particular, one investigation reported significantly greater H-CAL gain in the non-bioresorbable group (Bouchard *et al*. 1993), while another trial (Hugoson *et al*. 1995) showed a significantly greater H-CAL gain in the bioresorbable group. The remaining three investigations failed to detect any significant differences between the outcomes of treatment with bioresorbable or non-bioresorbable membranes. Generally, the results indicate that the predictability of GTR in the treatment of mandibular class II furcations is questionable if the treatment objective is the complete resolution of the furcation involvement.

Significant gain in V-CAL and reduction in PPD was also reported by several investigators following treatment of mandibular class II furcation defects (Pontoriero *et al*. 1988; Lekovic *et al*. 1989, 1990; Blumenthal 1993; Machtei *et al*. 1993; Black *et al*. 1994; Laurell *et al*. 1994; Machtei *et al*. 1994; Mellonig *et al*. 1994; Wang *et al*. 1994; Hugoson *et al*. 1995; Polson *et al*. 1995b). The reported mean values ranged from

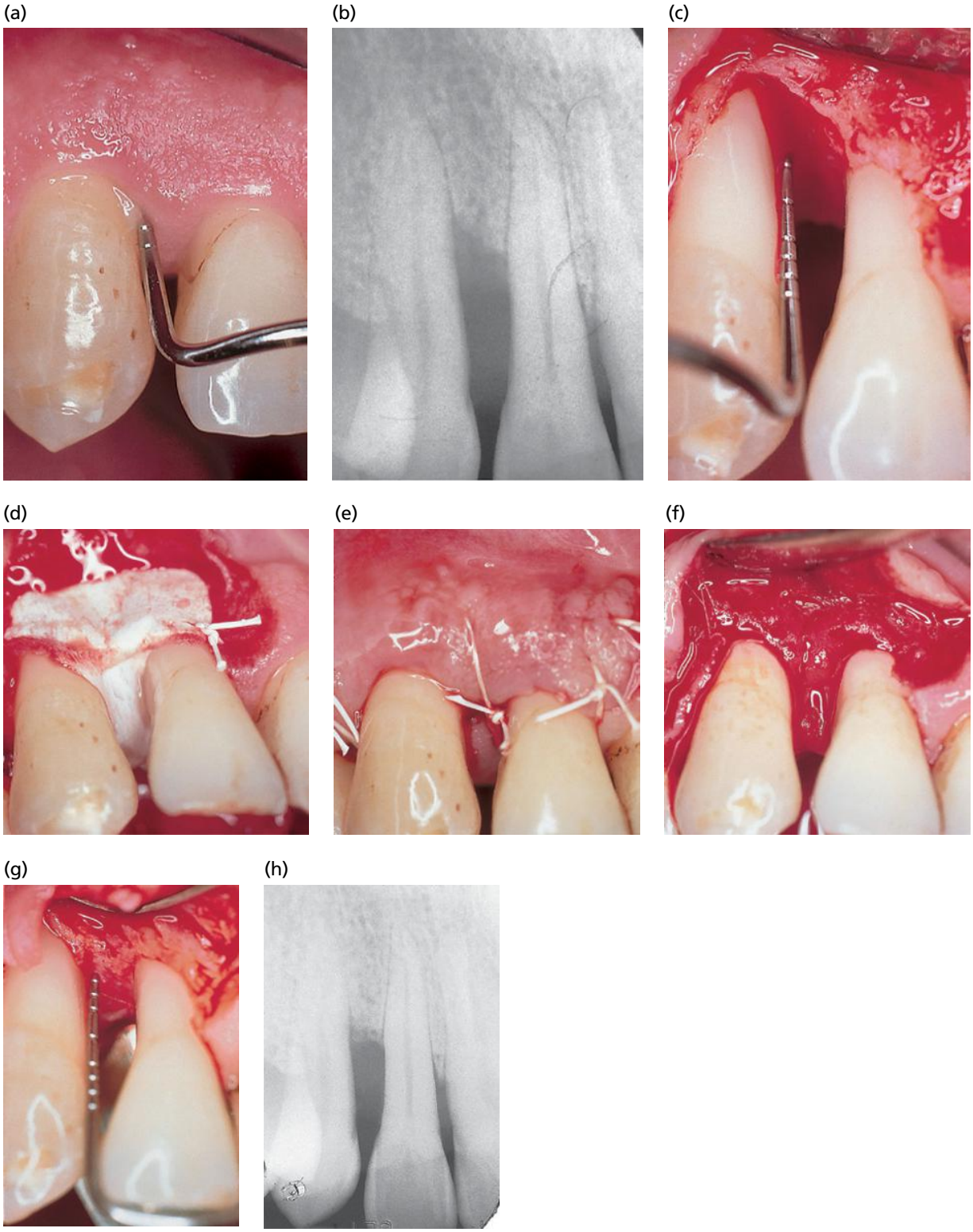


Fig. 45-36 Intrabony defect on the mesial aspect of a right maxillary canine treated with a non-bioresorbable barrier membrane. (a) Pocket depth was 9 mm and loss of clinical attachment was 10 mm. (b) Radiograph showing the presence of an interproximal intrabony defect. (c) After full-thickness flap elevation, defect debridement, and root planing, a 4-mm intrabony defect was evident. (d) An e-PTFE non-bioresorbable barrier membrane was tailored, positioned, and tightly sutured around the teeth adjacent to the defect. (e) Flap was repositioned and sutured to cover the membrane. Optimal preservation of the soft tissues was accomplished with an intrasulcular incision. (f) After removal of the membrane at 5 weeks, the defect appeared to be completely filled with newly formed tissue. (g) Treated site was surgically re-entered after 1 year. The intrabony defect was completely filled with bone. (h) One-year radiograph confirmed the complete resolution of the intrabony defect.

0.1 mm to 3.5 mm for V-CAL gain and from 1 mm to 4 mm for PPD reduction.

The effect of using barrier membranes for the treatment of mandibular class II furcations was investigated in six controlled randomized clinical trials in which GTR procedures were directly compared to flap surgery (Table 45-8). Sixty-six furcations treated with flap surgery and 87 treated with GTR

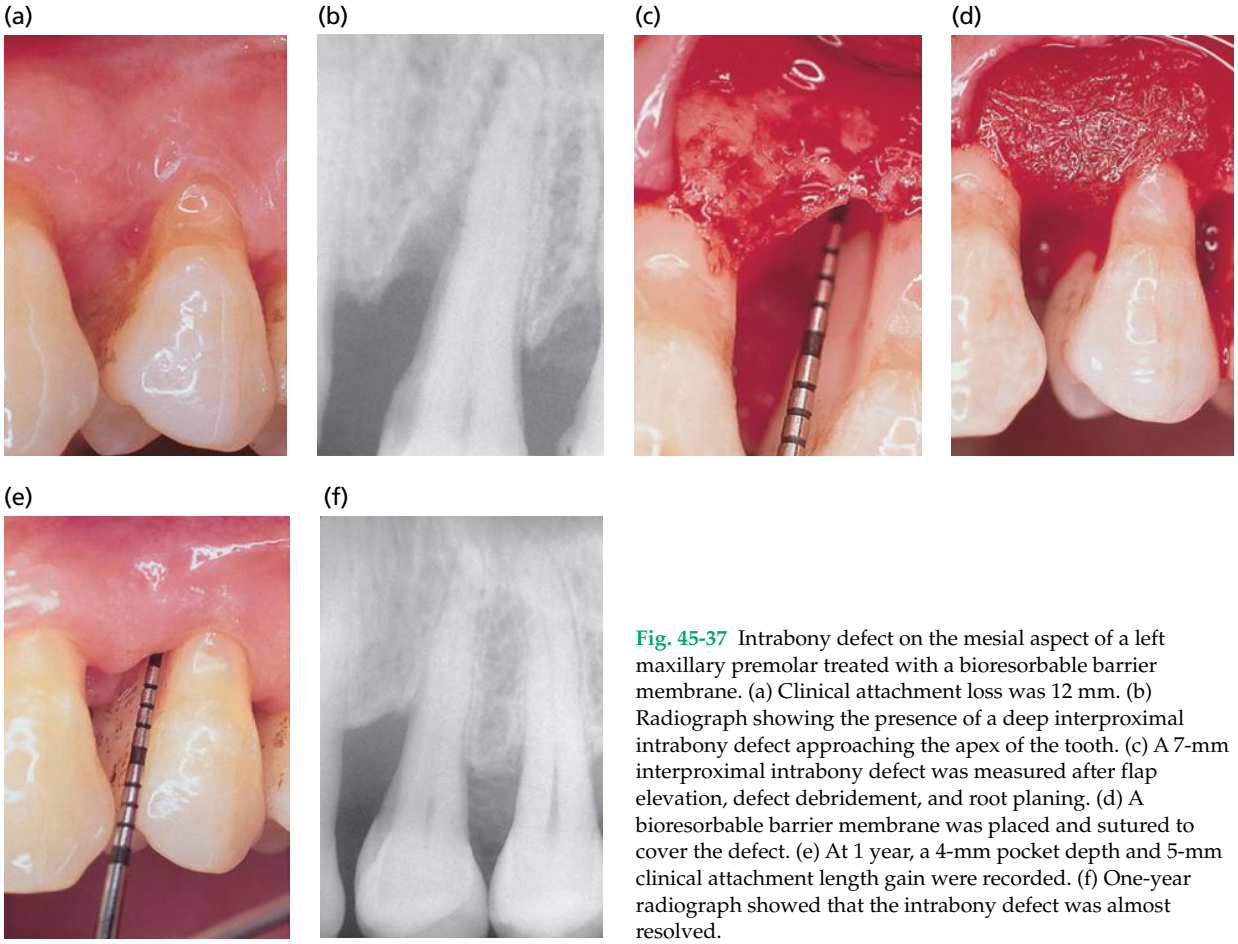


Fig. 45-37 Intrabony defect on the mesial aspect of a left maxillary premolar treated with a bioresorbable barrier membrane. (a) Clinical attachment loss was 12 mm. (b) Radiograph showing the presence of a deep interproximal intrabony defect approaching the apex of the tooth. (c) A 7-mm interproximal intrabony defect was measured after flap elevation, defect debridement, and root planing. (d) A bioresorbable barrier membrane was placed and sutured to cover the defect. (e) At 1 year, a 4-mm pocket depth and 5-mm clinical attachment length gain were recorded. (f) One-year radiograph showed that the intrabony defect was almost resolved.

were included. Three of the four studies reporting H-CAL gains concluded that GTR resulted in statistically significantly greater H-CAL gains than flap surgery (Pontoriero *et al*. 1988; Van Swol *et al*. 1993; Wang *et al*. 1994). The weighted mean of the results of these studies for H-CAL gain in furcations treated with GTR was 2.5 ± 1 mm (95% CI 2.1–2.9 mm), and 1.3 ± 1 mm (95% CI 0.8–1.8 mm) for furcations treated with flap surgery. These results indicate an added benefit from GTR in the treatment of mandibular class II furcations.

Maxillary class II furcations

Results reported in three controlled studies (Metzeler *et al*. 1991; Mellonig *et al*. 1994; Pontoriero & Lindhe 1995a) comparing GTR treatment of maxillary class II furcations with non-bioresorbable e-PTFE membranes and with OFD indicated that GTR treatment of such defects is generally unpredictable. In a study including 17 pairs of class II furcations, Metzeler *et al*. (1991) measured CAL gains of 1.0 ± 0.9 mm in the GTR-treated sites versus 0.2 ± 0.6 mm in the control sites. Following re-entry, horizontal PAL gains (H-OPAL) of 0.9 ± 0.4 mm and 0.3 ± 0.6 mm were detected in the GTR- and flap-treated furcations, respectively. None of the furcations of the two groups was completely resolved. Similarly, Mellonig *et al*. (1994) treated eight pairs of maxillary class II furcations and reported H-OPAL gains of 1.0 mm (GTR sites) and 0.3 mm (flap-treated sites). Again, none of the treated furcations in the two groups was completely closed. On the other hand, in a study of 28 maxillary class II furcations, Pontoriero and Lindhe (1995a) found a significant gain in CAL (1.5 mm) and horizontal bone (1.1 mm) in buccal class II furcations. Although these three investigations show a slight clinical improvement following treatment of class II maxillary furcations with GTR, the results are generally inconsistent.

Class III furcations

Four investigations of the treatment of mandibular class III furcations (Becker *et al*. 1988; Pontoriero *et al*. 1989; Cortellini *et al*. 1990; Pontoriero & Lindhe 1995b) indicate that the treatment of such defects with GTR is unpredictable. A controlled study by Pontoriero *et al*. (1989) showed that only eight of 21 "through-and-through" mandibular furcations treated with non-bioresorbable barrier membranes healed with complete closure of the defect. Another ten defects were partially filled and three remained open. In the OFD-treated control group, 10 were partially filled and 11 remained open. Similar results were reported by Cortellini *et al*. (1990) who, in a case cohort of 15 class III mandibular furcations, found that 33% of the defects had healed completely, 33% were partially

Table 45-5 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with access flap procedures in deep intrabony defects.

Study	Membranes	Number	Gains in CAL ± SD (mm)		Residual PPD ± SD (mm)	
			GTR	Access flap	GTR	Access flap
Chung *et al*. (1990)	Collagen	10	0.6 ± 0.6	–0.7 ± 0.9	4.0 ± 1.1	
	Collagen	9	2.4 ± 2.1			
	Control	14				
Proestakis *et al*. (1992)	e-PTFE	9	1.2 ± 1.3		3.5 ± 0.9	
	Control	9		0.6 ± 1.0		3.7 ± 3.0
Quteish & Dolby (1992)	Collagen	26	3.0 ± 1.5		2.2 ± 0.4	
	Control	26		1.8 ± 0.9		3.4 ± 0.6
Al-Arrayed *et al*. (1995)	Collagen	19	3.9	2.7	2.5	3.5
	Control	14				
Cortellini *et al*. (1995c)	e-PTFE	15	4.1 ± 1.9		2.7 ± 1.0	
	e-PTFE + titanium	15			2.1 ± 0.5	
	Control	15	5.3 ± 2.2	2.5 ± 0.8		3.7 ± 1.3
Mattson *et al*. (1995)	Collagen	13	2.5 ± 1.5		3.6 ± 0.6	
	Control	9		0.4 ± 2.1		4.5 ± 1.8
Cortellini *et al*. (1996b)	e-PTFE	12	5.2 ± 1.4		2.9 ± 0.9	
	Polylactic acid	12		4.6 ± 1.2		3.3 ± 0.9
	Control	12		2.3 ± 0.8		4.2 ± 0.9
Tonetti *et al*. (1998)	Polylactic acid	69	3.0 ± 1.6		4.3 ± 1.3	
	Control	67		2.2 ± 1.5		4.2 ± 1.4
Pontoriero *et al*. (1999)	Diff. barriers	30	3.1 ± 1.8		3.3 ± 1.3	
	Control	30		1.8 ± 1.5		4.0 ± 0.8
Ratka-Kruger *et al*. (2000)	Polylactic acid	23	3.1 ± 2.3		4.7 ± 1.4	
	Control	21		3.3 ± 2.7		4.9 ± 2.1
Cortellini *et al*. (2001)	Polylactic acid	55	3.5 ± 2.1		3.8 ± 1.5	
	Control	54		2.6 ± 1.8		4.7 ± 1.4
Weighted mean		**584**	**3.3 ± 1.8**	**2.1 ± 1.5**	**3.5 ± 1.1**	**4.1 ± 1.3**

CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; PPD, probing pocket depth; SD, standard deviation.

closed, and 33% were still through-and-through following treatment. Becker *et al*. (1988) did not observe complete closure of any of 11 treated class III mandibular furcations. Similarly, in a controlled clinical trial by Pontoriero and Lindhe (1995b) of 11 pairs of maxillary class III furcations randomly assigned to GTR or flap surgery, none of the furcation defects was closed.

Conclusion: Based on current evidence, it seems that mandibular class II furcations in the first or second molars, either buccal or lingual, with deep pockets at baseline and a gingival thickness of >1 mm, may benefit from GTR treatment.

Bone replacement grafts

Grafts for intrabony defects

BRGs comprise a heterogeneous group of materials of human (autologous or allogeneic), animal or synthetic origin. Some consist of bone or exoskeletal minerals; others contain mainly bone matrix. There is evidence for periodontal regeneration for only a few of these materials. A randomized controlled clinical trial provided histologic support that the healing outcome following application of DFDBA in intrabony defects has a regenerative component in the apical to middle portion of the depth of the defect (Bowers *et al*. 1989a–c). Isolated evidence also supports the fact that allograft and bovine bone mineral may yield a regenerative outcome when used alone [i.e. without other regenerative materials such as barrier membranes or biologically active regenerative materials (BARGs); see also Chapter 28] (Nevins *et al*. 2000).

BRGs were the first periodontal regenerative materials to be applied clinically. Today they are widely used in North America as DFDBAs and are frequently used in combination with other regenerative materials (GTR and/or BARG). Biologic principles supporting the use of *autologous and heterologous grafts* include osteoconductivity and osteoinductivity, but also their capacity for space provision and blood clot stabilization (Rosen *et al*. 2000; Trombelli & Farina 2008).

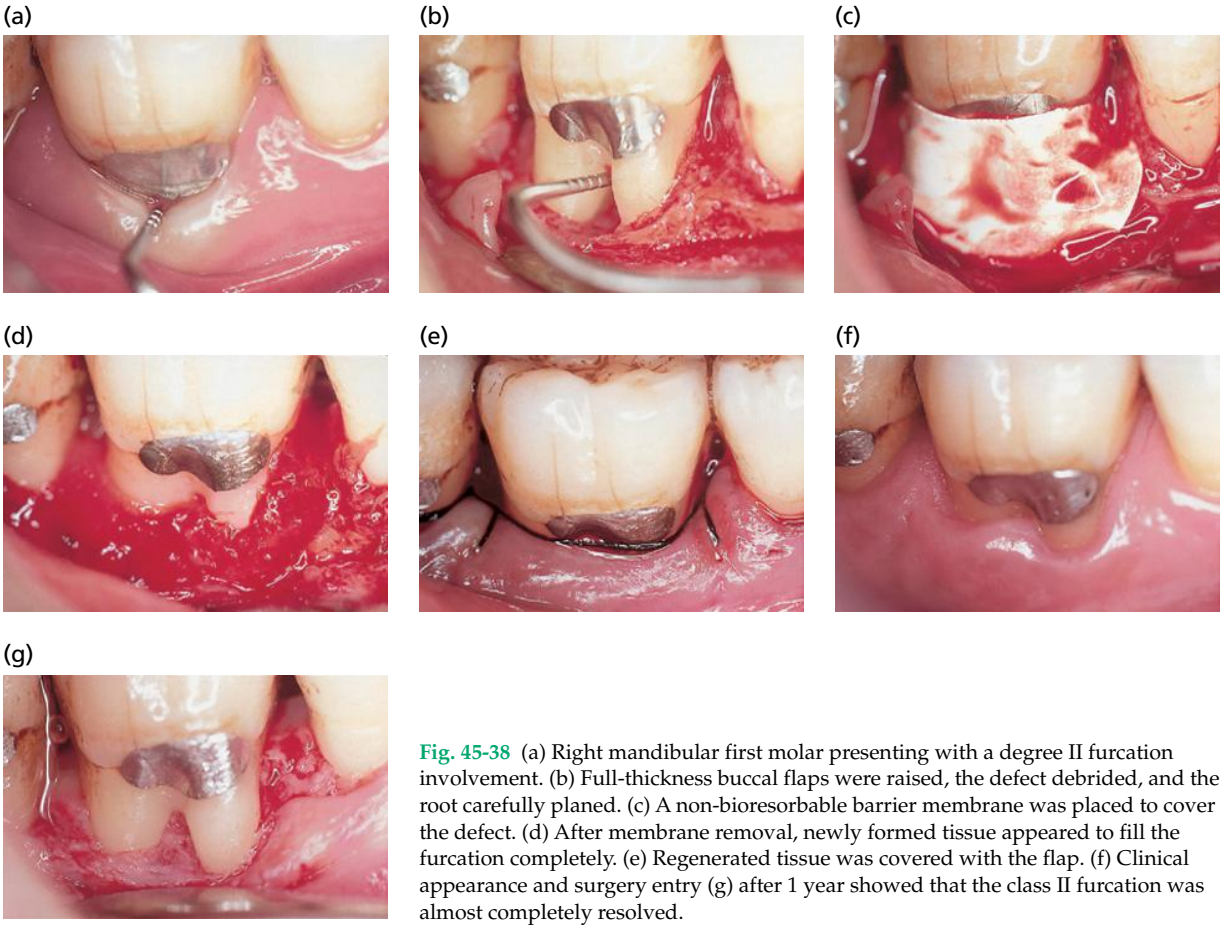


Fig. 45-38 (a) Right mandibular first molar presenting with a degree II furcation involvement. (b) Full-thickness buccal flaps were raised, the defect debrided, and the root carefully planed. (c) A non-bioresorbable barrier membrane was placed to cover the defect. (d) After membrane removal, newly formed tissue appeared to fill the furcation completely. (e) Regenerated tissue was covered with the flap. (f) Clinical appearance and surgery entry (g) after 1 year showed that the class II furcation was almost completely resolved.

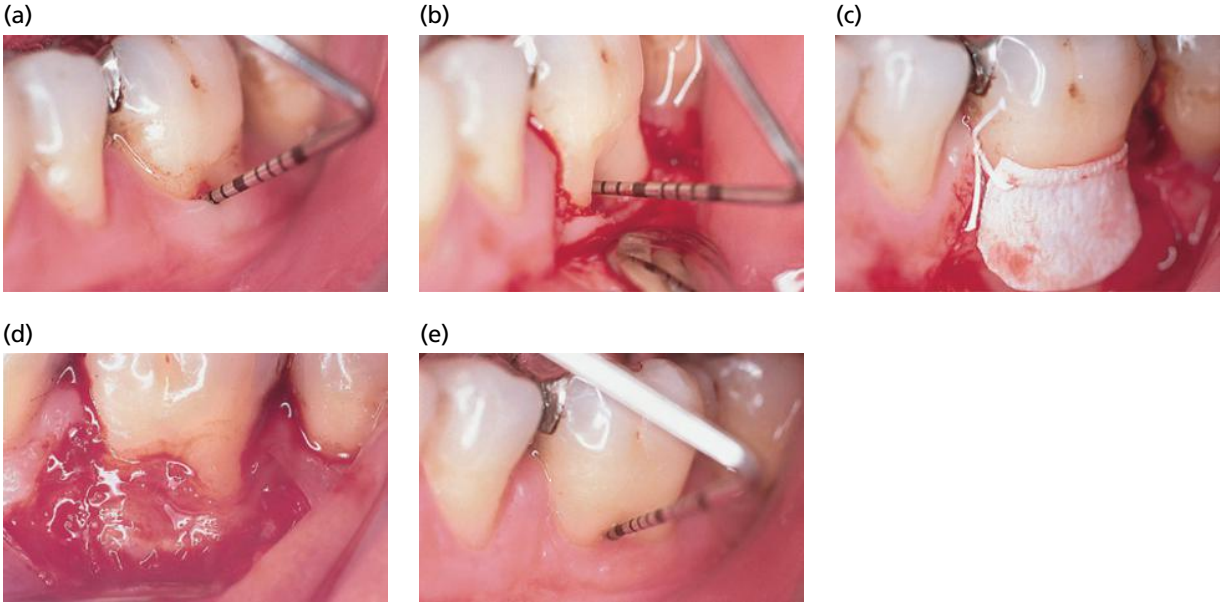


Fig. 45-39 (a) Left mandibular first molar presenting with a deep class II furcation involvement. (b) Horizontal loss of tooth support of 7 mm was probed. (c) An e-PTFE barrier membrane was trimmed and sutured to cover the furcation. (d) At membrane removal after 5 weeks, newly formed tissue filled the furcation completely. (e) At 1 year, a 3-mm gain of tooth support was measured, but a residual 4-mm class II furcation involvement was still present.

The clinical efficacy of allografts in terms of bone fill and CAL gain is supported by a meta-analysis of 27 controlled studies indicating that additional bone fill of 1 mm and additional CAL gain of 0.4 mm were observed (see Fig 45-8) (Reynolds *et al*. 2003). The total number of defects contributing to this meta-analysis however was relatively small (136 for CAL gain and 154 for bone fill). Furthermore, no large-scale multicenter trial has ever been performed and hence the

Table 45-6 Clinical outcomes and weighted mean of guided tissue regeneration (GTR) treatment of mandibular class II furcations.

Study		Treatment	Number	Defect depth (mm)	H-CAL gain (mm)	H-OPAL gain (mm)	No. of closed furcations
Pontoriero *et al*. (1988)	Controlled clinical trial	e-PTFE	21	4.4 ± 1.2	3.8 ± 1.2	NA	14 (67%)
Becker *et al*. (1988)	Case cohort	e-PTFE	6	8.3 ± 2.3	NA	1.8 ± 1.5	0
Schallhorn & McClain (1988)	Case cohort	e-PTFE	16	NA	NA	3.1 ± 1.7	5 (31%)
Lekovic *et al*. (1989)	Controlled clinical trial	e-PTFE	6	NA	NA	0.2 ± 0.5	NA
Lekovic *et al*. (1990)	Controlled clinical trial	e-PTFE	15	4.2 ± 0.2	NA	0.1 ± 0.1	NA
Caffesse *et al*. (1990)	Controlled clinical trial	e-PTFE	9	4.8 ± ?	0.8 ± ?	NA	NA
Anderegg *et al*. (1991)	Controlled clinical trial	e-PTFE	15	4.2 ± 2.2	NA	1.0 ± 0.8	NA
Yukna (1992)	Controlled clinical trial	e-PTFE	11	3.0 ± ?	NA	1.0 ± ?	0
		FDDMA	11	4.0 ± ?	NA	2.0 ± ?	0
Blumenthal (1993)	Controlled clinical trial	e-PTFE	12	4.4 ± 0.9	1.8 ± 1.0	1.7 ± 0.5	4 (33%)
		Collagen	12	4.5 ± 0.9	2.5 ± 0.8	2.5 ± 0.7	1 (8%)
Bouchard *et al*. (1993)	Controlled clinical trial	e-PTFE	12	NA	2.8 ± 1.3	2.2 ± 1.4	4 (33%)
		Conn. graft	12	NA	1.5 ± 1.5	1.5 ± 1.1	2 (17%)
Machtei *et al*. (1993)	Controlled clinical trial	e-PTFE	18	NA	2.3 ± 1.7	NA	NA
Parashis & Mitsis (1993)	Controlled clinical trial	e-PTFE	9	5.7 ± 0.7	4.7 ± 1.5	NA	4 (44%)
Van Swol *et al*. (1993)	Controlled clinical trial	Collagen	28	5.1 ± 1.4	2.3 ± 1.0	1.7 ± ?	NA
Wallace *et al*. (1994)	Controlled clinical trial	e-PTFE	7	NA	NA	2.3 ± ?	NA
Black *et al*. (1994)	Controlled clinical trial	e-PTFE	13	4.3 ± 2.0	0.8 ± 2.2	NA	NA
		Collagen	13	4.4 ± 1.5	1.5 ± 2.0	NA	NA
Laurell *et al*. (1994)	Case cohort	Polylactic acid	19	NA	3.3 ± 1.4	NA	9 (47%)
Machtei *et al*. (1994)	Controlled clinical trial	e-PTFE	30	7.7 ± 1.8	2.6 ± 1.7	NA	NA
Mellonig *et al*. (1994)	Controlled clinical trial	e-PTFE	11	8.4 ± 1.2	NA	4.5 ± 1.6	1 (9%)
Wang *et al*. (1994)	Controlled clinical trial	Collagen	12	6.0 ± 2.7	2.0 ± 0.4	2.5 ± ?	NA
Hugoson *et al*. (1995)	Controlled clinical trial	e-PTFE	38	5.9 ± 1.3	1.4 ± 2.2	NA	4 (11%)
		Polylactic acid	38	5.6 ± 1.4	2.2 ± 2.0	NA	13 (34%)
Polson *et al*. (1995)	Case cohort[a]	Polylactic acid	29	5.4 ± 0.2	2.5 ± 0.1	NA	0
Weighted mean			**423**	**5.4 ± 1.3**[b]	**2.3 ± 1.4**[c]	**1.9 ± 1**[d]	

[a] Mandibular and maxillary molars.
[b] n = mean (340) ± SD (302).
[c] n = mean (325) ± SD (316).
[d] n = mean (186) ± SD (177).
Conn graft, connective tissue graft; e-PTFE, expanded polytetrafluoroethylene; FDDMA, freeze dried dura mater allograft; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available.

applicability of these results to clinical practice settings remains to be established.

BRGs can be applied alone following elevation of a papilla preservation flap for the treatment of intrabony defects. The graft is applied to overfill the defect to compensate for an expected degree of shedding of the graft in cases of imperfect containment of the graft by the closed flap. A study has suggested using BRGs in combination with an antibiotic powder to enhance control of the bacterial contamination of the surgical wound (Yukna & Sepe 1982). This study reported improved outcomes from mixing the graft with tetracycline powder. DFDBAs have been successfully used along with minimally invasive surgery (Harrel 1999).

Grafts for furcation involvement

A series of controlled clinical trials has evaluated the clinical performances of BRGs in the flap approach to the treatment of furcation defects. Reynolds *et al*. (2003) in their review found an overall PPD reduction ranging from 1.9 mm to 2.31 mm in class II furcations treated with BRGs, compared to 0–1.8 mm for those

Table 45-7 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with e-PTFE non-bioresorbable barrier membranes with different types of bioresorbable barrier membranes in mandibular class II furcations

Study	Design and treatment (GTR C/GTR T)	n C/T	Defect depth (mm)		H-CAL gain (mm)		H-OPAL gain (mm)	
			GTR C	GTR T	GTR C	GTR T	GTR C	GTR T
Yukna (1992)	Intraindividual (e-PTFE/FDDMA)	11/11	3.0 ± ?	4.0 ± ?	NA	NA	1.0 ± ?	2.0 ± ?
Blumenthal (1993)	Intraindividual (e-PTFE/collagen)	12/12	4.4 ± 0.9	4.5 ± 0.9	1.8 ± 1.0	2.5 ± 0.8	1.7 ± 0.5	2.5 ± 0.7
Bouchard *et al*. (1993)	Intraindividual (e-PTFE/conn. graft)	12/12	NA	NA	2.8 ± 1.3[a]	1.5 ± 2.0	2.2 ± 1.4	1.5 ± 1.1
Black *et al*. (1994)	Intraindividual (e-PTFE/collagen)	13/13	4.3 ± 2.0	4.4 ± 1.5	0.8 ± 2.2	1.5 ± 2.0	NA	NA
Hugoson *et al*. (1995)	Intraindividual (e-PTFE/ polytetrafluoroethylene)	38/38	5.9 ± 1.3	5.6 ± 1.4	1.4 ± 2.2[a]	2.2 ± 2.0[a]	NA	NA
Weighted mean		**86/86**	**4.9 ± 1.4**[b]	**5 ± 1.3**[b]	**1.6 ± 1.9**[c]	**2 ± 1.7**[c]	**1.3 ± 1**[d]	**1.4 ± 0.9**[d]

[a] Statistically significant difference between treatments.
[b] n = mean (74) ± SD (63).
[c] n = mean (75) ± SD (75).
[d] n = mean (35) ± SD (124).
Conn graft, connective tissue graft; e-PTFE, expanded polytetrafluoroethylene; FDDMA, freeze dried dura mater allograft; GTR C, guided tissue regeneration control treatment; GTR T, guided tissue regeneration test treatment; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available; n C/T, number of defects in the control (C) and the test (T) treatment arms.

Table 45-8 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with access flap procedures in mandibular class II furcations.

	Design (GTR treatment)	n C/T	Defect depth (mm)		H-CAL gain (mm)		H-OPAL gain (mm)	
			Access flap	GTR	Access flap	GTR	Access flap	GTR
Pontoriero *et al*. (1988)	Intraindividual (e-PTFE)	21/21	4.0 ± 0.8	4.4 ± 1.2	2.0 ± 1.2	3.8 ± 1.2	NA	NA
Lekovic *et al*. (1989)	Intraindividual (e-PTFE)	6/6	NA	NA	NA	NA	–0.1 ± 0.3	0.2 ± 0.5
Caffesse *et al*. (1990)	Parallel (e-PTFE)	6/9	5.3 ± ?	4.8 ± ?	0.3 ± ?	0.8 ± ?	NA	NA
Van Swol *et al*. (1993)	Parallel (collagen)	10/28	5.7 ± 2.5	5.1 ± 1.4	0.7 ± 1.2[a]	2.3 ± 1[a]	0.8 ± ?	1.7 ± ?
Mellonig *et al*. (1994)	Intraindividual (e-PTFE)	6/6	7.5 ± 2.3	8.4 ± 1.2	NA	NA	1.1 ± 1.3[a]	4.5 ± 1.6[a]
Wang *et al*. (1994)	Intraindividual (collagen)	12/12	5.6 ± 2.7	6.0 ± 2.7	1.1 ± 0.6[a]	2.0 ± 0.4[a]	1.5 ± ?	2.5 ± ?
Weighted mean		**66/87**	**5.4 ± 1.8**[b]	**5.5 ± 1.5**[c]	**1.3 ± 1**[d]	**2.5 ± 1**[e]	**1 ± 1**[f]	**2.3 ± 1.2**[g]

[a] Statistically significant difference between treatments.
[b] n = mean (60) ± SD (54).
[c] n = mean (81) ± SD (72).
[d] n = mean (49) ± SD (43).
[e] n = mean (70) ± SD (61).
[f] >3n = mean (39) ± SD (17).
[g] n = mean (57) ± SD (17).
e-PTFE, expanded polytetrafluoroethylene; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available.

treated with OFD alone. For class III defects, BRGs produced a PPD change of 0.7–2.6 mm, as compared –1–2.6 mm in the controls. CAL changes were similar for mandibular class II and III furcations, ranging from 1.5 to 2.5 mm for grafted sites compared to 0–1.5 mm for the flap controls. The authors concluded that the results of these studies suggest that BRGs alone add relatively modest clinical benefit in the treatment of class II and III furcations, especially if complete closure of the furcation is the desired end point of treatment. More recently, Tsao *et al*. (2006b) tested a solvent-preserved, mineralized human cancellous bone allograft (MBA) with or without a collagen membrane in the treatment of 27 mandibular class II furcations. Their results indicated that solvent-preserved MBA, with or without a collagen membrane, can significantly improve bone fill in mandibular class II furcation defects.

Biologically active regenerative materials

Preclinical and clinical evidence for the use of BARGs has been reviewed (see also Chapter 28). The adoption of *biologic products/compounds* is based on their ability to induce or accelerate the processes of matrix formation and cell differentiation (Bosshardt 2008). These products promote the healing process, but lack mechanical properties to aid space provision and blood clot stabilization. Some of these, therefore, are

loaded on solid, bioresorbable carriers to add some mechanical properties (Palmer & Cortellini 2008; Trombelli & Farina 2008). Currently, preparations based on growth factors or amelogenins are available for use in periodontal regeneration. Significant preclinical evidence supports the positive effect of both on periodontal wound healing and regeneration (Howell *et al*. 1997; Bosshardt 2008).

Growth factors for intrabony defects

Support for the clinical use of growth factors comes from two multicenter studies on recombinant human-derived growth factor (Nevins *et al*. 2005; Jayakumar *et al*. 2011) and two on fibroblast growth factor-2 (FGF-2) (Kitamura *et al*. 2008, 2011). Nevins *et al*. (2005) treated 180 defects comprising both intrabony and furcation defects with one of two concentrations of PDGF (0.3 mg/mL and 1.0 mg/mL) combined with the β-TCPdelivery device or TCP alone. Results were assessed at 3 and 6 months and included both clinical and radiographic assessments. CAL gains at 6 months failed to demonstrate a significant benefit for either concentration of PDGF compared to the BRG alone. With regards to radiographic assessments, however, the lower tested concentration of PDGF resulted in significantly higher percentages of bone fill of the defect (57% versus 18%) and linear bone growth (2.6 mm versus 0.9 mm). The results of this study led to the approval of this material by the US Food and Drug Administration. The authors interpreted the dichotomy between the reported added benefit in terms of radiographic parameters and the lack of significant changes in CAL as the result of the biologic action of the growth factor formulation in shortening the healing time of the hard tissues.

In the Jayakumar *et al.* study (2011), 54 patients were treated with rhPDGF-BB1b combined with the β-TCP delivery device or tricalcium phosphate alone. CAL gain, bone growth, and percent bone fill at 6 months were significantly greater in the test group as compared to the TCP control group.

The study of 74 patients by Kitamura *et al*. (2008) compared three different concentrations of a FGF-2 vehicle with 3% hydroxypropylcellulose (HPC) to HCP alone. No difference was reported in terms of CAL gain between the test and control groups. However, a significant difference in terms of bone gain was reported in favor of the 0.3% concentration of FGF-2 as compared to HCP alone. The other two concentrations (0.03% and 0.1%) did not show any advantage in terms of bone gain. A second randomized, double-blind, placebo-controlled clinical trial on 253 adult patients compared 0.2%, 0.3%, or 0.4% FGF-2 to vehicle alone in two- or three-walled vertical bone defects (Kitamura *et al*. 2011). Each dose of FGF-2 showed significant superiority over vehicle alone (P <0.01) for the percentage of bone fill at 36 weeks after administration. No significant differences were observed between the groups in CAL gain.

No clinical safety problems were reported in any of the four cited studies.

Drawing conclusions from the four studies, it is apparent that both the tested growth factors resulted into a measurable added benefit compared to controls in terms of bone gain, while three of the four studies did not reach a significant difference in terms of CAL gain. Both efficacy and effectiveness of rhPDGF-BB1b and FGF-2 have to be further explored for use in private settings.

A recent controlled study evaluated clinical and histologic wound healing/regeneration following surgical implantation of recombinant human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a particulate β-TCP carrier (rhGDF-5/b-TCP) into periodontal defects in 28 patients (Stavropoulos *et al*. 2011). Control defects were treated with OFD alone. The authors reported greater PPD reduction, CAL gain, alveolar bone regeneration, and periodontal regeneration at sites that received rhGDF-5/β-TCP compared to control sites. However, these differences were not statistically significant. Block biopsies of the defect sites were collected at 6 months post surgery. Histologically, bone regeneration height was almost three-fold greater for the rhGDF-5/β-TCP treatment compared with OFD alone (2.19 ± 1.59 mm versus 0.81 ± 1.02 mm; $P = 0.08$). Similarly, an almost two-fold increase was observed for periodontal ligament (2.16 ± 1.43 mm versus 1.23 ± 1.07 mm; $P = 0.26$), cementum (2.16 ± 1.43 mm versus 1.23 ± 1.07 mm; $P = 0.26$), and bone regeneration area (0.74 ± 0.69 mm^2 versus 0.32 ± 0.47 mm^2; $P = 0.14$). Root resorption/ankylosis was not observed. Future studies with larger sample sizes need to be conducted to verify these findings.

Growth factors for furcation involvement

A human clinical trial (Camelo *et al*. 2003) was designed to evaluate the clinical and histologic response to rhPDGF-BB delivered in bone allograft for the treatment of advanced class II furcation defects. Three mandibular and one maxillary molar furcation defects were treated: two received 0.5 mg/mL and two 1.0 mg/mL of rhPDGF-BB, in all cases mixed with DFDBA. Both concentrations of rhPDGF-BB resulted in substantially improved horizontal (mean 3.5 mm) and vertical (mean 4.25 mm) probing depths and attachment levels (mean 3.75 mm). Histologic evaluation revealed periodontal regeneration, including new bone, cementum, and periodontal ligament coronal to the reference notch. This study documented the favorable tissue response to rhPDGF-BB treatment at both the clinical and microscopic levels, and demonstrated that periodontal regeneration can be achieved in advanced class II furcation defects using a combination of purified recombinant growth factor and bone allograft. These outcomes were confirmed by a second study of 15 sites presenting with class II furcations in which the PDGF was

loaded on DFDBA (Nevins *et al*. 2003), and in another study of four class III furcations in which the growth factor was loaded on TCP (Mellonig *et al*. 2009).

Promising histologic and clinical outcomes can be envisioned from these pilot studies. However, larger controlled clinical trials are needed to assess the real potential of growth factors in the treatment of teeth with furcation involvement.

Enamel matrix derivatives for intrabony defects

EMDs have been in clinical use for >10 years and its clinical efficacy is very well established. The benefit of use of EMD gel in the treatment of intrabony defects is supported by human histologic evidence, case report studies, meta-analysis of randomized controlled clinical trials, and a large multicenter trial (Heijl *et al*. 1997; Heden *et al*. 1999; Sculean *et al*. 1999b; Silvestri *et al*. 2000; Heden 2000; Tonetti *et al*. 2002; Giannobile & Somerman 2003; Heden & Wennström 2006) (Figs. 45-26, 45-27, 45-40). The prospective multicenter randomized controlled clinical trial (Tonetti *et al*. 2002) was designed to compare the clinical outcomes of papilla preservation flap surgery with or without the application of EMDs in 172 patients with advanced chronic periodontitis in 12 centers in seven countries. All patients had at least one intrabony defect of 3 mm or deeper. Heavy smokers (>20 cigarettes/day) were excluded. The surgical procedures included access for root instrumentation using either the SPPF or the MPPT in order to obtain optimal tissue adaptation and primary closure. After debridement, roots were conditioned for 2 minutes with a gel containing 24% EDTA. EMDs were applied to the test subjects and omitted in the controls. A total of 166 patients were available for the 1-year follow-up. On average, the test defects gained 3.1 ± 1.5 mm of CAL, while the control defects yielded a significantly lower CAL gain of 2.5 ± 1.5 mm. Pocket reduction was also significantly higher in the test group (3.9 ± 1.7 mm) compared to the controls (3.3 ± 1.7 mm). A multivariate analysis indicated that the treatment, the clinical centers, cigarette smoking, baseline PPD, and defect corticalization significantly influenced CAL gain. A frequency distribution analysis of the studied outcomes indicated that EMDs increased the predictability of clinically significant results (CAL gain >4 mm) and decreased the probability of obtaining negligible or no gain in CAL (CAL gain <2 mm). The results of this trial indicated that regenerative periodontal surgery with EMDs offers an additional benefit in terms of CAL gain, PPD reduction, and predictability of outcomes over papilla preservation flaps alone.

A secondary analysis of the multicenter trial has shown that, in intrabony defects, the added benefit of EMDs was greater in three-wall defects than in one-wall defects (Tonetti *et al*. 2002). Furthermore, another secondary analysis of the trial, but this time assessing the effect of the radiographic angle of the defect angle on the outcome (Tsitoura *et al*. 2004), uncovered a negative association between this angle and the CAL gain observed at 1 year. These data have questioned the suitability of the gel formulation of EMDs for the treatment of defects with a non-supporting anatomy (wide defects with missing bony walls) and spurred considerable research interest in the incorporation of EMDs into a variety of BRGs in order to enhance

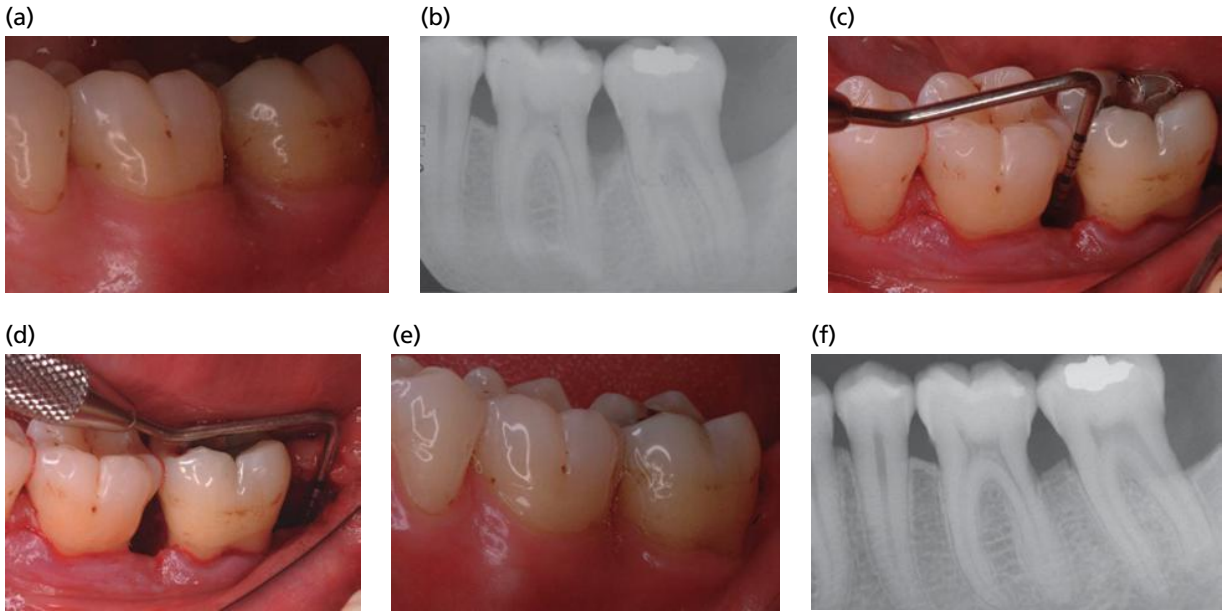


Fig. 45-40 Clinical case illustrating the use of enamel matrix derivatives (EMDs) to regenerate defects located on two adjacent teeth. At re-evaluation, deep pockets associated with deep intrabony defects were evident on the distal aspect of the first and second molars (a, b). Defects were accessed with the modified papilla preservation technique (MPPT) on the distal aspect of the first molar and with the use of a crestal incision in the retromolar area (c, d). Deep defects were exposed following debridement and root instrumentation (c, d). Following application of EMDs in gel form, primary closure was obtained with multilayered sutures. At 1-year follow-up, shallow probing depths associated with the elimination of the defects were observed (e, f).

wound stability and space maintenance. At this stage, however, no systematic evidence is available to support the use of such combinations.

More recently, EMDs have been successfully used in combination with minimally invasive techniques from MIS (Harrel et al 2005), to MIST (Cortellini & Tonetti 2007a, b, Cortellini *et al*. 2008; Ribeiro *et al*. 2011a), and to M-MIST (Cortellini & Tonetti 2009a, 2011). This product is very well suited to sites where flap reflection is minimal since its positioning does not require any flap extension and the improved stability provided by minimally invasive surgery to the wound seems to favor the expression of its activity (Cortellini *et al*. 2008; Cortellini & Tonetti 2009a).

Clinically, the rate of wound healing following application of EMDs seems to be enhanced. A study looking at soft tissue density in the surgical site by using underexposed radiographs (Tonetti *et al*. 2004b) found that the rate of increase in density following application of EMDs may be faster than in the access flap control. Such modulation has been interpreted as the outcome of the local release of growth and differentiation factors by the cells involved in local wound healing. Given their hydrophobic nature, enamel matrix proteins for clinical use are mixed in a gel carrier at low pH. Following an increase in pH in the periodontal wound and rapid elimination of the gel, enamel matrix proteins (consisting mainly of EMDs) are deposited in the wound environment and the root surface. While the mechanism(s) of action of EMDs are not fully understood, significant evidence suggests that periodontal ligament cells exposed to EMDs switch their phenotype by increasing expression of a host of growth and differentiation factor-related genes (Brett *et al*. 2002; Parkar & Tonetti 2004), including transforming growth factor-beta (Lyngstadaas *et al*. 2001). A recent review (Bosshardt 2008) concluded that (1) EMDs increase the cell proliferation of periodontal ligament and gingival fibroblasts and cells of osteoblast and chondrocyte lineage; (2) EMDs have biologic effects on cells of the osteoblast lineage, including up-regulation of markers of bone formation; (3) specific small amelogenin polypeptides (5 kDa) have osteoinductive properties when tested in an ectopic bone-forming model; (4) the evidence does not demonstrate an inductive role for EMDs on cementogenesis.

Enamel matrix derivatives for furcation involvement

Treatment of mandibular class II furcations with EMDs was attempted by Jepsen *et al*. (2004). A randomized intraindividual study of 45 patients was designed to compare EMDs and bioresorbable barriers. Both treatment modalities led to a significant clinical improvement. The authors reported a median reduction of open furcation depth of 2.8 mm in the EMD-treated sites compared to a reduction of 1.8 mm in the barrier-treated sites. Complete furcation closure was recorded in eight of 45 EMD-treated sites and three of 45 barrier-treated sites. Differences between test and control sites were not statistically significant. Chitsazi *et al*. (2007) reported an H-CAL gain that was significantly greater in EMD-treated mandibular class II furcations than in OFD controls ($P = 0.002$).

Another randomized study (Casarin *et al*. 2008) compared the use of EMDs to open flap alone in 15 patients with contralateral proximal maxillary class II furcations. At 6 months, the V-CAL gains in the control and test groups were 0.39 ± 1.00 mm and 0.54 ± 0.95 mm, respectively, while the H-CAL gains were 1.21 ± 2.28 mm and 1.36 ±1.26 mm, respectively ($P = 0.05$). The vertical bone level and horizontal bone level gains of the control group were 1.04 ± 1.12 mm and 1.00 ± 1.79 mm, respectively, and of the test group were 0.82 ± 1.82 mm and 1.17 ± 1.38 mm, respectively ($P = 0.05$). However, a statistically significantly greater number of reduced/closed furcations was observed in the test group ($P = 0.05$). The authors concluded that the use of EMDs in proximal furcations does not promote a superior reduction in PPD or a gain in clinical and osseous attachment levels, but can result in a higher rate of conversion of class II to class I furcations.

Controversial outcomes have been so far observed in the treatment of class II either maxillary or mandibular furcations with EMDs. Their use seems however to provide an added benefit compared to flap treatment alone.

Combination therapy

Combination therapy for intrabony defects

Biologic principles supporting *combination therapy* relate to the possibility of obtaining an additive effect from combining different regenerative principles, including osteoconductivity and osteoinductivity, capacity for space provision and blood clot stabilization, and ability to induce or accelerate the processes of matrix formation and cell differentiation that are inherent in barriers, grafts, and bioactive substances.

Compromised results after GTR may be observed in cases where the gingival flap, eventually supported by a membrane, collapses/falls (partially or totally) into the defect and/or towards the root surface, thereby reducing the space available for blood clot formation and growth of new tissues capable of forming periodontal ligament and bone in particular. Reduced amounts of regenerated bone due to membrane collapse were noted in early studies of GTR. In the study of Gottlow *et al*. (1984), it was observed that collapse of the membrane towards the root surface resulted in new cementum formation on the entire exposed root surface, whereas bone regeneration was minimal. Although the authors reported that the degree of coronal regrowth of bone was unrelated to the amount of new cementum formation, they did

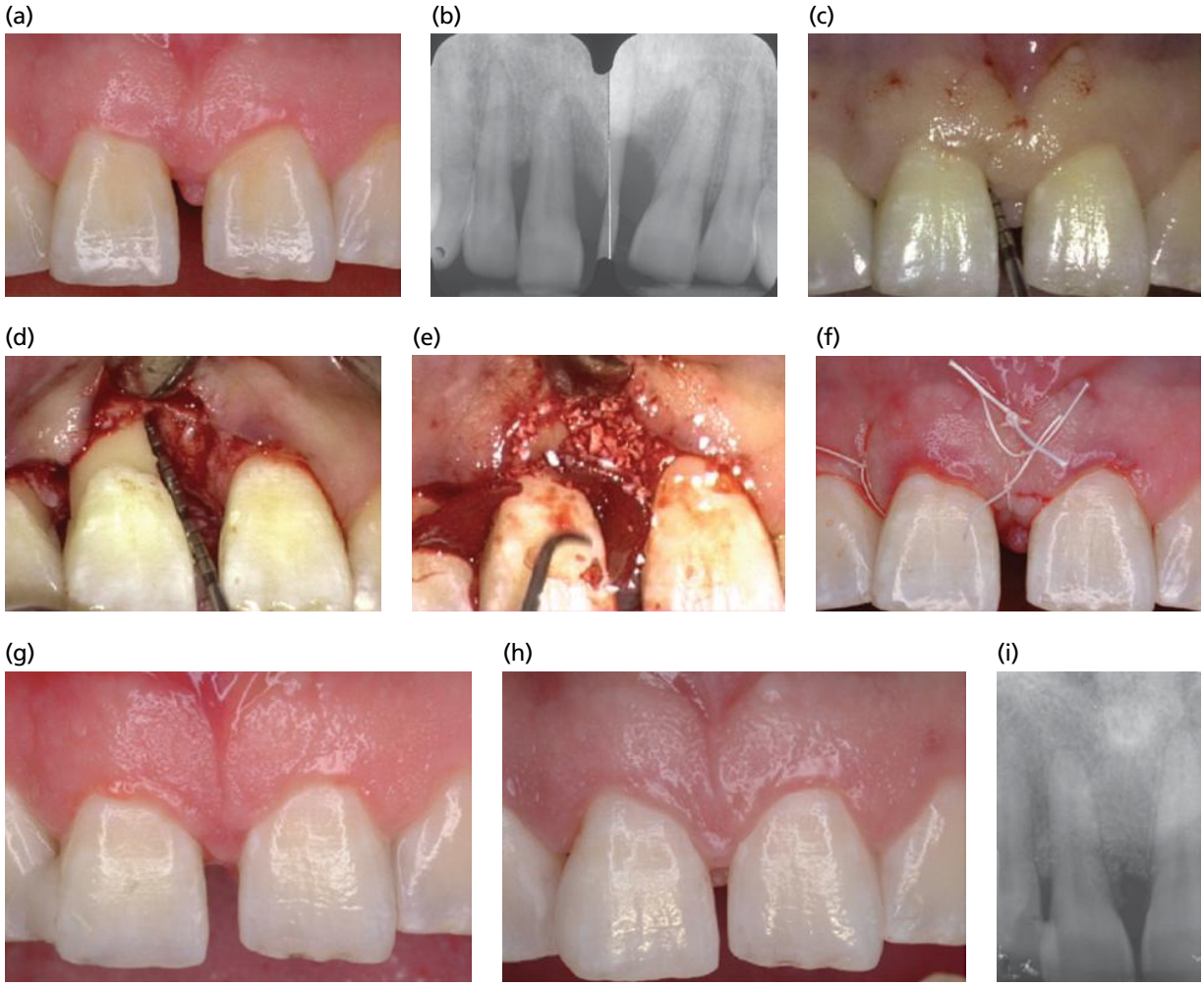


Fig. 45-41 Clinical case illustrating the application of a bone replacement graft (BRG) to support a bioresorbable membrane in a defect with poor space maintaining anatomy. Following control of periodontitis and risk factors, the upper right central incisor presented with a 12-mm deep pocket associated with a defect extending close to the apex of the tooth (a–c). The defect was accessed with the modified papilla preservation flap to reveal an 8-mm intrabony component (d). A BRG was placed under a bioresorbable collagen membrane (e). Primary closure was achieved with a multilayered suture technique (f). Excellent early healing was observed already at the 2-week follow-up (g). At 1 year, periodontal regeneration resulted in shallow probing depths and good resolution of the intrabony defect (h, i). Radio-opaque BRG particles were visible within the newly formed mineralized tissue.

not comment on what effect membrane collapse might have had. Experimental studies, however, recognized the negative effect of membrane collapse on periodontal regeneration generally and on bone formation in particular (Caton *et al*. 1992; Haney *et al*. 1993; Sigurdsson *et al*. 1994; Sallum *et al*. 1998). Haney *et al*. (1993) observed a highly significant correlation between the space provided by the membrane and the amount of regenerated alveolar bone in a supra-alveolar defect model in dogs. This finding corroborates that of Cortellini *et al*. (1995c) who reported that clinical application of self-supporting (reinforced with titanium) e-PTFE membranes, which could be positioned more coronally than ordinary e-PTFE membranes, yielded a statistically significant increase in PAL gain in intrabony defects. A particular risk for gingival flap/membrane collapse exists in cases where the configuration of the defect is incapable of supporting/preserving the membrane at the position where it was originally placed.

As already discussed, membrane materials must possess certain characteristics in order to be efficient. Among these, the membrane needs to be capable of keeping its shape and integral features, thereby maintaining the space created adjacent to the root surface. The e-PTFE membranes reinforced with titanium are the closest to meeting these requirements, but they have the disadvantage that they are non-bioresorbable. At present there are no bioresorbable membranes available that fulfil this requirement sufficiently, which means that the placement of a bioresorbable membrane on, for instance, a wide one-wall defect involves the risk of membrane collapse. The collapse may be prevented by implantation of a biomaterial into the defect to support the membrane so that it maintains its original position (Figs. 45-24, 45-41). While biologic products can enforce the healing process, they also lack mechanical properties to aid space provision and blood clot stabilization. A potential solution, therefore, could be to load the biologic

Table 45-9 Controlled clinical trials evaluating the combined effects of decalcified freeze-dried bone allografts (DFDBAs) and barrier membranes in deep intrabony defects.

Study	Design (GTR treatment)	Number[a]	Gains in CAL (mm)		*P* value	Residual PPD (mm)		*P* value
			GTR	GTR + DFDBA		GTR	GTR + DFDBA	
Chen *et al*. (1995)	Intraindividual (Collagen)	8	2.0 ± 0.4	2.3 ± 0.5	>0.05, NS	4.2 ± 0.4	4.2 ± 0.5	>0.05, NS
Mellado *et al*. (1995)	Intra-individual (e-PTFE)	11	2.0 ± 0.9	2.0 ± 1.4	0.86, NS	NA	NA	NA
Gouldin *et al*. (1996)	Intra-individual (e-PTFE)	26	2.2 ± 1.4	2.4 ± 1.6	NS	3.7 ± 1.6	3.7 ± 1.8	NS
Weighted mean		**45**	**2.1 ± 1.1**	**2.3 ± 1.4**		**3.8 ± 1.3**[b]	**3.8 ± 1.5**[b]	

[a] Defects per treatment arm.
[b] n = mean (34) ± SD (34).
CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; NA, not available; NS, not significant.

products onto solid, bioresorbable carriers to provide the necessary mechanical properties (Palmer & Cortellini 2008; Trombelli & Farina 2008). However, the biomaterial to be used for this purpose must not interfere with the process of periodontal regeneration and ideally it should also promote bone regeneration.

As previously described, periodontal regeneration has been attempted with a variety of grafting materials, among which DFDBAs apparently facilitate regeneration in humans (Ouhayoun 1996). In three controlled clinical trials, the treatment of a total of 45 pairs of intrabony defects with DFDBA grafting and GTR was compared to GTR treatment alone (Table 45-9). The weighted mean of the results of the reported investigations showed similar gain in CAL in the GTR group (2.1 ± 1.1 mm; 95% CI 1.6–2.6 mm) and in the GTR + DFDBA group (2.3 ± 1.4 mm; 95% CI 1.7–2.9 mm). The differences between the two treatments did not reach statistical significance, thus indicating no added effect of combining DFDBAs with barrier materials in the treatment of intrabony defects. Guillemin *et al*. (1993) compared the effect of DFDBAs alone with a combination of barrier materials plus DFDBAs in 15 pairs of intrabony defects. Both treatments resulted in significant CAL gain and bone fill at 6 months, but no difference was found between the treatments. Reynolds *et al*. (2003), in their systematic review, highlighted that clinical improvements from graft/barrier combinations were often obtained in large non-space maintaining defects. They concluded that the combination of graft and barriers can provide a significant gain in CAL and PPD reduction and a non-significant increase in bone fill when compared to graft alone.

Promising clinical results with a PAL gain of 1.0–5.5 mm were obtained in human case reports in which the GTR technique was combined with grafting of Bio-Oss®, an anorganic bovine bone xenograft, for the treatment of intrabony periodontal defects (Lundgren & Slotte 1999; Mellonig 2000; Paolantonio *et al*. 2001). The combined use of Bio-Oss® and GTR treatment resulted in greater PPD reduction, PAL gain, and defect fill compared to implantation of Bio-Oss® alone in case series (Camelo *et al*. 1998) and to flap surgery alone in a split-mouth study (Camargo *et al*. 2000).

In a randomized controlled clinical study including 60 patients (Stavropoulos *et al*. 2003), Bio-Oss® alone or impregnated with gentamicin was used as an adjunct to GTR in the treatment of one-wall or two-wall intrabony defects, and the outcomes were compared to those obtained following GTR or flap surgery alone. Treatment with a membrane alone (Fig. 45-42) resulted in a mean PAL gain of 2.9 mm, while it was 3.8 mm and 2.5 mm, respectively, when Bio-Oss® grafts with or without gentamicin were placed in the defects prior to membrane coverage (Fig. 45-43). The control defects treated with flap surgery demonstrated a PAL gain of only 1.5 mm. The clinical improvements in defects treated with GTR alone or in combination with Bio-Oss® grafting were significantly better than those obtained with flap surgery, whereas the differences between the groups treated with membranes were not statistically significant. A prospective multicenter randomized controlled clinical trial (Tonetti *et al*. 2004b) was designed to compare the clinical outcomes of papilla preservation flap surgery with or without the application of a GTR/bone replacement material. One hundred and twenty-four patients with advanced chronic periodontitis were treated in 10 centers in seven countries. All patients had at least one intrabony defect of at least 3 mm. One year after treatment, the test defects gained 3.3 ± 1.7 mm of CAL, while the control defects yielded a significantly lower CAL gain of 2.5 ± 1.5 mm. Pocket reduction was also significantly higher in the test group (3.7 ± 1.8 mm) when compared with the controls (3.2 ± 1.5 mm). A multivariate analysis indicated that the treatment, the clinical centers, baseline PPD and baseline full-mouth bleeding score (FMBS) significantly influenced CAL gains. The odds ratios (OR) for achieving above-median CAL gains were significantly improved by the test procedure (OR 2.6, 95% CI 1.2–5.4) and by starting with deeper PPD (OR 1.7, 1.3–2.2), but were decreased by receiving treatment at the worst-performing clinical center (OR 0.9, 0.76–0.99). The results of this trial indicated that regenerative periodontal surgery with a GTR/bone replacement material offers an additional

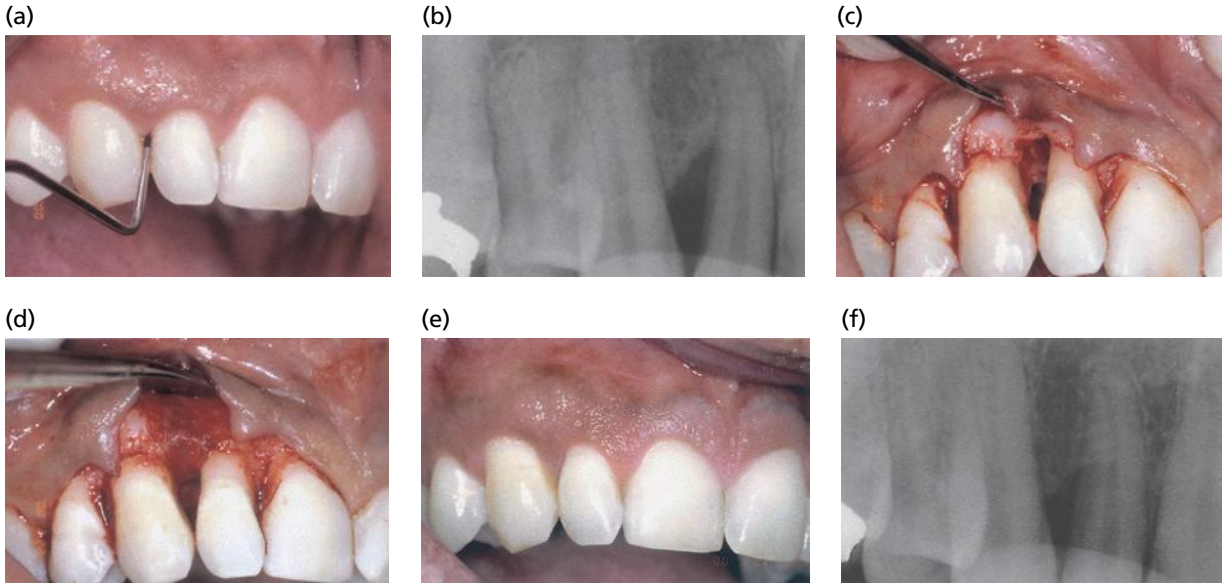


Fig. 45-42 Right lateral maxillary incisor with an 8-mm deep pocket associated with an intrabony defect on the distal aspect (a), as seen on the radiograph (b). Full-thickness buccal and palatal flaps were raised and the defect was debrided (c). A bioresorbable membrane was placed over the defect (d). The level of the interdental gingiva was maintained after 1 year (e) and the intrabony defect (f) had resolved.

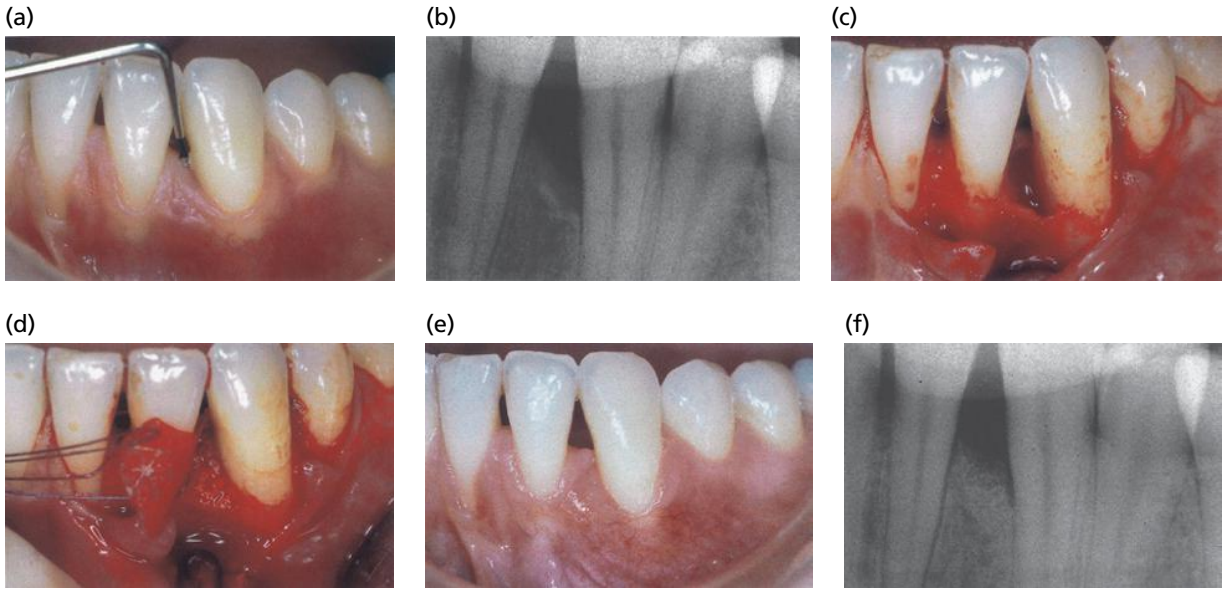


Fig. 45-43 Left mandibular canine with an 8-mm deep pocket (a) associated with an intrabony defect on its mesial aspect (b). The defect was debrided after flap elevation (c) and Bio-Oss® particles were placed in the defect (d) prior to placement of a bioresorbable membrane. After 1 year (e), no gingival recession had occurred and the intrabony defect had almost resolved (f).

benefit in terms of CAL gain, PPD reduction, and predictability of outcomes with respect to papilla preservation flaps alone.

In a controlled study (Pietruska 2001), similar clinical improvements were obtained when Bio-Oss® combined with GTR was compared with to the use of enamel matrix protein (Emdogain®).

Camelo *et al*. (1998) and Mellonig (2000) presented histologic data indicating that the use of Bio-Oss® under a membrane may result in partial regeneration of the periodontal apparatus, but in all the cases most of the defect was still occupied by deproteinized bone particles. Bone was not observed near the root, and the connective tissue fibers of the "new" periodontal ligament were mostly oriented parallel to the root surface. These results corroborate findings reported by Paolantonio *et al*. (2001), who observed only limited bone formation in the vicinity of the pre-existing bone in a biopsy, taken from a site treated 8 months earlier with Bio-Oss® and a collagen membrane. Most of the space in the defect was occupied by Bio-Oss® particles embedded in connective tissue. However, in a case report where intrabony defects were treated with Bio-Oss® combined with intraoral autogenous bone and GTR, new attachment formation had occurred consistently, but a major portion of the regenerated osseous tissue consisted of deproteinized bone particles (Camelo *et al*. 2001).

Combination therapy including use of EMDs plus barrier membranes and/or grafting materials have been tested. A systematic review (Trombelli & Farina 2008) concluded that there is evidence to support the use of EMDs either alone or in combination with grafts to effectively treat intraosseous defects and the additional use of a graft seems to enhance the clinical outcome with EMDs alone; the combined use of rhP-DGF-BB and P-15 with a graft biomaterial has shown beneficial effects in intraosseous defects; contrasting results were reported for PRP and graft combinations. A systematic review by Tu *et al*. (2010) concluded that there was little evidence to support the additional benefits of EMDs in conjunction with other regenerative materials when compared to EMDs alone. When different types of bone grafts and barrier membranes were used, EMDs with bovine bone grafts showed greatest treatment effects.

More recently, combination therapy has been successfully used in sites treated with minimally invasive surgeries. Cortellini and Tonetti (2011) proposed a combination of EMDs and Bio-Oss® with the M-MIST, and Trombelli *et al*. (2010) a combination of a bioresorbable barrier and a graft with the single flap approach.

Combination therapy for furcation involvement

Schallhorn and McClain (1988) reported on improved clinical results in intrabony defects and class II furcations, following a combination therapy including barrier membranes plus DFDBA and citric acid root conditioning. The authors reported a complete furcation closure in 75% of the treated sites (McClain & Schallhorn 1993).

In one study, barrier membranes alone were compared to combination therapy with hydroxyapatite. The difference in clinical outcomes between the two treatments was not statistically significant, but the combination therapy resulted in a greater extent of furcation fill (Lekovic *et al*. 1990).

In three studies on mandibular class II furcations, GTR treatment alone was compared with GTR treatment combined with DFDBA. In one of these investigations, a statistically significant improvement was found in terms of H-OPAL in the group of furcations treated with the combination therapy (Anderegg *et al*. 1991). In a second investigation, a non-bioresorbable barrier with and without DFDBA was tested in six patients with 17 mandibular class II buccal molar furcal invasions (Wallace *et al*. 1994). Ten teeth were randomly selected as test sites (ePTFE + DFDBA) and seven as controls (ePTFE alone). After 6 months, all sites were re-entered and both soft tissue and open surgical measurements were recorded. The addition of DFDBA to the GTR procedure did not significantly improve any of the mean soft tissue and open surgical measurements between the control and test groups. Both treatment procedures resulted in significant decreases in PPD, distance from the cementoenamel junction to the bottom of the defect (CEJ–BD), and horizontal bone fill (HBF) and a significant increase in REC. In a third study, a bioresorbable barrier with and without DFDBA was tested in 14 subjects with paired class II mandibular molar furcation defects (Luepke *et al*. 1997). When the bioresorbable barrier alone was compared to the bioresorbable barrier in combination with DFDBA, PPD reduction was significantly (P <0.01) in favor of the combination therapy. Vertical bone gain was significant greater with the combination treatment (P <0.02). The authors concluded that the combination therapy of bioresorbable barrier plus DFDBA is superior to the control therapy of bioresorbable barrier alone.

Lekovic *et al*. (2003) tested a combination of PRP, bovine porous bone mineral (BPBM), and GTR in 52 class II furcations (26 treated with the test material and 26 with OFD, which served as controls). The experimental group presented with significantly greater pocket reduction (4.07 ± 0.33 mm for experimental and 2.49 ± 0.38 mm for control sites), CAL gain (3.29 ± 0.42 mm for experimental and 1.68 ± 0.31 mm for control sites), vertical defect fill (2.56 ± 0.36 mm for experimental and −0.19 ± 0.02 for control sites), and horizontal defect fill (2.28 ± 0.33 mm for experimental and 0.08 ± 0.02 mm for control sites) than the control group. The authors concluded that the PRP/BPBM/GTR combined technique is an effective modality of regenerative treatment for mandibular grade II furcation defects. However, further studies are necessary to elucidate the role played by each component of the combined therapy in achieving these results.

Houser *et al*. (2001) compared the use of Bio-Oss® in combination with a bioresorbable collagen barrier (BioGide®) to OFD surgery in human mandibular class II furcation defects. A total of 31 furcations (18 test, 13 control) in 21 patients were treated. There was a statistically significant improvement in most clinical parameters for the experimental group, with minimal improvement noted for the flap control group. Vertical PPD reduction of 2.0 mm and horizontal PPD reduction of 2.2 mm were reported for the experimental group, while 0.3 mm and 0.2 mm reductions, respectively, were reported for the control group. Hard tissue measurements showed 2.0 mm of vertical furcation bone fill for the test group and 0.5 mm for control group. The test group had 3.0 mm of horizontal furcation bone fill and the control group had 0.9 mm. The test group had a defect resolution of 82.7% compared with 42.5% in the flap control group. There was a statistically significant difference between the two groups in all soft and hard tissue measurements with the exception of attachment level, recession, and alveolar crest resorption. The authors concluded that the combination of Bio-Oss® and Bio-Gide® is effective in the treatment of mandibular class II furcations.

Belal *et al*. (2005) treated 50 furcations in 20 patients with five different approaches (bioresorbable membrane or a connective tissue graft with or without bioresorbable hydroxylapatite, and flap alone as a control therapy). All experimental groups showed statistically significant improvement in the clinical parameters and bone density as compared to the control group. However, no statistically significant differences were observed between any of the experimental groups. Percentages of complete furcation closure ranged from 20% to 40% in the experimental groups, but was 0% in the flap control group.

Root surface biomodification

The effect of combining citric acid root biomodification with GTR treatment was evaluated in two randomized controlled clinical trials in intrabony defects. The first investigation (Handelsman *et al*. 1991) demonstrated significant CAL gain in both the test (e-PTFE membranes + citric acid; 3.5 ± 1.6 mm) and control sites (e-PTFE membranes alone; 4.0 ± 1.4 mm). Less favorable results following these two treatment modalities were reported by Kersten *et al*. (1992) who found CAL gains of 1.0 ± 1.1 mm in the test group and of 0.7 ± 1.5 mm in the control group. Both studies, however, failed to demonstrate any added effect of the use of citric acid in combination with non-bioresorbable barrier membranes.

Root surface biomodification with tetracycline alone and in combination with GTR was evaluated in two controlled studies on class II furcations (Machtei *et al*. 1993; Parashis & Mitsis 1993). Both investigations failed to show significant differences between sites treated with non-bioresorbable barrier membranes alone or in combination with tetracycline root surface biomodification. Similarly, the use of other surface-active chemicals like EDTA also failed to provide a significant added effect to GTR treatment in humans (Lindhe & Cortellini 1996).

The suggested role of root surface biomodification for improving periodontal regeneration has been assessed in a systematic review (Mariotti *et al*. 2003). The results of that exhaustive review of the evidence indicated that there was no evidence for a measurable improvement following root conditioning with agents like citric acid, tetracycline–HCl, phosphoric acid, fibronectin or EDTA.

Clinical potential and limits for regeneration

From the very beginning of modern periodontal regeneration it was apparent that periodontal tissues could express a surprising regenerative potential under favorable circumstances. Sparse case reports demonstrated that very deep defects reaching the apical third of the root could be filled with new bone and new clinical attachment (Pini Prato *et al*. 1988; Becker *et al*. 1988; Cortellini *et al*. 1990). Larger studies suggested that in deeper defects, greater clinical improvement is generally obtained (Tonetti *et al*. 1993a, 1996a; Garrett *et al*. 1998; Slotte *et al*. 2007). These observations raised a question about the "potential" for regeneration: is the potential greater in deeper defects? Cortellini *et al*. (1998) addressed this question in a controlled study and reported similar attachment gain in defects presenting with an intrabony component of ≤3 mm (76% defect resolution) and defects of ≥4 mm (77% defect resolution), indicating that the potential for regeneration is similar in both shallow and deep intrabony components. The conclusions of this study are indirectly supported by the results of large controlled clinical trials performed with the application of different successful regenerative approaches (Cortellini *et al*. 1995c, 1996b; Tonetti *et al*. 1998; Cortellini *et al*. 2001; Tonetti *et al*. 2002, 2004b). Unpublished subanalyses of these experimental populations, in which the treated defects were clustered according to defect depth, showed that CAL gain is obtained in all defects from shallow to deep, but deeper defects gain more attachment in millimeters than shallow ones. In other words, regeneration seems to express its potential as much as the "container" allows it, independent of the "regenerative approach" chosen, within the panel of the well tested, sound regenerative approaches. A recent controlled study has challenged the limits of the periodontium to repair or regenerate (Cortellini *et al*. 2011). The aim of this randomized, long-term clinical trial was to compare clinical and patient-based outcomes following periodontal regeneration or extraction and replacement of hopeless teeth with attachment loss to or beyond the apex. Twenty-five hopeless teeth were treated with a regenerative strategy. Most of the treated teeth had a periodontal lesion exceeding the apex of the tooth and involving three to four sides of the root (Fig. 45-44). Twenty-three of the 25 regenerated teeth obtained extensive clinical improvements. The average CAL gain was 7.7 ± 2.8 mm, the radiographic bone gain 8.5 ± 3.1 mm, and the PPD reduction 8.8 ± 3 mm. Most of the regenerated teeth showed a decrease in tooth mobility. Only two teeth showing unsatisfactory outcomes were extracted at 1 year. The 23 successfully regenerated teeth (92%) were in good health and function at the 5-year follow-up visit and 84% did not develop biologic complications during the recall period. The authors concluded that regenerative therapy can be successfully applied even to hopeless teeth and has the potential to change their prognosis. However, it should be underlined that the reported outcomes were obtained in a carefully selected patient population, and by applying "state of the art" regenerative therapy by very experienced clinicians, within a high quality program of periodontal and dental therapy and a strict periodontal supportive care program. In other words, it is apparent from the cited studies that to succeed in extreme conditions, a sound strategy has to be adopted.

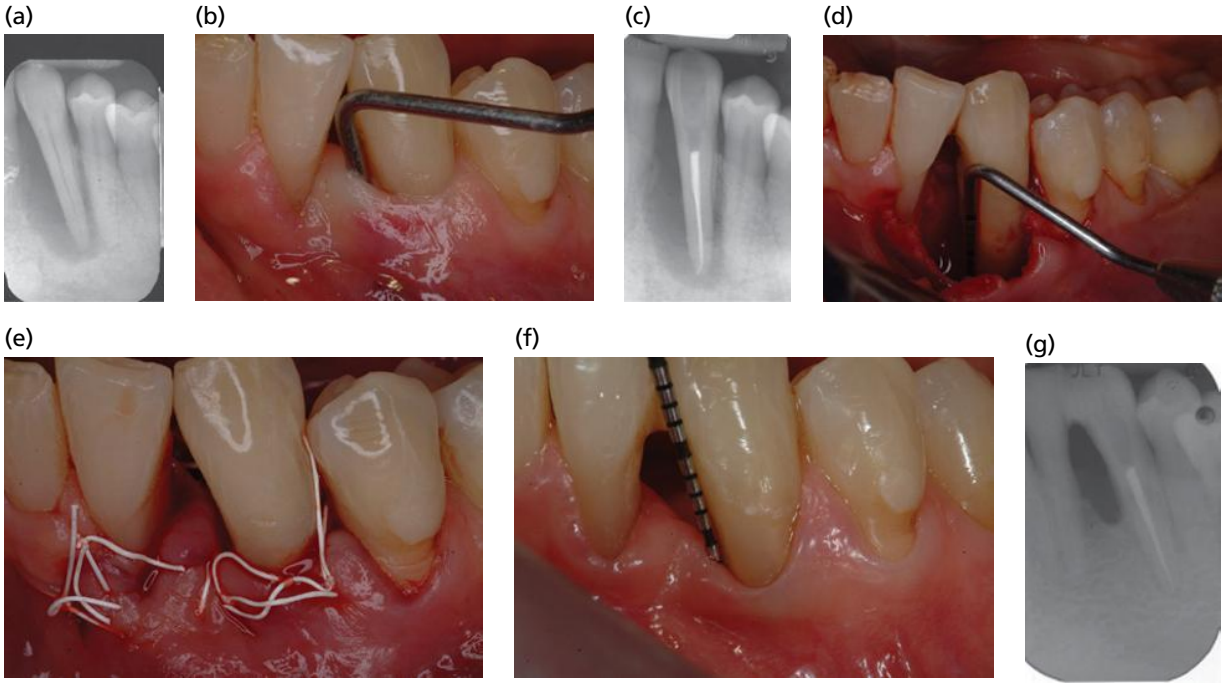


Fig. 45-44 Treatment of a very severe periodontal defect with periodontal regeneration. Baseline radiograph showed a very severe defect extending far beyond the apex of the tooth (a). A pocket deeper than 15 mm was evident at the mesial aspect of the lower left cuspid (b). The tooth was root canal treated (c). The area was accessed with a large flap: bone destruction almost all around is evident (d). The gingival flap was repositioned and sutured with a multilayer technique (e). At 1 year, a 4-mm pocket was probed (f). The radiograph showed the resolution of the periodontal defect (g).

Clinical strategies

Periodontal regeneration in intrabony defects has been successfully attempted with a variety of different approaches. As discussed, meta-analyses of randomized controlled clinical trials as well as human and animal histologic findings support the potential of barrier membranes (Nyman *et al*. 1982; Gottlow *et al*. 1986), DFDBAs (Bowers *et al*. 1989a–c), combinations of barrier membranes and grafts (Camelo *et al*. 1998; Mellonig 2000), and the use of EMDs (Mellonig 1999; Yukna & Mellonig 2000) or growth factors (Howell *et al*. 1997) to induce periodontal regeneration. Controlled clinical trials report that these approaches provide added benefits in terms of CAL gain as compared to OFD alone (Needleman *et al*. 2002; Trombelli *et al*. 2002; Giannobile & Somerman 2003; Murphy & Gunsolley 2003; Esposito *et al*. 2009; Needleman *et al*. 2006; Darby & Morris 2013). Comparisons between some of the regenerative approaches failed to demonstrate a clear superiority of any of the tested materials (Giannobile & Somerman 2003; Murphy *et al*. 2003; Reynolds *et al*. 2003).

The existing evidence, therefore, does not support any particular single regenerative approach. In addition, all the cited studies have shown a substantial degree of variability in terms of CAL gain, reporting failures or unsatisfactory outcomes in part of the treated population.

Research conducted mostly in the past decade has clearly established that the variability observed in outcomes of periodontal regenerative procedures is dependent on a variety of patient-, defect-, and surgical-associated factors. This is not unexpected since each individual patient presents with unique characteristics as well as each defect presenting with very different and unique anatomies. The outcomes of the randomized studies indicates clearly that none of the regenerative approaches can solve all the different patient/defect presentations. It is therefore mandatory to build up a clinical decision tree that allows clinicians to apply the regenerative strategy most appropriate to each individual case.

While relevant patient factors include cigarette smoking, residual periodontal infection, and oral hygiene, factors associated with the morphology of the defect are consistently found to be of relevance to the final outcome (Tonetti *et al*. 1998; Cortellini *et al*. 2001). Interestingly, however, the number of residual bony walls defining the defect seems to impact the outcomes of different periodontal regenerative materials in a divergent way. Non-bioresorbable (e-PTFE and titanium-reinforced e-PTFE) barrier membranes and bioresorbable barriers supported by a graft do not seem to be affected by the number of residual bony walls of the defect (Tonetti *et al*. 1993a, 1996a, 2004b), while EMDs result in better outcomes in three-wall defects (Tonetti *et al*. 2002). Furthermore, healing following application of bioresorbable barriers and non-bioresorbable e-PTFE barriers as well as EMDs is associated with the radiographic width of the intrabony defect (Tonetti *et al*. 1993a; Falk *et al*. 1997; Tsitoura *et al*. 2004). No such association has been found for the use of a xenogenic BRGs and bioresorbable barrier combination (Tonetti *et al*. 2004b).

Among the technical/surgical factors, membrane exposure and contamination have been associated with poorer outcomes (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). Similar problems were also encountered with bone grafting (Sanders *et al*. 1983). Poorer outcomes were also observed when the regenerated tissue was not properly protected with the flap on removal of non-bioresorbable barrier membranes (Tonetti *et al*. 1993a; Cortellini *et al*. 1995c).

A controlled clinical trial demonstrated that the combination of a papilla preservation flap and titanium-reinforced e-PTFE membrane resulted in greater CAL gain as compared to a conventional flap approach with an e-PTFE membrane (Cortellini *et al*. 1995c). This evidence, also partly supported by a systematic review (Murphy & Gunsolley 2003), strongly suggests that optimization of the surgical approach and control of surgical variables, particularly in relation to flap design and management and selection of the regenerative material, could improve outcomes. In the context of periodontal regeneration, several flap designs aimed specifically at the full preservation of the soft tissues during access to the defect have been described (Cortellini *et al*. 1995c, d, 1996c; Murphy 1996; Cortellini *et al*. 1999a; Cortellini & Tonetti 2007a, 2009b). Experimental testing of these regenerative flaps showed great improvements in achieving primary closure during the surgical session, with optimal interdental closure being obtained in virtually all cases (Cortellini *et al*. 1995c, d, 1999, 2001; Tonetti *et al*. 2004b). During the subsequent healing, however, dehiscence of the interdental tissue and membrane exposure was observed in up to a third of the cases. The ability to accomplish and maintain primary closure of the tissues over a GTR membrane was further improved by the use of a microsurgical approach that resulted in maintenance of primary wound closure in 92.3% of the treated sites for the whole healing period (Cortellini & Tonetti 2001, 2005, 2007a, b, 2009b, 2011).

This body of evidence has been utilized together with a degree of clinical experience to develop an "evidence-based regenerative strategy" to guide clinicians through a decision-making process aimed at the optimization of the clinical outcomes of periodontal regeneration in intrabony defects (Cortellini & Tonetti 2000a, 2005). Key steps of this process are the careful evaluation of the patient and of the defect, access to the defect with a papilla preservation flap, choice of the most appropriate regenerative technology/material, and ability to seal the regenerating wound from the contaminated oral environment with optimal suturing techniques.

The performance of this clinical strategy has been assessed in a 40-patient consecutive case series (Cortellini & Tonetti 2005). Following completion of initial, cause-related periodontal therapy, subjects presented full-mouth plaque scores of 10.2 ± 2.7% and full-mouth bleeding scores at baseline of 7.9 ± 2.8%. At the intrabony defects, CAL was 10.2 ± 2.4 mm and PPD 8.9 ± 1.8 mm. The radiographic defect angle was 29 ± 5.9°. CEJ–BD was 11.2 ± 2.7 mm and the intrabony component of the defects (INFRA) was 6.6 ± 1.7 mm. In this population, the SPPF could be used in 37.5% of sites, while the MPPT was selected in 45% of cases. The remaining sites, presenting with defects adjacent to edentulous areas, were accessed with a crestal incision.

Based on defect anatomy, non-bioresorbable titanium-reinforced e-PTFE barrier membranes were used in 30% of cases. In these cases, defect angles ranged from 27° to 42° (average 32.4 ± 4.3°), and eight of the 11 selected defects had a one-wall intrabony subcomponent of 1–3 mm (the average one-wall component of the 12 sites was 1.4 ± 1.2 mm). Ten of the 11 defects treated with bioresorbable membranes supported with a BRG presented a one-wall subcomponent of 1–5 mm (the average one-wall component of the 11 sites was 1.8 ± 1.3 mm); defect angles in this group ranged from 21° to 45° (average 31.4 ± 7°). Bioresorbable barriers alone were used in seven sites presenting with a prevalent two- and three-wall morphology and narrow defect angles, ranging from 20° to 28° (average 24.1 ± 3.7°). EMDs were applied to ten defects with a prevalent three-wall component. The defect angle in this group ranged from 19° to 31° (average 26.5 ± 4.3°).

Primary closure was obtained at completion of the surgical procedure for all treated sites. At the 1-week follow-up, when sutures were removed, two sites, both accessed with a SPPF, presented with a small interdental wound dehiscence: one had been treated with a bioresorbable membrane and BRG, the other with EMDs. At week 2, two additional small wound dehiscences were detected: one accessed with MPPT and treated with a bioresorbable membrane and BRG, the other accessed with SPPF and treated with a bioresorbable barrier alone. All the other sites (90%) remained closed during the entire early healing phase.

The 40 patients presented at the 1-year follow-up visit with excellent levels of plaque control and low levels of BoP. The 1-year CAL gain was 6 ± 1.8 mm (range 4–11 mm). No sites gained <4 mm of CAL; 77.5% gained ≥5 mm and 40% >6 mm. Residual PPDs were 2.7 ± 0.6 mm, with an average reduction of 6.1 ± 1.9 mm. Only four sites showed a residual PPD of 4 mm; all the other sites had a 1-year PPD of ≤3 mm. A minimal increase of 0.1 ± 0.7 mm in gingival recession between baseline and 1 year was recorded.

This study indicated that, whenever the treatment choice was made according to the protocol (i.e. based on: width of the interdental space to select the papilla preservation surgery; morphology of the defect to select the regenerative material; and choice of the material and local anatomy to select the suturing approach), all four approaches gave excellent results with CAL gains equal to 88–95% resolution of the original depth of the intrabony component of the defect (Cortellini & Tonetti 2005).

The CAL gain of 6 ± 1.8 mm at 1 year was obtained in defects with an intrabony component of 6.6 ± 1.7 mm. The percentage CAL gain therefore was 92.1 ± 12%. This indicates that a large part of the intrabony component of the defects was resolved. Using the Ellegaard criteria (Ellegaard *et al*. 1971), resolution of the intrabony component of the defect was either satisfactory or complete in all treated cases. In particular, 40.5% of defects had CAL gains equal to or greater than the baseline depth of the intrabony component, while the defect with the worst response showed a 71.4% CAL gain. Historical comparison with clinical experiments using bone grafting or GTR clearly indicates that the results of this trial approach were in the top percentiles in terms of CAL gains and defect resolution (Cortellini & Tonetti 2000a; Rosen *et al*. 2000).

A novel, more comprehensive clinical strategy has been developed to further improve the clinical capacity to ensure appropriate therapy for each patient/defect. This approach takes into proper account the relevance of the patient characteristics, as described earlier in this chapter, and is based on the need to satisfy the three major contributors to periodontal regeneration: (1) space for the formation of the blood clot at the interface between the flap and root surface (Haney *et al.* 1993, Sigurdsson *et al.* 1994, Cortellini *et al*. 1995b, c, Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al.* 2004); (2) stability of the blood clot to maintain a continuity with the root surface and thereby avoid the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993); (3) and soft tissue protection of the treated area to avoid bacterial contamination (Selvig *et al*. 1992; Nowzari *et al.* 1995; De Sanctis *et al*. 1996a, b; Sanz *et al*. 2004; Polimeni *et al*. 2006). *Space* and *blood clot stability* are self-provided in the so-called "containing defects", particularly the narrow three-wall defects (Goldman & Cohen 1958; Schallhorn *et al*. 1970; Selvig *et al*. 1993; Cortellini & Tonetti 1999; Tsitoura *et al*. 2004; Linares *et al*. 2006). The "non-containing defects", the large one- or two-wall defects, require an intervention to supplement the deficient anatomy (Tonetti *et al*. 1993, 1996; Falk *et al*. 1997; Tonetti *et al*. 2002, 2004a, b). The intervention can be based on the use of biomaterials such as "exoskeleton"-like barriers or "endoskeleton"-like grafts that are able to support the soft tissues and to stabilize the blood clot, or a combination of the two approaches. In other words, the anatomic deficiencies of the defects have to be supplemented by the additional use of biomaterials. The same goal could be obtained by adopting different surgical strategies in which tissues are minimally elevated to increase their stability (the MIST and the M-MIST approaches) (Cortellini & Tonetti 2007, 2009). Blood clot stability is also clearly influenced by tooth hypermobility: splinting teeth with class II or III mobility is mandatory to avoid the disruption of the blood clot in the early healing phase (Cortellini *et al*. 2001; Trejo & Weltman 2004).

Protection of the regenerating area has to be provided with the adoption of specifically designed surgical approaches. The different surgical approaches differ in terms of flap design and suturing technique. In addition to their ability to provide protection to the regenerating area, they could differently contribute to improving one or more of the many aspects potentially relevant to the wound healing process. The traditional papilla preservation flaps (Cortellini *et al*. 1995a, 1999) were designed as wide and very mobile flaps in order to allow for perfect visibility of the defect area, for easy placement of biomaterials, and for the coronal positioning of the buccal flap to cover barriers and biomaterials. In other words, papilla preservation flaps do not have the mechanical characteristics to improve wound stability or the capacity to independently create space for regeneration. The MIST (Cortellini & Tonetti 2007a, b), in contrast, was designed to reduce flap extension and mobility as much as possible to increase the capacity for primary wound closure and blood clot stability. This potential was illustrated in two studies that demonstrated the reduced impact of the number of residual bony walls and of the defect width on the outcomes obtained with EMDs under a MIST (Cortellini *et al*. 2008; Cortellini & Tonetti 2009a), and recently confirmed in a comparative study demonstrating similar outcomes between MIST alone and MIST plus EMDs (Ribeiro *et al*. 2011a).

A further development of the surgical approach was the M-MIST (Cortellini & Tonetti 2009b, 2011). This advanced flap design further enhanced the potential of the flap to provide space and stability for regeneration by leaving the interdental papillary soft tissues attached to the root surface of the crest-associated tooth and by avoiding any palatal flap elevation. The interdental soft tissues are the stable "ceiling" of a "room" into which blood flows and forms a clot. In addition, the hanging papilla prevents the collapse of the soft tissues, thereby maintaining space for regeneration: the anatomic bone deficiencies are potentially supplemented by the peculiar novel flap design that provides additional "soft tissue walls" in place of the missing bony walls and thus improves stability. The walls of the "room" are the residual bony walls, the root surface, and the buccal/lingual soft tissues. The minimal flap extension and elevation also reduces greatly the damage to the vascular system. It is clear that such a flap is not designed to allow the positioning of a barrier, but biologicals or grafts can easily be used with it.

Clinical flowcharts

Clinical flowcharts have been developed that take into account also the scientific contributions on surgical and post-surgical events, like chair time, side effects, and postoperative pain.

The step-by-step clinical approach to the treatment of intrabony defects includes two presurgical flow

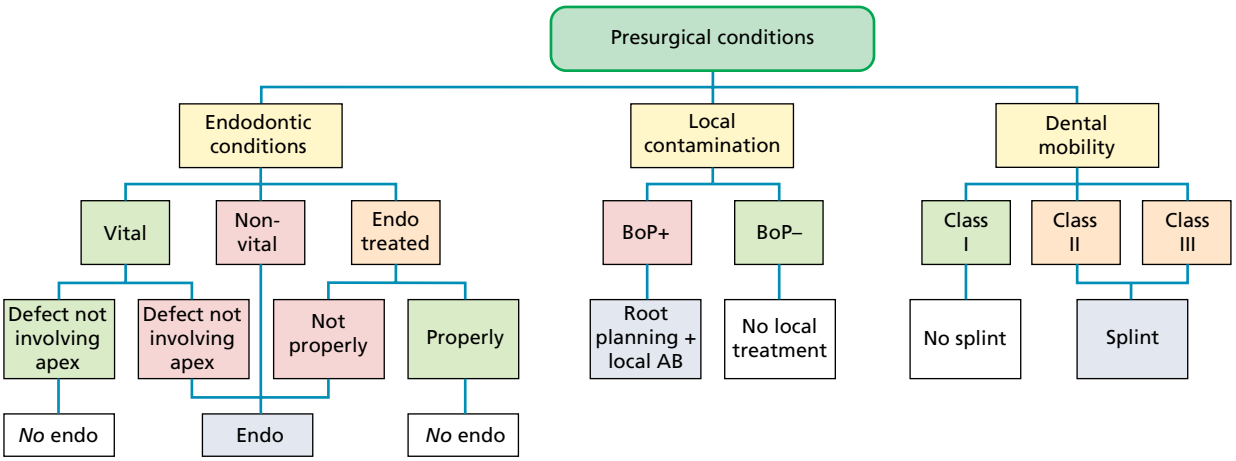


Fig. 45-45 Decision-making algorithm highlighting the clinical conditions to be checked before periodontal regeneration. These relate mainly to the endodontic status, presence of local contamination, and dental hypermobility of the tooth to be treated with periodontal regeneration. (BoP, bleeding on probing; AB, antibiotic.)

charts dealing with patient and local factors and four surgical flow charts (surgical nodes). The development of the surgical nodes was driven by the wish to treat any given defect with the procedure judged fastest, easiest, least burdened by side effects, and best tolerated by the patients. Lastly, postoperative care is suggested.

The step-by-step approach starts with control of patient-associated characteristics (see Fig. 45-10): low levels of plaque and residual infection, high levels of compliance, and absence of adverse conditions like smoking, stress, and uncontrolled diabetes or other systemic diseases have to be well established.

A few conditions, like endodontic condition, local contamination, and mobility of the involved tooth, must be controlled before surgery (Fig. 45-45). Endodontic diagnosis and eventual treatment should be performed well in advance of the regenerative approach (Cortellini & Tonetti 2001). Vital teeth should preferably be kept vital, with the only exception being a tooth whose apex is involved with the periodontal lesion (Cortellini *et al*. 2011). Non-vital teeth must be properly treated with root canal therapy. Existing root canal therapies should be carefully evaluated: improper treatments should be corrected. Local contamination of the defect-associated pocket should be as low as possible (Heitz-Mayfield *et al.* 2006). The presence of BoP (i.e. bacteria) should be controlled with additional gentle root planing and then the additional use of local antimicrobials (Tunkel *et al*. 2002; Hanes & Purvis 2003) a few weeks before regeneration (Cortellini *et al*. 2011). Teeth with mobility of class II or III should be splinted before or immediately after the surgical procedure (Cortellini *et al.* 2001; Trejo & Weltman 2004). Tooth hypermobility should be re-evaluated during the early healing phase: any detected increase in mobility should be taken care of.

The surgical access to the intrabony defects is selected from three different approaches: the SPPF

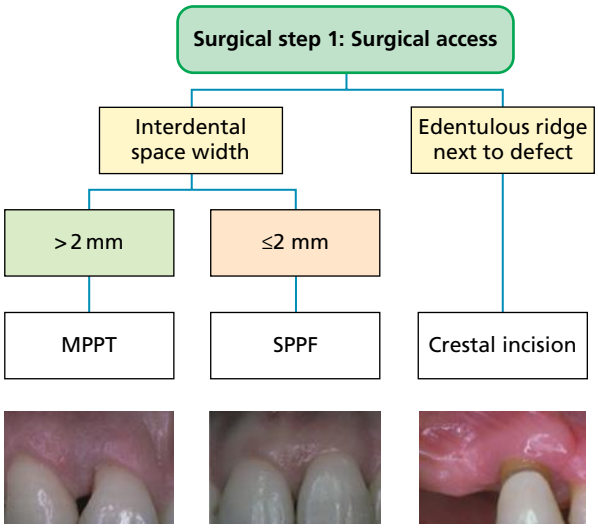


Fig. 45-46 Decision-making algorithm for obtaining access to an intrabony defect: the simplified papilla preservation flap (SPPF) is used for narrow interdental spaces (2 mm or narrower), while the modified papilla preservation technique (MPPT) is used to access defects associated with wider interdental spaces (3 mm or wider). Crestal incision is applied at a tooth neighboring an edentulous ridge.

(Cortellini *et al.* 1999a), the MPPT (Cortellini *et al.* 1995d), and the crestal incision (Cortellini & Tonetti 2000a) (Fig. 45-46). The SPPF is chosen whenever the width of the interdental space is 2 mm or less, as measured at the level of the supracrestal portion of the papilla. The MPPT is used at sites with an interdental width of >2 mm; the crestal incision is applied next to an edentulous area.

The next surgical step (Fig. 45-47) concerns the selection of the flap design. Whenever a defect involves one or two sides of a root and can be cleaned through a tiny buccal window, an M-MIST is applied (Cortellini & Tonetti 2009b, 2011). In some instances, the M-MIST can be applied to both the interdental spaces neighboring the defect-associated

tooth, allowing for instrumentation of a defect involving up to three sides of a root. If the defect cannot be cleaned through the buccal window, the interdental papilla is elevated by applying a MIST approach (Cortellini & Tonetti 2007a; Cortellini *et al*. 2008). A large flap, extended to the neighboring teeth and including also an eventual periosteal incision and/or vertical releasing incisions, is chosen in the presence of a very severe and deep defect, involving three or four sides of the root, which requires ample visibility for instrumentation and the use of either endo- or exo-skeletons (Cortellini *et al*. 1995d, 1999a).

Selection of the regenerative material is based on the defect anatomy and on the flap design chosen to expose the defect (Fig. 45-48). If an M-MIST approach is applied, EMDs or no regenerative materials are the elective choices (Cortellini & Tonetti 2009b, 2011). If a MIST is applied, EMDs can be used alone in containing defects or in combination with a filler in non-containing defects (Cortellini & Tonetti 2007a; Cortellini *et al*. 2008; Ribeiro *et al*. 2011a). If a large flap is elevated, the area should be stabilized by applying barriers or fillers, or a combination of barriers and fillers, or a combination of EMDs/growth factors and fillers. EMDs alone are preferred in defects with a prevalent three-wall morphology or in well-supported two-wall defects.

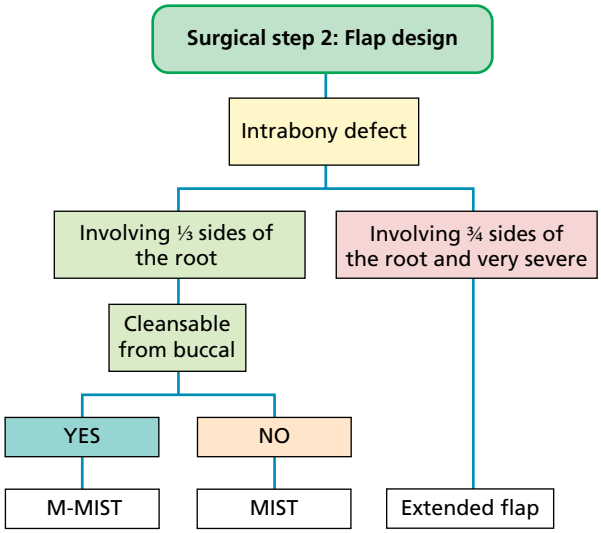


Fig. 45-47 Decision-making algorithm for choice of flap design. The type of surgical access from very small to very ample is chosen according to the severity and extension of the periodontal defect.

The suturing approach is selected according to the type of regenerative strategy applied (Fig. 45-49). It will consist of a single internal modified mattress suture when an M-MIST or an MIST approach is chosen and EMDs alone are applied (Cortellini & Tonetti 2007a; Cortellini et al 2008; Cortellini & Tonetti 2009a, 2011). When a large flap with a periosteal incision is used in association with a barrier or a graft or a combination of these, the suturing approach will consist of two internal mattress sutures applied at the defect-associated interdental area to achieve primary closure of the papilla in the absence of any tension (Cortellini *et al*. 1995b, c, 1999; Cortellini & Tonetti 2000a, 2005).

The surgical procedure is preferably performed with the aid of magnification such as loupes or an operating microscope (Cortellini & Tonetti 2001; Wachtel *et al*. 2003; Cortellini & Tonetti 2005). Microsurgical instruments and materials should be utilized to complement the normal periodontal set.

Post-surgical and early home-care protocols are derived from the experiences gained from running many controlled clinical trials (Cortellini *et al*. 1995c, 1996b; Tonetti *et al*. 1998; Cortellini *et al*. 2001; Tonetti *et al*. 2002, 2004b). An empirical protocol for the control of bacterial contamination consisting of doxycycline (100 mg b.i.d. for 1 week), 0.12%

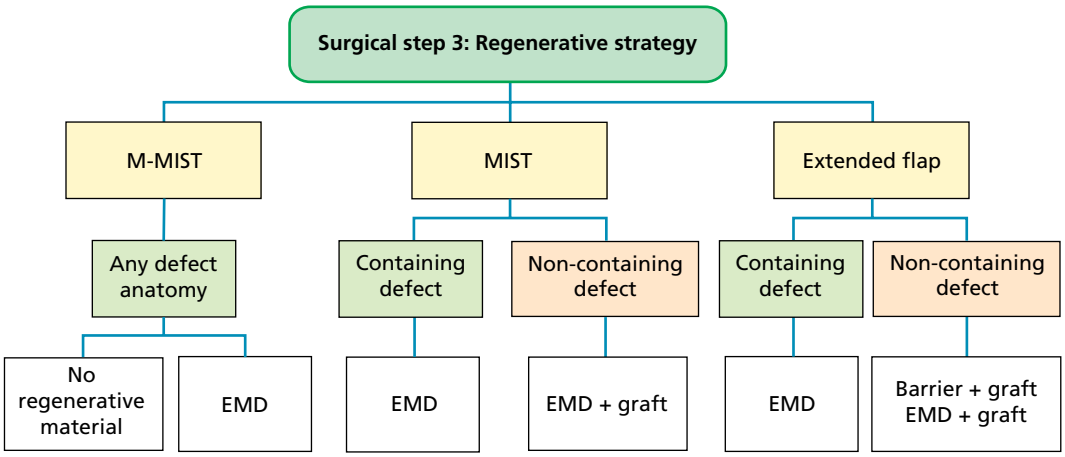


Fig. 45-48 Decision-making algorithm for choice of currently available technologies for application of regeneration in the treatment of intrabony defects. The clinical decision is based on two main parameters: (1) type of surgical access performed; (2) morphology of the periodontal defect. (MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique; EMD, enamel matrix derivative.)

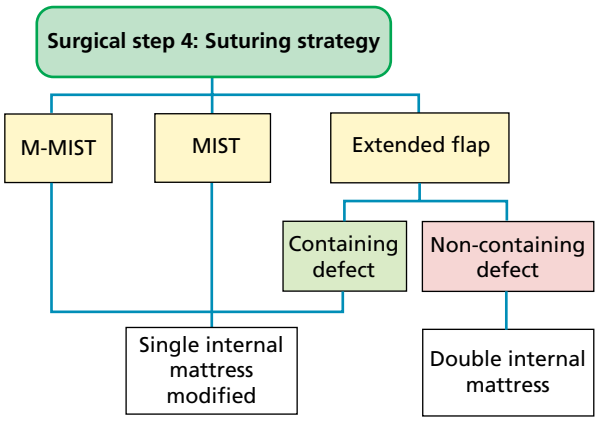


Fig. 45-49 Decision-making algorithm for the choice of suturing technique. (MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique.)

chlorhexidine mouth rinsing t.i.d., and weekly prophylaxis is prescribed. Sutures are removed after 1 week. Patients are requested to avoid normal brushing, flossing, and chewing in the treated area for periods of 6–10 weeks. A post-surgical soft toothbrush soaked in chlorhexidine is adopted from week 1 to gently wipe the treated area. Non-bioresorbable membranes are removed after 6 weeks. Patients can resume full oral hygiene and chewing function in the treated area 2–4 weeks after membrane removal or when bioresorbable membranes are fully resorbed. Patients treated with EMDs can resume full oral hygiene after a period of 4–5 weeks. At the end of the "early healing phase", patients are placed in a 3-month recall system. A general suggestion to avoid any invasive clinical maneuver, like hard subgingival instrumentation, restorative dentistry, orthodontics, and additional surgery, for a period of about 9 months is also part of the strategy to optimize the clinical outcomes of periodontal regeneration.

Conclusion

Periodontal regeneration has demonstrated significant clinical improvements in intrabony defects far beyond those achieved with debridement alone, with many different regenerative materials, including barrier membranes, grafts, active biologic compounds, and combinations of these. Different surgical approaches have been proposed and tested in combination with the various regenerative materials, but none has demonstrated a clear superiority over the others. Moreover, all of the proposed regenerative approaches have shown a high degree of clinical variability in terms of CAL gain: none has demonstrated the capacity to solve all the different and unique patient/defect presentations. Therefore, to treat a given defect, the regenerative strategy has to be chosen from a panel of options. The adoption of a clinical strategy for optimal application of materials and surgical approach could increase the efficacy of periodontal regeneration and give a clear advantage in terms of improved clinical outcomes. Periodontal regeneration expresses its potential in defects of any depth, from very shallow to very deep, and in extreme conditions can change the prognosis of teeth from hopeless to maintainable units.

Clinical outcomes obtained with periodontal regeneration can be maintained on a long-term basis, provided good oral hygiene and infection control within a stringent recall program are enforced. Current data indicate that, in patients participating in a supportive periodontal care program, 96% of teeth with severe intrabony defects and treated with a periodontal regenerative procedure could be retained for a period of up to 15 years.

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Chapter 46

Mucogingival Therapy: Periodontal Plastic Surgery

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Introduction

Mucogingival therapy is a general term used to describe periodontal treatment involving procedures for correction of defects in morphology, position, and/or amount of soft tissue and underlying bone support at teeth and implants (American Academy of Periodontology 2001).

A more specific term, *mucogingival surgery*, was introduced by Friedman (1957) and was defined as "surgical procedures designed to preserve gingiva, remove aberrant frenulum or muscle attachments, and increase the depth of the vestibule". Frequently, however, the term "mucogingival surgery" was used to describe all surgical procedures that involved both the gingiva and the alveolar mucosa. Consequently, not only were techniques designed (1) to enhance the width of the gingiva and (2) to correct particular soft tissue defects regarded as mucogingival procedures, but (3) certain pocket elimination approaches were also included in this group of periodontal treatment modalities. In 1993, Miller proposed the term *periodontal plastic surgery*, considering that mucogingival surgery had moved beyond the traditional treatment of problems associated with the amount of gingivae and recession type defects to also include correction of ridge form and soft tissue esthetics. Periodontal plastic surgery would accordingly be defined as "surgical procedures performed to prevent or correct anatomic, developmental, traumatic or disease-induced defects of the gingiva, alveolar mucosa or bone" (Proceedings of the 1996 World Workshop in Periodontics 1996). Among treatment procedures that may fall within this definition are various soft and hard tissue procedures aimed at:

- Gingival augmentation
- Root coverage
- Correction of mucosal defects at implants
- Crown lengthening
- Gingival preservation at ectopic tooth eruption
- Removal of aberrant frenulum
- Prevention of ridge collapse associated with tooth extraction
- Augmentation of the edentulous ridge.

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The focus of this chapter is mainly on treatment procedures for corrections of soft tissue defects in relation to the tooth and the edentulous ridge, while hard tissue augmentation procedures are covered in Chapter 50.

Gingival augmentation

The introduction of surgical procedures for gingival augmentation was based on the opinion that the presence of a wide band of keratinized and attached mucosa around the tooth is critical for maintaining gingival health and preventing attachment loss and soft tissue recession (Nabers 1954; Ochsenbein 1960; Friedman & Levine 1964; Hall 1981; Matter 1982). Hence, a discussion of the scientific evidence forming the basis for our current understanding of the role played by the gingiva in the protection of the periodontium proper seems appropriate.

Gingival dimensions and periodontal health

For many years the prevailing concept was that a narrow zone of gingiva (Fig. 46-1) was insufficient (1) to protect the periodontium from injury caused by friction forces encountered during mastication and (2) to dissipate the pull on the gingival margin created by the muscles of the adjacent alveolar mucosa (Friedman 1957; Ochsenbein 1960). Moreover, it was believed that an "inadequate" zone of gingiva would (1) facilitate subgingival plaque formation because of the improper pocket closure resulting from the movability of the marginal tissue (Friedman 1962) and (2) favor attachment loss and soft tissue recession because of less tissue resistance to apical spread of plaque-associated gingival lesions (Stern 1976; Ruben 1979). It was also considered that a narrow gingiva in combination with a shallow vestibular fornix might (1) favor the accumulation of food particles during mastication and (2) impede proper oral hygiene measures (Gottsegen 1954; Rosenberg 1960; Corn 1962; Carranza & Carraro 1970).

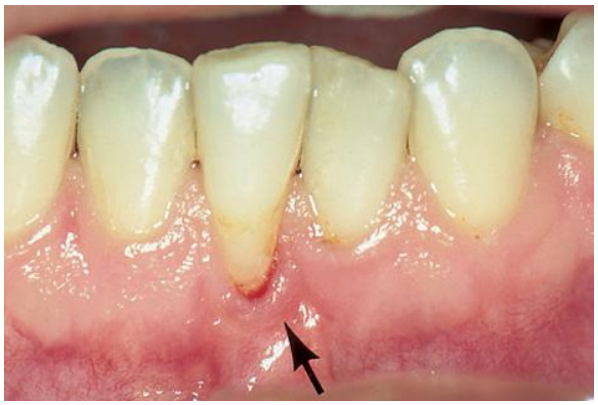


Fig. 46-1 Clinical photograph of a mandibular front tooth region. The gingiva on the buccal aspect of tooth 41 (arrow) has a narrow width and shows more pronounced signs of inflammation than adjacent gingival units with a wider zone of gingiva.

The opinions expressed concerning what could be regarded as being an "adequate" or "sufficient" dimension of the gingiva varied. While some authors suggested that <1 mm of gingiva may be sufficient (Bowers 1963), others claimed that the apicocoronal height of keratinized tissue ought to exceed 3 mm (Corn 1962). A third category of authors had a more biologic approach to the question and stated that an adequate amount of gingiva is any dimension that (1) is compatible with gingival health or (2) prevents retraction of the gingival margin during movements of the alveolar mucosa (Friedman 1962; De Trey & Bernimoulin 1980).

One of the first studies in which attempts were made to evaluate the significance of the gingival zone for the maintenance of periodontal health was carried out by Lang and Löe (1972) on dental students who had their teeth professionally cleaned once a day for 6 weeks. All buccal and lingual sites were examined for plaque, gingival conditions, and apicocoronal height of the gingiva. The results showed that despite the fact that the tooth surfaces were free from plaque, all sites with <2 mm of gingiva exhibited persisting clinical signs of inflammation. Based on this observation, the authors suggested that 2 mm of gingiva is an adequate width for maintaining gingival health. Subsequent clinical trials (Grevers 1977; Miyasato *et al*. 1977), however, failed to substantiate this concept of a required minimum dimension of gingiva. In fact, these clinical trials demonstrated that it is possible to maintain clinically healthy marginal tissues even in areas with <1 mm of gingiva.

The question whether a firmly attached portion of gingiva is critical for the protection of the periodontium proper was addressed by Wennström and Lindhe (1983a, b) utilizing the Beagle dog model. In these studies, dentogingival units with different clinical characteristics were experimentally established: (1) units with only a narrow and mobile zone of keratinized tissue and (2) units with a wide, firmly attached gingiva (Fig. 46-2). With mechanical plaque-control measures performed daily, the gingival units could be maintained free from clinical as well as histologic signs of inflammation irrespective of the presence or absence of an attached portion of gingiva. When bacterial plaque was allowed to accumulate (for 40 days), clinical signs of inflammation (redness and swelling) developed that were more pronounced in tooth regions with mobile gingiva (Fig. 46-3a) than in areas with a wide and firmly attached gingival zone (Fig. 46-3b). However, histologic analysis revealed that the size of the inflammatory cell infiltrate and its extension in an apical direction (an assessment which indirectly may be used as an estimate of the apical migration of the bacterial plaque) were similar in the two categories of dentogingival units. The finding that the clinical signs of gingival inflammation did not correspond with the

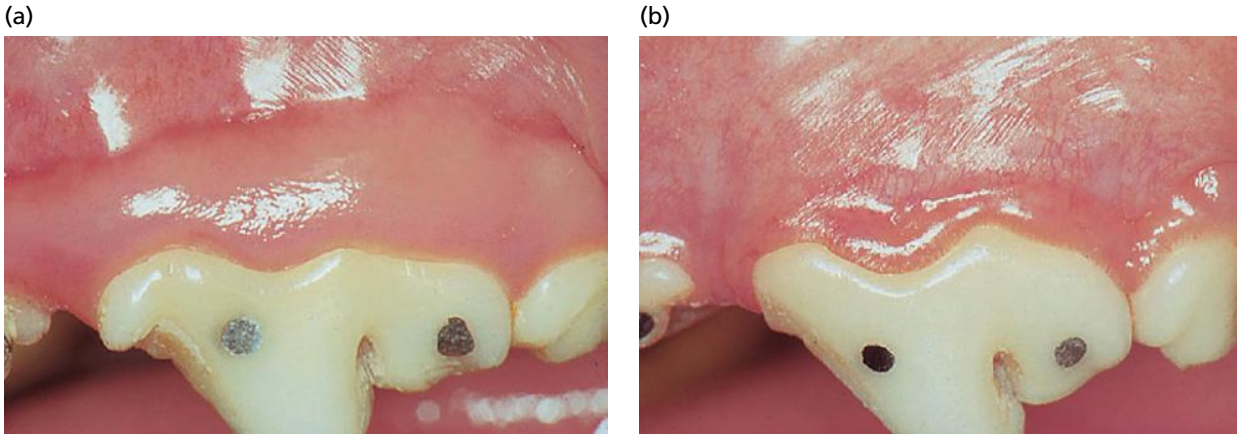


Fig. 46-2 Two teeth in a dog with varying dimensions of the marginal gingiva. (a) Buccal tooth site with a wide zone of attached gingiva. (b) Site with an unattached, narrow band of gingiva.

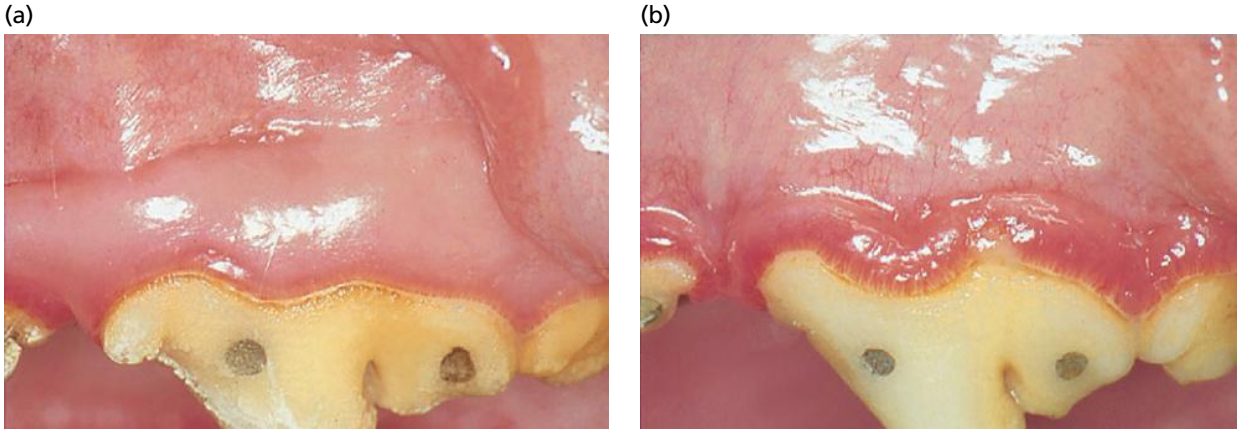


Fig. 46-3 Same teeth as in Fig. 44-2 after 40 days of plaque accumulation. The clinical signs of inflammation are more pronounced at the site with the narrow band of gingiva (b) than at the site with the wide zone of attached gingiva (a).

size of the inflammatory cell infiltrate illustrates the difficulties inherent in the interpretation of data from clinical examinations made in areas with varying gingival widths. This should be kept in mind when interpreting the data from the human study by Lang and Löe (1972) showing that clinically visible signs of inflammation, such as redness and swelling, were more frequent in areas with <2 mm of gingiva than in areas with a wider zone of gingiva.

The necessity for and effectiveness of gingival augmentation in maintaining periodontal attachment was examined by Dorfman *et al*. (1980). Ninety-two patients with bilateral facial tooth surfaces exhibiting minimal keratinized tissue (i.e. <2 mm) had a free gingival graft placed on one side, while the contralateral side served as the untreated control. Prior to and after surgery the patients were subjected to scaling and root planing and instruction in oral hygiene measures. Not surprisingly, the investigators found a significant increase (approximately 4 mm) in the width of keratinized tissue at the grafted sites. This increased width of gingiva, as well as the clinical attachment level, was maintained throughout the 2 years of follow-up. In the control sites, the gingival width was <2 mm and did not vary significantly during the observation period. However, the attachment level was also maintained unchanged in the non-grafted areas. Thus, the resistance to continuous attachment loss was not linked to the height (width) of the gingiva, a conclusion that was further substantiated by subsequent 4- and 6-year follow-up reports of this patient material (Dorfman *et al*. 1982; Kennedy *et al*. 1985).

Further support for the conclusion that a minimal zone of gingiva may not compromise periodontal health is available from a number of other longitudinal clinical studies (e.g. De Trey & Bernimoulin 1980; Hangorsky & Bissada 1980; Lindhe & Nyman 1980; Schoo & van der Velden 1985; Kisch *et al*. 1986; Wennström 1987; Freedman *et al*. 1999). Hence, Hangorsky and Bissada (1980), who evaluated the long-term clinical effect of free soft tissue grafts, concluded that while the free gingival graft is an effective method to widen the zone of the gingiva, there is no indication that this increase has direct influence upon periodontal health.

Conclusion: Gingival health can be maintained independent of its dimensions. Furthermore, there is evidence from both experimental and clinical studies that, in the presence of plaque, areas with a narrow zone of gingiva possess a similar degree of

"resistance" to continuous attachment loss as areas with a wide zone of gingiva. Hence, the traditional dogma of the need for an "adequate" width (in millimeters) of gingiva, or an attached portion of gingiva, for prevention of attachment loss is not scientifically supported.

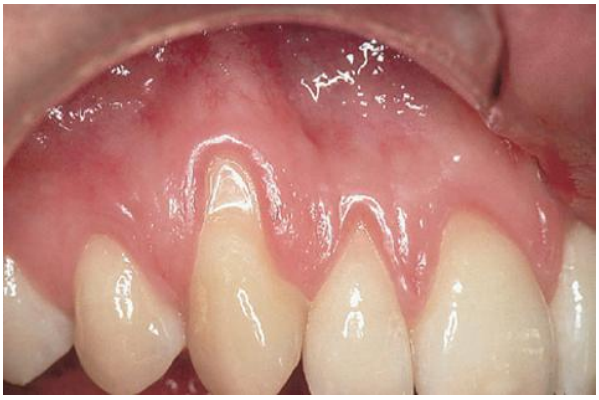
Marginal tissue recession

Marginal tissue recession, that is displacement of the soft tissue margin apical to the cementoenamel junction (CEJ) with exposure of the root surface, is a common feature in populations with high standards of oral hygiene (e.g. Sangnes & Gjermo 1976; Murtomaa *et al*. 1987; Löe *et al*. 1992; Serino *et al*. 1994), as well as in populations with poor oral hygiene (e.g. Baelum *et al*. 1986; Yoneyama *et al*. 1988; Löe *et al*. 1992; Susin *et al*. 2004). In populations maintaining high standards of oral hygiene, loss of attachment and marginal tissue recession are predominantly found at buccal tooth surfaces (Löe *et al*. 1992; Serino *et al*. 1994), and are frequently associated with the presence of a "wedge-shaped defect in the crevicular area of one or several teeth" (Sangnes & Gjermo 1976). In contrast, all tooth surfaces are usually affected by soft tissue recession in periodontally untreated populations, although the prevalence and severity is more pronounced at single-rooted teeth than at molars (Löe *et al*. 1978; Miller *et al*. 1987; Yoneyama *et al*. 1988; Löe *et al*. 1992).

Tissue trauma caused by vigorous toothbrushing is considered to be a predominant causative factor for the development of recessions, particularly in young individuals. Traumatizing toothbrushing and tooth malposition are the factors most frequently found to be associated with marginal tissue recession (Sangnes 1976; Vekalahti 1989; Checchi *et al*. 1999; Daprile *et al*. 2007). In addition, Khocht *et al*. (1993) showed that the presence of recessions is associated with the use of hard toothbrushes. Other local factors that have been associated with marginal tissue recession are (1) alveolar bone dehiscences (Bernimoulin & Curilivic 1977; Löst 1984), (2) high muscle attachment and frenal pull (Trott & Love 1966), (3) plaque and calculus (van Palenstein Helderman *et al*. 1998; Susin *et al*. 2004), and (4) iatrogenic factors related to restorative and periodontal treatment procedures (Lindhe & Nyman 1980; Valderhaug 1980). At least three different types of marginal tissue recessions may be defined:

1. *Recessions associated with mechanical factors, predominately toothbrushing trauma* (Fig. 46-4). Recessions resulting from improper toothbrushing techniques are often found at sites with clinically healthy gingiva and where the exposed root has a wedge-shaped defect, the surface of which is clean, smooth, and polished.
2. *Recessions associated with localized plaque-induced inflammatory lesions* (Fig. 46-5). Such recessions may be found at teeth that are prominently positioned, that is the alveolar bone is thin or absent (bone dehiscence), and where in addition the gingival tissue is thin (delicate). An inflammatory lesion that develops in response to subgingival plaque occupies the connective tissue adjacent to the dentogingival epithelium. Measurements made by Waerhaug (1952) suggest that the distance between the periphery of microbial plaque on the tooth surface and the lateral and apical extension of the inflammatory cell infiltrate seldom exceeds 1–2 mm. Thus, if the free gingiva is voluminous, the infiltrate will occupy only a small portion of the connective tissue. In a

(a)



(b)

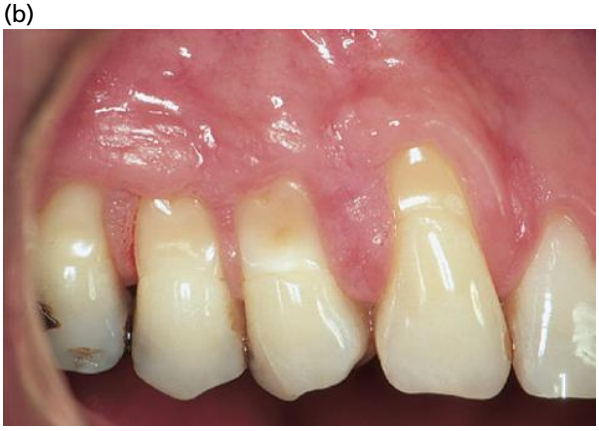


Fig. 46-4 Recessions associated with toothbrushing trauma. The marginal gingiva is clinically healthy and abrasion defects of various extensions can be noted in the exposed roots.

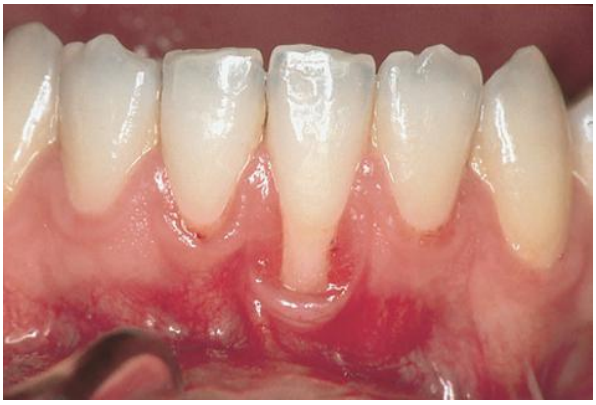


Fig. 46-5 Recession associated with localized plaque-induced inflammatory lesion.

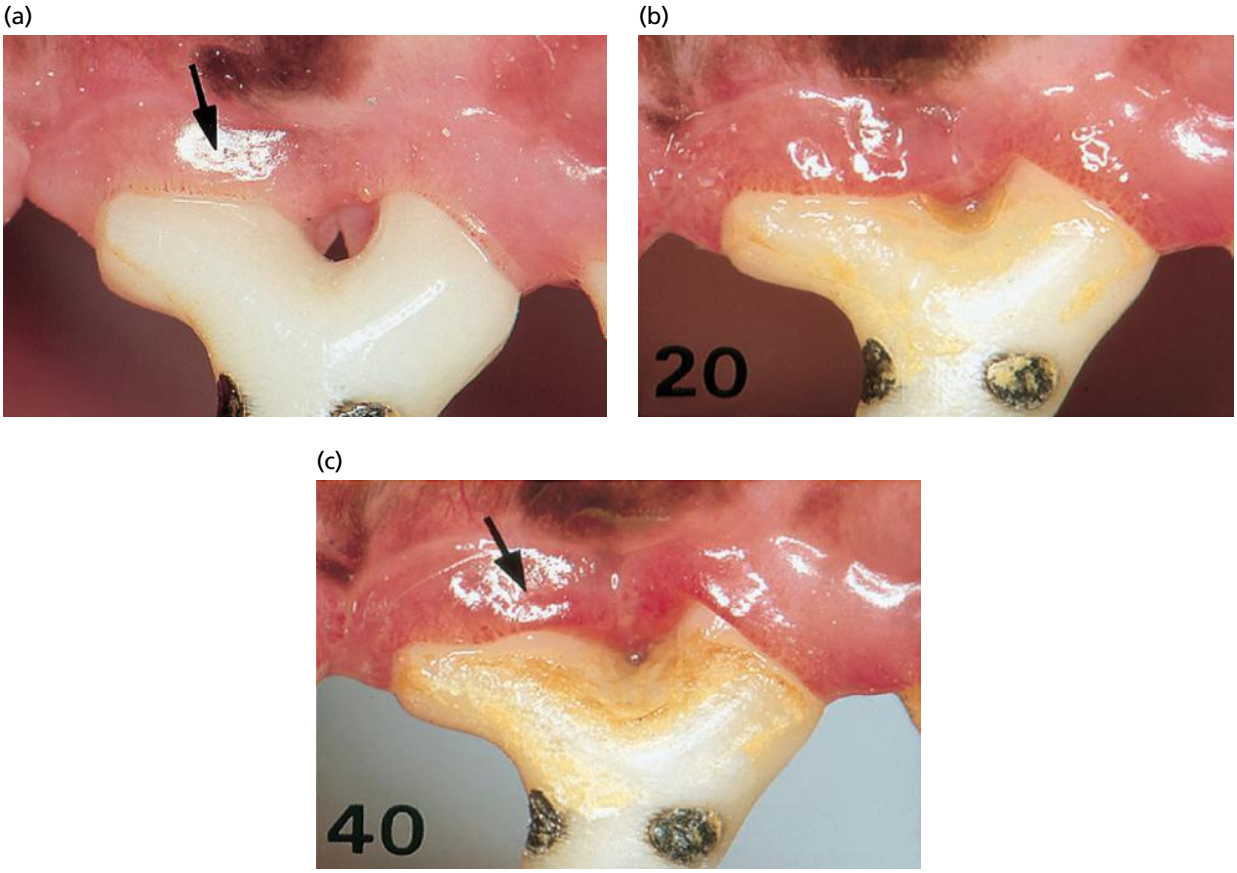


Fig. 46-6 Clinical photographs showing the development of a soft tissue recession as a result of plaque-induced inflammation in a Beagle dog. (a) Note the thin but healthy gingiva (arrow) at the start of the plaque accumulation period. (b) Pronounced clinical signs of inflammation are seen after 20 days. (c) After 40 days of no tooth cleaning, the gingival margin has receded (arrow).

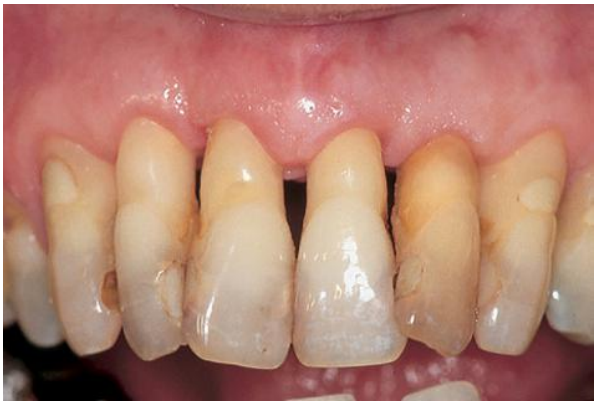


Fig. 46-7 Recessions associated with generalized forms of destructive periodontal disease. Recession of the soft tissue is found not only at the facial aspect of the teeth but also at proximal sites.

thin and delicate gingiva, on the other hand, the entire connective tissue portion may be engaged. Proliferation of epithelial cells from the oral as well as the dentogingival epithelium into the thin and degraded connective tissue may bring about a subsidence of the epithelial surface, which clinically becomes manifest as recession of the tissue margin (Baker & Seymour 1976) (Fig. 46-6).

3. *Recessions associated with generalized forms of destructive periodontal disease* (Fig. 46-7). The loss of periodontal support at proximal sites may result in compensatory remodeling of the support at the buccal/lingual aspect of the teeth, leading to an apical shift of the soft tissue margin (Serino *et al*. 1994). In addition, apical displacement of the soft tissue margin is an inevitable consequence of the resolution of periodontal lesions following treatment, and is independent of a non-surgical or a surgical treatment approach.

Cross-sectional studies showing that a correlation exists between the presence of recession defects and the height (width) of the gingiva (e.g. Stoner & Mazdyasna 1980; Tenenbaum 1982) have often been interpreted as evidence that a narrow zone of gingiva is a contributing factor in the development of soft tissue recessions (Fig. 46-8). It should be realized, however, that data derived from cross-sectional studies can neither prove nor disprove a cause–effect relationship. Consequently, the data reported from such studies may equally well be interpreted to demonstrate that the formation of a recession defect results in a reduced height of the gingiva. If this interpretation is valid, the rationale for increasing the height of the gingiva in an area *apical to an existing defect* as a method to prevent further recession may appear somewhat obscure.

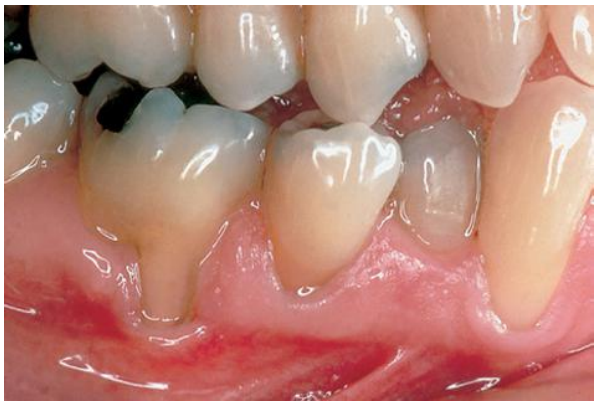


Fig. 46-8 Mandibular tooth segment with multiple buccal recessions illustrating the association proposed between recession depth and gingival height.

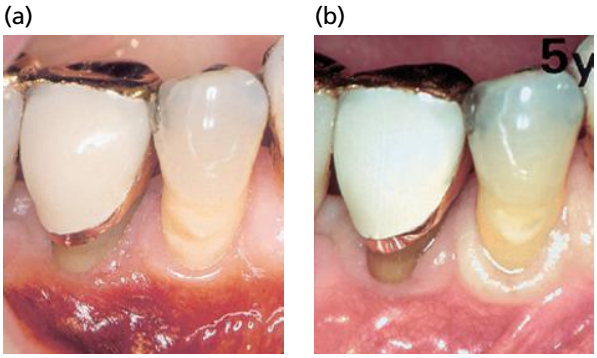


Fig. 46-10 (a) Mandibular canine and first premolar tooth region showing a very narrow zone of gingiva 6 months after surgical therapy. (b) No major change in the position of the soft tissue margin has occurred during a 5-year period despite the lack of attached gingiva.

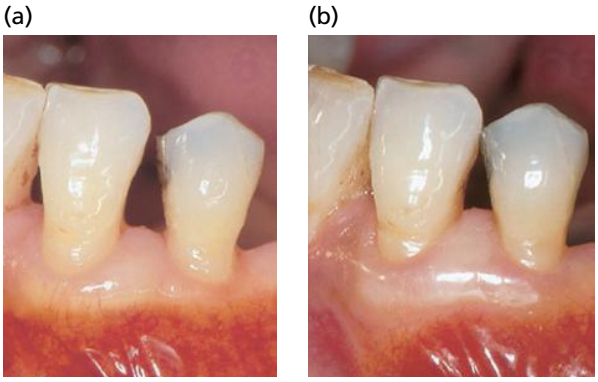


Fig. 46-9 (a) Clinical photograph of a canine and a first premolar in the mandibular jaw with <1 mm of attached portion of gingiva 6 months after surgical treatment. (b) Note the increase of the width of the gingiva at the facial aspect of the teeth and the more coronally positioned gingival margin 5 years later.

In fact, data obtained from prospective, longitudinal studies of patients showing areas with only a minimal zone of gingiva favor the conclusion that a certain quantity of gingiva is not essential for the preclusion of soft tissue recessions. Lindhe and Nyman (1980) examined the alterations of the position of the gingival margin following periodontal surgery in 43 patients with advanced periodontal breakdown. Following active treatment, all patients were recalled once every 3–6 months for maintenance care. The position of the soft tissue margin in relation to the CEJ was assessed on the facial aspect of all teeth after initial healing and after 10–11 years of maintenance. The results showed that both in areas with and without visible keratinized tissue after healing, a small coronal regrowth (≈1 mm) of the soft tissue margin had occurred during the period of maintenance. In other words, no recession was observed in this group of patients maintained on a careful prophylaxis program.

Dorfman *et al*. (1982) reported a 4-year follow-up study including 22 patients with bilateral tooth areas exhibiting gingival recession and lack of firmly attached marginal soft tissue. In conjunction with scaling and root planing, a free gingival graft was placed on one side, while the contralateral control side was treated by scaling and root planing only. All patients were recalled for prophylaxis once every 3–6 months during a 4-year period. The data obtained from the examinations of the non-grafted control areas revealed that no further recession of the soft tissue margin or loss of probing attachment had occurred despite the lack of attached marginal tissue. In fact, there was a slight gain of probing attachment. The authors concluded that recession sites without attached gingiva might not experience further attachment loss and recession if the inflammation is controlled. In a subsequent report, Kennedy *et al*. (1985) presented data on 10 patients who had not participated in the maintenance program for a period of 5 years. In these patients, plaque and clinical signs of inflammation as well as some further recession were noted at the 5-year examination as compared with the data obtained after termination of active treatment. However, except for the clinical signs of inflammation, which were more pronounced in non-grafted sites, no differences were observed between control sites with <1 mm or complete lack of attached gingiva and grafted sites.

The lack of relationship between the height of the gingiva and the development of soft tissue recession is further validated by results from longitudinal clinical studies (Schoo & van der Velden 1985; Kisch *et al*. 1986; Wennström 1987; Freedman *et al*. 1999). The prospective study by Wennström (1987) reported observations made at 26 buccal sites surgically deprived of all keratinized tissue. A baseline examination carried out 6 months after treatment revealed that these sites had regained a zone of gingiva which was, however, not attached or had only a minimal (<1 mm) portion attached to the underlying hard tissues (Figs. 46-9a, 46-10a). Adjacent teeth with a broad zone of attached gingiva were also included in the examinations. In most sites, the position of the soft tissue margin was maintained unchanged over 5 years

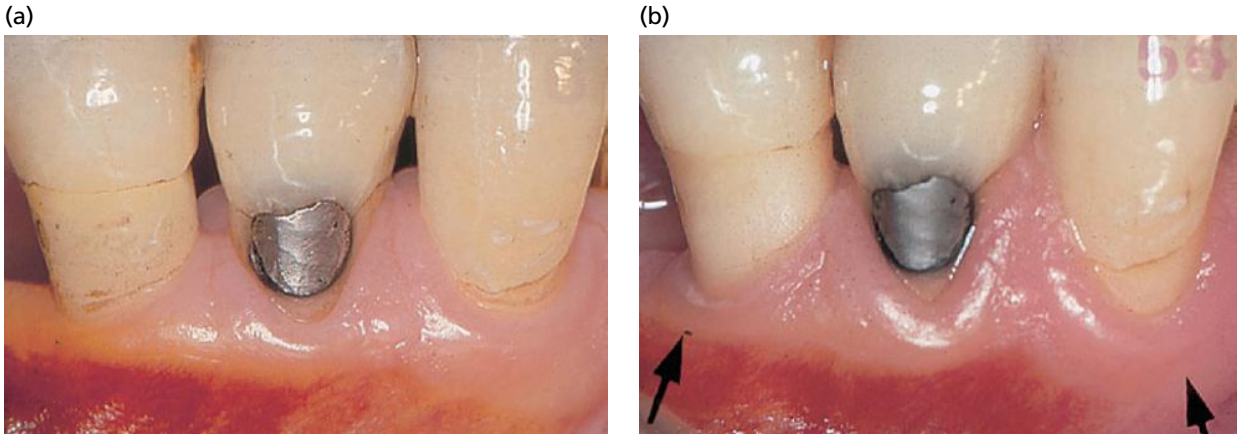


Fig. 46-11 Clinical photographs of the mandibular right canine–premolar tooth region in a patient showing several sites with apical displacement of the soft tissue margin during the 5 years of observation. (a) At the initial examination, the two premolars had <1 mm and the canine >1 mm of attached portion of gingiva. (b) After 5 years, recession and loss of keratinized tissue can be seen on the buccal aspect of the canine, which initially had a broad zone of gingiva (right arrow). The second premolar also showed further apical displacement of the soft tissue margin (left arrow).

(Figs. 44-9b, 44-10b). A further apical displacement of the soft tissue margin had occurred at two of 26 sites with no/a minimal attached portion of gingiva and at three of 12 adjacent control sites with a wide attached zone of gingiva. Since four of these five sites were found in one patient (Fig. 46-11), and all sites were free from clinical signs of inflammation, excessive toothbrushing was considered to be the causative factor, and following correction of the brushing technique no further progression of the recessions was observed. Furthermore, the development of soft tissue recession at the control sites resulted in a decreased gingival width, an observation that supports the concept that a narrow zone of gingiva apical to a localized recession is a consequence rather than a cause of the recession.

Conclusion: Marginal soft tissue recession is a common feature in populations with good as well as poor standards of oral hygiene. There is evidence to suggest that the predominant cause for localized recessions in young individuals is toothbrushing trauma, while periodontal disease may be the primary cause in older adults. Evidence from prospective longitudinal studies shows that the gingival height is not a critical factor for the prevention of marginal tissue recession, but that the development of a recession will result in loss of gingival height.

Marginal tissue recession and orthodontic treatment

Results from clinical and experimental research have documented that most forms of orthodontic therapy are innocuous to the periodontium (see Chapter 58). The clinician may observe, however, that some patients respond to frontal movements of incisors and lateral movements of posterior teeth by gingival recession and loss of attachment (Maynard & Ochsenbein 1975; Coatoam *et al*. 1981; Foushee *et al*. 1985) (Fig. 46-12). Based on the clinical observation that recession may occur during orthodontic therapy involving sites that have an "insufficient" zone of gingiva, it was suggested that a grafting procedure to increase the gingival dimensions should precede the initiation of orthodontic therapy in such areas (Boyd 1978; Hall 1981; Maynard 1987).

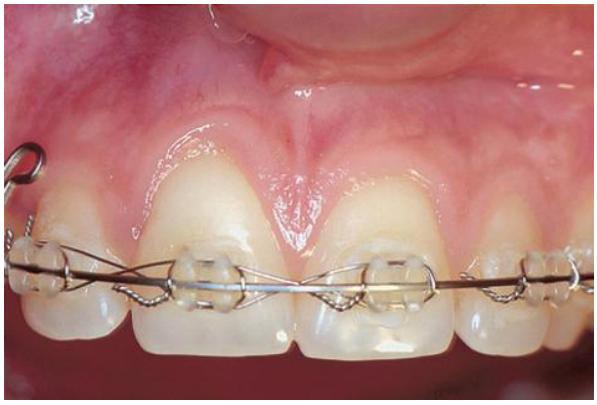


Fig. 46-12 Soft tissue recession at tooth 11 observed during the course of active orthodontic treatment.

As discussed previously, the presence of an alveolar bone dehiscence is a prerequisite for the development of a marginal tissue recession, that is a root dehiscence may establish an environment that is conducive for loss of gingival tissue. With respect to orthodontic therapy, this would imply that as long as a tooth is moved exclusively within the alveolar bone, soft tissue recession will not develop (Wennström *et al*. 1987). On the other hand, predisposing alveolar bone dehiscences may be induced by uncontrolled facial expansion of a tooth through the cortical plate, thereby rendering the tooth liable to the development of soft tissue recession. In this context it is interesting to note that experimental studies have shown that labial bone will reform in the area of a dehiscence when the tooth is retracted towards a proper positioning of the root within the alveolar process

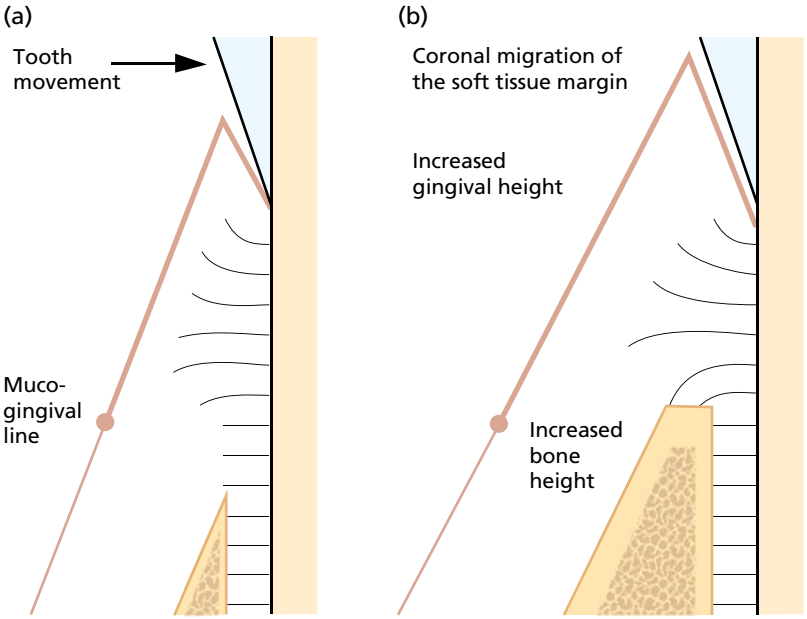


Fig. 46-13 (a) Schematic drawing illustrating alterations occurring in the marginal periodontal tissues following lingual movement of a tooth prominently positioned in the arch and having a bone dehiscence. (b) An increase in bone height and gingival height will be seen as well as a coronal migration of the soft tissue margin following lingual positioning of the tooth.

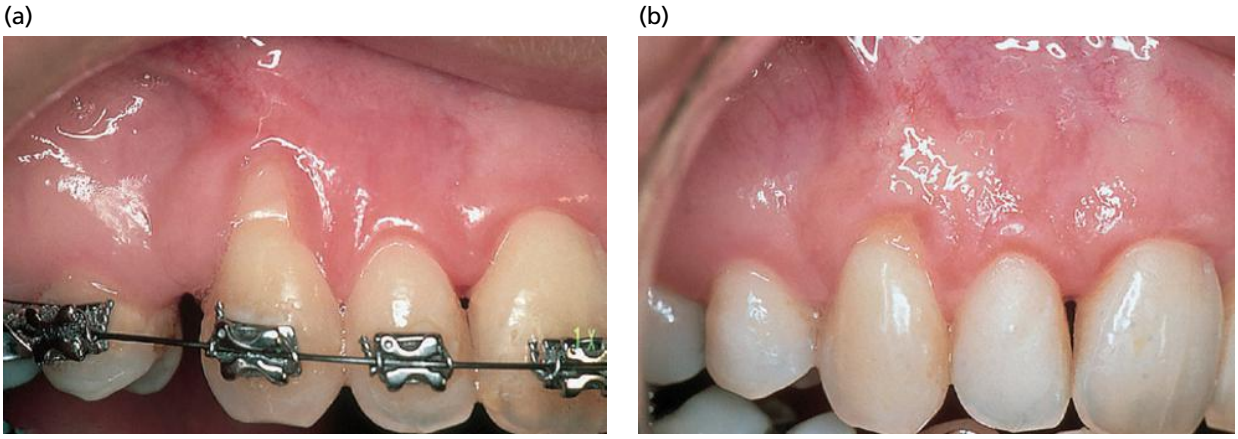


Fig. 46-14 (a) Prominently positioned tooth 13 showing soft tissue recession. (b) Same tooth following the completion of the orthodontic tooth movement. Note the reduction of the recession that has taken place as a consequence of the changed position of the tooth.

(Engelking & Zachrisson 1982; Karring *et al*. 1982) (Fig. 46-13). It is therefore likely that the reduction in recession seen at a previously prominently positioned tooth that has been moved into a more proper position within the alveolar process (Fig. 46-14) is also accompanied by bone formation.

Alterations occurring in gingival dimensions and marginal tissue position in conjunction with orthodontic therapy are related to the *direction of tooth movement*. Facial movement results in reduced facial gingival dimensions, while an increase is observed following lingual movement (Coatoam *et al*. 1981; Andlin-Sobocki & Bodin 1993). Recession of the labial gingival margin and loss of attachment were demonstrated in experimental studies in the monkey following either tipping and extrusion movements or bodily movements of incisors (Batenhorst *et al*. 1974; Steiner *et al*. 1981). However, similarly designed studies carried out in dogs (Karring *et al*. 1982; Nyman *et al*. 1982) and humans (Rateitschak *et al*. 1968) failed to demonstrate that labial tooth movement is accompanied by marginal tissue recession and attachment loss. The conflicting results may be related to differences with respect to, for example, (1) the amount of labial tooth displacement, (2) the presence/absence of plaque and gingival inflammation in the regions subjected to tooth movement, and/or (3) differences in gingival dimensions. Steiner *et al*. (1981) speculated on mechanisms by which gingival tissue could be lost as a result of labial tooth movement and suggested that tension in the marginal tissue created by the forces applied to the teeth could be an important factor. If this hypothesis is valid, obviously the volume (thickness) of the gingival tissue at the pressure side, rather than its apicocoronal height, would determine whether or not marginal tissue recession develops during orthodontic therapy.

Support for this hypothesis is obtained from an experimental study in monkeys (Wennström *et al*. 1987) in which teeth were orthodontically moved into areas with varying thickness and quality of the marginal soft tissue. Following extensive bodily

movement of incisors in a labial direction through the alveolar bone (Fig. 46-15), most teeth showed a small apical displacement of the soft tissue margin but no loss of connective tissue attachment (Fig. 46-16). In other words, the apical displacement of the gingival margin was the result of a reduced height of the free gingiva (Fig. 46-17), which in turn may be related to tension ("stretching") in the soft tissues during the facial tooth movement and reduced buccolingual tissue thickness. Similar to results presented by Foushee *et al*. (1985) from a study in humans, no relationship was found between the initial apicocoronal width (height) of the gingiva and the degree of apical displacement of the soft tissue margin during orthodontic therapy. Thus, the findings do not lend support to the concept of a certain zone of gingiva as

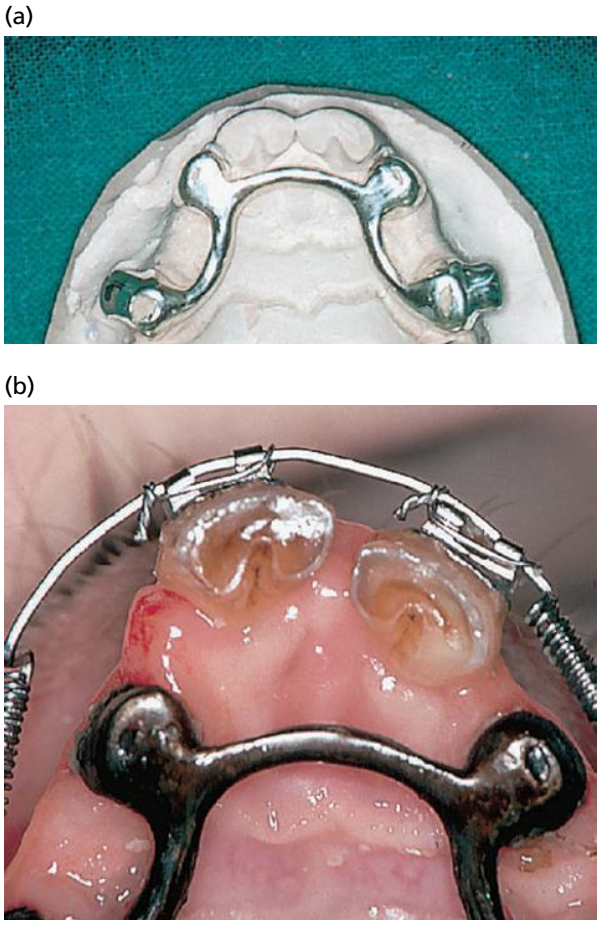


Fig. 46-15 Occlusal view of the maxillary jaw in a monkey showing the position of the central incisors before (a) and after (b) bodily movement in the labial direction. The canines and lateral incisors were joined in an individual fabricated silver splint and used as anchorage teeth.

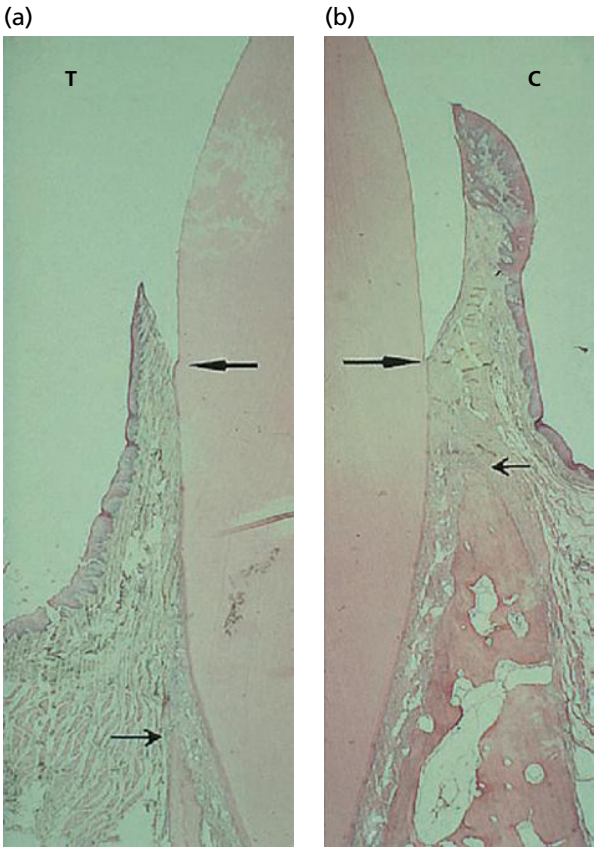


Fig. 46-17 Histologic specimens showing (a) reduced alveolar bone height at an incisor bodily moved in the labial direction and (b) normal alveolar bone height at a non-moved control tooth. Note the maintained level of connective tissue attachment and the reduced height of the free gingiva at the labially displaced incisor (a). Large arrows indicate the position of the cementoenamel junction and small arrows the position of the alveolar bone crest.

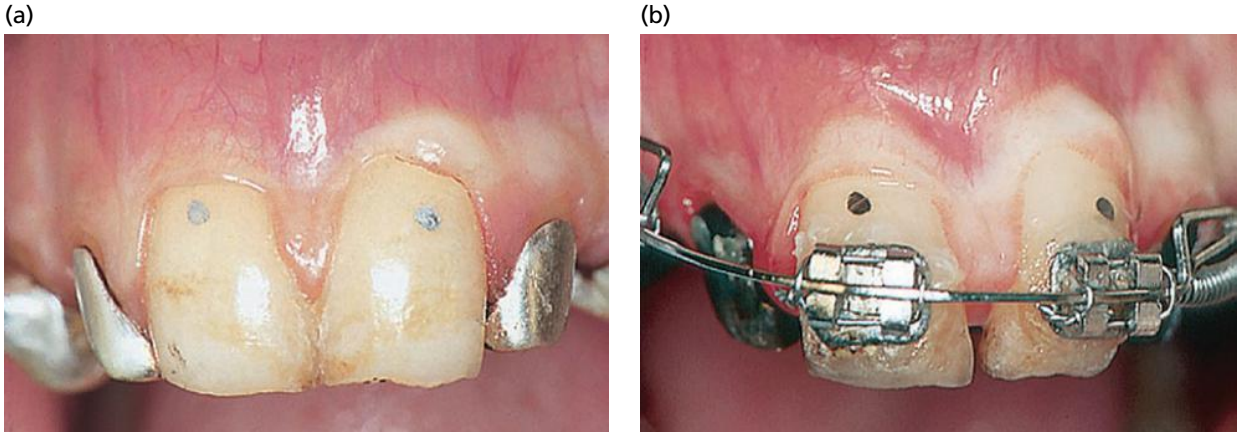


Fig. 46-16 Buccal aspect of the central incisors shown in Fig. 44-15 before (a) and after (b) the labial tooth movement. No obvious change in the location of the gingival margin has occurred despite the pronounced labial displacement of the incisors.

essential for the prevention of recession during orthodontic therapy, but rather corroborate observations reported by Coatoam *et al*. (1981) that the integrity of the periodontium can also be maintained during orthodontic therapy in areas which have only a minimal zone of gingiva.

In the experimental studies by Steiner *et al*. (1981) and Wennström *et al*. (1987), it was observed that teeth experiencing loss of connective tissue attachment when orthodontically moved facially, showed obvious clinical signs of inflammation throughout the experimental period. Since it has been demonstrated that, in the presence of plaque-induced suprabony lesions, orthodontic forces generating bodily tooth movement are not capable of causing accelerated destruction of the connective tissue attachment (Ericsson *et al*. 1978), a decreased buccolingual dimension of the border tissue due to "stretching" of the facial gingiva may have favored the destructive effect of the plaque-associated inflammatory lesion. This assumption is validated by the observations that, in the presence of plaque-induced gingivitis, a thin marginal soft tissue is more susceptible to complete breakdown than a thick one (Baker & Seymour 1976). Furthermore, no difference in attachment loss was observed at plaque-infected teeth that were bodily moved *within the alveolar bone*, irrespective of the type of bordering soft tissue (gingiva or lining mucosa) (Wennström *et al*. 1987). Hence, the *thickness rather than the quality* of the marginal soft tissue on the pressure side of the tooth is the determining factor for the development of the recession. The interpretation is supported by findings of clinical studies in humans analyzing factors of importance for the development of recessions during labial movement of mandibular incisors. Melsen and Allais (2005) found that gingival inflammation and a "thin gingival biotype" were significant predictors for gingival recession, and Yared *et al*. (2006) reported that 93% of the teeth that developed recession had a gingival thickness of <0.5 mm. Hence, the observations made in the studies discussed strongly emphasize the importance of adequate infection control during orthodontic treatment.

Conclusion: The clinical implication of the results from the studies discussed is that labial tooth movement should be preceded by careful examination of the dimensions of the tissues covering the facial aspect of the teeth to be moved. As long as a tooth can be moved within the envelope of the alveolar process, the risk of harmful side effects on the marginal tissue is minimal, irrespective of the dimensions and quality of the soft tissue surrounding the tooth. If, however, the tooth movement is expected to result in the establishment of an alveolar bone dehiscence, the volume (thickness) of the covering soft tissue should be considered as a factor that may influence the development of soft tissue recession during, as well as after, the phase of active orthodontic therapy. A thin gingiva may serve as a *locus minorus resistentia* to developing soft tissue defects in the presence of plaque-induced inflammation or toothbrushing trauma.

Gingival dimensions and restorative therapy

The placement of restoration margins subgingivally may not only create a direct operative trauma to the tissues (Donaldson 1974), but may also facilitate subgingival plaque accumulation, with resultant inflammatory alterations in the adjacent gingiva and recession of the soft tissue margin (Lang 1995; Parma-Benfenati *et al*. 1985; Günay *et al*. 2000). Over a 10-year period, Valderhaug (1980) evaluated longitudinally the soft tissue alterations taking place at facial sites of 286 teeth with subgingivally or supragingivally placed crown margins in 82 patients. The re-examination performed 1 year after insertion of the restorations revealed that the gingivae at teeth with subgingival restoration margins were more commonly inflamed than at those with supragingivally placed borders. Of the 150 teeth which had the facial crown margin located subgingivally at the time of cementation, 40% already showed supragingival exposure of the crown margin after 1 year, and at the 10-year examination as many as 71% had become supragingivally positioned due to recession of the soft tissue margin. Compared to teeth with supragingivally placed crown margins, the amount of recession and clinical attachment loss was greater at sites with subgingivally placed restoration margins.

Stetler and Bissada (1987) evaluated the periodontal conditions at teeth with subgingivally placed restoration margins and varying apicocoronal gingival height and found that teeth having a narrow (<2 mm) band of gingiva showed more pronounced clinical signs of inflammation than restored teeth with a wide gingival zone, but that there was no difference in loss of probing attachment. However, if subgingivally placed restorations favor plaque accumulation and the adjacent gingiva is thin, there may be a potential risk for the development of soft tissue recession. In fact, an experimental study in the Beagle dog (Ericsson & Lindhe 1984), in which metallic strips were inserted subgingivally in areas with varying widths of gingiva, showed that in sites with a thin gingiva, recession was a more likely consequence of the combined tissue trauma caused by the insertion of the strip and subsequent plaque accumulation during a 6-month period than in sites with a thick gingival margin. Accordingly, if recession is to be prevented, either the plaque-control standard has to be improved or the *thickness* of the gingival margin has to be increased. However, an increased gingival dimension *per se* will not prevent the apical propagation of the plaque-associated lesion and the associated loss of periodontal attachment.

The maintenance of stability and function of a load-carrying dental implant is dependent on a

well-functioning soft tissue barrier, established at the transmucosal passage of the implant unit (Berglundh 1993). In this respect, concern has been expressed that the lining mucosa may not provide a sufficient barrier function (Zarb & Schmitt 1990; Warrer *et al*. 1995), and that "keratinized tissue should be created with mucogingival surgical techniques prior to implant placement if not present in adequate amounts" (Meffert *et al*. 1992). With reference to the study by Lang and Löe (1972) on the relationship between width of keratinized mucosa and soft tissue health at teeth, an "adequate" dimension at dental implants was usually defined as ≥2 mm of keratinized mucosa. However, a reported prevalence of implant sites bordered by lining mucosa of 46–74% (e.g. Adell *et al*. 1986; Apse *et al*. 1991; Mericske-Stern *et al*. 1994), but a very high long-term success rate of implant therapy (e.g. Adell *et al*. 1990; Cochran 1996; Lekholm *et al*. 1999), give reasons to question the importance of an "adequate" width of keratinized mucosa for the success of implant therapy.

In a recent systematic review, the question regarding whether or not keratinized mucosa around dental implants is necessary to maintain health and tissue stability was addressed (Wennström & Derks 2012). According to this review, evidence suggests that with good oral hygiene habits, peri-implant soft tissue health can be maintained even when keratinized mucosa is lacking. Soft tissue recession mainly occurred during the early phase of follow-up (6–12 months after prosthesis delivery) and might be more pronounced at sites without keratinized mucosa. On the other hand, there is no evidence for a long-term effect of "inadequate" keratinized mucosa on the development of soft tissue recession, peri-implant bone loss, or implant loss. Also, there is a lack of evidence supporting the concept that grafting procedures aimed at increasing the amount of keratinized mucosa improve the outcomes of implant therapy. However, even if no studies have assessed patient-centered outcomes with regard to oral hygiene performance, one has to consider that some patients might experience pain and discomfort during brushing at implant sites facing the lining mucosa, which in turn may hamper adequate cleaning. In such cases, one might consider a grafting procedure to establish a firmer marginal tissue of keratinized mucosa.

Conclusion: Subgingival placement of the margin of a restoration is likely to result in soft tissue recession over time. Experimental and clinical data suggest that the thickness of the marginal gingiva, but not the apicocoronal width of the gingiva, may influence the magnitude of recession taking place as a result of direct mechanical trauma during tooth preparation and bacterial plaque retention. Evidence suggests that with good oral hygiene, peri-implant soft tissue health can be maintained even when keratinized mucosa is lacking. There is no evidence in support of an "adequate" width of keratinized mucosa as a superior protective soft tissue barrier around dental implants. However, it is recommended to maximize efforts to preserve existing keratinized mucosa during implant treatment procedures.

Indications for gingival augmentation

Scientific data obtained from well-controlled clinical and experimental studies have unequivocally demonstrated that the apicocoronal width of gingiva and the presence of an attached portion of gingiva are not of decisive importance for the maintenance of gingival health and the height of the periodontal tissues. Consequently, the presence of a narrow zone of gingiva *per se* cannot justify surgical intervention (Lang & Karing 1994; Proceedings of the 1996 World Workshop in Periodontics 1996). However, gingival augmentation should be considered in situations where, for example, the patient experiences discomfort during toothbrushing and/or chewing due to interference from a lining mucosa at teeth or implants. Furthermore, when orthodontic tooth movement is planned and the final positioning of the tooth can be expected to result in an alveolar bone dehiscence, an increase of the *thickness* of the covering soft tissue may reduce the risk for development of soft tissue recession. An increase of the *thickness* of the gingiva may also be considered when subgingival restorations are placed in areas with a thin marginal tissue.

Gingival augmentation procedures

Gingival augmentation operations comprise a number of surgical techniques, the majority of which have been developed mainly on an empiric basis. The earliest of these techniques are the "vestibular extension operations", which were designed mainly with the objective of extending the depth of the vestibular sulcus (Bohannan 1962a, b). In recent years, however, pedicle or free soft tissue grafts have become the most commonly used techniques in the management of "insufficient" gingival dimensions, because of higher predictability of the healing result.

Vestibular/gingival extension procedures

The "denudation techniques" included the removal of all soft tissue within an area extending from the gingival margin to a level apical to the mucogingival junction, leaving the alveolar bone completely exposed (Ochsenbein 1960; Corn 1962; Wilderman 1964) (Fig. 46-18). Healing following this type of treatment resulted often in an increased height of the gingival zone, although in some cases only a very limited effect was observed. However, the exposure of alveolar bone produced severe bone resorption with permanent loss of bone height (Wilderman *et al*. 1961; Costich & Ramfjord 1968). In addition, the recession of marginal gingiva in the surgical area often exceeded the gain of gingiva obtained in the

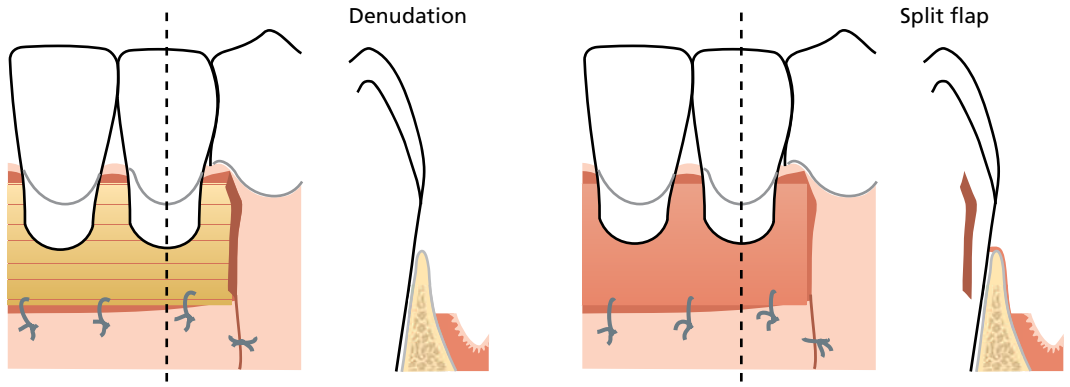


Fig. 46-18 Use of vestibular extension operations for increasing the width of the gingiva involves the production of a wound extending from the gingival margin to a level some millimeters apical to the mucogingival junction. With the "denudation" technique, all soft tissue is removed, leaving the alveolar bone exposed. With the "split-flap" procedure, only the superficial portion of the oral mucosa is removed, leaving the bone covered with connective tissue.

apical portion of the wound (Carranza & Carraro 1963; Carraro *et al*. 1964). Due to these complications and severe postoperative pain for the patient, the use of the "denudation technique" can hardly be justified.

With the "periosteal retention" procedure or "split-flap" procedure (Fig. 46-18), only the superficial portion of the oral mucosa within the wound area was removed, leaving the bone covered by periosteum (Staffileno *et al*. 1962; Wilderman 1963; Pfeifer 1965; Staffileno *et al*. 1966). Although the preservation of the periosteum implies that less severe bone resorption will occur than following the "denudation technique", loss of crestal bone height was also observed following this type of operation unless a relatively thick layer of connective tissue was retained on the bone surface (Costich & Ramfjord 1968). If a thick layer was not secured, the periosteal connective tissue tended to undergo necrosis and the subsequent healing closely resembled that following the "denudation technique" described above.

Other described gingival extension procedures may be considered as modifications of the "denudation" and "split-flap" techniques or combinations of these procedures. The apically repositioned flap procedure (Friedman 1962), for instance, involved the elevation of soft tissue flaps and their displacement during suturing in an apical position, often leaving 3–5 mm of alveolar bone denuded in the coronal part of the surgical area. This resulted in the same risk for extensive bone resorption as with other "denudation techniques". It was proposed by Friedman (1962) that a post-surgical increase of the width of the gingiva can be predicted with the "apically repositioned flap", but several studies indicated that the presurgical width most often was retained or was only slightly increased (Donnenfeld *et al*. 1964; Carranza & Carraro 1970).

The vestibular/gingival extension procedures referred to were based on the assumption that it is the frictional forces encountered during mastication that determine the presence of a keratinized tissue adjacent to the teeth (Orban 1957; Pfeifer 1963). Therefore, it was believed that by the displacement of muscle attachments and the extension of vestibular depth, the regenerating tissue in the surgical area would be subjected to physical impacts and adapt to the same functional requirements as those met by "normal" gingiva (Ivancie 1957; Bradley *et al*. 1959; Pfeifer 1963). Later studies, however, showed that the characteristic features of the gingiva are determined by inherent factors in the tissue rather than being the result of functional adaptation and that the differentiation (keratinization) of the gingival epithelium is controlled by morphogenetic stimuli from the underlying connective tissue (see Chapter 1).

Grafting procedures

The gingival and palatal soft tissues will maintain their original characteristics after transplantation to areas of the alveolar mucosa (see Chapter 1). Hence, the use of transplants offers the potential to predict the post-surgical result. The type of transplants used can be divided into (1) pedicle grafts, which maintain their connection to the donor site after placement at the recipient site (Fig. 46-19), and (2) free grafts that are completely deprived of their connection with the donor area (Fig. 46-20). For gingival augmentation, free grafts from the palate have been used most commonly (Haggerty 1966; Nabers 1966; Sullivan & Atkins 1968a; Hawley & Staffileno 1970; Edel 1974). As an alternative to the use of a mucosal graft from the palate, various allogenic graft materials, for example acellular freeze-dried dermal matrix (ADM) (Wei *et al*. 2000; Harris 2001) and human fibroblast-derived dermal substitute (McGuire & Nunn 2005) may be used, but the increase in the width of keratinized tissue following the use of these grafts may not be as predictable as with the use of autogenous grafts. Based on a systematic review of soft tissue augmentation techniques, Thoma *et al.* (2009) concluded that (1) there is evidence for an increased width of keratinized tissue and attached gingiva following apically repositioned flap/vestibuloplasty; (2) the addition of an autogenous tissue graft significantly increases the width of attached gingiva; and (3) the use of allogenic grafts produces dimensional increases in keratinized

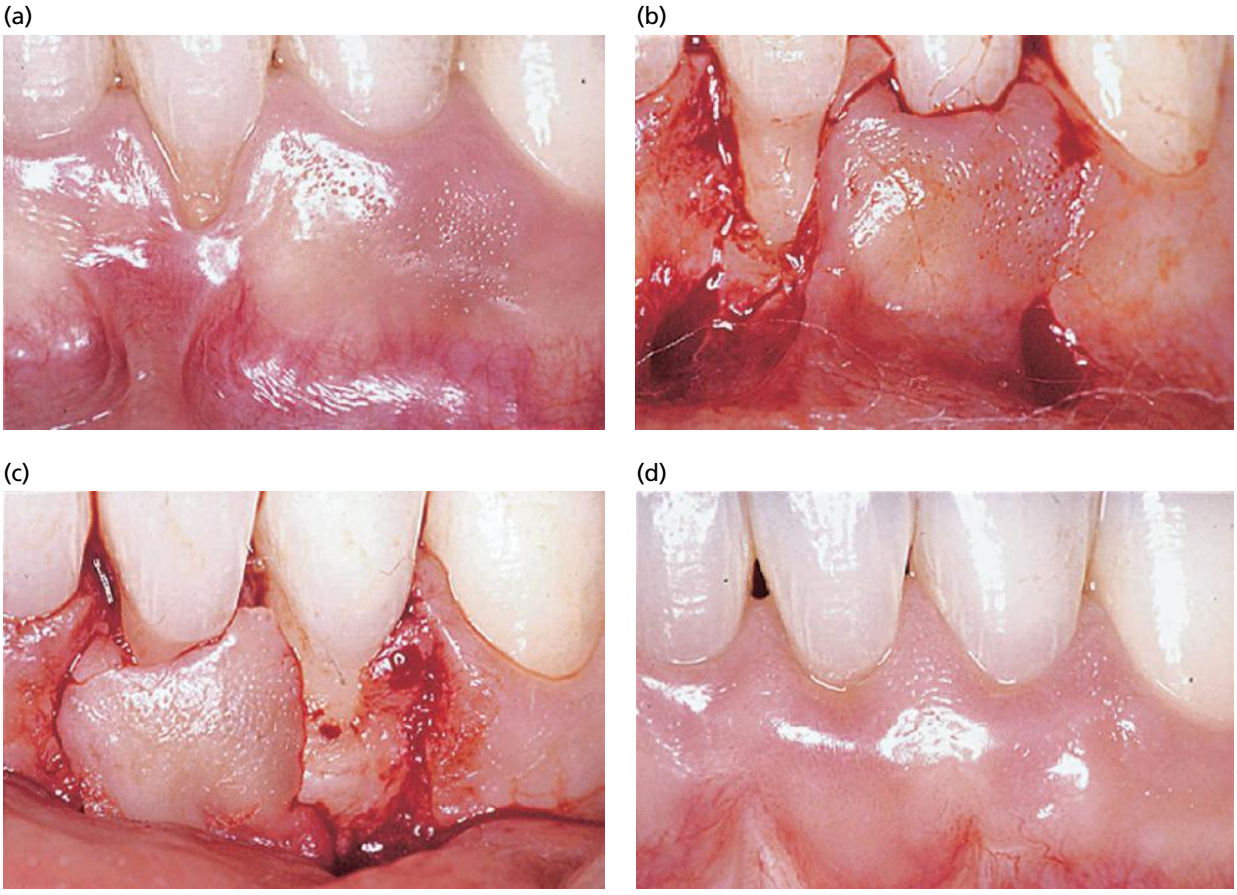


Fig. 46-19 Pedicle graft procedure for gingival augmentation. (a) Lower central incisor with facial soft tissue recession associated with high attachment of a frenulum. (b) Frenulum is released and a split flap of keratinized tissue is dissected from the area of the neighboring tooth. (c) Mobilized soft tissue flap is laterally moved and secured in position at the recipient site. (d) Healing result 1 year post-treatment shows the establishment of a broad zone of keratinized tissue without interfering frenulum.

tissue similar to those produced with autogenous tissue. More recently, a collagen matrix of porcine origin (Mucograft®) was shown to be as effective and predictable as the free autogenous graft in increasing the band of keratinized tissue at teeth and implants, but with significantly lower patient morbidity (Sanz *et al.* 2009; Nevins *et al.* 2011; Lorenzo *et al.* 2012). With the use of the alternative graft materials the preparation of the recipient site is similar to that using an autogenous graft.

Technique

1. The surgical procedure is initiated with the preparation of the recipient site (Fig. 46-20a, b). A periosteal bed free from muscle attachment and of sufficient size is prepared by sharp dissection. The partial-thickness flap is displaced apically and sutured.
2. In order to ensure that a graft of sufficient size and proper contour is removed from the donor area, usually the palatal mucosa in the region of the premolars, it is recommended to produce a foil template over the recipient site. The template is transferred to the donor site where it is outlined by a shallow incision (Fig. 46-20c). A graft with a thickness of approximately 1.5–2 mm is then dissected from the donor area (Fig. 46-20d). It is advocated to place the sutures in the graft before it is cut completely free from the donor area since this may facilitate its transfer to the recipient site.
3. The graft is immediately transferred to the prepared recipient bed and sutured (Fig. 46-20e). In order to immobilize the graft at the recipient site, the sutures must be placed in the periosteum or the adjacent attached gingiva. After suturing, pressure is exerted against the graft for 5 minutes in order to eliminate blood and exudate from between the graft and the recipient bed. The palatal wound is protected with a periodontal dressing. To retain the dressing, a stent usually has to be used.
4. The sutures and periodontal dressing are removed after 1–2 weeks.

For a description of the pedicle graft procedure, see "Root coverage procedures".

Healing following gingival augmentation procedures

Vestibular/gingival extension procedures

Since the specificity of the gingiva is determined by some inherent factor in the tissues, the postoperative results of vestibular extension procedures depend on

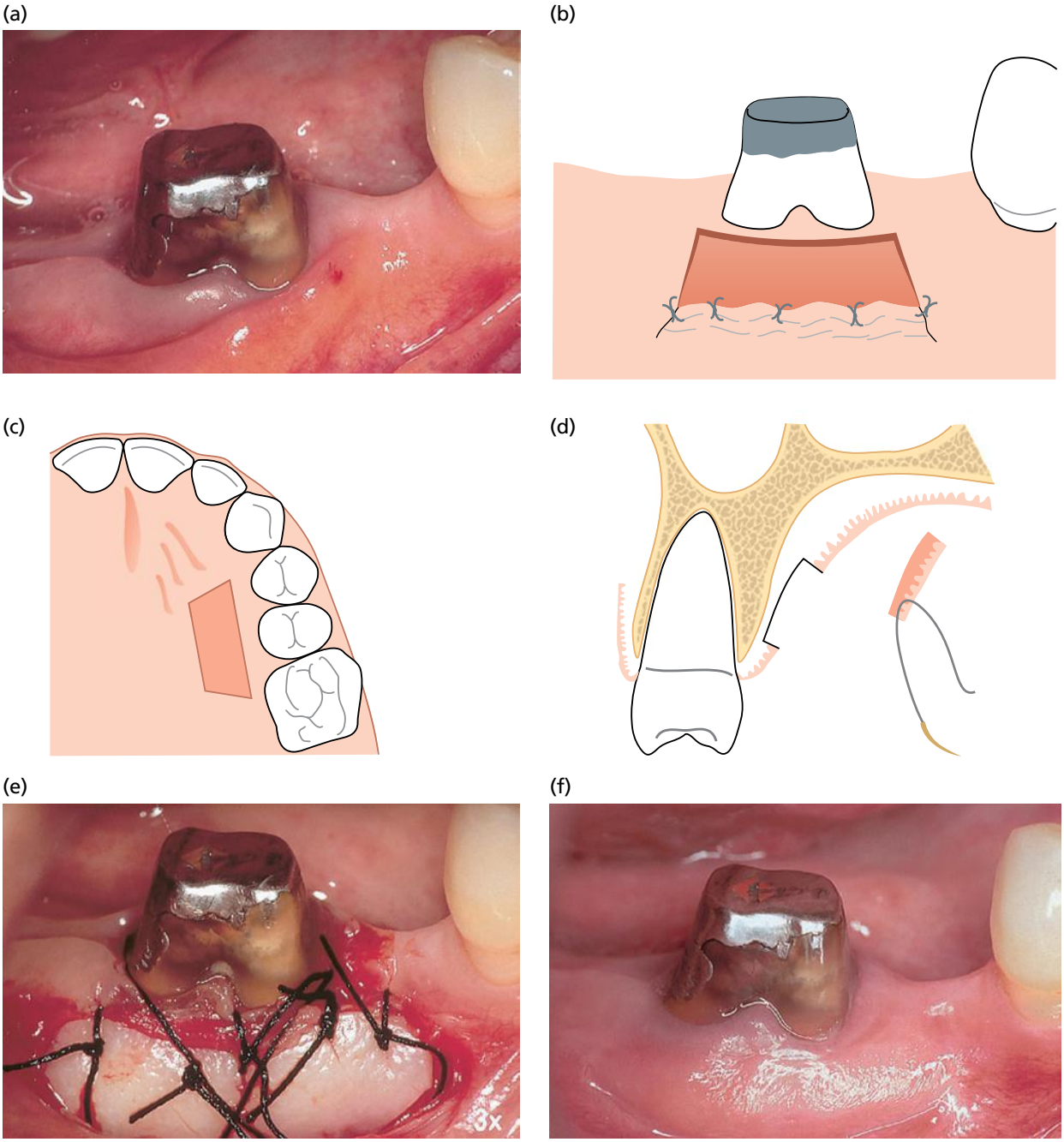


Fig. 46-20 Grafting procedure for gingival augmentation. (a) Lower molar at which the patient experiences discomfort during toothbrushing due to interfering lining mucosa and high attachment of a frenulum. The decision was made to displace the attachment of the frenulum apically and augment the gingival zone through the placement of a free graft. (b) Partial-thickness flap is dissected to prepare a recipient bed. The flap is displaced apically and sutured. (c, d) Graft with a thickness of 1.5–2 mm and of sufficient size and contour (a foil template of the recipient site may be used) is dissected from the palatal mucosa in the region of the premolars. (e) Graft is immediately transferred to the prepared recipient bed and anchored by sutures to secure a close adaptation of the graft to the recipient bed. (f) Periodontal dressing is applied to protect the graft. Following healing, a broad zone of keratinized tissue has been established.

the degree to which the various tissues contribute to the formation of granulation tissue in the wound area (Karring *et al*. 1975). Following the "denudation" or "split-flap technique", the wound area is filled with granulation tissue derived from the periodontal ligament, the tissue of the bone marrow spaces, the retained periosteal connective tissue, and the surrounding gingiva and lining mucosa (Fig. 46-21). The degree of bone resorption induced by the surgical trauma influences the relative amount of granulation tissue that grows into the wound from these various tissue sources. The resorption of crestal bone exposes varying amounts of the periodontal ligament tissue in the marginal area, allowing granulation tissue from the periodontal ligament to fill out the coronal portion of the wound. The greater the bone loss, the greater is the portion of the wound that becomes filled with granulation tissue from the periodontal ligament. This particular tissue possesses the capability to induce keratinization of the covering

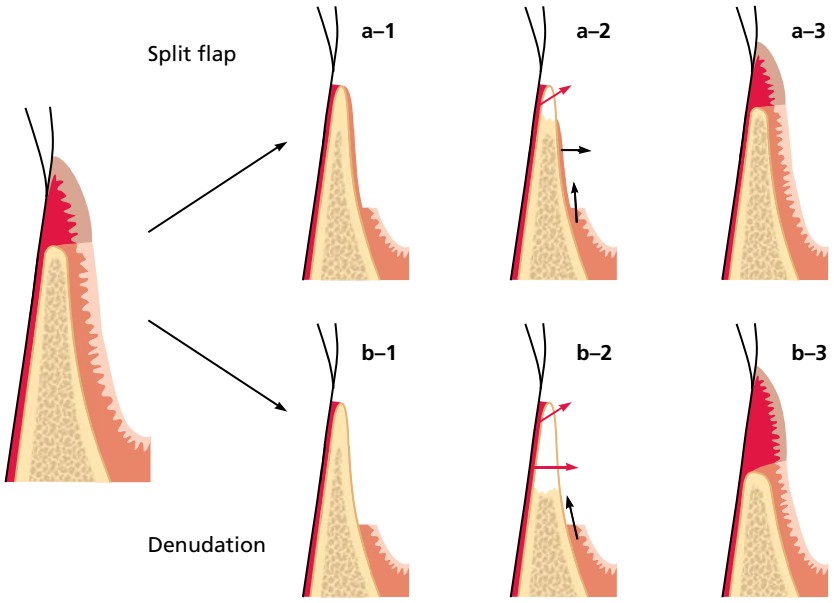


Fig. 46-21 Schematic drawing illustrating different stages of healing following the "split-flap" (a) and "denudation" (b) techniques. Cells from the oral mucosa, bone, and periodontal ligament (arrows) participate in granulation tissue formation. Due to the difference in the degree of bone resorption (a-2, b-2), a larger area of the coronal portion of the wound is filled with granulation tissue from the periodontal ligament following "denudation" than following the "split-flap" technique. Since granulation tissue from the periodontal ligament possesses the ability to induce a keratinized epithelium, "denudation" usually results in a wider zone of keratinized tissue than is the case following the "split-flap" technique (a-3, b-3).

epithelium. This means that the widening of the keratinized tissue following "denudation" and "split-flap" operations is achieved at the expense of a reduced bone height. The "denudation technique" usually results in more bone loss than the "split-flap technique". Therefore, a greater amount of granulation tissue with the capability of inducing a keratinized epithelium develops in the marginal area following the "denudation technique" than following the "split-flap technique". This is in accordance with the clinical observation that the "denudation technique" usually is superior to the "split-flap technique" in terms of increasing the width of keratinized tissue (Bohannan 1962a, b).

In a clinical study by Wennström (1983), periodontal pockets were eliminated by the use of a "gingivectomy" or a "flap" procedure, both of which involved the complete removal of the keratinized tissue. In the "gingivectomy" procedure, the wounded area was left to heal by second intention, while in the "flap" procedure the alveolar mucosa was repositioned to achieve complete coverage of the surgically exposed alveolar bone (Figs. 46-22a, 46-23a). Irrespective of the surgical technique used, healing resulted in the reformation of keratinized tissue, the width of which, however, was greater following the "gingivectomy" procedure than following the "flap" procedure (Figs. 46-22b, 46-23b). The gingiva was formed because granulation tissue from the periodontal ligament, with the capacity to induce a keratinized epithelium, had proliferated coronally along the root surface. This granulation tissue formation was obviously favored by a more pronounced bone resorption during the healing following the "gingivectomy" procedure.

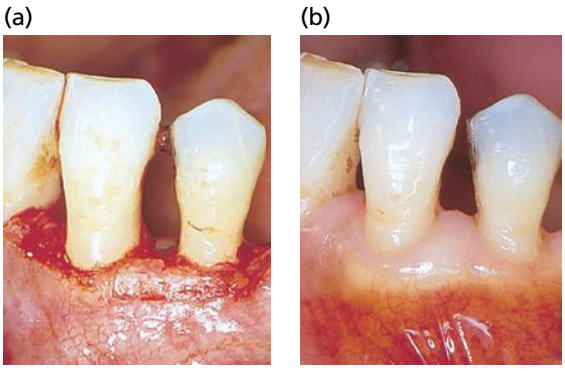


Fig. 46-22 (a) Clinical photograph of the buccal aspect of a canine and a premolar following the removal of the entire zone of gingiva by a gingivectomy procedure. (b) Healing result 9 months after surgery shows regained keratinized tissue.

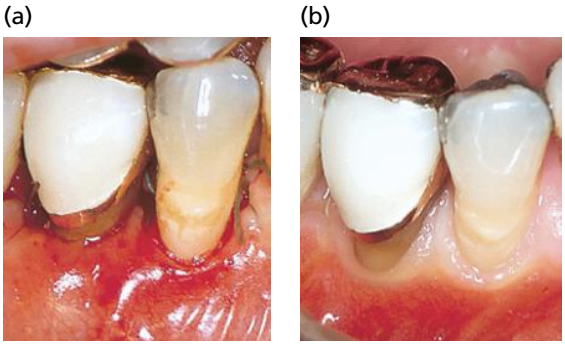


Fig. 46-23 Clinical photographs of a tooth region subjected to excision of the entire zone of gingiva by a flap procedure. (a) Alveolar mucosa has been displaced coronally to achieve complete coverage of the surgically exposed alveolar bone. (b) Healing has resulted in the reformation of a narrow zone of gingiva on the buccal aspect of the teeth, 9 months post surgery.

It can be concluded that the success or failure in extending the width of keratinized tissue by the "denudation" or "split-flap" techniques rests with the origin of the granulation tissue, which is related to the extent of bone loss induced by the surgical trauma. This in turn means that the result with respect to increasing the gingival width by methods involving periosteal exposure or denudation of the alveolar bone is unpredictable. The use of such methods is therefore not justified in periodontal therapy. The procedures discussed merely represent examples of how lack of knowledge about basic biologic principles may lead to the development of inappropriate therapeutic methods.

Grafting procedures

Healing of free soft tissue grafts placed entirely on a connective tissue recipient bed were studied in monkeys by Oliver *et al*. (1968) and Nobuto *et al*. (1988). According to these authors, healing can be divided into three phases (Fig. 46-24):

1. *Initial phase (from 0 to 3 days)*. During these first days of healing, a thin layer of exudate is present between the graft and the recipient bed. During this period the grafted tissue survives with an avascular "plasmatic circulation" from the recipient bed. Therefore, it is essential for the survival of the graft that a close contact is established to the underlying recipient bed at the time of operation. A thick layer of exudate or a blood clot may hamper the "plasmatic circulation" and result in rejection of the graft. The epithelium of the free graft degenerates early in the initial healing phase, and subsequently is desquamated. In placing a graft over a recession, part of the recipient bed will be the avascular root surface. Since the graft is dependent on the nature of its bed for diffusion of plasma and subsequent revascularization, the utilization of free grafts in the treatment of gingival recessions involves a great risk of failure. The area of the graft over the avascular root surface must receive nutrients from the connective tissue bed that surrounds the recession. Thus, the amount of tissue that can be maintained over the root surface is limited by the size of the avascular area.
2. *Revascularization phase (from 2 to 11 days)*. After 4–5 days of healing, anastomoses are established between the blood vessels of the recipient bed and those in the grafted tissue. Thus, the circulation of blood is re-established in the pre-existing blood

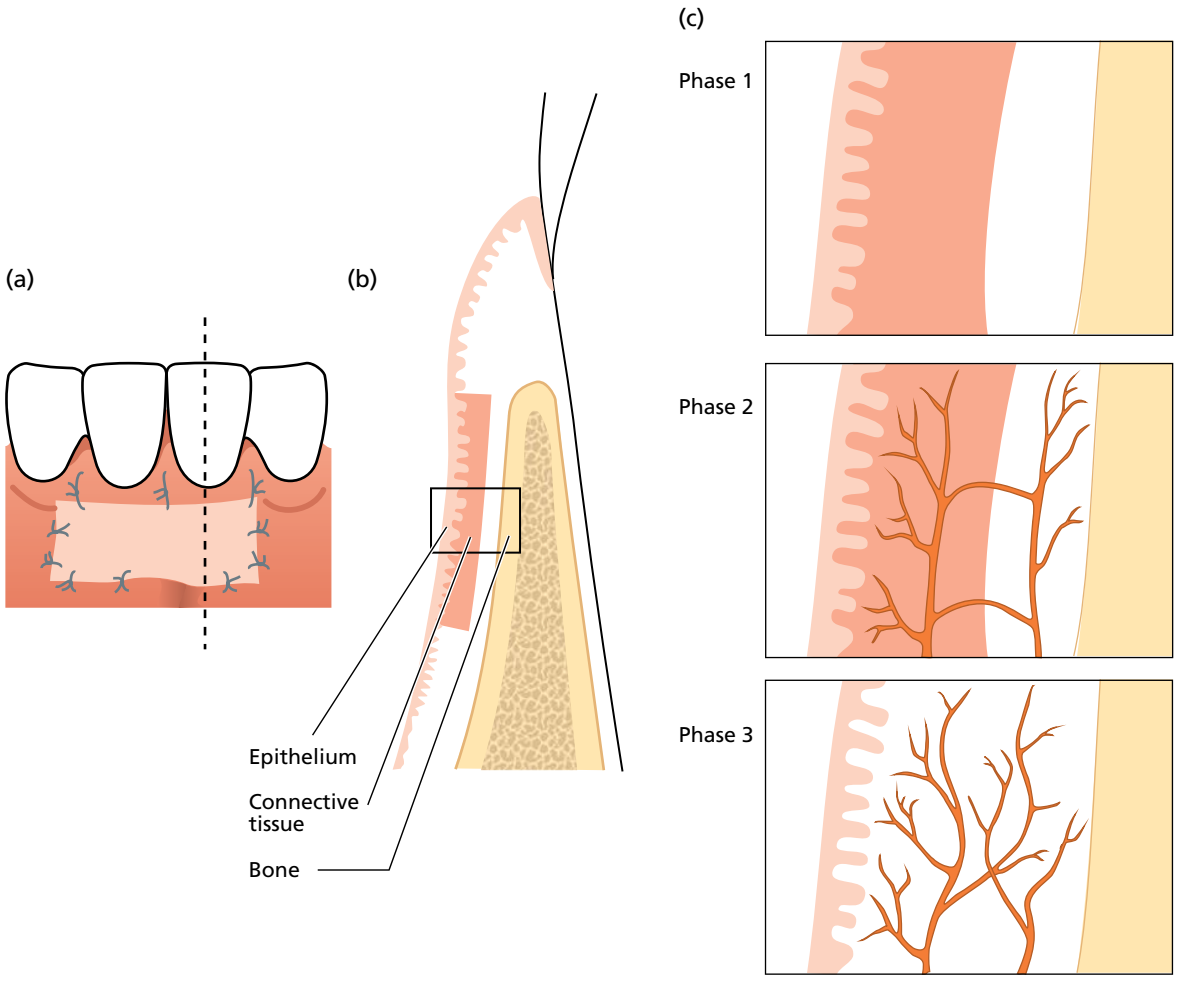


Fig. 46-24 Schematic drawings illustrating healing of a free gingival graft placed entirely on a connective tissue recipient bed (a). (b) Cross-section through the area. The framed areas (c) illustrate the three phases into which the healing process can be divided.

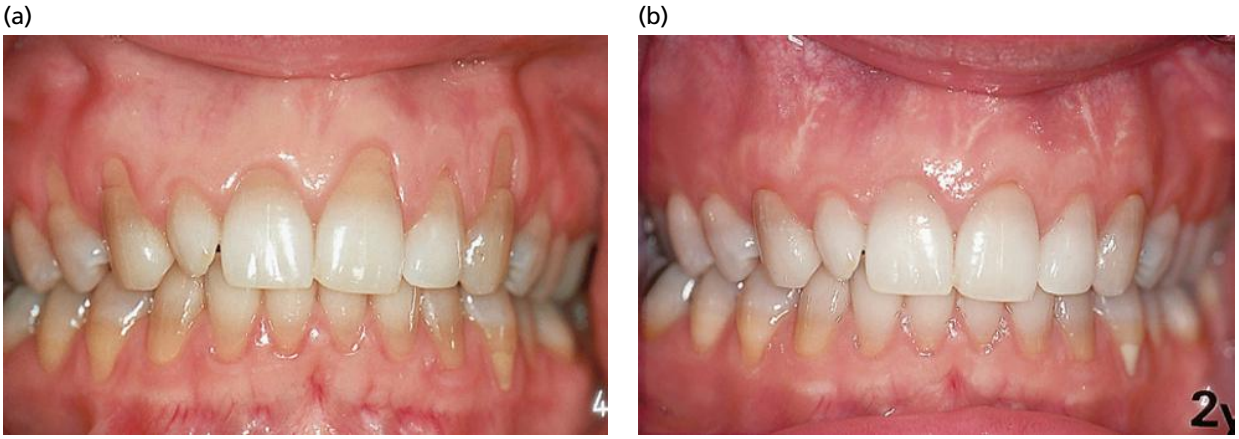


Fig. 46-25 (a) A 25-year-old woman with esthetic concerns due to multiple soft tissue recessions in the maxilla and a high lip line. The gingiva is healthy and several of the exposed root surfaces show abrasion defects, indicating toothbrushing trauma as the causative factor for the development of the recessions. The brushing technique was altered and root coverage was achieved surgically. (b) Two-year post-treatment view.

vessels of the graft. The subsequent time period is characterized by capillary proliferation, which gradually results in a dense network of blood vessels in the graft. At the same time, a fibrous union is established between the graft and the underlying connective tissue bed. The re-epithelialization of the graft occurs mainly by proliferation of epithelium from the adjacent tissues. If a free graft is placed over the denuded root surface, apical migration of epithelium along the tooth-facing surface of the graft may take place at this stage of healing.

3. *Tissue maturation phase (from 11 to 42 days)*. During this period, the number of blood vessels in the transplant is gradually reduced, and after approximately 14 days the vascular system of the graft appears normal. Also, the epithelium gradually matures with the formation of a keratin layer during this stage of healing.

The establishment and maintenance of a "plasmatic circulation" between the recipient bed and the graft during the initial phase of healing is critical in this kind of therapy. Therefore, in order to ensure ideal conditions for healing, blood between the graft and the recipient site must be removed by exerting pressure against the graft following suturing.

Root coverage

The main indications for root coverage procedures are esthetic/cosmetic demands (Fig. 46-25) and root sensitivity. Changing the topography of the marginal soft tissue in order to facilitate plaque control is also a common indication for root coverage procedures (Fig. 46-26).

It should be recalled that the two major causative factors in the development of marginal tissue recession are trauma caused by toothbrushing and plaque-induced periodontal inflammation. The control of these factors will prevent further progression of the

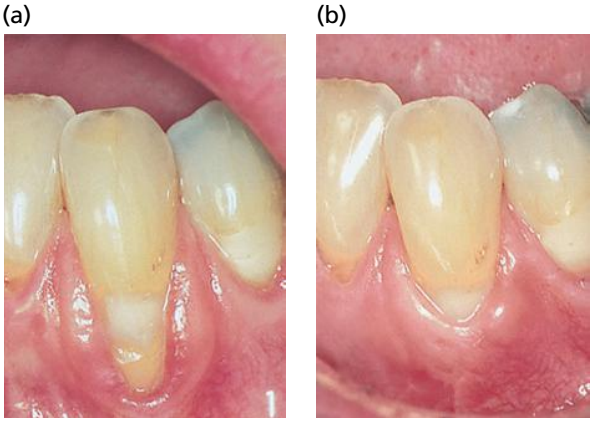


Fig. 46-26 (a) Mandibular canine with a deep recession, which makes self-performed plaque control difficult. (b) To facilitate plaque control, the position of the soft tissue margin was altered surgically.

recession in most cases. This means that in tooth regions with a thin covering of soft tissue, with or without an incipient recession, the patient should be encouraged to carry out effective, but at the same time non-traumatic, plaque-control measures. With respect to toothbrushing, the Bass method (see Chapter 36) should be avoided and the patient should be instructed to use a technique that creates as little apically directed pressure on the soft tissue margin as possible. A soft toothbrush should, of course, be used.

Miller (1985a) described a classification of recession defects taking into consideration the anticipated root coverage that it is possible to obtain with the use of a free gingival graft (Fig. 46-27):

- *Class I*: marginal tissue recession not extending to the mucogingival junction; no loss of interdental bone or soft tissue
- *Class II*: marginal tissue recession extending to or beyond the mucogingival junction; no loss of interdental bone or soft tissue
- *Class III*: marginal tissue recession extending to or beyond the mucogingival junction; loss of

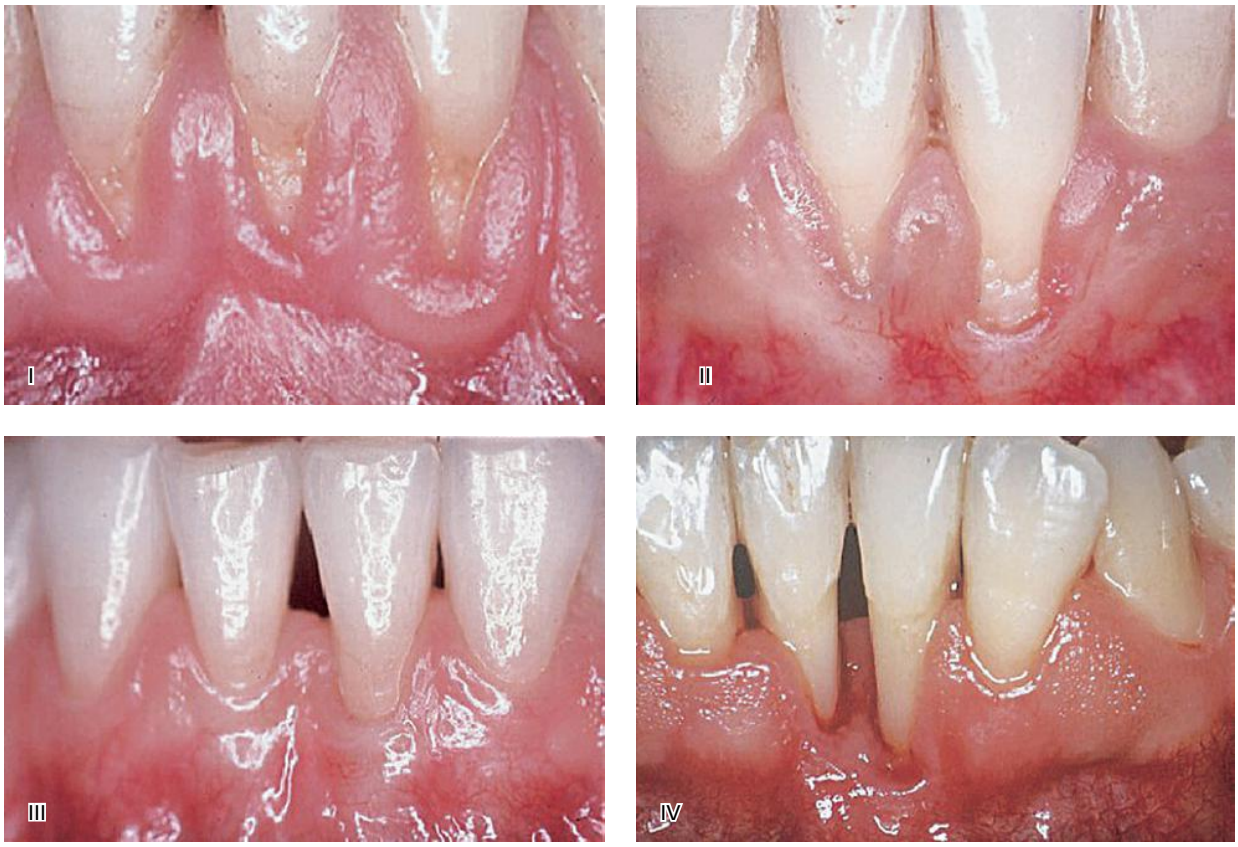


Fig. 46-27 Miller classification of recession defects (see text).

interdental bone/soft tissue or malpositioning of the tooth
- *Class IV*: marginal tissue recession extending to or beyond the mucogingival junction; severe loss of interdental bone/soft tissue or severe malpositioning of the tooth.

While complete root coverage was considered achievable in class I and II defects, only partial coverage could be expected in class III and IV recession defects. While there seems to be no reason to differentiate between class I and II recession defects, the critical clinical variable to assess in order to determine the possible outcome of a root coverage procedure is the level of periodontal tissue support at the proximal sites of the tooth. In line with this interpretation, Cairo *et al.* (2011) suggested a simplified classification of buccal recessions for prediction of the final root coverage outcome, based on clinical assessments of interproximal attachment levels:

- *Recession type 1 (RT1)*: buccal tissue recession with no loss of interproximal attachment
- *Recession type 2 (RT2)*: buccal tissue recession associated with loss of interproximal attachment less than or equal to the buccal attachment loss
- *Recession type 3 (RT3)*: buccal tissue recession associated with loss of interproximal attachment greater than the buccal attachment loss.

A consideration in relation to this classification and the prediction of complete root coverage is that not only is the clinical attachment level at the recession-affected tooth of importance, but also that at the neighboring teeth; in other words, whether or not there is loss of soft tissue height in the proximal site.

Recession defects in children need particular attention. In the growing child, recession defects may be eliminated spontaneously, provided adequate plaque control is established and maintained (Fig. 46-28). Andlin-Sobocki *et al*. (1991) reported from a 3-year prospective study that 25 of 35 recession defects with an initial depth of 0.5–3.0 mm healed spontaneously following improvement of the oral hygiene standard. Furthermore, all but three remaining recessions showed a decrease and no site demonstrated an increase in depth. Hence, reparative surgical treatment of soft tissue recessions in the developing dentition may not be necessary and should preferably be postponed until the growth is completed.

In an orthodontic case showing a recession defect and a thin (delicate) gingiva associated with a prominent, facially positioned tooth (Fig. 46-29a), surgical treatment for root coverage should be postponed until the orthodontic therapy is completed. The recession, as well as the dehiscence, will decrease as a consequence of the lingual movement of the tooth into a more proper position within the alveolar bone (Fig. 46-29b), and, if still indicated, the root coverage

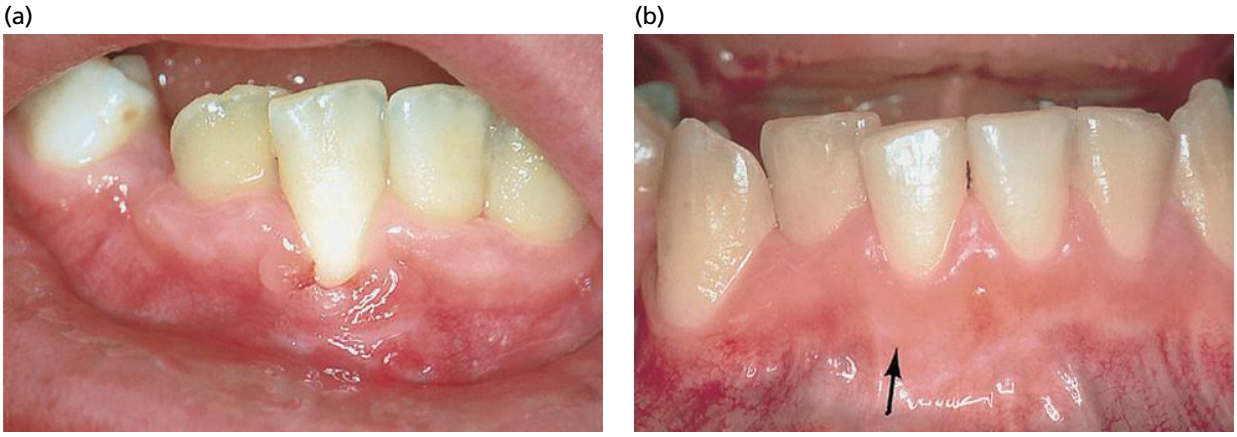


Fig. 46-28 A 9-year-old boy showing recession at tooth 41. (a) Tooth is rotated and buccally positioned. The minimal amount of gingiva found apical to the recession shows pronounced signs of inflammation. The plaque control in the region was improved but surgical intervention was postponed. (b) Same tooth area at the age of 14 years. Note the spontaneous soft tissue repair that has taken place at tooth 41 as a consequence of the improved plaque control and the growth in the alveolar process (arrow).

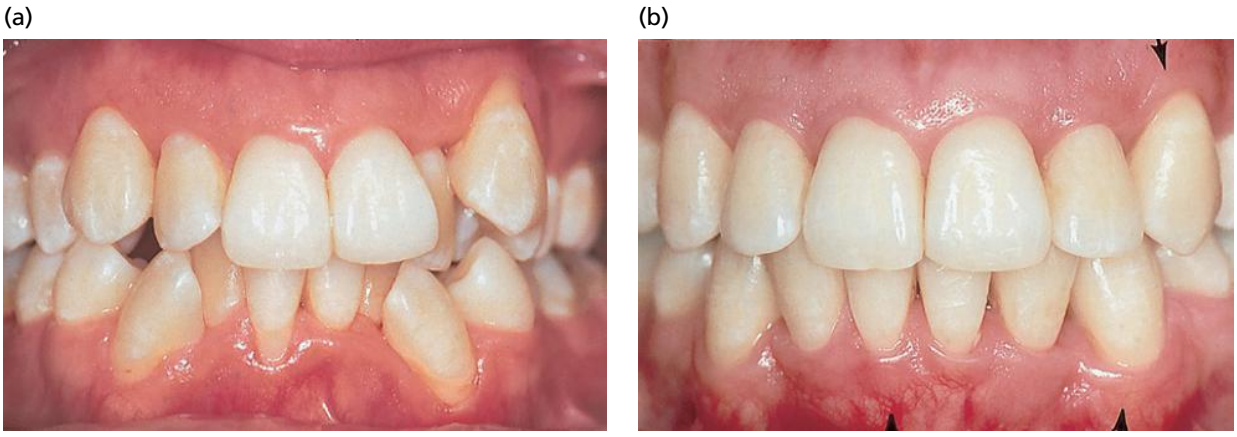


Fig. 46-29 Spontaneous repair of soft tissue recessions following orthodontic tooth movement. (a) A 22-year-old woman showing recessions and thin marginal tissues at prominently positioned teeth, particularly 23, 33, 41, and 43. (b) Following proper alignment of the teeth, the recessions have spontaneously been resolved and an increased gingival height can be noted.

procedure will show higher predictability of complete coverage if performed after rather than before the tooth movement.

Root coverage procedures

Surgical procedures used in the treatment of recession defects may basically be classified as (1) pedicle soft tissue graft procedures and (2) free soft tissue graft procedures.

The *pedicle graft procedures* are, depending on the direction of transfer, grouped as (1) *rotational flap procedures* (e.g. laterally sliding flap, double papilla flap, oblique rotated flap) or (2) *advanced flap procedures* (e.g. coronally repositioned flap, semilunar coronally repositioned flap). The latter procedures do not include rotation or lateral movement of the pedicle graft. Regenerative procedures are also included within the group of pedicle graft procedures, that is rotational and advanced flap procedures involving the placement of a barrier membrane between the graft and the root or the application of enamel matrix proteins.

The autogenous *free soft tissue graft procedures* may be performed as (1) an epithelialized graft or (2) a subepithelial connective tissue graft (non-epithelialized graft), both usually taken from the area of the masticatory mucosa in the palate.

Factors such as depth and width of recession, availability of donor tissue, presence of muscle attachments, and esthetics have to be taken into consideration in the selection of treatment procedure.

Treatment of the exposed root surface

Before root coverage is attempted, the exposed portion of the root should be rendered free from bacterial biofilms. Preferably, this is achieved by the use of a rubber cup and a polishing paste. Controlled clinical trials showed no differences in terms of root coverage or residual probing depth between teeth that had been instrumented (root planed) or polished only (Oles *et al*. 1988; Pini Prato *et al*. 1999). Extensive root planing may therefore only be performed in situations where a reduced root prominence would be considered beneficial for graft survival or tissue

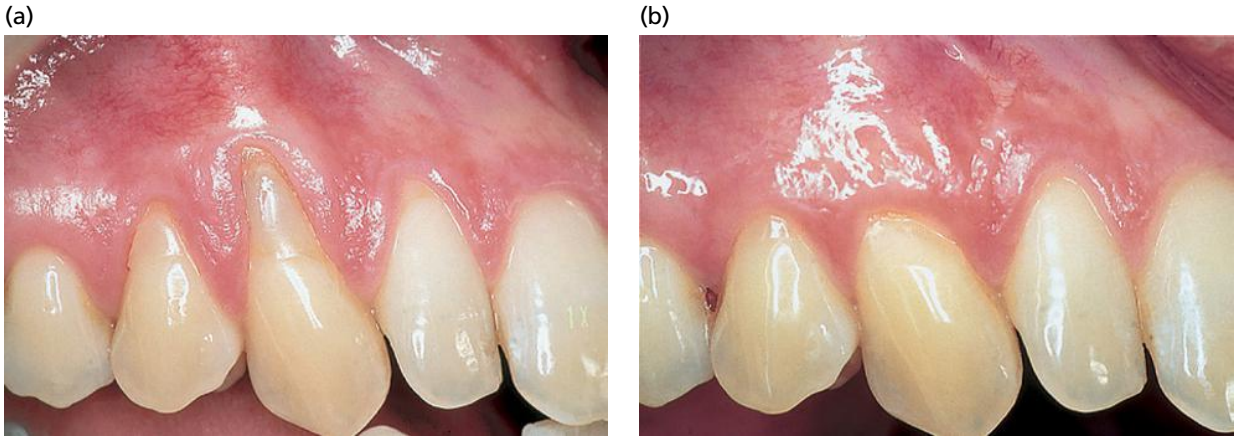


Fig. 46-30 (a) Canine showing pronounced recession and a composite resin restoration in the exposed root. Following removal of the restoration, the exposed root was surgically covered with soft tissue (pedicle graft). (b) Two-year postoperative healing result.

regeneration, or if a shallow root caries lesion is diagnosed. The presence of a filling in the root does not preclude the possibility of root coverage (Fig. 46-30), but preferably the filling should be removed before the root is covered with soft tissue.

The use of root surface demineralization agents has been advocated as important not only for the removal of the smear layer, but also to facilitate the formation of a new fibrous attachment through exposure of collagen fibrils of the dentin matrix and to allow subsequent interdigitation of these fibrils with those in the covering connective tissue. However, controlled clinical trials comparing the clinical outcome of root coverage procedures with and without root conditioning (Ibbott *et al*. 1985; Oles *et al*. 1985; Bertrand & Dunlap 1988; Laney *et al*. 1992; Bouchard *et al*. 1997; Caffesse *et al*. 2000) failed to demonstrate a beneficial effect from the use of acid root biomodification. Gottlow *et al*. (1986) evaluated the healing following treatment of localized gingival recessions with coronally positioned flaps and citric acid root biomodification in a controlled study in dogs. Histologic analysis after 3 months of healing disclosed no differences in the amount of root coverage or new connective tissue attachment between citric acid-treated sites and saline-treated control sites. Although root resorption was a common finding among the citric acid-treated teeth in this dog model, such a finding has not been reported to be common in humans. Based on a systematic review on the efficacy of root surface conditioning, Oliveira and Muncinelli (2012) concluded that there is no evidence that root surface biomodification by, for example, citric acid, EDTA or laser prior to soft tissue root coverage improves the clinical outcome of root coverage procedures.

Pedicle soft tissue graft procedures

Rotational flap procedures

The use of a laterally repositioned flap to cover areas with localized recession was introduced by Grupe and Warren (1956). This technique, which was called *the laterally sliding flap* operation, involved the reflection of a full-thickness flap in a donor area adjacent to the defect and the subsequent lateral displacement of this flap to cover the exposed root surface (see Fig. 46-19). In order to reduce the risk for recession on the donor tooth, Grupe (1966) suggested that the marginal soft tissue should not be included in the flap. Staffileno (1964) and Pfeifer and Heller (1971) advocated the use of a split-thickness flap to minimize the potential risk for development of dehiscence at the donor tooth. Other modifications of the procedure are the *double papilla flap* (Fig. 46-31) (Cohen & Ross 1968), the *oblique rotational flap* (Pennel *et al*. 1965), the *rotation flap* (Patur 1977), and the *transpositioned flap* (Bahat *et al*. 1990).

The technique is as follows:

1. The rotational flap procedure (Fig. 46-32) is initiated with the preparation of the recipient site. A reverse bevel incision is made all along the soft tissue margin of the defect (Fig. 46-32a). After removal of the dissected pocket epithelium, the exposed root surface is thoroughly curetted.
2. At a distance of approximately 3 mm from the wound edge, which delineates the defect at the side opposite the donor area, a superficial incision is performed extending from the gingival margin to a level approximately 3 mm apical to the defect (Fig. 46-32b). Another superficial incision is placed horizontally from this incision to the opposite wound edge. The epithelium together with the outer portion of the connective tissue within the area delineated by these incisions and the wound edges is removed by sharp dissection (Fig. 46-32c). In this way a 3-mm wide recipient bed is created at the one side of the defect, as well as apical to the defect.
3. A tissue flap to cover the recession is then dissected in the adjacent donor area. The preparation of this flap is initiated by a vertical superficial incision placed parallel to the wound edge of the recession and at a distance that exceeds the width of the recipient bed and the exposed root surface by approximately 3 mm (Fig. 46-32c). This incision is

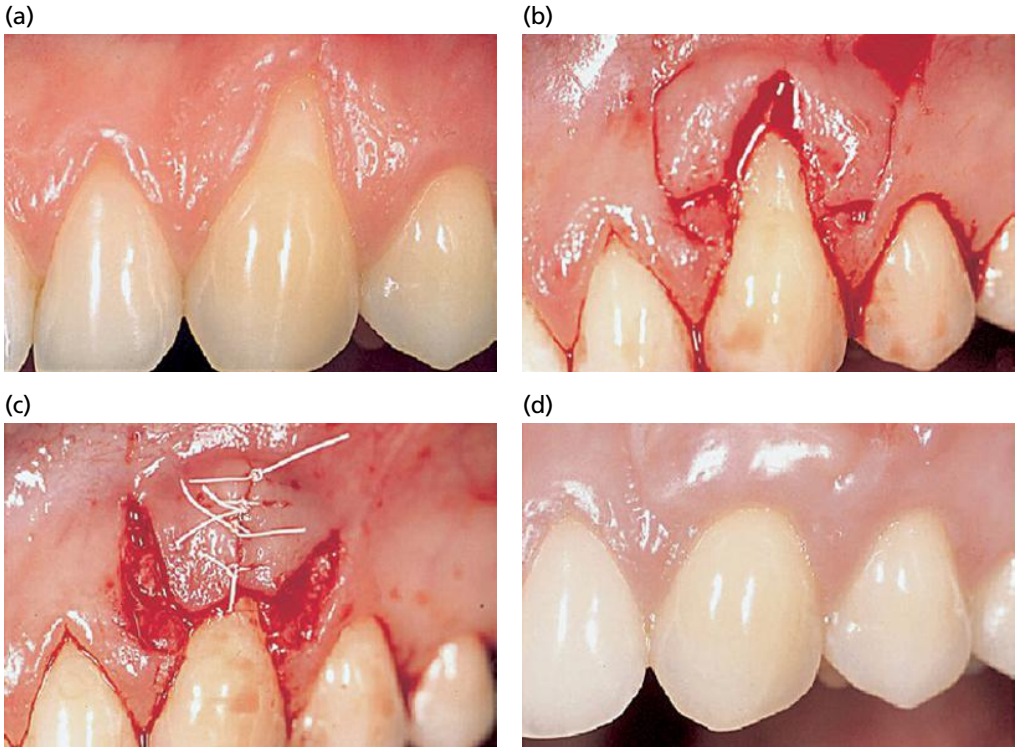


Fig. 46-31 Double papilla flap procedure. (a) Pretreatment view of a maxillary canine with facial soft tissue recession. Using split incisions, soft tissue flaps are mobilized from both sides of the recession (b) and sutured together for coverage of the exposed root (c). The healing result 6-month postoperatively shows complete root coverage (d).

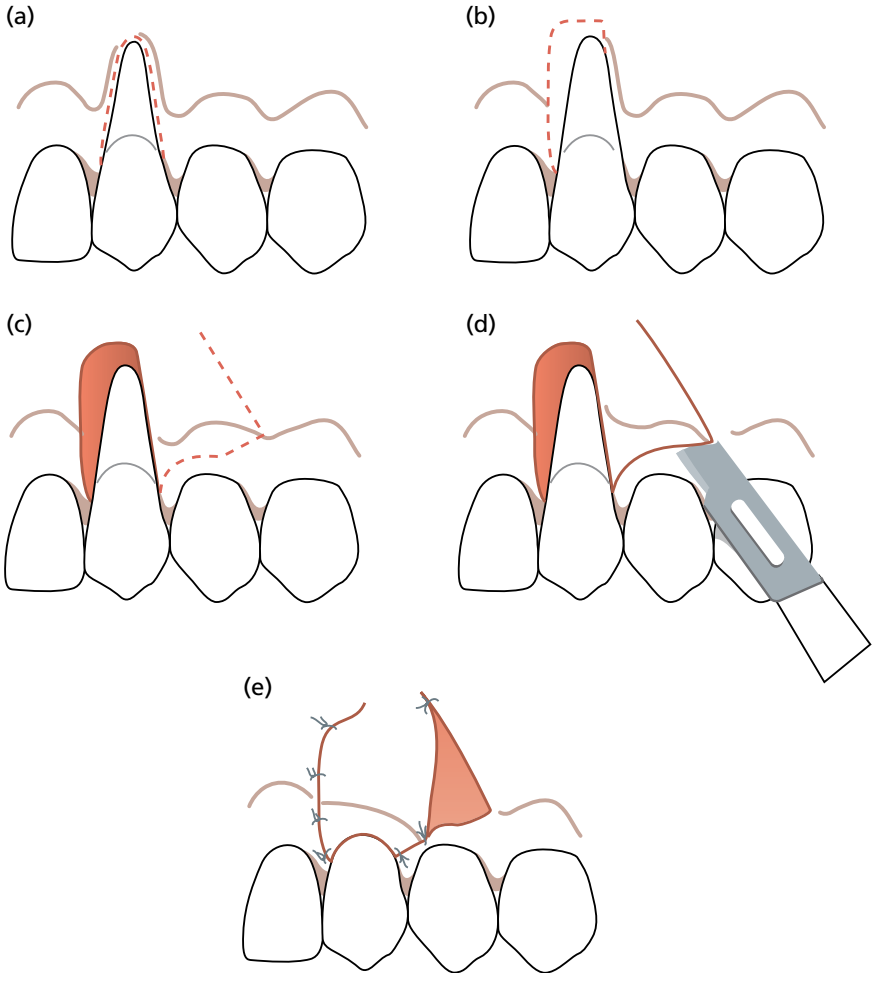


Fig. 46-32 (a–e) Rotational flap procedure. Schematic drawings illustrating the surgical technique for utilizing rotational pedicle grafts to cover localized recession defects (see text for explanation).

extended beyond the apical level of the recipient bed and is terminated within the lining mucosa with an oblique releasing incision directed towards the recession site. An incision connecting the vertical incision and the incision previously made around the recession is placed approximately 3 mm apical to the gingival margin of the donor site.

4. A split-thickness flap is then prepared by sharp dissection within the area delineated by these incisions so that a layer of connective tissue is left covering the bone in the donor area when the flap is displaced laterally over the denuded root surface (Fig. 46-32d). It is important that the oblique releasing incision is made far enough apically that the tissue flap can be placed on the recipient bed without being subjected to tearing forces when adjacent soft tissues are moved. The prepared tissue flap is rotated about 45° when sutured at the recipient bed (Fig. 46-32e).
5. The suturing of the flap should secure a close adaptation of the pedicle graft to the underlying recipient bed. Pressure is applied against the flap for 2–3 minutes in order to further secure a good adaptation. To protect the surgical area during the initial phase of healing, a periodontal dressing may be applied. A light-cured dressing material, for example Barricaid™ (Dentsply International Inc., Milford, DE, USA), is preferably used since this can be applied without dislocating the flap and has, in addition, a favorable esthetic appearance.
6. Following removal of the dressing and the sutures, usually after 10–14 days, the patient is instructed to avoid mechanical tooth cleaning for a further 2 weeks, but to rinse twice daily with a chlorhexidine solution as a method of infection control.

Advanced flaps

Since the lining mucosa is elastic, a mucosal flap raised beyond the mucogingival junction can be stretched in the coronal direction to cover the exposed root surfaces (Harvey 1965; Sumner 1969; Brustein 1979; Allen & Miller 1989; Wennström & Zucchelli 1996; De Sanctis & Zucchelli 2007). The coronally advanced flap can be used for root coverage of a single tooth as well as multiple teeth, provided suitable donor tissue is available. In situations with only shallow recession defects and minimal probing pocket depth labially, the *semilunar coronally repositioned flap* may offer an alternative approach (Harlan 1907; Tarnow 1986). For the treatment of an isolated deep gingival recession affecting a lower incisor, or the mesial root of the first maxillary molar, Zucchelli *et al*. (2004) suggested the use of a *laterally moved, coronally advanced flap*.

The technique for a *coronally advanced flap procedure* is as follows (Fig. 46-33):

1. The coronally advanced flap procedure is initiated with the placement of two apically divergent vertical releasing incisions, extending from a point coronal to the CEJ at the mesial and distal line axis of the tooth and apically into the lining mucosa (Fig. 46-33a).
2. A split-thickness flap is prepared by sharp dissection mesial and distal to the recession and

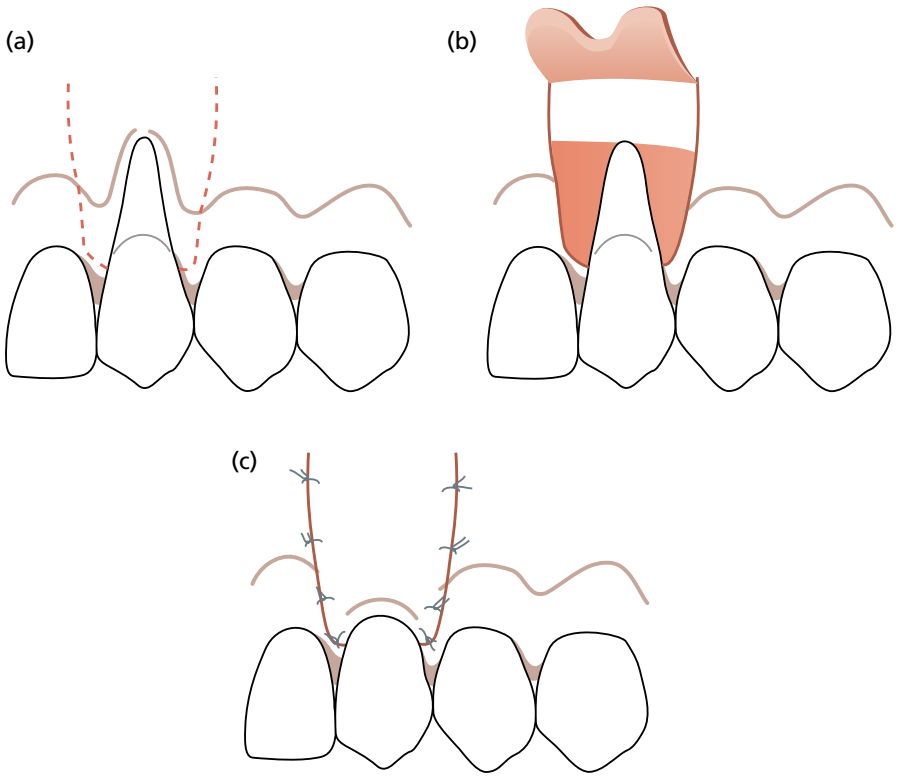


Fig. 46-33 (a–c) Coronally advanced flap procedure. Schematic drawings illustrating the surgical technique for utilizing coronally advanced pedicle grafts to cover localized recession defects (see text for explanation).

connected with an intracrevicular incision. Apical to the receded soft tissue margin on the facial aspect of the tooth, a full-thickness flap is elevated to maintain maximal thickness of the tissue flap to be used for root coverage (Fig. 46-33b). Approximately 3 mm apical to the bone dehiscence, a horizontal incision is made through the periosteum, followed by blunt dissection into the vestibular lining mucosa to release muscle tension. The blunt dissection is extended buccally and laterally to such an extent that the mucosal graft is tension-free when positioned coronally at the level of the CEJ. The facial portion of the interdental papillae is de-epithelialized to allow for a final placement of the flap margin coronal to the CEJ.

3. The tissue flap is coronally advanced, adjusted for optimal fit to the prepared recipient bed, and secured at a level 1-2 mm coronal to the CEJ by suturing the flap to the connective tissue bed in the papilla regions (Fig. 46-33c). Additional lateral sutures are placed to carefully close the wound of the releasing incisions. Mechanical tooth cleaning is avoided during the first 3–4 weeks of healing (rinsing with a chlorhexidine solution is prescribed), and when re-instituted, instructions in the use of a toothbrushing technique creating minimal apically directed trauma to the soft tissue margin is given.

Figure 46-34 illustrates the treatment of a recession defect with the use of the coronally advanced flap procedure. To allow the positioning of the flap margin coronal to the CEJ at the buccal surface, the interdental papillae have to be de-epithelialized before suturing (Fig. 46-35).

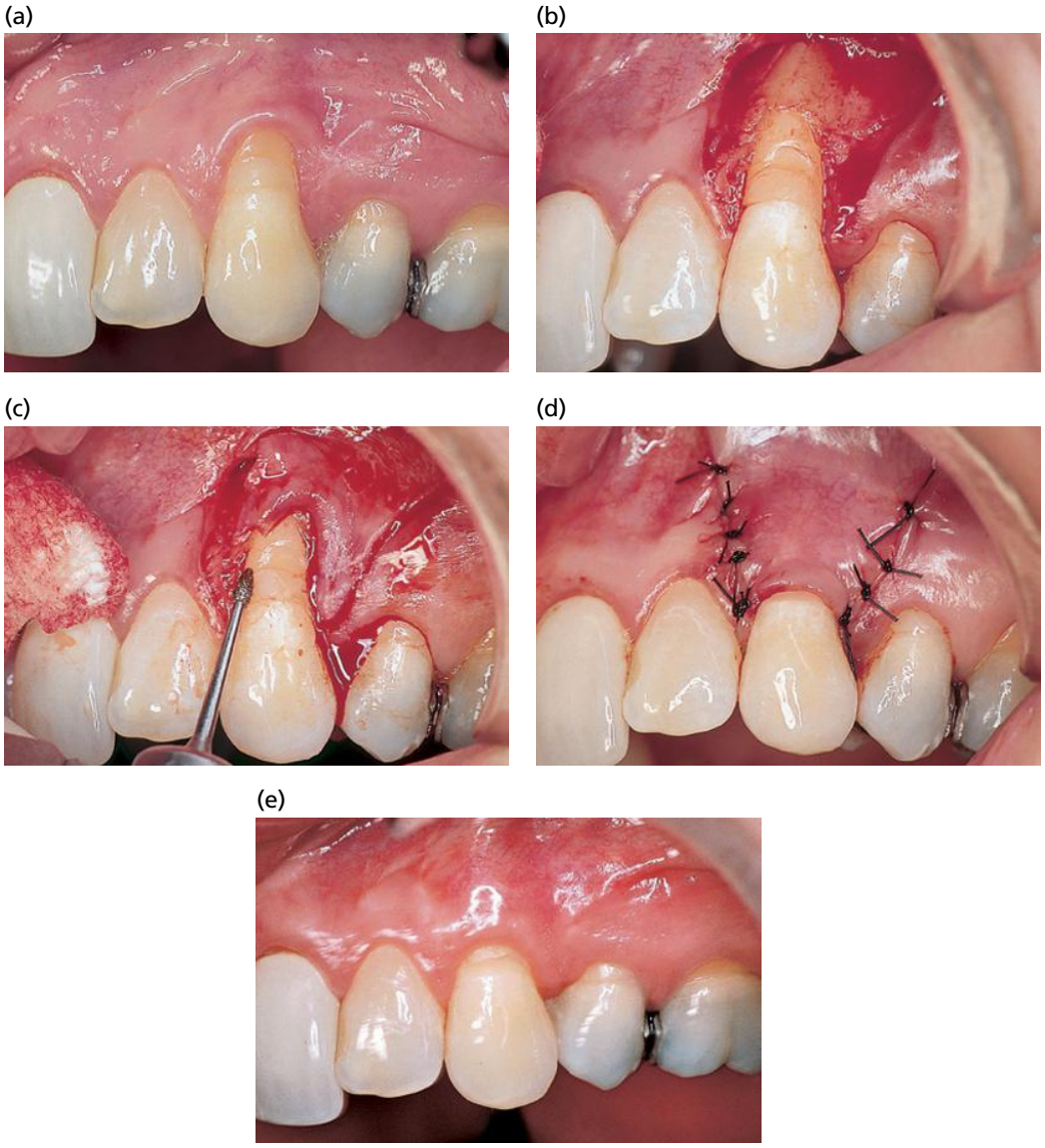


Fig. 46-34 Coronally advanced flap procedure. (a) Deep and wide recession defect on a canine with a composite resin restoration in the exposed root portion. Before preparation of the pedicle graft, the root is polished with pumice and a rubber cup. (b) Split flap has been dissected mesial and distal to the root, and a full-thickness flap apical to the recession. Approximately 4 mm apical to the bone dehiscence, the periosteum has been cut and a blunt dissection performed to facilitate the coronal positioning of the pedicle graft. (c) Composite resin restoration is removed. (d) Close suturing of the pedicle graft to cover the exposed root surface. (e) Healing outcome 1 year postoperatively.

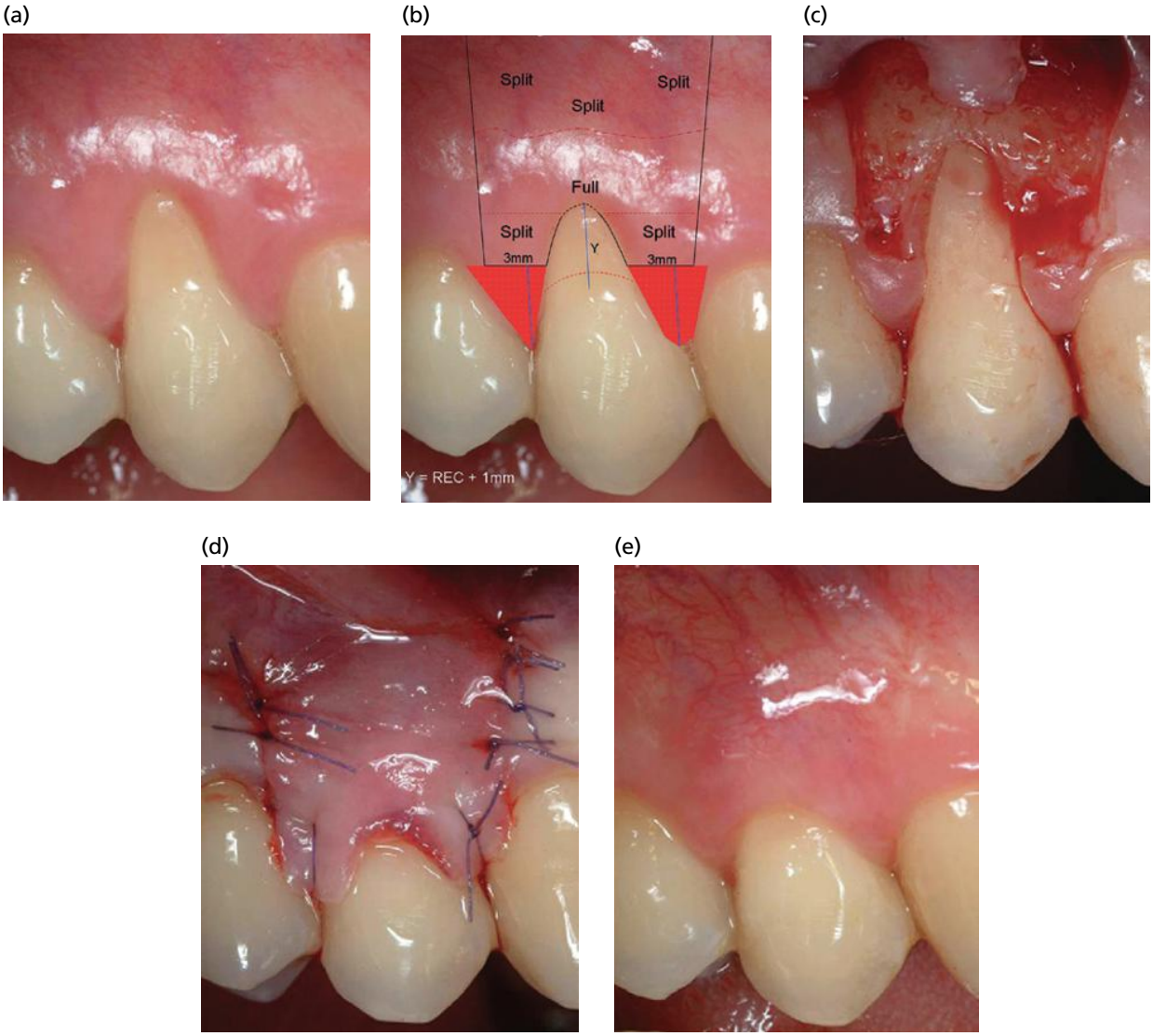


Fig. 46-35 Coronally advanced flap procedure. (a) Recession defect affecting a first premolar. (b) Schematic outline of the flap preparation. (Blue line, amount (in mm) of intended coronal advancement of the flap; dotted red area, de-epithelialized papillae; Split, split-thickness elevation; Full, full-thickness elevation.) (c) Flap elevated. The papilla areas are then de-epithelialized to allow anchorage of the flap coronal to the cementoenamel junction (CEJ). (d) Flap is advanced and anchored at a level coronal to the CEJ with a sling suture. (e) Clinical healing at 1 year.

The technique for a *laterally moved, coronally advanced flap* is as follows (Fig. 46-36):

1. A vertical incision is made approximately 3 mm from the lateral edge of the recession defect at the side opposite the donor area, and parallel to the lateral border of the recession defect. The incision is extended from the level of the CEJ to a point approximately 3 mm apical to the defect. At the marginal end of the vertical incision (at the level of the CEJ), a horizontal incision is made towards the recession defect. A third incision is made parallel to the lateral soft tissue margin of the recession defect on the donor side, from the bottom of the defect to the apical termination of the vertical incision on the recipient side. The area delineated by these incisions is de-epithelialized. In this way a 3-mm wide recipient bed is created lateral as well as apical to the defect.
2. A pedicle graft is harvested from the adjacent tooth site by the use of three incisions: (1) a beveled intrasulcular incision along the lateral edge of the recession defect; (2) a horizontal submarginal incision with a length 6 mm greater than the width of the recession defect; and (3) a beveled oblique vertical incision extending into the alveolar mucosa and parallel to the first incision. The outline of the submarginal incision should preserve 3 mm of marginal soft tissue at the donor tooth, and preferably provide at least 2 mm of keratinized tissue along the entire mesiodistal extension of the flap.
3. The flap is mobilized as a split-thickness flap in its lateral parts, while the center part, which will be placed over the exposed root, is elevated as a full-thickness flap. Apical to the mucogingival line, the elevation is continued as a split-thickness flap until it is possible to passively move the mucosal graft laterally to the recipient site.

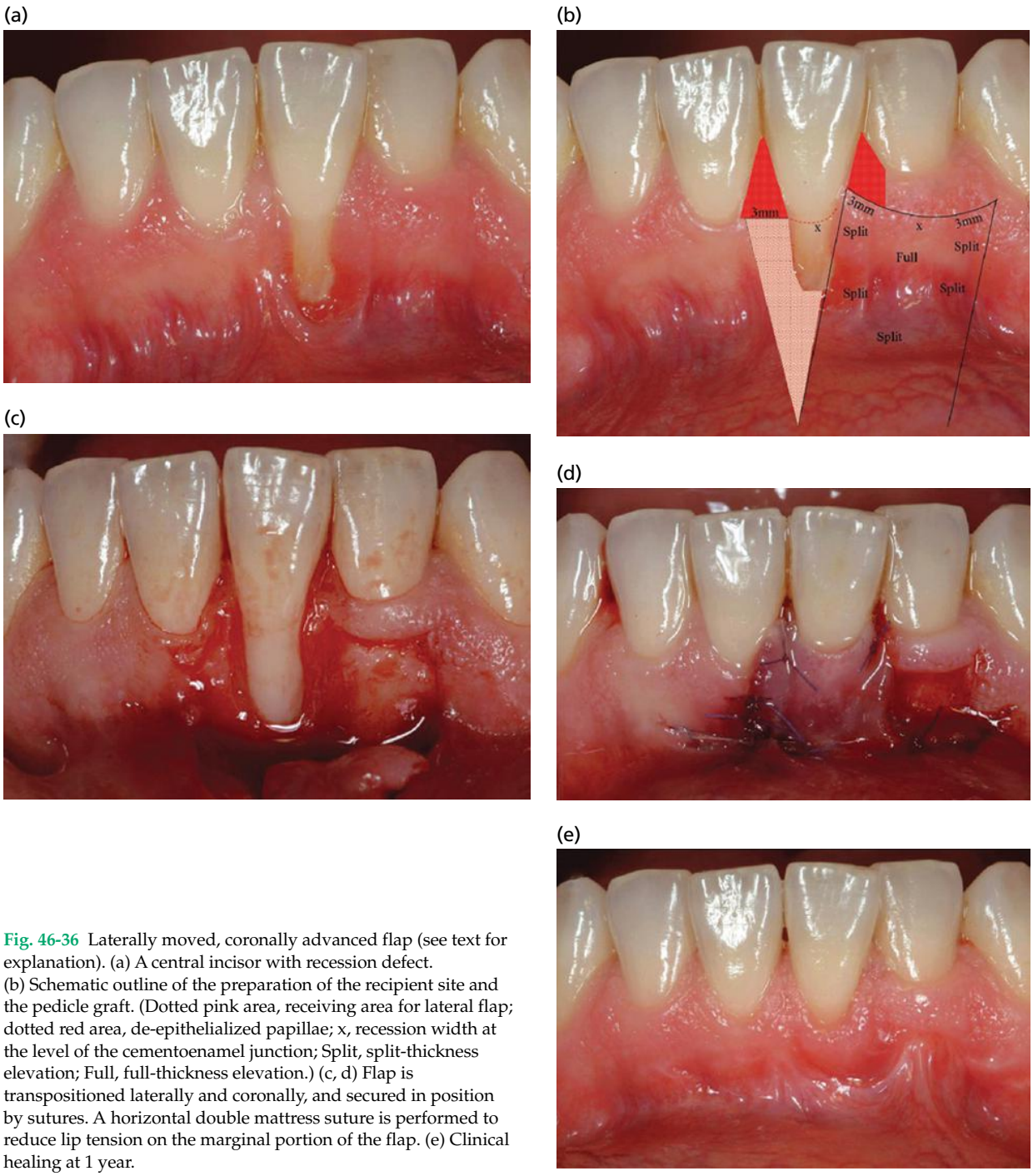


Fig. 46-36 Laterally moved, coronally advanced flap (see text for explanation). (a) A central incisor with recession defect. (b) Schematic outline of the preparation of the recipient site and the pedicle graft. (Dotted pink area, receiving area for lateral flap; dotted red area, de-epithelialized papillae; x, recession width at the level of the cementoenamel junction; Split, split-thickness elevation; Full, full-thickness elevation.) (c, d) Flap is transpositioned laterally and coronally, and secured in position by sutures. A horizontal double mattress suture is performed to reduce lip tension on the marginal portion of the flap. (e) Clinical healing at 1 year.

4. Blunt dissection is performed into the vestibular mucosa to release muscle tension and permit coronal advancement and passive adaptation of the flap to a level coronal to the CEJ.
5. The facial surface of the interdental papillae is de-epithelized to create connective tissue beds to which the laterally moved, coronally advanced flap can be sutured.
6. The suturing of the flap starts with the placement of two interrupted periosteal sutures in the most apical end of the vertical releasing incisions, and continues with a series of interrupted sutures, directed in an apicocoronal direction from the flap to the adjacent wound edge. A horizontal double mattress periosteal suture is placed apical to the vertical incisions to reduce lip tension on the root coverage portion of the flap. The coronal suture is a sling suture, which permits a precise adaptation of the flap against the root surface and the interdental connective tissue beds.

Figure 46-37 illustrates the treatment of a recession defect at a maxillary molar with the use of the *laterally moved, coronally advanced flap* procedure.

Zucchelli and De Sanctis (2000) described a flap design for the treatment of multiple recessions, which

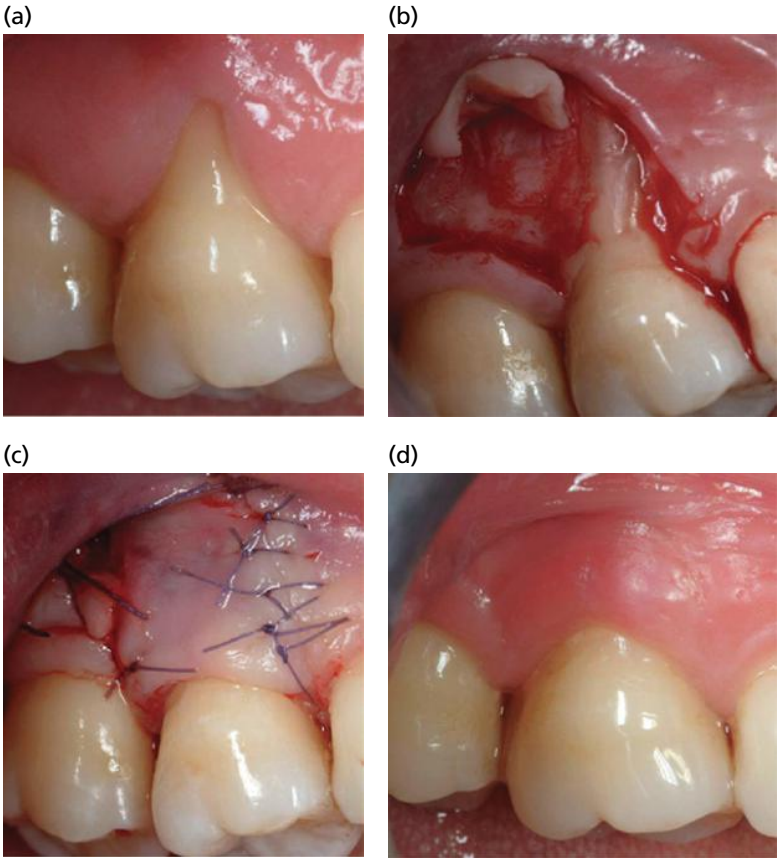


Fig. 46-37 Laterally moved, coronally advanced flap. (a–c) Recession defect at a first maxillary molar treated because of root sensitivity (see text for explanation). (d) Clinical healing at 1 year.

allows for optimal adaptation of the flap following its coronal advancement without placement of vertical releasing incisions. The technique for this *coronally advanced flap procedure for multiple recessions* is as follows (Fig. 46-38):

1. Oblique submarginal incisions are made in the interdental areas and connected with intracrevicular incisions at the recession defects. The incisions are extended to include one tooth on each side of the teeth to be treated to facilitate coronal repositioning of the flap. The oblique incisions over the interdental areas are placed in such a manner that the "surgically created papillae" mesial to the midline of the surgical field are dislocated apically and distally, while the papillae of the flap distal to the midline are shifted to a more apical and mesial position (Fig. 46-38b).
2. Starting at the oblique interdental incisions, a split-thickness flap is dissected (Fig. 46-38c). Apical to the level of the root exposures, a full-thickness flap is raised to provide maximum soft tissue thickness of the flap to be positioned coronally over the roots (Fig. 46-38d).
3. At the most apical portion of the flap, the periosteum is incised and this is followed by dissection into the vestibular lining mucosa to eliminate all muscle tension. The mobilized flap should be able to passively reach a level coronal to the CEJ at each single tooth in the surgical field.
4. The remaining facial portion of the interdental papillae is de-epithelialized to create connective tissue beds to which the flap can be sutured.
5. Sutures are placed to accomplish a precise adaptation of the coronally advanced flap against the teeth and to the interdental connective tissue beds (Fig. 46-38e). In addition, a horizontal double mattress suture may be placed to reduce lip tension on the marginal portion of the flap.

The technique for a *semilunar coronally repositioned flap procedure* is as follows (Fig. 46-39):

1. A semilunar incision is placed apical to the recession and at a distance from the soft tissue margin that should be approximately 3 mm greater than the depth of the recession. The outline of the incision should be parallel to the curvature of the gingival margin (Fig. 46-39a). The incision is extended into the papilla region on each side of the tooth, but care should be taken to maintain a broad base of anchorage to secure a collateral blood supply to the pedicle graft.
2. A split-thickness dissection of the facially located tissue is then made by an intracrevicular incision extending apically to the level of the semilunar incision (Fig. 46-39b). The mid-facial soft tissue graft is coronally repositioned to the level of the CEJ (Fig. 46-39c) and stabilized by light pressure for 5 minutes.
3. No suturing is needed but a light-cured dressing may be applied for wound protection.

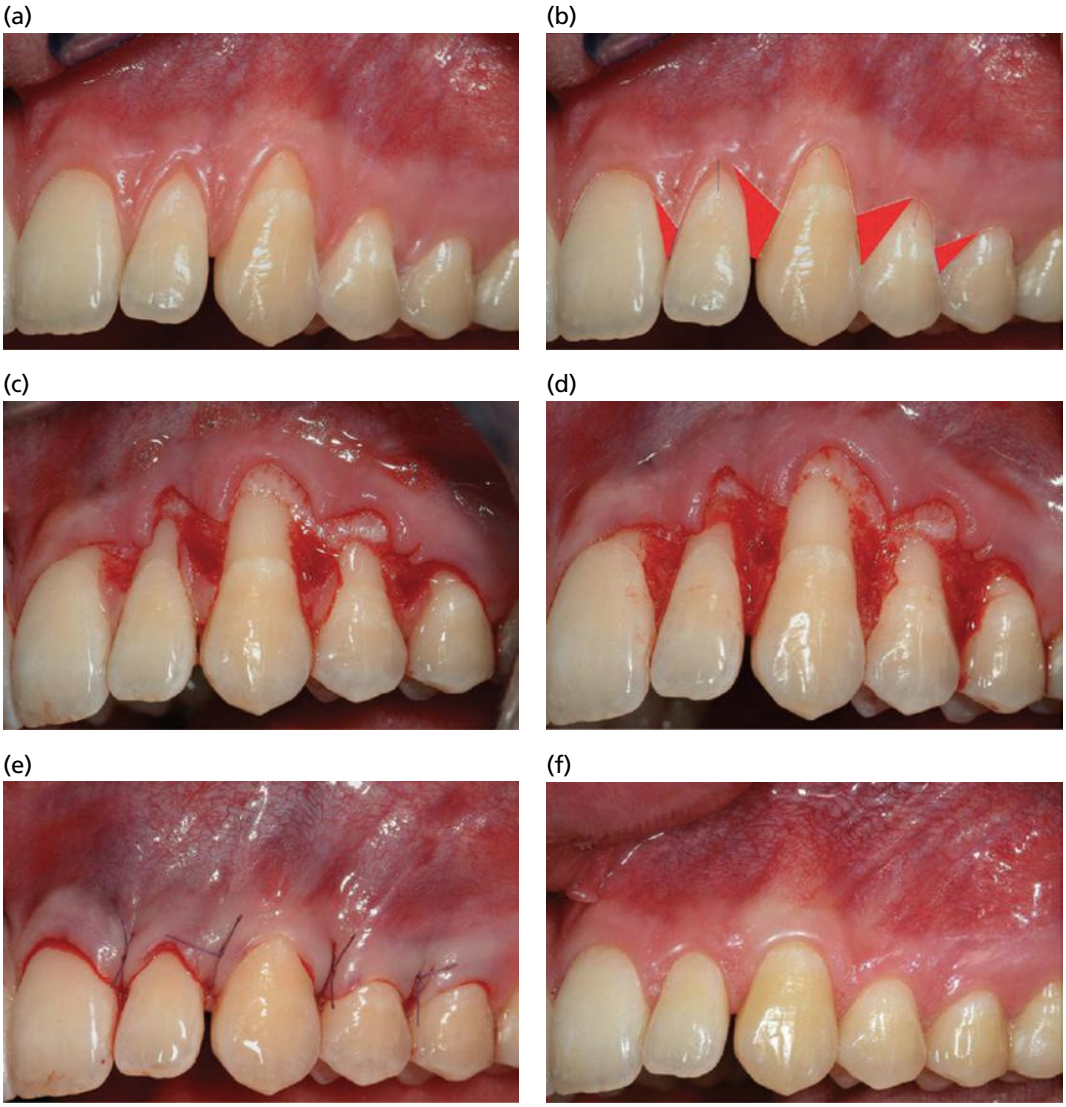


Fig. 46-38 Coronally advanced flap procedure for multiple recessions (see text for explanation). (a–e) Oblique incisions over the interdental areas are placed in such a manner that the "surgically created papillae" mesial to the midline of the surgical field are dislocated apically and distally, while the papillae of the flap distal to the midline are shifted to a more apical and mesial position. (f) One-year post-treatment view.

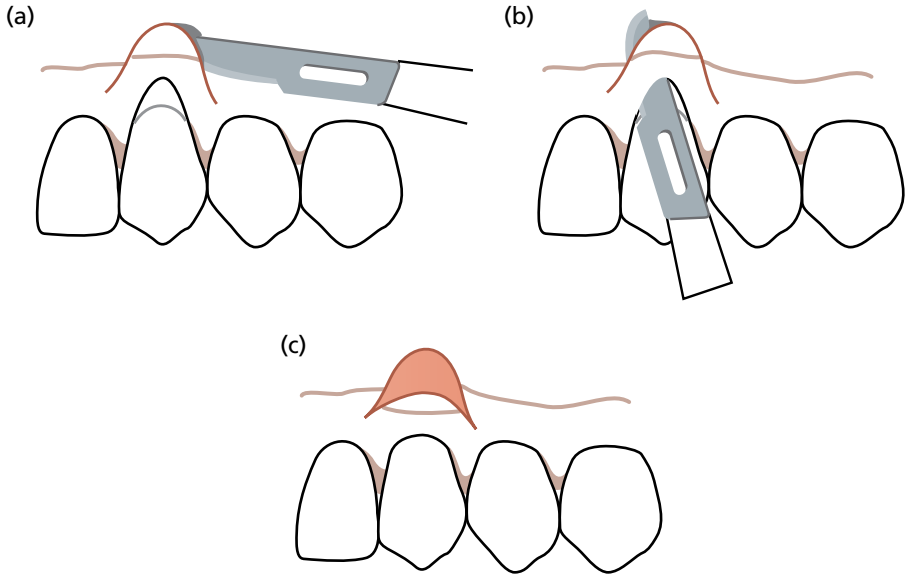


Fig. 46-39 Semilunar coronally repositioned flap procedure. Schematic drawings illustrating the surgical technique for utilizing coronally displaced pedicle grafts to cover shallow localized recession defects (see text for explanation).

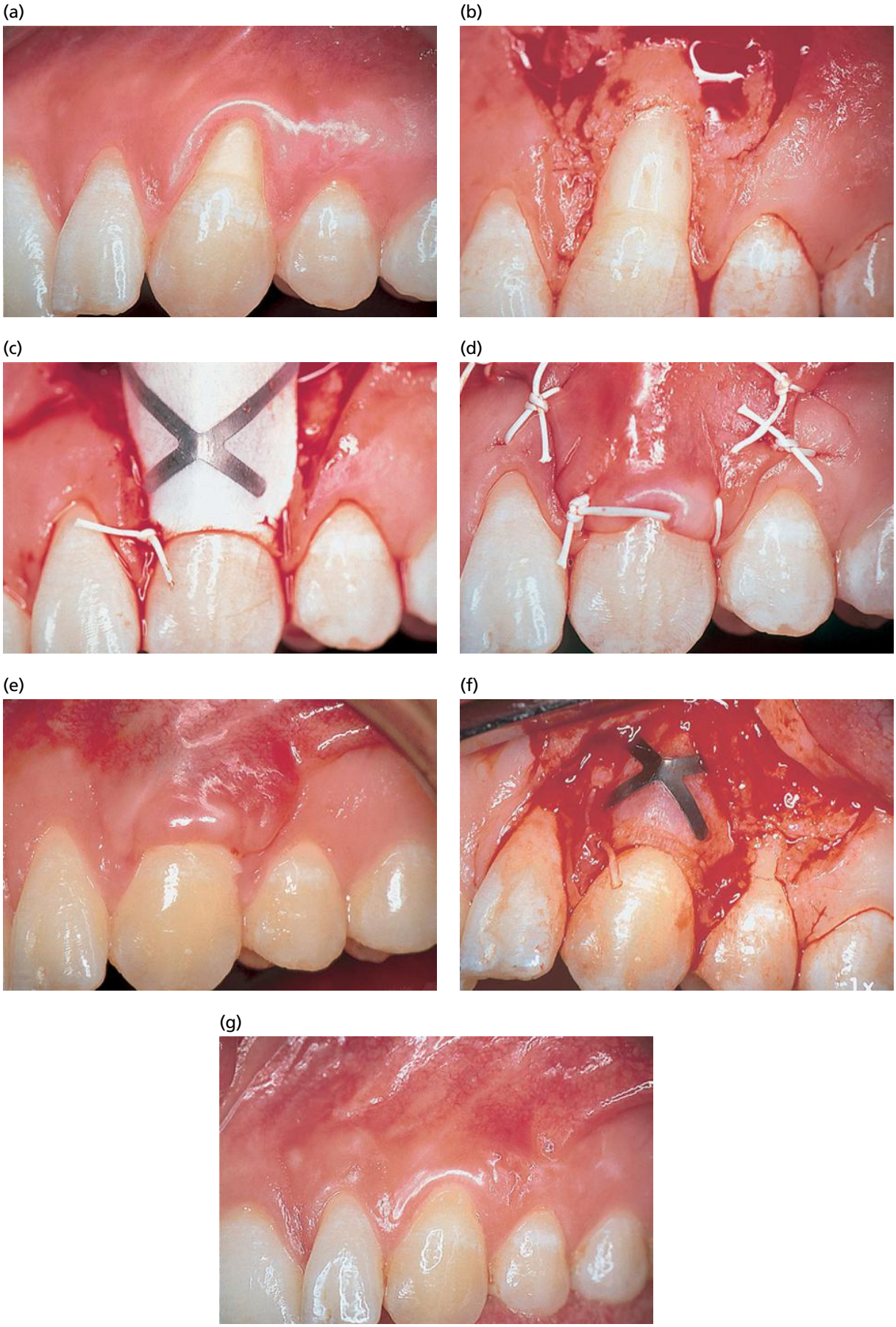


Fig. 46-40 Coronally advanced flap procedure combined with a titanium-reinforced non-biodegradable membrane barrier. (a–f) Recession defect at tooth 23 requiring treatment due to the patient's esthetic demands (see text for explanation). (g) One-year post-operative result.

Pedicle soft tissue graft procedures combined with a barrier membrane

The use of a barrier membrane, according to the principles of guided tissue regeneration (GTR; see Chapter 45), in conjunction with pedicle soft tissue graft procedures was introduced as a treatment modality for root coverage by Pini Prato *et al*. (1992). In order create space for tissue formation between the facial root surface and the membrane, the authors suggested that extensive root planing should be carried out to produce concave root morphology. Specially designed membranes for the treatment of recession-type defects are available, such as non-absorbable titanium-reinforced expanded polytetrafluoroethylene (e-PTFE) membranes (Fig. 46-40c). In addition, a variety of bioresorbable membranes are commercially available, but many of these may not be rigid enough to maintain the required space during healing.

The technique is as follows:

1. The pedicle graft used in the GTR procedure is generated through the preparation of a coronally advanced flap as described above (Fig. 46-40a, b). Depending on the degree of coronal repositioning, the facial portion of the interdental papillae may need to be de-epithelialized to prepare proper recipient beds for the pedicle graft.
2. The root is extensively planed or ground to obtain a concave profile of the root surface, thereby providing space for tissue formation. If a titanium-reinforced membrane is used, the root profile may not need to be changed to establish the required space between the root and the membrane.
3. The membrane barrier to be used is trimmed to cover the exposed root and approximately 3 mm of the bone lateral and apical to the dehiscence (Fig. 46-40c), and anchored to the tooth by a sling suture placed at the level of the CEJ.
4. The mobilized flap is positioned coronally and secured by interdentally placed interrupted sutures (Fig. 46-40d). The membrane should be completely covered by the flap to reduce the risk for bacterial contamination during healing. Additional sutures are placed to close the lateral wound of the releasing incisions.
5. The patient is advised to use a chlorhexidine mouth rinse for infection control and not to use any mechanical cleaning devices for at least 6 weeks in the tooth region subjected to surgery.
6. The use of non-biodegradable membrane barriers requires a second surgery for membrane removal, usually after 5–6 weeks (Fig. 46-40e, f). A partial-thickness trapezoidal flap is raised to expose the membrane. Following its removal, the flap is repositioned at the level of the CEJ to completely cover the newly formed tissue. Mechanical plaque control is re-instituted 4 weeks after membrane removal.

Pedicle soft tissue graft procedures combined with enamel matrix proteins

Abbas *et al*. (2003) described a surgical procedure for periodontal regenerative therapy of recession defects utilizing enamel matrix derivative (EMD) bioactive material (Emdogain®):

1. The surgical technique utilized is the coronally advanced flap as described above (see Fig. 46-33). The interdental papillae should be de-epithelialized to allow for maximum coronal positioning of the tissue flap over the exposed root surface at suturing.
2. Following preparation of the coronally advanced flap, the exposed root surface is conditioned with PrefGel™ (24% EDTA-gel, pH 6.7; Straumann Biologics, Switzerland) for 2 minutes to remove the smear layer.
3. After thorough rinsing with sterile saline, the EMD gel (Emdogain®; Straumann Biologics) is applied to the exposed root surface. The pedicle graft is advanced coronally and secured at a level slightly coronal to the CEJ by suturing the flap to the de-epithelialized papilla regions using non-irritating sutures. The vertical incisions are then closed with two to three sutures. Mechanical tooth cleaning is avoided during the first 3–4 weeks of healing (rinsing with a chlorhexidine solution is prescribed), and when re-instituted, a toothbrushing technique creating minimal apically directed trauma to the soft tissue margin is used.

Free soft tissue graft procedures

A free soft tissue graft of masticatory mucosa is usually selected when there is no acceptable donor tissue present in the area adjacent to the recession defect or when a thicker marginal tissue is desirable. The procedure can be used for the treatment of a single tooth as well as for groups of teeth. The graft used may either be (1) an epithelialized graft or (2) a subepithelial connective tissue graft of palatal masticatory mucosa.

Epithelialized soft tissue graft

The epithelialized free soft tissue graft procedure can be performed either as a two-step surgical technique, where an epithelialized free soft tissue graft is placed apical to the recession and following healing is positioned coronally over the denuded root (Fig. 46-41) (Bernimoulin *et al*. 1975; Guinard & Caffesse 1978), or as a one-step technique by which the graft is placed directly over the root surface (Sullivan & Atkins 1968a, b; Miller 1982) (Fig. 46-42). The latter technique has been the most commonly used.

The principles of utilizing free mucosal grafts were outlined by Sullivan and Atkins (1968a, b) and later modified by Miller (1982):

1. Before any incisions, the exposed root surface is carefully scaled and root planed (Fig. 46-42a). The convexity of the root may be reduced to minimize the mesiodistal avascular recipient bed.

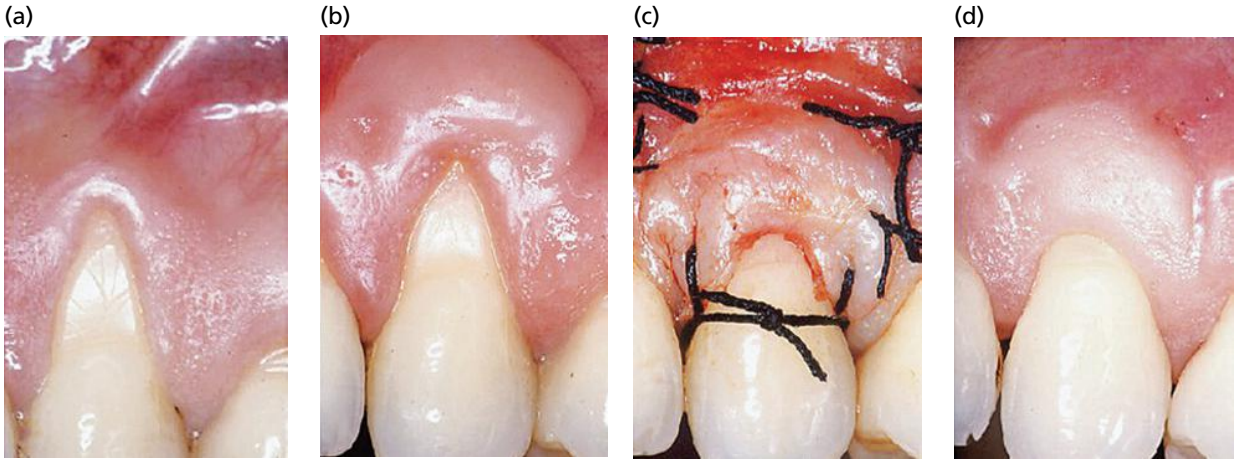


Fig. 46-41 Two-stage epithelialized free soft tissue graft procedure. (a–c) Epithelialized soft tissue graft is placed apical to the recession and allowed to heal. At a second-stage surgery, a coronally advanced flap procedure is performed to achieve coverage of the denuded root. (d) One-year postoperative result.

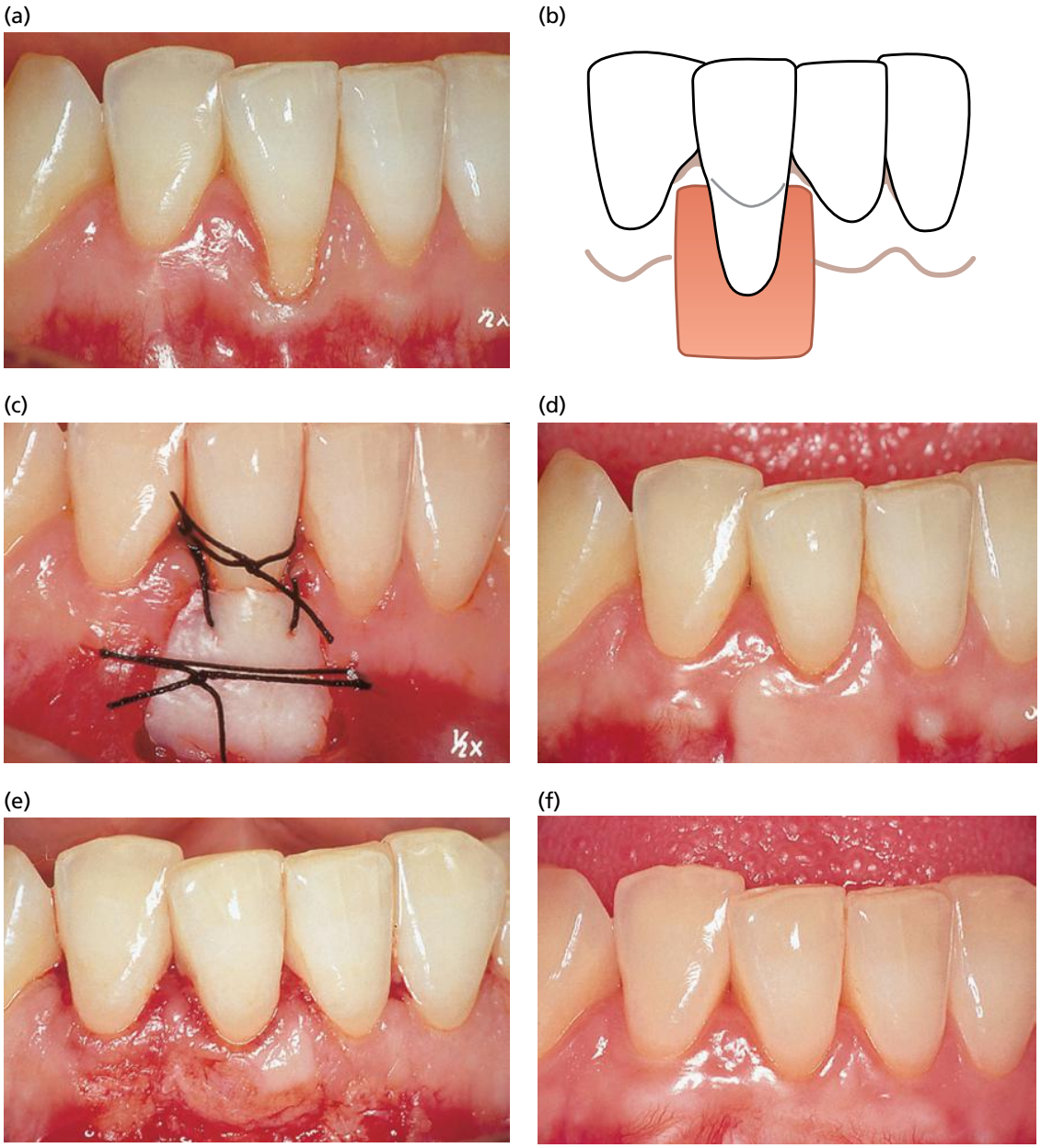


Fig. 46-42 (a–f) Epithelialized free soft tissue graft procedure. A recession defect at a mandibular central incisor treated with the free graft procedure (see text for explanation).

2. As in the treatment with pedicle grafts, the preparation of the *recipient bed* is crucial for the success of the free graft procedure. A 3–4-mm wide recipient connective tissue bed should be prepared apical and lateral to the recession defect (Fig. 46-42b). The area is demarcated by first placing a horizontal incision, at the level of the CEJ, in the interdental tissue on each side of the tooth to be treated. Subsequently, two vertical incisions, extending from the incision line placed in the interdental tissue to a level approximately 4–5 mm apical to the recession, are placed. A horizontal incision is then made connecting the two vertical incisions at their apical termination. Starting from an intracrevicular incision, a split incision is made to sharply dissect the epithelium and the outer portion of the connective tissue within the demarcated area.
3. To ensure that a graft of sufficient size and proper contour is removed from the donor area, a foil template of the recipient site is prepared. This template is transferred to the donor site, the palatal mucosa in the region of the premolars, and the required size of the graft is outlined by a shallow incision. A graft with a thickness of 2–3 mm is then dissected from the donor area (Fig. 46-20c, d). It is advocated to place sutures in the graft before it is cut completely free from the donor area since this may facilitate its transfer to the recipient site. Following the removal of the graft, pressure is applied to the wound area for control of bleeding.
4. The graft is immediately placed on the prepared recipient bed. In order to immobilize the graft at the recipient site, sutures must be anchored in the periosteum or in the adjacent attached gingiva. Adequate numbers of sutures are placed to secure close adaptation of the graft to the underlying connective tissue bed and root surface (Fig. 46-42c). Before the placement of a periodontal dressing, pressure is exerted against the graft for some minutes in order to eliminate blood from between the graft and the recipient bed. Following the control of bleeding, a periodontal dressing is applied to the wound in the donor area in the palate. An acrylic plate may be required to maintain the dressing in place during the healing phase.
5. The sutures and periodontal dressing are usually maintained for 2 weeks. The appearance of a grafted area after 3 months of healing is shown in Fig. 46-42d. A gingivoplasty may be indicated to achieve a satisfactory esthetic appearance of the grafted area (Fig. 46-42e, f).

Connective tissue graft

The techniques utilizing a subepithelial soft tissue graft, that is the connective tissue, involve the placement of the graft directly over the exposed root and the mobilization of a mucosal flap coronally (Fig. 46-43) or laterally (Fig. 46-44) for coverage of the graft (Langer & Langer 1985; Nelson 1987; Harris 1992; Bruno 1994; Zucchelli *et al*. 2003). An alternative technique is to place the base of the connective tissue graft within an "envelope" prepared by an undermining partial-thickness incision from the soft tissue margin, that is part of the graft will rest on the root surface coronal to the soft tissue margin (Fig. 46-45) (Raetzke 1985; Allen 1994). For the treatment of multiple adjacent recessions, a multi-envelope recipient bed ("tunnel") may be prepared (Zabalegui *et al*. 1999). The subepithelial connective tissue graft is harvested from the palate or the retromolar pad by the use of a "trap-door" approach (Fig. 46-46). Compared to the epithelialized graft, the connective tissue graft is preferable due to a less invasive palatal wound and an improved esthetic result. As an alternative to the connective tissue graft, xenogenic collagen matrix (e.g. Mucograft®) may be used (McGuire & Scheyer 2010; Jepsen *et al*. 2013).

The technique for the *connective tissue graft combined with a coronally advanced flap* is as follows (Fig. 46-43):

1. The surgical technique utilized is the coronally advanced flap as described above, but with the difference that the flap is elevated entirely as a split-thickness flap. The interdental papillae should be de-epithelialized to allow for maximum coronal positioning of the tissue flap over the exposed root surface at suturing (Fig. 46-43b).
2. A subepithelial connective tissue graft of masticatory mucosa is harvested on the palatal aspect of the maxillary premolars/first molar (or from the retromolar pad) by the use of a "trap-door" approach (Fig. 46-46). Before incisions are placed, the available thickness of the mucosa is estimated using the tip of the syringe. A horizontal incision, perpendicular to the underlying bone surface, is made approximately 3 mm apical to the soft tissue margin (Fig. 46-46a). The mesiodistal extension of the incision is determined from the graft size required, which is 6 mm longer than the width of the dehiscence measured at the level of the CEJ. To facilitate the removal of the graft, a vertical releasing incision may be made at the mesial termination of the primary incision. An incision is then placed from the line of the first incision and directed apically to perform a split incision of the palatal mucosa (Fig. 46-46b–f). A small periosteal elevator or scalpel is used to release the connective tissue graft from the bone.
3. The graft is immediately transferred to the recipient site and positioned at a distance from the CEJ equal to the height of keratinized tissue originally present apical to the recession defect. The graft is secured in position with two double vertical mattress sutures to adjacent soft tissue lateral to the dehiscence (Fig. 46-43c). A sling suture is placed in the papilla regions to position the margin of the covering advanced flap about 1 mm coronal to the CEJ. Interrupted sutures are used to close the wound along the vertical incisions (Fig. 46-43d).

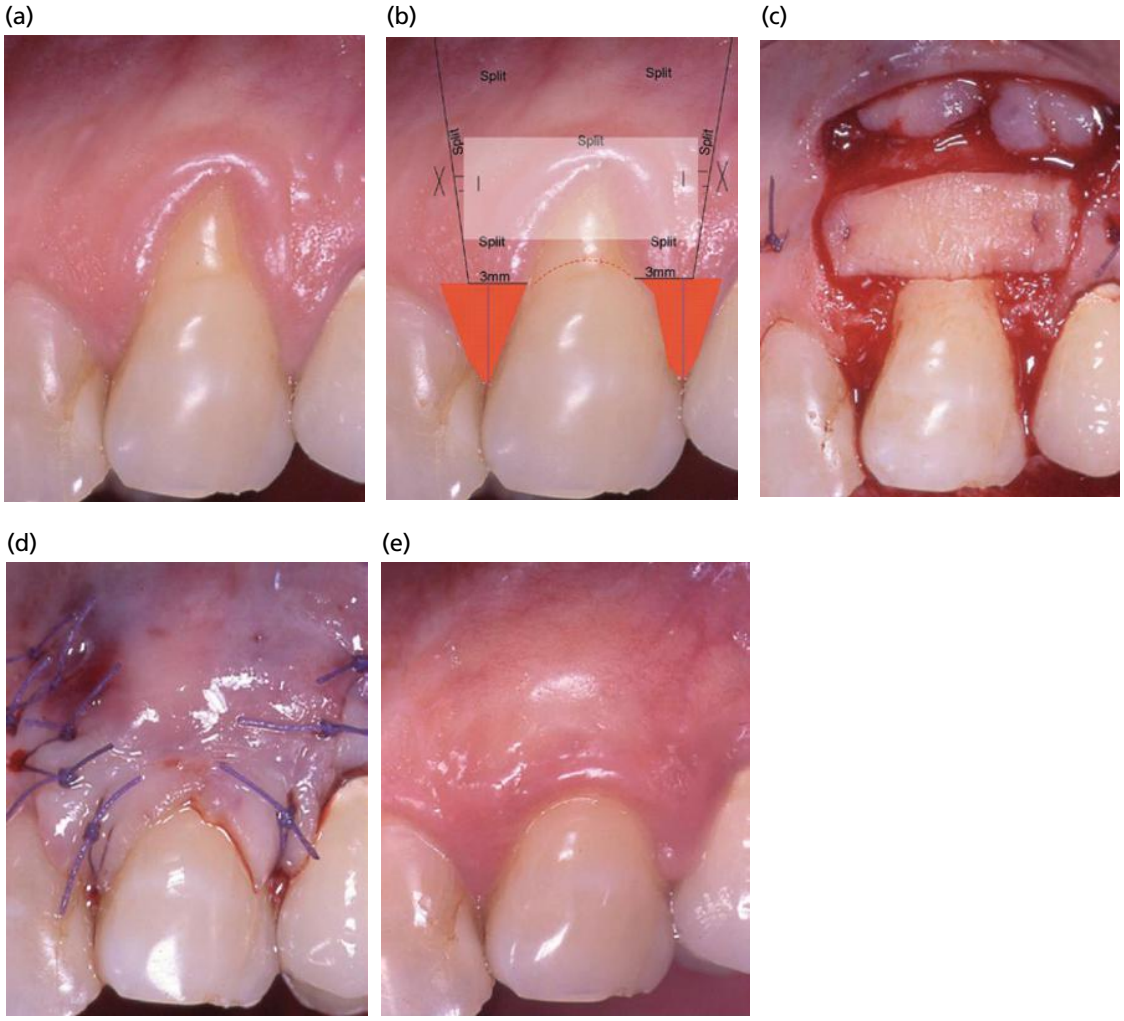


Fig. 46-43 Free connective tissue graft combined with a coronally advanced flap procedure: single recession (see text for explanation). (a, b) Deep gingival recession at a cuspid with minimal height of keratinized tissue apical to the root exposure. (c) Graft has been sutured to leave an area between the cementoenamel junction and the graft available for the marginal keratinized tissue of the flap. (d) Flap has been advanced coronally and sutured. (e) Clinical healing at 1 year.

Figure 46-47 illustrates the procedure applied to a case with multiple recession sites.

The "envelope" technique (Fig. 46-48) is as follows:

1. With the use of the "envelope" technique, the recipient site is prepared by first eliminating the sulcular epithelium by an internal beveled incision (Fig. 46-48a). Second, an "envelope" is prepared apically and laterally to the recession by split incisions (Fig. 46-48b). The depth of the preparation should be 3–5 mm in all directions. In an apical direction, the preparation of the site should extend beyond the mucogingival junction to facilitate the placement of the connective tissue graft and to allow for coronal advancement of the mucosal flap at the time of suturing.
2. A foil template may be used to harvest an appropriately sized connective tissue graft. The graft, which is obtained by the "trap-door" approach described above (Fig. 46-46), is inserted into the prepared "envelope" and positioned to cover the exposed root surface (Fig. 46-48c, d).
3. Sutures are placed to secure the graft in position (Fig. 46-48d). A crossed sling suture may be placed to advance the mucosal flap coronally. Pressure is applied for 5 minutes to adapt the graft closely to the root surface and covering soft tissue.

Figure 46-45 shows the treatment of a recession defect with the "envelope" technique.

The "*tunnel" technique* (Fig. 46-49) is as follows:

1. In case multiple adjacent recessions are to be treated, "envelopes" are prepared for each tooth as described above. However, the lateral split incisions are extended so that the multi-envelopes are connected mesially and distally to form a mucosal tunnel. Care should be taken to avoid detachment of the papillae.
2. The graft is gently positioned inside the tunnel and its mesial and distal extremities are fixed with two interrupted sutures. Sling sutures may be placed to advance the mucosal flap coronally over the exposed portions of the connective tissue graft. Pressure is applied for 5 minutes to closely adapt the graft to the root surface and covering soft tissue.

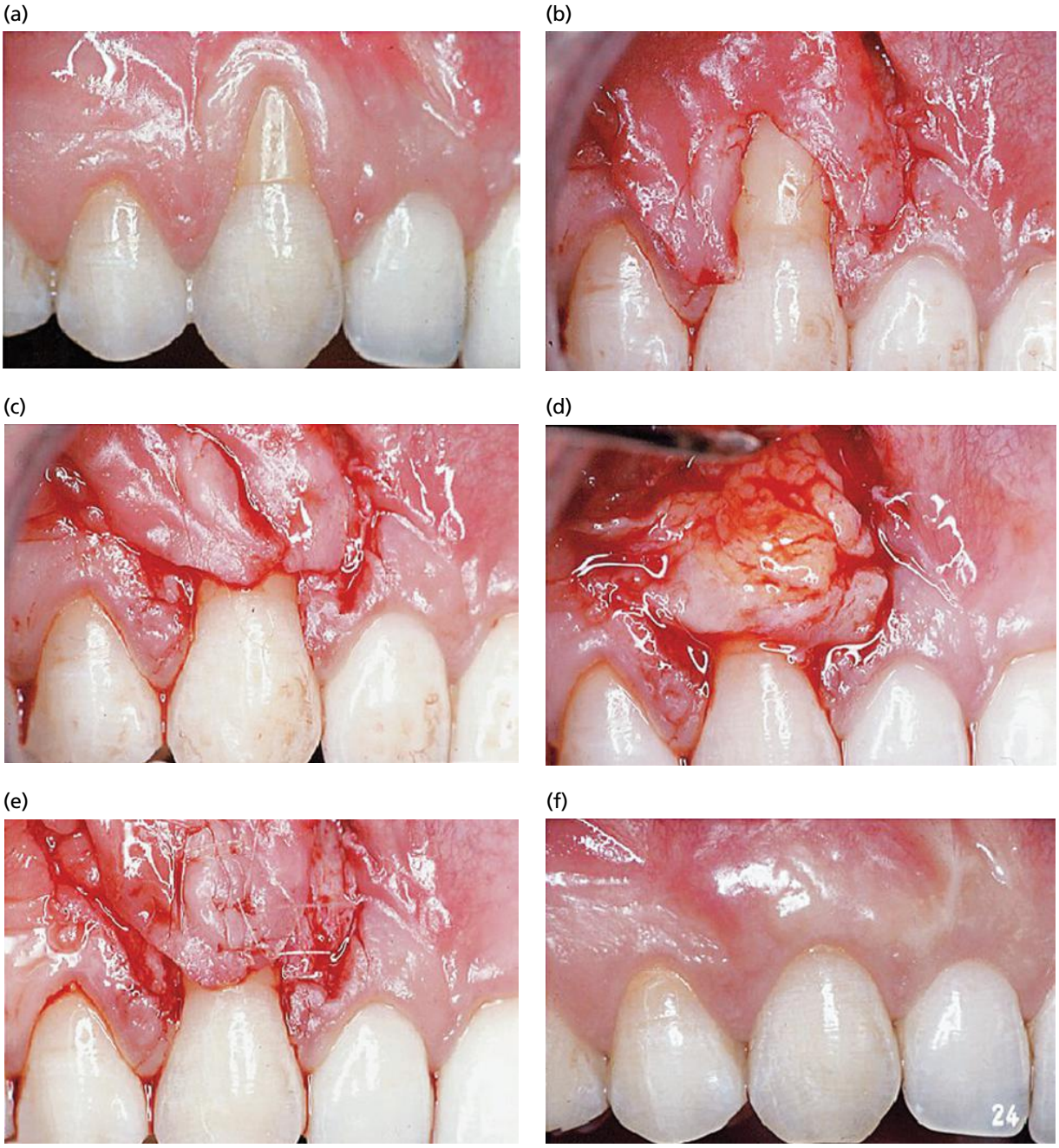


Fig. 46-44 (a–e) Free connective tissue graft combined with a double papilla flap procedure. (f) One-year post-treatment result.

Selection of surgical procedure for root coverage

For each individual case, several factors have to be taken into consideration when selecting the surgical procedure for achieving root coverage, for example jaw, tooth position, recession depth and width, tissue thickness and quality apical and lateral to the recession, esthetic demands, and compliance. From an esthetic point of view, the soft tissue coverage of exposed root surfaces should be in harmony with the adjacent tissue and hence a pedicle graft would be the preference.

For maxillary teeth, the coronally advanced flap may be considered as the basic procedure to be used for single as well as multiple recessions. If the quality of the mucosa apical to the recessions is considered inadequate for root coverage, the procedure is combined with the placement of a connective tissue graft.

In the mandible, the placement of a free connective tissue graft with an "envelope" or a "tunnel" preparation is preferred because of a thin mucosa apical to the recession and often the presence of multiple frenula, that is conditions not suitable for a coronally advanced flap. In case of a localized single recession defect of moderate depth, a rotational flap may be used if keratinized mucosa of sufficient dimensions are available lateral to the recession.

Soft tissue recessions at dental implants are commonly associated with a thin mucosa (Fig. 46-50) and hence the surgical approach to regain soft tissue

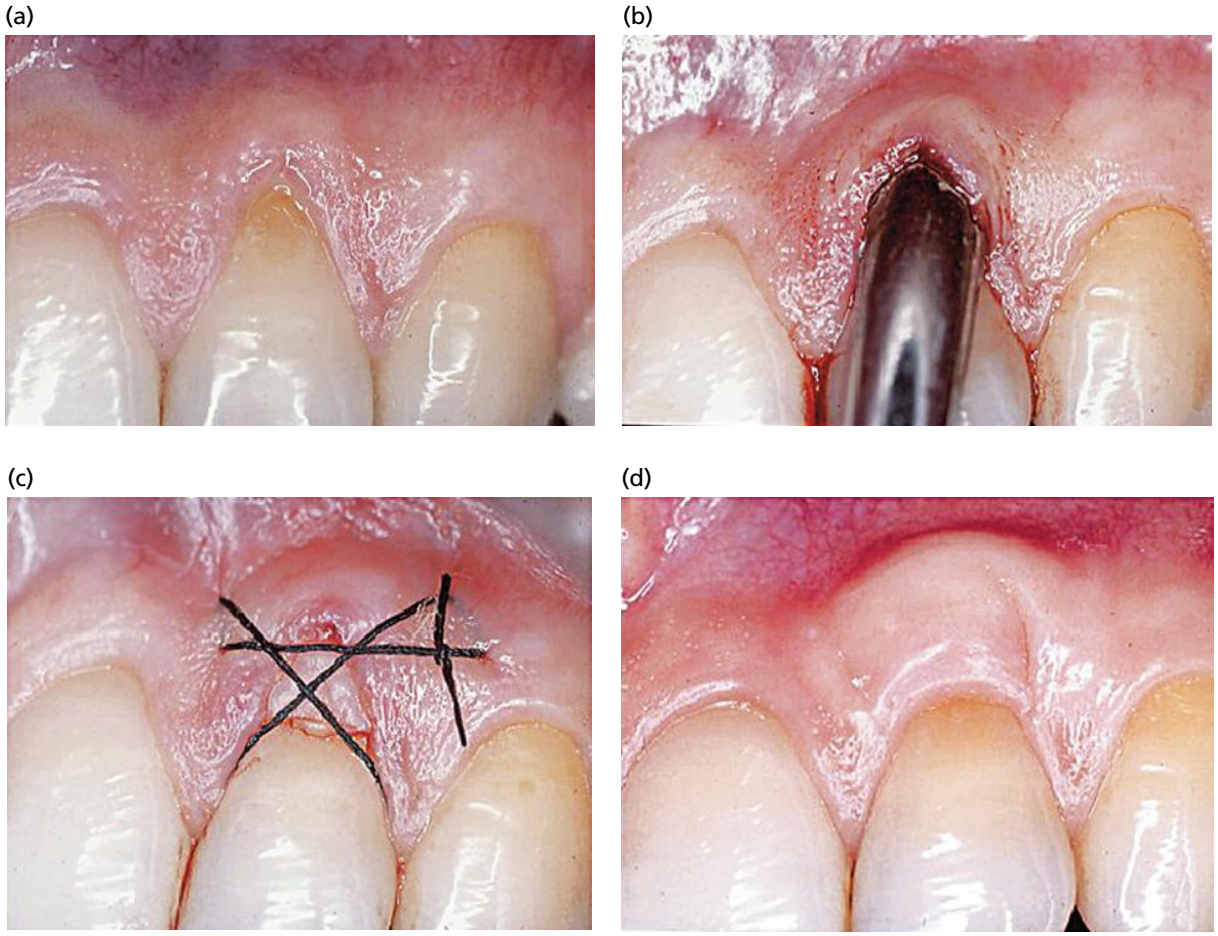


Fig. 46-45 (a–c) Free connective tissue graft procedure: the "envelope technique" (see text for explanation). (d) One-year post-treatment result. (Courtesy of P. Cortellini.)

coverage of the implant unit has to involve a connective tissue graft, either in a combined procedure with a coronally advanced flap or in a two-stage procedure with the placement of the connective tissue graft with an "envelope" procedure, followed by a coronally advanced flap as a second procedure.

Clinical outcome of root coverage procedures

Independent of the modality of surgical procedure used to obtain soft tissue root coverage, shallow residual probing depths, gain in clinical attachment, and increase in gingival height are the common characteristics of treatment outcome. Although the major indications for performing root coverage procedures are esthetic/cosmetic demands and root sensitivity, few studies have used assessments of these criteria as end points of treatment success. Instead, the common outcome variables used are the amount of root coverage achieved, expressed as a percentage of the initial depth of the recession defect, and the proportion of treated sites showing complete root coverage. Whereas complete root coverage may be a successful outcome with respect to root sensitivity, it is not necessarily equivalent to treatment success from an esthetic point of view because, besides root coverage in harmony with adjacent teeth, factors such as tissue thickness, color, and texture influence the appreciation of the esthetic result.

Root coverage

An overall comparison of the treatment outcome of various root coverage procedures is hampered by the fact that there is substantial heterogeneity between studies (Cairo *et al.* 2008; Chambrone *et al.* 2009). The variability in the treatment outcome for the various procedures, both within and between studies, is large, indicating that the procedures are operator sensitive and that various factors influencing the treatment outcome have not been adequately considered. An analysis with regard to initial Miller class I–II recession defects that may be successfully covered following treatment with coronally advanced flaps, based on the data from randomized controlled studies included in recent systematic reviews (Cairo *et al.* 2008; Chambrone *et al.* 2009), shows that on average about 70% root coverage may be expected (range 34–87%). Complete coverage of the recession defect, which is the ultimate goal of the therapy, may be reached in approximately 35% of treated cases (range 15–60%).

Evidence suggests that the treatment outcome can be improved by adjunctive use of connective tissue

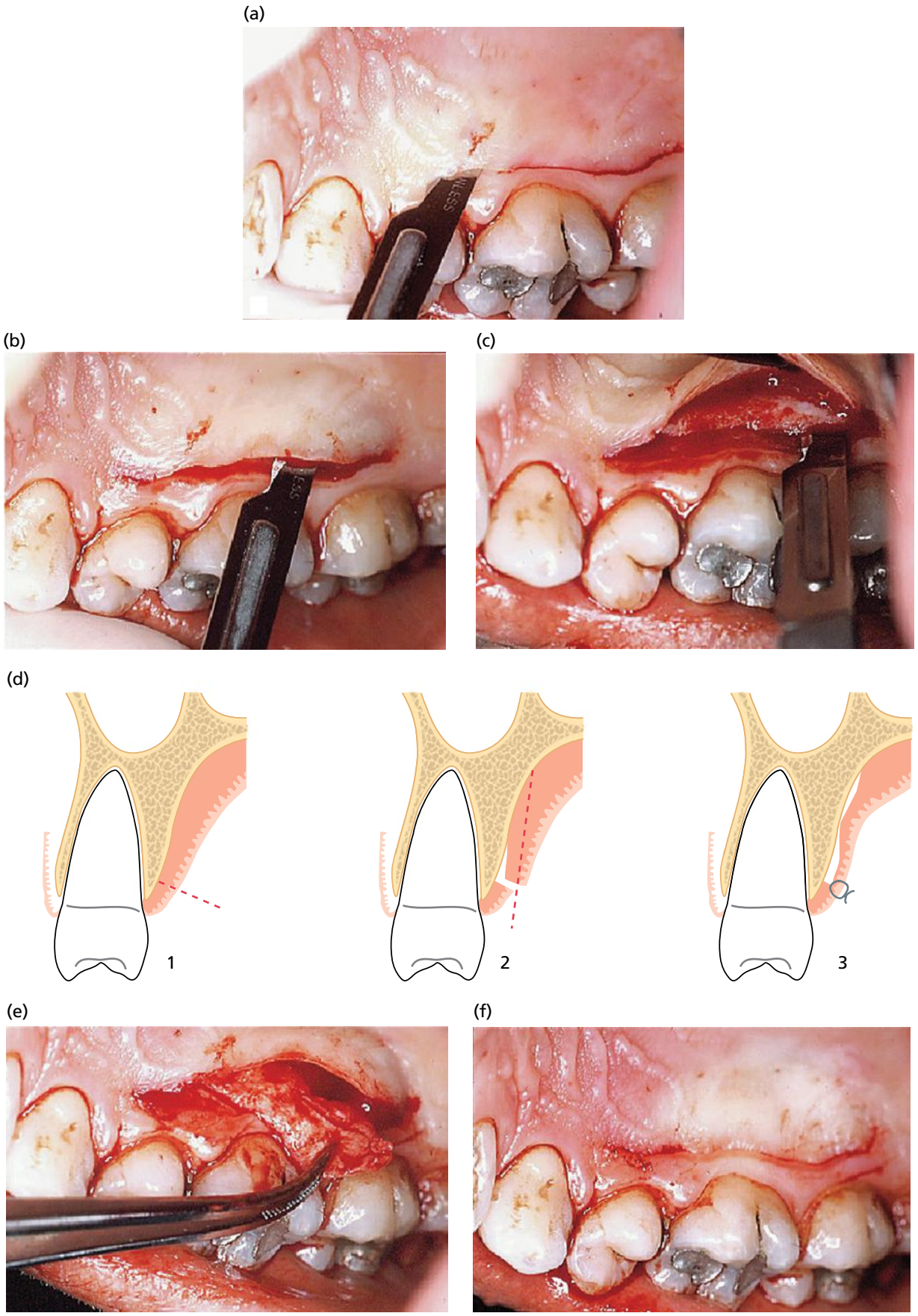


Fig. 46-46 (a–f) "Trap-door" technique for harvesting a free connective tissue graft (see text for explanation).

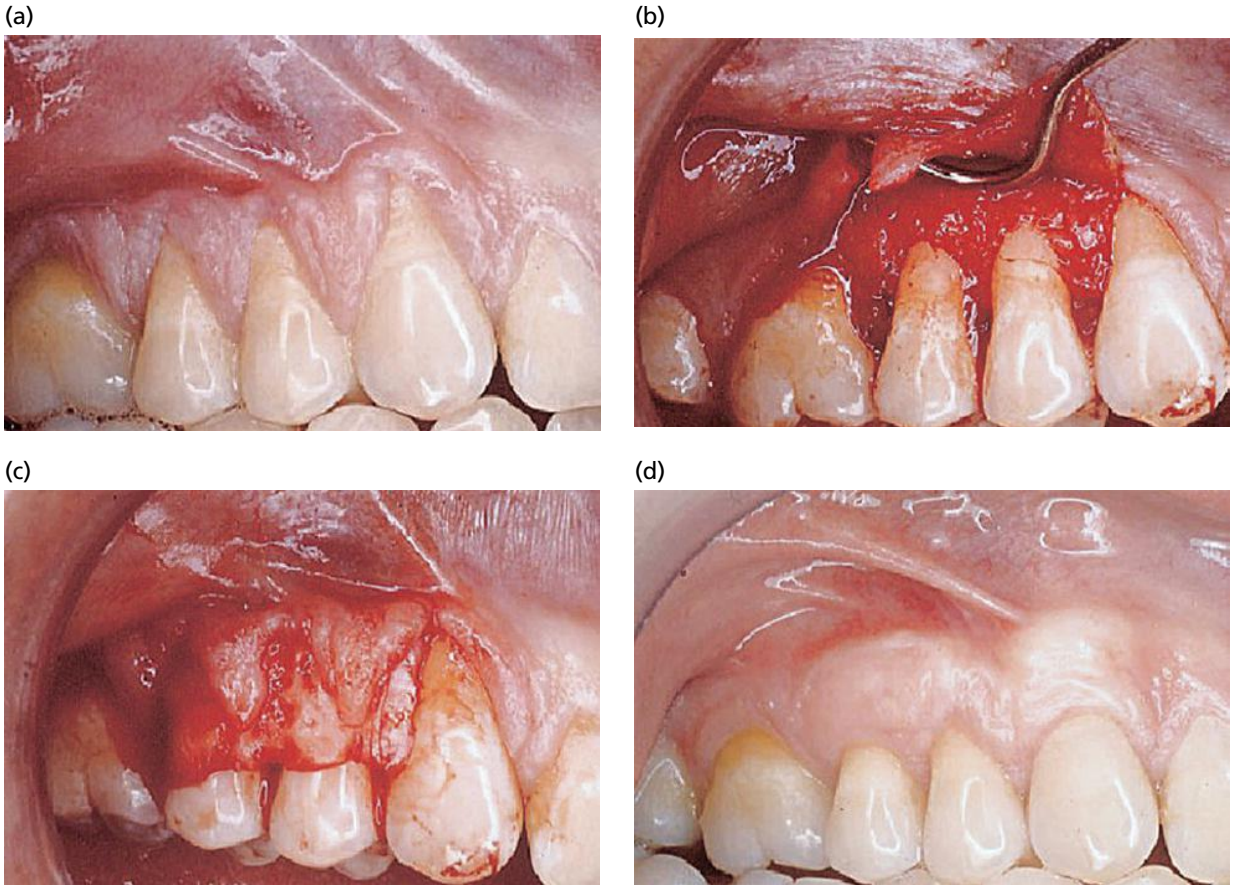


Fig. 46-47 (a–c) Free connective tissue graft combined with a coronally advanced flap procedure: multiple recessions (see text for explanation). (d) One-year post-treatment result.

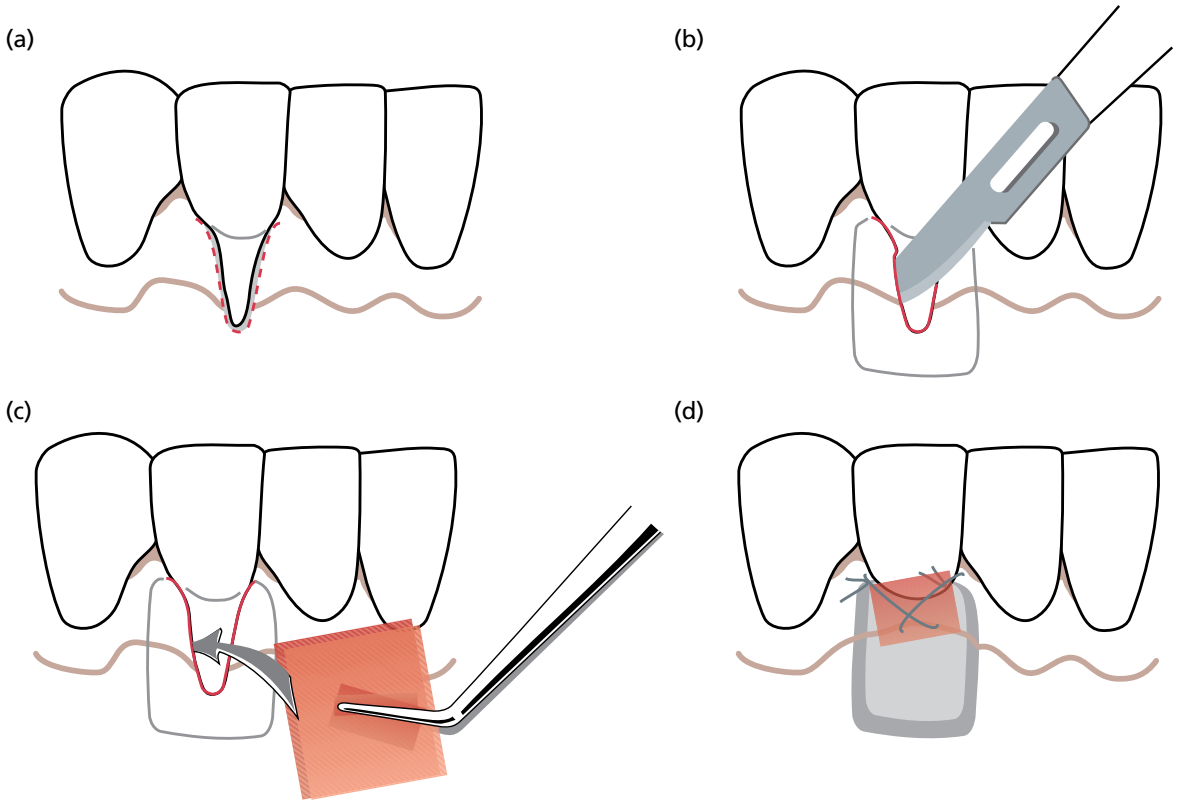


Fig. 46-48 (a–d) Free connective tissue graft procedure: the "envelope technique". Schematic drawings illustrating the surgical technique (see text for explanation).

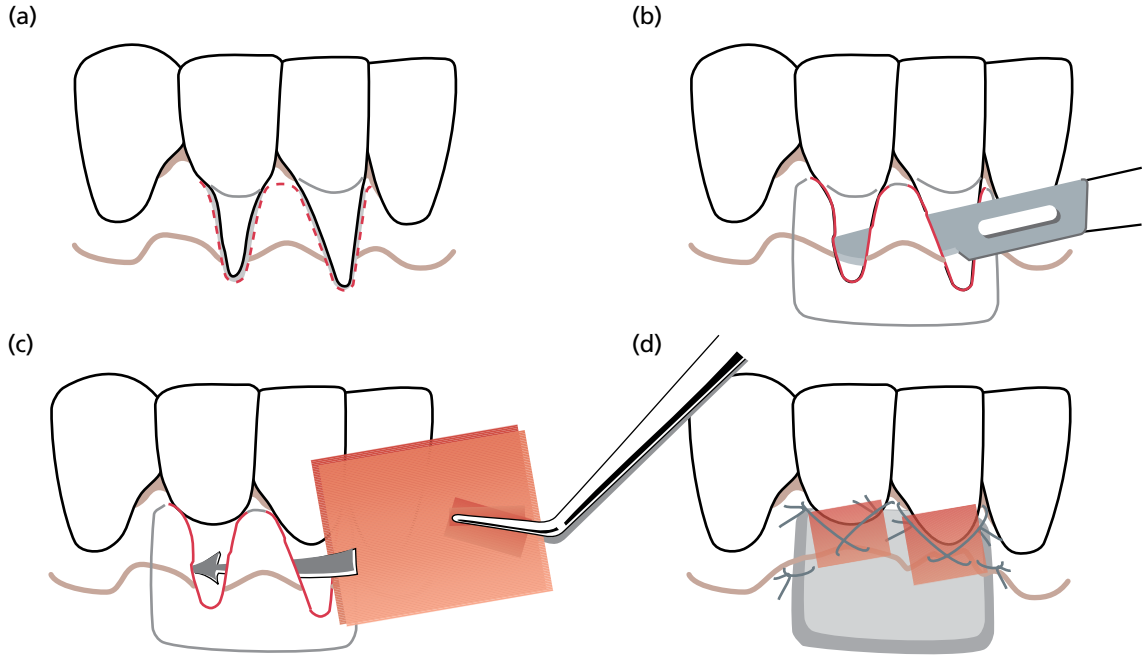


Fig. 46-49 (a–d) Free connective tissue graft procedure: the "tunnel technique". Schematic drawings illustrating the surgical technique (see text for explanation).

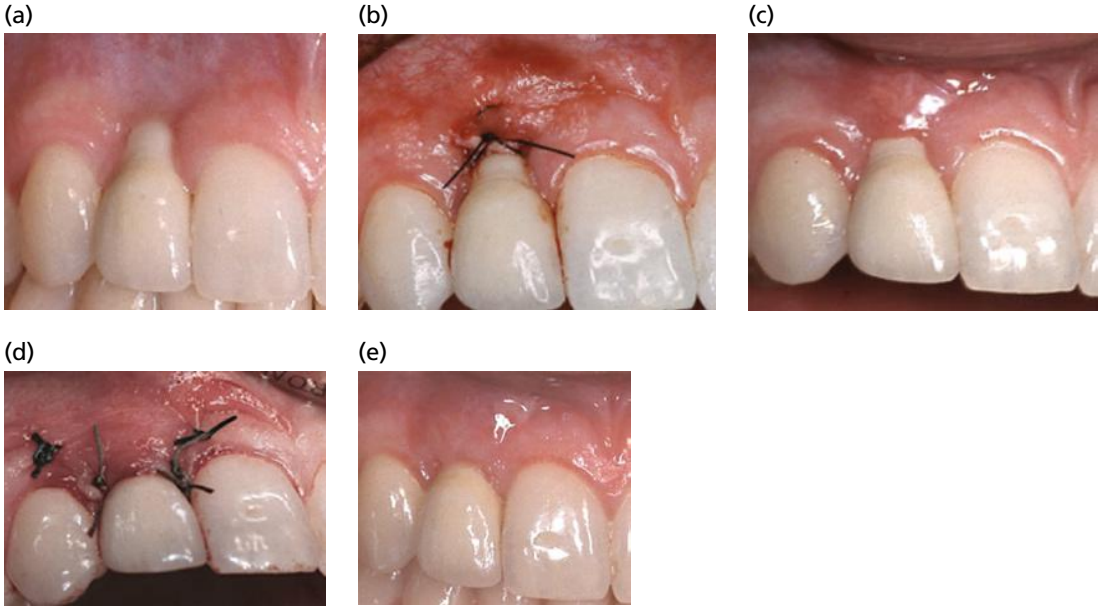


Fig. 46-50 (a) Soft tissue recession (dehiscence) defect at a dental implant in the lateral incisor position. Note the lack of facial keratinized mucosa and thin facial mucosa apical of the recession defect. (b) Connective tissue graft is placed by a pouch procedure in order to increase the thickness of the soft tissue apical to the soft tissue dehiscence. (c) Healing after 4 weeks when (d) the facial soft tissue was coronally advanced. (e) One-year follow-up. Note the increased volume of facial tissue and position of the soft tissue margin in harmony with the neighboring teeth.

graft or enamel matrix proteins, with an estimated mean absolute adjunctive effect of 15–25% for complete root coverage and 13–17% for reduction in recession depth (Cairo *et al.* 2008; Chambrone *et al.* 2009; Buti *et al.* 2013). The inclusion of barrier membranes, on the other hand, may not improve the treatment outcome. In fact, based on data from the systematic reviews referred to, the estimated mean absolute effect is –17% for complete root coverage compared to that with a coronally advanced flap alone. The lower mean predictability of complete root coverage achieved with the GTR procedure has been associated with the problem of membrane exposure during healing (Trombelli *et al.* 1995), but whether a bioresorbable or a non-bioresorbable barrier membrane is used does not seem to affect the treatment outcome (Roccuzzo *et al.* 1996).

With regard to the application of soft tissue coverage procedures for the treatment of soft tissue recessions/dehiscenses at dental implants, there is very limited data available in the literature on treatment outcomes. A limited case series by Burkhardt

et al. (2008) showed that complete coverage of the dehiscence was not obtained for any of the treated soft tissue recession defects at dental implants with a depth of 2–5 mm when a combined surgical procedure including connective tissue graft and coronally advanced flap was used. At the 6-month follow-up after surgery, the average gain in soft tissue coverage amounted to 66%.

Factors influencing the degree of root coverage

Patient-related factors. As with other surgical periodontal treatment procedures, poor oral hygiene will negatively influence the success of root coverage procedures (Caffesse *et al*. 1987). Further, a predominant causative factor in the development of gingival recession is toothbrushing trauma, and hence this factor has to be corrected to secure an optimal outcome for any root coverage procedure. Treatment outcome in terms of root coverage is usually less favorable in smokers than in non-smokers (Trombelli & Scabbia 1997; Zucchelli *et al*. 1998; Martins *et al*. 2004; Erley *et al*. 2006; Silva *et al*. 2006), although some studies showed no differences between these groups (Tolmie *et al*. 1991; Harris 1994).

Site related factors Among site-specific factors, the level of interdental periodontal support may be of greatest significance for the outcome of root coverage procedures. From a biologic point of view, complete root coverage is achievable in Miller class I–II recession defects (Fig. 46-51), while when loss of connective tissue attachment and soft tissue height also involves proximal tooth sites (class III–IV recession defects), only partial facial root coverage may be obtainable (Miller 1985b) (Fig. 46-52).

An additional factor shown to influence the degree of attainable root coverage is the dimensions of the recession defect. Less favorable treatment outcome has been reported at sites with wide (>3 mm) and deep (≥5 mm) recessions (Holbrook & Ochsenbein 1983; Pini Prato *et al*. 1992; Trombelli *et al*. 1995). In a study comparing the treatment effect of coronally advanced flap and free connective tissue graft procedures, Wennström and Zucchelli (1996) reported that complete root coverage was observed in only 50% of the defects with an initial depth of ≥5 mm compared to 96% for shallower defects. Pini Prato *et al*. (1992) suggested, based on clinical observations in a controlled clinical trial, that a more favorable result with respect to root coverage might be obtained with the GTR procedure in sites with deep (≥5 mm) recession defects as compared to the coronally advanced flap procedure alone. At the 18-month examination, the average coverage was 77% with and 66% without the inclusion of a membrane barrier. However, data presented from more recent systematic reviews and meta-analyses (Roccuzzo *et al*. 2002; Oates *et al*. 2003) showing that the predictability of root coverage is significantly reduced with the use of barrier membranes, limiting the justification for the use of the GTR procedure in the treatment of recession defects. The pretreatment gingival height apical to the recession defect is not correlated to the amount of root coverage obtained (Romanos *et al*. 1993; Harris 1994).

Technique-related factors Several technique-related factors may influence the treatment outcome of a pedicle graft procedure. In a systematic review including data from 15 studies (Hwang & Wang 2006), a positive correlation was demonstrated between the thickness of the tissue flap and recession reduction. For complete root coverage, the critical threshold thickness was found to be about 1 mm. However, whether a full- or a split-thickness pedicle graft is used for root coverage may not influence the treatment outcome (Espinel & Caffesse 1981).

Elimination of flap tension is considered an important factor for the outcome of the coronally advanced flap procedure. Pini Prato *et al*. (2000a) measured the tension in coronally advanced flaps to compare the

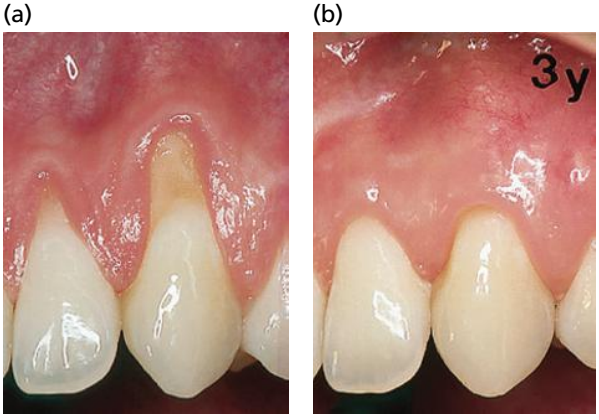


Fig. 46-51 (a) Buccal recession defects but no loss of periodontal support at proximal surfaces. Complete root coverage can be achieved. (b) Three-year follow-up.

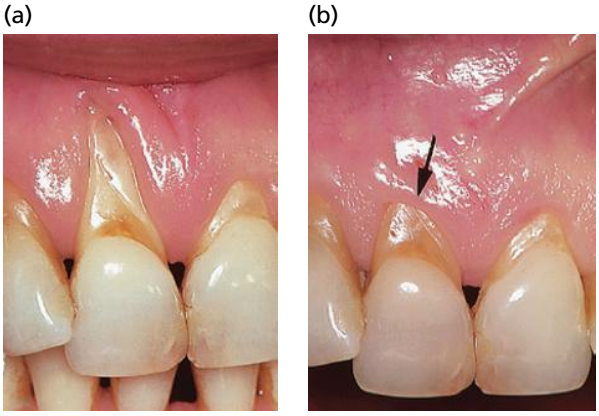


Fig. 46-52 (a) Deep buccal recession at tooth 11. The tooth has loss of support at proximal sites (Miller class III) and complete root coverage is not achievable. Also, neighboring teeth show recessions at all tooth surfaces. (b) Two-year healing result following attempted root coverage at the facial aspect of tooth 11 (arrow). The coronal position of the soft tissue margin is defined by the extension of proximal loss of periodontal support.

amount of root coverage in sites with and without residual flap tension. At sites that had residual tension (mean 6.5 g), the root coverage amounted to 78% 3 months post-surgically and 18% of the treated sites showed complete root coverage. Sites without tension demonstrated mean root coverage of 87% and complete root coverage in 45% of the cases. Furthermore, a statistically significant negative association was shown between the magnitude of residual tension in the flap and the amount of recession reduction.

Although the connective tissue areas lateral to the recession defect are considered important for the retention of the advanced flap when positioned over the root surface, the dimension of the interdental papilla area is not a prognostic factor for the clinical outcome of the root coverage procedure (Saletta *et al*. 2001). As can be expected, the position of the gingival margin relative to the CEJ after suturing affects the probability of complete root coverage following healing. Pini Prato *et al*. (2005) demonstrated that for 100% predictability of complete root coverage in the treatment of Miller class I recessions with a coronally advanced flap procedure, the flap margin has to be positioned at least 2 mm coronal to the CEJ.

With regard to free graft procedures, the thickness of the graft influences their success (Borghetti & Gardella 1990). A thickness of the free graft of about 2 mm is recommended.

Increased gingival height

An increased apicocoronal height of the gingiva is found following all procedures in which pedicle grafts of adjacent gingiva or free grafts from the palate have been placed over the recession defect. It is interesting to note, however, that an increased gingival height is also a common finding following a coronally advanced flap procedure only involving the existing gingiva apical to the recession (Fig. 46-53). This finding may be explained by several events taking place during the healing and maturation of the marginal tissue.

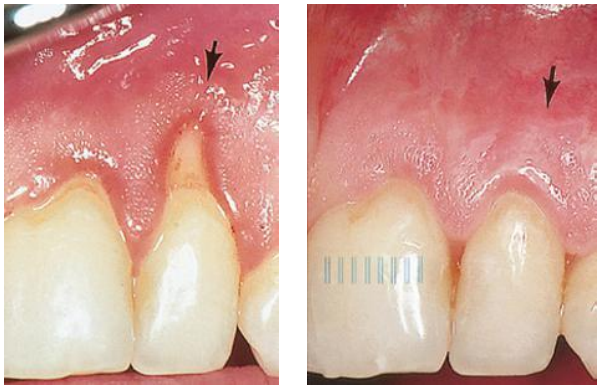


Fig. 46-53 Increased dimension of keratinized tissue 1 year following root coverage with a coronally advanced flap procedure. (a) Before and (b) One-year postoperatively. Arrows indicate the position of the mucogingival line.

Granulation tissue derived from the periodontal ligament tissue will form a connective tissue similar to the one of gingiva and with the potential to induce keratinization of the covering epithelium (Karring *et al*. 1971). A second factor to consider is the tendency of the mucogingival line to regain its "genetically"-defined position following its coronal "dislocation" with the coronally advanced flap procedure used to achieve root coverage. Support for the concept that the mucogingival line will regain its original position over time comes from a study by Ainamo *et al*. (1992). The authors performed an apically repositioned flap procedure in the lower anterior tooth region, which resulted in a 3-mm apical displacement of the mucogingival line. Re-examination after 18 years showed no differences in position of the mucogingival line between sites treated with the apically repositioned flap and contralateral control sites treated with a procedure not interfering with the mucogingival line, indicating that the mucogingival line had regained its original position.

Soft tissue healing against the covered root surface

Treatment of gingival recessions by pedicle grafts or free grafts may be clinically successful, but does the treatment result in a healing characterized by the formation of a connective tissue attachment or an epithelial attachment? Independent of the quality of attachment formed, however, root coverage procedures evidently rarely result in the formation of a deep periodontal pocket.

Healing of pedicle soft tissue grafts

In the areas surrounding the recession defect, that is where the recipient bed consists of bone covered by connective tissue, the pattern of healing is similar to that observed following a traditional flap operation. Cells and blood vessels from the recipient bed as well as from the tissue graft invade the fibrin layer, which is gradually replaced by connective tissue. After 1 week, a fibrous reunion is already established between the graft and the underlying tissue.

Healing in the area where the pedicle graft is in contact with the denuded root surface was studied by Wilderman and Wentz (1965) in dogs. According to these authors, the healing process can be divided into four different stages (Fig. 46-54):

1. *Adaptation stage (from 0 to 4 days).* The laterally repositioned flap is separated from the exposed root surface by a thin fibrin layer. The epithelium covering the transplanted tissue flap starts to proliferate and reaches the tooth surface at the coronal edge of the flap after a few days.
2. *Proliferation stage (from 4 to 21 days).* In the early phase of this stage, the fibrin layer between the root surface and the flap is invaded by connective

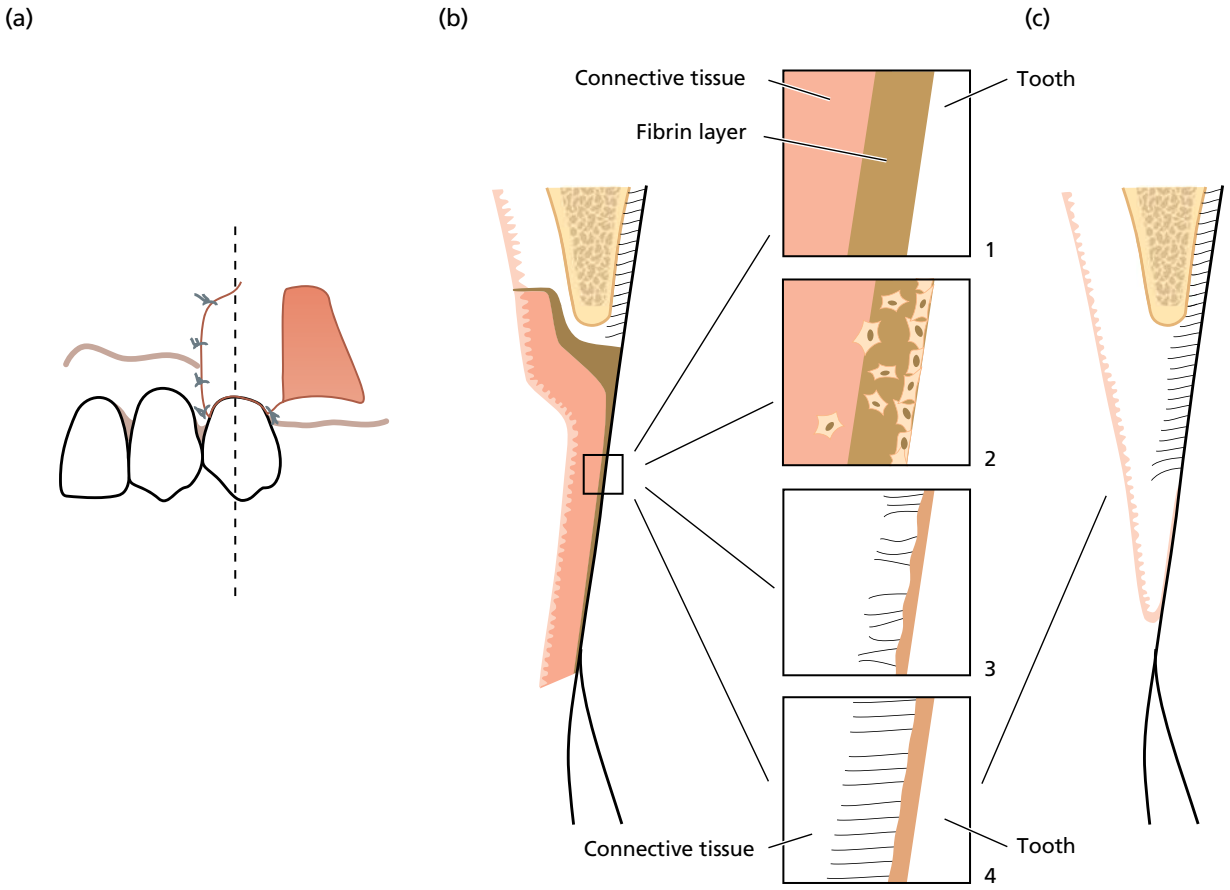


Fig. 46-54 (a) Schematic drawing illustrating healing following treatment of a localized soft tissue recession with a pedicle graft. (b) Cross-section through the area immediately after operation. The framed areas (1–4) illustrate the four stages into which the healing process can be divided. (c) Area after healing. Approximately 50% of the successfully covered defect may show new connective tissue attachment.

tissue proliferating from the subsurface of the flap. In contrast to areas where healing occurs between two connective tissue surfaces, growth of connective tissue into the fibrin layer can only take place from one surface. After 6–10 days, a layer of fibroblasts is seen in apposition to the root surface. These cells are believed to differentiate into cementoblasts at a later stage of healing. At the end of the proliferation stage, thin collagen fibers are formed adjacent to the root surface, but a fibrous union between the connective tissue and the root has not been observed. From the coronal edge of the wound, epithelium proliferates apically along the root surface. According to Wilderman and Wentz (1965), the apical proliferation of epithelium may stop within the coronal half of the defect, although further down-growth of epithelium was also frequently observed.

3. *Attachment stage (from 27 to 28 days).* During this stage of healing, thin collagen fibers become inserted into a layer of new cementum formed at the root surface in the apical portion of the recession.
4. *Maturation stage.* This last stage of healing is characterized by continuous formation of collagen fibers. After 2–3 months, bundles of collagen fibers insert into the cementum layer on the curetted root surface in the apical portion of the recession.

Results of experimental studies in monkeys and dogs on the healing characteristics of the periodontal wound have been interpreted to indicate that gingival connective tissue lacks the ability to form a new connective tissue attachment to the root, but may induce root resorption (see Chapter 28). This finding is of particular interest when considering the rationale for the treatment of recession defects by free or pedicle soft tissue grafts. Since, in these surgical procedures, gingival connective tissue is placed in contact with a denuded root surface, root resorption should be expected to occur. The reason why it is not a common complication following this type of treatment can be explained by two possible events: either cells from the periodontal ligament form a fibrous attachment to the root surface or epithelial cells proliferate apically, forming a root-protective barrier (long junctional epithelium) towards the gingival connective tissue.

Histologic studies to determine whether it is one or the other type of attachment that results following treatment of recessions with pedicle grafts indicate that new connective tissue attachment may form in part of the defect. In the study by Wilderman and Wentz (1965), a connective tissue attachment of around 2 mm and an epithelial attachment of the same height had formed in the soft tissue-covered

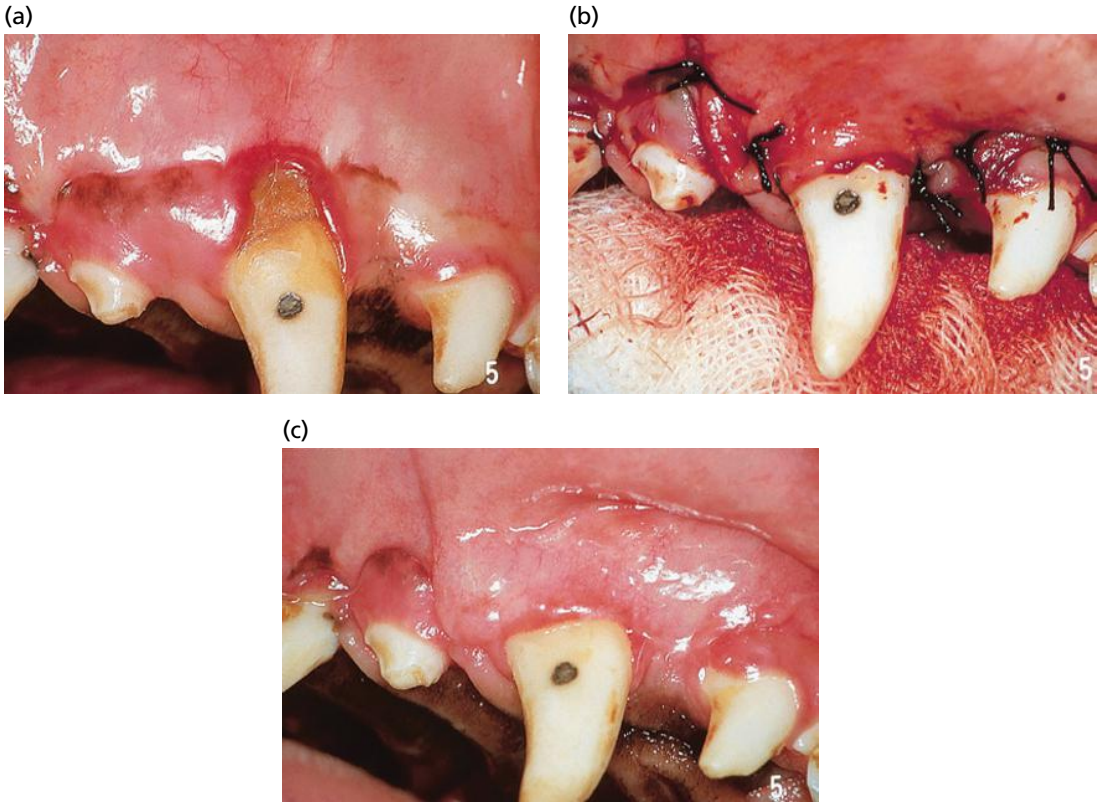


Fig. 46-55 Clinical photographs showing the treatment of an experimentally induced localized recession defect in a dog with a coronally displaced flap. (a) Presurgical appearance of the localized recession defect. (b) Site following flap closure of the defect and (c) following 3 months of healing.

portion of the defect, that is about 50% of the successfully covered defect showed new connective tissue attachment. Gottlow *et al*. (1986) examined the result of healing following treatment of experimentally produced recession type defects with a coronally advanced flap in dogs (Fig. 46-55). The histologic analysis after 3 months of healing disclosed that, on average, 20% of the apicocoronal length of the original defect had been exposed due to recession during healing (i.e. about 80% root coverage was achieved), 40% was covered by epithelium, and 40% demonstrated connective tissue attachment with cementum formation (Fig. 46-56). Determining factors for the type of healing result were the size and the shape of the defect. The possibility of achieving a new connective tissue attachment in the apical portion of the defect seemed to be considerably better in narrow recession defects than in wider ones, most likely because the periodontal ligament at the lateral parts of the defect will serve as a source of granulation tissue from which a new connective tissue attachment can develop.

Healing following pedicle graft procedures has also been histologically studied in monkeys (Caffesse *et al*. 1984; Gottlow *et al*. 1990), and in these studies 38–44% of the successfully covered recession defects demonstrated formation of new connective tissue attachment. The study by Gottlow *et al*. (1990) also showed that the use of a GTR membrane between the root surface and the pedicle graft generated

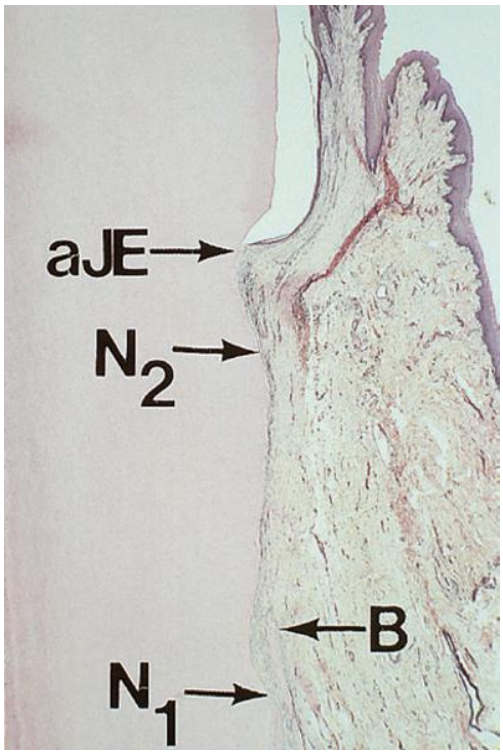


Fig. 46-56 Microphotograph of the healing following a coronally displaced flap in the same dog as in Fig. 44-54. A new connective tissue attachment is formed and extends coronally from the apical border of the notch prepared at the bottom of the bone dehiscence (N_1) to the apical termination of the epithelium (aJE) located within the notch indicating the presurgical level of the soft tissue margin (N_2). (B, alveolar bone crest.)

significantly more new connective tissue attachment (79% of the covered part of the recession defect). A significantly increased amount of cementum formation with inserting collagen fibers was also demonstrated following the utilization of enamel matrix proteins in combination with a coronally advanced flap for treatment of experimentally produced recession defects in dogs (Sallum *et al*. 2004).

Some case reports with human block sections provide further evidence that new connective tissue attachment may be formed following pedicle graft procedures. Histologic evaluation of two teeth treated with a laterally positioned flap revealed that connective tissue attachment was re-established in the apical quarter of the successfully covered portion of the root (Sugarman 1969). Cortellini *et al*. (1993) examined histologically a tooth treated with the GTR procedure and showed that connective tissue faced 74% of the length of the recession defect. New cementum with inserting collagen fibers, that is new connective tissue attachment, covered 48% of the distance between the apical border of the root instrumentation and the soft tissue margin. In addition, histomorphometric assessments of a tooth treated with enamel matrix proteins revealed that new cementum covered 73% of the original defect (Heijl 1997).

Healing of free soft tissue grafts

Survival of a free soft tissue graft placed over a denuded root surface depends on diffusion of plasma and subsequent revascularization from those parts of the graft that are resting on the connective tissue bed surrounding the dehiscence. The establishment of collateral circulation from adjacent vascular borders of the bed allows the healing phenomenon of "bridging" (Sullivan & Atkins 1968a). Hence, the amount of tissue that can be maintained over the root surface is limited by the size of the avascular area (Oliver *et al*. 1968; Sullivan & Atkins 1968). Other factors considered critical for the survival of the tissue graft placed over the root surface are that a sufficient vascular bed is prepared around the dehiscence and that a thick graft is used (Miller 1985b).

Another healing phenomenon frequently observed following free graft procedures is "creeping attachment", that is coronal migration of the soft tissue margin. This occurs as a consequence of tissue maturation over a period of about 1 year post treatment.

There are few histologic evaluations of the nature of the attachment established to the root surface following the use of free grafts for root coverage. Sugarman (1969) reported from a histologic evaluation of a human tooth treated with a free soft tissue graft that new connective tissue attachment was found in the apical quarter of the successfully covered recession defect. Harris (1999) and Majzoub *et al*. (2001), each reporting the histologic outcome of free connective tissue grafts in two cases, found only minimal amounts of new cementum formation in the most apical part of the recession defect and that healing resulted in a long junctional epithelium occupying the interface between the covering soft tissue and the root. Carnio *et al*. (2002) performed a histologic evaluation of four cases of root coverage with a connective tissue graft combined with application of enamel matrix proteins (Emdogain®). They reported that the healing resulted in connective tissue adhesion to the root surface and that the formation of new cementum was observed only in the most apical end of the grafted area.

Thus, the limited histologic information available from humans on the healing of free soft tissue grafts indicates that a healing pattern similar to the one discussed above following pedicle graft procedures may result, namely that connective tissue attachment may be established in the most apical and lateral parts of the recession defect, but that an epithelial attachment is formed along the major portion of the root. Further, the application of enamel matrix proteins may prevent the apical migration of the epithelium, but may not favor the formation of a true connective tissue attachment between the free graft and the root surface.

Interdental papilla reconstruction

There may be several reasons for loss of papilla height and the establishment of "black triangles" between teeth. The most common reason in the adult individual is loss of periodontal support due to plaque-associated lesions. However, abnormal tooth shape, improper contours of prosthetic restorations, and traumatic oral hygiene procedures may also negatively influence the outline of the interdental soft tissues.

Nordland and Tarnow (1998) proposed a classification system regarding the papillary height adjacent to natural teeth, based on three anatomic landmarks: the interdental contact point, the apical extent of the facial CEJ, and the coronal extent of the proximal CEJ (Fig. 46-57):

- *Normal*: the interdental papilla occupies the entire embrasure space apical to the interdental contact point/area
- *Class I*: the tip of the interdental papilla is located between the interdental contact point and the level of the CEJ on the proximal surface of the tooth
- *Class II*: the tip of the interdental papilla is located at or apical to the level of the CEJ on the proximal surface of the tooth but coronal to the level of the CEJ mid-buccally
- *Class III*: the tip of the interdental papilla is located at or apical to the level of the CEJ mid-buccally.

In an observational study in humans, Tarnow *et al*. (1992) analyzed the correlation between the presence of interproximal papillae and the vertical distance between the contact point and the interproximal bone crest. When the vertical distance from the contact

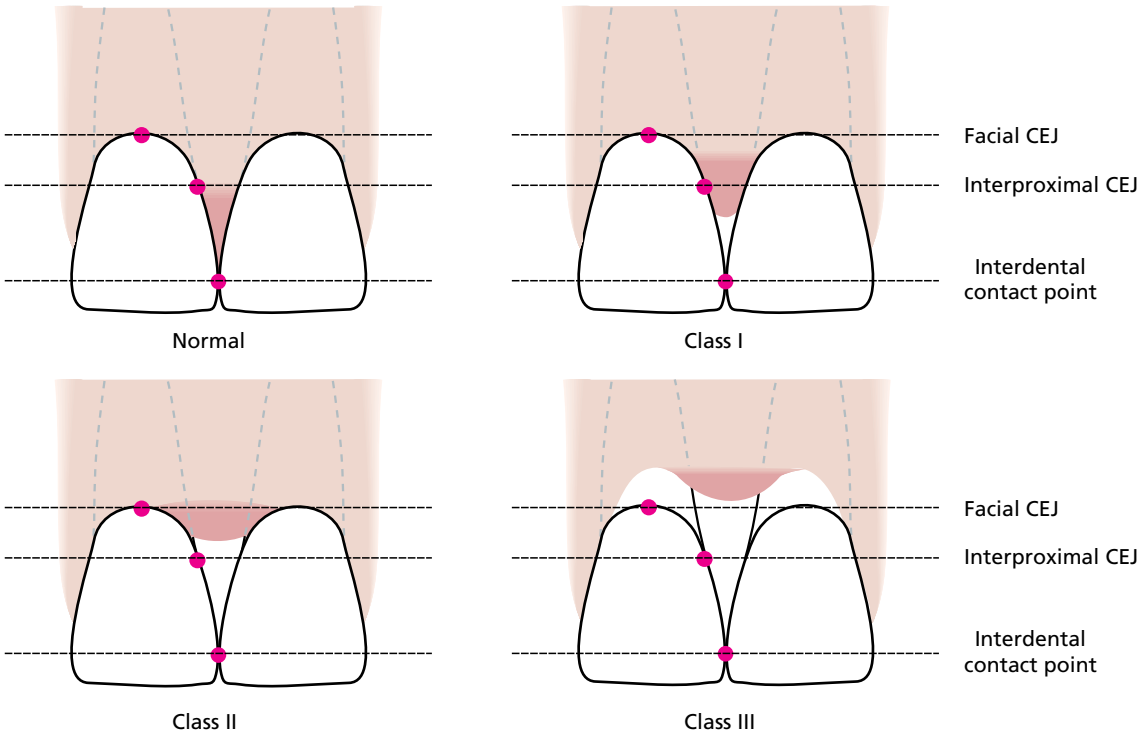


Fig. 46-57 Schematic drawing illustrating the classification system for papilla height. (CEJ, cementoenamel junction.) (Source: Nordland & Tarnow 1998.)

point to the crest of bone was ≤5 mm, the papilla was present almost 100% of the time, whereas if the distance was ≥6 mm only partial papilla fill of the embrasure between the teeth was most commonly found. Considering that a supracrestal connective tissue attachment zone of approximately 1 mm is normally found (Gargiulo 1961), the observation indicates that the biologic height of the interdental papilla may be limited to about 4 mm. This interpretation is supported by the observation that in interdental areas denuded following an apically repositioned flap procedure, an up-growth of around 4 mm of soft tissue had taken place 3 years after surgery (Van der Velden 1982). Hence, before attempts are made to surgically reconstruct an interdental papilla, it is important to carefully assess (1) the vertical distance between the bone crest and the apical point of the contact area between the crowns and (2) the soft tissue height in the interdental area. If the bone crest–contact point distance is ≤5 mm and the papilla height is <4 mm, surgical intervention for increasing the volume of the papilla could be justified in order to solve the problem of an interdental "black triangle". However, if the contact point is located >5 mm from the bone crest, because of loss of periodontal support and/or an inappropriate interdental contact relationship between the crowns, methods to lengthen the contact area apically between the teeth should be selected rather than a surgical attempt to improve the topography of the papilla.

If loss of papilla height is only caused by soft tissue damage from oral hygiene devices, interproximal hygiene procedures must be initially discontinued to allow soft tissue recovery and then successively modified in order to eliminate/minimize traumatic injury to the papillae.

Surgical techniques

Several case reports have been published regarding surgical techniques for the reconstruction of deficient papillae (e.g. Beagle 1992; Han & Takei 1996; Azzi *et al*. 1999). However, the predictability of the various procedures has not been documented and no data are available in the literature providing information on the long-term stability of surgically regained interdental papillae.

Beagle (1992) described a pedicle graft procedure utilizing the soft tissues palatal to the interdental area (Fig. 46-58). A split-thickness flap is dissected on the palatal aspect of the interdental area. The flap is elevated labially, folded, and sutured to create the new papilla at the facial part of the interdental area. A periodontal dressing is applied on the palatal aspect only, in order to support the papilla.

Han and Takei (1996) proposed an approach for papilla reconstruction ("semilunar coronally repositioned papilla") based on the use of a free connective tissue graft (Fig. 46-59). A semilunar incision is placed in the alveolar mucosa facial to the interdental area and a pouch-like preparation is performed into the interdental area. Intrasulcular incisions are made around the mesial and distal half of the two adjacent teeth to free the connective tissue from the root surfaces to allow coronal displacement of the gingival–papillary unit. A connective tissue graft, taken

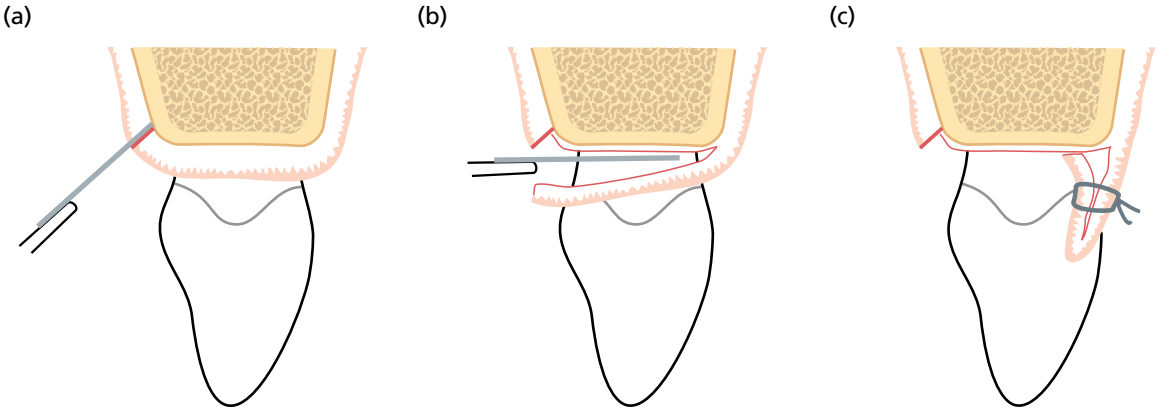


Fig. 46-58 (a–c) Papilla reconstruction: pedicle graft technique. Schematic drawings illustrating the surgical technique (see text for explanation).

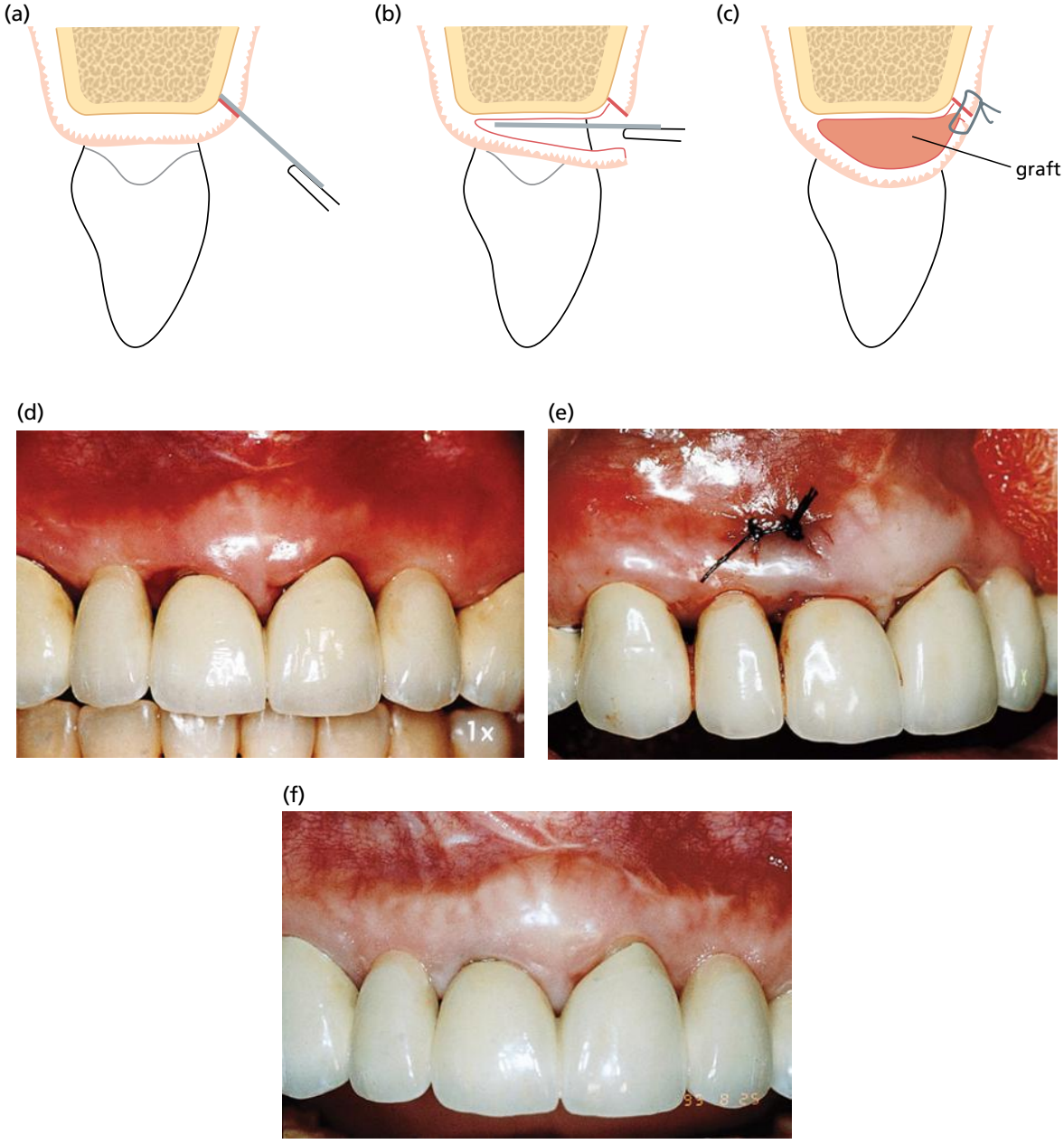


Fig. 46-59 Papilla reconstruction: "semilunar coronally repositioned papilla" technique. (a–c) Schematic drawings illustrating the surgical technique (see text for explanation). (d–f) Reconstruction of papillae distal to the central incisors with the use of the semilunar coronally repositioned papilla technique in a patient with a fixed bridge reconstruction.

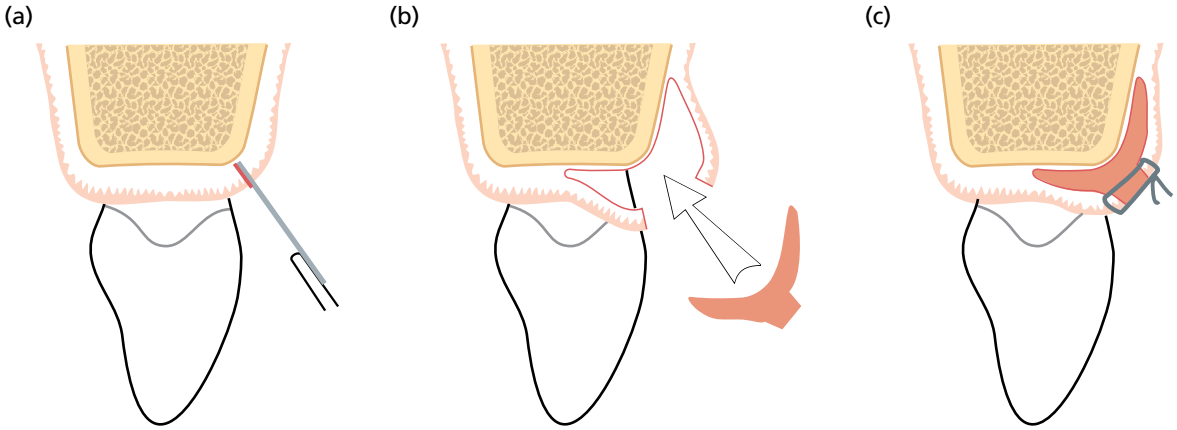


Fig. 46-60 Papilla reconstruction: "envelope" technique. (a–c) Schematic drawings illustrating the surgical technique (see text for explanation).

from the palate, is placed into the pouch to support the coronally positioned interdental tissue.

Azzi *et al*. (1999) described a technique in which an envelope-type flap is prepared for coverage of a connective tissue graft (Fig. 46-60). An intrasulcular incision is made at the tooth surfaces facing the interdental area to be reconstructed. Subsequently, an incision is made across the facial aspect of the interdental area and an envelope-type split-thickness flap is elevated into the proximal site as well as apically to a level beyond the mucogingival line. A connective tissue graft is harvested from the tuberosity area, trimmed to adequate size and shape, and placed under the flaps in the interdental papilla area. The flaps are brought together and sutured with the connective tissue graft underneath.

Crown-lengthening procedures

Excessive gingival display

In most patients, the lower edge of the upper lip assumes a "gum-wing" profile which limits the amount of gingiva that is exposed when a person smiles. Patients who have a high lip line expose a broad zone of gingival tissue and may often express concern about their "gummy smile" (Fig. 46-61). The form of the lips and the position of the lips during speech and smiling cannot be easily changed, but the dentist may, if necessary, modify/control the form of the teeth and interdental papillae as well as the position of the gingival margins and the incisal edges of the teeth. In other words, it is possible by a combination of periodontal and prosthetic treatment measures to improve dentofacial esthetics in this category of patient.

As a base for treatment decisions, a careful analysis of the dentofacial structures and how they may affect esthetics should be performed. It should include the following features:

- Facial symmetry
- Interpupillary line; even or uneven
- Smile line: low, median or high
- Dental midline in relation to facial midline
- Gingival display during speech and during a broad, relaxed smile
- Harmony of gingival margins
- Location of gingival margins in relation to the CEJ
- Periodontal phenotype
- Tooth size and proportions/harmony
- Incisal plane/occlusal plane.

If excessive gingival exposure is due to insufficient length of the clinical crowns, a crown-lengthening procedure is indicated to reduce the amount of gingiva exposed, which in turn will favorably alter the shape and form of the anterior teeth. To select the proper treatment approach for crown lengthening, an analysis of the individual case with regard to crown–root–alveolar bone relationships should also be included.

In the young adult with an intact periodontium, the gingival margin normally resides about 1 mm coronal to the CEJ. However, some patients may have a height of free gingiva that is >1 mm, resulting in a disproportional appearance of the clinical crown. If such a patient complains about his/her "small front teeth" and the periodontium is of a thin phenotype, full exposure of the anatomic crown can be accomplished by a gingivectomy/gingivoplasty procedure (Fig. 46-61).

An assessment should also be made regarding the amount and pattern of pigmentation existing within the gingival tissues, and the patient's desire to maintain or lessen the pigmentation contained within the tissues. The externally beveled path of incision that is usually employed in a gingivectomy procedure will remove the pigmentation and produce pink gingival tissue upon initial healing (Fig. 46-62). The surgically induced color change in the tissues comes about rapidly and markedly affects esthetic values. For this reason, an externally beveled gingivectomy procedure should not be terminated at the midline in patients who have pigmented gingival tissues. It should be extended across the midline to the premolar area to avoid a color mismatch in the esthetic zone of the anterior teeth. The color change may be permanent

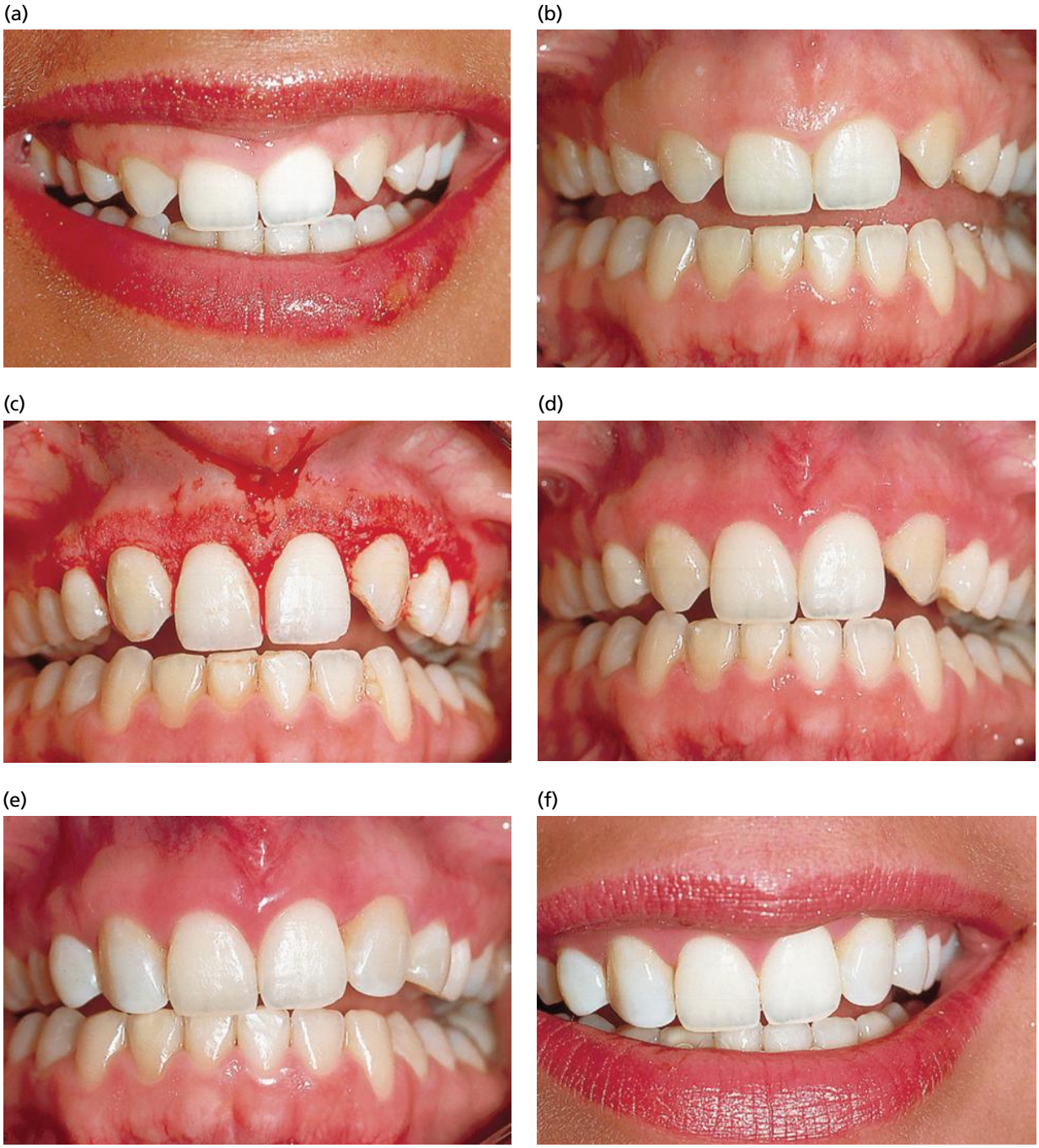


Fig. 46-61 Crown-lengthening procedure. (a, b) Pretreatment views. The clinical crowns are considerably shorter than the anatomic crowns. The lateral incisors were congenitally missing and orthodontic treatment had been carried out to move the posterior teeth anteriorly. The canine teeth in the position of the lateral incisors added to the esthetic disharmony. (c) Gingivectomy was performed to expose the anatomic crowns of the teeth. (d) One month post surgery. At this appointment, the canine and first premolar teeth were reshaped and bonded. (e) Tooth form and proportional balance were improved by bonding. (f) At 3 years post treatment, the gingival tissues exhibited no rebound and retained the architectural form sculpted into the tissue at the time of the surgical procedure.

or the pigmentation may slowly return over a period of a year or more. Patients should be informed of the changes in tissue color that will occur and be allowed to make a choice as to the color of the tissue they will have post-surgically. If they wish to maintain their pigmentation, an internally beveled path of incision (internal gingivectomy) should be employed (Fig. 46-63).

If the periodontium is of the thick phenotype and there is a bony ledge at the osseous crest, an apically positioned flap procedure (see Chapter 39) should be performed. This will allow for osseous recontouring (Fig. 46-64).

More extensive bone recontouring is required to solve esthetic problems found in patients who do indeed have short anatomic crowns in the anterior section of the dentition. In this category of patients, prosthetic measures must be used after resective periodontal therapy to increase the apicocoronal dimension of the crowns (Fig. 46-65). Patients who are

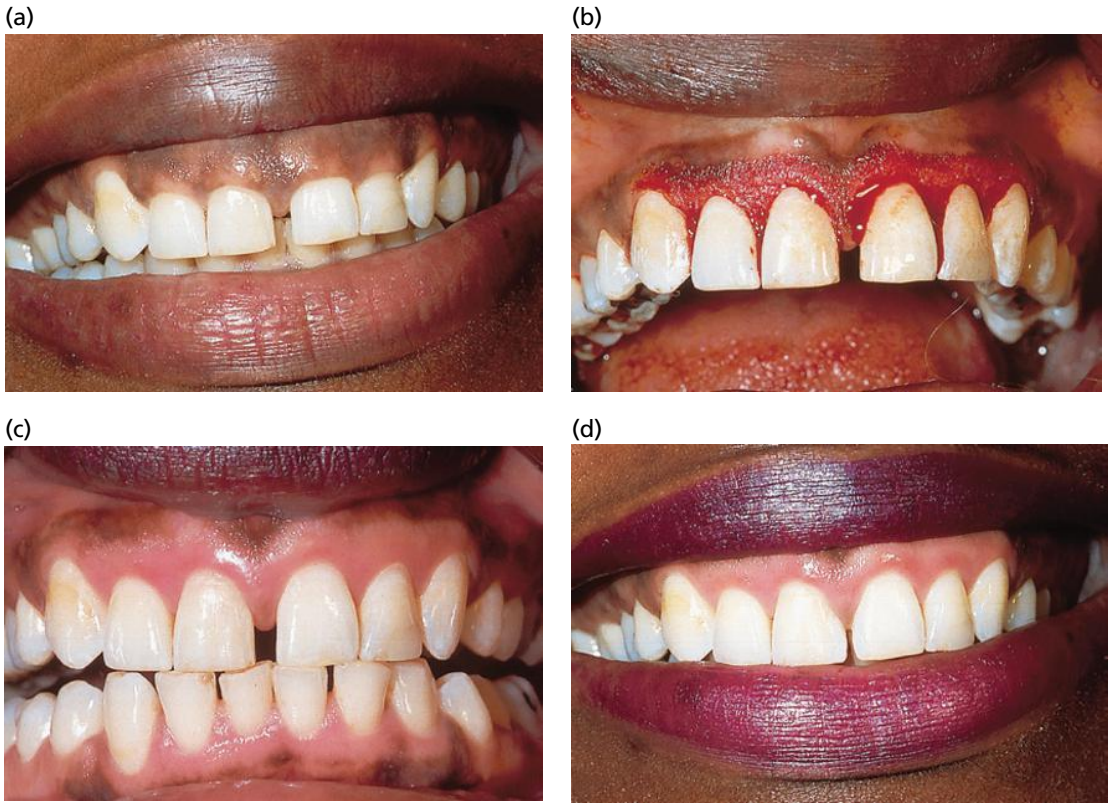


Fig. 46-62 (a) Pretreatment view. The patient disliked her "small front teeth" and diastema. Radiographs and probing indicated the gingival tissues were covering the cervical one-third of the crowns. Crestal bone was thin and in normal relationship to the cementoenamel junctions. The patient preferred "pink gums" if she could possibly have them. (b) A long externally beveled path of incision was used to accomplish the gingivectomy. (c) View showing the color changes and pleasing architecture produced in the anterior gingiva at 2 months post surgery. The diastema was partially closed by direct bonding at this time. (d) Post-treatment view showing the enhancement of esthetic values for the patient.

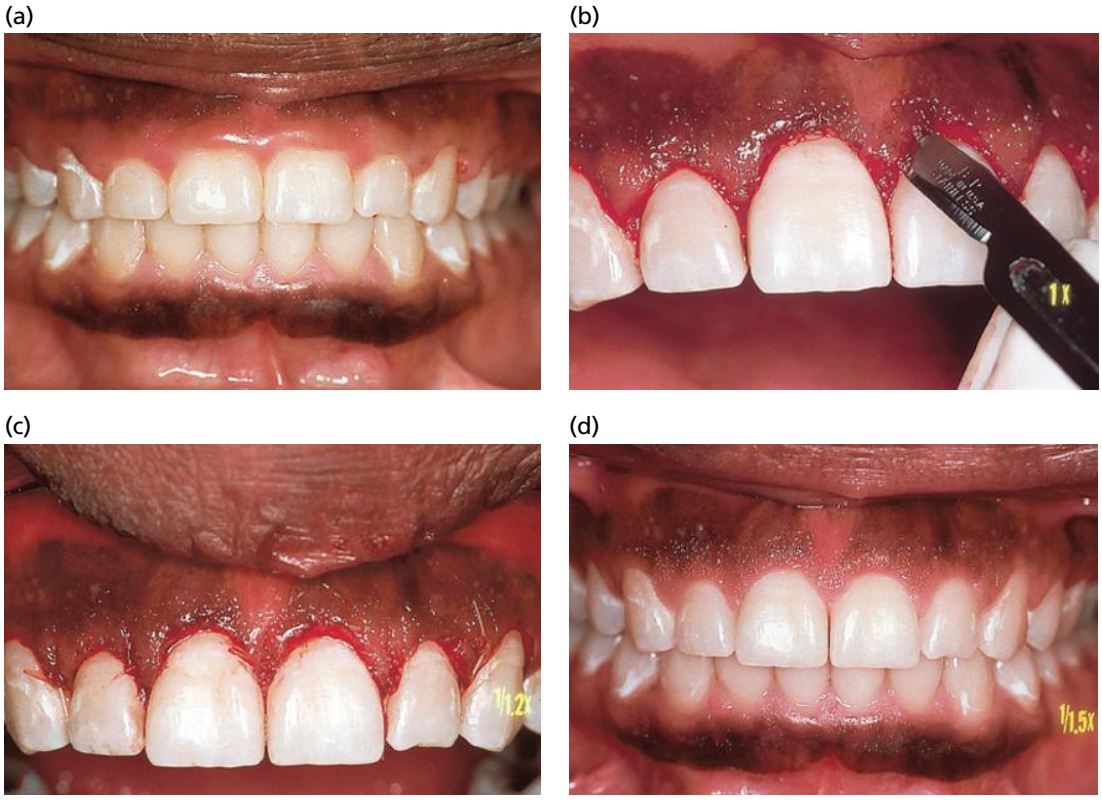


Fig. 46-63 (a) Pretreatment view. This patient disliked her "small front teeth"; she sought consultation to have her teeth made longer by crowning them. Probing and radiographs revealed normal osseous morphology and a wide zone of attached gingiva that covered the cervical one-third of the incisors. It was explained to the patient that a surgical solution was preferred to restorative procedures to make her teeth longer. The patient made a request that the color of her gingival tissues remain unchanged. (b) An internally beveled path of incision was use to effect an "internal gingivectomy" to maintain the pigmentation in the tissues. This created mini flaps in the areas of the papillae. (c) 5-0 gut sutures were used to stabilize the papillae. (d) Crown lengthening that was achieved with maintenance of color harmony can be seen in this view at 3 months post surgery. (Courtesy of E. Saacks.)

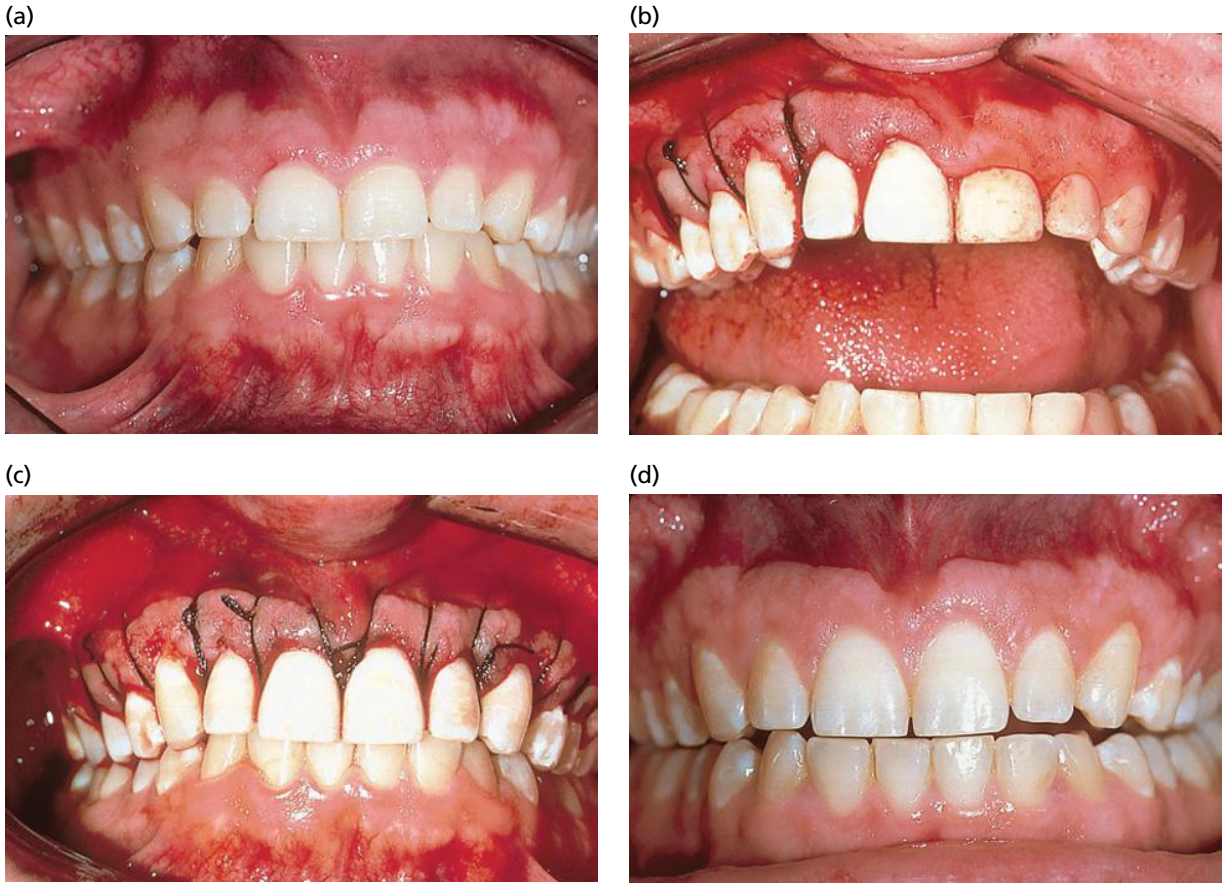


Fig. 46-64 (a) Pretreatment view. The patient, a dentist, requested crown lengthening to lessen his "gummy smile" and give him a more masculine appearance. The patient had a wide zone of attached gingiva and thick crestal bone. Palpation indicated bony exostoses. (b) An apically positioned flap and osseous resective surgery, from second premolar to second premolar, were used to lengthen the teeth. The surgery was confined to the labial surfaces. This view shows one-half of the completed surgery. (c) Vertical mattress sutures were utilized to hold the flap apically. (d) Three years post-treatment. Note that the gingival tissues retain the morphology created at the time of surgery.

candidates for this kind of resective therapy can be divided into two categories:

1. *Subjects who have normal occlusal relationships and incisal guidance*. In this category, the incisal line of the front teeth must remain unaltered, but the clinical crowns can be made longer by surgically exposing the root structure and by locating the cervical margins of the restorations apical to the CEJ (Fig. 46-65).
2. *Subjects who have abnormal occlusal relationships with excessive interocclusal space in the posterior dentition when the anterior teeth are in edge-to-edge contact*. In this category, the length of the maxillary front teeth can be reduced without inducing posterior occlusal interferences. In addition, the marginal gingiva can be resected or relocated to an apical position before crown restorations are made.

In some individuals with an excessive display of gingiva, the size and shape of the teeth and the location of the gingival margins may be perfectly normal. The excessive display of gingiva in these cases is often caused by vertical maxillary excess and a long mid-face (Fig. 46-66). Periodontal crown-lengthening procedures will not suffice to solve their problems, but rather the maxilla must be altered by a major maxillofacial surgical procedure. The risk-to-benefit and cost-to-benefit ratios must be thoroughly evaluated before recommending this type of surgical therapy to correct esthetic problems.

Exposure of sound tooth structure

Crown-lengthening procedures may be required to solve problems such as (1) inadequate amount of tooth structure for proper restorative therapy, (2) subgingival location of fracture lines, and (3) subgingival location of carious lesions. The techniques used to accomplish crown lengthening include (1) an apically positioned flap procedure including bone resection and (2) forced tooth eruption with or without fiberotomy.

Apically positioned flap with bone recontouring

The apically positioned flap technique with bone recontouring (resection) may be used to expose sound tooth structure. As a general rule, at least 4 mm of sound tooth structure must be exposed at the time of

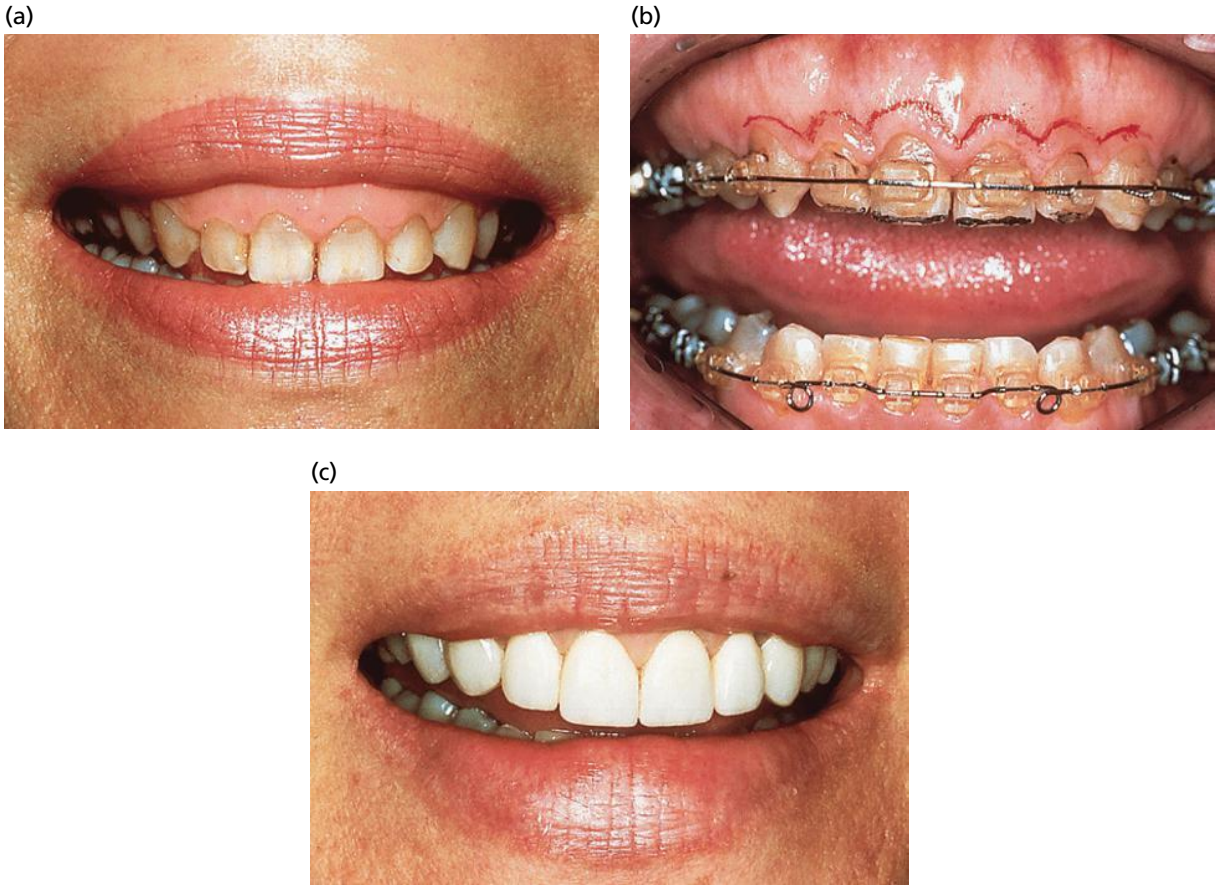


Fig. 46-65 Crown lengthening by surgical and prosthetic procedures. (a) Pretreatment view. The patient displayed "short front teeth" and a broad exposure of gum tissue. The full anatomic crown is exposed in this case and the surgically-induced recession will expose root structure. (b) Patient had an unusually wide zone of attached gingiva. The gingival margins were positioned apically by making an internally beveled flap with a submarginal entrance incision as outlined in red ink. The crest of the bone was reduced in height. (c) After the tissues had matured following surgery, individual crowns were prepared for each of the anterior teeth. Crown lengthening was achieved and the patient no longer exposed a broad expanse of gum tissue. (Courtesy of D. Garber.)

surgery. During healing, the supracrestal soft tissues will proliferate coronally to cover 2–3 mm of the root (Herrero *et al*. 1995; Pontoriero & Carnevale 2001; Lanning *et al*. 2003), thereby leaving only 1–2 mm of supragingivally located sound tooth structure. When this technique is used for crown lengthening, it must also be realized that gingival tissues have an inherent tendency to bridge abrupt changes in the contour of the bone crest. Thus, in order to retain the gingival margin at its new and more apical position, bone recontouring must be performed not only at the problem tooth but also at the adjacent teeth to gradually reduce the osseous profile (Fig. 46-67). Consequently, substantial amounts of attachment may have to be sacrificed when crown lengthening is accomplished with an apically positioned flap technique. It is also important to remember that, for esthetic reasons, symmetry of tooth length must be maintained between the right and left sides of the dental arch. This may, in some situations, call for the inclusion of even more teeth in the surgical procedure.

- *Indication:* crown lengthening of multiple teeth in a quadrant or sextant of the dentition.

Fig. 46-66 Patient displays a large expanse of gingival tissue when smiling or speaking. The patient has a long mid-face and vertical maxillary excess. The gingival margins reside 1 mm coronal to the cementoenamel junction and the anatomic and clinical crowns are approximately equal.

- *Contraindication:* surgical crown lengthening of single teeth in the esthetic zone (Fig. 46-68).
- *Technique:* the apically positioned flap technique and methods used for bone recontouring are discussed in Chapter 39.

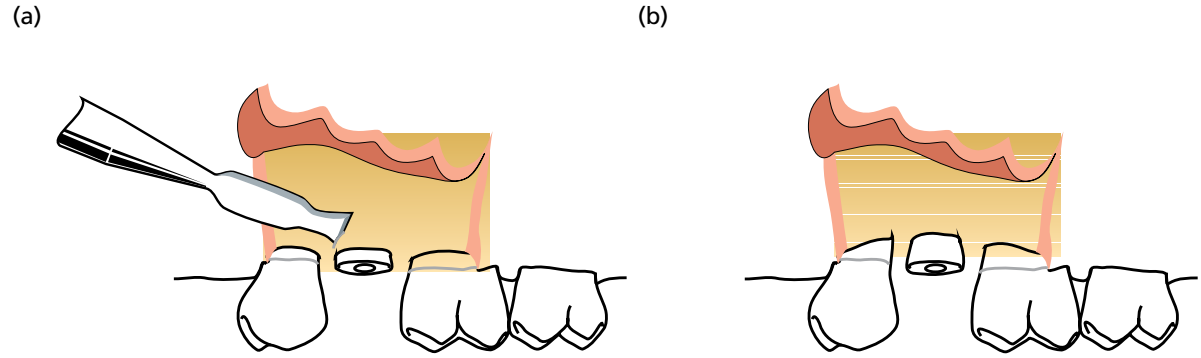


Fig. 46-67 Surgical resective therapy for crown lengthening cannot be confined to the tooth in need of treatment. (a, b) The principles of osseous resection require that bone be removed from the adjacent teeth to create a gradual rise and fall in the profile of the osseous crest. This causes a loss of attachment apparatus and recession of the adjacent teeth as well.

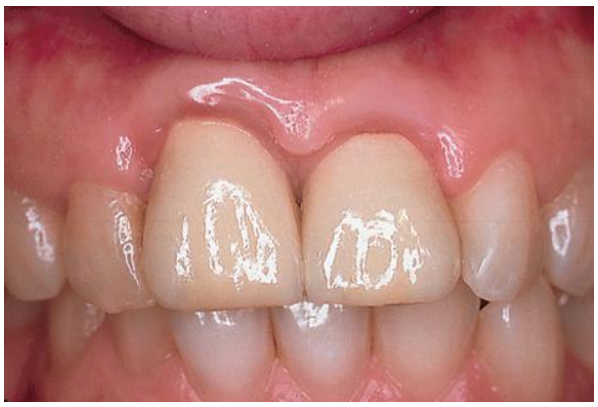


Fig. 46-68 Deformity which interfered with dentofacial esthetics was created at the right central incisor by using a surgical crown lengthening procedure at one single tooth to expose sound tooth structure. The soft tissues cannot follow the abrupt and steep changes in the osseous profile. The crown preparation invaded the zone of normal supracrestal connective tissue. This created a chronic periodontal pocket and adversely affected esthetics. (Courtesy of A. Winnick.)

Forced tooth eruption

Orthodontic tooth movement can be used to erupt teeth in adults (Reitan 1967; Ingber 1974, 1976; Potashnick *et al*. 1982). If moderate eruptive forces are used, the entire attachment apparatus will move in unison with the tooth. The tooth must be extruded a distance equal to or slightly longer than the portion of sound tooth structure that will be exposed in the subsequent surgical treatment. After the tooth has reached the intended position and has been stabilized, a full-thickness flap is elevated and bone recontouring is performed to expose sound root structure. For esthetic reasons it is important that the bone and soft tissue levels at adjacent teeth remain unchanged.

Forced tooth eruption can also be used to level and align gingival margins and the crowns of teeth to obtain esthetic harmony. Instead of using surgical procedures to position the gingival margins of unaffected normal teeth apically to the level of a tooth with recession or orthodontic malalignment, the tooth that is malpositioned or has sustained recession is erupted to the level of the normally positioned teeth. The entire attachment apparatus and dentogingival junction will follow the root of the tooth as it is moved coronally (Fig. 46-69).

- *Indication:* crown lengthening at sites where removal of attachment and bone from adjacent teeth must be avoided. The forced eruption technique can also be used as a method to reducing pocket depth at sites with angular bony defects (Brown 1973; Ingber 1974, 1976). The angular bony defect at the problem tooth can be reduced, while the attachment level at the adjacent tooth surface remains unchanged (Fig. 46-70).
- *Contraindication:* the forced eruption technique requires the use of fixed orthodontic appliances. Thus, in patients who only have a few teeth remaining, an alternative approach for crown lengthening has to be selected.
- *Technique:* orthodontic brackets are bonded to the problem tooth and to adjacent teeth, and are combined with an archwire. Another type of mechanical system can be utilized by placing a heavy gauge bar or wire in grooves prepared in the adjacent teeth and over the problem tooth. A power elastic is tied from the bracket to the archwire (or the bar), which pulls the tooth coronally. If most of the crown structure is lost, root canal therapy is required. A post placed in the root canal is fitted with a power elastic, which is also joined with the archwire. The direction of the tooth movement must be carefully checked to ensure that the problem tooth is not tilted or moved toward the adjacent tooth surfaces.

Forced tooth eruption with fiberotomy

If fiberotomy is performed during the forced tooth eruption procedure, the crestal bone and the gingival margin are retained at their pretreatment locations, and the tooth–gingiva interface at adjacent teeth is unaltered. Fiberotomy is performed using a scalpel at 7–10-day intervals during the forced eruption to sever the supracrestal connective tissue fibers, thereby preventing the crestal bone from following

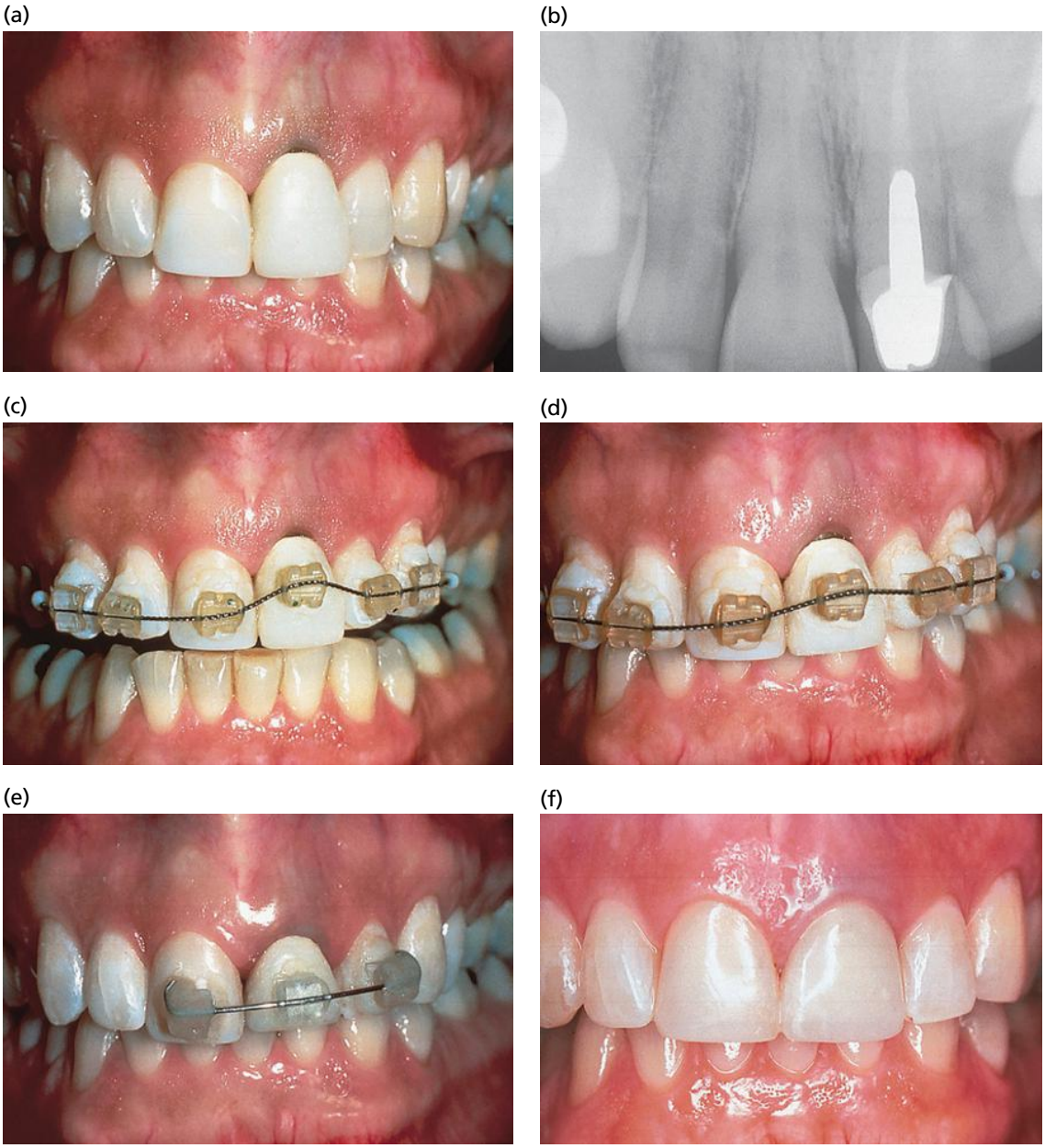


Fig. 46-69 Forced tooth eruption (show method) used to level gingival margins, treat recession on a single tooth, and create esthetic harmony. (a, b) Recession on the left central incisor exposed the root surface darkened from root canal treatment. The uneven gingival margins and dark root surface detracted from an otherwise attractive smile. (c) Nitol wire with an offset bracket was used to slowly extrude the incisor. (d) Occlusal adjustment was made on the lingual side of the crown to create room for the tooth to erupt. This view, after 1 month in tooth movement, shows the gingival tissues moving with the root of the tooth. (e) Sufficient eruption had occurred by 3 months to level the gingival margins. The orthodontic brackets were used for temporary stabilization and a new crown was prepared. (f) New crown masked the show-through of the dark root. The even gingival margins and beautiful crown created esthetic harmony. (Courtesy of J. Ingber.)

the root in a coronal direction. In the case presented in Fig. 46-71, fiberotomy was performed only at the mesial half of the root. Radiographs obtained after 9 weeks demonstrate that crestal bone migration has occurred at the distal but not at the mesial surface of the erupted tooth (Pontoriero *et al*. 1987).

- *Indication:* crown lengthening at sites where it is important to maintain the location of the gingival margin at adjacent teeth unchanged.
- *Contraindication:* fiberotomy should not be used at teeth associated with angular bone defects.
- *Technique:* similar to the technique described for the forced tooth eruption procedure. Fiberotomy is performed once every 7–10 days during the phase of forced tooth eruption.

Ectopic tooth eruption

Surgical intervention is often indicated for teeth erupting ectopically, that is with an eruption position facial to the alveolar process (Fig. 46-72). To create a satisfactory width of the gingiva for the permanent tooth, the tissue entrapped between the erupting tooth and the

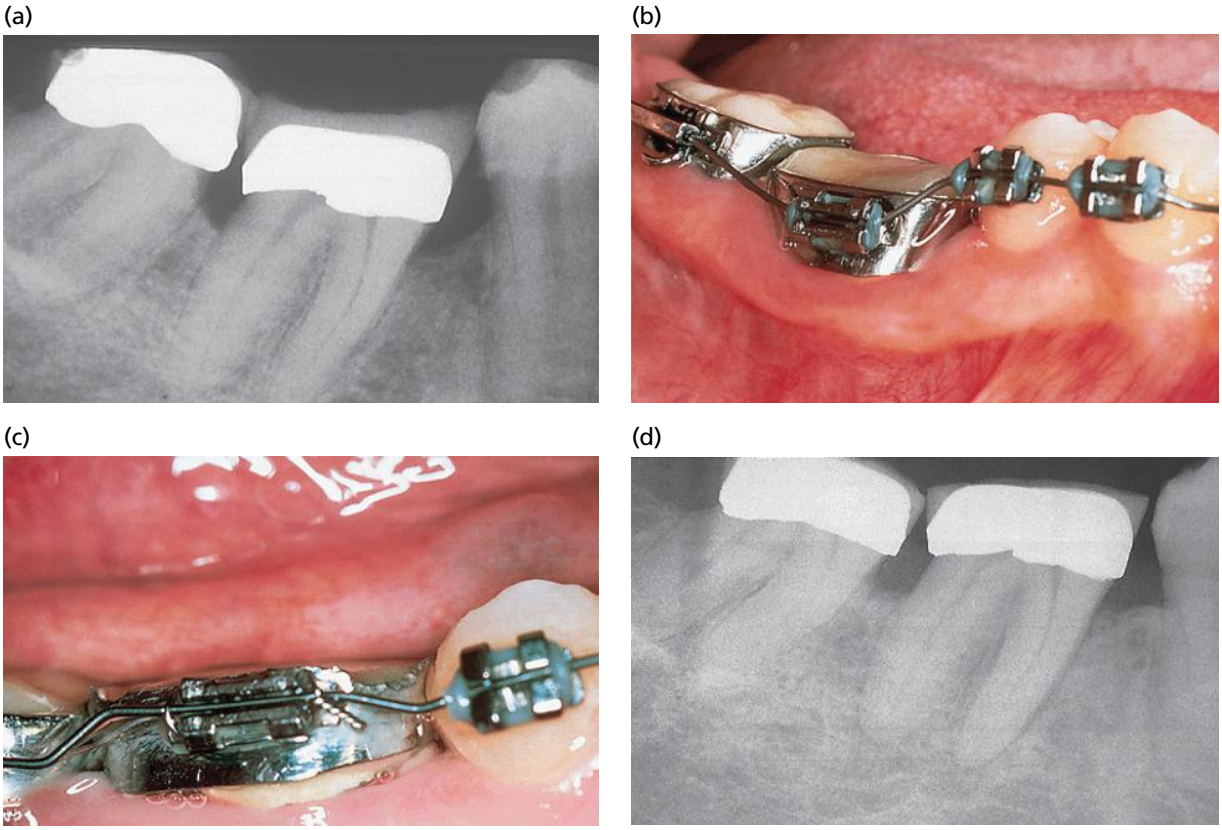


Fig. 46-70 Slow tooth eruption procedure used to level cementoenamel junctions and angular bone crests. (a) Pretreatment radiograph. (b) Nitol wire was used to erupt the molar. (c) Crown was shortened over a period of 4 months by selective grinding. (d) Radiograph taken 8 months after the start of treatment. The angular bone defects were leveled.

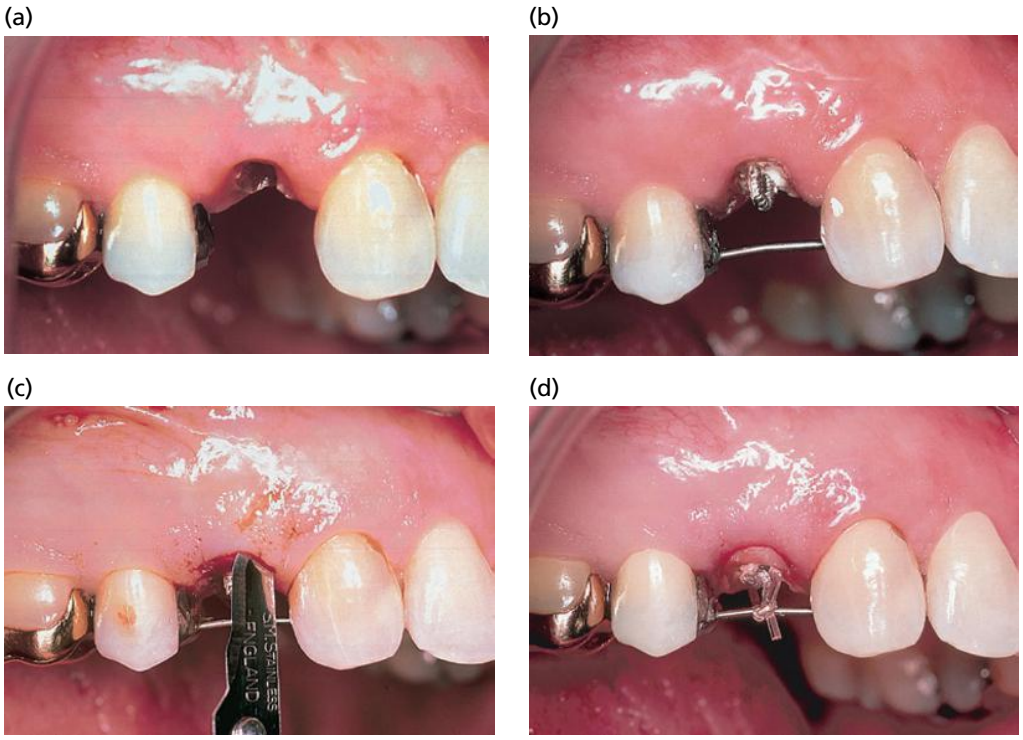


Fig. 46-71 Rapid tooth eruption procedure in conjunction with fiberotomy procedure. (a) Buccal view, the fracture on the first premolar extended subgingivally. (b) Soft tooth structure was excavated and a twisted wire with an occlusal hook was temporarily cemented in the root canal. A bar was placed into the amalgam restoration on the premolar and bonded to the lingual surface of the canine. (c, d) Sulcular fiber resection was performed at the mesial half of the tooth to the level of the bone crest. The distal half remained as a control surface. The fiber resection was repeated once a week during the 3-week eruption phase.

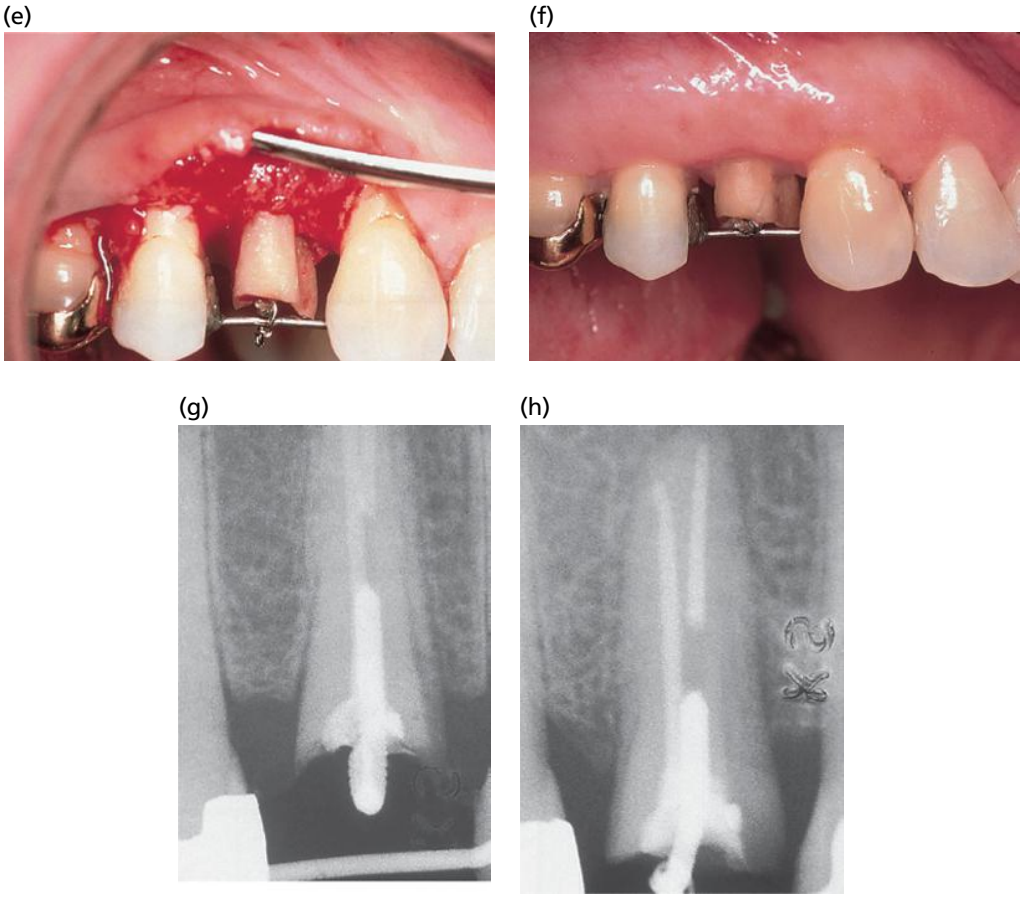


Fig. 46-71 (*Continued*)(e) Tooth was stabilized for 6 weeks, and at that time a full-thickness flap was raised. The bone crest had a "positive" angulation at the distal surface and remained unchanged at the "test" mesial surface. Osseous resection was used to level the bony septum on the distal surface. (f) Ample crown lengthening was obtained and the gingival margins healed to their former shape and location. (g) Pretreatment radiograph enlarged to show the normal shape of the crests of the interdental septae. (h) Enlargement of the post-eruption radiograph (3 weeks of rapid eruption and 6 weeks of stabilization) to show the "positive" angular crest on the "control" distal side and the unchanged crest on the mesial "test" side. (Courtesy of R. Pontoriero)

deciduous tooth is usually utilized as donor tissue (Agudio *et al*. 1985; Pini Prato *et al*. 2000b).

Three different techniques have been described for the interceptive mucogingival treatment of buccally erupting teeth, depending on the distance from the donor site (entrapped gingiva) to the recipient site (area located facially–apically to the erupting permanent tooth) (Agudio *et al*. 1985; Pini Prato *et al*. 2000b):

- *Double pedicle graft* (Fig. 46-73). This flap procedure is indicated when the permanent tooth erupts within the zone of keratinized tissue but close to the mucogingival junction. An intrasulcular incision is performed at the deciduous tooth and extended laterally to the gingival crevice of the adjacent teeth and apically to the erupting permanent tooth. By mobilization of the flap apical to the mucogingival line, the entrapped gingiva can be elevated and transposed for positioning apically to the erupting tooth. Sutures may be placed to secure the position of the gingival tissue facial to the erupting tooth.
- *Apically positioned flap* (Fig. 46-74). When the permanent tooth is erupting apical to the mucogingival junction, vertical releasing incisions have to be placed to allow for apical positioning of the keratinized tissue. Two lateral releasing incisions are made and extended apically beyond the mucogingival junction. An intrasulcular incision is performed at the deciduous tooth and a partial-thickness flap is elevated beyond the ectopically erupting tooth. The mobilized gingival flap is moved apical to the erupting tooth and secured in position by sutures.
- *Free gingival graft* (Fig. 46-75). If the tooth is erupting within the alveolar mucosa distant to the mucogingival junction, a free gingival graft procedure may be selected. The entrapped gingiva is removed by a split incision and used as an epithelialized connective tissue graft. The free gingival graft is placed at a prepared recipient site facial/apical of the erupting tooth. Careful suturing is performed to secure close adaptation of the graft to the underlying connective tissue bed.

All these procedures have been proven to be effective in establishing a facial zone of gingiva following the alignment of teeth erupting in an ectopic position (Pini Prato *et al*. 2000b, c).

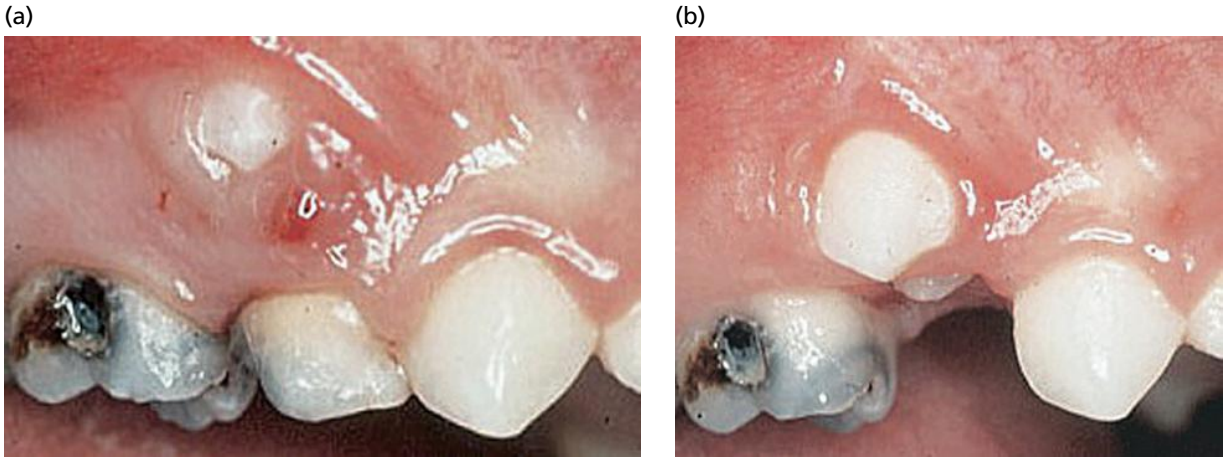


Fig. 46-72 (a, b) Ectopic tooth eruption. The permanent tooth is erupting close to the mucogingival junction.

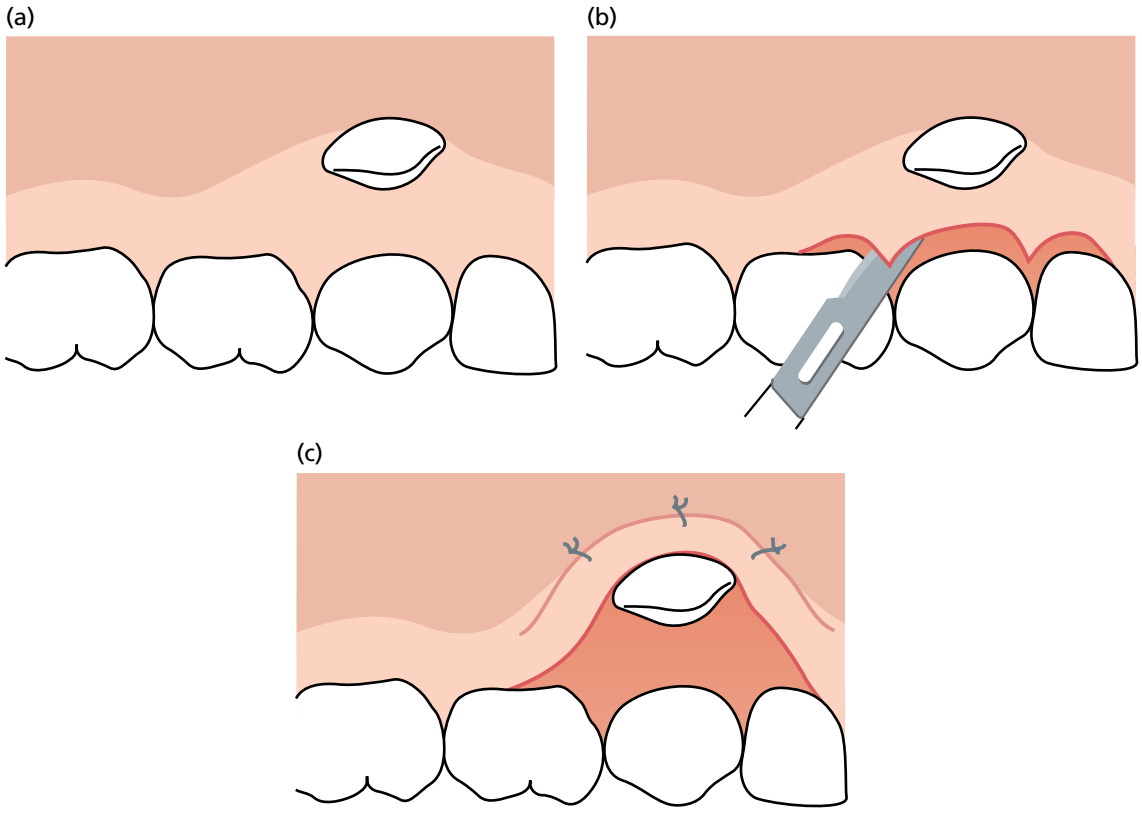


Fig. 46-73 (a–c) Ectopically erupting tooth: double pedicle graft. Schematic drawings illustrating the surgical technique (see text for explanation).

Deformed edentulous ridge

A partially edentulous ridge may retain the general shape of the alveolar process. Such a ridge is traditionally referred to as a normal ridge. Even though this normal ridge has retained the buccolingual and apicocoronal dimensions of the alveolar process, it is not normal in many other respects; the eminences that existed in the bone over the roots are no longer present and the interdental papillae are missing.

The smooth contours of the normal ridge create problems for the restorative dentist. In a fixed bridge the pontics (1) frequently give the impression that they rest on the top of the ridge rather than emerge from within the alveolar process, (2) lack a root eminence, and (3) lack marginal gingivae and interdental papillae. Dark triangles, which almost always interfere with dentofacial esthetics, are present in the embrasure area between the pontics and between the abutments and the pontics. In other words, in the presence of a normal ridge, it may be difficult or impossible to produce a fixed prosthesis which truly restores the esthetics and function of the natural dentition.

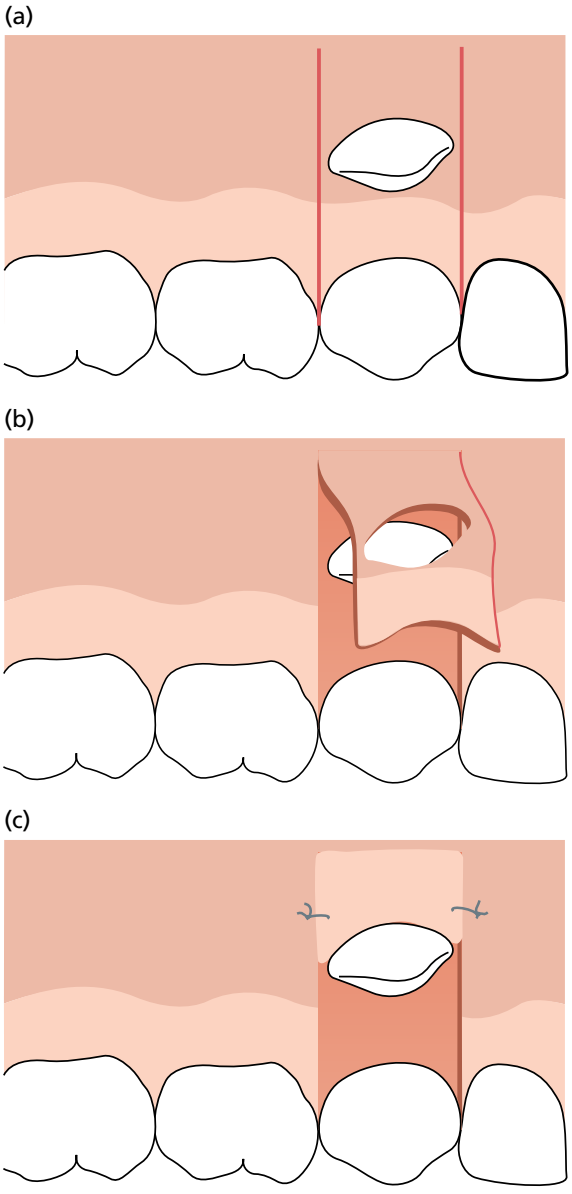


Fig. 46-74 (a–c) Ectopically erupting tooth: apically positioned flap. Schematic drawings illustrating the surgical technique (see text for explanation).

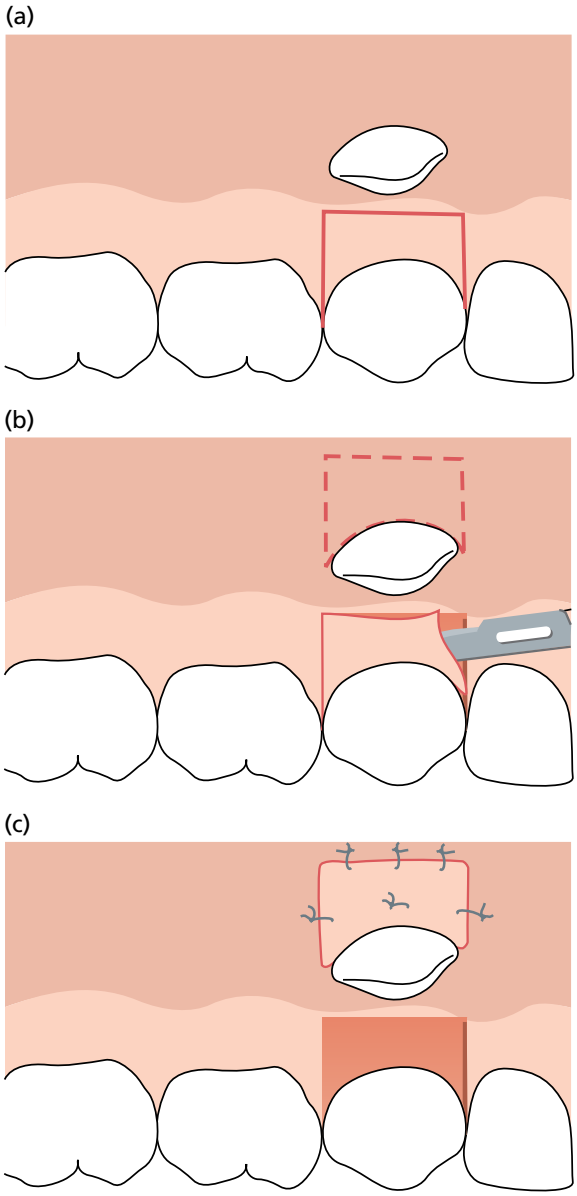


Fig. 46-75 (a–c) Ectopically erupting tooth: free gingival graft. Schematic drawings illustrating the surgical technique (see text for explanation).

Prevention of soft tissue collapse following tooth extraction

Following extraction of a tooth, the topography of the surrounding soft and hard tissues will be altered. The soft tissue margin will collapse and the height of the adjacent papillae will be reduced. This soft tissue collapse may be prevented by immediate post-extraction placement of an ovate pontic to support the soft tissues. Figure 46-76 shows such a situation where a central incisor had to be extracted due to root fracture. With the immediate placement of the pontic, the facial soft tissue margin and the papillae were maintained almost unchanged following the healing of the extraction site. Also, in situations where several adjacent teeth have to be extracted, insertion of ovate pontics may facilitate the preservation of the outline of the soft tissue ridge (Fig. 46-77).

Prevention of ridge collapse due to alveolar bone resorption following tooth extractions must also be considered. Borghetti and Laborde (1996) recommended methods for prevention of bone ridge collapse after tooth extraction in any case of:

- Fracture of the vestibular osseous plate during tooth extraction or due to trauma
- Resorption of the vestibular osseous plate
- Presence of a thin vestibular bone plate.

Procedures proposed for prevention of ridge collapse in conjunction with tooth extractions include (1) flap elevation for complete soft tissue closure of the extraction sites (Borghetti & Glise 2000), (2) placement of connective tissue grafts over the extraction sites (Nevins & Mellonig 1998), (3) placement of bone grafts (Becker *et al*. 1994), and (4) utilization of barrier membranes (Lekovic *et al*. 1997). Procedures for preservation of the bone dimensions following tooth extraction are discussed in Chapter 50.

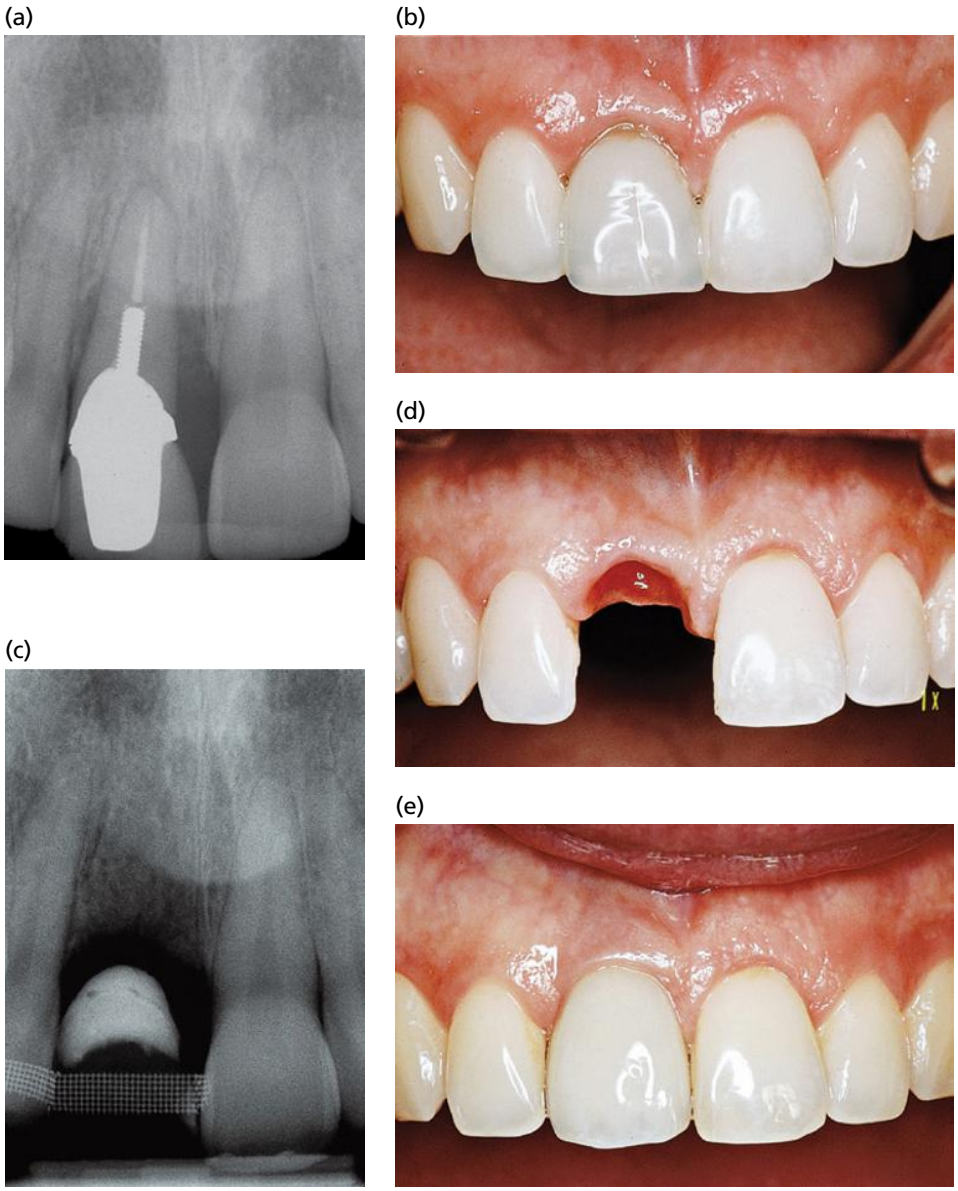


Fig. 46-76 (a) Central incisor that cannot be maintained because of root fracture which also caused pronounced periodontal destruction. (b) Immediately following tooth extraction, an ovate pontic was inserted to support the facial and proximal soft tissues. (c, d) Radiographic and clinical view of the area 6 weeks after tooth extraction. (e) Follow-up 1 year after the placement of the permanent prosthetic reconstruction (single implant).

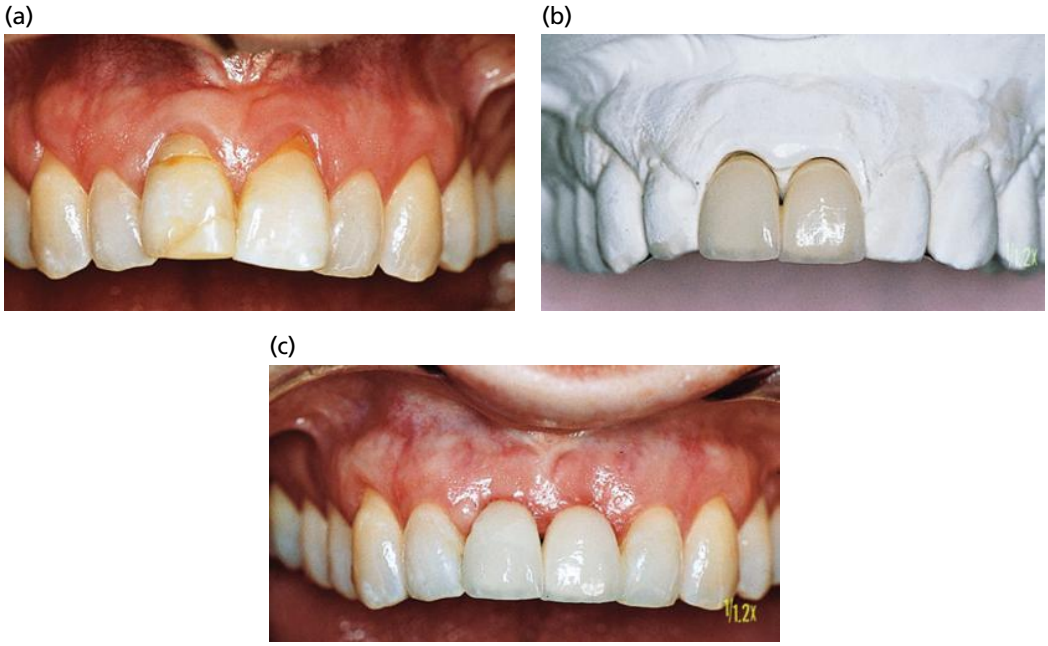


Fig. 46-77 (a) A 26-year-old female patient who had a trauma against the maxillary central incisors. Due to root fracture and endodontic complications, both central incisors had to be extracted. (b) A Rochette bridge with ovate pontics was fabricated as a temporary replacement for the incisors. (c) Clinical view of the front tooth region 8 weeks after tooth extraction and placement of the resin-bonded temporary bridge.

Correction of ridge defects by the use of soft tissue grafts

A deformed ridge may result from tooth extractions, advanced periodontal disease, abscess formations, etc. The deformity that exists in the ridge is directly related to the volume of root structure and associated bone that is missing or has been destroyed. According to Seibert (1983) ridge defects can be divided into three classes:

- *Class I*: loss of buccolingual width but normal apicocoronal height
- *Class II*: loss of apicocoronal height but normal buccolingual width
- *Class III*: a combination of loss of both height and width of the ridge.

Ridge augmentation procedures should be preceded by careful surgical–prosthetic treatment planning with joint consultations involving the surgeon and the restorative dentist in order to attain an optimal esthetic result. The following factors should be determined prior to the initiation of therapy:

- Volume of tissue required to eliminate the ridge deformity
- Type of graft procedure to be used
- Timing of various treatment procedures
- Design of the provisional restoration
- Potential problems with tissue discolorations and matching tissue color.

Ideally, a provisional restoration should be made prior to surgery. The shape of the teeth in the provisional restoration, the axial inclination and emergence profile of the teeth, and embrasure form should be an exact prototype of the final prosthesis that is to be constructed. It is the task of the clinician performing the surgery to augment the tissues to meet the provisional prosthesis in the most exact manner possible. If a gingival flange of pink-colored acrylic is used around single or multiple pontics on a temporary removable partial denture, the flange must be cut away in order to avoid pressure on the graft and give the tissues room to swell during the immediate post-surgical phase of healing. The soft tissue at the surgically-treated recipient site for a graft will undergo considerable swelling during the early phase of healing and the tissues will conform to the tissue-facing surfaces of the bridge or partial denture. The prosthesis is thus used to help in shaping the outline of the augmented ridge to the desired form. The location and shape of interproximal embrasure areas in the provisional bridge will determine where the "papillae" created in the ridge will be located.

Surgical procedures for ridge augmentation

Numerous surgical graft and implant procedures attempting to reconstruct a partially edentulous ridge or ridge defect have been described in the literature over the years. The procedures may be grouped according to the methods used for ridge augmentation as (1) soft tissue augmentation procedures and (2) hard tissue augmentation procedures. In this chapter, only soft tissue augmentation procedures will be addressed, while hard tissue augmentation procedures are covered in Chapter 50. To illustrate the various approaches utilizing soft tissues for ridge augmentation, the following procedures will be discussed:

- Pedicle graft procedure:
  - Roll flap procedure
- Free graft procedures:
  - Pouch graft procedure
  - Interpositional graft procedure
  - Onlay graft procedure.

Studer *et al*. (1997) proposed the use of the pedicle graft procedure for correction of a single-tooth ridge defect with minor horizontal and vertical loss, whereas submerged free connective tissue graft procedures should be selected for larger defects. The onlay full-thickness graft procedure is indicated primarily for ridge augmentation in the presence of additional mucogingival problems such as insufficient gingival width, high frenum, gingival scarring, or tattoo. These recommendations were based on short-term evaluation of the obtained volumetric increase of the edentulous ridge following various augmentation procedures, which demonstrated superior results with the use of submerged connective tissue grafts compared to the use of full-thickness grafts (Studer *et al*. 2000).

"Roll flap procedure"

Surgical concept

The "roll flap procedure" (Abrams 1980) involves the preparation of a de-epithelialized connective tissue pedicle graft, which is subsequently placed in a subepithelial pouch (Fig. 46-78). This procedure is used in the treatment of small-to-moderate class I ridge defects, primarily in cases with a single-tooth space. The technique enables the surgeon to augment tissue apically and labially to the cervical area of a pontic and to give the recipient site the appearance of a normal tooth–gingiva interface. Hence, a buccolingual ridge concavity can be converted into a ridge convexity resembling the eminence produced by the roots of the adjacent teeth (Fig. 46-79).

Technique

A rectangular pedicle of connective tissue is prepared on the palatal side of the defect (Fig. 46-78). The length of the pedicle must match the amount of apicocoronal augmentation that is planned. This, in turn, is related to the amount of root eminence that exists on either side of the defect. If a two- or three-tooth pontic space is treated with the roll technique, two or three separate pedicles are raised. Each of these pedicles will form a new "root–cervical margin".

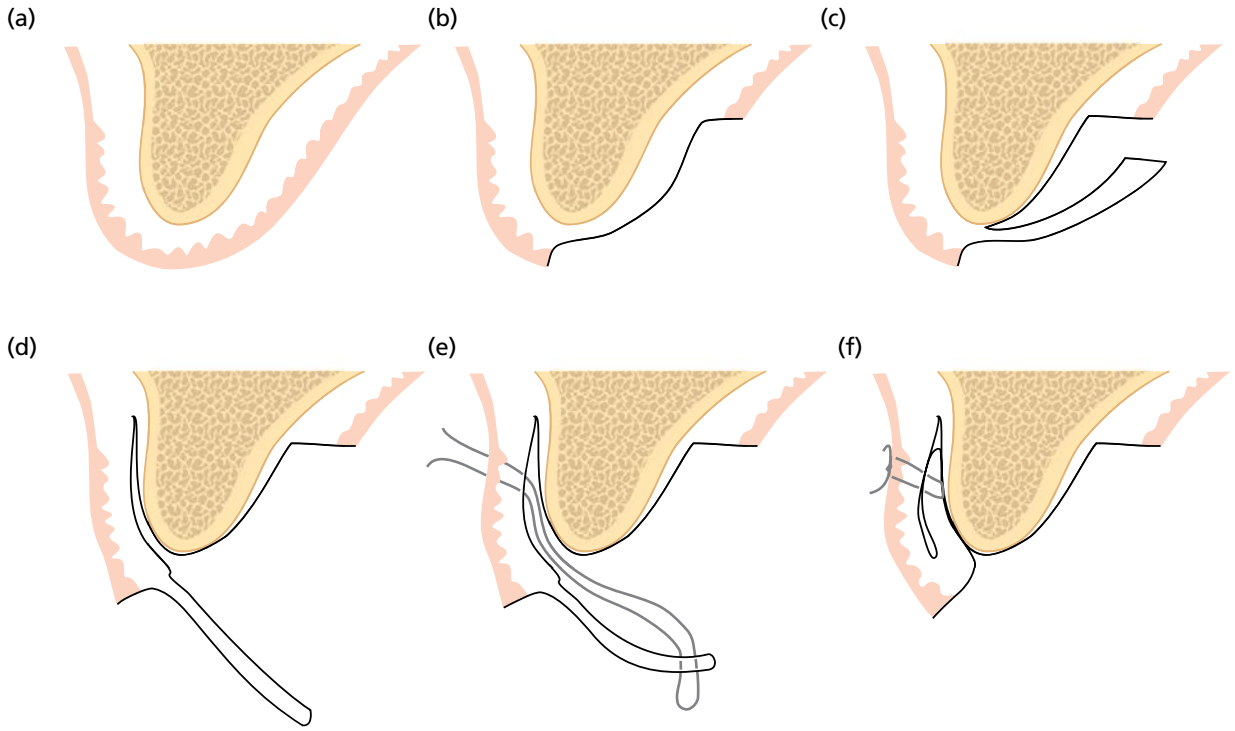


Fig. 46-78 Sequence of steps in the "roll flap procedure". (a) Cross-section of the residual edentulous ridge prior to treatment. (b) Removal of the epithelium. (c) Elevation of the pedicle. (d) Pouch is created. (e) Sutures are placed at the mucogingival junction to catch the tip of the pedicle flap and pull it into place in the pouch. (f) Flap is secured. A convexity in the ridge was created.

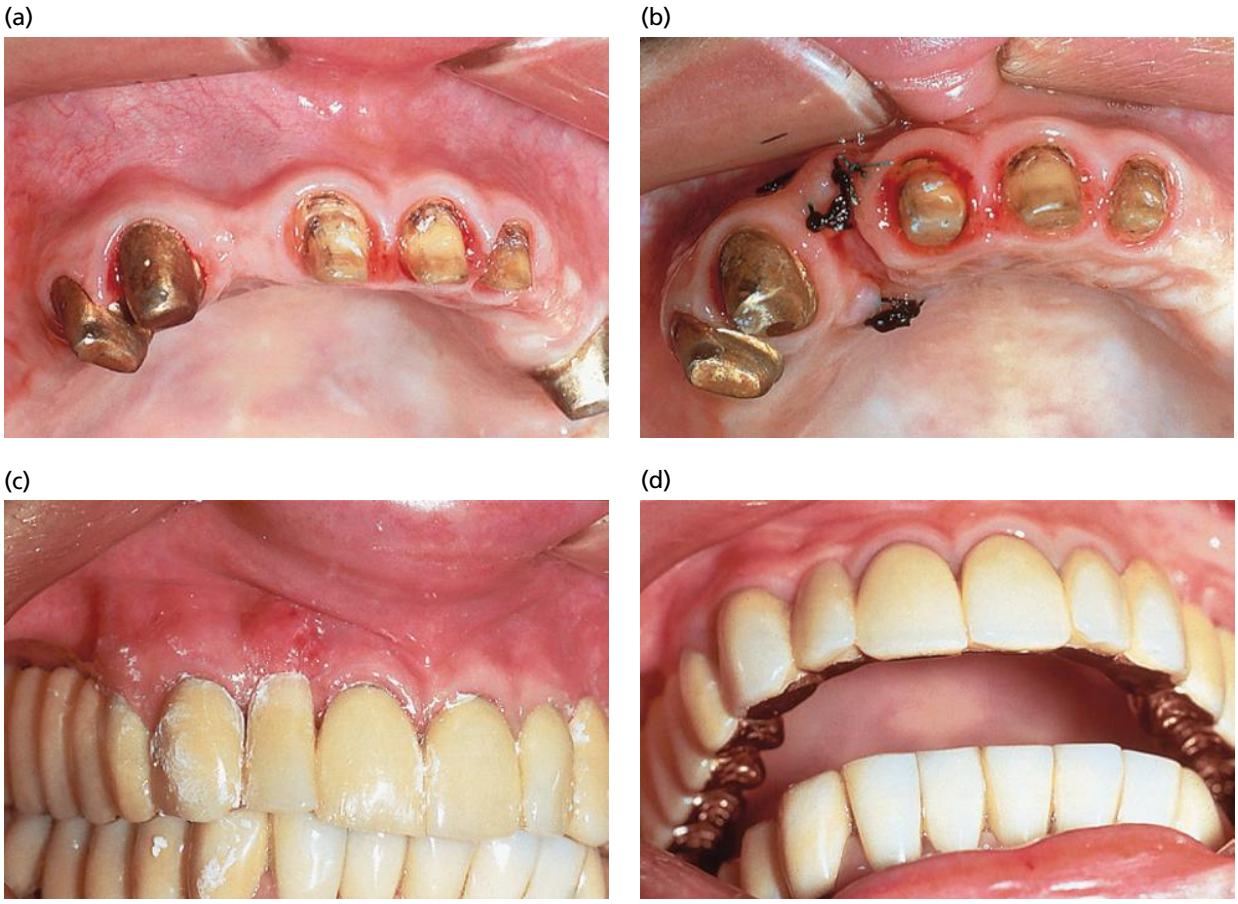


Fig. 46-79 "Roll flap procedure". (a) Pretreatment view of a class I ridge defect in the area of the right lateral incisor. Note the marked concavity in the ridge. (b) View shows the surgical site 1 week after surgery and prior to the removal of the sutures. (c) Tissue surface of the pontic was relined with autopolymerizing resin. (d) Final prosthesis in place. Note the illusion of a root eminence and a free gingival margin apical to the lateral incisor pontic tooth. (Courtesy of L. Abrams.)

The epithelium on the palatal surface of the donor site is first removed. A maximum amount of supraperiosteal connective tissue is raised from the palate using sharp dissection. The void that is produced at the donor site will gradually fill in with granulation tissue. Caution must be exercised in dissection of the pedicle flap so that tissue perforation is avoided when the plane of dissection approaches the facial (labial) surface. A pouch is made in the supraperiosteal connective tissue at the facial (labial) surface of the ridge. In order to preserve as much connective tissue and blood supply as possible at the recipient site, the dissection must be made as close as possible to the periosteum of the facial bone.

The pedicle is tucked into the pouch as a try-in procedure. Adjustment of pedicle size should now be made. Once the pedicle fits as desired, it is made ready for the stabilizing suture. The suturing scheme is shown in Fig. 46-78. The suture must be positioned close to the mucobuccal fold. This enables the surgeon to pull the pedicle to the apical portion of the pouch. The suture should not be tied tightly, since it only serves as a positioning and stabilizing device. The use of a resorbable suture material is recommended.

Adjustment of pontic contours

Measures used to adapt the tissue surface of the pontic to the contour of the surgically treated ridge are common to all soft tissue ridge augmentation procedures in patients with fixed bridgework. A light contact is maintained between the pedicle graft and the tissue surface of the pontics. The postoperative swelling will cause the tissue to conform to the shape of the pontic. This enables the clinician to shape the soft tissue into a form that is intended for the augmented site. Autopolymerizing resin is added to the tissue surface of the pontics and is allowed to cure until the resin reaches a dough-like state. The bridge is then seated and pressed into the grafted site. When the resin has set to a firm consistency, the bridge is removed and placed in hot water to complete the process of polymerization (Fig. 46-79). The tissue surface of the pontics and the embrasure areas are then carved to the shape that is intended for the final bridge. The surface of the pontic is polished and the bridge placed using appropriate temporary cement.

Postoperative care

A periodontal dressing is placed over the donor site. No dressing should be placed over the facial (labial) surface of the grafted area where swelling will occur. The dressing at the donor site should be changed at weekly intervals and maintained until wound healing has progressed to a point where the tissue is no longer tender to touch.

Pouch graft procedures

Surgical concept

A subepithelial pouch is prepared in the area of the ridge deformity, into which a free graft of connective tissue is placed and molded to create the desired contour of the ridge. The entrance incision and the plane of dissection may be made in different ways (Kaldahl *et al*. 1982; Seibert 1983; Allen *et al*. 1985; Miller 1986; Cohen 1994):

- *Coronoapically*: the horizontal incision is made on the palatal or lingual side of the defect and the plane of dissection carried in an apical direction (Fig. 46-80)
- *Apicocoronally*: the horizontal incision is made high in the vestibule near the mucobuccal fold and the plane of dissection is carried coronally to the crest of the ridge
- *Laterally*: one or two vertical entrance incisions are started from either side of the defect (Fig. 46-81).

The plane of dissection is made laterally across the span of the deformity.

Indication

The technique is used to correct class I defects. Patients with large-volume defects may have thin palatal tissues, which are insufficient to provide the volume of the donor tissue necessary to fill the deformity. In such cases, various procedures for hard tissue augmentation may be selected (see Chapter 50).

Technique

The pouch is prepared as described above. The mesiodistal entrance incision for the edge of the pouch should be made with a long bevel and must be started well to the palatal (lingual) side of the defect (Fig. 46-80). After the pouch has been filled with graft, the facial tissue will be stretched. The long bevel of the entrance incision permits the palatal edge of the flap to slide toward the facial surface without opening a gap at the incision line. Sometimes, vertical releasing incisions have to be made lateral to the border of the defect.

A suitable donor site is selected in the palate, the tuberosity area, or in an edentulous area and a free graft of connective tissue is excised using a "trapdoor" approach. The graft is immediately transferred to the recipient site and properly positioned. The palatal entrance incision and the releasing incisions are closed with sutures.

Interpositional graft procedure

Surgical concept

Interpositional grafts are not completely submerged and are covered in the manner that a subepithelial connective tissue graft is placed (Fig. 46-82) (Seibert 1991, 1993a, b). Therefore, there is no need to remove the epithelium from the surface of the donor tissue. If augmentation is required not only in the buccolingual but also in the apicocoronal direction, a portion of the graft must be positioned above the surface of the tissue surrounding the recipient site (Fig. 46-83).

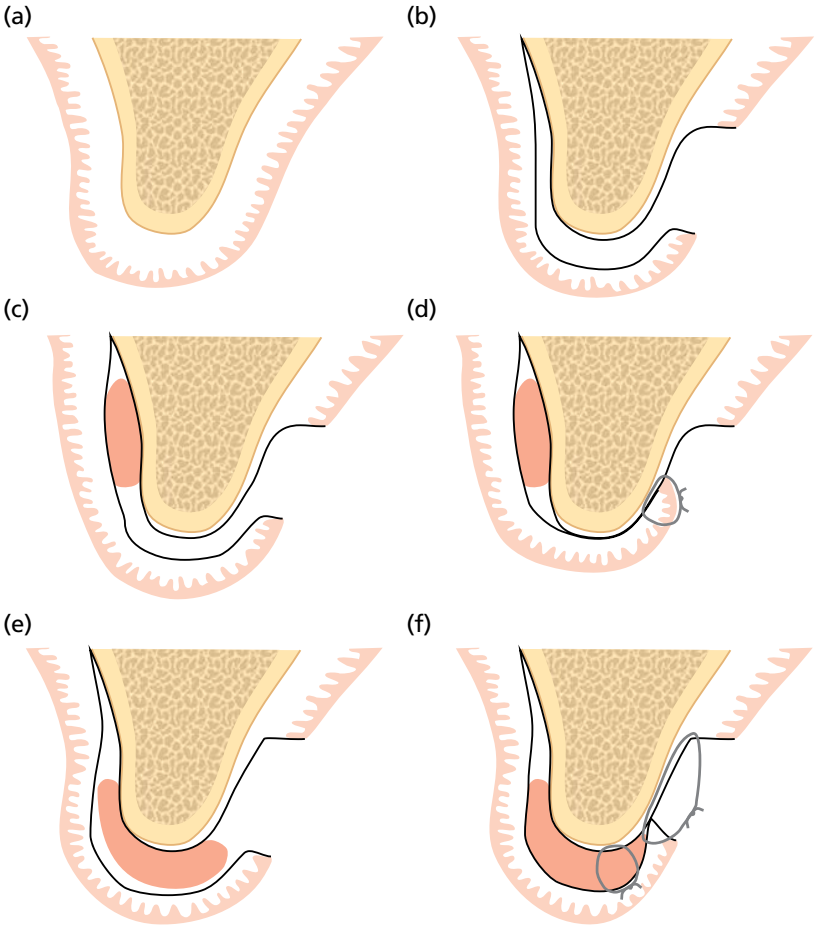


Fig. 46-80 Sequence of steps in the "pouch graft procedure" utilizing a free graft of connective tissue to expand the ridge. (a) Cross-section of the residual edentulous ridge prior to treatment. (b) Horizontal incision to create the pouch is made well to the palatal side of the defect. The incision is started partial-thickness to leave connective tissue to suture to when the flap is closed. The dissection is made supraperiosteal on the labial side of the ridge to (1) ensure an adequate blood supply within the pedicle and (2) permit the flap to expand labially or labially and coronally free of tension. (c, d) Connective tissue graft can be placed as shown for maximal buccolingual augmentation. (e, f) If vertical augmentation is desired, the connective tissue implant can be placed closer to the crest of the ridge. As is shown in (d) and (f), the more the flap is stretched or extended to gain augmentation, the more difficult it is to gain primary flap closure.

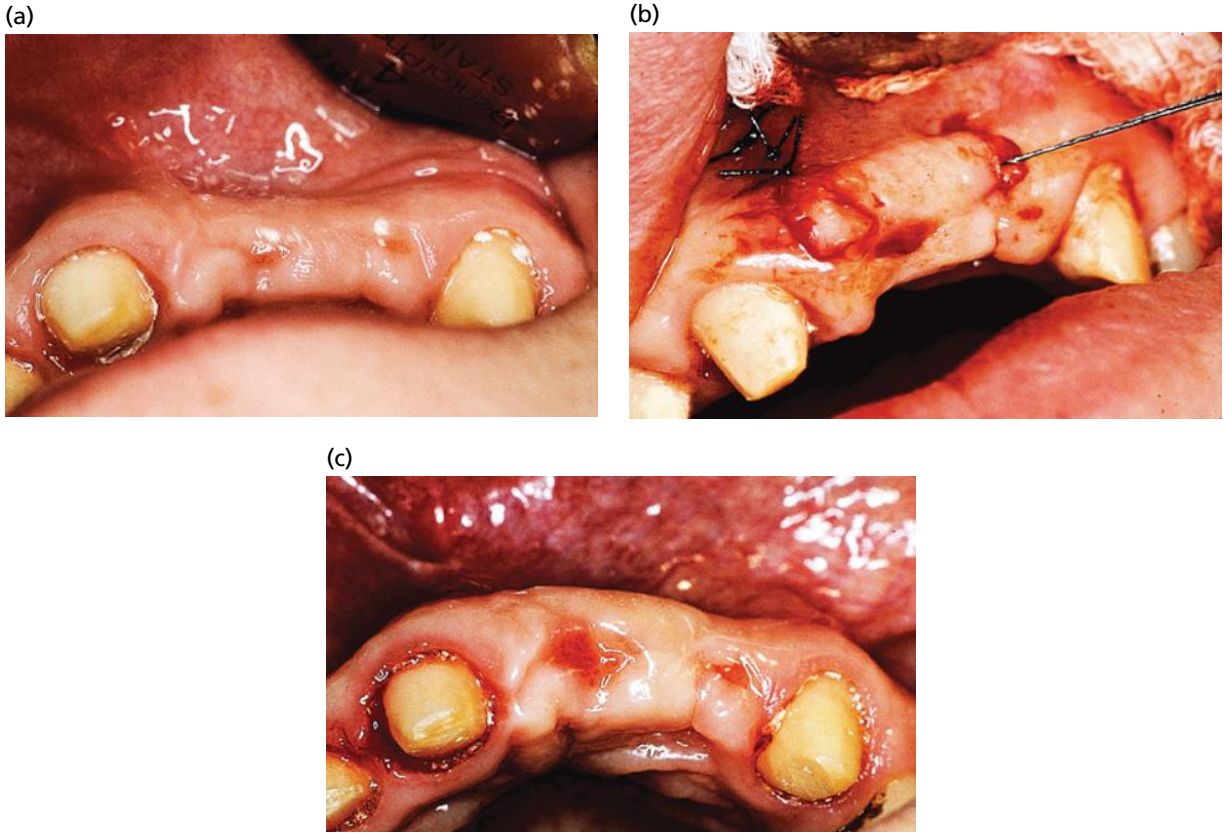


Fig. 46-81 Pouch graft procedure. (a) Pretreatment view of a class I ridge deformity. (b) Placement of the free connective tissue graft in a tunnel prepared by split incision between the two vertical incisions. The graft is brought into position by the use of a suture placed in one end of the free graft. (c) Four months post treatment showing restored facial dimension of the edentulous ridge.

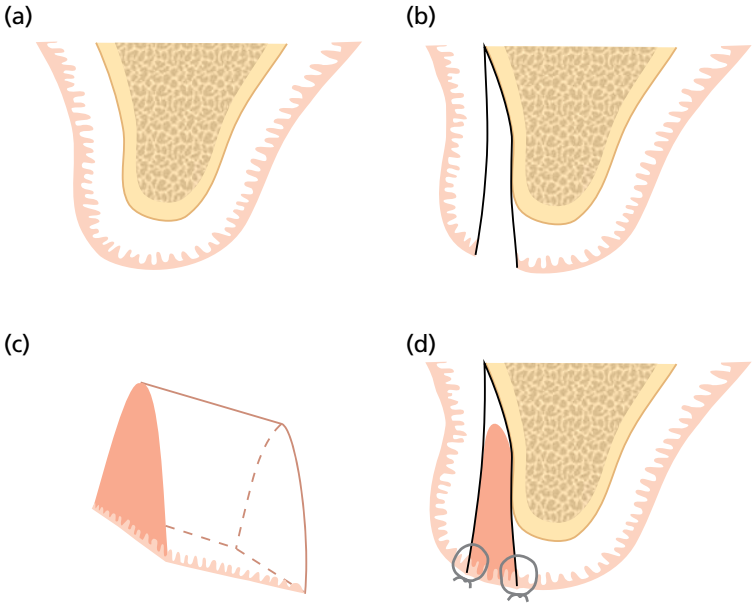


Fig. 46-82 Schematic drawings of the interpositional graft procedure. (a) Cross-section of class I ridge defect. (b) Labial flap (partial-thickness dissection preferred) is used to create the pouch. (c) Wedge-shaped graft is removed from the palate. (d) Epithelial surface of the graft is placed flush with the surface of the tissue surrounding the pouch and sutured around its circumference.

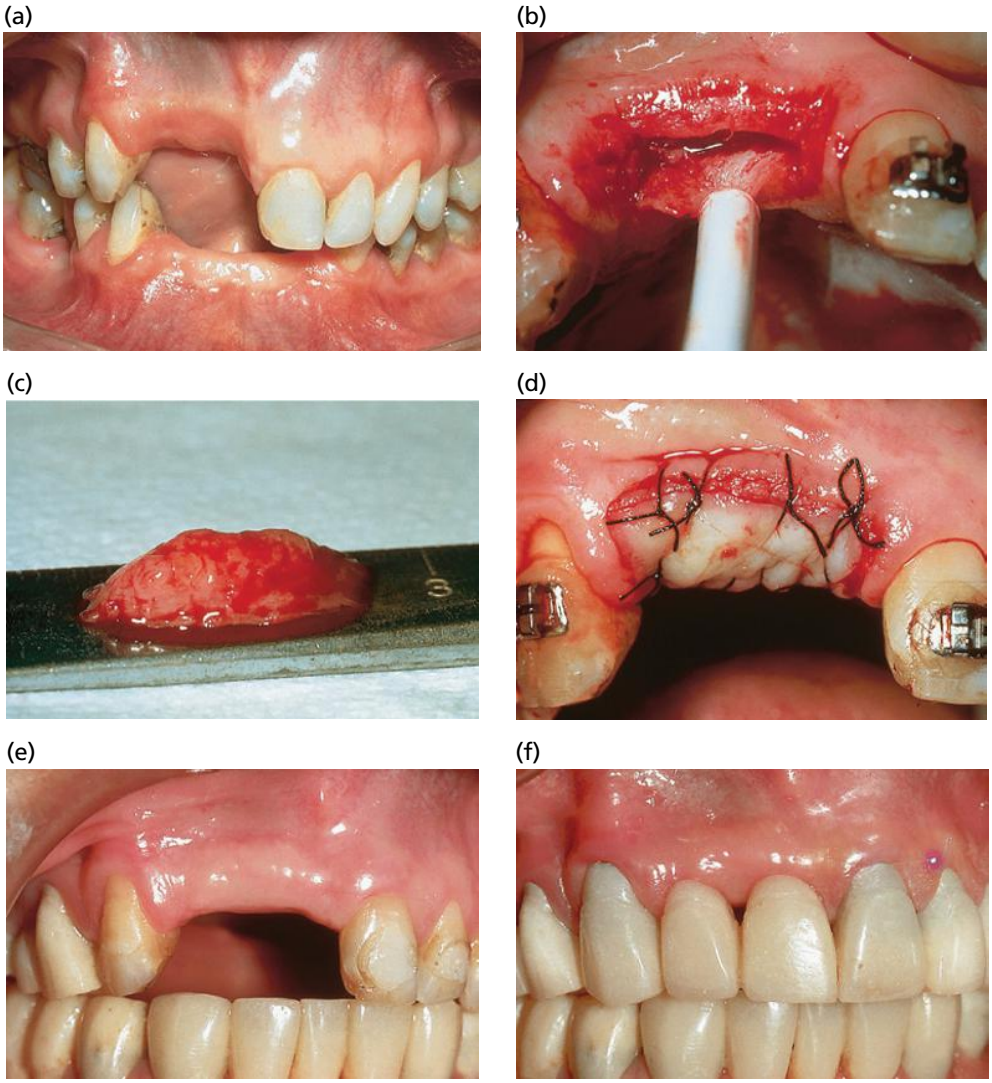


Fig. 46-83 (a) Pretreatment view, class III ridge defect. A two-stage procedure was used to augment the ridge. (b) Pouch was prepared to receive an interpositional graft. Epithelium was removed from the borders of the recipient site to permit some of the graft to be placed above the level of the surrounding tissue in order to gain apicocoronal augmentation. (c) Wedge-shaped graft was 10 mm thick at its center. (d) Interpositional graft was both displacing the labial surface of the pouch in the labial direction as well as adding height to the ridge. (e) Two months post treatment. Additional augmentation was needed apicocoronally. (f) Second-stage onlay graft was used to create a papilla and fill the dark triangle between the pontics.

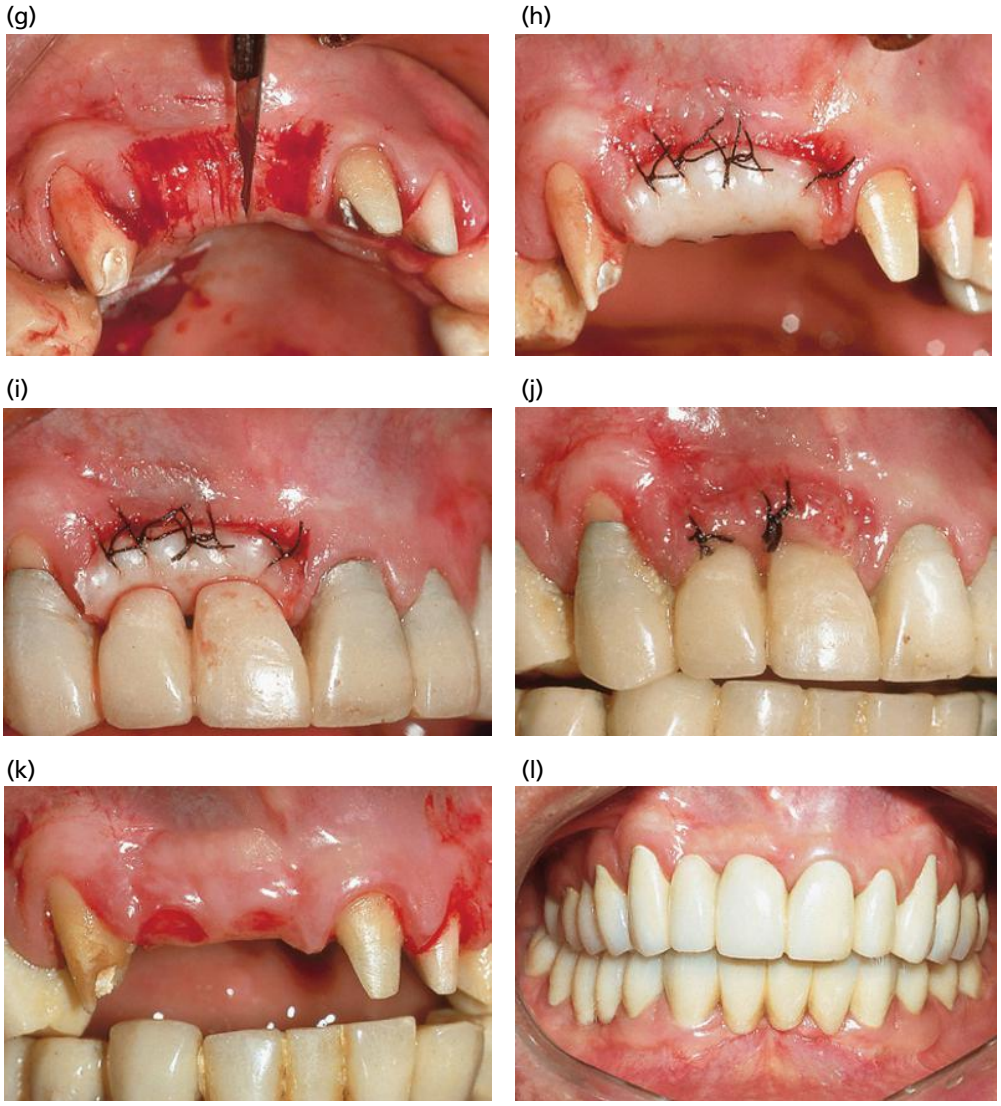


Fig. 46-83 (*Continued.*) (g) Two months after the first surgical procedure, the ridge was de-epithelialized and cuts were made into the connective tissue prior to placing the second-stage onlay graft into position. (h) Onlay graft was sutured into position. (i) Pontics were adjusted and brought into light contact with the graft. (j) Marked swelling occurred within the graft at 14 days post surgery. (k) Two months following the second surgical procedure, a gingivoplasty was performed to deepen the pontic receptacle sites for the ovate pontics. (l) Post-treatment view 1 year after the final surgical procedure. (Courtesy of J. Seibert and P. Malpeso.)

A certain amount of the grafted connective tissue will thus be exposed in the oral cavity.

Indications

Interpositional graft procedures are used to correct class I as well as small and moderate class II defects.

Technique

An envelope flap, or a split-thickness flap with releasing incisions, is prepared at the facial surface of the defect area. The provisional bridge is placed in position to serve as a reference when estimates are made regarding the amount of tissue that has to be grafted to fill the defect. A periodontal probe may be used to measure the length, width, and depth of the void of the pouch. A suitable donor site is selected in the palate or the tuberosity area, and a free graft of epithelium–connective tissue is excised (Fig. 46-82).

The donor tissue is transferred to the recipient site and placed in position. If gain in ridge height is not intended, the epithelial surface for the graft is placed flush with the surrounding epithelium. The graft is sutured along its entire circumference to the tissues of the recipient site. The provisional bridge is placed in position and the pontics are trimmed and adjusted as discussed above. No dressing is used to cover the recipient site.

If gain also in ridge height is intended, a certain portion of the graft has to be kept above the surface of the surrounding tissue (Fig. 46-83d). Granulation tissue formed during healing will eventually make the border between the graft and the adjacent tissue smooth and properly epithelialized. The swelling, which occurs postoperatively, will assist in sculpting the contour of the ridge.

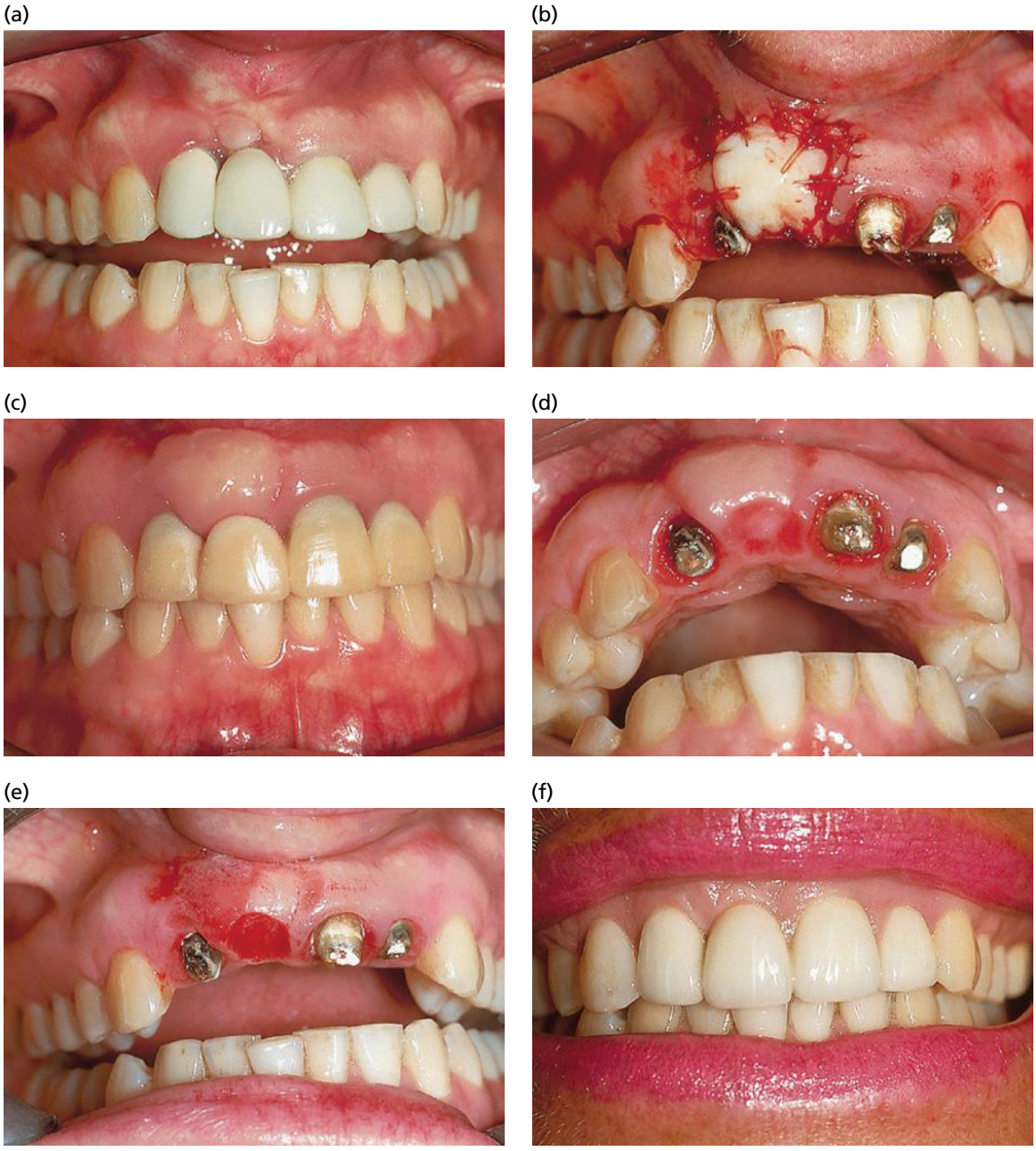


Fig. 46-84 Onlay graft procedure. (a) Pretreatment view. The gingival tissues were distorted from previous attempts at esthetic reconstruction. The patient wished to have a papilla between the right maxillary lateral and central incisor and a natural looking bridge. (b) Pontic area, including the papilla on the mesial of the right lateral incisor, was de-epithelialized and a thick (5-mm) onlay graft was sutured into position. (c) Pontic was shortened at the time of surgery to accommodate the thick graft. At 3 months post surgery, the graft had undergone maximum shrinkage and gingivoplasty could now be done. (d) Incisal view at 3 months post surgery. Note the "papilla" that has been created. The indentation in the ridge was naturally created by the tissue swelling against the pontic tooth. (e) Rotary diamond point gingivoplasty was done to reshape the bulky graft to normal contours, deepen the receptacle site for the ovate pontic, and level the gingival margins. (f) View shows the esthetic harmony that was obtained in the soft tissues and tooth form at 2 years post treatment. (Courtesy of J. Seibert and C. Williams.)

Onlay graft procedures

Surgical concept

The onlay procedure was designed to augment ridge defects in the apicocoronal plane, that is to gain ridge height (Meltzer 1979; Seibert 1983). Onlay grafts are epithelialized free grafts which, following placement, receive their nutrition from the de-epithelialized connective tissue of the recipient site. The amount of apicocoronal augmentation that can be obtained is related to the initial thickness of the graft, the events of the wound healing process, and the amount of graft tissue that survives (Figs. 46-83, 46-84, 46-85). If necessary, the grafting procedure can be repeated at 2-month intervals to gradually increase the ridge height.

Indications

Onlay graft procedures are used in the treatment of large class II and III defects. They are not suitable in areas where the blood supply at the recipient site has

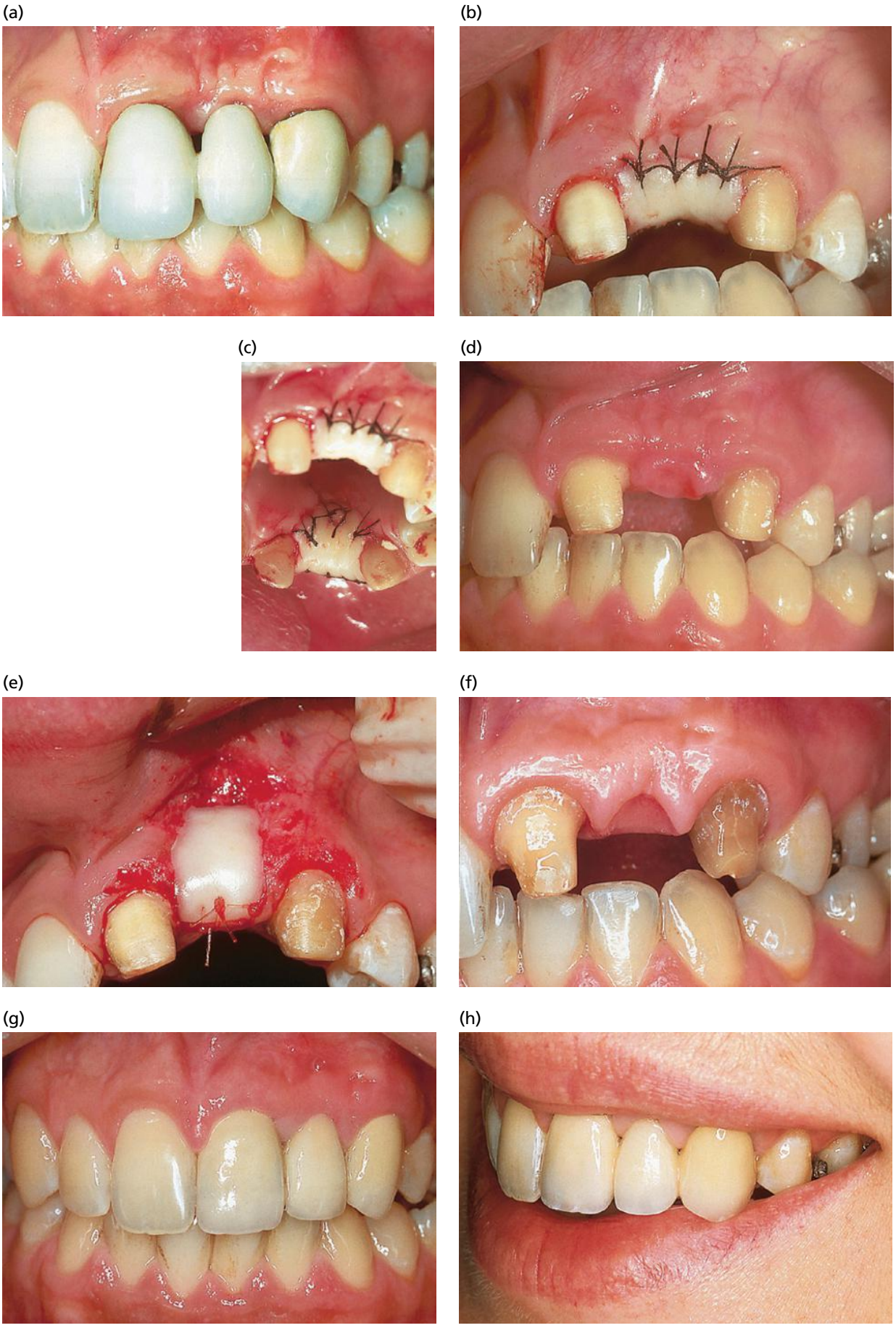


Fig. 46-85 Onlay graft procedures utilized to augment ridge and create papillae. (a) Pretreatment view. The left lateral incisor was extracted after a traumatic injury. The patient detested the dark triangle on the mesial of the pontic, the poor tooth form in the bridge, and the irregular contours in her gingival tissue. (b, c) An onlay graft was used to gain apicocoronal and buccolingual ridge augmentation as well as to develop papillae. Note how the graft was extended to the palatal side of the ridge to gain greater blood supply from a larger connective tissue base. (d, e) At 2 months post surgery, a second-stage veneer graft was used to eliminate the surface irregularities on the surface of the gingiva and gain greater buccolingual augmentation. (f) At 4 months post second-stage surgery, gingivoplasty was done to prepare the area for an ovate form pontic. (g, h) One year post treatment, esthetics have been restored for this patient. (Courtesy of J. Seibert and D. Garber.)

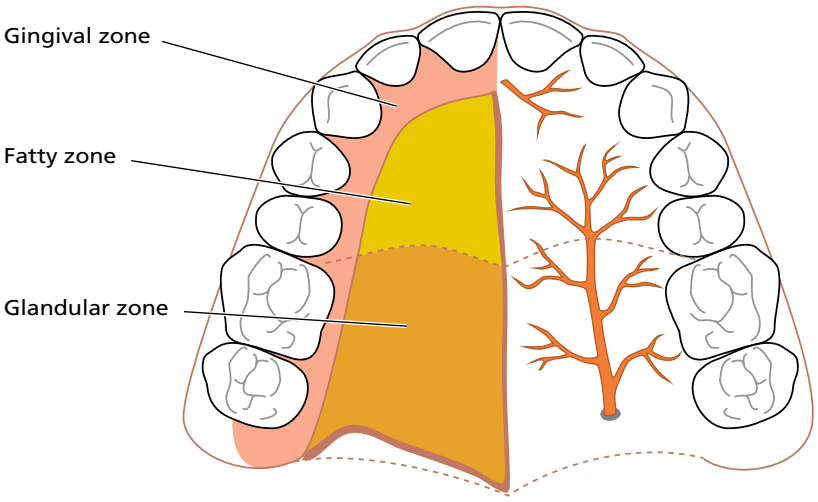


Fig. 46-86 Basic anatomic–histologic zones of the palate. Note the normal location of the greater palatine foramen.

been compromised by scar tissue formation from previous wound healing.

Technique

An attempt must be made to retain as much of the lamina propria of the recipient site as possible. The anesthetic solution should be placed high in the vestibular fornix and in the palate, thus keeping vasoconstriction in the recipient site to a minimum. A scalpel blade is used to remove the epithelium. The scalpel is moved with short, saw-like strokes across the recipient site at a level approximately 1 mm below the outer surface of the epithelium. The least amount of connective tissue possible should be excised. The margins of the recipient site can be prepared with either a butt joint or a beveled margin. The prepared recipient site should be covered with a surgical gauze moistened with isotonic saline while the donor tissue is dissected (Fig. 46-83g–i).

Selection of donor site

Onlay graft procedures, as well as interpositional graft procedures, require large amounts of donor tissue. As a general rule, the palatal vault region of premolars and first molars, midway between the gingival margin and the midline raphae, is the only area in the maxilla that contains the necessary volume of tissue required to augment large ridge defects. During the presurgical planning phase, the tissue of the palate should be probed with a 30-gauge syringe needle to ensure that an acceptable volume of tissue can be obtained at the time of surgery.

The major palatine artery emerges from the posterior palatine foramen located adjacent to the distal surface of the maxillary second molar, midway between the gingival margin and the midline raphae (Fig. 46-86). The artery passes in an anterior direction close to the surface of the palatal bone. It is important therefore that the second and third molar regions are not used as donor sites for large volume grafts.

Planing in graft preparation

As a rule, the graft should be made a few millimeters wider and longer than the dimensions required at the recipient site. The dimensions of the graft are outlined on the palate with the use of a scalpel and light bleeding is provoked to define the surface borders. In order to avoid interference with the palatine artery, the borders of the graft must be planed in such a way that its thinner portions are located high in the palatal vault or in the first molar area. The thicker portions should be harvested from the premolar areas.

Dissection of donor tissue

The base of the graft should be V- or U-shaped to match the shape of the defect in the ridge. The different planes of incision prepared in the palate must therefore converge towards an area under the center or toward one edge of the donor site. It is comparatively easy, with the use of a scalpel, to dissect in an anteroposterior or, from an area high in the palate, in a lateral direction towards the teeth. It is, however, difficult to dissect in an anterior direction from the distal edge of the donor site. There are a variety of blade holders available which permit the scalpel blade to be positioned at different angles to the holder and which enable the surgeon to cut with a back-action. When the donor tissue has been removed, it must be stored in pieces of surgical gauze moistened in isotonic saline at all times.

Treatment of the donor site

Since it is difficult to anchor and maintain a periodontal dressing at the donor site in the palatal vault, an acrylic stent should be fabricated prior to surgery. The stent should be made with wrought wire clasps on each side to add retention and to aid the patient in removing and inserting the device.

The donor site must be inspected carefully for signs of arterial bleeding. If any small vessel bleeding is observed, a circumferential suture must be placed around the vessel distal to the bleeding point. Immediately thereafter, the void at the donor site should be packed with a suitable hemostatic agent

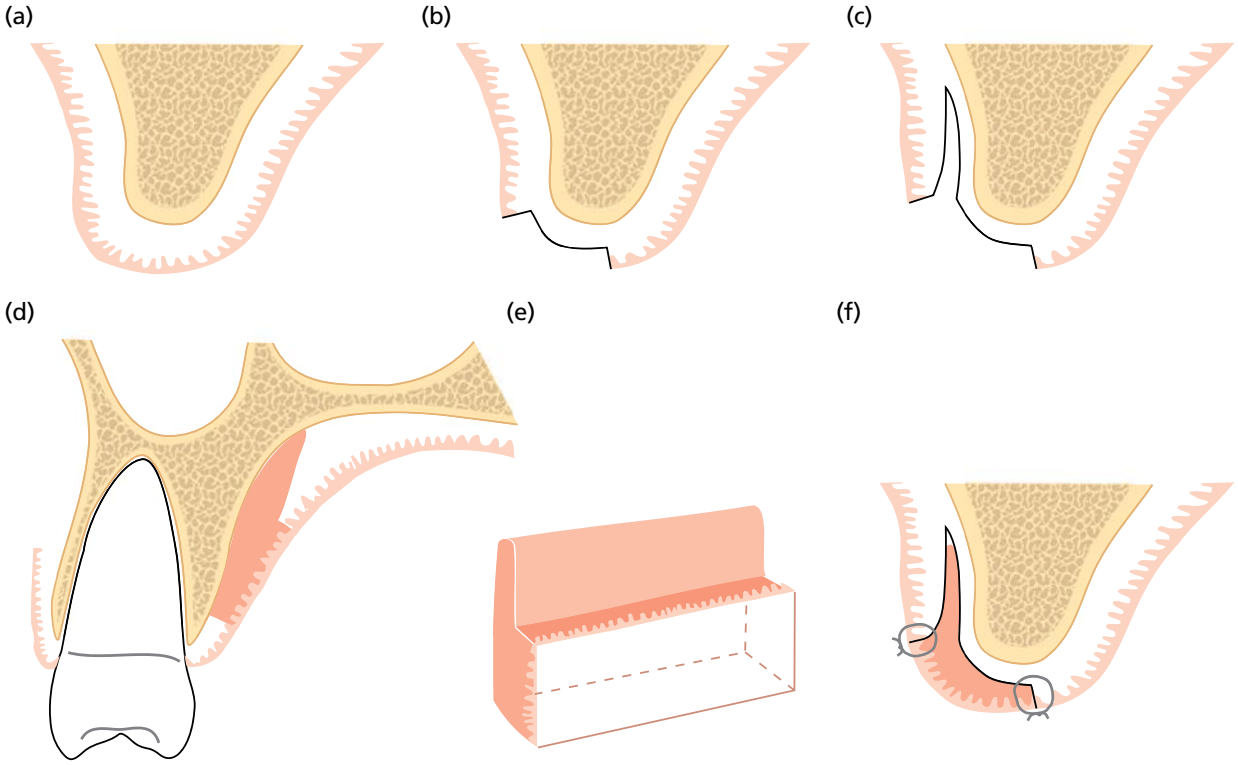


Fig. 46-87 Schematic diagram of the combination onlay–interpositional graft procedure. (a) Cross-section of a class III ridge defect. (b) Epithelium is removed on the labial–crestal side of the ridge to prepare the recipient bed for the onlay segment of the graft. (c) Partial-thickness dissection was then used to create a pouch for the interpositional section of the graft. (d) Dissection for the graft is started at right angles to the surface of the palate. The scalpel blade is then angled to remove a long connective tissue segment for the graft. (e) Three-dimensional view of the onlay section of the graft (including epithelium) and the connective tissue segment for buccolingual augmentation. (f) Graft sutured into position. (Reproduced from Quintessence Pub. Co.)

and the edges of the wound brought closer together with sutures. The stent is then put into position.

Try-in and stabilization of graft

The graft is transferred with tissue forceps to the recipient site for a try-in. The graft is trimmed to the proper shape and adjusted to fit the connective tissue surface of the prepared ridge. A series of parallel cuts may be made deep into the exposed lamina propria of the recipient site to sever large blood vessels (Fig. 46-83g) immediately before suturing. A series of interrupted sutures is placed along the borders of the graft. The dental assistant should stabilize the onlay graft against the surface of the recipient site, while the surgeon completes the placement of sutures.

Wound healing in the recipient site

Considerable postoperative swelling often occurs during the first week after pouch and onlay augmentation procedures. The epithelium of the graft will slough to form a white film on the surface of the graft. Patients should rinse two to four times per day with an antimicrobial mouth wash during the first week after surgery and refrain from mechanical cleaning measures in the area until a new epithelial covering has formed over the graft, which will not occur until a functional capillary circulation has been re-established in the graft (4–7 days after the surgery). The grafted tissue will assume a normal color as the epithelium thickens via stratification. Tissue form is usually stable after 3 months, but further shrinkage may occur over a period of several months. Final restorative measures should therefore not be initiated until after 6 months.

Wound healing in the donor site

Granulation tissue will gradually fill the donor site. Initial healing is usually complete within 3–4 weeks after the removal of a 4–5-mm thick graft. Patients should wear the surgical stent for about 2 weeks to protect the healing wound. The palate returns to its presurgical contour after about 3 months.

Combined onlay–interpositional graft procedures

Class III ridge defects pose a major challenge to the clinician since the ridge has to be augmented in both vertical and horizontal dimensions. The combined onlay–interpositional graft procedure (Fig. 46-87, 46-88) may successfully be used in such a situation (Seibert & Louis 1996). The combined graft procedure may offer the following advantages:

- Submerged connective tissue section of the interpositional graft aids in the revascularization of the onlay section of the graft, thereby gaining a greater percentage take of the overall graft

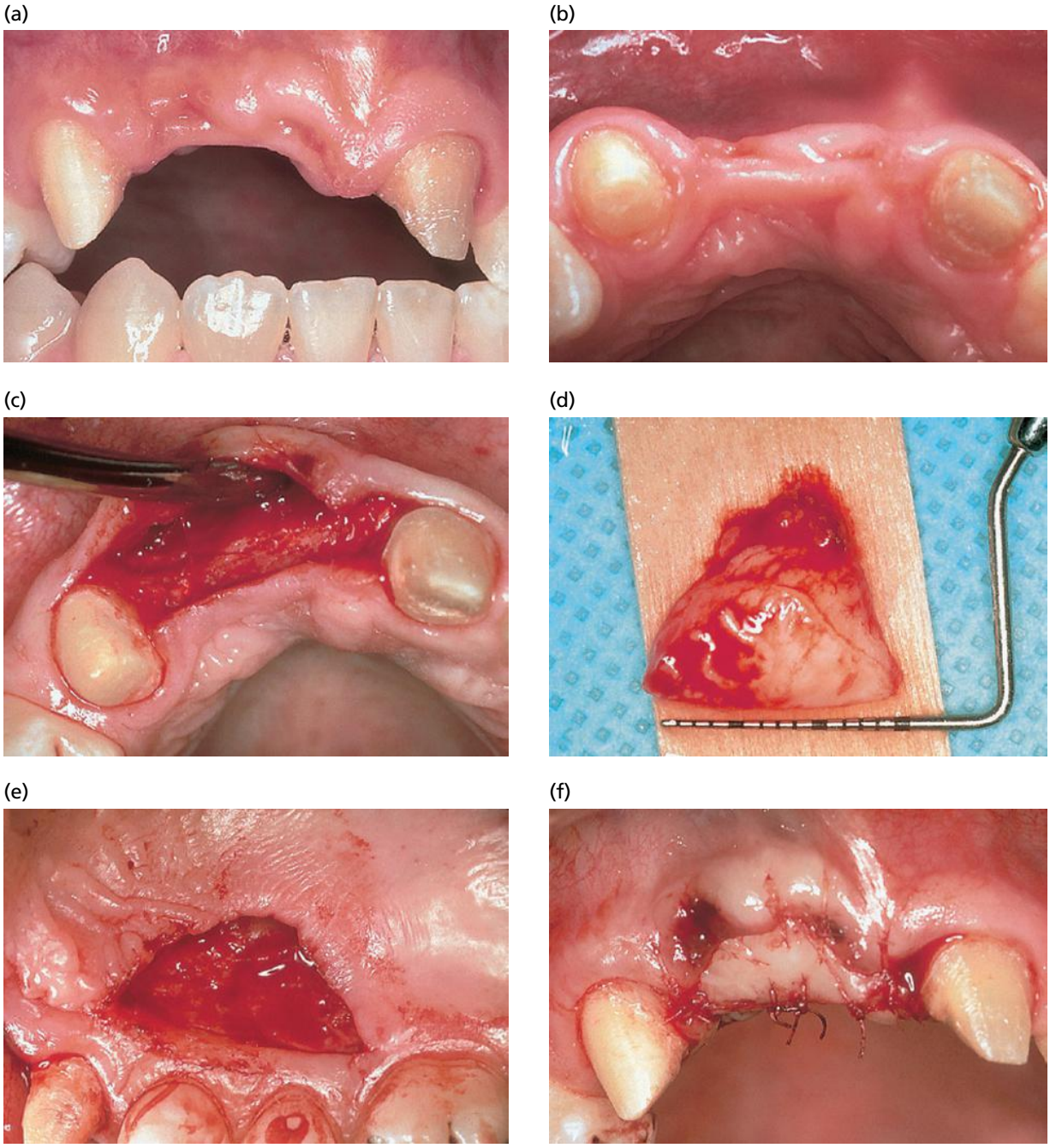
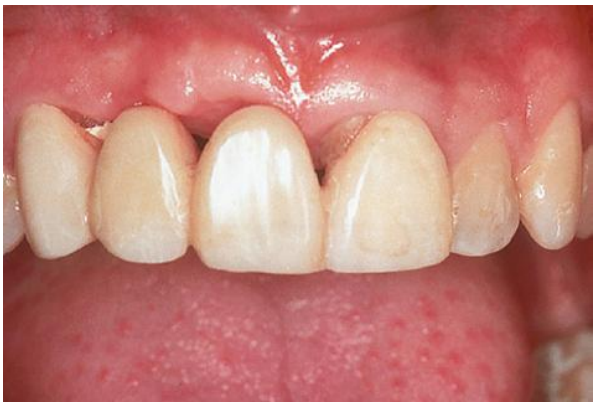


Fig. 46-88 (a, b) Right maxillary lateral and central incisors were lost due to trauma. These views show the horizontal and vertical loss of ridge tissue 10 months after the extractions. (c) Partial-thickness path of incision was extended labially and apically to create a pouch. The amount of space created within the pouch and the degree of relaxation of the flap was then tested with a periosteal elevator. (d) Epithelialized section of the graft can be seen in this view. (e) Premolar area, maxillary right side, was used as a donor area. The area of exposed connective tissue corresponded to the onlay section of the graft. The incisions were extended another 5–7 mm towards the midline on a long bevel to obtain the interpositional segment of the graft. (f) Graft was tucked into the labial pouch and sutured first along its palatal border. The labial flap was then sutured along the epithelial connective border of the graft. The residual labial socket defect in the flap created a soft tissue discontinuity defect along the labial margin of the flap. (g) At 6 weeks post surgery, it can be seen that further augmentation would be required to gain additional soft tissue in both the vertical and horizontal planes. A second-stage procedure was done at this time. (h) An incision 1.5 mm in depth was utilized to de-epithelialize the crestal surface of the ridge. Note that the papillae were not included within the surgical field. The mesial and distal borders of the onlay section of the recipient site were then extended apically to create vertical releasing incisions. The overall recipient site was to be trapezoidal in shape. A labial flap to create the pouch section of the recipient site was made using partial-thickness dissection. (i) The left maxillary premolar area was used as the donor site for the second-stage surgery. (j) This side view clearly shows the epithelialized onlay section of the graft and the de-epithelialized connective tissue section of the graft, as well as tissue thickness. (k) Graft was sutured first along the fixed palatal border to gain initial stabilization. Then the connective tissue interpositional section was sutured along the lateral borders. The flap was then sutured over the interpositional section of the graft at the epithelialized edge of the onlay section of the graft and along the vertical incisions. (l) At 6 weeks post surgery, the provisional prosthesis was modified to bring the tissue surface of the pontics into contact with the healing ridge. (m) At 2 months post surgery, tooth form was further modified on the provisional prosthesis and gingivoplasty was done to sculpt the tissues to their final form and smooth out surface irregularities. (n) Final ceramo-metal prosthesis was inserted 4 months later. The life-like reconstruction of the soft tissues and dentition restored dentofacial esthetics for the patient. (Courtesy of J. Seibert, J. Louis, and D. Hazzouri. Reproduced from Quintessence Pub. Co.)

(g)



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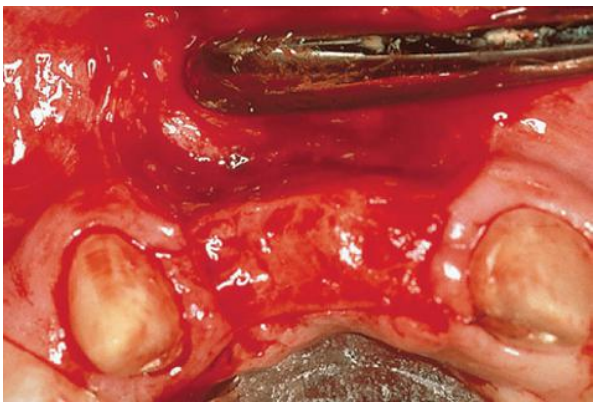

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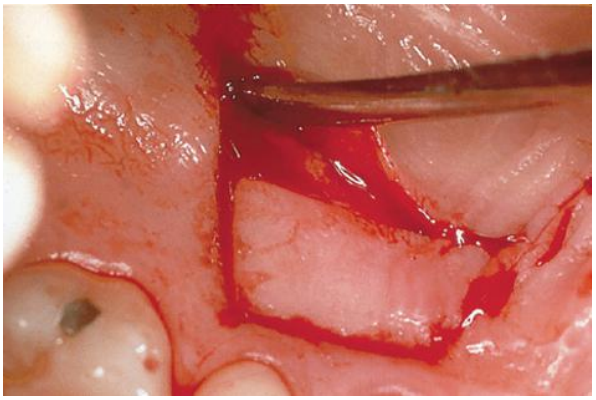

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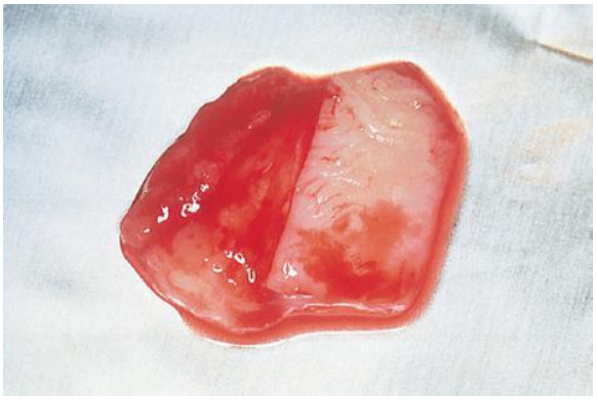

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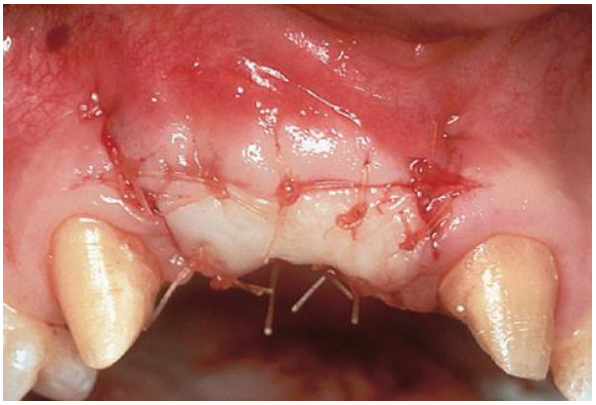

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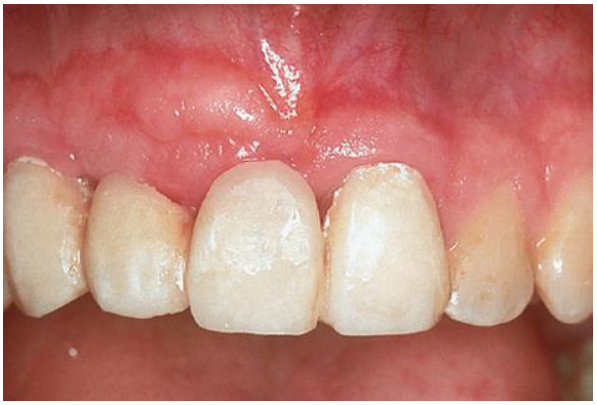

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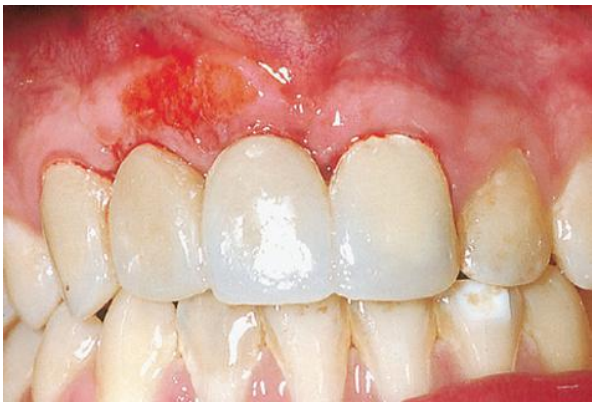

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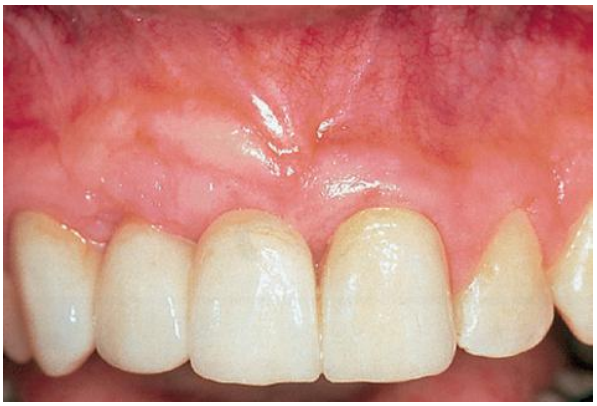

Fig. 46-88 *Continued*

- Smaller postoperative open wound in the palate donor site
- Faster healing in the palate donor site with less patient discomfort
- Greater latitude or ability to control the degree of buccolingual and apicocoronal augmentation within a single procedure
- Vestibular depth is not decreased and the mucogingival junction is not moved coronally, thereby eliminating the need for follow-up corrective procedures.

Refinement of pontic contours and gingivoplasty soft tissue sculpting procedures

It is desirable, when reconstructing defects within a partially edentulous ridge, to moderately overcorrect the ridge in the area of the deformity. This will compensate for wound contraction and provide the necessary bulk of tissue within the ridge to sculpt the ridge to its final form. Gingivoplasty techniques using rotary coarse diamond stones in an ultraspeed handpiece with copious water spray are used to smooth out incision lines and perfect the fit and shape of the pontic teeth to the crest of the ridge (Figs. 46-84, 46-88). Adjustments are made to shape the cervical contour and emergence profile of the pontic teeth to match those of the contralateral teeth. The tissue-contacting surfaces of the pontic teeth are immediately rebased with autopolymerizing resin and polished. This final tissue sculpting procedure and reshaping of the provisional prosthesis is minor in nature but aids greatly in defining the shape of the papillae and creating the illusion of the presence of a cuff of free gingiva at the pontic–ridge interface.

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Chapter 47

Periodontal Plastic Microsurgery

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Microsurgical techniques in dentistry: development of concepts

In general, the main aim of a surgical intervention is no longer just the survival of the patient or one of his/her organs, but the preservation of maximum function and improvement of patient comfort. In many surgical specialties, these demands have been met by a minimally invasive surgical approach.

Microsurgery in general is not an independent discipline, but a technique that can be applied to different surgical disciplines. It is based on the fact that the human hand, with appropriate training, is capable of performing finer movements than the naked eye is able to control. First reports on microsurgery go back to the 19th century when a microscope for use in ophthalmology was developed (Tamai 1993). Later, to correct otosclerotic deafness, the first surgical operation with a microscope was performed in Sweden (Nylén 1924). The microsurgical technique, however, did not attract the interest of surgeons until the 1950s, when the first surgical microscope, OPMI 1, with a co-axial lighting system and the option for a stereoscopic view was invented and commercialized by the Carl Zeiss company.

The microvessel surgery that later revolutionized plastic and transplantation surgery was mainly developed by neurosurgeons (Jacobsen & Suarez 1960; Donaghy & Yasargil 1967). With microsurgically-modified techniques, small vessels of a diameter of <1 mm could be successfully anastomosed on a routine basis (Smith 1964). As a consequence, a completely amputated thumb could be successfully replanted for the first time in 1965 (Komatsu & Tamai 1968). Between 1966 and 1973, a total of 351 fingers were replanted at the Sixth People's Hospital in Shanghai without magnification, resulting in a healing rate of 51% (Zhong-Wei *et al.* 1981). Since 1973, this replantation was performed solely with surgical microscopes and the corresponding success rates increased to 91.5%. These results documented the importance of a fast and successful restoration of the blood circulation in replanted extremities and free tissue grafts. Further achievements of the microsurgical technique in plastic reconstructive surgery included transplantation of toes to replace missing thumbs (Cobbett 1969), interfascicular nerve transplantation (Millesi 1979), microvascular transplantation of toe joints (Buncke & Rose 1979), micro-neurovascular transplantation of the pulp of a toe to restore the sensitivity of the finger tips (Morrison *et al.* 1980), and microvascular transplantation of the nail complex (Foucher 1991). Positive results for microsurgically modified interventions have led to today's routine clinical applications in orthopedics, gynecology, urology, plastic reconstructive, and pediatric surgery.

Clinical Periodontology and Implant Dentistry, Sixth Edition. Edited by Niklaus P. Lang and Jan Lindhe.

After a few early single reports (Bowles 1907; Baumann 1977; Apotheker & Jako 1981), the surgical microscope was introduced in dentistry in the 1990s. Case reports and the application of the microscope were described in the prosthetic (Leknius & Geissberger 1995; Friedman & Landesman 1997, 1998; Mora 1998), endodontic (Carr 1992; Pecora & Andreana 1993; Ruddle 1994; Mounce 1995; Rubinstein 1997), and periodontal literature (Shanelec 1991; Shanelec & Tibbetts 1994; Tibbetts & Shanelec 1994; Shanelec & Tibbetts 1996; Burkhardt & Hürzeler 2000).

Treatment outcomes in endodontics were statistically analyzed in prospective studies following the introduction of microendodontic techniques (Rubinstein & Kim 1999, 2002). Within 1 year after apical microsurgery, 96.8% of cases were considered to be healed. At the re-evaluation 5–7 years after the first postoperative year, a success rate of 91.5% measured by clinical and radiographic parameters was still evident (Rubinstein & Kim 2002). The corresponding percentage of healed cases treated with conventional apical surgery without a surgical microscope was only 44.1% 6 months to 8 years post surgery (Friedman *et al*. 1991). Today, the better outcomes of a microscope-enhanced approach in endodontics is well supported by systematic reviews and meta-analyses (Del Fabbro & Taschieri 2010; Setzer et al. 2012).

Despite the positive results in prospective studies (Cortellini & Tonetti 2001; Rubinstein & Kim 2002; Burkhardt & Lang 2005), the surgical microscope was only slowly accepted in prosthodontics, endodontics (Seldon 2002), and periodontal surgery. Possible reasons for this were the long learning curve, impaired maneuverability of the devices, and high costs for purchasing the instrument.

Concepts in microsurgery

The continuous development of operating microscopes, refinement of surgical instruments, production of improved suture materials, and suitable training laboratories have had a decisive role in the worldwide establishment of the microsurgical technique in many specialties. The three elements, that is *magnification, illumination*, and *instruments*, are called the *microsurgical triad* (Kim *et al*. 2001), the improvement of which is a prerequisite for improved accuracy of surgical interventions. Without any one of these, microsurgery is not possible.

Magnification

Optimal vision is a stringent necessity in periodontal practice. More than 90% of the sensations of the human body are perceived by visual impressions. Vision is a complex process that involves the integration of multiple links between the eye, retina, optic nerve, and brain. An important measure of human eyesight is visual acuity (measured in angular degrees), defined as the ability to perceive two objects separately. The visual acuity is influenced by anatomic and physiologic factors, such as the density of cells packed on the retina and the electrophysiologic processing of the image on the retina. If necessary, it may be improved with corrective lenses.

Another important factor influencing visual acuity is the lighting. The relation between visual acuity and light density is well established: at both low and high light densities, visual acuity decreases. Maximum visual acuity can be achieved at a light density of 1000 cd/m^2 and optimal lighting conditions should be implemented.

Visualization of fine details is enhanced by increasing the image size of the object. This can be done in two ways: (1) moving closer to the objects and (2) magnification. Using the former method, the ability of the lens of the eye to accommodate becomes important and influences the visual capacity. By changing the shape of the lens, the refraction of the optical apparatus increases, allowing it to bring nearer objects into focus. With aging, the ability to focus on near objects is compromised because the lens of the eye loses flexibility (Burton & Bridgeman 1990). This phenomenon is called presbyopia. Presbyopia affects all people in middle age, and becomes especially noticeable when the nearest point at which the eye can focus accurately exceeds the ideal working distances (Burton & Bridgeman 1991). To see small objects accurately, the focal length must be increased. As an example, an older individual reading without glasses must hold the reading matter farther away to see the print, but the longer working distance results in the print being seen in a smaller size. This decrease in image size, resulting from the increased working distance, needs to accommodate the limitations of presbyopia and is especially hindering in clinical practice. In periodontal practice, the tissues to be manipulated are usually very fine and cannot be distinguished easily with normal visual acuity. Therefore, the clinical procedure may only be performed successfully with the use of magnification, which improves precision and, hence, the quality of work.

Optical principles of loupes

In dentistry, two basic types of magnification systems are commonly used: the surgical microscope and loupes. The latter can further be classified into (1) single-lens magnifiers (clip-on, flip-up, jeweler's glasses) and (2) multilens telescopic loupes. Single-lens magnifiers produce the described diopter magnification by adjusting the working distance to a set length. As diopters increase, the working distance decreases. With a set working distance, there is no range and no opportunity for movement, which makes it difficult to maintain focus and, therefore, may cause neck and back strain from poor posture (Basset 1983; Diakkow 1984; Shugars *et al*. 1987). Additionally, diopter magnifiers give poor image quality, which restricts the quality of surgery with them (Kanca & Jordan 1995). These types of glasses cannot be considered to be a true means of magnification.

Fig. 47-1 Compound loupes, inclinable and adjustable in the interpupillary distance (Galilean principle).

(a)

(b)

Fig. 47-2 (a) Prism loupes, sealed to avoid leakage of moisture, front frame mounted and fully adjustable (Prism principle). (b) Sterilizable guards against contact for a safe rotation of the loupe during the surgical intervention.

Telescopic loupes (compound or prism loupes), however, allow good ergonomic posture as well as significant advancements in optical performance (Shanelec 1992). Instead of increasing the thickness of a single lens to increase magnification, compound loupes use multiple lenses with intervening air spaces (Fig. 47-1). These allow adjustment of magnification, working distance, and depth of the field without excessive increase in size or weight. Prism loupes are the most optically advanced type of loupe magnification available (Fig. 47-2). While compound loupes use multiple refracting surfaces with intervening air spaces to adjust optical properties, prism loupes are actually low-power telescopes. They contain Pechan or Schmidt prisms that lengthen the light path through a series of mirror reflections within the loupes (Fig. 47-3). Prism loupes produce better magnification, larger fields of view, wider depths of field, and longer working distances than do other loupes. To guarantee a proper adjustment of loupes, knowledge of some basic definitions and key optical features of loupes is necessary (Fig. 47-4).

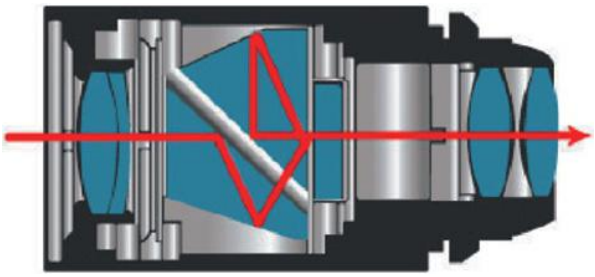

Fig. 47-3 Light path through a prism loupe. Even though the distance the light travels has increased, there is no decrease in brightness or image contrast, even at ×4 or ×5 magnification. This is due to the fact that the light does not travel through air, but rather through the glass of the prism.

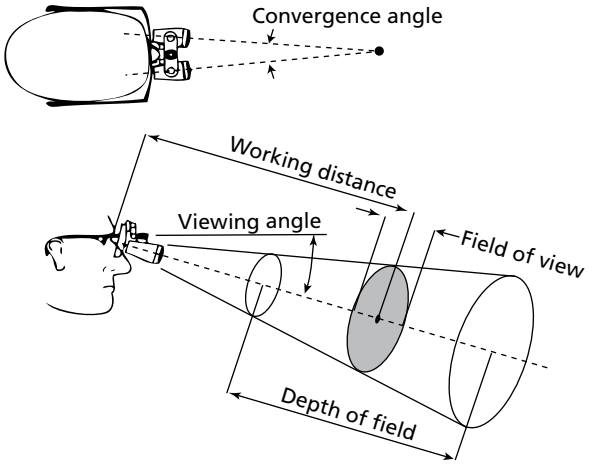

Fig. 47-4 Principal optical features of loupes.

Working distance

The working distance (Fig. 47-4) is the distance between the eye lens and the object in vision. There is no set rule for how much the working distance may be increased. Depending on the height and the resulting arm length of the dentist, the working distance with slightly bent arms usually ranges from 30 to 45 cm. At this distance, postural ergonomics are greatly improved and eye strain reduced due to less eye convergence. The multitude of back, neck, shoulder, and eye problems that dentists suffer when working without using loupes, frequently originate from the need to assume a short working distance to increase visual acuity (Coburn 1984; Strassler 1989). By wearing surgical loupes, the dentist's head can be held in the center of the body's balance over the spine and is stabilized against gravity.

Working range

The working range (depth of field) (Fig. 47-4) is the range within which the object remains in focus. The depth of field of normal vision ranges from working distance to infinity. When moving back from a close working distance, the eyes naturally accommodate and refocus to the new working distance. Normally, eye position and body posture are not frozen in one place for an extended period, but vary constantly. Wearing loupes changes this geometry. Body posture

and position of the extraocular muscles are confined to a range determined by the loupe's characteristics. It is important to understand that each individual's vision is limited to his/her own internal working range, which means that he/she may only be able to maintain focus on an object within a 15-cm range, even though the loupes have a 23-cm depth of field. With any brand of loupe, the depth of field decreases as the magnification increases.

Convergence angle
The convergence angle (Fig. 47-4) is the pivotal angle aligning the two oculars, such that they point at the identical distance and angle. At a defined working distance, the convergence angle varies with interpupillary distance. Wider-set eyes will have more eye convergence at short working distances. Therefore, the convergence angle defines the position of the extraocular muscles and this may result in tension of the internal and external rectus muscles; this may be an important source of eye fatigue.

Field of view
The field of view (Fig. 47-4) is the linear size or angular extent of an object when viewed through the telescopic system. It also varies depending on the design of the optic lens system, the working distance, and the magnification. As with depth of field, when magnification increases, the field of view decreases.

Interpupillary distance
The interpupillary distance (Fig. 47-4) depends on the individual's eye position within the head and is a key adjustment that allows long-term, routine use of loupes. The ideal setting, as with binoculars, creates a single image with a slightly oval-shaped viewing area. If the viewing area is adjusted to a full circle, excess eye muscle strain would inhibit the ability to use the loupes for long periods of time.

Viewing angle
The viewing angle (Fig. 47-4) is defined as the angular position of the optics that allows comfortable working. The shallower the angle, the greater the need to tilt the neck to view the object being worked on. Therefore, loupes for dental clinicians should have a greater angulation than loupes designed for industrial workers. Only slight or no angulation, which results when magnifiers are embedded in the lenses of the eyeglasses, may cause the operator to unduly tilt his/her head to view a particular object. This, again, may lead not only to neck discomfort, but also to pain in the shoulder muscles and possibly to headaches. As the working posture is likely to change over time, the loupes should be adjustable to any posture.

Illumination
Most manufacturers offer collateral lighting systems or suitable fixing options. These systems may be helpful, particularly for higher magnification in the range of ×4 or more. Loupes with a large field of view will have better illumination and brighter images than those with narrower fields of view. Important considerations in the selection of an accessory lighting source are total weight, quality, and brightness of the light, ease of focusing and directing the light within the field of view of the magnifiers, and ease of transport between surgeries (Strassler *et al*. 1998).

It has to be realized that with each surface refraction in a lens, 4% of the transmitted light will be lost due to reflection. In telescopic loupes, this could amount to as much as a 50% reduction in brightness. Antireflective coatings have been developed to counteract this effect by allowing lenses to transmit light more efficiently. The quality of lens coatings varies and should be evaluated when selecting loupes (Shanelec 1992).

Choice of loupes

Before choosing a magnification system, different loupes and appropriate time for a proper adjustment have to be considered. Ill-fitting or improperly adjusted loupes as well as the quality of the optics will influence the performance. For use in periodontal surgery, an adjustable, sealed prism loupe with high-quality, coated lenses offering a magnification between 4× and 4.5×, either headband- or front frame-mounted, with a suitable working distance and a large field of view, seems to be the instrument of choice. The information in Table 47-1 serves as a basic guide to making an appropriate selection.

Optical principles and components of a surgical microscope

The surgical microscope is a complicated system of lenses that allows stereoscopic vision at a magnification of approximately ×4–40 with excellent illumination of the working area. In contrast to loupes, the light beams fall parallel onto the retinas of the observer so that no eye convergence is necessary and the demand on the lateral rectus muscles is minimal (Fig. 47-5). The microscope consists of optical components, lighting unit, and mounting system. To avoid unfavorable vibration of the microscope during use, it should be firmly attached to a wall, ceiling or floor stand. When mounted on the floor, the position of the microscope in the room must allow quick and easy access.

The optical unit includes the following components (Fig. 47-6): (1) magnification changer, (2) objective lenses, (3) binocular tubes, (4) eyepieces, and (5) lighting unit (Burkhardt & Hürzeler 2000).

Magnification changer
The magnification changer or "Galilean" changer consists of one cylinder into which two Galilean telescope systems (consisting of a convex and

Table 47-1 Features to consider in the selection of a magnifying loupe system.

Compound loupes (Galilean)	Magnification range ×2–3.5 Lighter in weight Shorter working distance Shorter loupe barrel
Prism loupes (Keplerian)	Magnification range 3–5× Heavier in weight Longer working distance Longer loupe barrel
Front-frame mounted	Allow up to 90% of peripheral vision Not to be used with prescription glasses Require soft and cushioned nose piece Better weight distribution
Head-band mounted	Restricted peripheral vision Allow use with prescription glasses Better weight distribution Require adjustment more often
Fixed-lens magnifiers	No adjustment options when changing posture Minimum weight
Flip-up capability	Require removable, sterilizable handle Allow switch from magnified to regular vision
Quality of the lenses	Corrected for chromatic and spherical aberration No drop-off in clarity when approaching the edges Sealed system to avoid leakage of moisture Option for disinfection
Adjustment options	Interpupillary distance Viewing angle Vertical adjustment Lock in adjusted position Convergence angle (preset angle may be more user-friendly)
Lens coating	Brighter image More light
Accessories	Transportation box Side and front shields for protection Mounted light source Removable cushions

concave lens) with various magnification factors are built. These systems can be used in either direction depending on the position of the magnification changer. A total of four different magnification levels are available. Straight transfer without any optics yields no magnification. The combination of the magnification changer with varying objective lenses and eyepieces yields increasing magnification when the control is adjusted.

The stepless motor-driven magnification changer must achieve a magnification of ×0.5–2.5 with one optical system, which is operated with either a foot pedal or an electric rotating control, mounted on the

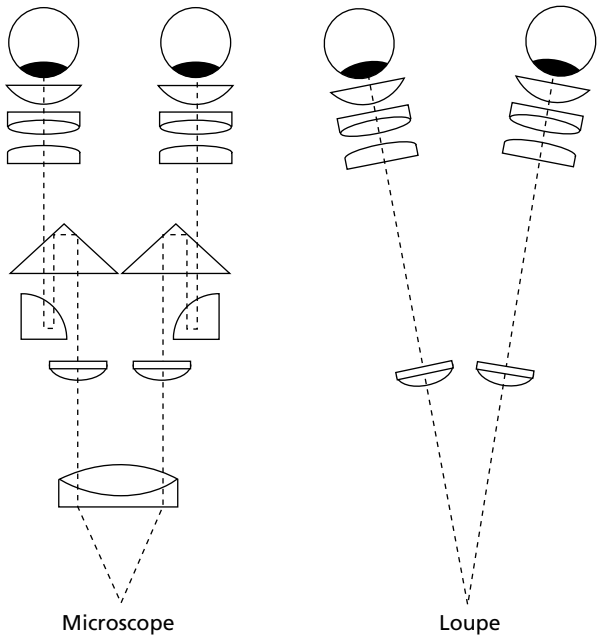

Fig. 47-5 Comparison of vision enhancement with loupes and a microscope. The loupes necessitate eye convergence, while vision is paralleled through the microscope.

microscope. The operator should decide whether to use the manual or motorized magnification changer. If the magnification must be changed frequently, it can be accomplished more quickly with the manual than with the motorized changer, the former not having in-between levels. While the motorized system improves the focus and comfort over the manual system, the former is more expensive.

Objective lenses

As processed by a magnification changer, the image is only projected by a single objective. This simultaneously projects light from its source twice for deflection by the prisms into the operation area (i.e. coaxial lighting). The most frequently used objective is 200 mm (f = 200 mm). The focal length of the objective generally corresponds to the working distance of the object.

Binocular tubes

Depending on the area of use, two different binocular tubes are attached (i.e., straight and inclined tubes). With straight tubes, the view direction is parallel to the microscope axis. Using inclined tubes, an angulation to the microscope axis of 45° is achieved. In dentistry, only inclined, swiveling tubes that permit continuous adjustable viewing are used for ergonomic reasons. The latest configuration consists of a foldable binocular tube with integrated 360° rotation function. This allows a precise increase or decrease of the working distance and adjusts for eye discrepancies between surgeon and assistant, an important aspect for improving ergonomics in periodontal microsurgery (Fig. 47-7). The precise adjustment of the interpupillary distance is the basic prerequisite for stereoscopic vision of the operation area.

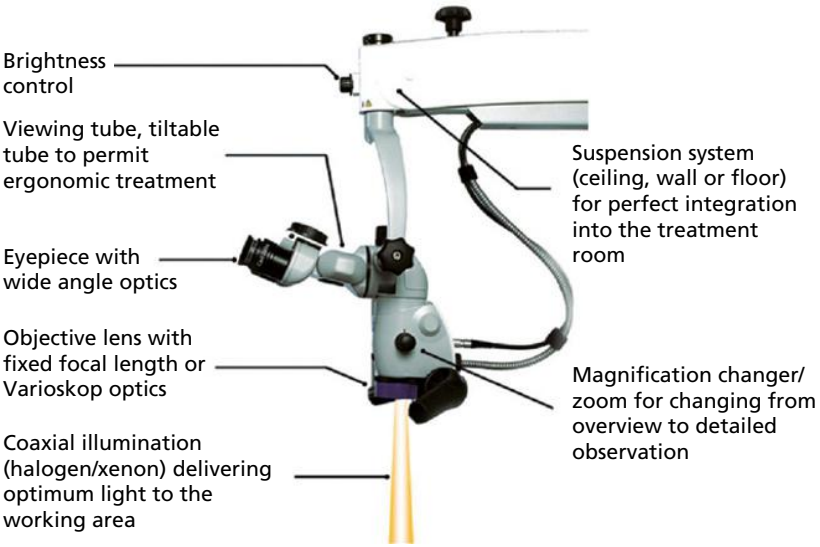

Fig. 47-6 System components of a surgical microscope.

Fig. 47-7 Tiltable and foldable viewing tube allowing an ergonomic posture during clinical work, which is a prerequisite for optimal performance using microsurgical technique.

Eyepieces

The eyepieces magnify the interim image generated in the binocular tubes. Varying magnifications can be achieved (×10, ×12.5, ×16, ×20) using different eyepieces. Eyepiece selection not only determines the magnification, but also the size of the field of view. As with loupe spectacles, an indirect relationship exists between the magnification and the field of view. The 10× eyepiece generally provides a sufficient compromise between magnification and field of view. Modern eyepieces allow a correction facility within −8 to +8 diopters that is a purely spherical correction.

The majority of surgical microscopes are modules that can be equipped with attachments that include integrated video systems, photographic adapters for cameras, units for image storage, color printers, and powerful lighting sources. Prior to purchasing attachments, inexperienced clinicians should research what it is that they need. It is recommended that magnifying loupes are used prior to purchasing a microscope to become accustomed to working under magnification.

Lighting unit

Optimal illumination is necessary with high magnifications. The use of halogen lamps has become popular. These lamps provide a whiter light than lamps using conventional bulbs due to their higher color temperature. As halogen lamps emit a considerable portion of their radiation within the infrared spectrum, microscopes are equipped with cold-light mirrors to keep this radiation from the operation area. An alternative to the halogen light is the xenon lamp that functions for up to ten times longer than the halogen lamp. The light emitted has daylight characteristics with an even whiter color and delivers a brighter, more authentic image with more contrast.

Advantages and disadvantages of loupes and surgical microscopes

A substantial number of periodontists have adopted the use of low magnification in their practices and recognize its great benefits. Most results are based on subjective statements from patients or observations of the attending surgeons. At present, it can only be speculated how significantly the selection of magnification influences the result of the operation. The magnification recommended for surgical interventions ranges from ×2.5 to ×20 (Apotheker & Jako 1981; Shanelec 1992). In periodontal surgery, magnifications of ×4–5 for loupe spectacles and ×10–20 for surgical microscopes appear to be ideal depending on the type of intervention. As the depth of field decreases with increasing magnification, the maximum magnification for a surgical intervention is limited to about ×12–15 when dealing with a localized problem, for example coverage of a single soft tissue recession or interdental wound closure after a guided tissue regeneration of an infrabony defect. A magnification range of ×6–8 seems appropriate for clinical inspections or surgical interventions when the entire quadrant is under operation. Higher magnifications of ×15–25 are more likely required for the visual

examination of clinical details only, such as in endodontic interventions.

Advantages of loupes over the microscope are reduced technique sensitivity, expense, and learning phase. The lighting of the operation field is often insufficient, however, and this may limit the usefulness of magnifications above ×4.5. The surgical microscope guarantees a more ergonomic working posture (Zaugg *et al*. 2004), optimal lighting of the operation area, and freely selectable magnification levels. These advantages are countered by the increased expenses of the equipment and the extended learning phase for the surgeon and his/her assistant. In order to visualize lingual or palatal sites that are difficult to access, the microscope must have sufficient maneuverability. Developments have enabled direct viewing of oral operation aspects. By means of these optical devices, it will most likely be possible to perform all periodontal interventions with the surgical microscope.

Instruments

Technical aspects

Proper instrumentation is fundamental to microsurgical intervention. While various manufacturers provide sets of microsurgical instruments, these are generally conceived for vascular and nerve surgery and, therefore, are inappropriate for use in plastic periodontal surgery. Appropriate sets of steel or titanium instruments for periodontal surgery are available from different manufacturers. A basic set comprises a needle holder, microscissors, microscalpel holder, anatomic and surgical forceps, and a set of various elevators.

As the instruments are primarily manipulated by the thumb, index and middle finger, their handles should be round, yet provide traction so that finely controlled rotating movements can be executed. The rotating movement of the hand from 2 o'clock to 7 o'clock (for right handed persons) is the most precise movement that the human body is able to perform. The instruments should be approximately 18 cm long and lie on the saddle between the operator's thumb and the index finger, and also be slightly top heavy to facilitate accurate handling (Fig. 47-8). In order to avoid an unfavorable metallic glare under the light of the microscope, the instruments often have a colored coating surface. The weight of each instrument should not exceed 15–20 g (0.15–0.20 N) in order to avoid hand and arm muscle fatigue.

The needle holder should be equipped with a precise working lock that should not exceed a locking force of 50 g (0.5 N). High locking forces generate tremor, and low locking forces reduce the ability to sense movement. In order to avoid the thread slipping when tying a knot, the tips of the forceps have flat surfaces or can be finely coated with a diamond grain that improves the security with which the needle holder holds a surgical needle (Abidin *et al*. 1990).

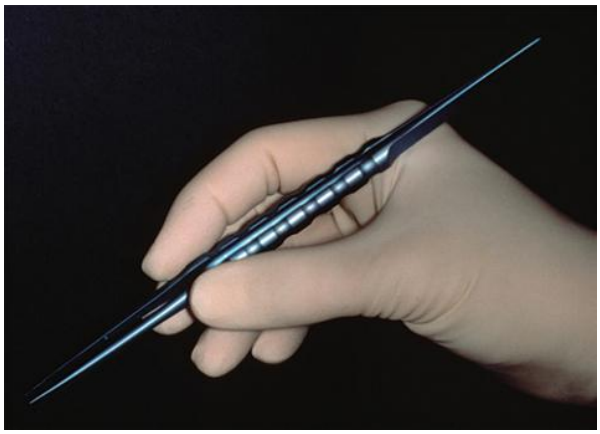

Fig. 47-8 Correct hand position for utilizing microsurgical instruments. Fine rotary movements using a pencil-like grip are needed for precise movements.

The configuration of the needle holder jaw has considerable influence on this security. Teeth on the tungsten carbide inserts provides the greatest resistance to either twisting or rotation of the needle between the needle holder jaws, but this benefit must be weighed against the potential damaging effects of the teeth on suture material. Smooth jaws without teeth cause no demonstrable damage to 6-0 monofilament nylon sutures, whereas needle holder jaws with teeth ($7000/in^2$) markedly reduced the suture breaking strength (Abidin *et al*. 1990). Additionally, the sharp outer edges of the needle holder jaws must be rounded to avoid breakage of fine suture materials (Abidin *et al*. 1989). When the needle holder jaws are closed, no light must pass through the tips.

Locks aid in the execution of controlled rotation movements on instrument handles without pressure. The tips of the forceps should be approximately 1–2 mm apart when the instrument lies in the hand without any pressure.

Various shapes and sizes of microscalpels can be acquired from ophthalmic or plastic surgery instrument sets and supplemented with fine instruments (fine chisels, raspatories, elevators, hooks, and suctions) from conventional surgery.

Microinstruments are stored in a sterile container or tray to protect them against damage. The tips of the instruments must not touch each other during sterilization procedures or transportation. The practice staff should be thoroughly instructed about the cleaning and maintenance of such instruments, as cleansing in a thermo disinfector without instrument fixation can irreparably damage the tip of these very expensive microinstruments.

Suture materials

Suture material and technique are essential factors to consider in microsurgery (Mackensen 1968). Wound closure is a key prerequisite for healing following surgical interventions and is most important for the avoidance of complications (Schreiber *et al*. 1975;

Kamann *et al*. 1997). The most popular technique for wound closure is the use of sutures that stabilize the wound margins sufficiently and ensures a proper closure over a defined period of time. However, the penetration of a needle through the soft tissue in itself causes trauma, and the presence of foreign materials in a wound may significantly enhance the susceptibility to infection (Blomstedt *et al.* 1977; Österberg & Blomstedt 1979). Hence, it is obvious that needle and thread characteristics also influence the wound healing and surgical outcome.

Characteristics of the needle

The needle consists of a swage, body, and tip, and can differ in terms of material, length, size, tip configuration, body diameter, and nature of the connection between needle and thread. In *atraumatic* sutures, the thread is firmly connected to the needle through a press-fit swage or fixed in a laser-drilled whole. There is no difference concerning stability between the two attachment modalities (Von Fraunhofer & Johnson 1992). The body of the needle should be flattened to prevent twisting or rotation in the needle holder. The needle tips differ widely depending on the specialty in which they are used. Tips of cutting needles are appropriate for coarse tissues or atraumatic penetrations. In order to minimize tissue trauma in periodontal microsurgery, the sharpest needles, namely reverse cutting needles with precision tips or spatula needles with micro tips (Fig. 47-9), are preferred (Thacker *et al*. 1989).

The shape of the needle can be straight or bent to various degrees. For periodontal microsurgery, the 3/8″ circular needle generally ensures optimum results. A wide range of lengths, as measured along the needle curvature from the tip to the proximal end of the needle lock, are available. For papillary sutures in the posterior area, needle lengths of 13–15 mm are appropriate. The same task in the front aspect requires needle lengths of 10–12 mm, and for closing a buccal releasing incision, needle lengths of 5–8 mm are adequate. To guarantee perpendicular penetration through the soft tissues, which prevents tearing, an asymptotic curved needle is advantageous in areas where narrow penetrations are required (e.g. margins of gingivae, basis of papillae). To fulfil these prerequisites for ideal wound closure, at least two different sutures are used in most surgical interventions. Table 47-2 serves as a basic guide to the selection of the appropriate suture material.

Characteristics of the thread

The thread may be classified in either *resorbable* or *non-resorbable* materials. Within these two categories, the materials can be further divided into *monofilament* and *polyfilament* threads. The bacterial load of the oral cavity also demands attention when choosing the suture material. Generally, in the oral cavity the wound healing processes are uneventful, thereby reducing the risk of infection introduced by contamination of the thread. As polyfilament threads are characterized by a high capillarity, monofilament threads are preferred (Mouzas & Yeadon 1975). *Pseudomonofilaments* are coated polyfilament threads that aim to reduce mechanical tissue trauma. During suturing, their coating breaks and the properties of the pseudomonofilament thread then correspond to those of polyfilament threads (Macht & Krizek 1978). However, fragments of the coating may invade the surrounding tissues and elicit a foreign body reaction (Chu & Williams 1984).

Resorbable sutures

Resorbable threads may be categorized as *natural* or *synthetic*. Natural threads (i.e. surgical gut) are produced from the intestinal mucosa of sheep or cattle. The twisted and polished thread loses stability within 6–14 days due to enzymatic breakdown (Meyer & Antonini 1989). Histologic examinations have confirmed inflammatory tissue reactions with a distinct infiltrate when using these threads. For this reason, use of natural resorbable threads is generally obsolete (Bergenholtz & Isaksson 1967; Helpap *et al*. 1973; Levin 1980; Salthouse 1980).

Synthetic threads have the advantage of constant physical and biologic properties (Hansen 1986). They are made from polyamides, polyolefines or polyesters that disintegrate on hydration

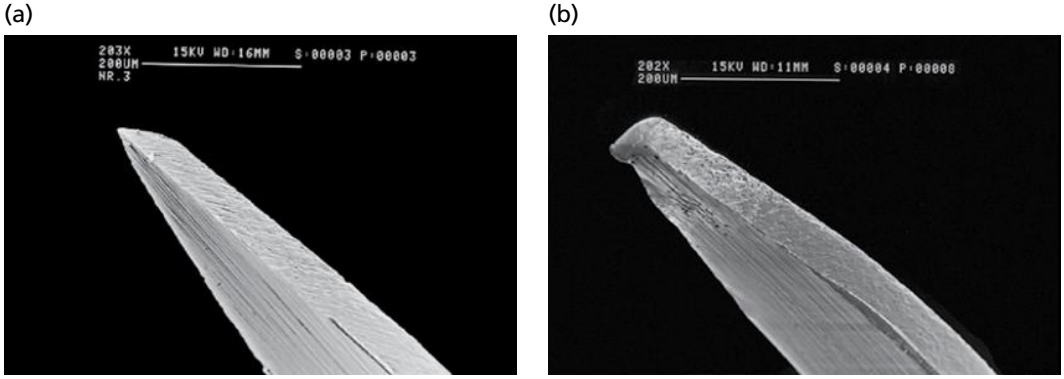

Fig. 47-9 (a) Intact sharp spatula needle. (b) Damaged needle tip after sticking it into the enamel surface.

Table 47-2 Ideal needle-thread combinations (non-resorbable) for use in periodontal microsurgery.

Indications	Suture strength	Needle characteristics	Thread materials	Product name
Buccal releasing incisions	7-0	3/8 curvature, cutting needle with precision tip, needle length of 7.6 mm	Polypropylene	Prolene®
	7-0	Asymptotic curved needle, cutting needle tip, round body, needle length of 8.9 mm	Polypropylene	Prolene®
	9-0	3/8 curvature needle, spatula needle, needle length of 5.2 mm	Polyamide	Ethilon®
Interdental sutures, front area	6-0	3/8 curvature, cutting needle with precision tip, needle length of 11.2 mm	Polypropylene	Prolene®
	7-0	3/8 curvature, cutting needle with precision tip, needle length of 11.2 mm	Polyamide	Ethilon®
Interdental sutures, premolar area	6-0	3/8 curvature, cutting needle with precision tip, needle length of 12.9 mm	Polyamide	Ethilon®
	6-0	3/8 curvature, cutting needle with precision tip, needle length of 12.9 mm	Polypropylene	Prolene®
Interdental suture, molar area	6-0	3/8 curvature, cutting needle, needle length 16.2 mm	Polyamide	Ethilon®
Crestal incisions	7-0	3/8 curvature, cutting needle with precision tip, needle length 11.2 mm	Polyamide	Ethilon®
	6-0	3/8 curvature, cutting needle with precision tip, needle length 12.9 mm	Polypropylene	Prolene®
Papilla basis incisions	7-0	Asymptotic curved needle, cutting needle tip, round body, needle length 8.9 mm	Polypropylene	Prolene®
	9-0	½ curvature, cutting needle with micro tip, needle length 8.0 mm	Polyamide	Ethilon®

into alcohol and acid. Polyester threads are mechanically stable and, based on their different hydrolytic properties, loose their firmness over different but constant times. A 50% reduction of breaking resistance can be expected after 2–3 weeks for polyglycolic acid and polyglactin threads, 4 weeks for polyglyconate, and 5 weeks for polydioxanone threads. The threads are available in twisted, polyfilament forms and monofilament forms when finer sutures are required. The capillary effect is limited and hardly exists for polyglactin sutures (Blomstedt & Österberg 1982).

Non-resorbable sutures

A commonly used material for fine monofilament threads (0.1–0.01 mm) that shows adequate tissue properties is polyamide. Tissue reactions seldom occur, except when errors occur in the polymerization process (Nockemann 1981). Polyolefines are inert materials that remain in the tissues and are not subjected to hydrolytic degradation (Salthouse 1980; Yu & Cavaliere 1983). Materials with excellent tissue properties are polypropylene and its newest further development, polyhexafluoropropylene. After suturing, the thread is encapsulated in connective tissues and maintains its stability for a longer period. Threads that are 5-0 and thicker are relatively stiff and, for that reason, may impact patient's comfort.

A substance with similar biologic, but improved handling, properties is polytetrafluoroethylene. Due to its porous surface structure, the monofilament threads should only be used in conjunction with measures to restrict bacterially loaded oral cavity.

Intraoral tissue reactions around suture materials

The initial tissue reaction after suturing is the result of trauma.If a resorbable suture remains *in situ* for >2 weeks after wound closure, an acute inflammatory reaction may continue. This phenomenon is caused by bacteria entering the stitch canal and penetrating along the thread (Chu & Williams 1984; Selvig *et al*. 1998). The reaction culminates on the third postoperative day (Selvig *et al*. 1998). It is comparable for resorbable and non-resorbable suture threads (Postlethwait *et al*. 1975). Histologically, this early response is characterized by three zones of tissue alteration (Selvig *et al*. 1998): (1) an intensive cellular exudation in the immediate vicinity of the entry of the stitch canal, followed by (2) a concentric area, harboring damaged cells as well as intact tissue fragments, and (3) a wide zone of inflammatory cells in the surrounding connective tissues.

A bacteriostatic effect of glycolic acid during the resorption process of polyglactin threads (Lilly *et al*. 1972) could not be established (Thiede *et al*. 1980), and the resorption of the polyglycolic thread was inhibited by the acid environment caused by the infection (Postlethwait & Smith 1975). Such studies confirm the increased risk for bacterial migration along the thread in the humid and bacterially-loaded oral cavity. Experimental and clinical data indicate that most wound infections begin around suture material left within the wound (Edlich *et al*. 1974; Varma *et al*. 1974). Polyfilament threads additionally facilitate the bacterial migration, and bacteria can also penetrate the inner compartment of the thread, which impairs the immunologic response of the host (Blomstedt *et al*. 1977; Haaf & Breuninger 1988). This is just one reason why monofilament, non-resorbable sutures are preferred and they should be removed at the earliest biologically acceptable time (Gutmann & Harrison 1991). The infectious potential can further be reduced by using an anti-infective therapy based on daily rinsing with or topical application of chlorhexidine (Leknes *et al*. 2005).

Another promising option to reduce the bacterial migration along the suture is coating it with a bacteriostatic substance. Vicryl® Plus (Ethicon®, Norderstedt, Germany) is a resorbable suture material coated with triclosan that inhibits bacterial growth for up to 6 days by damaging the membrane of the bacterial cells (Rothenburger *et al*. 2002; Storch *et al*. 2002).

Training concepts: Surgeons and assistants

The benefits of the operating microscope in periodontal surgery seem to be obvious. What then are the reasons for the delay in taking advantage of periodontal surgery under the microscope? The main reason is that most surgeons do not adjust to the surgical microscope and those who have been using microscopes successfully, have not made adequate in-depth practical recommendations to help other periodontal surgeons overcome their initial problems. Working under magnification changes the clinical settings as the visual direction during the surgical intervention does not meet the working ends of the instruments and the field of view has a smaller diameter. Additionally, the small size of the tissue structures and sutures threads requires movement to be guided by visual rather than tactile control. This altered clinical situation requires adjustment from the surgeon.

The three most common errors in the use of the surgical microscope are: (1) using magnification that is too high, (2) inadequate task sharing between surgeon and assistant, and (3) lack of practice.

High magnification

There is a tendency to use magnification which is too high. As described above, one of the fundamental optical principles is the higher the magnification, the narrower the field of vision and the smaller its depth. This concept is important because high magnification makes surgery more difficult, especially when it involves considerable movement. In these circumstances, low magnification of ×4–7 should be used. On the other hand, higher magnification of ×10–15 may be useful when dissecting within a small area and less movement is required, for example in papilla preservation techniques. In general, the magnification should be that which allows the surgeon to operate with ease and without increasing his/her usual operating time required for a particular surgical procedure. Surgical time does not have to be increased once the surgeon has adapted fully to the microscope. The more experienced and skilled the surgeon is with the microscope, the higher the magnification he/she can use with ease.

It may take 6 months or more for surgeons to become familiar with a magnification of 10×, which usually is the maximum used in plastic periodontal surgery. A point of diminishing return will eventually be reached where the advantages of magnification are outweighed by the disadvantages of a narrower field of vision.

Task sharing between surgeon and assistant (teamwork)

In microendodontics during root canal treatment, the whole procedure is performed with a minimum change in position changes by the operating persons. Focusing can easily be achieved by moving the mirror towards or away from the objective lenses. In periodontal surgery, both hands are used to hold the instruments and changes in position are more frequently required, which increase the demands on the operating team and require an ideal cooperation between surgeon and assistant.

In all surgeries, at least two operating persons are involved: a surgeon and an assistant, who assists the surgeon in the most rudimentary tasks of the operation. Among the tasks undertaken by the assistant, those that he/she performs for almost all operations and requiring varying levels of skill, should be considered: flap retraction, suction, rinsing and cutting the sutures. To guarantee a continuous work flow during the surgical intervention, a second assistant who organizes the instruments is frequently desirable.

In periodontal microsurgery, where inherently the surgeon has very little access, retraction is vital. The retraction should be done from different positions and must be devoid of all tremor or movement. This is an exceptionally strenuous task as the assistant is expected to maintain the same posture for a period of time which can extend to 1 hour. Fatigue experienced by the assistant will increase the chances of tremor as time goes by.

For optimal working conditions, the assistant also needs to view the operation under magnification. An assistant wearing loupes is also able to use open

peripheral vision to arrange the instruments and to check the patient's facial expression during the operation. On the other hand, the surgeon and assistant will only have the same view if co-observer tubes are used; the assistant is then able to point the suction tube to the right place and keeping the view clear; this is also an issue during suturing when the air intake of the suction tube can easily suck the fine threads.

Lack of practice

When working under high magnification, the surgeon has to adjust to the narrow field of vision with a new coordination between eye and hand. This adjustment comes only after much regular practice with simple surgical procedures. The practice unit consists of a microscope, microinstruments, and different suitable models. At the start of training, a two-dimensional model, such as a rubber dam, is appropriate for learning how to manipulate the instruments, pick up the needles, and tie knots. After the initial training, practicing on three-dimensional models (fruit, eggs, chickens) helps the surgeon become accustomed to the restricted depth of the field.

Another aim of training is to reduce tremor. Its physiologic basis is uncertain, but it is important to be aware of the causes in order to prevent it. An important factor is body posture, which must be natural, with the spinal column straight and the forearms and hands fully supported. An adjustable chair, preferably on wheels, is recommended for the surgeon who should place him/herself in the most comfortable position. Tremor varies between individuals and even in the same individual under different conditions. In some people, the intake of coffee, tea or alcohol may increase tremor; in others, emotions, physical exercises or the carrying of heavy weights can cause it.

After completion of an appropriate training during which instrument handling has become automatized, the surgeon can be said to have adjusted to the new conditions and will then be able to fully concentrate on the surgical procedure in clinical practice without requiring additional time.

Clinical indications and limitations

The clinical benefits of a microsurgical approach in periodontal practice have mainly been evaluated from case reports (Shanelec & Tibbetts 1994; Michaelides 1996; Shanelec & Tibbets 1996; de Campos *et al*. 2006) and case cohort studies (Cortellini & Tonetti 2001; Wachtel *et al*. 2003; Francetti *et al.* 2004). The procedures described were surgical coverage of buccal root recessions and flap closure after regenerative interventions. Both of these interventions have in common the manipulation during surgery of delicate soft tissue structures, which could be refined by selecting a less traumatic surgical approach. All of the studies confirmed the beneficial effects of the microsurgical approach. When covering a root recession, vascularization of the injured tissues becomes critical as there is no blood supply from the underlying root surface. Frequently, the coverage is performed by a connective tissue graft from the palate, which has different vascular characteristics compared to the supracrestal gingiva and is the only tissue, naturally created and specifically designed, that can survive and function over avascular root surfaces. As graft survival depends upon early plasmatic diffusion (Oliver *et al*. 1968; Nobutu *et al*. 1988), firm and stable flap or graft adaptation is of crucial importance to minimize the coagulum and facilitate the ingrowth of new vessels. A minimally traumatic approach allows a more precise flap preparation and suturing with a reduction in tissue and vessel injuries, resulting in faster and more complete anastomosis of new capillary buds from the recipient bed with the existing, but severed, vessels of the graft or the flap. There is strong evidence supporting the hypothesis that the mechanical properties of the extracellular matrices are important for capillary morphogenesis, while factors like pH (acidic condition), ionic strength, and other biochemical parameters primarily stimulate the proliferation and migration of endothelial cells (Nehls & Herrmann 1996).

The interdental gingiva is also a delicate tissue with a limited vascular network. As the gingival plexus does not extend interproximally, the central part of the interdental soft tissue is only supplied by vessels from the periodontal ligament space and arterioles that emerge from the crest of the interdental septa (Folke & Stallard 1967; Nuki & Hock 1974). These anatomic factors influence the wound healing capacity of the tissues after surgical dissection and the small size of the structures (i.e. papilla or col) complicates the precise adaptation of the flap margins. Therefore, wound dehiscences, resulting in healing at secondary intention, are a common finding after suturing the papilla in papilla preservation techniques (Tonetti *et al.* 2004). Using microsurgery to form a modified or simplified papilla preservation flap, primary wound closure could be noted in 92.3% of all treated sites 6 weeks after the intervention (Cortellini & Tonetti 2001).

Historical comparisons with studies performed by the same authors without the use of an operating microscope showed a clear advantage for the use of a microsurgical approach. Complete primary wound closure was observed in only 67% of the cases treated with a simplified preservation flap (Cortellini *et al*. 1999b), and in 73% of the cases treated with a modified papilla preservation flap (Cortellini *et al*. 1999a). These results clearly demonstrated the improvement in tissue preservation and handling using a minimally invasive approach to achieve primary closure of the interdental space (Fig. 47-10).

A cohort study evaluating a flap design for regeneration with enamel matrix derivatives [*minimally invasive surgical technique* (MIST)] combined with the microsurgical technique, confirmed the previous positive results with primary wound closure of the interdental tissues in all of the treated sites 6 weeks postoperatively (Cortellini & Tonetti 2007) (Fig. 47-11).

Subjective observations of clinicians have found there is a less traumatic approach in periodontal surgery when magnification aids and fine suture materials are used. These ensure passive wound closure in most surgical interventions. This speculation was substantiated by an *in vitro* experiment evaluating the tearing characteristics in mucosal tissue samples subjected to applied tension forces with sutures of different sizes and needles of different characteristics (Burkhardt *et al.* 2006). The pig jaw mucosal tissue samples were attached to a test-tearing apparatus of a Swiss textile company and the tension tearing diagrams were traced for 3-0, 5-0, 6-0, and 7-0 sutures with forces of up to 20 N. While the 3-0 sutures almost exclusively led to tissue breakage at an average of 13.4 N, the 7-0 sutures broke before tissues were torn in every instance at a mean applied force of 3.6 N. With 5-0 and 6-0 sutures, both events occurred randomly at a mean force of 10 N. This indicates that a clinician will influence the amount of damage to the tissue depending on his/her selection of a thick or thin suture material. Considering this fact, it may be speculated that wound dehiscence may be prevented and a passive flap adaptation may be improved by the choice of thinner sutures; this inevitably requires magnification if its benefits are to be fully appreciated.

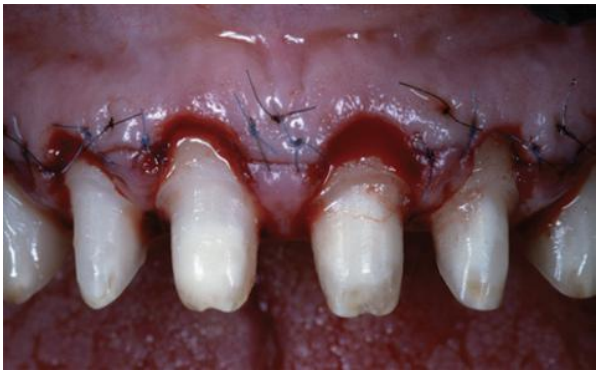

Fig. 47-10 Primary closure of the buccal papilla after a crown lengthening procedure. Modified mattress suture (according to Laurell) with 7-0 polyamide thread (black) and two single knot closures with 8-0 polypropylene thread (blue).

Wound healing in periodontal and peri-implant defects following flap surgery is conceptually a more complex processes than wound healing in most other sites in the body due to fact that the wound is constituted of several interfaces of tissues that differ fundamentally in composition. While connective tissue flaps opposing vascular surfaces are more resistant to mechanical forces, blood clot adhesion to avascular surfaces like dentin, enamel, ceramic or titanium, seems to be impaired and this, therefore, leaves the wound interfaces more susceptible to tearing (Wikesjö & Nilvéus 1990; Wikesjö *et al*. 1991; Werfully *et al*. 2002). It is evident that control of flap tension requires careful attention and has to be controlled in situations where mechanical stability of the flap is required.

The role of flap tension in primary wound closure was recently investigated in humans (Burkhardt & Lang 2010). Sixty patients scheduled for single implant installation were recruited. Before suturing, the tensile forces on the flap were recorded with an electronic tension device. After 1 week, the wounds were inspected with regards to complete closure. While only a few (10%) wound dehiscences resulted for flaps subjected to minimal initial tension of 0.01–0.1 N, flaps subjected to higher closing forces (>0.1 N) yielded significantly increased percentages of wound

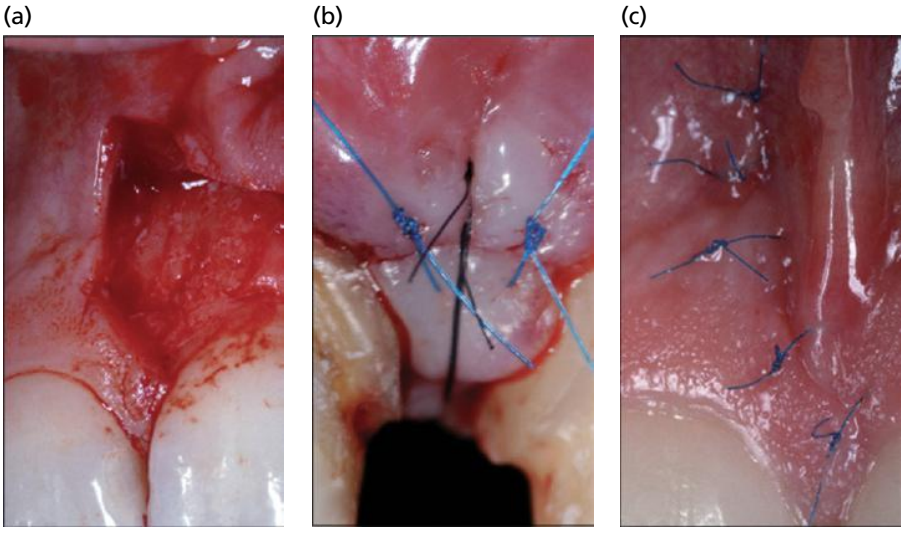

Fig. 47-11 Minimally invasive surgical technique (Cortellini & Tonetti 2007). (a) Suturing with 8-0 polypropylene thread (blue). (b) Clinical appearance 7 days postoperatively. (c) Clinical appearance of the releasing incision 4 days postoperatively.

dehiscences (>40%). This study also revealed that flaps with a thickness of >1 mm demonstrated significantly lower proportions of flap dehiscences at higher closing forces (>15 g) than thinner flaps (≤1 mm). This study supports the need to control closing forces at the wound margins. In order to minimize tissue trauma, the use of finer suture diameters and magnification aids may be helpful owing to the fact that thinner sutures (6-0, 7-0, 8-0) tend to break rather than tear tissue (Burkhardt *et al*. 2006).

Opponents of periodontal microsurgery often mention the adverse effect of a prolonged intervention time when working with microscopes. It has been shown that the incidence and severity of complications and pain following periodontal surgery correlate closely with the duration of the surgical procedure (Curtis *et al*. 1985). It can be speculated that an extended operation time may counter the beneficial treatment effect of minimally invasive techniques. However, studies comparing micro- and macrosurgical approaches do not support this concern (Burkhardt & Lang 2005).

Considering all these facts, there are no clinical contraindications for the use of magnification in periodontal surgery. From a user's point of view, a few aspects in the oral cavity are difficult to access with an operating microscope. In these circumstances and in surgical interventions which require a frequent change of position, the use of loupes may be preferable.

Comparison to conventional mucogingival interventions

Today's *plastic periodontal surgery,* evolving from *mucogingival surgery*, includes all surgical procedures performed to prevent or correct anatomic, developmental, traumatic or disease-induced defects of the gingiva, alveolar mucosa or bone (Proceedings of the 1996 World Workshop on Periodontics 1996). To verify the beneficial effects of a microsurgical approach, the results with a conventional technique in all the different indications have to be evaluated first. The variables to be used as descriptors of the therapeutic end point of success may vary, depending on the specific goal of the mucogingival therapy. Some results, such as volume changes after ridge augmentation procedures, are clinically difficult to assess due to a lack of a defined end point and therefore are documented in the literature by qualitative measurements only. Plastic surgical interventions with clearly defined landmarks for measurement, and thus well investigated in the literature, are guided tissue regeneration procedures (Needleman *et al*. 2006) and coverage of buccal root recessions (Roccuzzo *et al*. 2002; Clauser *et al*. 2003; Oates *et al*. 2003; Pagliaro *et al*. 2003; Cairo *et al*. 2008). While the former results in a reduction in probing measures, improved attachment gain, and less increase in gingival recession compared to open flap debridement, the latter yields a significant reduction in recession depth and also improvement in clinical attachment level measures. However, there is a marked variability between the studies, indicating the influence of case selection, materials used, applied techniques, and surgeon's dexterity. As a result, it is difficult to draw general conclusions because the factors affecting the outcomes are unclear from the literature and may include study conduct issues such as bias. Among these factors, the dexterity of the surgeon ranks high and seems to strongly influence the results. Dexterity is a complicated, proprioceptive reflex involving the eye, hand, and brain, and therefore is difficult to assess in clinical settings. To eliminate its influence and to estimate the magnitude of the real benefits of a microsurgical approach, micro- and macro-surgical techniques need to be compared in controlled studies.

Concerning the coverage of mucosal recessions, a comparison between the two approaches (micro- and macro-surgery) was performed in a randomized controlled clinical trial (Burkhardt & Lang 2005). The study population consisted of 10 patients with bilateral class I and class II recessions at maxillary canines. In a split-mouth design, the defects were randomly selected for recession coverage with either a microsurgical (test) or macrosurgical (control) approach. Immediately after the surgical procedures and after 3 and 7 days of healing, fluorescent angiograms were performed to evaluate graft vascularization. The results at the test sites revealed vascularization in 8.9 ± 1.9% immediately after the procedure. After 3 days and after 7 days, this had risen to 53.3 ± 10.5% and 84.8 ± 13.5%, respectively. The corresponding results at control sites were 7.95 ± 1.8%, 44.5 ± 5.7%, and 64.0 ± 12.3%, respectively (Fig. 47-12). All the differences between test and control sites were statistically significant. In addition, clinical parameters were assessed before the surgical intervention, and 1, 3, 6, and 12 months postoperatively. Mean recession coverages of 99.4±1.7% for the test and 90.8±12.1% for the control sites were seen after the first month of healing. Again, this difference was statistically significant. The percentage of root coverage at both test and control sites remained stable during the first year at 98% and 90%, respectively.

This clinical study clearly demonstrated that mucogingival surgical procedures designed for the coverage of exposed root surfaces and performed using a microsurgical approach, improved the treatment outcomes substantially and to a clinically relevant level when compared with the clinical performance under routine and macroscopic conditions. However, the choice of micro- and macro-surgical approaches must consider not only treatment outcomes, but also logistics, cost, and patient-centered parameters. Future comparative studies will provide the evidence as to whether or not the use of the surgical microscope will further increase surgical effectiveness and thus become an indispensable part of periodontal surgical practice.

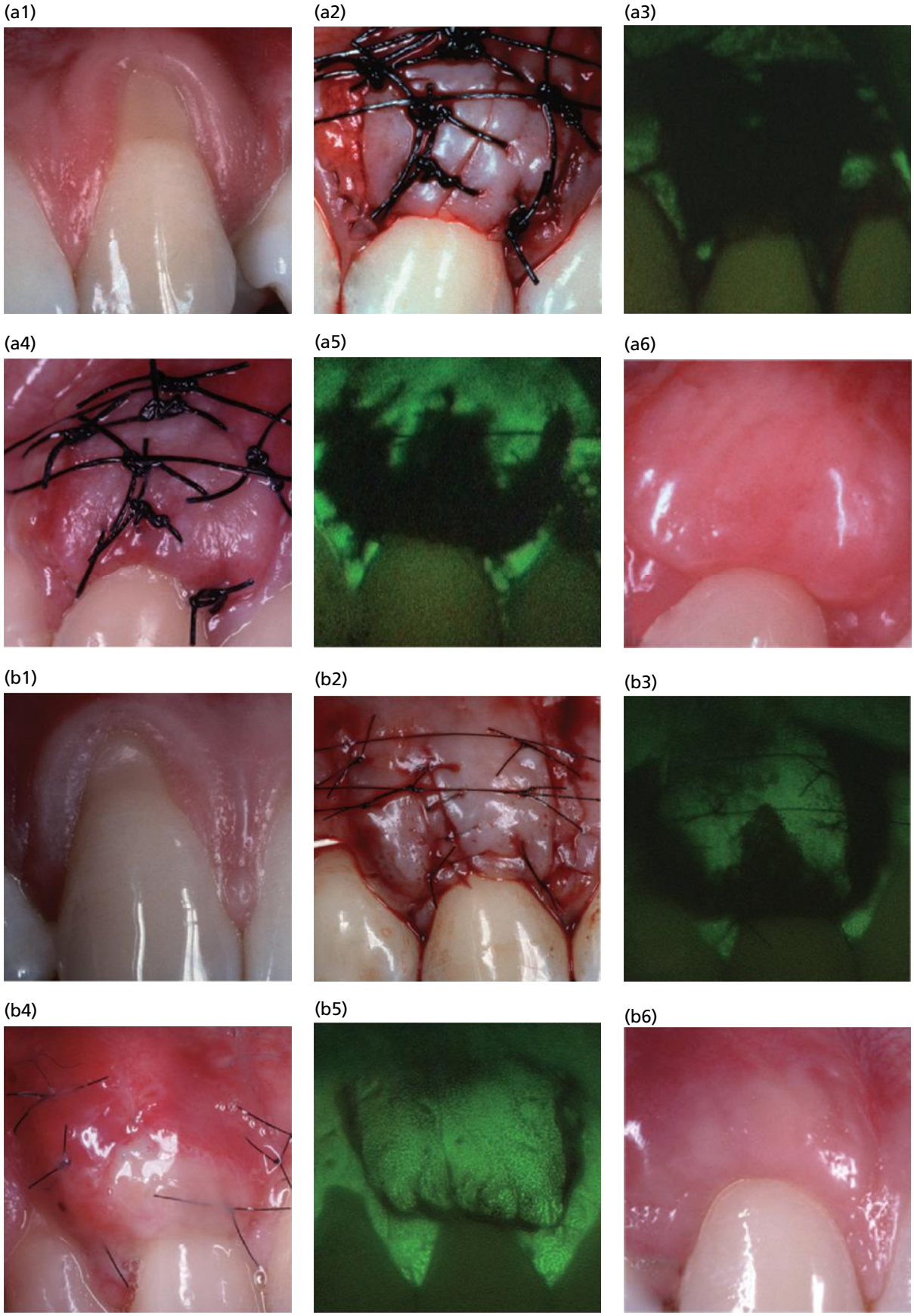

Fig. 47-12 Recession coverage: comparison of macro- and micro-surgery (Burkhardt & Lang 2005). (a) Macrosurgical recession coverage. (a1) preoperative clinical photograph; (a2) immediately after the surgical intervention; (a3) angiographic evaluation immediately after the intervention; (a4) healing after 7 days; (a5) angiographic evaluation after 7 days; (a6) clinical photograph at 3 months (visible contours of incision lines). (b) Microsurgical recession coverage: (b1) preoperative clinical photograph; (b2) immediately after the surgical intervention; (b3) angiographic evaluation immediately after the intervention: (b4) healing after 7 days; (b5) angiographic evaluation after 7 days; (b6) clinical situation after 3 months (no traces of the intervention visible).

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Part 14: Surgery for Implant Installation

Chapter 48

Piezoelectric Surgery for Precise and Selective Bone Cutting

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Background and physical principles

The oscillating sound pressure wave of ultrasound is above the upper human audible level (30–20 KHz). The use of ultrasonics has now largely established itself in periodontology (Flemming *et al*. 1998; Lea *et al*. 2003) and endodontics (Walmsley *et al*. 1992). The first results of ultrasound-assisted periodontal therapy date back to 1955 (Zinner 1955). High-frequency sound waves were used for mechanical debridement of dental hard tissues (Catuna 1953). Clinically, clear advantages for ultrasonic waves in calculus removal were seen compared to conventional scaling (Johnson & Wilson 1957). Certain beneficial effects were also demonstrated for removal of root canal fillings and fractured instruments from root canals using ultrasonic waves (Walmsley *et al*. 1990).

By converting electrical energy into ultrasonic waves, usually by magnetostriction or piezoelectricity, ultrasound can be used for thermal, mechanical, and chemical applications. Whereas magnetostriction alters the physical dimensions of a material in a magnetic field, piezoelectricity is based on the so-called piezo effect. French physicists Jean and Marie Curie first mentioned this effect in 1880 (Hoigne *et al*. 2006). They described the development of an electric current on the surface of certain crystals and many substances when subjected to mechanical strain. The reversion of this effect, which occurs when crystals are deformed under an electric current, was discovered a while later.

An alternating voltage applied to a polarized crystalline piezo-ceramic causes expansion in the direction of polarity and, perpendicular to it, contraction of the material. This vibrating movement and behavior of the crystals lead to oscillation at a specific frequency and amplitude (Stübinger *et al*. 2005). The transmission and reflection of this oscillating beam can be used in medical imaging, and its detection and measurement from tissues inside the human body gives useful information. The specific acoustic impedance of the permeated tissues causes beam diversification at their boundaries through a complex interaction of absorption, reflection, refraction, diffusion, and diffraction (Bains *et al*. 2008).

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Technical characteristics of piezoelectric bone surgery

The use of piezoelectric physical process was effectively applied in dentistry for ablation and abrasion of hard tissue by Catuna (1953). A few years later, the use of traditional ultrasonic vibration technology for cutting mineralized tissue was studied in animals (Mazorow 1960; McFall 1961; Horton *et al*. 1975, 1981).

Horton *et al.* (1981) demonstrated that ultrasound-based osteoplastic surgery safely and precisely removed hard tissue with little intraoperative interference from bleeding. The same group also demonstrated histologically that ultrasonic osteotomy of buccal alveolar process defects in dogs showed a favorable healing tendency in comparison to when this was performed with a low-speed rotary cutting bur. Even though the osteotomy sites cut with a rotary bur revealed the smoothest bone surface, bone healing after ultrasonic osteotomy was enhanced.

However, all these studies using magnetostrictive ultrasonic instruments did not result in any clinical applications due to the limits of the technology. In order to overcome these technological limits, Vercellotti *et al*. (2001a) conducted research to develop a new clinically effective ultrasonic and sonic piezoelectric bone-cutting instrument in animals, called Piezosurgery®. In 2000, the first human clinical study introducing the Piezoelectric Bone Surgery procedure was published (Vercellotti 2000). This well-accepted and revolutionary surgical method was introduced in a split ridge split case report in which the edentulous ridge was so narrow that it had previously not been possible to cut it using other cutting instruments and at the same time maintain its integrity.

Today piezosurgery represents an innovative bone-cutting technique based on the use of microvibrations at a specific ultrasonic frequency modulated by sonic waves (Fig. 48-1). After a short learning curve, the cutting effectiveness of piezosurgery is comparable to that of other bone-cutting instruments, but in addition it offers greater control in the handling of small and delicate bone fragments.

The piezoelectric cutting action is the result of bone micronization produced by mechanical shock waves that vibrate in a linear manner at a sonic and ultrasonic frequency (from 30 to 30 000 Hz). The reduced vibration amplitude (20–80 µm) of the cutting tips is the main reason for the most interesting surgical characteristics: selective cutting action, precision, intraoperative control, and safety. The selective cutting action is a result of the limited amplitude of the mechanical microvibrations: at these amplitudes only mineralized tissue can be cut and damage to soft tissue is avoided because of their elasticity. The ultrasonic technology to cut soft tissues requires higher frequencies >50 kHz (Labanca *et al.* 2008).

Moreover, the mechanical micro-movements at a frequency of about 24–30 kHz generates a cavitation effect in the irrigation solution, which reduces intraoperative overheating and bleeding, thus increasing surgical visibility and safety, and facilitating healing mechanisms.

Fig. 48-1 Mectron Piezosurgery® device.

Application of piezosurgery

While the piezoelectric device commonly has a similar design to that of conventional surgical hand pieces, due to the different cutting principle with this device, the surgeon still needs to be trained in its operation. While Salami *et al*. (2010) found that especially well-trained otologic surgeons do not need any defined learning period before successfully performing straight osteotomy lines using piezosurgery, they still concluded that, "an audited training period should exist for all surgeons who undertake the piezoelectric device for the first time".

For ultrasonic osteotomy, the optimal rake angle between the piezoelectric device and the orthogonal preparation axis is 0–10° (Khambay & Walmsley 2000). Outside this angle range, both cutting performance and precision fall off in quality. In contrast to rotating burs, increasing the manual pressure exerted on the piezoelectric device does not accelerate the cutting speed. Rather, with increased manual pressure the cutting tip is no longer able to operate freely and its vibration is massively constrained, resulting in overheating. Furthermore, increased manual pressure will diminish haptic sensitivity and fragile bone as well as soft tissue structures are commonly iatrogenically damaged as a result. Thus, great care needs to be taken when applying contact pressure. Periodic interruptions will slow the cutting vibrations and are particularly recommended when performing comprehensive and deep cuts (Robiony *et al*. 2004). Such intervals also give the surgeon the opportunity to refine the most appropriate osteotomy design with superior levels of precision and tissue protection.

In terms of both dexterity and tactile sensitivity, piezosurgery offers certain advantages. In micrometric osteotomy, easy handling with increased maneuverability is achieved with reduced contact pressure and macro-vibrations. Reduced contact pressure supports this effect. Thereby, not only is accidental trauma to adjacent soft tissue structures reduced, but also the invasiveness of the surgical procedure can be minimized. There is no need to supplement the applied force to balance the rotation or oscillation of the instrument so as to avoid tissue damage from lack of control. In contrast, a bone bur rotating at a speed of about 20 000 rpm applies approximately 320 shock waves/minute, and generates macrovibrations that reduce precision and intraoperative control. In fact, during the cutting action, the surgeon must exert a pressure on the hand piece in the order of several kilograms. Together with the small and sophisticated cutting tips, ultrasonic microvibrations reduce the chipping effects at the osteotomy rims. Spalling of brittle mineralized hard tissue structures is marginal and only occurs in exceptional cases of forced insert tilting or lever movements by the surgeon.

Thus, delicate handling and practical experience are vital to maximizing the advantages of piezosurgery. Only then can very precise cuts be made in anatomically difficult-to-reach areas or previously inaccessible locations. In this regard, the acoustic feedback from the cutting process allows the most suitable operating pressure to be defined for the treatment of cortical or cancellous bone structures.

Bone quality as well as the physical characteristics of the working tip have a tremendous influence on the mode, shape, and magnitude of the oscillation. Claire *et al*. (2013) explored the effect of the oscillation patterns of a universal OP3 piezosurgery tip on morphologic cutting characteristics. Qualitatively, cutting of cortical bone produced a narrow defect with a clear bony demarcation of the cut as compared to cancellous bone. Physical loads of up to 100 g on the working tip were found to be ideal for cortical bone; a 200-g load significantly decreased tip oscillation. This effect with increasing load was not seen for spongious bone. The lower limit of the load must also be carefully considered, as when too low the tip starts to slide across the surface of the bone and as a result the sharpness of the incision will be lost and osteotomy margins will be irregular (Romeo *et al*. 2009).

Clinical and biologic advantages of piezosurgery

Execution of osteotomies with marginal tissue damage and low blood loss promotes optimal healing conditions in the postoperative phase. The associated reduction of pain and swelling will improve patient comfort. Furthermore, the constant and adjustable irrigation cooling gives a clear intraoperative view, allowing precise removal of blood and cutting debris. Ultrasound-induced cavitational bubble activity in the liquid irrigation solution additionally facilitates visibility around the osteotomy site (Fig. 48-2).

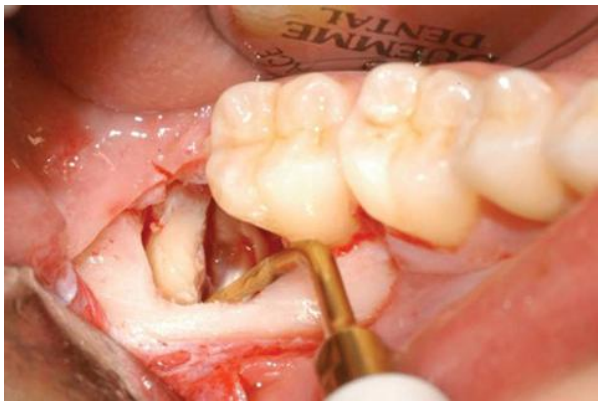

Fig. 48-2 Cavitation effect of saline solution gives good intraoperative visibility.

Beyond the technical precision of piezosurgery, however, biologic outcomes, including prevention of bone necrosis and thermal or mechanical injury to adjacent tissues, are of utmost importance. Especially in the wake of the trend toward less invasive surgery with advanced precision and less accidental damage, piezosurgery offers a safe technique that avoids overheating and tissue trauma. Surgical stress has a great influence on the viability of cells and the regeneration processes following trauma. For this reason, any manipulation of bone should be as atraumatic as possible to stimulate a fast and unimpeded healing.

In a series of different *in vitro* and *in vivo* studies, several authors have demonstrated that piezoelectric bone cutting does not impair bone remodeling or cell viability. Chiriac *et al*. (2005) analyzed the morphology, viability, and differentiation of cells growing out of the bone chips generated by piezoelectric surgery or use of a conventional rotating drill. The bone chips were mainly from cortical donor sites. The authors demonstrated that autogenous bone chips harvested from both piezoelectric surgery and use of a conventional drill contained vital cells that differentiated into osteoblasts *in vitro*. Overall, they did not find any significant differences between the viability of the chips harvested using the two methods.

von See *et al*. (2010) performed further analyses on the viability of endochondral (femoral) and membranous (mandibular) bone cells harvested from piezoelectric surgery, compared to those harvested with a rotating drill or a scraper. Morphometric evaluation showed a smooth surface after the use of the drilling device or the piezoelectric device. In contrast, small cracks and an irregular bone surface were seen following use of the scraper method. Overall, endochondral and membranous osteoblast proliferation did not show any differences between the harvesting methods; however, cell count showed significantly more osteoblast-like cells in specimens harvested with a scraper or piezoelectric device than with a bur. Therefore, the osteogenic potential of autogenous

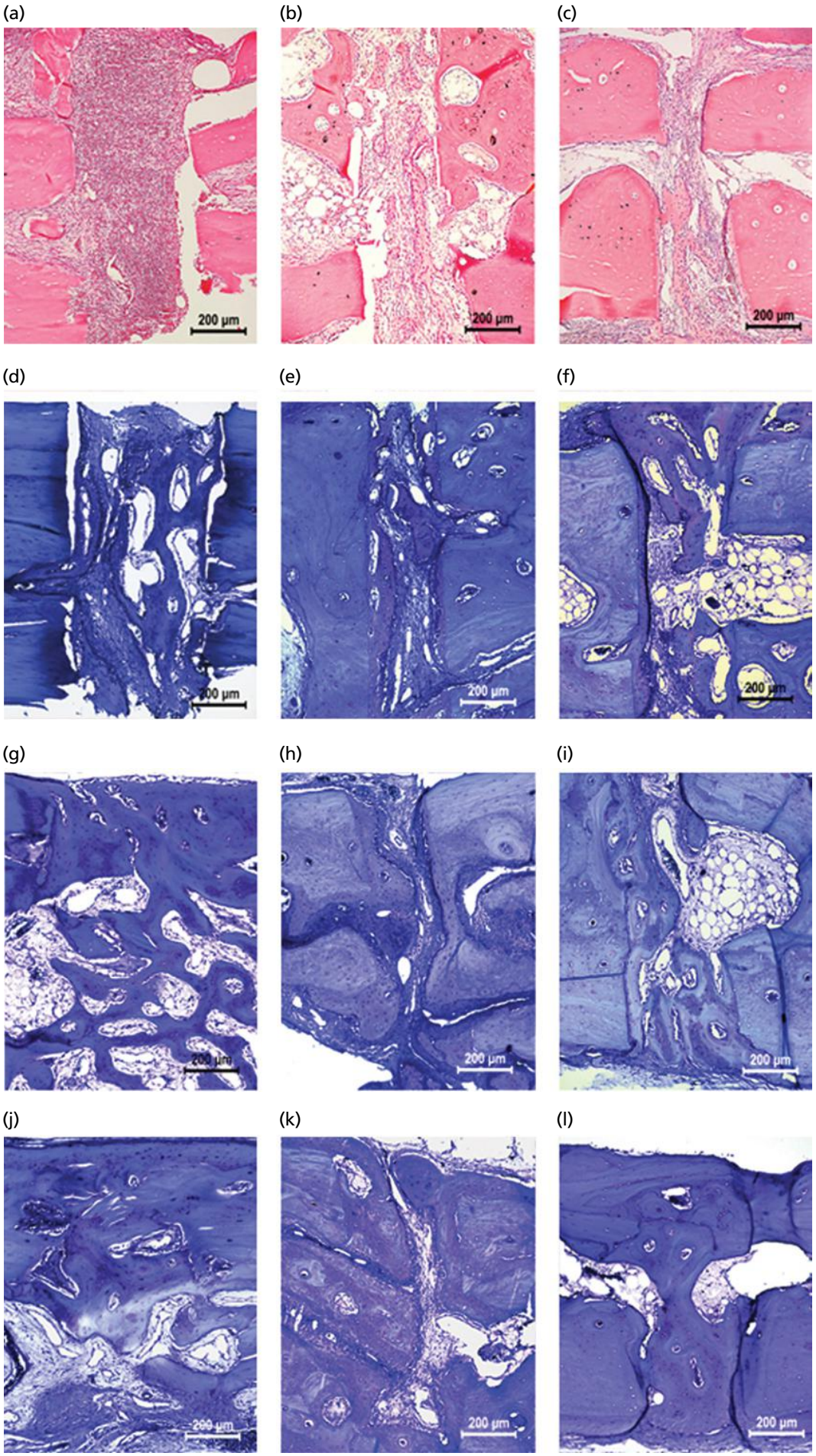

Fig. 48-3 Summary of histologic results following osteotomies performed with piezosurgery (a, d, g, j), a novel saw blade (b, e, h, k), or a conventional saw blade (c, f, i, l). (a–c) Specimens after 1 week were stained with hematoxylin and eosins to clearly identify the soft tissue structures and matrix in the early healing phase. (d–f) Specimens after 2 weeks, (g–i) 3 weeks, and (j–l) 5 weeks were stained with toluidine blue to evaluate new bone formation and bone remodeling. All three osteotomy techniques showed characteristic gap healing with bridging of the osteotomy site with immature and woven bone in the initial healing stage. After 5 weeks, all techniques revealed an advanced remodeling with lamellar structures (Reproduced with permission of Springer.).

bone harvested by piezosurgery appears promising for any regenerative procedure.

Concerning heat generation in close vicinity to the osteotomy gap and the corresponding biologic tissue reactions, Heinemann *et al.* (2012) compared different sonic and ultrasonic systems with conventional rotary burs in fresh porcine jaw segments. Even though histologic investigations indicated intact osteocytes adjacent to the osteotomy rims with all three instruments, piezosurgery showed the highest temperature rise (18.17° C). In contrast to sonic surgery, the walls of the funnel-shaped piezoelectric osteotomy sites showed a conspicuous stained defect zone of about 30 µm at the lateral aspect. Additionally, a clear undulation of the trabecular bone structure could be observed. In a further cadaver study in sheep mandibles, Metzger *et al*. (2006) found that the "pneumatic hammer"-effect of the piezoelectric device produced a significantly rougher surface with loosened bone edges and a defect zone of about 170 µm, in comparison to a conventional rotary bur.

Vercellotti *et al.* (2005) evaluated histologically the reparative potential and osseous response following resective periodontal piezoelectric ostectomy and osteoplasty in a dog model. After elevation of full-thickness mucoperiosteal flaps and soft tissue degranulation, about 4 mm of bone was removed from around each tooth by applying randomly either piezosurgery, a carbide bur, or a diamond bur. Whereas in the early (14 days) as well in the late (56 days) wound healing phase, both bur groups revealed a certain histologically detectable bone loss, the group subjected to piezoelectric bone surgery demonstrated a slight mean gain in bone level at both time points. Based on their results, the authors suggested that piezosurgery might be highly beneficial for the physiologic restructuring of the osseous architecture of the alveolar crest after resective periodontal therapy.

In a further experiment in rabbit skulls, Ma *et al*. (2013) compared bone healing following osteotomies performed with either piezosurgery or with two different oscillating saw blades. After 1 week, the osteotomy gap in the piezoelectric group showed a large number of inflammatory cells, a high degree of vascularized tissue structures (72.8%), and provisional matrix (21.8%). In some cases, small and scattered islands of the start of centripetal osteoid formation could be observed near the osteotomy rims. After 2 weeks, the gap was mostly filled with a mixture of immature woven bony structures, and the amount of new osteoid and mineralized bone tissue had increased. After 5 weeks, the osteotomy gaps had almost completely filled with newly formed bone with a high degree of mineralization. Consolidation of the osteotomy gap was in many cases almost complete and in some cases new bone structures revealed a lamellar orientation (Fig. 48-3). The same group demonstrated similar results with piezoelectric osteotomy in a sheep tibia model (Stübinger *et al*. 2010a). Three months after piezoelectric osteotomy, advanced bone remodeling with the distinct formation of lamellar bone was seen. The original mid-shaft osteotomy line marked the border for healing with early-stage longitudinal alignment of remodeled lamellar bone.

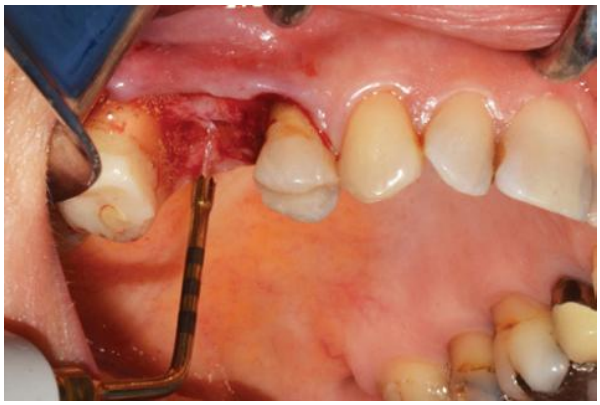

Fig. 48-4 IM2 insert to obtain pilot osteotomy with the ultrasonic implant site preparation technique (UISP).

Piezoelectric implant site preparation

In addition to conventional osteotomy, piezosurgery can also be used for implant site preparation (Vercellotti *et al*. 2014). This application, however, calls for special surgical tips with an adapted shape and geometry to allow a symmetrical implant hole to be drilled with minimal thermal and mechanical damage to the bone (Fig. 48-4).

Preti *et al.* (2007) analyzed neo-osteogenesis and inflammatory reactions after implant site preparation using either piezosurgery or a conventional drill. The authors evaluated the levels of bone morphogenetic protein-4 (BMP-4), transforming growth factor-beta 2 (TGF-ß2), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1ß) and IL-10. Notably in the early phase (7–14 days), piezoelectric implant sites revealed more newly formed bone with larger amounts of osteoblasts. Except for IL-1ß and TNF-α, levels of BMP-4, TGF-ß2, and IL-10 were increased in the piezoelectric group at this time period. Overall, piezoelectric bone surgery was more effective in stimulating peri-implant osteogenesis with a clear reduction in pro-inflammatory cytokines. Similar good biologic and biomechanical results for piezoelectric implant site preparation have been reported in a pelvic sheep model (Stübinger *et al.* 2010b).

Clinical applications of piezoelectric surgery

The results of several experimental and clinical studies investigating bone healing and biologic behavior of hard and soft tissue structures following piezoelectric osteotomy provide a sound clinical basis for the clinical application of piezoelectric surgery. However, in spite of the proven and obvious advantages of piezosurgery, individualized patient medical care and the experience of the surgeon are of vital importance

in determining the surgical outcome and overall acceptance by the patients.

One of strongest criticisms of piezosurgery is the time-consuming nature of the technique. As the surgeon cannot accelerate piezoelectric cutting by advanced manual customization, which usually is a practicable scheme for conventional drilling devices, the overall efficiency is dependent on the preselected power settings. Therefore, when removing large amounts of bone, the combined use of piezosurgery with conventional high-speed drills is an approved and advocated approach.

Nonetheless, the intraoperative safety of piezosurgery makes it the preferred technique in all types of bone surgery. The use of autologous bone to correct and reconstruct bony defects is still a widely preferred and approved method to replace lost bone volume. Harvesting of bone fragments *en bloc* as well as particulate bone has certain advantages in different clinical indications. However, the regenerative capability of harvested bone fractions and the harvesting technique demand specific surgical and technical requirements if a successful treatment outcome is to be guaranteed (Berengo *et al.* 2006; Bacci *et al.* 2011). Whereas conventional rotating or oscillating devices allow easy and fast harvesting of block grafts, their use in harvesting bone chips is more limited. For collecting an adequate amount of particulate bone, scrapers show superior performance, but osteotomy of complete bone structures is not possible with these instruments. Piezosurgery overcomes these limitations as custom-designed cutting tips allow an individualized surgical approach depending on the situation. Shape, width, and thickness of piezosurgical tips are optimized for typical and common intraoral applications using adjusted power settings. For this reason, piezoelectric technology is used widely in routine dental surgery (Fig. 48-5).

Piezosurgery had gained a wide acceptance in implant dentistry for maxillary sinus elevation, bone grafting, lateralization of the inferior alveolar nerve, alveolar ridge expansion, and orthodontic microsurgical osteotomies.

Sinus floor elevation

In oral surgery, and particularly in implant dentistry, the need for micrometric, selective cutting makes piezosurgery an ideal and less invasive method, especially for maxillary sinus elevation. The technique of maxillary sinus floor elevation is used to rehabilitate the edentulous posterior maxilla with implant-borne prostheses when there is insufficient bone volume due to the reduced height of the residual edentulous ridge. The clinical success of implants placed in the bone-grafted maxillary sinus is similar to that reported for implants placed in pristine bone (Pjetursson *et al.* 2008). An essential condition for this is that the surgical technique is performed correctly at each step. The most frequent complication in standard sinus lift surgery using conventional drilling devices is perforation of the Schneiderian membrane, which can occur both during the access osteotomy and during elevation maneuvers. Bone grafting performed in the presence of a perforation is, most of the time, responsible for an inflammatory complication during the healing period, which may require re-intervention. To reduce the risk of perforation, Vercellotti *et al.* (2001b) studied a new surgical protocol using piezoelectric surgery. The study sample showed a clear reduction in the rate of membrane perforation (5%). Even though this was a pilot study in a small number of patients, its results can be regarded as promising. To avoid any accidental, iatrogenic tearing or perforation of the Schneiderian membrane, specific blunt cutting tips secure an effective osteotomy with preservation of the underlying delicate sinus soft tissue structures (Fig. 48-6).

Even though most studies report clinically favorable results using piezosurgery for the access osteotomy and loosening the membrane, some studies have shown no clear surgical benefit for the piezosurgical approach (Rickert *et al.* 2013). The latter, however, should not deter surgeons from routinely using piezosurgery for maxillary sinus elevation (Fig. 48-7).

The lateral window technique is probably the most established and approved application of piezosurgery, although other approaches, including from

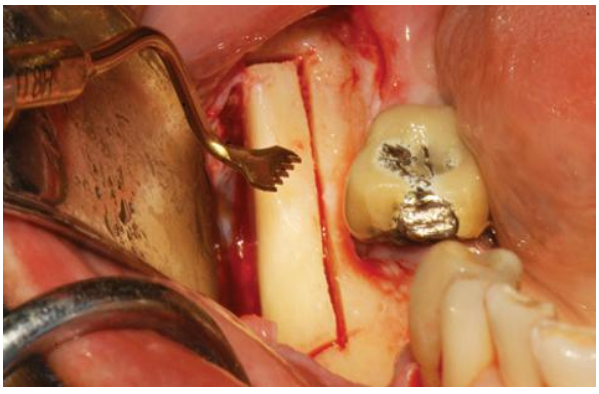

Fig. 48-5 OT8R insert cutting action to simplify the bony block osteotomy and reduce soft tissue damage.

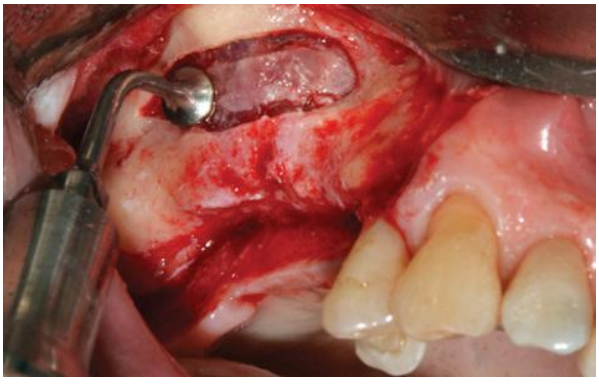

Fig. 48-6 EL1 insert for sinus membrane separation following use of the safe piezoeletric bony window osteotomy technique.

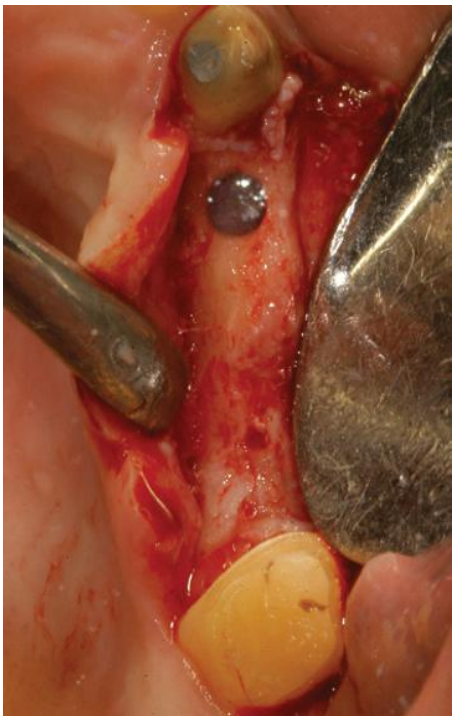

Fig. 48-7 Sinus lift crestal approach using the piezosurgery OT9 tip to preserve the Schneiderian membrane.

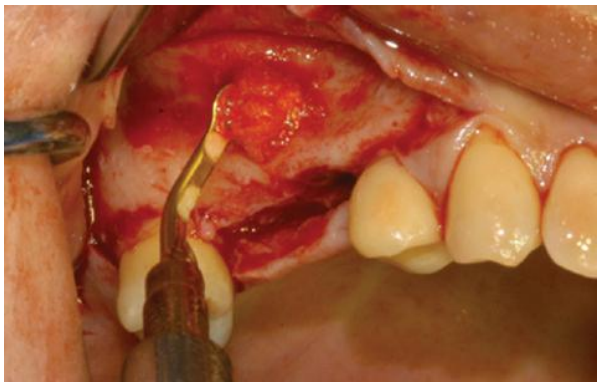

Fig. 48-8 Lateral sinus wall osteoplasty using the OP3 insert to reduce the bony wall thickness for a safer antrostomy technique and simultaneous bone chip harvesting.

the crestal and palatal sides, have been described (Stübinger *et al.* 2009; Baldi *et al.* 2011; Cassetta *et al.* 2012). Notably, the thin and precise cutting with piezosurgery allows proper repositioning of the lateral window lid into the former defect site (Sohn *et al.* 2010). This surgical procedure facilitates graft stabilization when particulate augmentation techniques are used to fill the sinus cavity. Use of a shielding membrane can then in many cases be regarded as facultative or even dispensable. A further advantage of piezosurgery is that, as well as opening the bony window, particulate bone can be simultaneously harvested from the adjacent surface of the edentulous ridge in a scraping–pulling fashion (Stacchi *et al.* 2013). The autologous bone material can then be used either alone or in combination with various biomaterials (Fig. 48-8). With slight variations in the overall osteotomy design, numerous authors have highlighted and supported the effectiveness and success of piezoelectric sinus grafting (Wallace *et al.* 2007; Cortes *et al.* 2012; Wallace *et al.* 2012).

Bone grafting

Rehabilitation of fully and partially edentulous patients by means of endosseous implants has proven to be a predictable treatment option with convincing long-term results (Adell *et al.* 1990; Blanes *et al.* 2007). Yet, a major precondition for the success and sustainability of dental implants is the availability of enough and adequate residual bone volumes. Several techniques for ridge augmentation have been promoted to overcome the problem of insufficient bone volume at the implantation site. In this regard, autogenous bone grafts from the chin or ramus region for bony reconstruction of intraoral defects have proved to be a safe and reliable method due to their osteogenic properties, good long-term stability, and minor resorption. For all interventions, including harvesting, where thin and fragile bony structures are susceptible to fracture as a result of the application pressure or vibration, an accurate and atraumatic osteotomy is a major prerequisite. Piezosurgery offers a potentially safe bone processing technique in such cases, with its high precision allowing individual geometries to be cut. Especially in esthetically demanding zones, the former contour can be preserved or ideally reconstructed using customized bone blocks harvested with customized piezoelectric cut designs (Majewski 2012). With custom-built cutting tips, it is possible to perform osteotomies in difficult-to-access anatomic areas, with minimal trauma to surrounding soft tissue structures. This enables the surgeon to safely harvest bone grafts from, for example, the ramus region or the zygomaticomaxillary region (Stübinger *et al.* 2006). Furthermore, the thorough and comprehensive osteotomy lines achieved reduces the use of hammers and chisels for loosening the bone fragments, thus reducing patient discomfort and the accidental risk of harming underlying vital tissues like the inferior alveolar nerve. Thus, piezosurgery gives the surgeon unprecedented opportunities to harvest intraoral autologous bone grafts with high precision and safety.

Lateralization of the inferior alveolar nerve

Avoidance of iatrogenic damage is of utmost importance and demands not only great skills from the surgeon, but also a minimally invasive osteotomy technique. This is particularly important to avoid damage to the inferior alveolar nerve during surgical removal of impacted molars, spacious tumors or cysts, as well as during implant placement into severely vertically atrophic alveolar ridges. Generally, the inferior alveolar nerve is at risk of harm during

conventional removal of deeply impacted third molars in 1–22% of cases (Degerliyurt *et al.* 2009). The close proximity of the nerve to the impacted teeth together with the reduced manual control over rotating or oscillating instruments makes it difficult for the surgeon to safely preserve this vital structure.

The same problem confronts the surgeon during a lateralization procedure for implant placement. Lateralization of the inferior alveolar nerve is often performed as an alternative to the augmentation technique (Metzger *et al.* 2006). Especially in the posterior areas, conventional instruments limit the visibility and surgical control necessary to distinguish between hard and soft tissue structures. This often leads to surgical damage to the nervous structures. The precise and selective piezoelectric cut with an additional cavitation effect affords much greater safety (Bovi 2005). By creating a replaceable cortical lateral bone lid over the neurovascular bundle, the surgeon obtains free and clear access to the nerve. The bone window is easily relocated to its former position and this protects the nerve structures following nerve retraction, transposition, and subsequent implant placement. Even if there is unintentional contact with the nerve, the negative side effects are much lower than when a conventional rotating or oscillating instruments comes into contact with the nerve (Salami *et al.* 2008).

Edentulous ridge splitting

Split-crest techniques avoid the need for bone augmentation of atrophic edentulous ridges with autologous bone grafts from intra- or extra-oral donor sites. Thereby, the disadvantage of requiring a second surgical donor site can be overcome. During a bone-splitting procedure, the compromised edentulous ridge is cut crestally and the lingual plate is separated from the buccal plate. The dental implant is inserted in the resulting expanded space.

Clinically, edentulous ridge-splitting techniques have been proven to be especially successful for the trabecular bone of the maxilla (Fig. 48-9). The high elasticity and flexibility of cancellous bone structures in the upper jaw allow an effective and fast osteotomy with atraumatic ridge expansion (Amato *et al.* 2012). In the cortical mandible, bone splitting is much more challenging, as mechanical trauma as well as the shape and design of the cutting tools often fracture the thin and fragile bone segments. In contrast, bone sectioning with piezoelectric devices ensuring micrometric osteotomies with no macrovibrations allows easy handling with an increased maneuverability even in delicate cases. Piezosurgery is ideally suited to providing a stable and sound placement and integration of dental implants in these conditions. Thus, even though edentulous ridge splitting using conventional instruments has proven to be a successful treatment regimen (Simion *et al.* 1992; Scipioni *et al.* 1999), the application of piezoelectric osteotomy has improved and refined the surgical procedure.

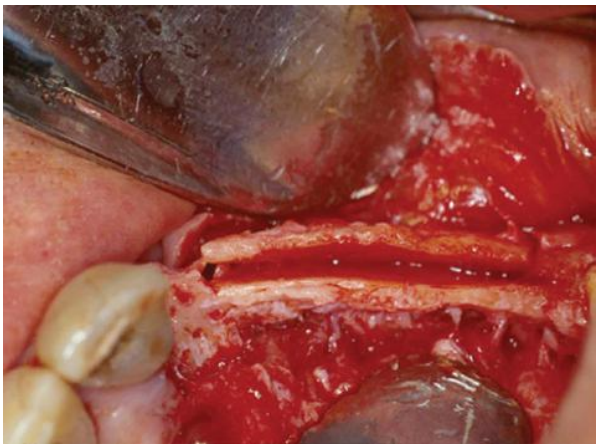

Fig. 48-9 Piezoelectric ridge expansion technique in the maxilla.

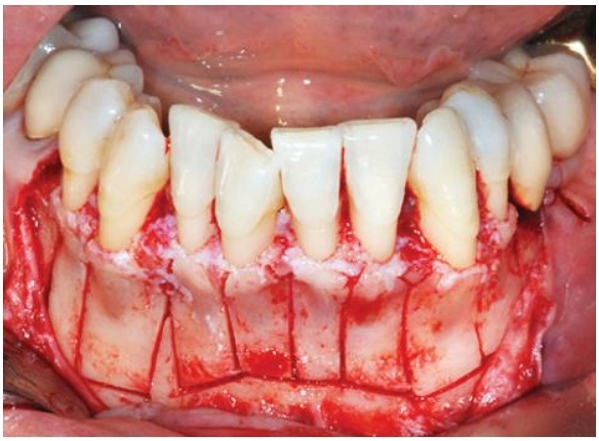

Fig. 48-10 Piezoelectric corticotomy for monocortical tooth dislocation and ligament distraction.

Orthodontic microsurgery

The precise and selective cutting with minimal pressure and vibration also advocate ultrasound-based osteotomy for selective alveolar decortication associated with alveolar augmentation in accelerated orthodontic treatment (Wilcko *et al.* 2001). Rapid achievement of a functionally and esthetically stable occlusion plays a vital role in modern orthodontic therapy. Monocortical tooth dislocation with dentoalveolar compensation is a common procedure in orthognathic surgery to correct dental malpositions, and several orthodontic approaches to correcting tooth malpositions or inclinations are available (Lai *et al.* 2008; Wilmes *et al.* 2009). However, certain features, such as hard and soft tissue dehiscences, fenestration defects, root resorptions, and gingival recession, detract from a favorable treatment outcome. A possible surgical alternative that reduces the required orthodontic forces as well as treatment time is interdental or vestibular corticotomy combined with orthodontic treatment (Ahn *et al.* 2012). With the increased precision of piezoelectric osteotomy,

microsurgical orthodontic therapy has emerged as a promising and reliable treatment concept (Vercellotti & Podesta 2007; Bertossi *et al*. 2011). With simple vertical interdental incisions and minimal soft tissue manipulation, individual teeth can be loosened and separated from each other with vertical and basal monocortical osteotomies (Fig. 48-10). Alveolar augmentation with bone blocks or bone chips can be simultaneously performed. The different designs and shapes of cutting tips offer a wide range of osteotomy patterns for an ideal repositioning and stabilization of bone–tooth blocks.

Conclusion

The advantages of piezosurgery allow numerous modifications of proven surgical procedures, but also novel surgical techniques for common and standard surgical interventions in oral and maxillofacial surgery. Clinical application of piezosurgery has enhanced the handling of delicate structures. Regarding osteotomies of thin and fragile bones, the application of ultrasound is superior to that of other mechanical instruments, because it is easy to handle, provides efficient bone ablation, and minimizes accidental harm to adjacent soft tissue structures.

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Chapter 49

Timing of Implant Placement

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Introduction

Restorative therapy performed on implant(s) placed in a fully healed and non-compromised alveolar process has high clinical success and survival rates (Pjetursson *et al.* 2004). Currently, however, implants are also being placed in (1) sites with ridge defects of various dimensions, (2) fresh extraction sockets, (3) the area of the maxillary sinus, etc. Although some of these clinical procedures were first described many years ago, their application has only relatively recently become common. Accordingly, one issue of primary interest in current clinical and animal research in implant dentistry includes the study of tissue alterations that occur following tooth loss and the proper timing thereafter for implant placement.

In the optimal case, the clinician will have time to plan for the restorative therapy (including the use of implants) prior to the extraction of one or several teeth. In this planning, a decision must be made whether the implant(s) should be placed immediately after the tooth extraction(s) or if a certain number of weeks (or months) of healing of the soft and hard tissues of the alveolar process should be allowed prior to implant installation. The decision regarding the timing for implant placement, in relation to tooth extraction, must be based on a proper understanding of the structural changes that occur in the alveolar process following the loss of the tooth (teeth). Such adaptive processes are described in Chapter 3.

The removal of single or multiple teeth will result in a series of alterations within the edentulous segment of the alveolar process. Hence, during socket healing, the hard tissue walls of the alveolus will resorb, the center of the socket will become filled with cancellous bone, and the overall volume of the site will become markedly reduced. In particular, the buccal wall of the edentulous site will be diminished not only in the buccolingual/palatal direction but also with respect to its apicocoronal dimension (Pietrokovski & Massler 1967; Schropp *et al.* 2003). In addition to hard tissue alterations, the soft tissue in the extraction site will undergo marked adaptive changes. Immediately following tooth extraction, there is a lack of mucosa and the socket entrance is thus open. During the first weeks following the removal of a tooth, cell proliferation within the mucosa will result in an increase of its connective tissue volume. Eventually, the soft tissue wound will become epithelialized and a keratinized mucosa will cover the extraction site. The contour of the mucosa will subsequently adapt to follow the changes that occur in the external profile of the hard tissue of the alveolar process. Thus, the contraction of the ridge is the net result of bone loss as well as loss of connective

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tissue. Figure 49-1 illustrates the tissue alterations described above. It is obvious that no ideal time point exists following the removal of a tooth, when the extraction site has (1) maximum bone fill in the socket and (2) voluminous mature covering mucosa.

A consensus report was published in 2004 describing issues related to the timing of implant placement in extraction sockets (Hämmerle *et al.* 2004). Attempts had previously been made to identify the advantages and disadvantages of early, delayed, and late implant placements. Hämmerle and co-workers considered it necessary, however, to develop a new concept (classification) that incorporated the growing knowledge in this field of implant dentistry. This new classification took into consideration data describing structural alterations that occur following tooth extraction as well as knowledge derived from clinical observations.

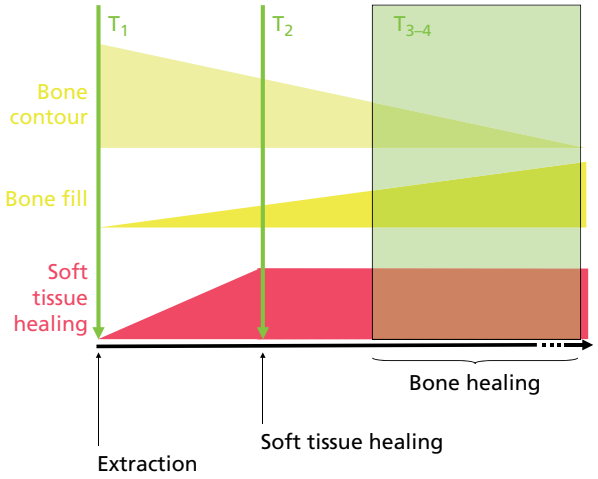

Fig. 49-1 Schematic drawing depicting the changes in the soft and hard tissues following tooth extraction over time. $T_{1–4}$ represent the four different time points for implant placement.

The classification presented in Table 49-1 was introduced in the consensus report. Important aspects included:

- In clinical practice, the decision to place an implant following tooth extraction is usually determined by some soft and hard tissue characteristics of the healing socket. Healing does not necessarily follow rigid time frames, and may vary according to site and patient factors.
- To avoid temporal-based descriptions, this new classification used numerical descriptors – types 1, 2, 3, and 4 – that reflect the conditions of the hard and soft tissues:
  - Type 1 placement: the implant is placed immediately following the extraction of a tooth
  - Type 2 placement: the implant is placed in a site where the soft tissues have healed and a mucosa is covering the socket entrance
  - Type 3 placement: the implant is placed in an extraction site at which substantial amounts of new bone have formed in the socket
  - Type 4 placement: the implant is placed in a fully healed ridge.
- It was further recognized that there is a clear separation between hard tissue healing and soft tissue healing within and around the extraction socket.

This classification has since been refined (Chen *et al.* 2009).

Advantages and disadvantages of the various timings are shown in Table 49-1.

Two methods for flap closure at implant sites have been described. One approach requires primary

Table 49-1 Classification of types 1–4 implant placements, and advantages and disadvantages of each type.

Classification	Definition	Advantages	Disadvantages
Type 1	Implant placement as part of the same surgical procedure as and immediately following tooth extraction	Reduced number of surgical procedures Reduced overall treatment time Optimal availability of existing bone	Site morphology may complicate optimal placement and anchorage Thin tissue biotype may compromise optimal outcome Potential lack of keratinized mucosa for flap adaptation Adjunctive surgical procedures may be required Technique-sensitive procedure
Type 2	Complete soft tissue coverage of the socket (typically 4–8 weeks)	Increased soft tissue area and volume facilitates soft tissue flap management Allows resolution of local pathology to be assessed	Site morphology may complicate optimal placement and anchorage Increased treatment time Varying amounts of resorption of the socket walls Adjunctive surgical procedures may be required Technique-sensitive procedure
Type 3	Substantial clinical and/or radiographic bone fill of the socket (typically 12–16 weeks)	Substantial bone fill of the socket facilitates implant placement Mature soft tissues facilitate flap management	Increased treatment time Adjunctive surgical procedures may be required Varying amounts of resorption of the socket walls
Type 4	Healed site (typically >16 weeks)	Clinically healed ridge Mature soft tissues facilitate flap management	Increased treatment time Adjunctive surgical procedures may be required Large variation in available bone volume

would closure, whereas the other one allows for a transmucosal position of the implant or the healing cap. No differences regarding survival rates and interproximal bone levels were found when these two methods were compared in a split-mouth design (Ericsson *et al.* 1997; Astrand *et al.* 2002; Cecchinato *et al.* 2004). These studies did not, however, analyze in detail the differences between submerged or transmucosal healing in sites of high esthetic importance. Hence, not only the width of the gap but also the width of the alveolar process is a parameter to be considered during treatment planning.

A recent review analyzed the clinical outcomes of implants placed according to the timing scheme described above (Chen & Buser 2009). Based on the analysis of 91 studies, it was found that bone augmentation procedures were more effective in type 1, 2, and 3 placements than in type 4 placement. Furthermore, it appeared that recession of the facial mucosal margin was more frequent when implants were placed according to the type 1 timing.

Type 1 placement as part of the same surgical procedure as and immediately following tooth extraction

Ridge alterations in conjunction with implant placement

It has become common practice to insert implants immediately after the removal of teeth that were scheduled for extraction for various reasons. Over the years, many claims have been made regarding the advantages of immediate implant placement (Chen *et al.* 2004). These advantages include easier definition of the implant position, reduced number of visits to the dental office, reduced overall treatment time and costs, preservation of bone at the site of implantation, optimal soft tissue esthetics, and enhanced patient acceptance (Werbitt & Goldberg 1992; Barzilay 1993; Schwartz-Arad & Chaushu 1997b; Mayfield 1999; Hämmerle *et al.* 2004).

It was proposed that placement of an implant in a fresh extraction socket may stimulate bone tissue formation and osseointegration, and hence counteract the adaptive alterations that occur following tooth extraction. In other words, type 1 implant installation may allow the preservation of bone tissue of the socket and the surrounding jaw. It was in fact recommended (e.g. Denissen *et al.* 1993; Watzek *et al.* 1995; for review see Chen, *et al.* 2004) that implant installation should be performed directly following tooth extraction as a means to avoid bone atrophy.

Clinical studies in humans (Botticelli *et al.* 2004; Covani *et al.* 2004) and experiments in dogs (Araújo & Lindhe 2005; Araújo *et al.* 2006a, b) have examined the influence of implant installation in the fresh extraction socket on bone modeling and remodeling in the surgical site.

Botticelli *et al.* (2004) examined hard tissue alterations that occurred in the alveolar process during a 4-month period of healing following implant placement in fresh extraction sockets. Eighteen subjects (21 extraction sites) with moderate chronic periodontitis were studied. The treatment planning of all 18 subjects called for extraction of single teeth, and restoration by means of implants in the incisor, canine, and premolar regions of the dentition. Following sulcus incisions, full-thickness mucosal flaps were raised and the tooth was carefully mobilized and removed with forceps. The site was prepared for implant installation with pilot and twist drills. The apical portion of the socket was pre-tapped. A non-cutting solid-screw implant (Straumann®, Basel, Switzerland) with a rough surface topography was installed. The implant was positioned in such a way that the marginal level of its rough surface portion was located apical to the marginal level of the buccal and lingual/palatal walls of the socket (Fig. 49-2a). After implant installation (1) the distance between the implant and the inner and outer surface of the buccal and/or lingual bone plates and (2) the width of the marginal gap that was present between the implant and the buccal, lingual, mesial, and distal bone walls were determined with the use of sliding calipers. The soft tissue flaps were replaced and the implants were "semi-submerged" during healing (Fig. 49-2b). After 4 months of healing, a surgical re-entry procedure was performed (Fig. 49-2c). The clinical measurements were repeated so that alterations

Fig. 49-2 Clinical views of (a) implant position in the fresh extraction socket; (b) flaps replaced and sutured; (c) implant site after 4 months of healing (buccal view).

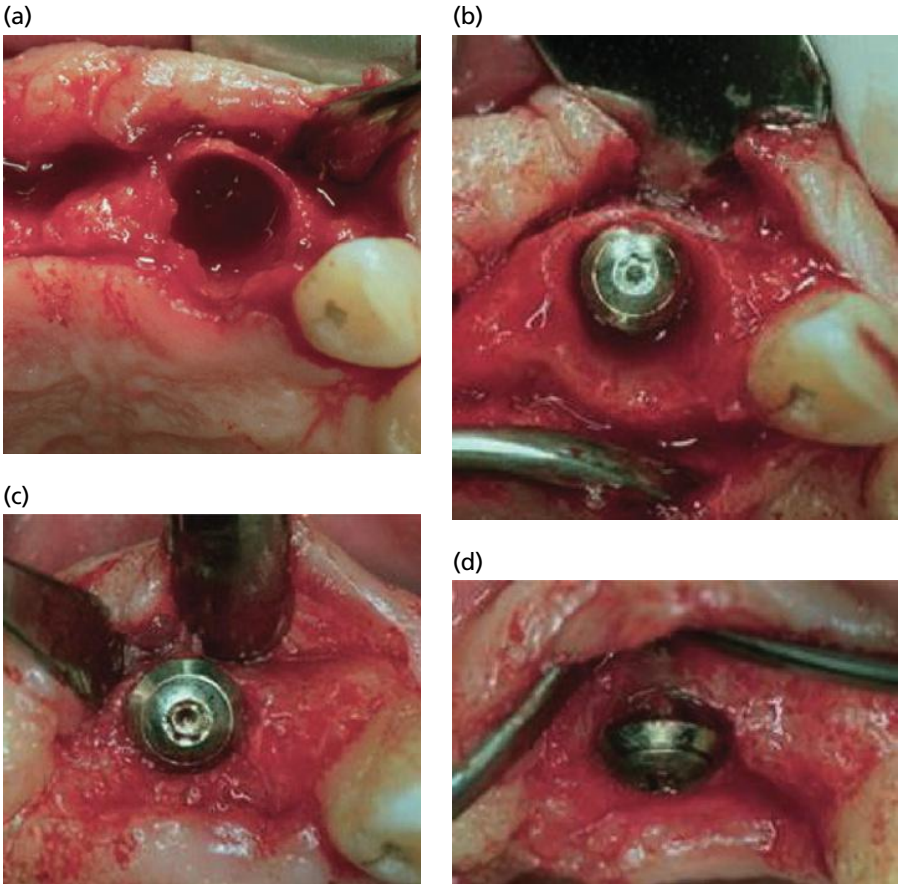

Fig. 49-3 Clinical views of (a) alveolar socket of a maxillary canine; (b) implant position in the fresh extraction socket; (c) implant site after 4 months of healing (occlusal view); (d) implant site after 4 months of healing (buccal view). Note the very thin bone covering the buccal aspect.

that had occurred during healing regarding (1) the thickness and height of the buccal and lingual/palatal socket walls and (2) the width of the marginal gap could be calculated.

Figure 49-3a shows an extraction socket immediately after the removal of a maxillary canine tooth. At re-entry it was realized that the marginal gap had completely resolved. Furthermore, the thickness of the buccal as well as the palatal bone walls had markedly reduced (Fig. 49-3c, d). In Fig. 49-3d, the implant surface can be seen through the very thin remaining buccal bone wall.

Another site from this clinical study is shown in Fig. 49-4. The first maxillary premolar (tooth 14) was removed (Fig. 49-4a) and one implant was placed in the palatal socket of the fresh extraction site. A second implant was placed in the healed edentulous ridge and in position 15 (Fig. 49-4b). At re-entry, it was observed that (1) the marginal gap had completely resolved and (2) the distance between the implant and the outer surface of the buccal bone plate had markedly reduced (Fig. 49-4c).

Botticelli *et al.* (2004) reported that during the 4 months of healing following tooth extraction and implant installation practically all marginal gaps had resolved. At the time of implant placement, the mean distance (18 subjects, 21 sites) between the implant and the outer surface of the buccal bone wall was 3.4 mm, while the matching dimension on the lingual/palatal aspect was 3.0 mm. At re-entry after 4 months, the corresponding dimensions were 1.5 mm (buccal) and 2.2 mm (lingual). In other words, the reduction of the buccal dimension was 1.9 mm (56%), while the equivalent reduction of the lingual dimension was 0.8 mm (27%). The findings by Botticelli *et al.* (2004) strongly indicate that implant placement in a fresh extraction socket may, in fact, not prevent the physiologic modeling/remodeling that occurs in the ridge following tooth removal.

In a recent randomized controlled clinical study, parallel-walled and conical implants were placed immediately into 93 extraction sockets of maxillary non-molar teeth (Sanz *et al.* 2010). Detailed clinical measurements taken at implant placement and 16 weeks thereafter assessed the changes in the relationship between the bone of the socket and the implant surface. A pronounced reduction of the buccal bone dimension occurred over this time period. A smaller reduction of external bone dimension was observed at the lingual aspect. No differences were found between the parallel-walled and conical implants with respect to reduction of the ridge contour. In contrast to the reduction of the external dimensions of the ridge, the gaps between the walls of the socket and the implant surface at the time of placement had partially been filled with newly formed bone at the 16-week follow-up examination (Huynh-Ba *et al.* 2010; Sanz *et al.* 2010).

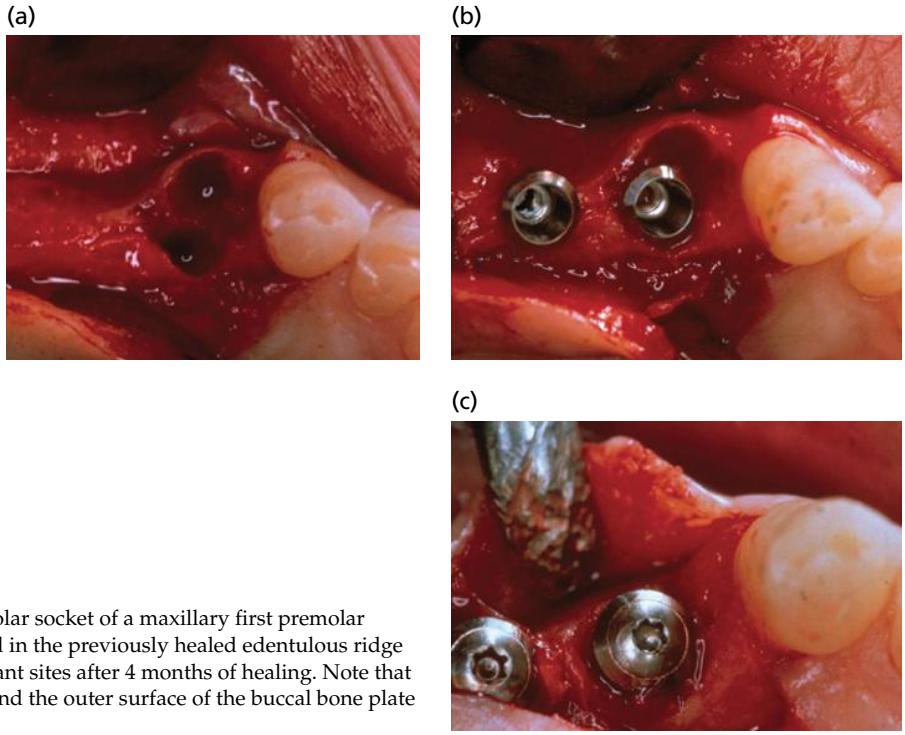

Fig. 49-4 Clinical views of (a) alveolar socket of a maxillary first premolar (occlusal view); (b) implants placed in the previously healed edentulous ridge and in the alveolar socket; (c) implant sites after 4 months of healing. Note that the distance between the implant and the outer surface of the buccal bone plate was markedly reduced.

In a subsequent paper analyzing the same patient groups, it was found that the bone fill of the gap between the implant and the bone walls of the socket as well as the maintenance of the buccal bone height were more favorable at premolar as compared to canine and incisor sites (Ferrus *et al.* 2010; Tomasi *et al.* 2010). Furthermore, the thickness of the buccal bone wall and the dimension of the gap described above favorably influenced the amount of bone fill during the 4-month healing period. A 3-year follow-up examination reported minimal implant failures and stable soft and hard tissue conditions in both groups of implants (Sanz *et al.* 2014).

In order to study the bone modeling/remodeling that occurs in the fresh extraction site following implant placement in more detail, Araújo and Lindhe (2005) used histologic means to determine the magnitude of the dimensional alterations that occurred in the alveolar process following the placement of implants in fresh extraction sockets in the Beagle dog. Buccal and lingual full-thickness flaps were elevated in both quadrants of the mandible. The distal roots of the third and fourth premolars were removed (Fig. 49-5a). In the right jaw quadrants, implants (solid screw, Straumann®) with a rough surface were placed in the sockets so that the marginal border of the rough surface was below the buccal and lingual bone margin (Fig. 49-5b). The flaps were replaced to allow a "semi-submerged" healing (Fig. 49-5c). In the left jaws, the corresponding sockets were left without implantation and the extraction sockets were fully submerged under the mobilized flaps (Fig. 49-5d). After 3 months, the mucosa at the experimental sites in the right and left jaw quadrants appeared to be properly healed (Fig. 49-6). The animals were sacrificed and tissue blocks containing the implant sites and the edentulous socket sites were dissected and prepared for histologic examination. Figure 49-7 shows a buccolingual section of one edentulous site after 3 months of healing. Newly formed bone covers the entrance of the socket. The lamellar bone of the buccal cortical plate is located about 2.2 mm apical to its lingual counterpart. Figure 49-8a presents a similar section from an implant site in the same dog. The marginal termination of the buccal bone plate is located about 2.4 mm apical to the lingual crest. In other words, the placement of an implant in the fresh extraction socket failed to influence the process of modeling that occurred in the hard tissue walls of the socket following tooth removal. Thus, after 3 months of healing the amount of reduction of the height of the buccal bone wall (in comparison to the lingual bone alteration) was similar at the implant sites and the edentulous sites. At 3 months, the vertical discrepancy between the buccal and lingual bone margins was >2 mm in both categories of sites (edentulous sites 2.2 mm, implant sites 2.4 mm).

In a follow-up experiment in the dog, Araújo *et al.* (2006a) studied whether osseointegration, once established following implant placement in a fresh extraction socket, could be lost as a result of continued tissue modeling of the bone walls during healing. As was the case in their previous study (Araújo & Lindhe 2005), the distal roots of the third and fourth premolars in both quadrants of the mandible were removed following flap elevation. Implants were installed in the fresh extraction sockets, and initial stability of all implants was secured. The flaps were

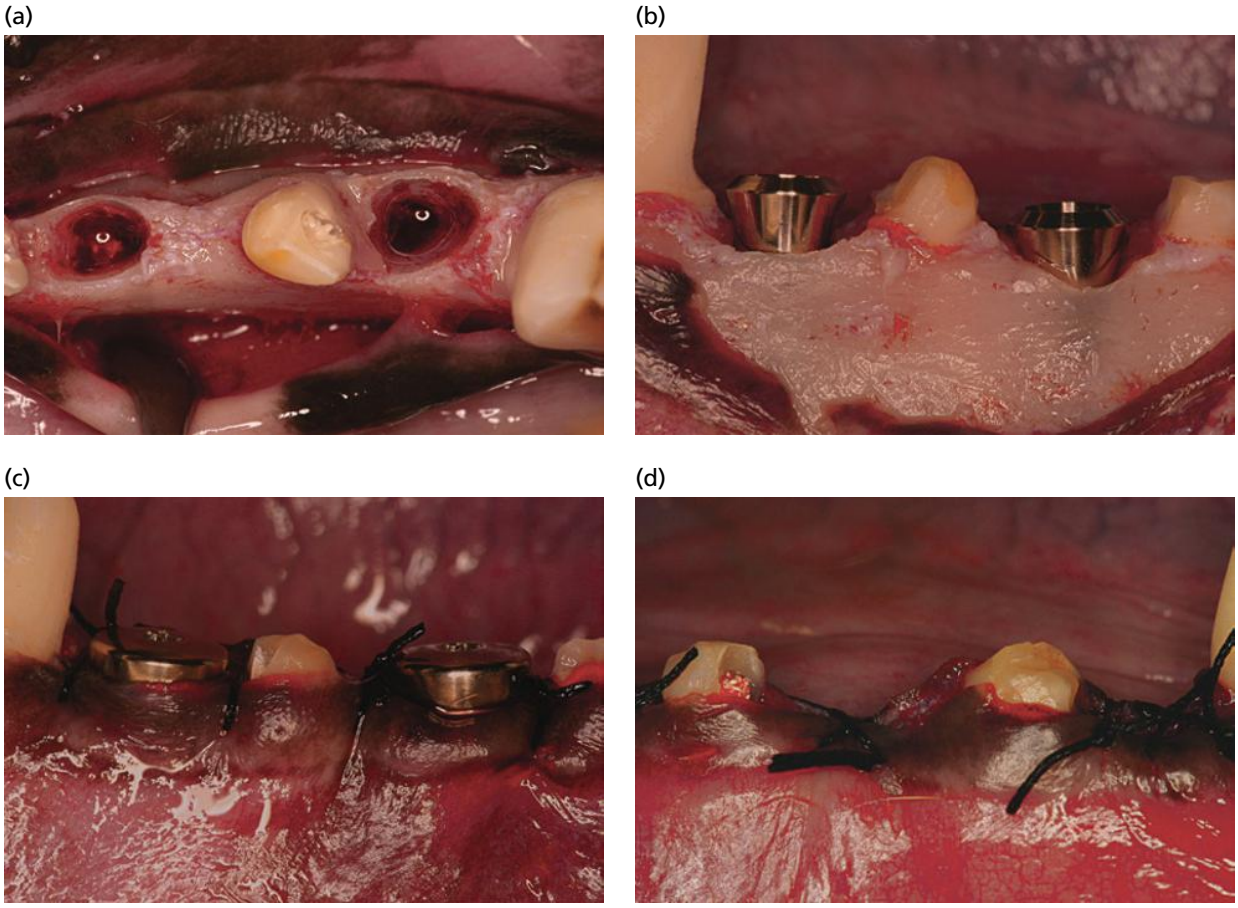

Fig. 49-5 (a) Mandibular premolar site (in a dog experiment) from which the distal root of the fourth premolar was removed. (b) In the test side of the mandible, the implant was placed in the socket in such a way that the rough surface marginal limit was flush with the bone crest. (c) Mucosal, full-thickness flaps were replaced and sutured to allow a "semi-submerged" healing. (d) On the contralateral side of the mandible, the sockets were left without implantation.

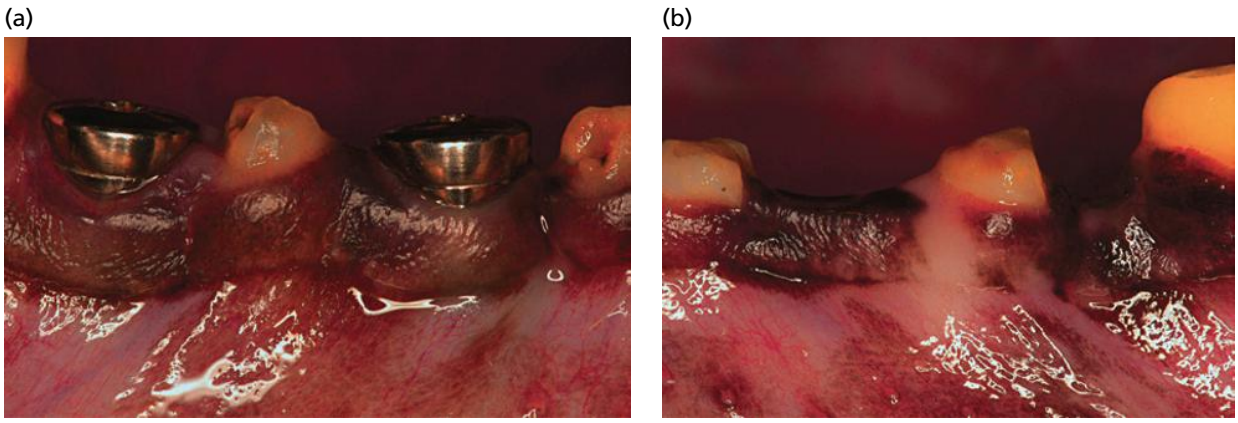

Fig. 49-6 (a) Implant and (b) edentulous sites after 6 months of healing.

replaced and "semi-submerged" healing of the implant sites was allowed. Immediately following flap closure, biopsies were obtained from two dogs, while in five dogs healing periods of 1 month and 3 months were permitted prior to biopsy. Figure 49-9a shows a buccolingual aspect of an extraction site immediately after implant installation. Contact was established between the pitch on the surface of the implant body and the walls of the socket. A coagulum resided in the void between the contact regions (Fig. 49-9b) and also in the marginal gap. In sections taken after 4 weeks of healing, it was observed that this void had become filled with woven bone that made contact with the rough surface part of the implant (Fig. 49-10). In this 4-week interval, (1) the buccal and lingual bone walls had undergone marked surface resorption, and (2) the height of the thin buccal hard tissue wall had been reduced. In the interval between 4 weeks and 12 weeks of healing, the buccal bone crest shifted further in an apical

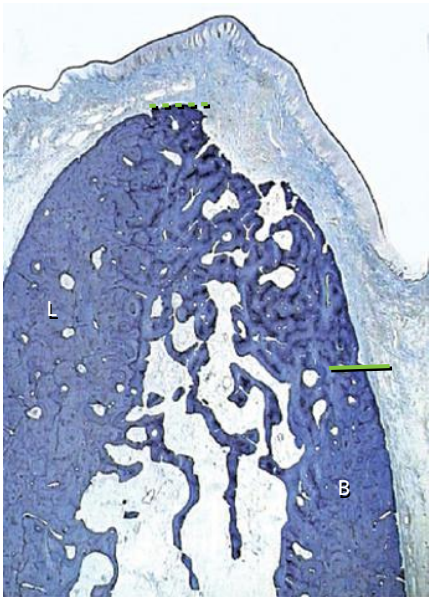

Fig. 49-7 Buccolingual section of the edentulous site. Note that the remaining buccal crest (continuous line) is located far below the lingual counterpart (dotted line). (B, buccal aspect; L, lingual aspect.)

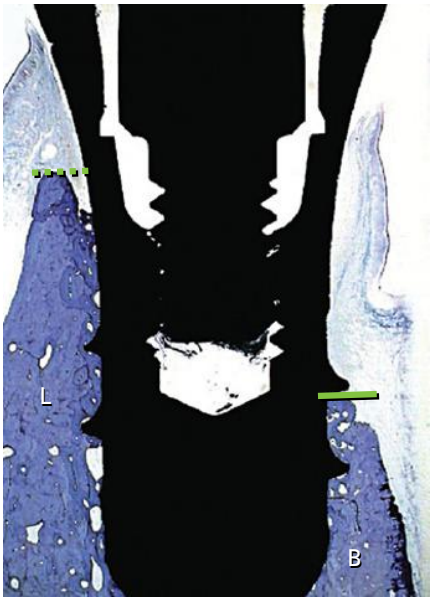

Fig. 49-8 Buccolingual section of the implant site. Note that the remaining buccal crest (continuous line) is located far below the lingual counterpart (dotted line). (B, buccal aspect; L, lingual aspect.)

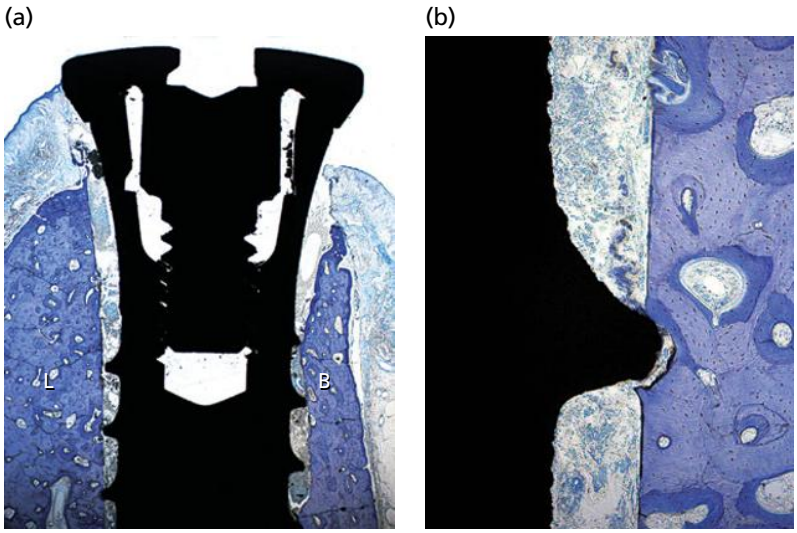

Fig. 49-9 (a) Buccolingual section of an extraction site immediately after implant installation. (b) Contact was established between the pitch on the surface of the implant body and the walls of the socket. (B, buccal aspect; L, lingual aspect.)

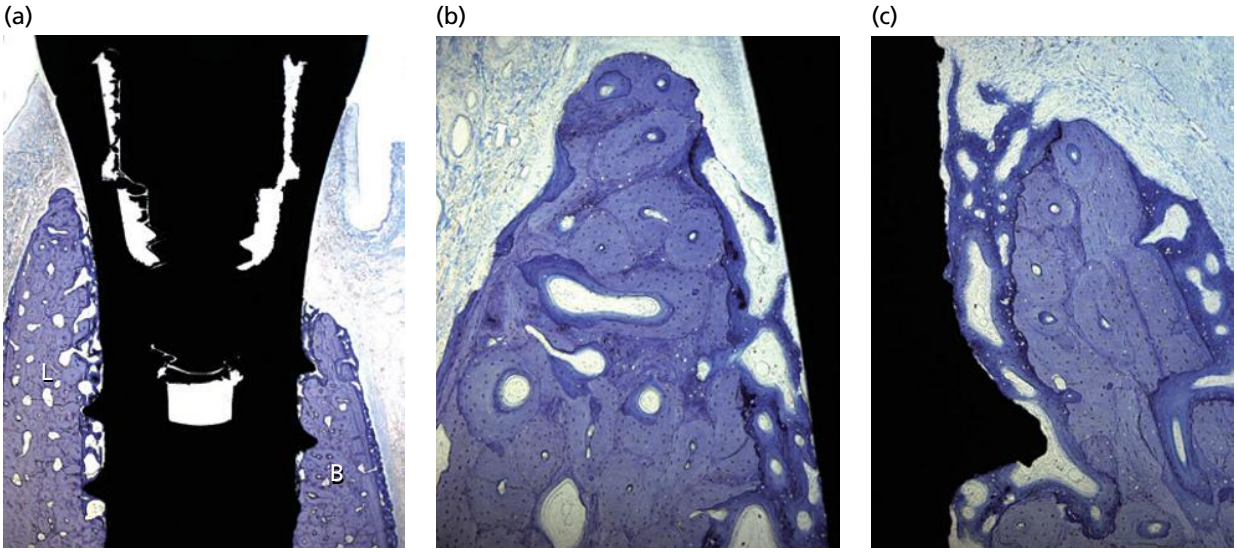

Fig. 49-10 (a) Buccolingual section 4 weeks after implant installation. The void between the implant surface and the bone wall was completely filled with newly formed bone in both lingual (b) and buccal (c) aspects. (B, buccal aspect; L, lingual aspect.)

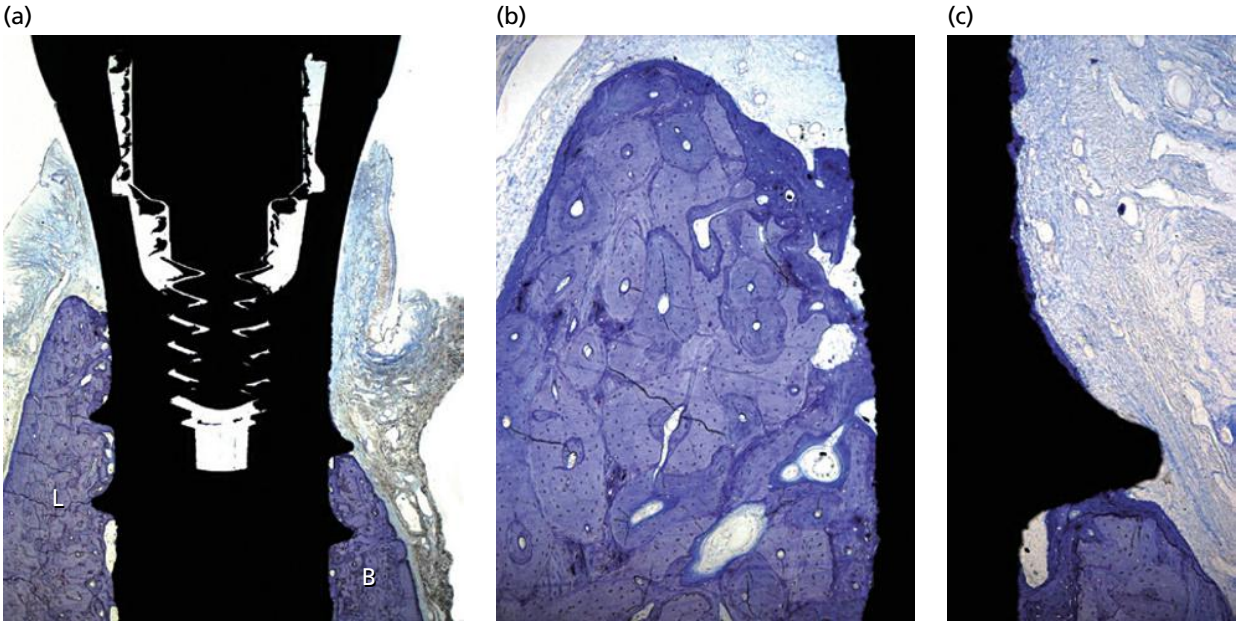

Fig. 49-11 (a) Buccolingual section 12 weeks after implant installation. Note that the buccal bone crest shifted in an apical direction and fragments of it can be seen on the denuded implant surface (c). The lingual bone crest, however, remained stable (b). (B, buccal aspect; L, lingual aspect.)

direction (Fig. 49-11). The woven bone at the buccal aspect that in the 4-week sample made contact with the implant in the marginal gap region had modeled and only fragments of this bone remained (Fig. 49-11c). At the end of the study, the buccal bone crest was located >2 mm apical to the marginal border of the rough implant surface.

These findings demonstrate that the bone (woven bone)-to-implant contact that was established during the early phase of socket healing following implant installation was in part lost when the buccal bone wall underwent continued atrophy. It is obvious, therefore, that the alveolar process following tooth extraction (loss) will adapt to the altered functional demands by atrophy and that an implant, in this respect, is unable to substitute for the tooth. The clinical problem with type 1 placement is that the bone loss will frequently cause the buccal portion of the implant to gradually lose its hard tissue coverage, and that the metal surface may become visible through a thin peri-implant mucosa and cause esthetic concerns (Fig. 49-12).

The question now arises whether it is possible to overcome this problem. This issue was studied in a Beagle dog experiment by Araújo *et al.* (2006b). The distal root of the third mandibular premolar and the distal root of the first mandibular molar were removed and implants placed in the fresh extraction sockets. The third premolar socket in this dog model is comparatively small, and hence the implant inserted (Straumann® Standard Implant, diameter 4.1 mm) occupied most of the hard tissue wound (Fig. 49-13). During healing, resorption of the buccal bone wall occurred (Fig. 49-14) and >2 mm of the marginal portion of the implant became exposed to peri-implant mucosa.

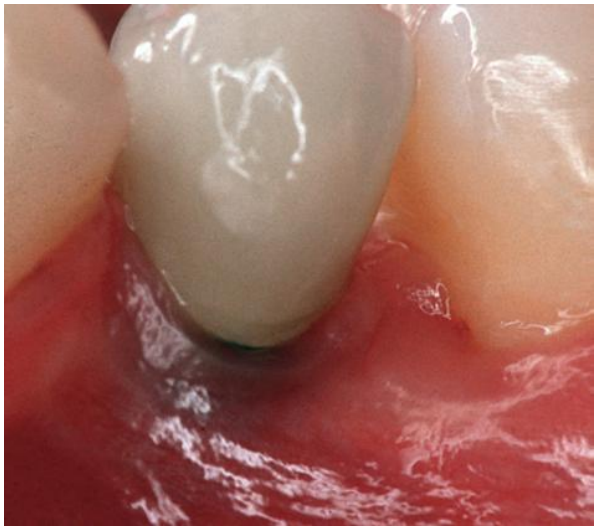

Fig. 49-12 Clinical view of an implant lacking the buccal bone. Note that the metal surface had become visible through the thin mucosa.

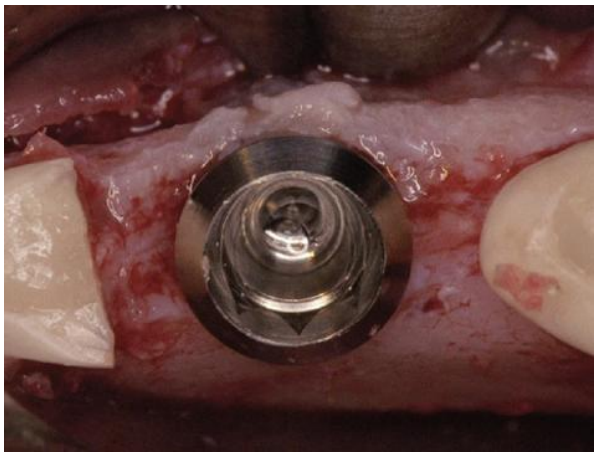

Fig. 49-13 Implant installation in the narrow, third premolar alveolar socket.

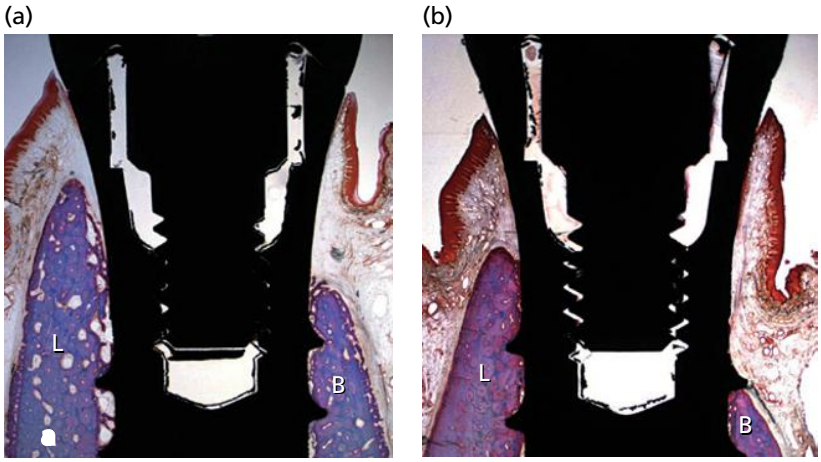

Fig. 49-14 Buccolingual section of the healed premolar sites (a) 4 and (b) 12 weeks after implant installation. (B, buccal aspect; L, lingual aspect.)

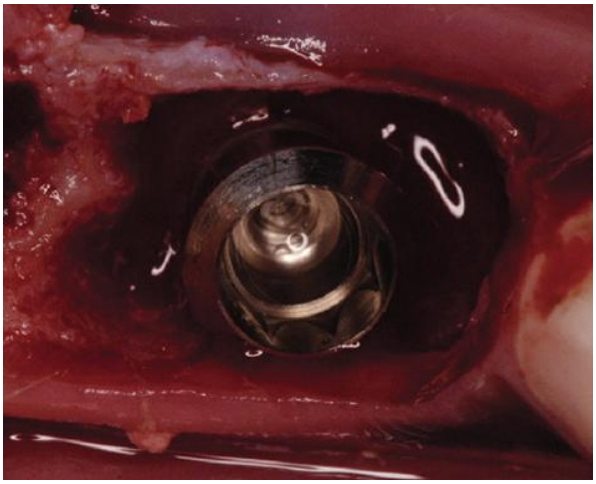

Fig. 49-15 Implant installation in the wide, first molar alveolar socket.

The molar socket, on the other hand, is very large (Fig. 49-15) and hence after implant (Straumann® Standard Implant, diameter 4.1 mm) placement, a >1-mm wide marginal gap occurred between the metal body and the bone walls (Fig. 49-16b). Primary stability of the implant was achieved through contacts between the metal body and the bone in the apical (periapical) portions of the socket. During the early phase of healing, this gap in the molar site became filled with woven bone. In the interval during which the buccal bone wall underwent programmed atrophy, the newly formed bone in the gap region maintained osseointegration and continued to cover all surfaces of the implant (Fig. 49-16a, b).

Conclusion: The data reported illustrate an important biologic principle. Atrophy of the edentulous ridge will occur following tooth loss. This contraction of the ridge cannot be prevented by placing an implant in the fresh extraction socket. The atrophy includes a marked reduction of the width and height of both the buccal and lingual bone plates; in particular, the buccal bone plate will undergo marked change. To some extent the problem with buccal bone resorption can be overcome by placing the implant deeper into the fresh socket and in the lingual/palatal portion of the socket.

As a consequence of the above-described healing, bone regeneration procedures may be required to improve or retain bone volume and the buccal contour at a fresh extraction site. Such bone augmentation is sometimes mandatory in the esthetic area.

Stability of implant

Another issue with type 1 (and also type 2) placement is the anchorage of the implant to obtain primary stability in a position in the jaw that will enable the subsequent restoration to meet high demands regarding esthetics and function. In most cases of type 1 placement, the implants are fixed in native bone apical to the alveolus (Fig. 49-17). Additional retention may be achieved by anchoring the implant in the bony structures of the alveolar walls or interradicular septa.

Another critical issue with type 1 placement is related to how to deal with the presence of periapical pathology at the tooth to be extracted. In a controlled clinical trial, it was observed that primary stability of some implants in a type 1 procedure could not be achieved (Siegenthaler *et al.* 2007). In this study, implants were inserted to replace teeth either exhibiting periapical pathology (test) or presenting healthy periapical conditions (control) (Siegenthaler *et al.* 2007). Apart from the finding that in four implant sites in the test group and one in the control group no implants could be placed due to an unfavorable bone morphology that precluded primary implant stability, no differences were found between the test and the control groups. At 5-year follow-up of the same group of patients, 100% implant survival was recorded in both groups. Furthermore, low levels of marginal bone loss and favorable clinical parameters with no statistically significant difference between the implants in the test and control groups were observed.

Data from a recent study analyzing 418 sites where implants were immediately placed into

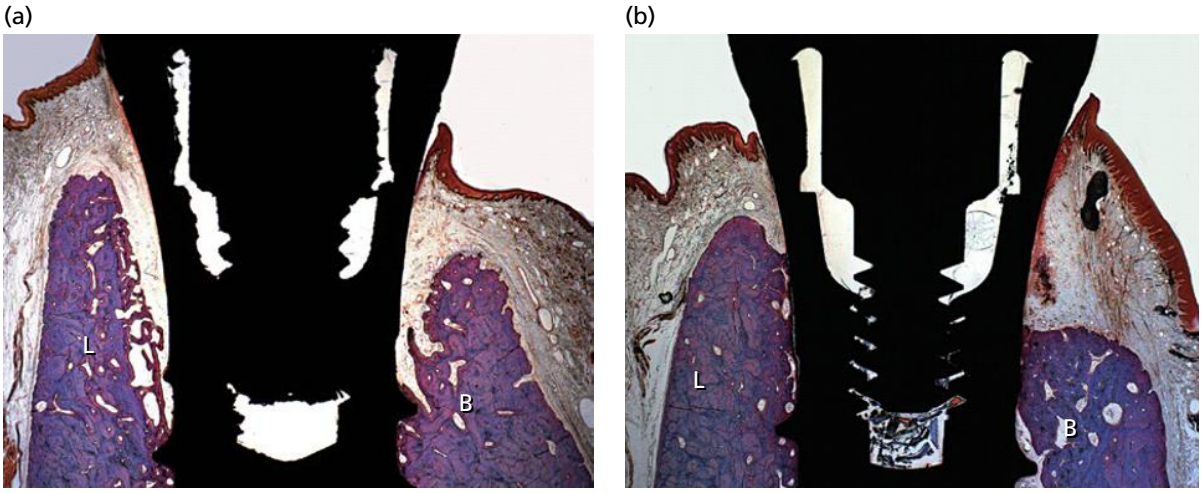

Fig. 49-16 Buccolingual section of the healed molars sites (a) 4 and (b) 12 weeks after implant installation. (B, buccal aspect; L, lingual aspect.)

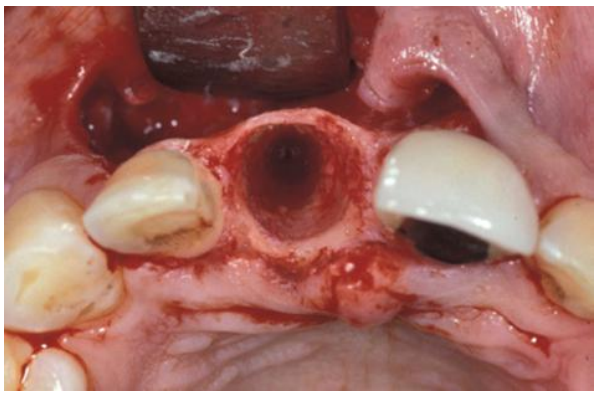

Fig. 49-17 Type 1 implant placement provides optimal availability of existing bone contours. Note the presence of a thin buccal bone plate. Anchorage of an implant can be achieved by engaging the bone apical to the apex of the extracted tooth and the palatal wall of the socket.

extraction sockets with periapical pathology revealed 97.8% survival after a mean follow-up of >5 years (Fugazzotto 2012).

A recent systematic review analyzed data from eight human trials with implants immediately placed into extraction sockets in the presence of periapical pathology (Waasdorp *et al.* 2010). Treatment regimens consistently included thorough debridement of the site prior to implant placement. Bone defects present were normally treated with guided bone regeneration (GBR) procedures. In the majority of cases, an antibiotic regimen was prescribed. Clinical and radiographic results revealed survival and success rates similar those for implants placed in non-infected sites. In contrast, studies have reported a higher occurrence of periapical lesions at implants, when the tooth replaced by the implant had exhibited periapical pathology, or when the tooth next to the implant site exhibited periapical pathology (Lefever *et al.* 2013).

Hence, it appears that the presence of periapical pathology at the tooth to be extracted may represent a higher risk for periapical problems at implants immediately placed into the extraction socket. An important body of evidence, however, suggests that by applying a meticulous treatment regimen, implants placed into the site where teeth with periapical pathology have been extracted, can be maintained with high survival and success rates over time.

How to deal with teeth exhibiting marginal periodontal pathology is another important clinical question regarding type 1 implant placement. In a recent study, implants were immediately placed to replace two groups of teeth (Crespi *et al.* 2010). In one group, the marginal periodontium showed signs of infection, but in the other group the marginal periodontium was clinically healthy. Four years after implant placement, no significant differences between the two groups were found regarding implant survival, marginal bone levels, and peri-implant soft tissue parameters. Hence, properly performed immediate implant placement may lead to successful outcomes when replacing teeth affected by marginal periodontitis.

Type 2 placement: Completed soft tissue coverage of the tooth socket

There are several reasons why the type 2 approach is often recommended. At this stage of healing, the socket entrance is covered with a mucosa. The soft tissue is (1) comparatively mature, (2) has proper volume, and (3) can be easily managed during flap elevation and replacement procedures. Furthermore, the type 2 timing permits an assessment of the resolution of periapical lesions that may have been associated with the extracted tooth. The disadvantages inherent in the type 2 approach include (1) resorption of the socket walls and (2) an extended treatment time (see Table 49-1).

Following tooth extraction, the socket becomes filled with a coagulum that is then replaced with granulation tissue within a few weeks. In the normal case, it takes about 4–8 weeks before the soft tissue

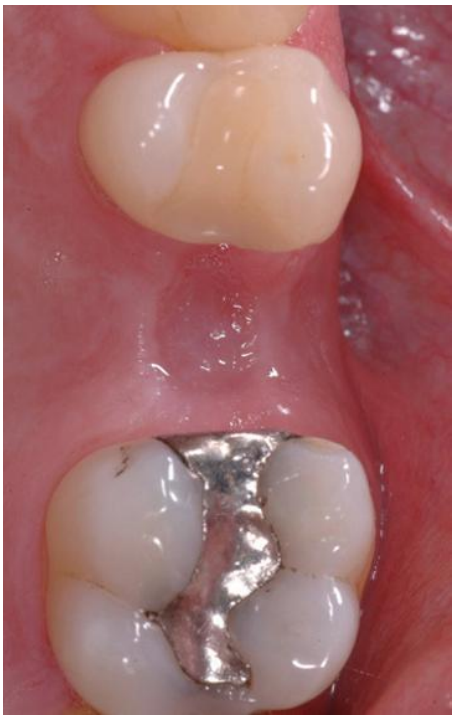

Fig. 49-18 Soft tissues have completely healed over the extraction socket 8 weeks after tooth removal (type 2).

(granulation tissue, provisional connective tissue; see Chapter 3) fills the socket and its surface becomes covered with epithelium (Amler 1969; Zitzmann, *et al.* 1999; Hämmerle & Lang 2001; Nemcovsky & Artzi 2002). The maturation of the soft tissue (further deposition and orientation of collagen fibers) that can facilitate flap management may require an even longer healing time.

The larger amount of soft tissue that is present at the site of implant placement when the type 2 approach is used allows for precise management of the mucosal flap and hence optimal soft tissue healing (Fig. 49-18). This advantage with the type 2 timing must be matched against the hard tissue reduction and the change of the ridge contour that results from the resorption of the socket walls and of the buccal bone plate. It must be noted that at some extraction sites the mucosa may remain adherent via scar tissue to the underlying bone or to the provisional connective tissue of the socket. In such cases, it may be difficult to separate the soft tissue from the bone and to mobilize the flap. In such a situation, the trauma caused in conjunction with flap elevation may rupture the soft tissue and compromise healing. This in turn may result in soft tissue dehiscence, local infection, and inflammation (Zitzmann *et al.* 1997).

As shown in Fig. 49-1, the initial gain in mucosa (area and volume) is later followed by an overall loss of soft tissue volume. This is evidenced by the fact that the volume of the alveolar process – including the bone as well as the mucosal compartments – markedly decreases during the first 12 months following tooth extraction (Schropp *et al.* 2003).

During the 4–8 weeks between tooth extraction and type 2 implant placement, only small amounts of new bone (woven bone) will form in the socket. This means that the risk of not achieving primary implant stability is similar in type 1 and type 2 approaches. Thus, in sites where the available bone height apical to the tip of the root is <3 mm, it is frequently impossible to obtain primary implant stability in the bone beyond the apex of the extracted tooth. When, in addition, a wide alveolus is precluding the engagement of its bony walls, the type 3 approach may be favored.

Type 3 placement: Substantial bone fill has occurred in the extraction socket

The type 3 time frame is chosen for implant installation at sites where, for various reasons, bone fill is required within the extraction socket. Newly formed woven bone will occupy the socket area after healing periods extending from 10 to 16 weeks (Evian *et al.* 1982). In this period, however, the walls of the socket are frequently completely resorbed and replaced with woven bone. The entrance to the socket is closed with a cap of woven bone that is in the process of remodeling. The mucosa that covers the extraction site is (1) residing on a mineralized ridge, and (2) mature and easier to manage during surgical flap elevation and replacement procedures.

The type 3 approach often allows the clinician to place the implant in a position that facilitates the prosthetic phase of the treatment. The disadvantages with this approach encompass (1) a prolonged treatment time, (2) additional resorption and diminution of the ridge, including a substantial change of its contour, and (3) a concomitant loss of soft tissue volume.

Type 4 placement: Alveolar process is healed following tooth loss

In the type 4 approach, the implant is placed in a fully healed ridge. Such a ridge can be found after 4 months, but more likely after 6–12 months of healing following tooth extraction (loss). After 6–12 months of healing following tooth extraction, the clinician will find a ridge that is lined by a mature, often well-keratinized mucosa that resides on dense cortical bone. Beneath the cortical bone plate, cancellous bone occupies a varying portion of the alveolar process (see Chapter 3).

In a study of human volunteers it was observed that the rate of formation of new bone within the extraction site started to decrease after 3–4 months of healing. At this stage, the newly formed bone and the remaining bone of the socket walls entered into a phase of remodeling (Evian *et al.* 1982). Concomitant with the remodeling of this centrally located bone tissue, extra-alveolar resorptive processes leading to

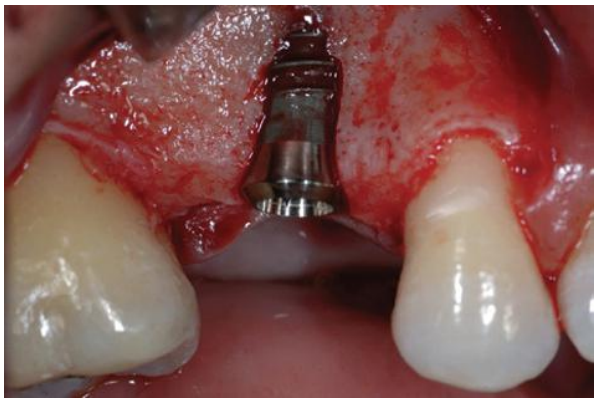

Fig. 49-19 Buccal dehiscence defect is present at an implant placed into a ridge, which has undergone substantial buccal bone resorption since tooth extraction several months ago (type 4).

a further contraction of the ridge and change of its contour continued for at least 12 months (Schropp *et al.* 2003).

The advantage of type 4 installation is that healing is more or less complete and only minor additional change of the ridge may occur. The disadvantages include (1) increased treatment time and (2) further reduction of the overall volume of the ridge and change of its external contour. This pronounced additional loss of ridge volume may at times require complicated bone augmentation procedures (Fig. 49-19). As a consequence, type 4 placement is avoided in most cases when the tooth (teeth) to be replaced is (are) present at the time of examination and treatment planning.

Clinical concepts

When implants are to be placed in the edentulous portion of the ridge, factors in addition to the tissue changes over time must be considered. Thus, in the treatment planning phase, aspects such as the (1) overall objective of the treatment, (2) location of the tooth within the oral cavity – in the esthetic or non-esthetic zone, and (3) anatomy of the bone and the soft tissue at the site(s) to be treated, must be evaluated.

Aim of therapy

Dental implants are most commonly used to restore health and function. During the surgical phase of therapy, therefore, ideal conditions must be established for successful bone and soft tissue integration with the implant. In a growing number of cases, however, treatment must also satisfy patient demands regarding the esthetic outcome. In such cases, the overall surgical and prosthetic treatment protocol may become more demanding, since factors other than osseointegration and soft tissue integration may play an important role.

Restoration of health and function

In cases where the restoration of health and function constitutes the primary goal of the treatment, the location and volume of available hard and soft tissues are the important factors to consider. In such cases, the type 1 approach is usually selected (Wichmann 1990).

The replacement of a single-rooted tooth with an implant in a fully healed ridge will, in most cases, ensure proper primary stability with the implant in a correct position. In addition, the soft tissues are sufficient in volume and area. The mucosal flap can be adapted to the neck (or the healing cap) of the implant (one-stage protocol). When primary wound closure is intended (two-stage protocol), mobilization of the soft tissue will allow tension-free adaptation and connection of the flap margins.

When an implant is placed in the unhealed site of a multirooted tooth, the surgical procedure becomes more demanding. Often, the ideal position for the implant is in the area of the inter-radicular septum. If the septa are delicate, anchorage for primary implant stability may be difficult to achieve (Fig. 49-20). In addition, in molar sites there is often only a small amount of soft tissue present. This may create a problem with respect to wound closure with a mobilized, tension-free flap. In some molar sites, primary wound closure may not be possible following implant installation.

The presence of marginal defects (gaps) between the implant and the fully healed ridge following type 4 placement was regarded in the past as a significant problem that could compromise osseointegration. However, studies in humans and animals have demonstrated that in such a horizontal marginal defect (gap) of ≤2 mm, new bone formation as well as defect resolution and osseointegration of the implant (with a rough titanium surface) will occur (Wilson *et al.* 1998; Botticelli *et al.* 2004; Cornelini *et al.* 2005).

Esthetic importance and tissue biotype

The replacement of missing teeth with implants in the esthetic zone is a demanding procedure. Deficiencies in the bone architecture and in the soft tissue volume and architecture may compromise the esthetic outcome of treatment (Grunder 2000). Hence, when an implant is to be placed in the esthetic zone, not only the anatomy of the hard tissues but also the texture and the appearance of the soft tissues must be considered.

In a recent systematic review including patients with intact facial bone walls and a thick soft tissue biotype, a limited risk for advanced mid-facial soft tissue recession was reported (Cosyn *et al.* 2012). Furthermore, it was stated that the literature was scarce regarding the effect of different parameters on mid-facial soft tissue recession, like thin or thick tissue biotype, flapless or flap surgery, and immediate or late provisionalization. In another study of a specific treatment protocol that included type 1 implant

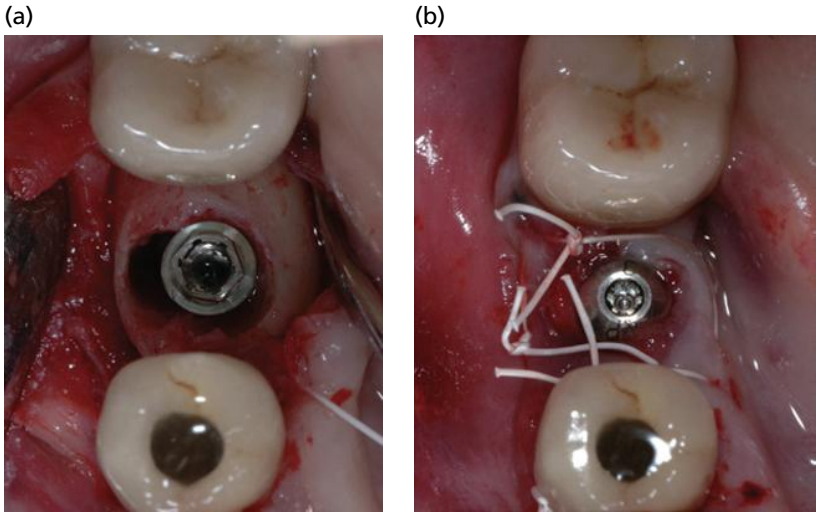

Fig. 49-20 (a) Immediate implant placement (type 1) in a mandibular premolar extraction socket. Note the buccal bone deficiency, where bone will be augmented by guided bone regeneration. (b) Same site as in (a) following adaptation of the flap around the neck of the implant, obtaining a transmucosal mode of healing.

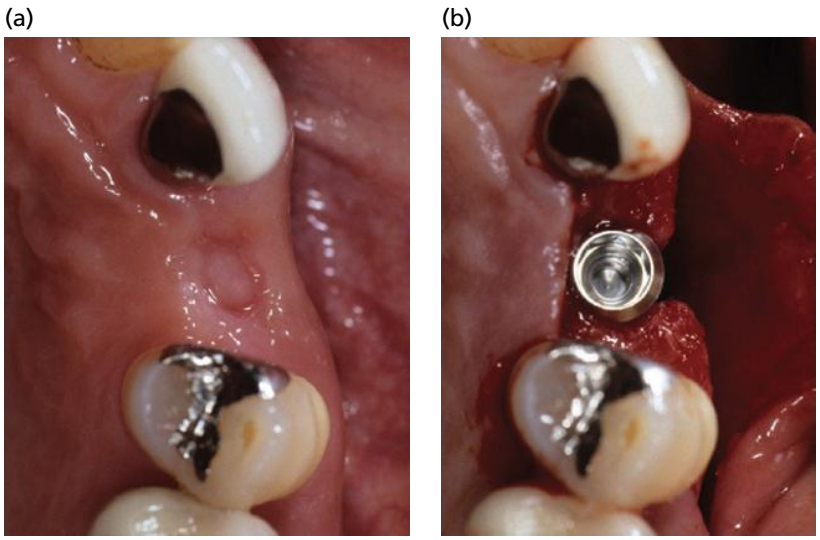

Fig. 49-21 (a) Single-tooth gap 8 weeks following tooth extraction. The soft tissues have completely healed over the extraction socket. (b) Same site as in (a). An implant has been placed in the edentulous gap. The resulting buccal dehiscence defect will be augmented with bone by applying guided bone regeneration.

placement, flapless surgery, and immediate provisionalization, Cabello *et al.* (2013) reported good esthetic outcomes with only small changes in the height of the interproximal papillae and the level of the mid-facial mucosal margin.

Type 2 installation is often preferred when implants are placed in the esthetic zone (Fig. 49-21). The key advantage of type 2 (as opposed to type 1) installation is the increased amount of soft tissue that will have formed during the first weeks of healing following tooth extraction. It must be emphasized, however, that no randomized controlled studies comparing the treatment outcomes in type 1 or type 2 placements have so far been reported.

Apart from obtaining soft tissue coverage of the previous entrance to the alveolus, type 2 installation has also been claimed to reduce facial soft tissue recession compared to type 1 implant placement. In a comparative study assessing esthetic outcomes of immediate and conventional implant placement, no treatment was favored over any other with respect to overall esthetic results (Raes *et al.* 2011). Interestingly, conventional implant placement was associated with more mid-facial recession than immediate implant placement. In a clinical study of implants placed in fresh extraction sockets (Botticelli *et al.* 2004), during healing, they became clinically osseointegrated within the borders of the previous extraction socket. However, significant loss of buccal bone height (contour) also occurred. In esthetically critical situations, this loss of contour may lead to a compromised outcome. Hence, not infrequently, tissue augmentation procedures must be performed in the esthetic zone.

In this context, it is important to realize that when a two-stage implant placement protocol is used, the labial mucosa will recede following abutment connection surgery. Mean values of recession between 0.5 mm and 1.5 mm, but with large variations, have been reported in several clinical studies (Grunder 2000; Oates *et al.* 2002; Ekfeldt *et al.* 2003). These findings additionally stress the necessity for a careful treatment approach when implants are placed in the esthetic zone. The biotype (see Chapter 4) of the soft and hard tissues may play a role in the esthetic outcome of implant therapy. Characteristics of soft and hard tissues at teeth were described and classified into two biotypes: the flat thick or the pronounced scalloped, thin biotype (Olsson & Lindhe 1991; Olsson

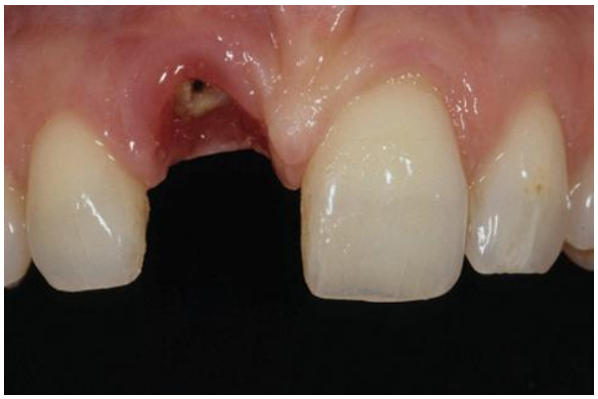

Fig. 49-22 Patient exhibiting a thin tissue biotype as characterized by a thin free gingiva, a narrow zone of keratinized and attached mucosa, shallow probing depths, and a pronounced "scalloped" contour of the gingival margin, including recessions at some maxillary anterior teeth. Tooth 11 is scheduled for extraction and replacement by an implant using a type 2 or 3 approach.

et al. 1993; Weisgold *et al.* 1997). The thin tissues in the latter type include a thin free gingiva, a narrow zone of attached mucosa, and a pronounced "scalloped" contour of the gingival margin. In addition, the scalloped thin biotype is associated with a delicate bone housing. In a recent study it was found that buccal tissue recession at single-tooth implants was more pronounced in patients exhibiting a thin biotype compared to patients with a thick biotype (Evans & Chen 2008). Based on these findings and on clinical experience, it was proposed that patients exhibiting a pronounced scalloped biotype should be treated with a type 2, 3, or 4 rather than a type 1 implant installation approach (Fig. 49-22). Currently, the paucity of data from well-controlled clinical studies precludes clear statements regarding the effect of the different types of implant placement on the stability and the height of the soft tissues at the implant sites.

Success of treatment and long-term outcomes

Numerous clinical studies have demonstrated that type 1 implant placement is a successful and predictable clinical method (Lang *et al.* 1994; Schwartz-Arad & Chaushu 1997a; Hämmerle *et al.* 1998; Covani *et al.* 2004). In addition, success and survival rates for type 1 implants have been reported to be of the same magnitude as those for implants placed in healed ridges (Gelb 1993; Grunder 2000; Gomez-Roman *et al.* 2001; Gotfredsen 2004; Schwartz-Arad *et al.* 2004). Histologic studies in animals confirmed the viability of type 1 placement. Unloaded titanium implants placed in extraction sockets showed a high degree of osseointegration (Anneroth *et al.* 1985), that is similar to that for implants placed in healed sites. Furthermore, a few studies analyzing survival rates for type 2 and 3 placements have shown survival rates similar to those reported for type 1 and 4 placements (Watzek *et al.* 1995; Nir-Hadar *et al.* 1998; Polizzi *et al.* 2000).

Conclusion

In situations where teeth are to be replaced with implants, various factors govern the decision regarding the optimal time point for implantation following tooth extraction. Of special importance are the overall objective of the treatment, the location of the tooth within the oral cavity, the anatomy of the bone and the soft tissue at the site, and the adaptive changes of the alveolar process following tooth extraction. The decision regarding the timing for implant placement needs to be based on a thorough understanding of the structural changes that occur in the alveolar process following tooth extraction, with and without implant placement, as presented in this chapter.

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Part 15: Reconstructive Ridge Therapy

Chapter 50

Ridge Augmentation Procedures

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Introduction: Principles in alveolar bone regeneration

The alveolar process is sensitive to a variety of environmental and physiologic factors that influence its ability to function and maintain its integrity. Before implant therapy became available, the physiology and healing patterns of the edentulous ridge after a tooth was extracted were often neglected or not dealt with properly (Amler *et al*. 1960; Amler 1969). Today, implant placement in severe cases of alveolar resorption is a well-understood and recognized challenge that significantly impacts the success of implant therapy. Although alveolar bone loss can be congenital, the result of trauma, pathology, and chronic/acute infection, or a consequence of periodontal disease, the loss of mechanical function following a tooth extraction is the most widely experienced scenario that leads to this clinical deficiency. In fact, after a tooth is extracted, approximately 25% of the bone volume has been reported to be lost after the first year. Over time, this deterioration may progress and is often reported to be responsible for a 40–60% loss of alveolar volume during the first 3 years after a tooth is lost. The resulting ridge deficiency is primarily the result of the gradual loss of the horizontal dimension accompanied by a rapid loss of bone height (Carlsson *et al*. 1967). Therefore, clinicians have suggested protocols to minimize ridge resorption or correct clinically unfavorable deficiencies (Tarnow & Eskow 1995; Sclar 2004; Seo *et al*. 2004) (Fig. 50-1).

Successful ridge augmentation procedures consider basic biologic and physical principles of bone to enhance the regenerative potential of the host. The placement of bone grafting materials to favor healing in osseous defects or to augment atrophic edentulous ridges to allow dental implant installation has been evaluated in a number of experimental and clinical studies, and has become a gold standard treatment in implant dentistry (Fig. 50-2).

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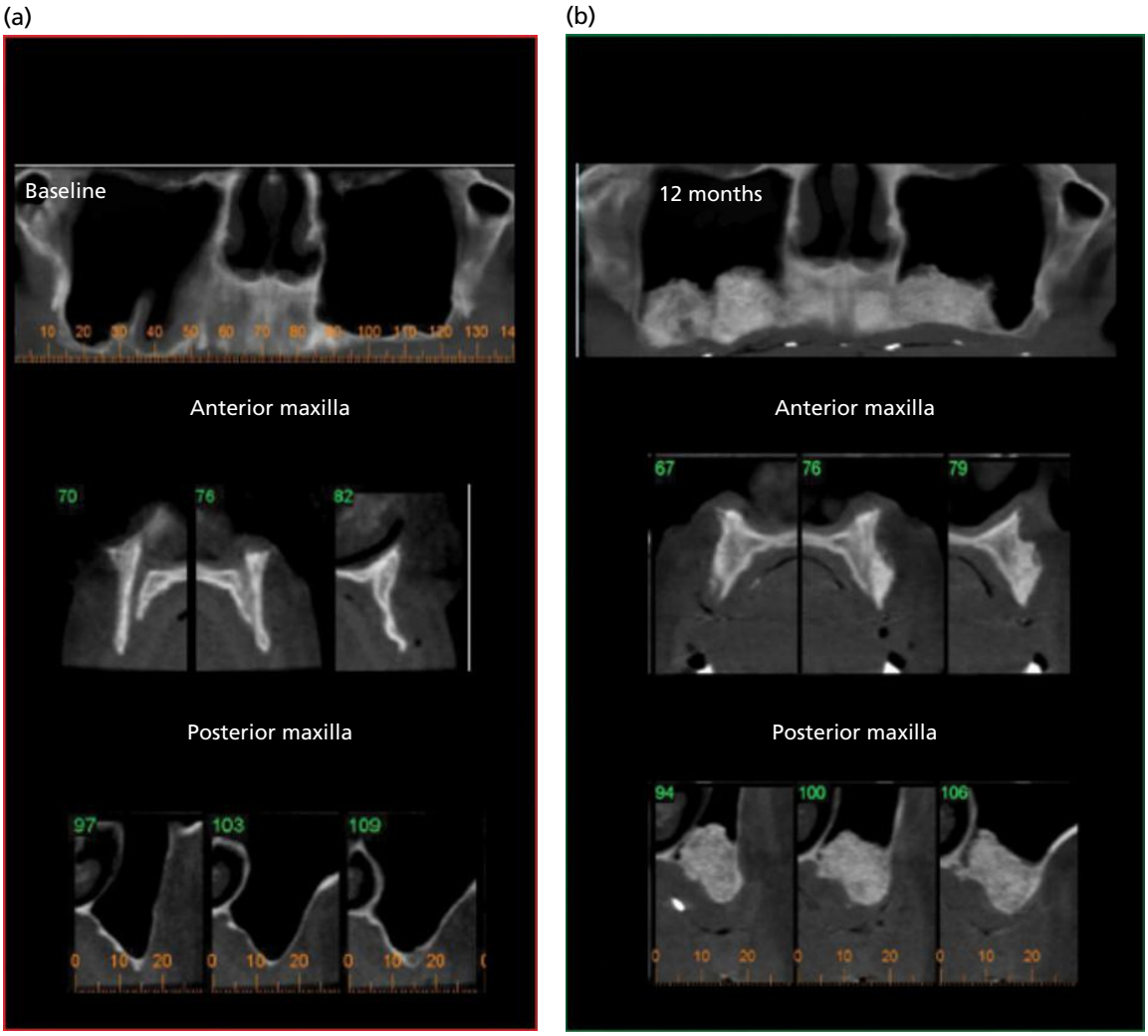

Fig. 50-1 (a) Preoperative and (b) postoperative after cone-beam computer tomography images of an adequately corrected anterior and posterior ridge deficiency. Advanced bone grafting protocols have evolved to allow predictable implant placement in severe ridge deficiencies that would have otherwise prevented implant therapy.

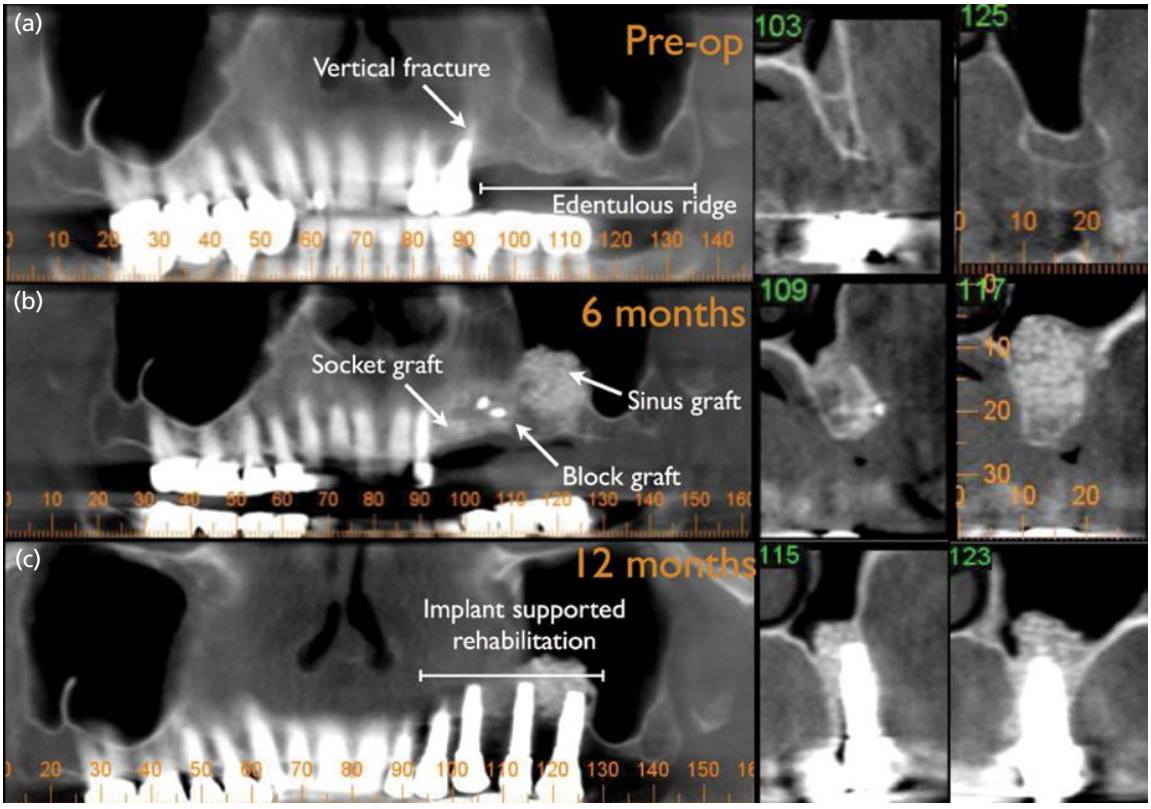

Fig. 50-2 Availability of diverse bone grafting materials. This has significantly contributed to the development of successful ridge augmentation techniques. (a) Baseline radiographic image highlights the edentulous deficient ridge. (b) Six months after the required grafting procedures. (c) Twelve months after surgery and implant-supported rehabilitation.

It has been found that the osteogenic environment that maximizes the bone regenerative potential of traditional advanced grafting procedures is often affected by local as well as systemic factors. In some cases, the incorporation of the bone graft in the recipient site may be partially or completely impaired, and in turn there may be bone resorption and bone loss associated with the donor grafting material. As a consequence, much of the intended volume is lost, and frequently, the defects heal with fibrous connective tissue instead of bone. The surgical principles that favor bone regenerative therapies have been discussed and have helped to create awareness of the physical and biologic factors that are determinants of adequate healing (Wang & Boyapati 2006). The molecular wound healing events following tooth extraction and eventual consolidation and bone repair of the residual ridge occur through an orderly sequence of expression of osteogenic factors associated with angiogenesis, cell survival, matrix synthesis, and maturation (Lin *et al.* 2011). Some of the most important modifiable factors to consider and assist in proper wound management are discussed below.

Promoting primary wound closure

Primary closure is primordial for bone regeneration because it provides an undisturbed environment for healing (Gelb 1993; Becker & Becker 1996; Fugazzotto 1999; Goldstein *et al*. 2002). Ideal flap closure should be relatively passive and tension-free. In this way, the risk of membrane exposure, wound contraction, collagen formation and remodeling, re-epithelialization, and patient discomfort are decreased. In order to ensure primary closure, the presence of adequate soft tissue should be assessed prior to surgery. It may be recommended to augment the soft tissues prior to bone augmentation in cases where the soft tissue is lacking.

Enhancing cell proliferation and differentiation

Proper cell proliferation and differentiation not only provides blood, oxygen, and nutrients to the tissues, but also acts as a source of angiogenic and osteogenic cells. Sources of osteogenic cells include the periosteum, endosteum, and undifferentiated pluripotent mesenchymal cells. The bone marrow is an excellent source of these mesenchymal cells, which can differentiate into osteoblasts and osteoclasts. In order to increase important early healing events, perforations of the cortical plate have been recommended to facilitate the migration of cells to the healing site (Buser *et al.* 1995). This is a process referred to in the literature as the regional acceleratory phenomenon (RAP). These perforations act as a mechanical or non-infective stimulus that increases blood perfusion to the healing site. Therefore, important growth factors are released, allowing the tissue to heal faster than the normal unperturbed regeneration process (Frost 1983; Shih & Norrdin 1985).

Currently, a number of biologically active products are available clinically to overcome common intrinsic wound healing limitations by enhancing cell proliferation and differentiation, and by allowing a more rapid and predictable bone anabolic signaling process between the graft and the host tissue.

Protecting initial wound stability and integrity

One factor that affects wound healing is stability of the blood clot, and the barrier membrane helps stabilize the blood clot (Wang *et al*. 2004). This is important because the clot contains a multitude of cytokines [e.g. interleukin-1 (IL-1), IL-8, tumor necrosis factor], growth factors [e.g. platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2)], and signaling molecules that aid in recruiting cells to promote healing. Moreover, the blood clot is important for the formation of granulation tissue and subsequent formation of bone (Schenk *et al.* 1994).

Additionally, to allow proliferation of bone-forming cells, a physical space is necessary (Oh *et al.* 2003). This is typically achieved through the use of membranes that exclude epithelial and connective tissue cells, or a proper scaffold. As will be discussed later, membrane collapse is problematic as it compromises the space available for the osteogenic cells. Hence, the use of titanium-reinforced membranes helps in space maintenance, especially in cases of severe bone loss (Jovanovic *et al.* 1995), compared to the collapse reported with collagen membranes alone (Oh *et al*. 2003).

This chapter discusses the growing evidence in the area of bone augmentation procedures that are frequently employed by clinicians to augment the deficient residual ridges prior to implant therapy.

Treatment objectives

The rationale behind any crestal bone augmentation procedure is to establish sufficient bone availability for safe and predictable dental implant therapy, as well as for attaining adequate bone thickness around the installed implant. Spray *et al*. (2000) evaluated the influence of bone thickness on the marginal bone response at second-stage uncovering surgeries, and reported that as the bone thickness approached 1.8–2 mm, bone loss (i.e. implant dehiscence) decreased significantly. Although the "adequate" bone thickness may vary depending on the macroscopic and microscopic implant configurations, as well as the clinical indication, it is generally agreed that at least 2 mm of bone on the buccal side of the implant are needed to achieve long-term stability of peri-implant health and good esthetics.

This rationale is further justified by the growing evidence for biologic complications around functional implants. The prevalence of these peri-implant

diseases affecting the implant-supporting bone (peri-implantitis) ranges between 28% and 56% of patients and between 12% and 43% of implants (Zitzmann & Berglundh 2008). Among the potential risk factors for peri-implantitis, rough implant surfaces exposed to the oral environment are at a higher risk of accumulating bacterial plaque biofilms and hence the development of mucosal inflammation (Renvert *et al*. 2011). Schwarz *et al*. (2012) evaluated the influence of residual marginal dehiscence bone defects after guided bone regeneration (GBR) on the long-term stability of peri-implant health, and reported that implants exhibiting residual defect heights of >1 mm were at higher risk of presenting mucosal clinical attachment loss, marginal recession, and deepened probing pocket depths 4 years after treatment. Therefore, the implant surgeon should ensure that there is enough bone to fully cover the implant surface and in case of limited availability, carry out a bone augmentation procedure.

Diagnosis and treatment planning

Patient

In general, there are no specific contraindications for ridge augmentation procedures provided the patient can withstand a conventional oral surgical procedure. For bone augmentation procedures as well as for other types of oral implant operations, there are some relative contraindications that need to be taken into consideration, mainly medical conditions that might impair normal bone healing. For example, in patients with diabetes, there is evidence that implant success rates are similar to those in healthy patients, provided there is appropriate glycemic control. Experimental studies, however, have provided histologic evidence of impaired healing in implants placed in diabetic animals when compared to healthy controls, although osseointegration was achieved in both groups (Colombo *et al*. 2011; Schlegel *et al*. 2013). Recently, the effect of experimental diabetes and metabolic control on the potential for *de novo* bone formation following GBR was investigated in the rat mandible (Retzepi *et al*. 2010). These authors did not observe statistically significant differences in the amount of vertical bone regeneration when uncontrolled diabetic, insulin-controlled diabetic, and healthy animals were compared. The uncontrolled diabetes group, however, showed an increased rate of infectious complications and a less predictable outcome. When metabolic control of the systemic condition was achieved, the detrimental effects on healing were reversed.

Smoking has also been found to negatively affect the long-term prognosis of osseointegration (Bain & Moy 1993). Clinical studies have reported that smokers present not only higher rates of implant failure when compared with non-smokers (De Bruyn & Collaert 1994; Lambert *et al*. 2000), but also a greater number of complications around successfully integrated implants (Roos-Jansaker *et al*. 2006), such as a higher incidence of peri-implant mucositis and peri-implantitis (Heitz-Mayfield 2008). Although there is ample evidence on the negative effects of tobacco smoking on the clinical outcomes of periodontal regenerative therapies, such as guided tissue regeneration (GTR) (Patel *et al*. 2012), few studies have directly evaluated its effect on GBR. A meta-analysis, based on six studies, evaluated the effects of smoking on dental implants placed on augmented bone and reported an odds ratio (OR) of 3.61 (95% CI 2.26–5.77) for implant failures (Strietzel *et al*. 2007). In this systematic review, the impact of smoking on the outcomes of different bone regeneration techniques (horizontal and/or vertical augmentation) was assessed in four retrospective studies: three studies reported more failures and complications in smokers compared with non-smokers. Moreover, the amount of bone augmentation in smokers was inferior when compared with that in non-smokers. Similarly, a recent clinical case series evaluated the outcomes of a GBR procedure combining autogenous bone and an expanded polytetrafluoroethylene (ePTFE) membrane (Lindfors *et al*. 2010). In the group of non-smokers, the augmentation procedure was successful in 95% of the cases, whereas in smokers it was successful in only 63% of the cases. Moreover, signs of soft tissue inflammation were present in ten (37%) of the augmentation sites, and this occurred more often in smokers (75%) than in non-smokers (21%).

These patient-related factors are not absolute contraindications for bone augmentation procedures, but they should be taken into consideration during diagnosis and treatment planning. When a bone augmentation procedure is indicated, the patient's systemic status should be optimized.

Defect classification

Bone availability is the main prerequisite for safe and predictable implant placement. There are, however, many clinical situations where bone quantity is limited and therefore, bone augmentation procedures are indicated. In order to decide on the appropriate bone augmentation strategy, the available bone crest must be carefully evaluated with careful clinical examination and three-dimensional (3D) radiography (see Figs. 50-1, 50-2) of the bone morphology.

According to Seibert (1983), alveolar crest defects are classified into three categories (Fig. 50-3):

- *Class 1 defects*: when the bone deficiency is predominantly in the horizontal dimension
- *Class 2 defects*: when the bone deficiency is predominantly in the vertical dimension
- *Class 3 defects*: when the bone deficiency affects both the vertical and horizontal dimensions.

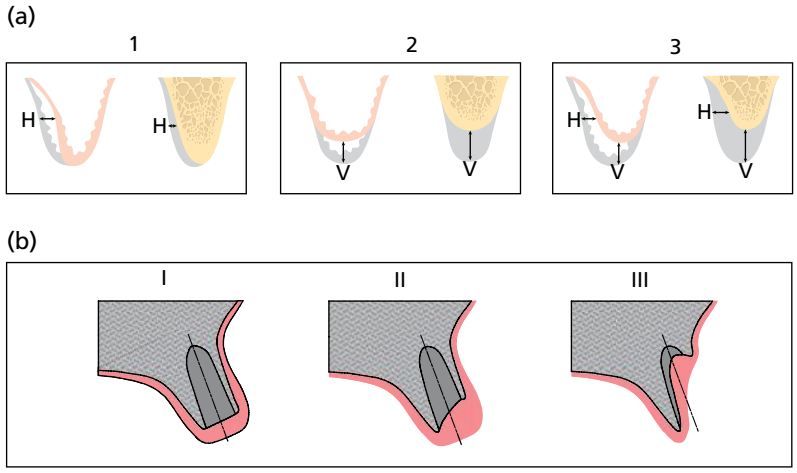

Fig. 50-3 (a) Alveolar crest defects, Seibert classification. (b) Extraction sockets defect, Hämmerle & Jung classification.

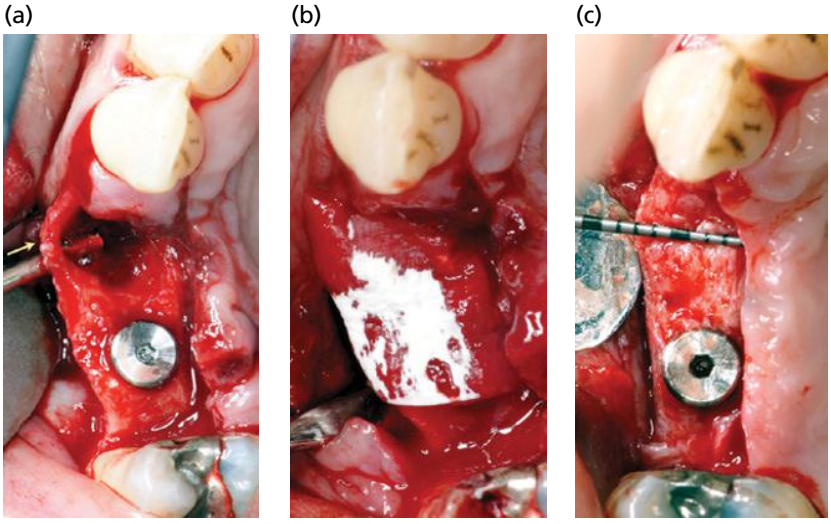

Fig. 50-4 (a, b) Socket preservation (deproteinized bovine bone mineral + non–cross-linked collagen membrane) in position 13 due to fenestration (arrow) of the buccal bone wall of the socket (class II defect, Hämmerle & Jung) and immediate implant (no graft) in position 14. (c) Re-entry surgery at 4 month. Outcome of the socket preservation procedure. Note the bone remodeling at the implant site.

Depending on the amount of available bone and the defect type, the treatment strategy may consider implant placement and a concomitant bone augmentation procedure (one-step GBR procedure) or bone augmentation and delayed implant placement once the bone volume has been augmented (two-step GBR procedure). The one-step procedure is indicated in class 1 defects when there is enough vertical bone for placing an implant with appropriate primary stability and the bone regenerative procedure is intended for horizontal bone augmentation. In class 2 and 3 defects, depending on the amount of vertical augmentation needed, the delayed approach is usually indicated (Fig. 50-4).

Bone augmentation procedures could also be considered when placing implants in fresh extraction sockets. In most of these clinical situations, the morphology of the socket does not match the implant diameter and, depending on the resulting bone defect, a different bone augmentation procedure might be indicated.

Hämmerle and Jung (2008) (Fig. 50-3) have classified these defects in fresh extraction sockets as:

- *Class I*: extraction socket that has intact bone walls after tooth extraction
- *Class II*: extraction socket that has a marginal dehiscence/fenestration of the buccal bone wall after tooth extraction
- *Class III*: extraction socket that has a large dehiscence of the buccal bone wall after tooth extraction.

A one-step GBR procedure is usually indicated for class I and II defects, while in large class III defects the delayed approach might be indicated.

When placing implants in extraction sockets, timing of the bone augmentation procedure is also very important since, depending on the time elapsed from tooth extraction, different soft tissue conditions may be encountered. For details regarding the different implant treatment strategies in extraction sockets, see Chapter 49.

Bone augmentation therapies

In the mid-1980s, the GTR principle was applied in periodontal regeneration, based on the early studies of Melcher (1976), who developed the concept of using barrier membranes to "guide" the biologic process of wound healing. These early experimental studies demonstrated that the exclusion of soft tissue invasion of the defect by means of a barrier membrane, allowed the cells with regenerative potential to migrate to the site (derived from the periodontal ligament or bone marrow) and promoted periodontal regeneration (Nyman *et al*. 1982). Based on the same biologic principle, the GBR treatment concept was mechanical exclusion of the soft tissues from filling the osseous defect, thus allowing the cells with osteogenic cells to colonize the wound (Dahlin *et al*. 1988). The key prognostic factor in GBR was enough space under the barrier membrane to allow for bone regeneration of the crestal defect. Depending on the morphology of the defect, this space could be maintained with either a particulated graft or a block graft. Different biomaterials, natural and/or synthetic, have been developed, investigated, and used as grafts for bone augmentation procedures.

The following sections describe the biologic principles of GBR using different preclinical models and also the biomaterials that have been most frequently investigated and used as graft materials.

Biologic principles of guided bone regeneration

Seibert and Nyman (1990) demonstrated successful reconstruction of surgically-created, buccolingual defects in the edentulous ridge of dogs after 90 days of healing, with newly formed bone filling the space created beneath e-PTFE (Gore-Tex®) non-resorbable barrier membranes. Furthermore, Smukler *et al*. (1995) reported that the application of barrier membranes in class III ridge defects led to a mean vertical augmentation of 3.31 mm (Buser *et al.* 1995), and demonstrated that this regenerated bone could successfully integrate dental implants when these were placed 6 months after the GBR procedure.

The sequence and pattern of bone regeneration in GBR procedures has been investigated in experimental studies. Schenk *et al.* (1994) investigated surgically-created, membrane-protected defects in the edentulous ridge in dogs. The histologic analysis showed a sequence of events starting with the organization of a blood clot that filled the protected space beneath the membrane. A connective tissue matrix rich in new vascular structures replaced this blood clot and later, deposition of woven bone started from the surrounding bony walls and concentrically filled the defect. This woven bone was later replaced by parallel-fibered lamellar bone, resulting in a new cortical structure at the periphery of the defects. This pattern of intramembranous bone growth shown in GBR was described also in the healing of an alveolar socket after tooth extraction (Cardaropoli *et al*. 2003).

Dahlin *et al.* (1989) were the first to provide evidence to support the effectiveness of GBR around implants. e-PTFE membranes were applied around exposed implant threads inserted in rabbit tibiae and peri-implant bone formation was observed provided enough space was secured under the membrane. Becker *et al*. (1990) also assessed the potential of GBR in treating exposed threads of implants placed in dog mandibles. They reported a mean increase of 1.37 mm in bone height for the GBR-treated test sites, versus 0.23 mm for the sham-operated controls.

Vertical bone augmentation using this principle was also demonstrated by Jovanovic *et al*. (1995) who reported regeneration of the mandibular process when applying e-PTFE membranes around supracrestally placed implants in dogs. The new bone formed supracrestally amounted to 1.82 mm (SD 1.04) and 1.9 mm (SD 0.3) when using titanium-reinforced and standard e-PTFE membranes, respectively. GBR was also studied histologically in monkeys with e-PTFE membranes placed around dental implants inserted immediately into fresh extraction sockets (Warrer *et al*. 1991): bone regeneration was seen around the implant circumference in GBR-treated sites, compared with a lack of bone contact in non–GBR-treated control sites. Similar experimental studies in dogs also showed successful bone regeneration using e-PTFE membranes in implants immediately placed in fresh extraction sockets (Becker *et al*. 1991; Gotfredsen *et al*. 1993).

Regenerative materials

Barrier membranes

Different types of barrier membranes have been tested for GBR. These membranes must fulfil specific criteria for promoting bone regeneration of the edentulous ridge, such as biocompatibility, cell occlusion properties, integration by the host tissue, and space-making capacity. Their specific composition falls into two broad categories: non-resorbable and resorbable. e-PTFE has been the most frequently used material for *non-resorbable membranes* in both periodontal and bone regeneration clinical applications. e-PTFE membranes are flexible with an external porous structure allowing for tissue integration and an internal occlusive layer providing the barrier mechanism. They are composed of a chemically stable and biologically inert polymer that resists microbiologic and enzymatic degradation and does not elicit any immunologic reactions. To enhance the space-making capacity of these devices, a titanium scaffold is applied between the two ePTFE layers, adding stiffness and reinforcing the membrane structure. These non-degradable barrier membranes require a second surgical intervention to remove them. This disadvantage, together with the high occurrence of postoperative complications, mainly from early membrane

exposure, has limited their clinical use and has led to the development and broader use of resorbable membranes.

Bioresorbable membranes must ensure that the tissue reactions during the process of membrane resorption or biodegradation are minimal and do not affect the outcome of bone regeneration (Hardwick *et al*. 1995). Several bioresorbable materials have been tested with varying success in bone regeneration applications. Bioresorbable membranes are either natural (xenogeneic collagen type I or III) or made of synthetic polymers, including polyurethane, polyglactin 910, polylactic acid, polyglycolic acid, polyorthoester, polyethylene glycol, and different combinations of polylactic and polyglycolic acid (Sandberg *et al*. 1993; Zellin *et al*. 1995; Brunel *et al*. 1998; Jung *et al*. 2006). When inserted into an aqueous environment, such as a biologic system, the biodegradable polymers undergo enzymatic degradation by hydrolysis. The natural collagen membranes undergo resorption by enzymatic degradation. This membrane degradation process depends on many factors, such as membrane composition, pH, temperature, degree of polymer crystallization, cross-linking in collagen membranes, and membrane volume (Warrer *et al.* 1992; Hämmerle & Jung 2003). The duration of the barrier function is, therefore, variable and the resorption process may interfere with the wound healing and bone regenerative outcome.

Several experimental studies have compared the potential of these barrier membranes for promoting bone regeneration. When non-resorbable e-PTFE membranes were compared with synthetic bioresorbable membranes made of poly D,L-lactide-co-trimethylencarbonate, significantly more bone was formed around implants covered with e-PTFE membranes, although both test and control implants exhibited new direct bone-to-implant contact (Hurzeler *et al.* 1997). These differences are mainly due to the lack of stiffness and space-making capacity of bioresorbable membranes, which when placed directly over the implant threads, tend to collapse and occlude the space available for bone regeneration. This problem is usually overcome by using a scaffold or graft material under the membrane that provides the space for tissue in-growth and subsequent bone formation. Experimental studies comparing non-resorbable and collagen resorbable membranes, with and without the use of a scaffold, have shown similar bone regenerative outcomes for the non-resorbable membranes and the collagen resorbable membranes used with a scaffold (Hurzeler *et al*. 1998).

For collagen membranes, the biodegradation and concomitant tissue integration depends on the degree of collagen cross-linking. A comparative study evaluated different collagen membranes: (1) BioGide (BG) (non–cross-linked porcine type I and III collagens, bilayered) (Geistlich Biomaterials, Wolhusen, Switzerland); (2) BioMend (BM) (glutaraldehyde cross-linked bovine type I collagen) Sulzer Medica, Colla-Tec Inc., Plainsboro, NJ, USA); (3) BioMendExtend (BME) (glutaraldehyde cross-linked bovine type I collagen) (Sulzer Medica); (4) Ossix (OS) (enzymatic cross-linked bovine type I collagen) (3i, Colbar R&D Ltd, Ramat Hush-aron, Israel); (5) TutoDents (TD) (non–cross-linked bovine type I collagen, bilayered) (Tutogen, Carlsbad, CA, USA); (6) VN(1); (7) VN(2); and (8) VN(3) (1, 3, 4 × chemical cross-linked porcine type I and III collagens, bilayered, respectively) (Geistlich Biomaterials) (Rothamel *et al*. 2004). The non–cross-linked porcine-derived collagen types I and III exhibited good tissue integration (without observable foreign body reactions), rapid neoangiogenesis, and almost complete biodegradation 4 weeks after implantation. The vascularization and biodegradation of chemical and enzymatically cross-linked collagen membranes, however, were slower and the resorption rate was directly related to the degree of cross-linking.

The choice of membrane material usually depends on the amount of bone regeneration needed, mainly in the vertical dimension. e-PTFE barrier membranes have demonstrated more favorable results when compared with resorbable devices, mainly due to their better space-making capacity, longer barrier function, and lack of a resorption process that may negatively affect bone formation (Hämmerle & Jung 2003). Nevertheless, a high rate of soft tissue dehiscence was observed with the use of ePTFE membranes. When this complication occurs, early contamination of the exposed membrane usually jeopardizes the regenerative outcome. A meta-analysis evaluating the influence of membrane exposure on the outcomes of regenerative procedures reported that new bone formation was six-fold greater when no soft tissue dehiscence occurred (Machtei 2001).

As already mentioned, these frequent complications and the need for a second surgery to remove the membrane with non-resorbable membranes make resorbable membranes the current gold standard, provided they are used with an adequate space-making graft material. The choice of non–cross-linked resorbable collagen membranes should be based on their advantages in terms of earlier neoangiogenesis, lack of inflammatory response, and fast biodegradation/integration within the host tissue.

Bone grafts and bone substitutes

Bone grafts

Autogenous bone grafts (autografts) have historically been the gold standard in bone regeneration therapies since they have well-documented osteoconductive, osteoinductive, and osteogenic properties (Yukna 1993). In alveolar bone augmentation surgeries, autogenous bone is used either as a particulate or a block graft. Particulate bone grafts are normally harvested from intraoral sites and used in combination with barrier membranes following the principles of

GBR. These bone chips have the disadvantages that their availability is limited within the oral cavity and, as they lack a rigid and supportive structure, they do not provide the space-making capacity necessary for the treatment of class II and III defects. In these cases, rigid titanium-reinforced ePTFE barrier membranes or other space maintenance strategies, such as tenting screws or microimplants, have been used in conjunction with particulate bone autografts. Another drawback with the use of autografts is their fast resorption rate, which requires early implant placement to assure functional loading to the regenerated bone, thus preventing its resorption.

Monocortical block autografts may be harvested from intra- or extra-oral sites. Common intraoral donor sites are the mandibular chin or the ascending ramus area, whereas common extraoral donor sites are the iliac crest or the calota. They may be used in combination with barrier membranes or alone, and they require fixation to the recipient crestal site with mini-screws to avoid micro-movements during healing. These grafts, due to their excellent space maintenance capacity, are indicated in large crestal defects in which there is a need for vertical bone augmentation. Their main disadvantage is the morbidity associated with their harvesting, mainly from the chin area. As with particulate autografts, their resorption rate is high, although when combined with a barrier membrane or with bone particulate xenografts, resorption is slowed.

Bone substitutes

In order to avoid the morbidity associated with the harvesting of autogenous bone grafts, allografts, xenografts, and alloplasts have been indicated and tested.

Allografts are bone grafts harvested from cadaver donors and processed by freezing or demineralization and freezing. These grafts are then sterilized and supplied by specially licensed tissue banks as bone particles or large blocks. Demineralized freeze-dried bone allografts (DFDBAs) have shown osteoconductive as well as osteoinductive properties due to the release of bone morphogenetic proteins (BMPs) during the demineralization process. There is some concern, however, regarding their absolute non-infectivity, although there have been no reported cases of disease transmission from DFDBAs used for dental purposes among over 1 million cases over 25 years (Yukna 1993). These allografts are usually used in combination with barrier membranes following the principles of GBR.

Xenografts are graft biomaterials of animal origin, mainly bovine and equine. These graft materials are deproteinized in order to completely remove the organic component and thus avoid any immunogenic reaction. This chemical or low heat process preserves the original bone architecture and the inorganic mineral composition, which assures the osteoconductive properties of the biomaterial. Inorganic bovine bone grafts are usually particulate and utilized according to the principles of GBR in combination with resorbable collagen membranes. Different preclinical and clinical studies have demonstrated their safety and efficacy as bone substitutes for both periodontal and peri-implant augmentation procedures (Baldini *et al*. 2011). Recently, highly purified porcine collagen type I has been added to xenografts to enhance their clinical handling by improving the cohesion between the mineral granules.

Alloplasts are synthetic bone substitutes that include different combinations of calcium phosphates fabricated under different sintering conditions, which yields different physical properties and resorption rates. The combination of hydroxyapatite and beta-tricalcium phosphate (β-TCP) provides a scaffolding function (hydroxyapatite) as well as osteoconductive properties (β-TCP). These biomaterials are usually resorbable and delivered as granules. They should be always used in combination with barrier membranes.

Choice of material

This choice should be based on the clinical indication. For small bone defects requiring mainly horizontal bone augmentation, the use of xenografts and alloplasts has demonstrated excellent results. When the objective is to preserve the socket walls after tooth extraction, experimental studies have evaluated the histologic healing when the sockets are filled with different graft materials. The use of autogenous bone chips alone does not counteract the physiologic process of bone remodeling that occurs at the socket bone walls after tooth extraction (Araújo & Lindhe 2011). Indeed, the healing process at these sites filled with autografts showed characteristics similar to those of the sockets without any filling. In contrast, the use of xenografts with a much slower resorption rate demonstrated significantly better preservation of the socket walls than the non-grafted sites. Histologically, these xenograft granules were integrated and fully surrounded by newly formed bone (Araújo & Lindhe 2009). In a similar experimental model, a β-TCP alloplast demonstrated limited bone promotion properties, with the graft particles being encapsulated with connective tissue (Araújo *et al.* 2010).

In crestal defects requiring horizontal augmentation, particulate bone grafts should be utilized in combination with barrier membranes. Experimental studies testing different graft materials [biphasic hydroxyapatite + β-TCP (BCG)] or collagen-coated deproteinized bovine bone mineral (DBBM) (BOC) showed that both biomaterials increased bone fill and the percentage of osseointegrated bone–graft particles, and it was concluded that both BCG and BOC provide an osteoconductive scaffold to support GBR procedures at dehiscence-type defects (Schwarz *et al.* 2007).

In large crestal defects for which the aim is both horizontal and vertical bone augmentation, the use of

monocortical autogenous corticocancellous block grafts is recommended. In experimental studies comparing the use of these block grafts with and without a barrier membrane, a significant buccocrestal resorption and limited bone augmentation were demonstrated in the non–membrane-protected group, thus demonstrating the clear indication for always protecting the block graft with a resorbable barrier device (von Arx *et al.* 2001).

Evidence-based results for ridge augmentation procedures

These procedures have been used in five main clinical applications: ridge preservation, bone regeneration in fresh extraction sockets, horizontal bone augmentation, ridge splitting/expansion, and vertical ridge augmentation.

Ridge preservation

Important structural changes of the edentulous ridge take place after tooth extraction and eventually lead to dimensional changes of the alveolar crest. A recent systematic review assessed the hard and soft tissue changes occurring 6 months after tooth extraction in humans and demonstrated a horizontal bone loss of 29–63% and vertical bone loss of 11–22% from the dimensions of the alveolar bone crest at the time of extraction (Tan *et al*. 2012). With the goal of preventing these physiologic hard and soft tissue changes, different bone augmentation techniques have been proposed to preserve the alveolar architecture after tooth extraction. In general, these ridge preservation techniques have been defined as: "Any therapeutic approach carried out immediately after tooth extraction aimed to preserve the alveolar socket architecture and to provide the maximum bone availability for implant placement" (Vignoletti *et al*. 2012).

These ridge preservation approaches have utilized GBR principles using the following regenerative technologies:

- Resorbable and non-resorbable barrier membranes alone
- Resorbable barrier membranes in combination with bone substitutes
- Bone substitutes alone
- Bone substitutes in combination with soft tissue grafts.

Furthermore, different surgical techniques have been proposed, such as flap/flapless approaches allowing for primary/secondary healing.

Results from a systematic review evaluating the efficacy of these socket preservation therapies concluded that these techniques may reduce the bone dimensional changes that occur after tooth extraction, although some degree of vertical and horizontal bone loss can still be expected (Ten Heggeler *et al.* 2011). These results are consistent with those from another recent systematic review that compared the outcomes of socket preservation therapies with the spontaneous healing of the post-extraction socket (Vignoletti *et al.* 2012). A statistically significant greater reduction in bone height and width for the control groups compared to the test groups treated with socket preservation therapies was demonstrated: weighted mean differences between test and control groups were 1.47 mm and 1.84 mm, respectively. Furthermore, in an attempt to assess the influence of the different factors that may influence this outcome, a subgroup analysis with meta-regression was performed. The potential factors included in the meta-regression were: (1) the socket site, that is the integrity/non-integrity of the socket bone walls and presence/absence of adjacent teeth; (2) the surgical protocol, that is flapped/flapless surgery or primary flap closure/secondary intention healing; and (3) the biomaterial used, that is membrane/no membrane or type of graft material. The conclusions from the subgroup analysis were:

- Use of membranes gave better results than for use of grafts alone in terms of horizontal bone changes.
- A slight tendency towards less bone loss in the horizontal direction was observed when the sockets healed by primary intention.
- Flapped surgical procedures demonstrated significantly less horizontal bone resorption of the socket, when compared to flapless surgeries.

Based on this evidence, it is not possible to indicate which type of surgical procedure or biomaterial is most suitable for socket preservation, but the use of barrier membranes and a flapped surgical procedure should be suggested.

Bone regeneration in fresh extraction sockets

According to the classification proposed at the Third ITI Consensus Conference (Hämmerle *et al*. 2004), immediate and early implant placement (type 1 and 2) protocols have been indicated as the most suitable for implant placement following tooth extraction. The type 1 protocol (immediate implant placement) was first presented in 1976 by Schulte and Heimke (1976). The several advantages inherent to placing the implant immediately after tooth extraction have led to a growth in popularity of this protocol in the last decade and this has attracted the interest of clinicians and investigators (Fig. 50-5).

Based on preclinical and human studies, it is well accepted that implant placement into a fresh extraction socket does not counteract the physiologic bone remodeling in the alveolar bone crest. Results from human trials have demonstrated that both vertical and horizontal dimensional changes of the alveolar

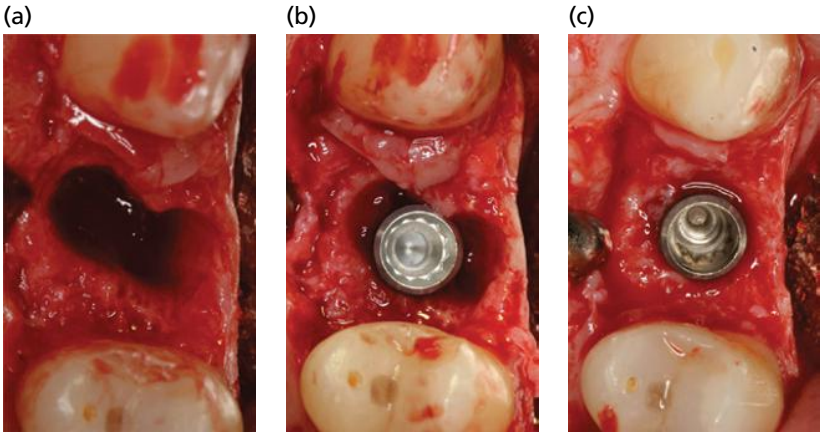

Fig. 50-5 (a) Class I defect (Hämmerle & Jung). Extraction of tooth 14. (b) Immediate implant placement and (c) re-entry procedure after 4 months of healing. Note the overall contraction of the maxillary ridge.

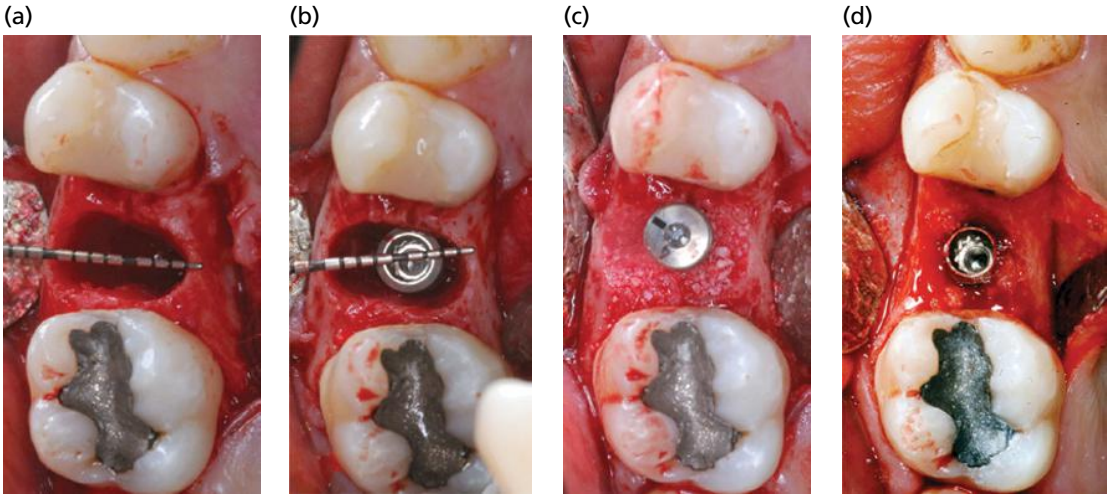

Fig. 50-6 (a) Class I defect (Hämmerle & Jung). Extraction of tooth 15. (b, c) Immediate implant placement with deproteinized bovine bone and porcine collagen fibers. (d) Re-entry surgery at 4 months. Outcome of the grafting procedure.

crest may be expected. Botticelli *et al*. (2004) demonstrated a horizontal resorption of approximately 56% and 30% of the original dimension of the buccal and lingual bone walls of the sockets, respectively, when placing single-tooth immediate implants in the anterior region of the maxilla. These results are consistent with data from a similar study demonstrating 36% and 14% hard tissue resorption at the buccal and palatal bone walls, respectively. Furthermore, the vertical bone resorption of the buccal bone crest was also investigated and amounted to a mean value of 1 mm (SD 2) (Sanz *et al*. 2010). These changes in the horizontal and vertical dimension were mainly influenced by the thickness of the buccal bone plate (>1 mm) and the gap that occurs between the implant surface and the buccal socket wall. Hence, implants placed into sockets with a <1-mm buccal thickness/gap are at higher risk of presenting a dehiscence defect that exposes the implant surface to the oral environment and a greater overall horizontal resorption of the alveolar crest.

This type 1 immediate implant surgical protocol combined with other treatment concepts has also been proposed:

- Immediate implant placement with a graft and/or barrier membranes and/or a soft tissue graft (Fig. 50-6)
- Immediate implant placement with immediate loading.

A recent systematic review has estimated survival and success rates of implants and the implant-supported prostheses; the prevalence of biologic, technical, and esthetic complications; and the magnitude of soft and hard tissue changes following implant placement immediately into fresh extraction sockets (Lang *et al*. 2012). On the basis of 46 included clinical trials, the 2-year survival rate of implants placed into extraction sockets was 98.4% (97.3–99%). Unfortunately, only limited long-term data were available for the occurrence of biologic complications. In terms of esthetic results, it was reported that about 20% of patients who underwent immediate implant placement suffered from suboptimal esthetic outcomes due to buccal soft tissue recession in studies with observation periods of 3 years or more. Gingival biotypes and a buccolingual position of the implants were the most relevant factors for buccal soft tissue levels.

The effect of regenerative therapies combined with type 1 immediate implant placement has been evaluated in a multicenter prospective clinical study (De Angelis *et al.* 2011). In this study, patients received a resorbable membrane alone or in conjunction with a bone substitute, and were followed up to 1 year after implant loading. The authors reported an more favorable outcome when using a membrane in conjuction with the bone substitute. However, they disclosed that single post-extractive implants might be at a higher risk for implant complications.

Although a high survival rate for type 1 immediate implants has been reported in the literature, long-term outcomes based on peri-implant health and esthetics are still not available. Based on the available evidence, important risk factors for unpredictable esthetic outcomes are the thickness of the buccal bone plate, gingival biotype, and buccolingual positioning of the implant. Although many authors advocate the use of horizontal bone augmentation techniques (GBR) in conjunction with immediate implant placement, the evidence for this additional treatment is unclear from controlled clinical trials.

To overcome some of these surgical/clinical limitations of the immediate implant protocol, the type 2 or early implant placement protocol has been advocated. This surgical protocol consists of performing the extraction and thoroughly cleaning the extraction socket, then waiting 4–6 weeks before placing the implant, which allows for soft tissue coverage and full healing of the extraction wound. The rationale for this surgical approach lies in the elimination of any infectious tissue, mostly in situations where the reason for the extraction was periapical or very deep periodontal pathology, and at the same time having enough soft tissue to allow for primary intention healing during the implant therapy through a tension-free flap closure without altering the mucogingival line. This is particularly important since, in many clinical situations, the cause of extraction is deep periodontal or periapical pathology where the availability of bone is limited and bone augmentation will be required in conjunction with the implant placement. The importance of early implant placement lies in the availability of the socket walls, since 4 weeks after extraction the socket walls will be preserved and this facilitates the placement of the implant and the required bone augmentation. Moreover, the recent evidence for a usually very thin (1 mm) maxillary buccal bone wall (Huynh-Ba *et al*. 2010; Januario *et al*. 2011) makes the requirement for bone augmentation almost the norm whenever implants are placed in critically esthetic areas in the anterior maxilla, in spite of having enough vertical bone availability. The type 2 implant placement protocol is therefore very appropriate in this indication. Not only is the bone height and width of the ridge mostly preserved, but there is also enough keratinized mucosa to allow for a successful bone augmentation procedure during the implant placement; the results of augmentation techniques depend on a tension-free primary wound closure (Buser *et al*. 2008).

The efficacy of this surgical protocol has been recently studied in a systematic review comparing it to the standard type 3 or delayed protocol (implant placement at least 3 months after tooth extraction). This reported the pooled mean difference between the type 2 versus type 3 protocols to be a 13.11% reduction of defect bone height and a 19.85% reduction of defect bone width in favor of the type 2 protocol (Sanz *et al.* 2012). In terms of esthetic outcomes, based on two studies (Schropp *et al.* 2004; Schropp & Isidor 2008), at 2-year follow-up patients were significantly more satisfied with the early placement protocol, both in terms of the appearance of the restoration and the overall experience with treatment. These differences, however, were lost at the 5-year follow-up.

Horizontal ridge augmentation

Horizontal ridge augmentation can be performed using particulate or block grafts with or without barrier membranes (Fig. 50-7). The use of particulate grafts together with barrier membranes (GBR) is especially indicated in conjunction with the placement of an implant in class I defects, when there is enough bone width to allow good implant primary stability. In severe class I defects, a delayed bone regeneration approach (staged) is indicated and a block graft is often advocated to assure enough space maintenance to allow significant horizontal augmentation. Both GBR and block grafts have been demonstrated to be a successful and predictable treatment modality to augment a horizontally deficient ridge (Fig. 50-7, 50-8). (Fiorellini & Nevins 2003; Schwartz-Arad & Levin 2005; Schwartz-Arad *et al*. 2005). According to Donos *et al*. (2008), the implant survival rate for staged GBR was 99–100%, while that for one-stage ridge augmentation was 87–95%, but this systematic review was hindered by a lack of randomized clinical controlled trials and heterogeneity of the available studies, thus restricting the number of studies included in the systematic review.

Different authors have published case series utilizing bone grafts for horizontal bone augmentation and have concluded that it is a reliable procedure. In 15 partially edentulous patients, 18 alveolar ridges were augmented with ramus or symphysis block grafts. The mean horizontal ridge augmentation was 6.5 ± 0.33 mm. At implant placement surgery, the graft had resorbed to 5.0 ± 0.23 mm, which is a reduction of 23.5%, but it was still sufficient for implant placement (Cordaro *et al*. 2002). Raghoebar *et al*. (2000) performed horizontal ridge augmentation on the edentulous mandibles of seven patients using autogenous block grafts. The bone width increased from 1.3 ± 0.3 mm to 5.6 ± 0.6 mm. Although after 3 months of healing, at implant placement, there had been a slight resorption of the bone width by 0.5 ± 0.3 mm, it was still sufficient for implant placement. In a controlled

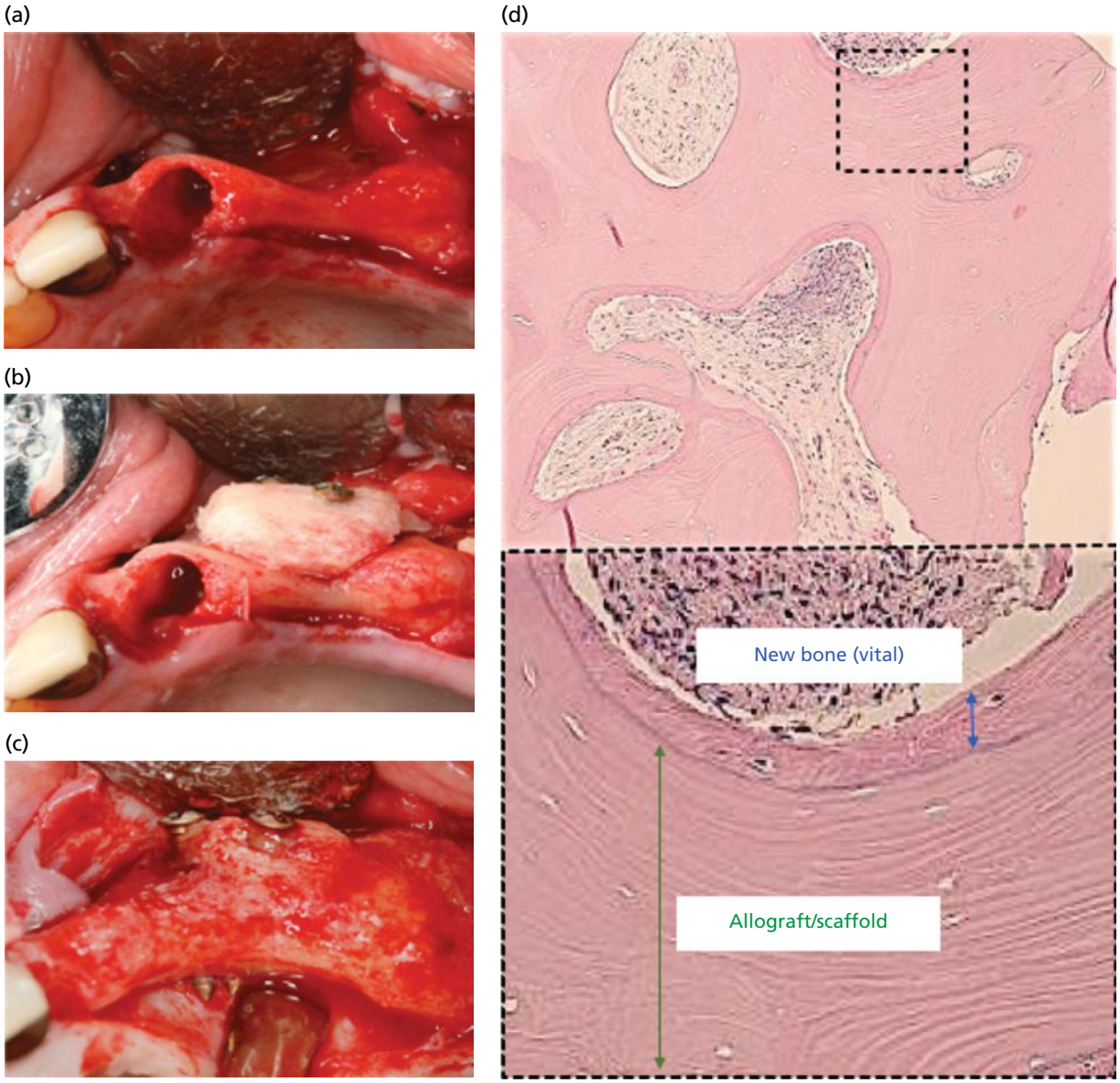

Fig. 50-7 (a, b) Use of an allograft block in the posterior maxilla. (c) Re-entry after 6 months. (d) Histologic evaluation of the regenerated bone shows significant osteoconductivity and incorporation of the allograft block particles with new/vital bone. Use of block grafts to overcome severe horizontal ridge deficiencies have proven very predictable.

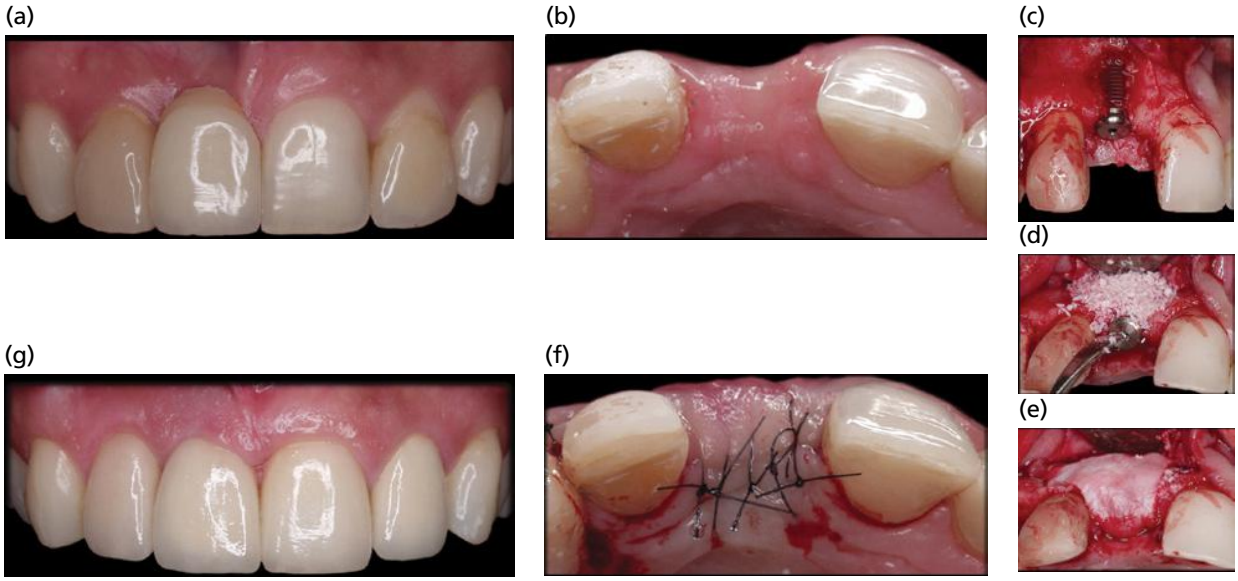

Fig. 50-8 (a, b) Class 2 defect (Seibert). (c–e) Implant placement and horizontal guided bone regeneration procedure with deproteinized bovine bone mineral + non–cross-linked collagen membrane. (g) Implant-supported prosthesis.

clinical study, 30 patients with inadequate bone width were assigned to two different groups: (1) GBR + e-PTFE + autograft and (2) autogenous onlay grafts only: 2.7 mm of horizontal bone gain was attained in the GBR group compared to 4.0 mm in the onlay graft group. The authors also found that the graft resorption was greater in the GBR group compared to the block graft group (40% vs 25%) (Chiapasco *et al*. 1999).

The use of autografts is currently somewhat limited due to the morbidity associated with their harvesting and their high resorption rate (mainly when used as bone chips). The use of bone substitutes, mainly of xenogeneic origin, together with resorbable membranes (collagen), has demonstrated good results in one-stage or delayed horizontal bone augmentation techniques with minimal patient morbidity and few postoperative complications. Moreover, these xenogeneic grafts have a very slow resorption rate, which assures their long-term stability. In a prospective case series, 12 patients with 15 implant sites receiving horizontal ridge augmentation using DBBM with or without barrier membrane were followed for 9–10 months before placement of dental implants (Hämmerle *et al*. 2008). The mean crestal bone width was significantly increased from 3.2 mm at baseline to 6.9 mm, demonstrating the effectiveness of using boned substitutes for horizontal ridge augmentation

Ridge splitting/expansion

Another technique used in the maxilla to augment bone width through bone condensation is ridge splitting or ridge expansion osteotomy. Summers (1994a, b) first used this technique, osteocondensation, to augment bone width and elevate sinus floors in an attempt to avoid the lateral window sinus lift. This technique is preferably used in the maxilla because this bone is frequently type III or IV, which is more amendable to osteocondensation compared to type I or II bone. Chisels and osteotomes are used to produce longitudinal greenstick fractures in the bone and create osteotomy sites without the need for drilling. This preserves the compromised bone volume. The bone is compressed to the lateral surfaces with the use of osteotomes of increasing diameters, thus increasing its strength and density. The advantage of this technique is that it allows for the ideal implant diameter to be placed in the restoratively driven position. In addition, the cancellous bone and marrow are exposed to grafting of the site, which improves revascularization and healing (Engelke *et al*. 1997). Summers (1994b) proposed the use of this technique if the alveolar bone is at least 3 mm wide on the basis of the assumption that this is the minimum width for cancellous bone found between the cortical plates. However, in a more recent study on cadavers, Katranji *et al*. (2007) found that the buccal plates in the edentulous maxilla and mandible had a mean cortical thickness of 1.0–2.1 mm. Therefore, it may be prudent to use this technique when the lateral ridge width is 4–5 mm as at this width there is some cancellous bone between the cortical plates. This procedure is accompanied by simultaneous implant placement.

Ridge splitting and/or expansion are frequently described together because of their common treatment outcome: increase in lateral bone width. Ridge splitting is essentially the fracture of the buccal cortical plate and its displacement laterally to accommodate implant placement. The spaces created between the cortical plates and the implants are subsequently filled with particulate bone graft materials (Scipioni *et al*. 1994; Engelke *et al*. 1997). Ridge expansion involves the creation of an osteotomy site with the initial implant drill and expansion of the site with osteotomes or the implant fixture. According to Donos *et al*. (2008), the implant survival rate ranged from 86.2% to 100%, while the success rate for the split osteotomy in achieving adequate ridge width for implant placement ranged from 87.5% to 97.8%.

Vertical ridge augmentation

In general, there is a lack of randomized controlled clinical trials evaluating the efficacy of these surgical techniques. Moreover, the available studies are very heterogeneous and with relatively small sample sizes, which limits the ability to draw valid conclusions. From the limited information available, it appears that vertical augmentation is a highly technique-sensitive procedure which may give successful treatment outcomes, like adequate gain in vertical bone height and successful implant placement (Fig. 50-9).

A recent systematic review evaluated clinical outcomes of vertical bone augmentation to enable dental implant placement (Rocchietta *et al.* 2008). The review evaluated clinical, histologic, and long-term outcomes of implants placed in vertically regenerated bone and identified three main groups of vertical bone augmentation techniques: (1) GBR (seven studies), (2) onlay bone-block grafting (five studies), and (3) distraction osteogenesis (13 studies). The lack of clinical trials, the heterogeneity of the studies, and the small sample sizes limited the ability to perform any meta-analysis, although the authors reported that there was clinical and histologic evidence corroborating that vertical ridge augmentation may be achieved successfully. Nevertheless, a broad range of technique-related complications were highlighted. For GBR, the reported complication rates were 0–45.5% and complications were mainly related to membrane exposure. For distraction osteogenesis, complication rates were higher (10–75.7%), and complications included fractures or infection of the distractor, neurologic alterations, fractures of the distracted or basal bone, and lingual or palatal inclination of the distracted bone. Minor complications were reported after onlay block bone grafting and these were related to the morbidity from harvesting the block and graft shrinkage. These results are consistent with data

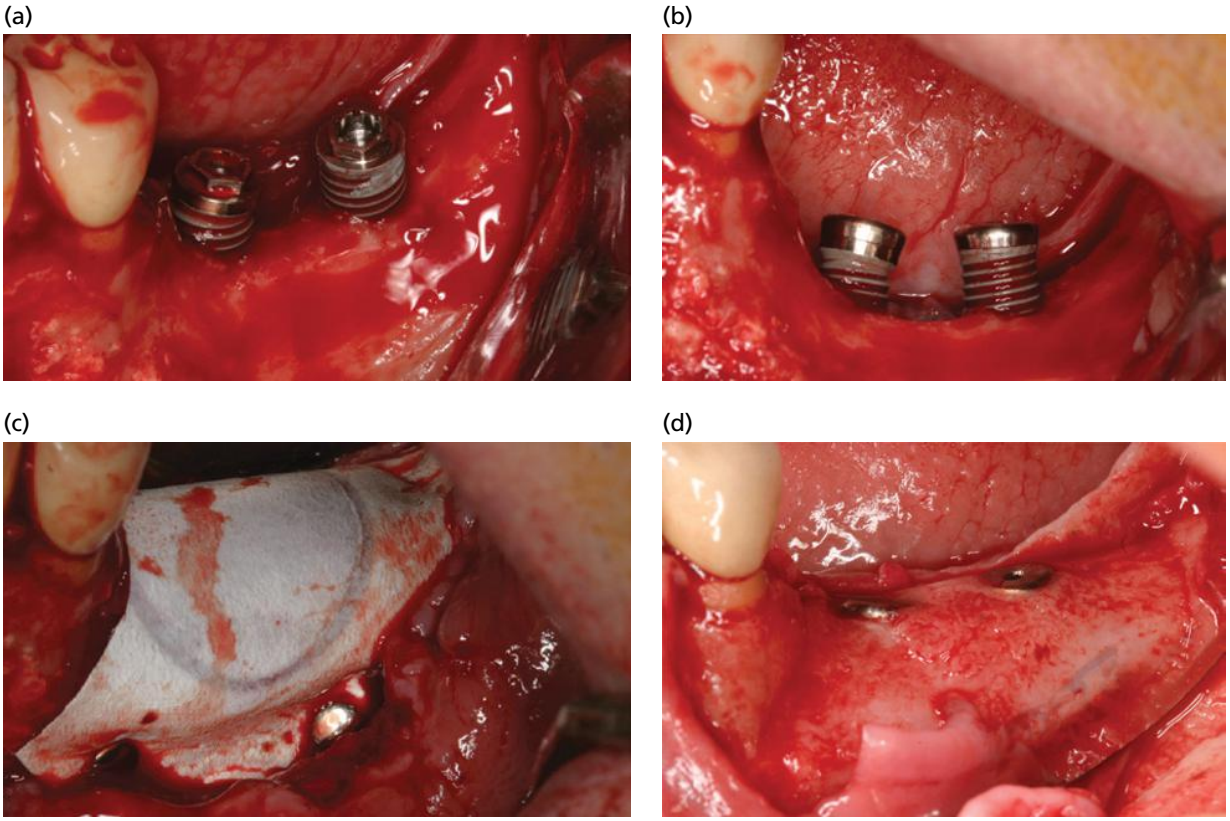

Fig. 50-9 (a–c) Class 3 defect (Seibert). Implant placement and vertical guided bone regeneration with an ePTFE membrane and autologous bone. (d) Re-entry surgery at 12 months. (Courtesy of S. Morante.)

from an earlier systematic review that evaluated the outcomes of horizontal and vertical augmentation procedures (Esposito *et al*. 2009). From this review it was concluded that no specific technique was superior and the complexity of these techniques and the high frequency of complications was highlighted.

There are several published case series demonstrating the possibility of attaining a significant vertical bone augmentation, but also highlighting the technical difficulties and the high number of postoperative complications of this technique. In a small clinical study, six partially edentulous patients were recruited and 14 implants were placed leaving the coronal third exposed circumferentially. Autogenous bone grafts covered with titanium-reinforced e-PFTE membranes were used to cover the implants and the flaps were raised to allow for a submerged healing. An average of 4.95 mm of bone height was gained after 12 months in areas where the membranes were not exposed (Tinti *et al*. 1996). In a similar study, Simion *et al*. (1994) placed implants protruding 4–7 mm above the bone crest in five patients. e-PTFE membranes were used to cover the exposed implant threads. At 9 months, the histologic assessment showed bone formation up to 3–4 mm above the previous bone crest and the implant fixture was osseointegrated with the new bone. In a multicenter long-term study, Simion *et al*. (2001) evaluated the survival rate of implants placed at the time of the vertical ridge augmentation. The 123 implants with 2–7 mm of exposed implant thread were assigned to three groups: titanium-reinforced e-PTFE, allograft, and autograft. The overall implant success rate was 97.5% in the group with e-PTFE membranes, and this was the group demonstrating the least amount of bone loss.

Distraction osteogenesis was initially used in orthopedics, and more recently adapted to augment deficient edentulous ridges. The technique involves three stages: (1) latency, (2) distraction, and (3) consolidation (Cano *et al*. 2006) (Fig. 50-10). In the latency phase, once the osteotomy has been performed, undisturbed healing takes place over 1 week. This is followed by the activation of the distractor, which is placed into the prepared site during surgery, with a daily controlled force that aims to separate the bone segments at a rate of 0.5–1 mm/day. Distraction is usually performed over a period of 30 days and significant bone gain can be attained (4–7 mm) (Gaggl *et al*. 2000). In the consolidation phase, a callus forms in the space between the bone segments and subsequently remodels into mature bone. This technique has the advantage of not requiring a donor site and the significant bone gain obtained can be in the vertical, horizontal, or both directions. However, distraction osteogenesis has frequent complications, sometimes of a severe nature, such as fracture of the mandible or the moveable segment. Increased patient discomfort during the activation of the device and the incorrect direction of the distractor leading to excessive bone on the lingual side are also frequent complications; the latter leads to inadequate bone formation (Saulacic *et al*. 2009).

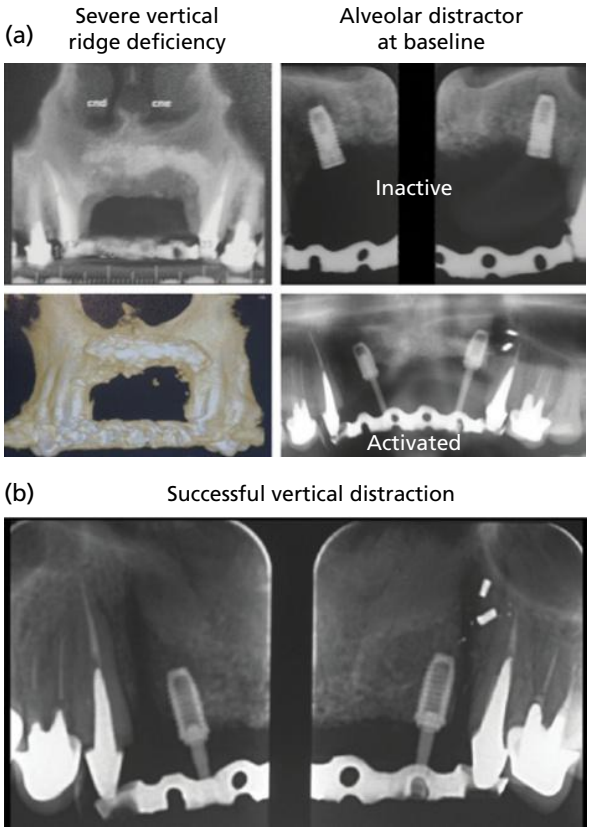

Fig. 50-10 Distraction osteogenesis. Stabilization of the ridge using a unidirectional vector distractor and successful vertical ridge compensation in the anterior maxilla. (Courtesy of T. Valcanaia.)

Taking into consideration the difficulties in performing these techniques, the frequent complications, and the heterogeneity and lack of quality of the available scientific evidence, their use should not be generalized, but rather limited to very experienced operators.

Emerging technologies

Growth factors

Wound healing approaches using growth factors to increase bone volume have significantly advanced the field of periodontal regenerative medicine. A major focus of periodontal research has been the impact of tissue growth factor on bone and tissue regeneration (Giannobile 1996; Anusaksathien & Giannobile 2002; Nakashima & Reddi 2003; Raja *et al*. 2009). Advances in molecular cloning have made available unlimited quantities of recombinant growth factors for applications in tissue engineering. Recombinant growth factors known to promote skin and bone wound healing, such as PDGF (Rutherford *et al*. 1992; Giannobile *et al*. 1994; Camelo *et al*. 2003; Ojima *et al*. 2003; Nevins *et al*. 2005; Judith *et al*. 2010), insulin-like growth factors (IGFs) (Lynch *et al*. 1991; Giannobile *et al*. 1994; 1996; Howell *et al*. 1997), fibroblast growth factors (FGFs) (Terranova *et al*. 1989; Sigurdsson *et al*. 1995; Giannobile *et al*. 1998; Takayama *et al*. 2001; Murakami *et al*. 2003), and BMPs (Gao *et al*. 1995; Wikesjo *et al*. 2004; Huang *et al*. 2005), have been used in preclinical and clinical trials for the treatment of large ridge and alveolar deficiencies (Jung *et al*. 2003; Fiorellini *et al*. 2005; Nevins *et al*. 2005). Currently, two recombinant proteins are clinically used to enhance and promote edentulous ridge regeneration, BMP-2 and PDGF-BB.

Biologic effects of PDGF

PDGF is a member of a multifunctional polypeptide family that binds to two cell membrane tyrosine kinase receptors (PDGF-Rα and PDGF-Rβ) and subsequently exerts its biologic effects on cell proliferation, migration, extracellular matrix synthesis, and antiapoptosis (Kaplan *et al*. 1979; Seppa *et al*. 1982; Heldin *et al*. 1989; Rosenkranz & Kazlauskas 1999). PDGF-α and -β receptors are expressed in regenerating periodontal soft and hard tissues (Parkar *et al*. 2001). In addition, PDGF initiates cell chemotaxis (Nishimura & Terranova 1996), mitogenesis (Oates *et al*. 1993), matrix synthesis (Haase *et al*. 1998), and attachment (Zaman *et al*. 1999). More importantly, *in vivo* application of PDGF alone or in combination with (IGF-1 enhances mineralized tissue repair (Lynch *et al*. 1989, 1991; Rutherford *et al*. 1992; Giannobile *et al*. 1994, 1996). PDGF has been shown to have a significant regenerative impact on periodontal ligament cells as well as on osteoblasts (Matsuda *et al*. 1992; Oates *et al*. 1993; Marcopoulou *et al*. 2003; Ojima *et al*. 2003).

Biologic effects of BMPs

BMPs are multifunctional polypeptides belonging to the TGF-β superfamily of proteins (Wozney *et al*. 1988). The human genome encodes at least 20 BMPs (Reddi 1998). BMPs bind to type I and II receptors that function as serine–threonine kinases. The type I receptor protein kinase phosphorylates intracellular signaling substrates called Smads (*Sma* gene in *Caenorhabditis elegans* and *Mad* gene in *Drosophila*). The phosphorylated BMP-signaling Smads enter the nucleus and initiate the production of other bone-related matrix proteins, leading to bone morphogenesis. The most remarkable feature of BMPs is their ability to induce ectopic bone formation (Urist 1965). BMPs are not only powerful regulators of cartilage and bone formation during embryonic development and regeneration in postnatal life, but also participate in the development and repair of other organs such as the brain, kidney, and nerves (Reddi 2001).

Studies have demonstrated the expression of BMPs during tooth development and periodontal repair, including alveolar bone (Aberg *et al*. 1997; Amar *et al*. 1997). Investigations in animal models have shown the potential repair of alveolar bony defects using rhBMP-12 (Wikesjo *et al*. 2004) or rhBMP-2 (Lutolf *et al*. 2003; Wikesjo *et al*. 2003). In a clinical trial, rhBMP-2 delivered by a bioresorbable collagen sponge revealed significant bone formation in a human buccal wall defect model following tooth

extraction when compared to the collagen sponge alone (Fiorellini *et al*. 2005). Furthermore, BMP-7, also known as osteogenic protein-1, stimulates bone regeneration around teeth and endosseous dental implants, and in maxillary sinus floor augmentation procedures (Rutherford *et al*. 1992; Giannobile *et al*. 1998; van den Bergh *et al*. 2000).

Cell therapy

The cell is central to new tissue growth and differentiation. In cell-based regenerative medicine, cells are delivered to a defective site with the goal of improving the regeneration process (Mao *et al*. 2006). Cell delivery approaches are used to accelerate edentulous ridge regeneration through two primary mechanisms: (1) use of cells as carriers to deliver growth or cellular signals; and (2) provision of cells which are able to differentiate into multiple cell types to promote regeneration. The use of cells as vehicles to deliver growth factors can stimulate an endogenous regeneration process (Discher *et al.* 2009). This strategy has been intensively investigated in both soft and hard periodontal tissue regeneration. Stem cell research has soared in the past few years and the effects of these cells on healing and regenerative potential have been extensively studied.

Mesenchymal stem cells (MSCs) are self-renewable and can differentiate into a variety of cell types that form mesenchymal and connective tissues (Pittenger *et al.* 1999; Mao *et al*. 2006). Bone marrow stromal cells are the most widely investigated MSCs because they are easily accessible. These cells were initially isolated and described over 50 years ago based on their ability to adhere to plastic substrates of cell culture plates (Becker *et al*. 1963). Since then, this simple protocol has been widely used to isolate MSCs from many tissues, such as adipose tissue, muscle, liver, pancreas, and cartilage (Ward *et al*. 2010). MSCs have a tremendous potential in regenerative medicine owing to their multipotency and capability to form a variety of tissues. Regarding periodontal tissue engineering, both extraoral and intraoral stem cells can be harvested and then subjected to enrichment and expansion techniques. Within this context, multiple sources of stem cells have been evaluated for the treatment and regeneration of the edentulous ridge (Huang *et al*. 2009). There is strong potential for the use of MSC sources from outside the oral cavity for transplantation to the oral and craniofacial complex (Noth *et al.* 2010; Ward *et al*. 2010).

Bone marrow stromal cells have also been shown to promote bone healing and dental implant osseointegration (Bueno & Glowacki 2009). In a series of studies, Yamada *et al*. (2004) used a combination of platelet-rich plasma as an autologous scaffold with *in vitro*-expanded bone marrow stromal cells to increase osteogenesis in dental implant surgery. This "autogenous injectable bone treatment" resulted in higher marginal bone levels, better bone–implant contact, and increased bone density compared to controls. Recently, cells harvested from the bone marrow were driven down MSC pathways via a single-pass perfusion process to promote bone regeneration in tooth extraction socket and sinus floor augmentation procedures (Kaigler *et al*. 2010).

Just as periodontal ligament is essential for osteogenesis and cementogenesis during development and remodeling, cells derived from this tissue are necessary for the appropriate healing response to injury (Shimono *et al*. 2003). Transplantation of periodontal ligament cells has shown the potential to regenerate alveolar bone *in vivo* (Nakahara *et al.* 2004).

Besides stem cell delivery, other cell-based therapy strategies have been developed based on the concept that transplanted cells will promote regeneration by secreting growth factors via autocrine and paracrine pathways. Allogenic foreskin fibroblasts have been shown to be safe and able to promote keratinized gingiva formation at gingival recession defects (Nevins *et al*. 2005). A tissue-engineered living cellular construct composed of viable neonatal keratinocytes and fibroblasts was reported to achieve a comparable clinical outcome to that with a gingival graft (McGuire *et al*. 2008), with strong potential to promote tissue neogenesis through the stimulation of angiogenic signals (Morelli *et al*. 2011).

These investigations support the use of this approach to deliver important cues to drive the regenerative process, and illustrate the significant potential of cell-based therapy to form a variety of periodontal tissues.

Scaffolding matrices to deliver cells and genes

Scaffolding matrices are used in tissue engineering to provide an environment where space is created and maintained over a period of time for cellular growth and tissue in-growth. These matrices serve as 3D template structures to physically support and facilitate periodontal tissue regeneration when combined with cell- or gene-based tissue engineering. Over the past two decades, scaffolds have been extensively developed, studied, and utilized. Several fundamental requirements of scaffold design have been proposed (Murphy & Mooney 1999). When applied to tissue engineering, scaffolds should (1) provide a 3D architecture that supports a desired volume, shape, and mechanical strength; (2) have a high porosity and surface-to-volume ratio with a well-interconnected open-pore structure to promote high seeding density and embrace bioactive molecules; (3) be biocompatible; and (4) degrade at a controlled rate and pattern that allows sufficient support until tissue defects are fully resolved.

Transplantation of cells can be carried out via tissue-engineered scaffolds (Murphy & Mooney 1999) that provide adhesion and anchorage for interacting stem cells in order to control the presentation of adhesion sites, thereby improving cell survival and participation (Alsberg *et al*. 2003; Davis *et al*. 2005). Through similar cell therapy approaches, extensive reconstructions are becoming more predictable, as demonstrated by the

regeneration of a mandible formed in a patient by using a metal and polymer scaffold seeded with stem cells and BMPs (Warnke *et al*. 2004).

Bioactive molecules, such as growth factors, may also be encapsulated into nano-/micro-particles that are embedded in matrices to aid their sustained release, thereby enhancing stimuli for tissue formation. Other approaches using scaffolds include mimicking stem cell niches to regulate daughter cell proliferation, differentiation, and dispersion into surrounding tissue or attracting useful cells to a desired anatomic site (Discher *et al*. 2009).

Scaffold fabrication technologies as applied to periodontal tissue engineering include conventional prefabricated scaffolds, such as particulated, solid form; injectable scaffolds that are adapted or administered into a periodontal defect; and novel image-based designs that result in a 3D printed scaffold that is customized to fit into a defect .

Prefabricated scaffolding matrices

Conventional scaffolds used to regenerate tissue *in vivo* are prefabricated, and many techniques have been described that produce both natural and synthetic polymeric scaffolds. Naturally-derived scaffolds include autografts, allografts, and xenografts. Alloplasts and other polymers are synthetically engineered materials consisting of bioactive molecules that serve a function similar to that of natural scaffolds.

Naturally-derived scaffolds

There are many naturally-derived scaffolds used for tissue engineering applications. Freeze-dried bone allograft (FDBA) is a mineralized bone graft that has been suggested to promote osteoinductive and osteoconductive bone regeneration, although reports of its regenerative effectiveness have been mixed (Altiere *et al*. 1979; Dragoo & Kaldahl 1983; Goldberg & Stevenson 1987). Variability in preparations of the allograft, and its regenerative potential and osteoinductive ability are seen between different bone banks (Shigeyama *et al*. 1995; Schwartz *et al*. 1996). Nonetheless, FDBA appears to be a practical material for regeneration of periodontal attachment apparatus. Xenogenic grafts show physical and chemical similarities to human bone matrix, and they have been successful in various periodontal and implant-related bone repair cell delivery applications (Nevins *et al*. 2006). DBBM has osteoconductive properties (Hämmerle *et al*. 1998).

Synthetic biomimetic polymer scaffolds

Synthetic polymers have been studied extensively as gene therapy delivery systems since it is easier to modify their properties, such as by controlling their macrostructure and degradation time, compared to naturally derived scaffolds (Jang *et al*. 2004). Furthermore, the release mechanism and exposure duration of bioactive molecules, such as growth factors, can be controlled (Ramseier *et al*. 2006). By acting as a localized gene depot, synthetic polymer scaffolds have the ability to maintain the therapeutic level of encoded proteins, which limits unwanted immune responses and potential side effects (Ghali *et al*. 2008).

Polymers such as poly(lactic-co-glycolic acid) (PLGA) have drawn much attention for their excellent properties for encapsulation of genes (Mundargi *et al*. 2008). PLGA microspheres have been used to deliver antibiotics, as an occlusive membrane for GTR, as a growth factor carrier for periodontal regeneration, and for cementum and complex tooth structure engineering (Williams *et al*. 2001; Kurtis *et al*. 2002; Young *et al*. 2002; Jin *et al*. 2003; Cetiner *et al*. 2004; Moioli *et al*. 2006). However, while microsphere systems have demonstrated promising results, new microtechnology approaches today are focusing on nano-sized particles (Agarwal & Mallapragada 2008). Nanotechnology has been attracting much attention for therapeutic agent and gene delivery, and a number of studies and reviews have delineated its contribution and capability to meet challenges of current regeneration therapy (Agarwal & Mallapragada 2008; Mundargi *et al*. 2008; Sanvicens & Marco 2008).

The nanoscaled fibrillar structure of collagen shows promising effects on cellular biologic activities, and suggests potential as a synthetic polymer scaffold that mimics the nanofibrous structure of collagen (Woo *et al*. 2007). Furthermore, a recent study has developed macroporous polymer scaffolds with varying pore wall architecture in order to enhance the environment for induction of cellular activity and provide guidance for 3D regeneration (Wei & Ma 2009). Therefore, a delivery scaffold can provide a suitable environment for targeted cells and tissues, as well as controlling the dynamic release of entrapped biologics. Periodontal therapy based on these systems, however, remains in its infancy.

The use of hyaluronic acid (HA) in the dental field has been demonstrated to restore periodontal defects and to carry and deliver growth factors such as BMP and FGF-2 (Wikesjo *et al*. 2003). A recent *in vitro* study has shown an HA and collagen (Col) combination scaffold to be a suitable environment for the growth of human periodontal ligament cells and therefore its potential in periodontal tissue engineering (Wang *et al*. 2009).

Inorganic calcium phosphate-based materials have also been used as delivery systems. Materials such as β-TCP are synthetic scaffolds that can be used to repair osseous defects around teeth or dental implants by acting as a bone substitute or as a carrier for growth factor delivery (Gille *et al*. 2002).

Hydrogels, formed by the cross-linking or self-assembly of a variety of natural or synthetic hydrophilic polymers to produce structures that contain >90% water, are obtained from natural materials such as collagen chitosan, dextran, alginate or fibrin. They are favorable for tissue engineering due to their innate ability to interact with cells while undergoing controlled degradation (De Laporte & Shea 2007; Moioli *et al*. 2007; Agarwal & Mallapragada 2008). Vector release from hydrogels is dependent upon the physical structure and

degradation of the hydrogel, and its interactions with the vector (De Laporte & Shea 2007).

Computer-based applications in scaffold design and fabrication

Computer-based applications in tissue engineering are some of the most recent developments in scaffold design and fabrication for cell and gene delivery (He *et al*. 2010). This type of technology, image-based design, has been used to define virtual 3D models for surgical planning by utilizing data from computed tomography (CT) and magnetic resonance imaging (MRI). Specifically, in tissue engineering, CT or MRI data are used to define the 3D anatomic geometry of a defect and then to create a template for a scaffold at a global anatomic level. This 3D printed scaffold, since it is produced from the 3D model, will precisely fill the defect space. Furthermore, the architecture of the scaffold can be defined to design the heterogeneous internal structure in such a way that creates region-specific variations in porous microstructures and scaffold surface topography, thereby altering the material and biologic properties in specific regions of the scaffold, such as modulus, permeability, and cell orientation (Hollister *et al*. 2002).

Future perspective

Tissue engineering is making an important impact on bone regeneration therapy. The use of cell and gene therapy to enhance and direct periodontal wound healing into a more predictable regenerative path is being exploited in bioengineering efforts aimed at developing a therapeutic system to promote bone repair (Rios *et al*. 2011). Various novel delivery scaffolding systems are being extensively studied and fabricated, and are demonstrating capabilities to meet the challenges of current regeneration therapy. However, numerous challenges remain. A major obstacle is how to maximize the utility of cells/genes delivered to a passive or permissive environment where there is context for the type of cell needed, but in which very few biologic signals are given to encourage normal cell function (Ramseier *et al*. 2005). Other obstacles, such as identifying cell sources and clinically relevant cell numbers, the integration of new cells into existing tissue matrices, and the achievement of functional properties of tissue equivalents using an expanded repertoire of biomaterials, also need to be confronted in the field of tissue engineering. Practical and regulatory requirements will also need to be met before the technologies of cell and gene transfer can be applied in the clinical arena.

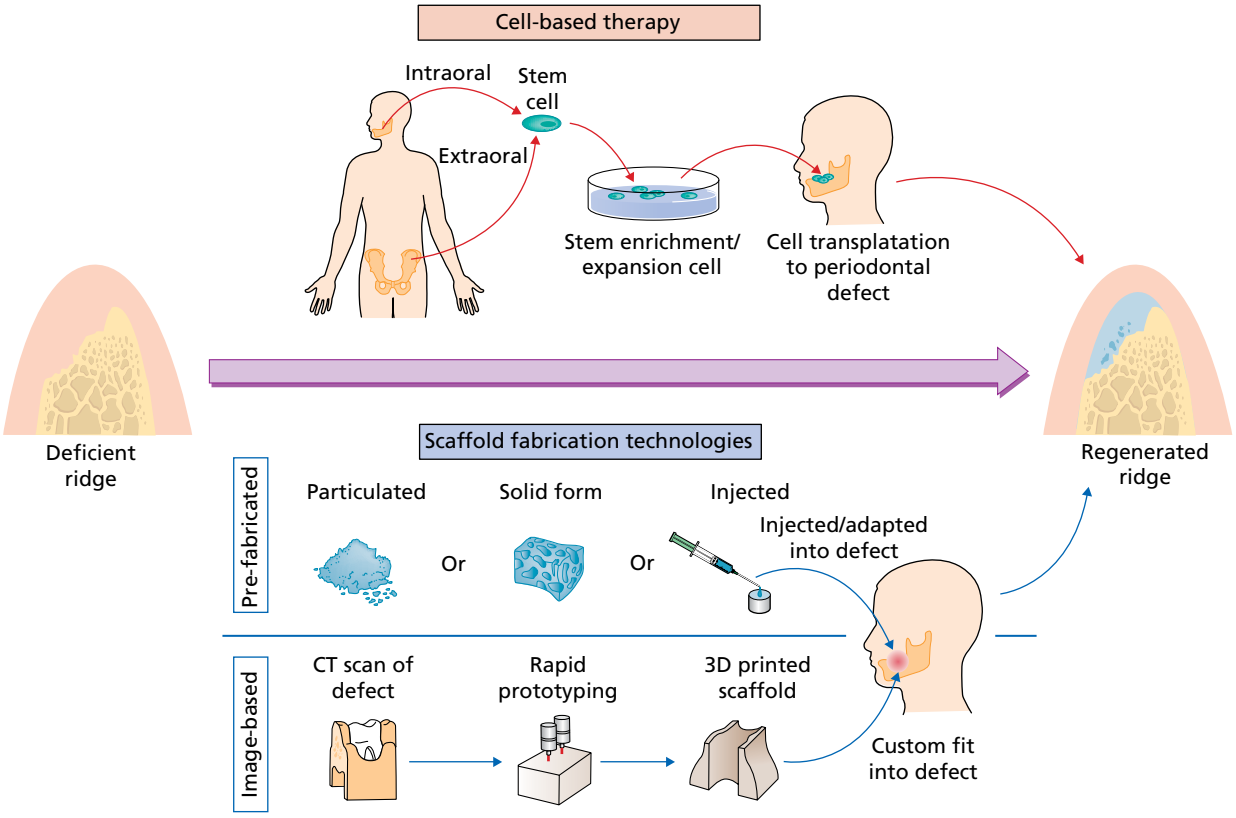

Fig. 50-11 New emerging technology for the treatment of edentulous ridge deficiencies. Research advances enable the integration of cell therapy and novel scaffold fabrication technologies. This promising modality could enhance predictable rapid tissue regeneration and ultimately the outcome of implant therapy. Extraoral and intraoral stem cells represent a viable and accessible source from which to harvest and expand multipotent colonies. Adequate cell density could be reached *in vitro* in a controlled environment and made readily available. Prefabricated and image-based scaffolds are becoming an essential component in regenerative medicine. A defined supporting structure allows the localization and guidance of the appropriate cells and proteins, and the establishment of a mechanically competent environment.

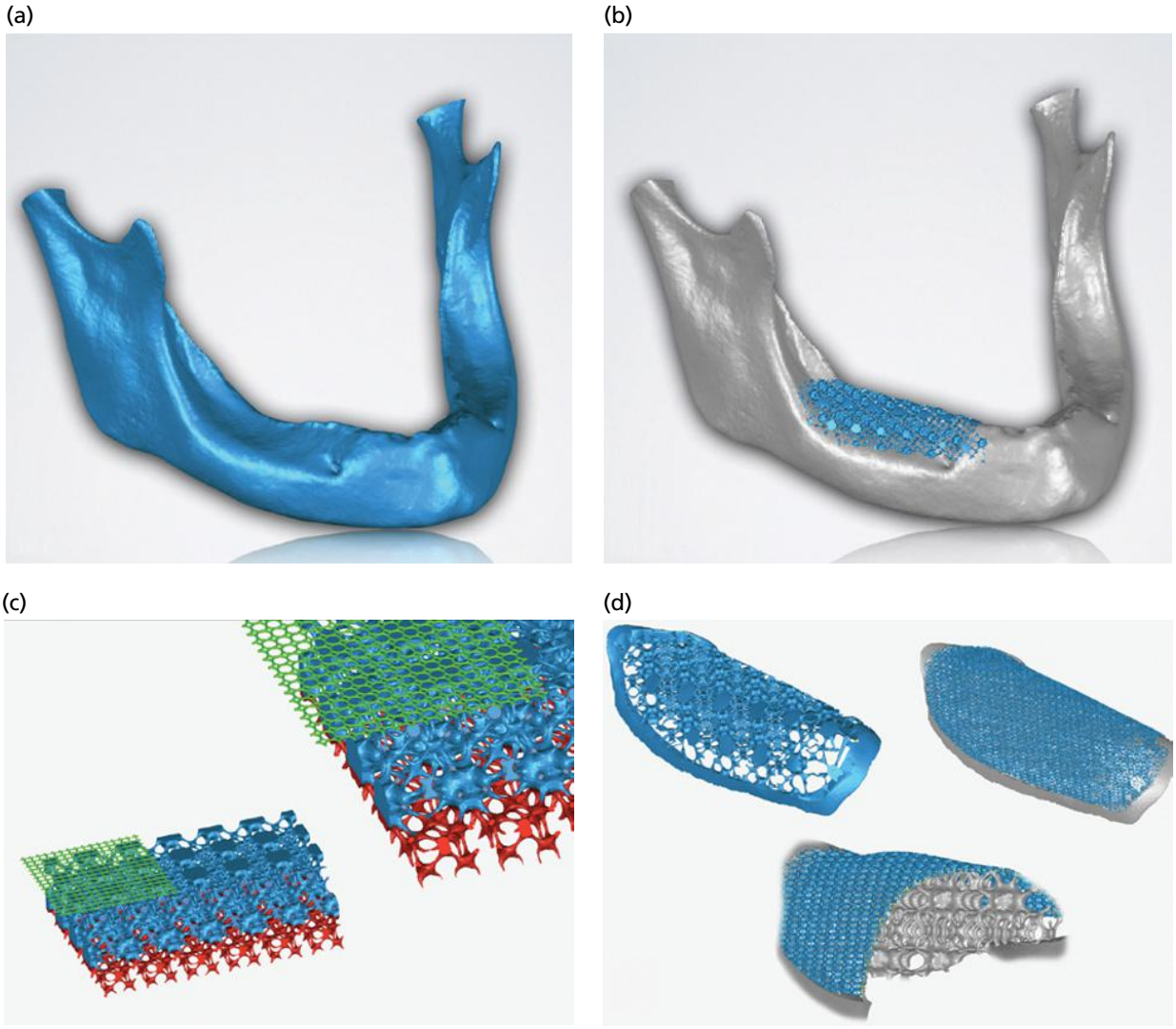

Fig. 50-12 (a) Volume rendering of cone-beam computed tomography (CBCT) scan of an edentulous ridge deficiency. CT provides a reliable digitized image dataset that is adequate for the assessment of mineralized tissue defects. (b) Custom-fit scaffold design. (c) Multilayer design. Based on 3D image data, a scaffold structure is designed using a computer-aided design (CAD) system. Scaffold topography could be used to enhance or modulate cell/tissue incorporation. (d) Enhanced scaffold topography. (Courtesy of I. Rudek.)

Collectively, the cell-based, scaffold, and gene therapy methods interface and complement each other to enhance the potential to restore tissue function and structure in a predictable manner (Figs. 50-11, 50-12). It is expected that in the future that there will be greater usage of bioactive molecules such as BMPs and PDGF to accelerate and enhance the healing potential of the defects, bringing about faster, easier, and predictable treatment outcomes. The success and the future of periodontal regenerative therapy will need to be supported by understanding of and ability to recognize clinical situations that will benefit from one or an integration of these new emerging technologies.

Conclusion

In general, ridge augmentation procedures have become increasingly predictable. The correct selection and application of the available techniques and biomaterials are key determinants of implant survival/success rates. Currently, research in the field of advanced bone grafting is directed at overcoming the technical and biologic limitations that continue to challenge implant dentistry. The use of novel scaffolding biomaterials, bioactive molecules, and advanced surgical techniques offers potential in the creation of increased bone volume and predictability in the treatment of challenging bone defects. Only through further research and development in the area of scaffold fabrication, along with cell-based and gene therapy, can tissue engineering continue to advance.

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Chapter 51

Elevation of the Maxillary Sinus Floor

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Introduction

Elevation of the maxillary sinus floor was first reported by Boyne in the 1960s. Fifteen years later, Boyne and James (1980) reported on the elevation of the maxillary sinus floor in patients with large, pneumatized sinus cavities as a preparation for the placement of blade implants. The authors described a two-stage procedure: the maxillary sinus was grafted using autogenous particulate iliac bone in the first stage of surgery, and in the second stage of surgery after approximately 3 months, the blade implants were placed and later used to support fixed or removable reconstructions (Boyne & James 1980).

As implant dentistry developed, it became more evident that the posterior maxillary region was often limited for standard implant placement, since the residual vertical bone height was reduced (Fig. 51-1). An elevation of the maxillary sinus floor was an option in solving this problem. Several surgical techniques have been presented for entering the sinus cavity, elevating the sinus membrane, and placing bone grafts.

A transalveolar approach for sinus floor elevation with subsequent placement of implants was first suggested (Tatum 1986). Utilizing this approach, a "socket former" for the selected implant size was used to prepare the implant site. A "green-stick fracture" of the sinus floor was accomplished by hand tapping the "socket former" in a vertical direction. After preparation of the implant site, a root-formed implant was placed and allowed to heal in a submerged way.

Summers (1994) later described another transalveolar approach, using tapered osteotomes with increasing diameters (Fig. 51-2). Bone was conserved by this osteotome technique because drilling was not performed. Adjacent bone was compressed by pushing and tapping as the sinus membrane was elevated. Then, autogenous, allogenic or xenogenic bone grafts were added to increase the volume below the elevated sinus membrane. A follow-up of 173 press-fit submerged implants, placed using this technique, reported a success rate of 96% at 18 months after loading (Rosen *et al*. 1999).

Today, two main procedures of sinus floor elevation for dental implant placement are in use: (1) a

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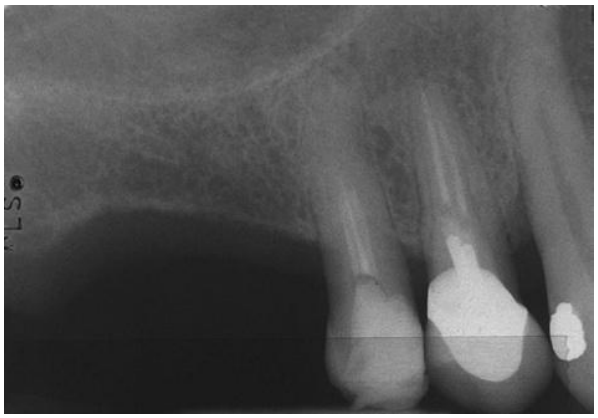

Fig. 51-1 Radiograph of a posterior maxilla, showing reduced residual bone height which will not allow standard implant placement.

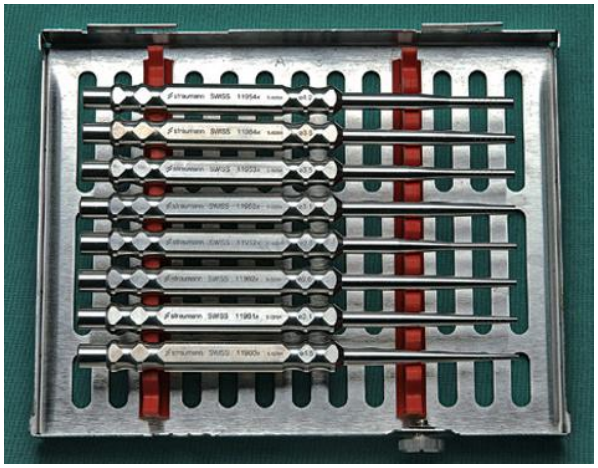

Fig. 51-2 Set of tapered osteotomes with different diameters to compress and push the residual bone from the implant preparation into the sinus cavity and to elevate the sinus membrane (introduced by Summers in 1994).

two-stage technique using the lateral window approach, and (2) a one-stage technique using a lateral or a transalveolar approach. The decision to use the one- or the two-stage technique is based on the amount of residual bone available and the possibility of achieving primary stability for the inserted implants.

Treatment options in the posterior maxilla

Implant placement in the posterior maxilla remains a challenge. Reduced bone volume due to alveolar bone resorption and pneumatization of the sinus cavity makes it more difficult to place implants to support a dental prosthesis.

Several treatment options have been used in the posterior maxilla to overcome the problem of inadequate bone quantity. The most conservative treatment option is placement of short implants to avoid entering the sinus cavity. For placement of short implants, there is still a need for at least 6 mm of residual bone height, however. Another way of

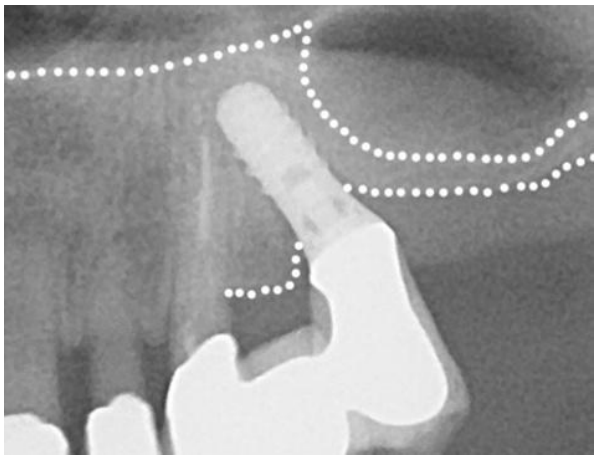

Fig. 51-3 Radiograph showing a tilted implant placed in the position of tooth 25 to avoid entering the sinus cavity. After remodeling, the bone level on the distal aspect of the implant is more apical than at the time of implant placement. This may lead to increased probing pocket depths around tilted implants. The dotted lines represent the outlines of the residual bone.

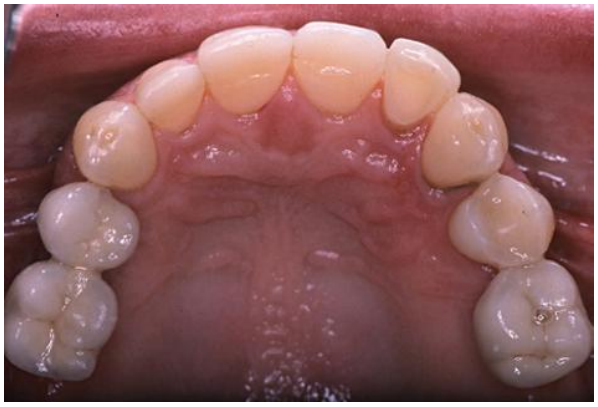

Fig. 51-4 Patient with a shortened dental arch. Three implants were placed in the positions of teeth 15, 14, and 25 without elevating the maxillary sinus floor and, subsequently, the patient's second premolar was restored.

avoiding grafting the maxillary sinus is to place tilted implants in a position mesial or distal to the sinus cavity if these areas have adequate bone (Fig. 51-3). Furthermore, extra-long zygomatic implants can be placed in the lateral part of the zygomatic bone.

However, in patients with appropriate residual bone height, minor augmentation of the sinus floor can be accomplished via the transalveolar approach using the osteotome technique (Summers 1994; Rosen *et al*. 1999; Ferrigno *et al*. 2006; Pjetursson *et al*. 2009a). The problem of inadequate bone height may be overcome by elevating the maxillary sinus floor via the closed technique to provide sufficient quantity of bone to support dental implants.

A more invasive treatment option in the posterior maxilla is the one- or two-stage sinus floor elevation with a lateral approach.

By mastering these different methods, most edentulous areas in the maxilla can by restored with implant-supported reconstructions. The concept of

a shortened dental arch must also be kept in mind. The work of Käyser (1981) has shown that patients maintained adequate (51–80%) chewing capacity with a premolar occlusion (Fig. 51-4).

Sinus floor elevation with a lateral approach

Anatomy of the maxillary sinus

The maxilla consists of a variety of anatomic structures, including the maxillary sinus, lateral nasal walls, pterygoid plates, associated vasculature structures, and teeth.

The maxillary sinus is pyramidal in shape. The base of the pyramid is the medial wall of the sinus and also the lateral wall of the nasal cavity, and its apex points towards the zygomatic bone. The roof of the sinus is also the floor of the orbit. The sinus has a non-physiologic drainage port high on the medial wall (maxillary ostium) that opens into the nasal cavity between the middle and lower nasal conchae.

The maxillary sinus maintains its overall size while the posterior teeth remain in function. It is, however, well known, that the sinus expands with age, and especially when posterior teeth are lost. The average volume of a fully developed sinus is about 15 mL but may range between 4.5 and 35.2 mL. The sinus cavity expands both inferiorly and laterally, potentially invading the canine region. This phenomenon is possibly the result of atrophy caused by reduced strain from occlusal function. One or more septa, termed "Underwood's septa", may divide the maxillary sinus into several recesses.

The overall prevalence of one or more sinus septa is between 26.5% and 31% (Ulm *et al*. 1995; Kim *et al*. 2006) and is most common in the area between the second premolar and the first molar. Edentulous segments have a higher prevalence of sinus septa than dentate maxillary segments.

The sinus is lined with respiratory epithelium (pseudo-stratified ciliated columnar epithelium) that covers a loose, highly vascular connective tissue (Fig. 51-5). Underneath the connective tissue, immediately next to the bony walls of the sinus, is the periosteum. These structures (epithelium, connective tissue, and periosteum) are collectively referred to as the Schneiderian membrane.

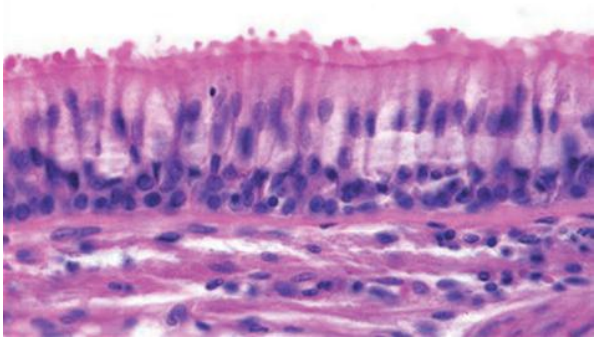

Fig. 51-5 Pseudostratified, ciliated columnar epithelium.

The blood supply to the maxillary sinus is derived primarily from the maxillary artery and, to a lesser degree, from the anterior ethmoidal and superior labial arteries. The sinus floor receives blood supply from the greater/lesser palatine and sphenopalatine arteries. These vessels penetrate the bony palate and ramify within the medial, lateral, and inferior walls of the sinus (Fig. 51-6). The posterior superior alveolar artery has tributaries that perfuse the posterior and lateral walls. The posterior superior alveolar and infraorbital arteries anastomose in the bony lateral wall, on average 19 mm from the alveolar bone crest (Solar *et al*. 1999). The dense vascular network of the maxilla reduces after tooth loss and with increased age. The vast majority of the blood vessels in the maxilla (70–100%) come from the periosteum (Chanavaz 1990, 1995). Venous drainage is into the sphenopalatine vein and pterygomaxillary plexus. Neural supply comes from branches of the maxillary nerve.

Non-hemolytic and alpha-hemolytic streptococci and *Neisseria* spp. are the normal commensal microbiota of the maxillary sinus. Staphylococci, diphtheroids, *Hemophilus* spp., pneumococci, *Mycoplasma* spp., and *Bacteroides* spp. are also found in varying amounts (Timmenga *et al*. 2003).

The healthy maxillary sinus is self-maintaining by postural drainage and actions of the ciliated epithelial lining, which propel bacteria toward the ostium. The maxillary sinus also produces mucus containing lysozymes and immunoglobulins. The significant vascularity of the Schneiderian membrane helps maintain its healthy state by allowing lymphocyte and immunoglobulin access to both the membrane and the sinus cavity.

The fact that the maxillary sinus opening to the nasal cavity is not in the lower part of the sinus (where a graft may be placed) is important and provides an anatomic rationale for sinus floor elevation, as the grafting procedure does not interfere with

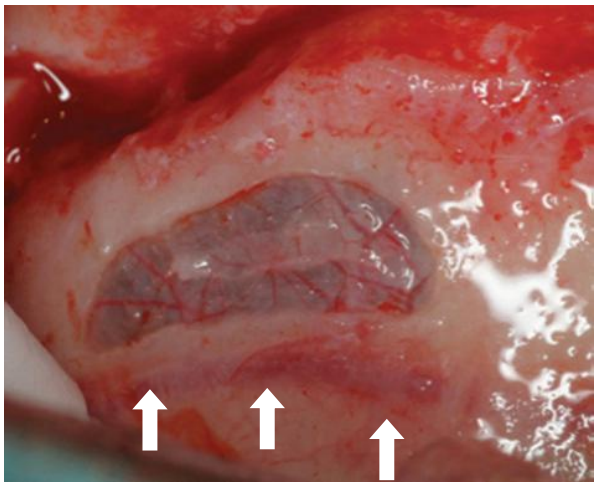

Fig. 51-6 Relatively large vessel integrated into the lateral wall of the sinus (arrows). Perforation of this vessel during preparation of the lateral window would cause excessive bleeding.

normal sinus function. In fact, a maxillary sinus floor elevation may improve symptoms of sinusitis/congestion by bringing the floor of the sinus closer to the drainage port.

Presurgical examination

Prior to planning complicated surgical procedures like elevation of the maxillary sinus floor, a thorough examination, including medical and dental history, should be obtained (see Chapters 28–30).

The dental and periodontal status is evaluated using clinical and radiologic examination methods. The vitality of the neighboring teeth has to be tested. The infraorbital, lateral nasal, and superior labial areas of the face must be examined regarding tenderness to palpation, swelling or asymmetry. The patient's history along with findings made during the clinical examination should provide sufficient information for diagnosing acute, allergic, and chronic sinusitis.

Preoperative screening to assess a potential pathologic condition in the maxillary sinus should include radiographic examination, such as orthopantomography (OPT), tomography, computed tomography (CT), cone-beam computed tomography (CBCT) or aquitomo-scans (see Chapter 30).

Before performing the sinus floor elevation surgery, all dentate patients should receive cause-related therapy (see Chapters 35–38).

Medical or surgical therapy of sinusitis, and removal of polyps and tumors must be completed prior to sinus floor elevation.

Indications and contraindications

The main indication for maxillary sinus floor elevation utilizing a lateral approach is reduced residual bone height, which does not allow standard implant placement or placement of implants in combination with minor sinus floor elevation using the osteotome technique. In cases of reduced bone height due to alveolar bone resorption and pneumatization of the sinus cavity, the so-called lateral approach, with or without horizontal bone augmentation, is indicated.

Contraindications for sinus floor elevation can by divided into three groups: intraoral contraindications, medical conditions, and local contraindications.

The *medical* contraindications include: chemotherapy or radiotherapy of the head and neck area at the time of sinus floor elevation or in the preceding 6 months, depending on the field of radiation; immunocompromised patients; medical conditions affecting bone metabolism; uncontrolled diabetes; drug or alcohol abuse; patient non-compliance; and psychiatric conditions.

Whether or not smoking is an absolute contraindication for maxillary sinus floor elevation remains controversial. In a case series, Mayfield *et al.* (2001) evaluated survival of implants placed in combination with bone augmentations (horizontal, vertical, and sinus elevations). The survival rate of these implants was 100% for non-smokers compared to only 43% for smokers after 4–6.5 years of functional loading. This reduced survival rate has been corroborated by several other authors (Bain & Moy 1993; Jensen *et al*. 1996; Gruica *et al*. 2004). However, a large study evaluating 2132 implants after sinus floor elevation with simultaneous implant placement found conflicting results (Peleg *et al*. 2006). Two hundred and twenty-six sinus floor elevations (627 implants) were performed on smokers, and 515 sinus floor elevations (1515 implants) on non-smokers. After a follow-up time of up to 9 years, the survival rate of the implants was 97.9%, and there were no statistically significant differences between survival rates in smokers and in non-smokers. A recent systematic review (Pjetursson *et al.* 2008) investigated the survival rate of implants inserted in combination with sinus floor elevation utilizing the lateral approach. Five of the included studies reported on the influence of smoking status of the patients, although not clearly defined, on implant survival after sinus floor elevation. A group of non-smokers who received 2159 implants and a group of smokers who received 863 implants were analyzed. The smokers had a higher annual failure rate (3.54%) compared with non-smokers (1.86%).

Alteration of the nasal–maxillary complex such that it interferes with normal ventilation as well as mucociliary clearance of the maxillary sinus, may be a contraindication for sinus floor elevation. However, such abnormal conditions may be clinically asymptomatic or only present with mild clinical symptoms. These conditions include viral, bacterial, and mycotic rhinosinusitis, allergic sinusitis, sinusitis caused by intrasinus foreign bodies, and odontogenic sinusitis resulting from necrotic pulp tissue. All odontogenic, periapical, and radicular cysts of the maxillary sinus should be treated prior to sinus floor elevation.

A sinus floor elevation under any of the above conditions may disturb the fine mucociliary balance, resulting in mucus stasis, suprainfection or a subacute sinusitis.

Absolute local contraindications for sinus floor elevation are: acute sinusitis; allergic rhinitis and chronic recurrent sinusitis; scarred and hypofunctional mucosae; local aggressive benign tumors; and malignant tumors.

Surgical techniques

The original Caldwell–Luc technique, commonly referred to as the lateral window or lateral approach, describes an osteotomy prepared in a superior position just anterior to the zygomatic buttress. Two other positions have also been described: a mid-maxillary position between the alveolar crest and zygomatic buttress area, and a low anterior position near the level of the existing alveolar ridge (Lazzara 1996;

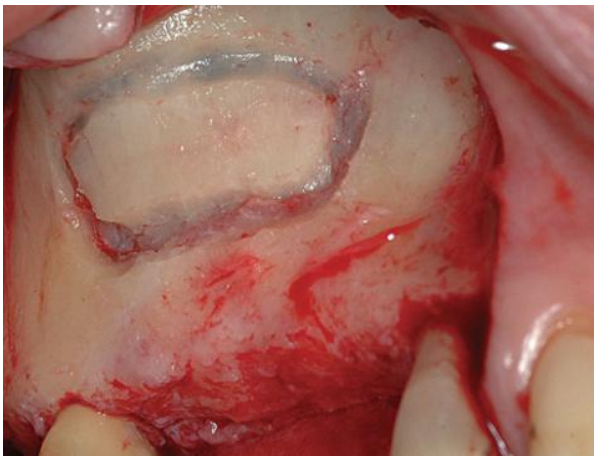

Fig. 51-7 Outline of the lateral window has been marked with a round bur.

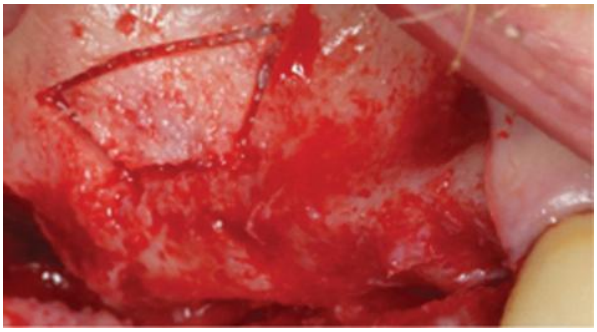

Fig. 51-8 Outline of the lateral window is made with a piezoelectric surgical tip, taking care not to perforate the membrane.

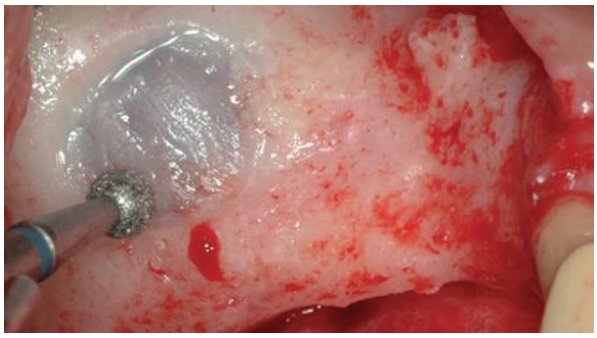

Fig. 51-9 Buccal bony plate is trimmed to a paper-thin lamella with a fine grit round diamond bur, avoiding perforation of the sinus membrane.

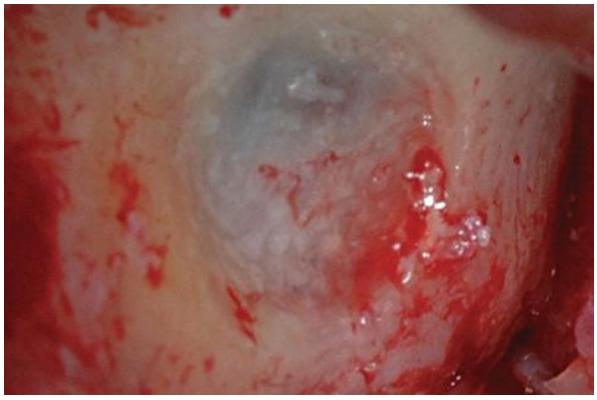

Fig. 51-10 After removing the buccal bony plate, the bluish hue of the sinus membrane becomes clearly visible.

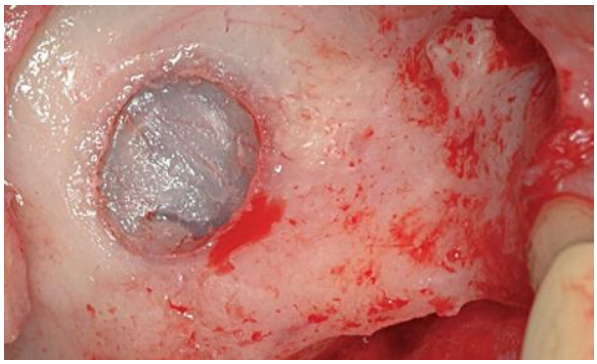

Fig. 51-11 Before elevating the sinus membrane, the entire buccal bone is removed to gain access to the membrane.

Zitzmann & Schärer 1998). The technique described below is a modification of these techniques:

1. A presurgical rinse with chlorhexidine 0.1% is performed for a period of 1 minute.
2. Local anesthesia is delivered buccal and palatal to the surgical area and tuberosity block anesthesia is performed.
3. The initial incision is mid-crestal, extending well beyond the planned extension of the osteotomy. The incision is carried on forward beyond the anterior border of the maxillary sinus. Releasing incisions are made anteriorly, extending into the buccal vestibulum to facilitate reflection of a full-thickness mucoperiosteal flap.
4. A mucoperiosteal flap is raised slightly superior to the anticipated height of the lateral window.
5. After the lateral sinus wall has been exposed, a round carbide bur (Fig. 51-7) in a straight hand piece or a piezoelectric surgical tip (Fig. 51-8 are used to mark the outline of the osteotomy. When the bone has been trimmed down to a thin bony plate, the preparation is continued with a round diamond bur (Fig. 51-9) in a straight hand piece or a diamond-coated piezoelectric surgical tip until the bluish hue of the sinus membrane is observed (Fig. 51-10). Three methods for handling the buccal cortical bone plate have been proposed. The most common one is thinning of the buccal bone to a paper-thin bone lamella using a round bur, and removing it prior to the elevation of the sinus membrane (Fig. 51-11). The second method is to fracture the cortical bony plate like a trap-door and use it as the superior border to the sinus compartment, leaving it attached to the underlying mucosa. Since the cortical bony plate is resistant to bone resorption, this may protect the graft. The third method is to remove the cortical bony plate during sinus floor elevation and replace it on the lateral aspect of the graft at the end of the grafting procedure. The rationale for this method was the notion that the lateral window would not completely heal without

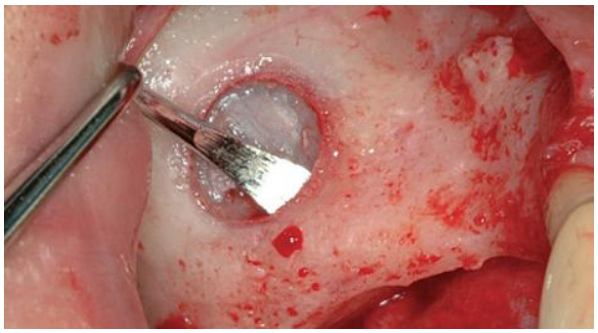

Fig. 51-12 Sinus membrane is carefully elevated using a blunt instrument. To avoid penetration, it is essential to keep contact with the underlying bone at all times during this procedure.

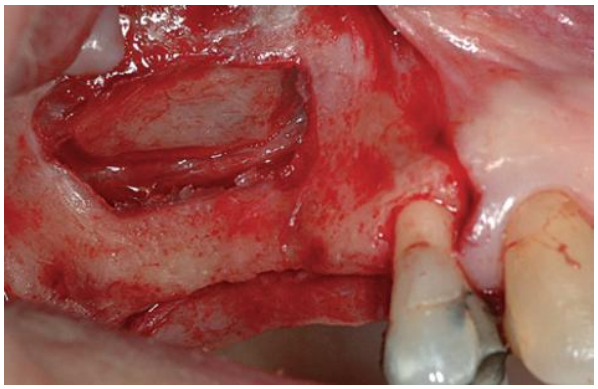

Fig. 51-13 Buccal cortical bony plate was fractured and moved upwards and inwards like a "trap-door". The cortical bony plate delineates the superior border of the maxillary sinus compartment.

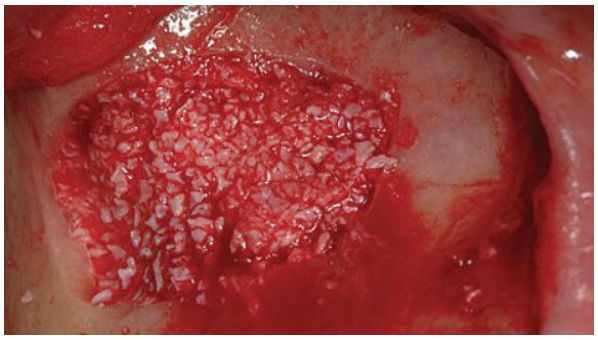

Fig. 51-14 Sinus compartment has been filled with a loosely packed 1 : 1 mixture of particulate autogenous bone and a xenograft.

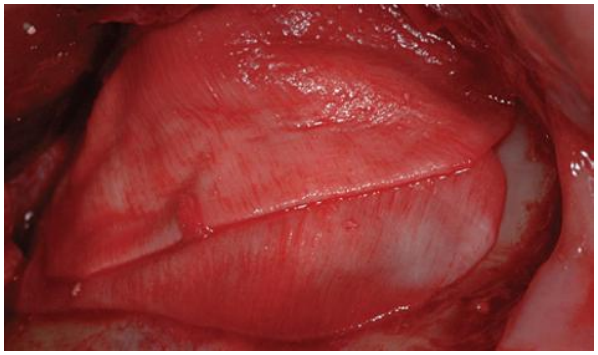

Fig. 51-15 Lateral window has been covered with single or double layer of resorbable barrier membrane.

replacement of its cortical plate. However, healing of the lateral window by bone apposition has been demonstrated to occur without replacing the cortical bony plate (Boyne 1993).

6. The next step is chosen according to the technique used. If the buccal wall is eliminated, the sinus membrane is elevated directly with blunt instruments (Fig. 51-12). On the other hand, gentle tapping is continued until movement of the bony plate is observed if the "trap-door" technique is used. Then, in combination with the elevation of the sinus membrane in the inferior part of the sinus, the bony plate is rotated inwards and upwards to provide adequate space for the grafting material (Fig. 51-13). Care should be taken not to perforate the sinus membrane.

Depending on the clinical condition and the surgeon's preference, a delayed (two-stage) or a one-stage sinus floor elevation simultaneously with the implant installation is chosen.

Two-stage sinus elevation (delayed installation of the implant)

1. Grafting material is placed in the compartment made by the elevation of the sinus membrane. The grafting material should not be densely packed, because this reduces the space needed for in-growth of newly forming bone. In addition, pressurizing the thin sinus membrane may result in a late perforation.
2. After the compartment has been filled with grafting material (Fig. 51-14), the lateral window is closed by covering it with a resorbable or a non-resorbable barrier membrane (Fig. 51-15). Subsequently, the flap is closed free of tension. In most conditions, there is a need for deep periosteal incisions to achieve tension-free closure.

One-stage sinus floor elevation with simultaneous implant placement

1. After the sinus membrane has been elevated, the implant sites are prepared. If rotary instruments are used, the sinus membrane has to be protected using a periosteal elevator (Fig. 51-16). Osteotomes of different diameters may be used to prepare the implant site, and then the membrane can be protected by inserting sterile gauze into the sinus compartment (Fig. 51-17).
2. The appropriate implant length is measured with a blunt depth gauge (Fig. 51-18). Before placing the implant, the grafting material is inserted into the medial part of the sinus compartment (Fig. 51-19). After implant placement (Fig. 51-20), the lateral part of the compartment is filled with grafting material (Fig. 51-21).
3. The subsequent steps coincide with those described for the two-stage procedure.

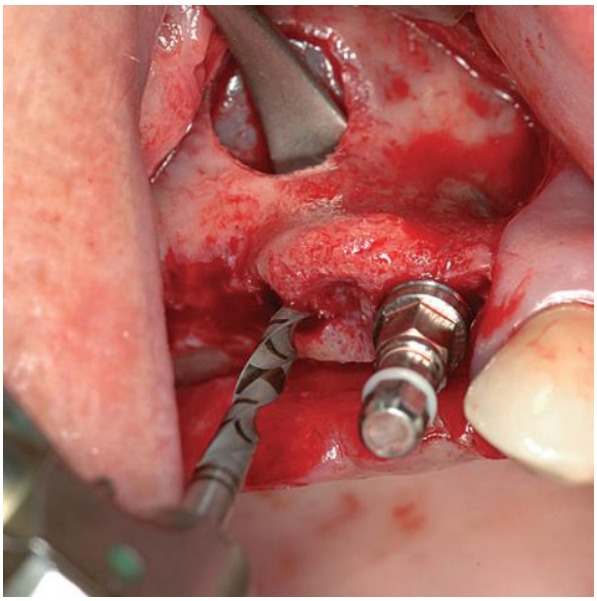

Fig. 51-16 Protection of the sinus membrane with a periosteal elevator in the sinus compartment when using rotary instruments to prepare the implant site.

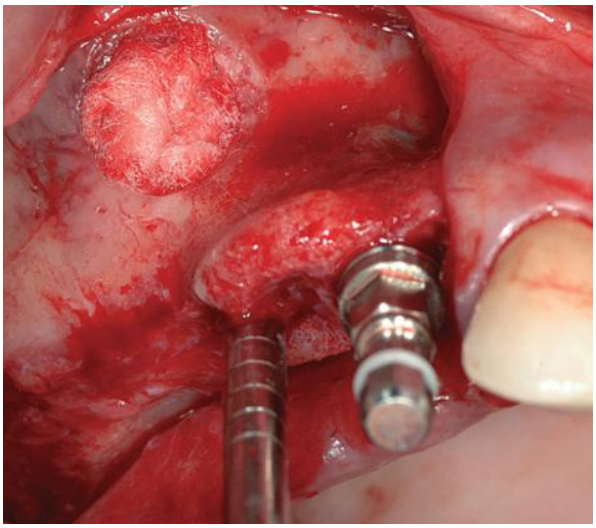

Fig. 51-17 Protection of the sinus membrane with sterile gauze inserted into the sinus compartment when using osteotomes to prepare the implant site.

The main differences between the methods used currently are the position and technique used to prepare the lateral window, the amount of sinus membrane elevation, the type of graft utilized, and the choice of one-stage or two-stage approaches.

Histomorphometric evidence of enhanced bone formation following membrane placement over the lateral window is available. In a randomized controlled clinical trial (Tarnow *et al*. 2000), a split-mouth design with bilateral sinus grafts was performed for 12 patients with or without covering the lateral window using a membrane. After 12 months, histologic samples were taken through the lateral window. The mean percentage of vital bone formation was 25.5% with and 11.9% without a covering barrier. Similar results were obtained in a controlled clinical trial (Froum *et al*. 1998) measuring bone formation in 113 sinuses grafted either with xenograft alone or a

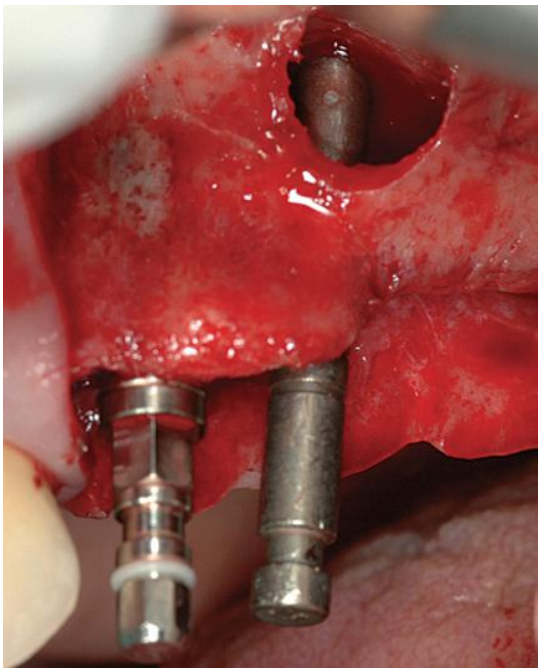

Fig. 51-18 Simultaneous sinus floor elevation and implant placement: height of the sinus compartment and implant length can be determined by inserting a blunt depth gauge into the implant site. Care must be taken not to apply too much pressure on the sinus membrane.

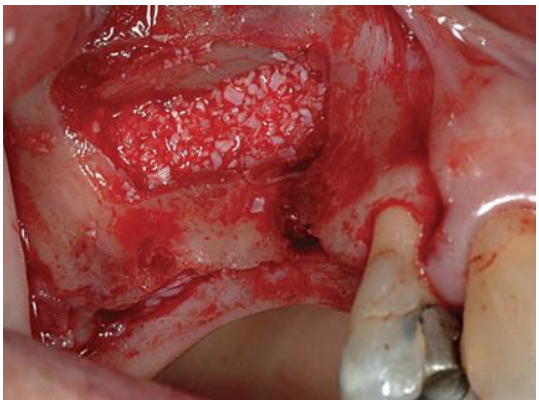

Fig. 51-19 Before placing the implants, grafting material has to be inserted into the medial part of the sinus compartment, because access to the medial part of the sinus compartment is restricted after implant installation.

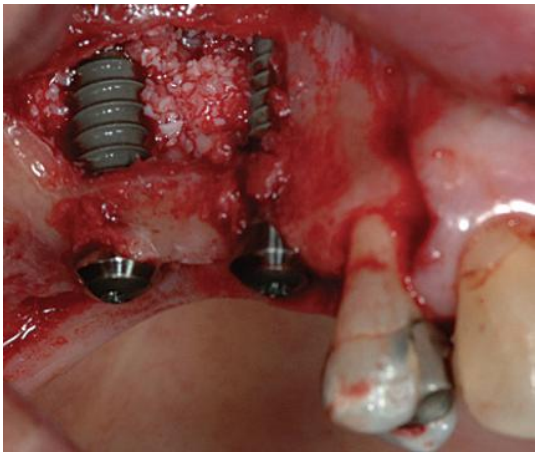

Fig. 51-20 Two implants have been installed after filling the medial part of the sinus compartment.

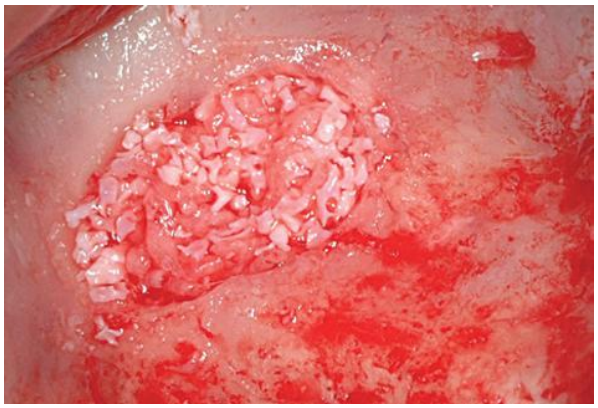

Fig. 51-21 After implant installation, the lateral part of the sinus compartment is filled with loosely packed grafting material.

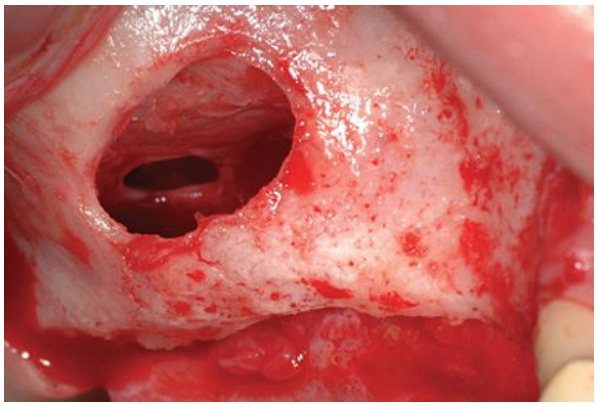

Fig. 51-22 Perforation of the sinus membrane. A medium-sized perforation can be detected after elevation of the membrane.

composite of xenograft and autograft. The mean vital bone formation was 27.6% when a membrane was used compared to 16% without. In a recent systematic review (Pjetursson *et al.* 2008), comparison of the failure rates of dental implants inserted in sinuses where the lateral access window was covered with a membrane with the survival rates of dental implants where the access window was not covered revealed annual failure rates of 0.79% and 4.04%, respectively.

Post-surgical care

In order to minimize postoperative pain and discomfort for the patient, surgical handling should be as atraumatic as possible. Precautions must be taken to avoid perforation of the flap and the sinus membrane. The bone should be kept moist during the surgery, and a tension-free primary flap closure is essential. The pain experienced by patients is mostly limited to the first days after surgery. Swelling and bruising of the area are usually the chief postoperative sequelae. Often, swelling and bruising extend from the inferior border of the orbit to the lower border of the mandible or even to the neck. In order to reduce swelling, it is important to cool the area with cooling pads, at least over the first postoperative hours. Occasionally, minor bleeding may arise from the nose. It is important to inform patients that some irritation in the nasal area may be expected. If the patient needs to sneeze, the nose should not be covered so that air pressure is allowed to escape. After the surgery, patients are placed on antibiotic prophylaxis and prescribed pain killers and non-steroidal anti-inflammatory drugs (NSAIDs). It remains controversial whether or not patients need steroidal anti-inflammatory administration after such a procedure. Furthermore, antiseptic rinses with 0.1–0.2% chlorhexidine twice daily are indicated for the first 3 weeks after surgery.

Complications

When performing sinus floor elevation, the risk of complications must be considered and their appropriate treatment foreseen.

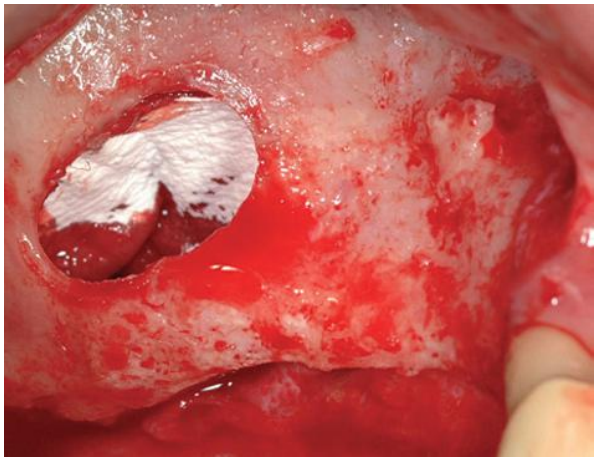

Fig. 51-23 Closure of small-to-medium-sized sinus membrane perforations by applying a resorbable barrier membrane.

The most common intraoperative complication is perforation of the sinus membrane (Fig. 51-22). The presence of maxillary sinus septa and root apices penetrating into the sinus may increase the risk of membrane perforation. The risk of perforation has been reported to be between 10% and 40% during surgery (Block & Kent 1997; Timmenga *et al.* 1997; Pikos 1999). In a recent systematic review (Pjetursson *et al.* 2008), the mean prevalence of membrane perforation, based on 20 of the included studies, was 19.5% and ranged from 0% to 58.3%. Whether or not this complication influences the survival rate of the implants is still controversial. Some authors (Khoury 1999) have reported a correlation between membrane perforation and implant failure, while other studies reported no correlation.

In the event of membrane perforation, it is recommended to elevate the membrane in the opposite direction to prevent further enlargement of the perforation. Smaller perforations (<5 mm) may be closed by using tissue fibrin glue, suturing or by covering them with a soft resorbable barrier membrane (Fig. 51-23). In cases of larger perforations, larger barrier membranes, lamellar bone plates or suturing may be used either alone or in combination with tissue fibrin glue to provide a superior border for the

grafting material. In instances of larger perforations, where a stable superior border cannot be achieved, the grafting of the maxillary sinus must by aborted and a second attempt at sinus floor elevation may be performed 6–9 months later (Tatum *et al*. 1993; van den Bergh *et al*. 2000).

Other complications that have been reported during surgery include excessive bleeding from the bony window or the sinus membrane, and wound dehiscences. Iatrogenic complications include injury to the infraorbital neurovascular bundle from deep dissection to free the flap from tension or blunt trauma due to the compression of the neurovascular bundle during retraction. Implant migration, hematoma, and adjacent tooth sensitivity have also been reported.

Infection of the grafted sinuses is a rare complication. In a meta-analysis based on 24 studies, the prevalence of infection was 2.9%, ranging from 0% to 7.4% (Pjetursson *et al.* 2008). The risk for infection increases with a membrane perforation. Hence, it is recommended to avoid sinus grafting and simultaneous implant placement in situations of large membrane perforations (Jensen *et al*. 1996). Infection of the grafted sinuses is usually seen 3–7 days post surgically and may lead to failure of the graft. A possible complication secondary to infection is parasinusitis with the spread of the infection to the orbita or even to the brain. For these reasons, infected sinus grafts must be treated immediately and aggressively. Surgical removal of the entire graft from the sinus cavity and administration of high doses of antibiotics are essential.

Sinusitis is another complication that may occur after sinus grafting. In a study evaluating the function of the maxillary sinus after sinus floor elevation (Timmenga *et al*. 1997), 45 patients who had received 85 sinus grafts underwent endoscopic examination. Of these, five were diagnosed with sinusitis. In these five patients, the endoscopic examination revealed oversized turbinates and septal deviation. Hence, the result of this study showed that the incidence of sinusitis was low and mainly found in patients with an anatomic or functional disorder prior to the sinus grafting.

Reported causes of late failure include chronic infection, graft exposure, loss of the entire bone graft, oroantral fistula, in-growth of soft tissue through the lateral window, granulation tissue replacing the graft, and sinus cysts.

Grafting materials

There are differences in opinion on the need to graft material when elevating the maxillary sinus floor.

Sinus floor elevation without grafting material

Studies in monkeys (Boyne 1993) showed that implants protruding into the maxillary sinus following elevation of the sinus membrane without grafting material, exhibited spontaneous bone formation over more than half of the implant's height. Hence, protrusion of an implant into the maxillary sinus does not appear to be an indication for bone grafting. In the same study, it was also seen that the design of the implant influenced the amount of spontaneous bone formation. Implants with open apices or deep-threaded configurations did not reveal substantial amounts of new bone formation. On the other hand, implants with rounded apices that penetrated 2–3 mm into the maxillary sinus tended to show spontaneous bone formation around their entire circumference. However, when the same implants penetrated 5 mm into the maxillary sinus, only a partial (51%) growth of new bone was seen towards the apex of the implant. This has also been demonstrated in clinical studies in humans.

Lundgren and co-workers (Lundgren *et al*. 2004; Hatano *et al*. 2007; Cricchio *et al.* 2011) have performed studies in which the lateral bone window was removed during the procedure and the sinus membrane was elevated and sutured against the lateral wall in an elevated position to create and maintain a compartment for blood clot formation. Finally, the bony lid was moved into its former position and secured with the overlying mucosa. Comparisons of pre- and post-operative CT radiography 6 months after the procedure clearly demonstrated new bone formation within the compartment created by the sinus membrane elevation procedure.

In a clinical study, 131 implants were placed using the lateral approach (Ellegaard *et al*. 2006). The sinus membrane was elevated and implants were inserted and left to protrude into the sinus cavity. The sinus membrane was allowed to settle onto the apex of the implants, thus creating a space to be filled with a blood coagulum. After a mean follow-up of 5 years, the survival rate of these implants was 90%. It must be kept in mind, however, that the residual bone height in this study was at least 3 mm to allow for a primary stability of the implants.

A recent longitudinal study following 84 patients who underwent 96 sinus floor elevations procedures with simultaneous placement of 239 implants without using grafting materials, demonstrated on intraoral radiographs an average intrasinus bone gain of 5.3 mm after 6 months of healing (Cricchio *et al.* 2011). After a mean follow-up of 3 years, the implant survival was 98.7%.

Autogenous bone

Autogenous bone grafts are considered the gold standard for grafting due to their maintenance of cellular viability and presumptive osteogenic capacity. The use of autogenous grafts in sinus floor elevation was first reported by Boyne and James (1980) and Tatum (1986).

Grafts may be harvested intraorally or extraorally. Common intraoral donor sites are the maxillary

tuberosity, the zygomatico-maxillary buttress, the zygoma, the mandibular symphysis, and the mandibular body and ramus (Fig. 51-24). Bone may be harvested in block section or in particulate form. The extraoral donor sites that have been utilized are the anterior and posterior iliac crest, tibial plateau, rib, and calvaria.

Autologous bone grafts contain bone morphogenic proteins (BMPs) that are capable of inducing osteogenic cells in the surrounding tissues. They also contain other growth factors essential for the process of graft incorporation. Processing of autograft, with grinding or morselizing, does not seem to disturb the viability of the osteogenic cells (Springer *et al*. 2004). The main source of osteogenic cells during graft consolidation is the periosteum which includes mesenchymal progenitor cells and provides a rich source of blood vessels. Osteoclasts are then required for remodeling of the graft–woven bone complex. The consolidation of the graft depends on the properties of the graft material and the osteogenic potential of the recipient bed. Initially, cortical bone grafts act as weight-bearing space fillers and remain a mixture of necrotic and viable bone for a prolonged period of time. The ideal graft material has to allow in-growth of blood vessels and formation of bone on its surfaces for integration into the recipient bed (osteoconductivity).

Where sinus floor elevations do not eventually receive dental implants, the bone grafts may resorb due to the lack of functional load and strain.

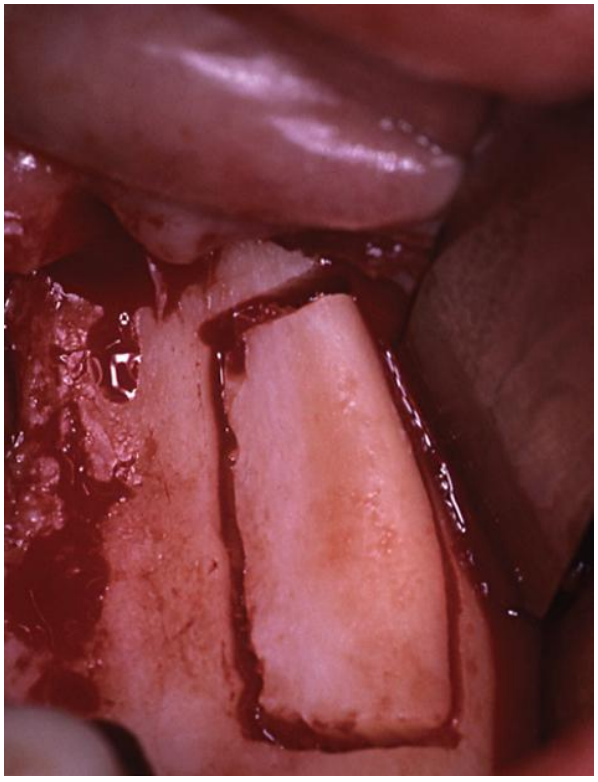

Fig. 51-24 Most suitable sites used to harvest block or particulate bone grafts intraorally are the mandibular body and the mandibular ramus.

Bone substitutes

Loss of autografts during healing occurs when resorption of the autograft exceeds new bone formation during the consolidation phase. Thus, to overcome excessive resorption of autografts, bone substitutes that are known for their slow resorption process are added to autografts to increase the stability of grafts during the consolidation phase.

Tricalcium phosphate was the first bone substitute to be applied successfully for sinus floor elevation (Tatum 1986). Over the years, allografts, alloplasts, and xenografts of various types have been used alone or in combination with autografts. Studies in animal models showed that the use of bone substitutes, such as bovine bone mineral, either alone or in combination with autografts, preserved the vertical height of the graft over time (Fig. 51-25). In a human study, sinus grafts consisting of autografts and demineralized allografts were observed over a period of time. A graft resorption of up to 25% was seen. Furthermore, a human study also showed significant reduction in graft volume when either autogenous bone alone or a mixture of autogenous bone and xenografts were used (Hatano *et al*. 2004). A recent study comparing the use of bone-added osteotome sinus floor elevation (BAOSFE) with sinus floor elevation utilizing the lateral approach, concluded minimal bone resorption was seen for both methods: 1.35 mm and 1.36 mm, respectively, over a period of 2 years after the procedure was performed (Kim *et al.* 2011). There is a definitive need for good long-term studies that address the stability of the different types of grafting materials in the maxillary sinuses over time.

Histologic analysis of human biopsy specimens from sinuses augmented with xenografts revealed that xenograft particles were mostly surrounded by mature compact bone (Fig. 51-26). In some Haversian canals, it was possible to observe small capillaries, mesenchymal cells, and osteoblasts in conjunction with new bone. No gaps were noted at the interface between the xenograft particles and the newly formed bone (Piattelli *et al*. 1999).

Fig. 51-25 1 : 1 mixture of particulate autologous bone and bone substitute. The autologous bone particles include viable osteogenic cells, bone morphogenic proteins, and other growth factors. The bone substitute is supposed to decrease the resorption of the grafting material.

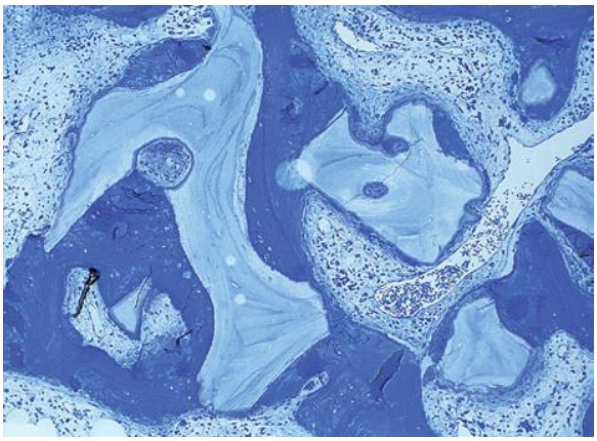

Fig. 51-26 Bovine bone mineral particles (xenograft) are mostly surrounded by new mature compact bone. No gaps can be seen at the interface between the xenograft particles and the newly formed bone. (Courtesy of D. D. Bosshardt.)

A human study evaluating bone formation after sinus floor elevation using xenografts alone or in combination with autogenous bone and/or demineralized freeze-dried bone allografts (DFDBAs) reported a statistically significant increase in vital bone formation when as little as 20% of autologous bone was added to the bone substitutes (Froum *et al*. 1998). The mean vital bone formation was 27.1% after a healing period of 6–9 months. However, comparative studies (Hising *et al*. 2001; Hallman *et al*. 2002a, b; Valentini & Abensur 2003) reported higher survival rates for implants placed into sinuses grafted with 100% xenograft as compared to those placed in sinuses grafted with 100% autogenous bone or composite graft of xenograft and autogenous bone.

In a recent systematic review (Pjetursson *et al*. 2008), an attempt was made to compare the survival rates of implants inserted into maxillary sinuses that had been grafted utilizing different grafting materials. The relative failure rates of the different types of grafting materials were analyzed with multivariable random-effect Poisson regression. In order to avoid the confounding factor of implant surfaces, only studies reporting on rough textured implants were included and machined-surface implants were excluded. Bone substitutes, a combination of autogenous bone and bone substitutes, and autogenous bone blocks all showed similar low annual failure rates of 1.13%, 1.10%, and 1.27%, respectively. The particulated autogenous bone graft, based on two studies, showed significantly lower annual failure rates of 0.06%. It must, however, be kept in mind that all types of grafting materials had high implant survival rates ranging between 96.3% and 99.8% after 3 years.

Another indication for using bone substitutes is to reduce the volume of bone that must be harvested. When a large sinus cavity is grafted with autologous bone alone, 5–6 mL of bone may be necessary. By using bone substitutes alone or in combination with autografts, the amount of autogenous bone to be harvested is greatly reduced.

Success and implant survival

Jensen *et al*. (1996) published the findings from the Consensus Conference of the Academy of Osseointegration. Retrospective data were collected from 38 clinicians who collectively performed 1007 sinus floor elevations and placed 2997 implants over a 10-year period. The majority of the implants had been followed for 3 years or more. Two hundred and twenty-nine implants were lost, resulting in an overall survival rate of 90.0%. However, the data were so variable that no definitive conclusions regarding the grafting material, type of implants, and timing of implant placement could be drawn.

Survival of implants cannot be the sole criterion for success of maxillary sinus floor elevation. Factors such as the preoperative residual bone height, long-term stability of the bone graft, and incidence of failing two-stage sinus grafting due to graft resorption must also be considered.

Of the 900 patient records that were screened for the Consensus Conference in 1996, only 100 had radiographs of adequate quality for analysis of the residual bone height. In total, only 145 sinus grafts in 100 patients with 349 implants were analyzed. After a mean follow-up period of 3.2 years, 20 implants were lost. Of the implants lost, 13 had been placed in residual bone with a height of 4 mm and seven in residual bone with a height of 5–8 mm. None of the implants placed in residual bone height of >8 mm were lost. There was a statistically significant difference in implant loss when residual bone height was ≤4 mm as compared to ≥5 mm (Jensen *et al*. 1996).

A critical appraisal of the dental literature on maxillary sinus floor elevation shows that the two-stage approach (delayed implant installation) is more likely to be used in situations with less residual bone height compared to the one-stage approach (simultaneous implant placement).

The efficacy of performing a one-stage sinus floor elevation in patients whose residual alveolar bone height in the posterior maxilla was between 3 and 5 mm was assessed (Peleg *et al*. 1999). Using the modified Caldwell–Luc technique, the maxillary sinus was elevated with composite grafts of symphysal autograft and DFDBA in a 1 : 1 ratio. One hundred and sixty implants were placed in 63 elevated sinuses. A 100% survival rate of the implants was reported after 4 years. In a second study using a similar protocol for 55 implants placed into 20 elevated sinuses, the residual alveolar bone height was only 1–2 mm (Peleg *et al*. 1998). All implants osseointegrated successfully, and no implants were lost after 2 years of functional loading.

One randomized controlled clinical trial has compared one- and two-stage sinus floor elevation, in 40 patients divided into groups (Wannfors *et al*. 2000). The residual bone height ranged from 2 to 7 mm. The reported survival rate for the one-stage protocol (Fig. 51-27) in 75 implants was 85.5%, as compared to

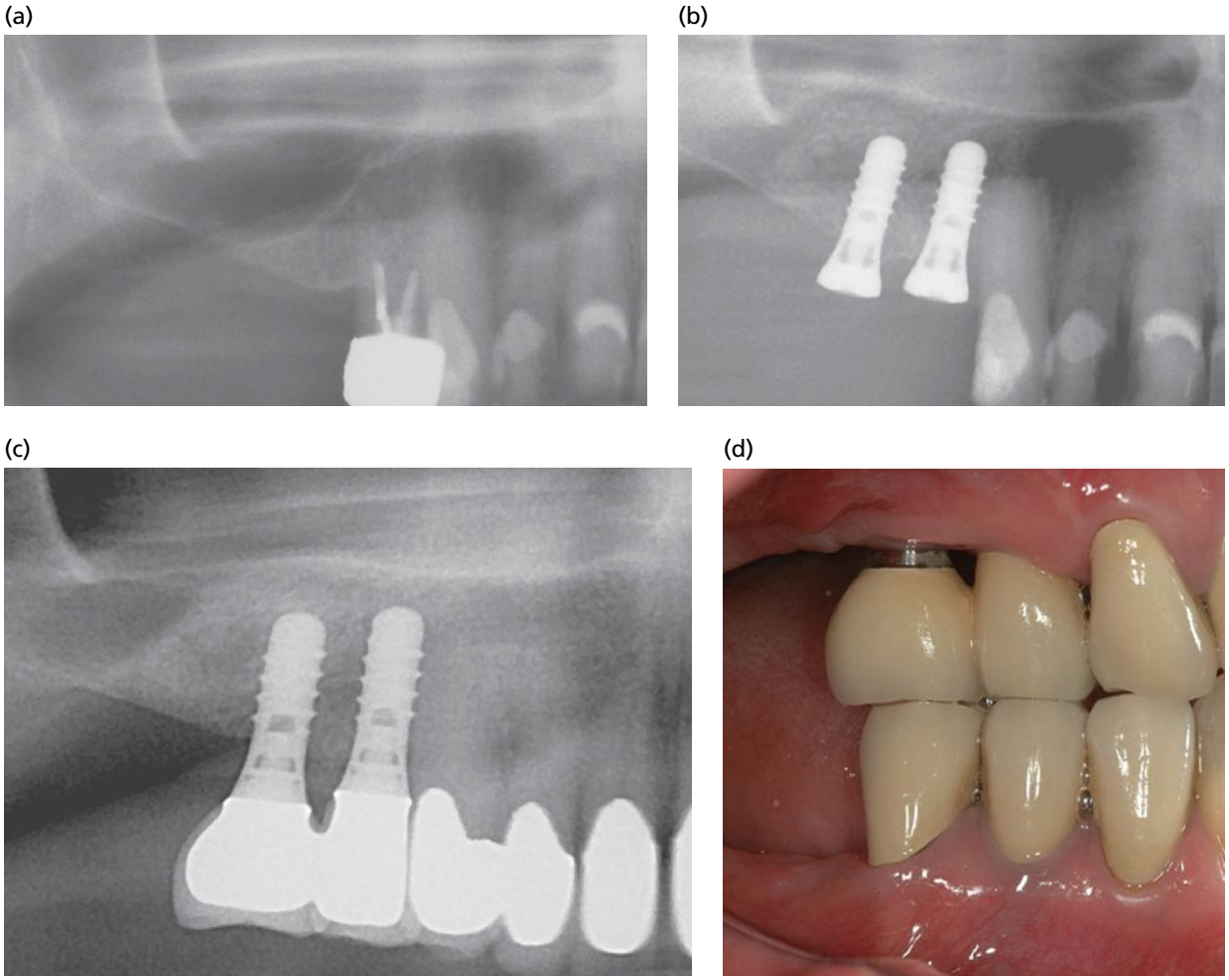

Fig. 51-27 One-stage sinus floor elevation. (a) Panoramic radiograph showing oblique inferior sinus borders and a residual bone height between 2 and 6 mm in the position of tooth 25. (b) Two implants were placed: a standard implant placement in the position of tooth 24 and an implant installed in combination with sinus floor elevation in the position of tooth 25. A 1 : 1 mixture of particulate autologous bone harvested from the maxillary tuberosities and the zygomatic bone combined with bovine bone mineral was used as the grafting material. (c) Panoramic radiograph taken 1 year after functional loading. A new inferior border of the maxillary sinus and a stable graft volume were evident. (d) Clinical picture at the 1-year follow-up visit.

90.5% for the two-stage protocol (Fig. 51-28) in 74 implants after 1 year in function. Apparently, the risk of implant failure in grafted areas was greater for the one-stage procedure than for the two-stage procedure, although the results did not reach statistical significance. In the systematic review previously mentioned (Pjetursson *et al.* 2008), one- and two-stage sinus floor elevations were compared (24 studies with 5672 implants using the one-stage approach and 24 studies with 3560 implants using the two-stage approach). The annual failure rates for the two methods were similar: 4.07% versus 3.19%, respectively. It must, however, be kept in mind that the one-stage approach is usually only applied when the residual bone height gives enough primary implant stability. Hence, the two-stage approach is usually used in more challenging situations with limited residual bone.

The stability of the sinus graft height was evaluated on panoramic radiographs for 349 implants. After a mean follow-up period of 3.2 years, the reduction of the graft height varied between 0.8 mm (autograft and alloplast) and 2.1 mm (autograft). This indicated that all of the graft materials appeared to be stable, with only 1–2 mm of the graft height being lost over the 3-year period (Jensen *et al*. 1996). Further studies evaluating the long-term stability of sinus grafts (Block *et al*. 1998; Hatano *et al*. 2004) yielded similar results.

Wallace and Froum (2003) published a systematic review of the effect of maxillary sinus floor elevation on the survival of dental implants. The inclusion criteria were human studies with a minimum of 20 interventions, a follow-up time of 1 year of functional loading, and implant survival as an outcome measure. The main results indicated:

- Survival rate of implants placed in conjunction with sinus floor elevation with the lateral approach varied between 61.7 and 100%, with an average of 91.8%.
- Implant survival rates compared favorably to reported survival rates for implants placed in the non-grafted maxilla.

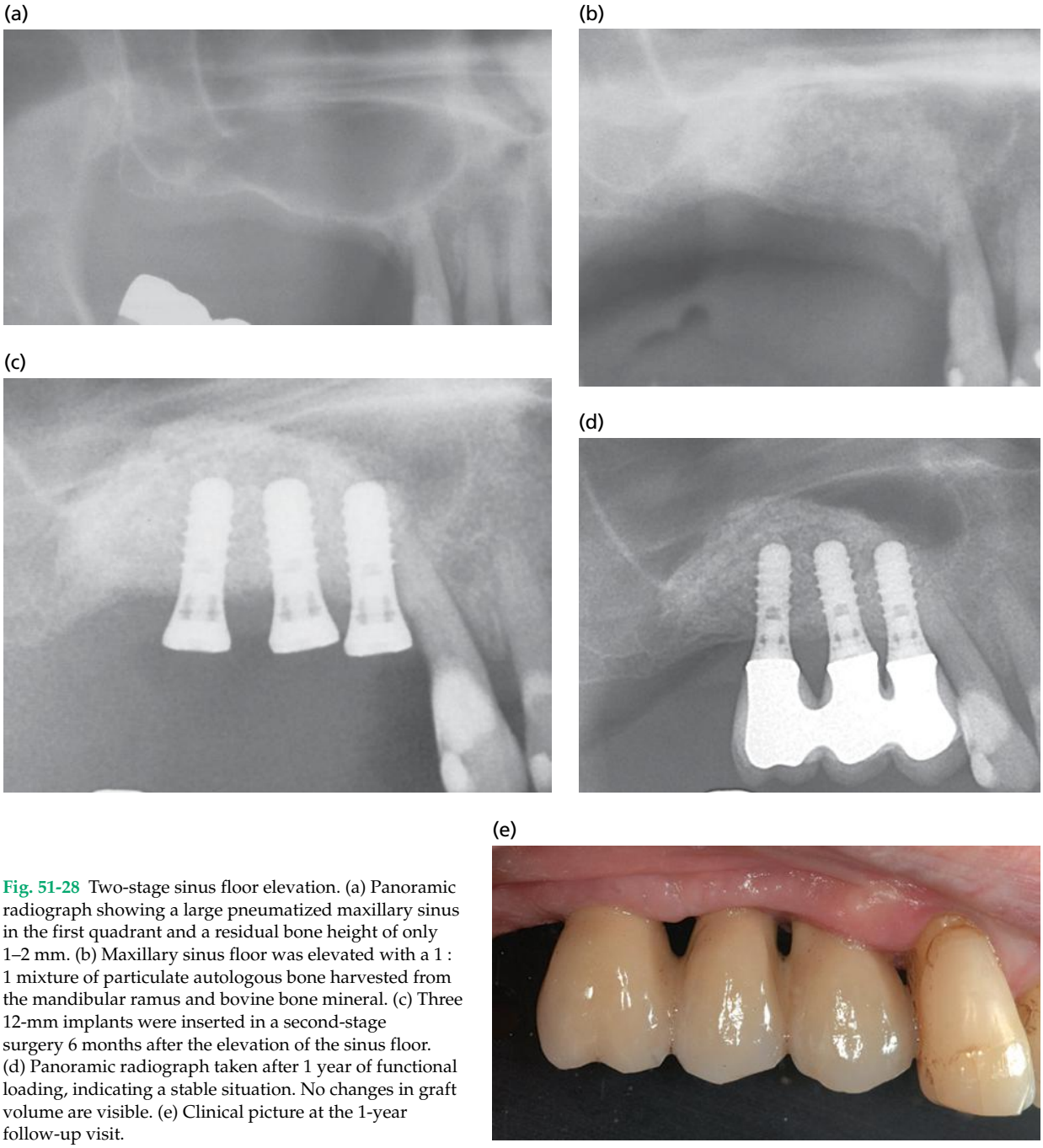

Fig. 51-28 Two-stage sinus floor elevation. (a) Panoramic radiograph showing a large pneumatized maxillary sinus in the first quadrant and a residual bone height of only 1–2 mm. (b) Maxillary sinus floor was elevated with a 1 : 1 mixture of particulate autologous bone harvested from the mandibular ramus and bovine bone mineral. (c) Three 12-mm implants were inserted in a second-stage surgery 6 months after the elevation of the sinus floor. (d) Panoramic radiograph taken after 1 year of functional loading, indicating a stable situation. No changes in graft volume are visible. (e) Clinical picture at the 1-year follow-up visit.

- Rough-surface implants yielded higher survival rates than machined-surface implants when placed in grafted sinuses.
- Implants placed into sinuses augmented with particulate autografts showed higher survival rates than those placed in sinuses that had been augmented with block grafts.
- Implant survival rates were higher when barrier membranes were placed over the lateral window.
- The utilization of grafts consisting of 100% autogenous bone or the inclusion of autogenous bone as a component of composite grafts did not affect implant survival.

A systematic review (Pjetursson *et al*. 2008) included 48 prospective and retrospective studies reporting on 12 020 implants inserted in combination with sinus floor elevation using the lateral approach. Meta-analysis of the included studies indicated an estimated annual failure rate of 3.48%, translating into a 3-year implant survival rate of 90.1% (95% CI 86.4–92.8%). However, when failure rates were analyzed at the subject level, the estimated annual failure rate was 6.04%, which translates to 16.6% of the subjects experiencing implant loss over a period of 3 years. One of the main conclusions of the meta-analysis was that the implant surface significantly affected the outcome of the treatment. The annual failure rate of machined-surface implants was 6.86% compared with an annual failure rate of 1.20% for rough-surface implants, which was a highly significant difference. The 3-year survival rate for rough-surface implants was 96.4% (95% CI 94.6–97.7%).

Sinus floor elevation with the transalveolar approach (osteotome technique)

The osteotome technique was first developed to compress soft, type III and IV maxillary bone. The concept is intended to increase the density of bone in the maxilla, leading to better primary stability of inserted dental implants.

In the maxilla, the bone crest in edentulous ridges is often narrow in the buccopalatal dimension. This limits the possibility of standard drilling when preparing an implant site. Thus, to address this difficult situation, tapered round osteotomes of increasing diameters have been used to expand the compactible cancellous maxillary bone and gently move it in a lateral direction to increase crestal width. This procedure is known as the "ridge expansion osteotome technique" and will not be addressed further in this chapter.

Tatum (1986) described the transalveolar approach to elevate the sinus floor. The osteotome technique for sinus floor elevation, using a set of osteotomes of varying diameters (Fig. 51-29) to prepare the implant site, was first presented by Summers (1994). The bone-added osteotome sinus floor elevation (BAOSFE), today referred to as the *Summers technique*, may be considered to be a more conservative and less invasive approach than the conventional lateral approach of sinus floor elevation. A small osteotomy is made through the crest of the edentulous ridge, at the inferior region of the maxillary sinus. This intrusion osteotomy procedure elevates the sinus membrane, thus creating a "tent" and space for bone graft placement and/or blood clot formation. It should be noted that the bone grafts are placed blindly into the space below the sinus membrane. Hence, the main disadvantage of this technique is the possibility of perforation of the sinus membrane. However, an endoscopic study has shown that the sinus floor can be elevated by up to 5 mm without perforating the membrane (Engelke & Deckwer 1997).

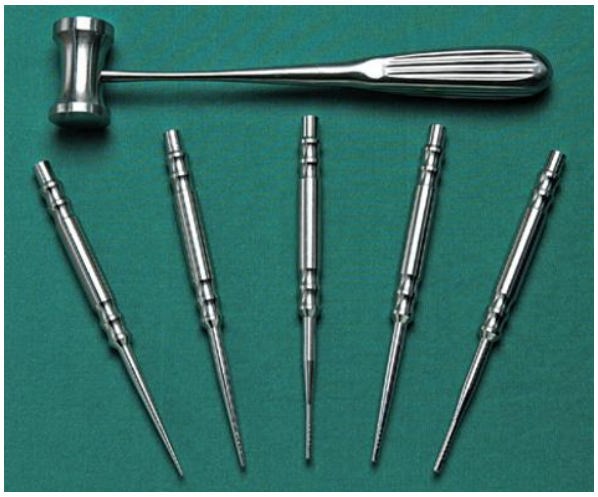

Fig. 51-29 Set of straight and tapered osteotomes used to prepare the implant site and to elevate the maxillary sinus floor.

Indications and contraindications

Indications for the transalveolar osteotome technique include a flat sinus floor with a residual bone height of at least 5 mm and adequate crestal bone width for implant installation.

Contraindications for the graft placement and/or blood clot formation technique are similar to those previously described for the lateral approach. In addition, however, patients with a history of inner ear complications and positional vertigo are not suitable for the osteotome technique. Regarding local contraindications, an oblique sinus floor (>45° inclination) is not suitable for the osteotome technique (Fig. 51-30), because osteotomes first enter the sinus cavity at the lower level of an oblique sinus floor, while still having bone resistance at the cranial level of the sinus floor. In this situation, there is a high risk of perforating the sinus membrane with the sharp margin of the osteotomes (Fig. 51-31).

Surgical technique

Only minor modifications (Rosen *et al*. 1999; Fugazzotto 2001; Chen & Cha 2005; Pjetursson *et al.* 2009a) to the original technique (Summers 1994) have been presented. The following describes a modification of the original technique:

1. Presurgical patient preparation includes oral rinsing with 0.1% chlorhexidine for a period of 1 minute.
2. Local anesthesia is administered into the buccal and palatal regions of the surgical area.
3. A mid-crestal incision with or without releasing incision is made and a full-thickness mucoperiosteal flap is raised.
4. With a surgical stent or a distance indicator, the implant positions are marked on the alveolar crest

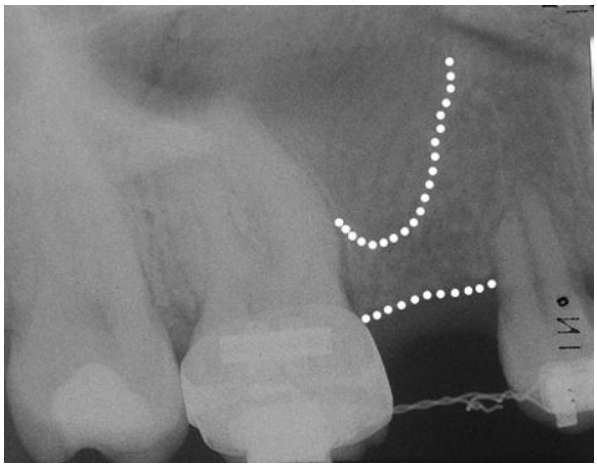

Fig. 51-30 Edentulous space in the position of tooth 15. The oblique inferior border of the maxillary sinus lies at approximately 60° to the inferior border of the alveolar crest (dotted lines represent the outlines of the residual bone). In a clinical situation like this, it is difficult to elevate the maxillary sinus floor with osteotomes and carries a high risk for perforating the sinus membrane.

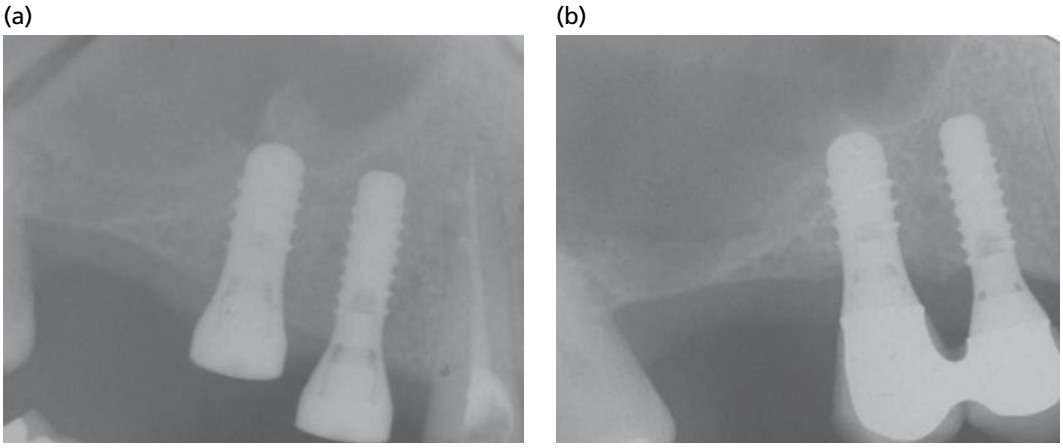

Fig. 51-31 (a) Sinus floor elevation was performed with the osteotome technique in a case with an oblique sinus floor. The cortical bone of the sinus floor was in-fractured and rolled-up, causing perforation of the sinus membrane. Due to the membrane perforation, no grafting material was utilized. (b) Same patient at the 5-year follow-up visit. The implant was stable, but only minor new bone formation is visible at the distal aspect of the implant.

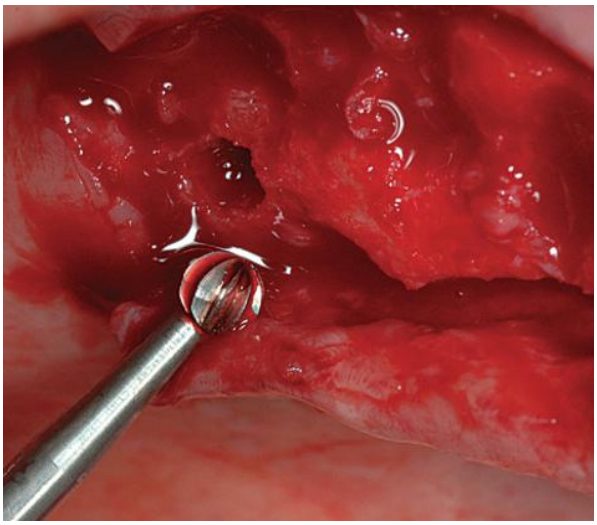

Fig. 51-32 Exact position of the implant site is first marked with a small round bur (#1) and then extended with two sizes of round burs (#2 and #3) to a diameter about 0.5–1 mm smaller than that of the implant to be installed.

with a small round bur (#1). After precisely locating the implant positions, the openings of the preparations are widened with two sizes of round burs (#2 and #3) to a diameter about 0.5–1 mm smaller than the implant diameter to be placed (Fig. 51-32).

5. The distance from the crestal floor of the ridge to the floor of the maxillary sinus, measured on the preoperative radiograph prior to implant site preparation, can, in most cases, be confirmed at surgery by penetrating the opening of the preparation with a blunt periodontal probe through the soft trabecular bone (type III or IV bone) to the floor of the maxillary sinus.
6. After confirming the distance to the sinus floor, pilot drills with small diameters (1–1.5 mm smaller than the implant diameter) are used to prepare the implant site to a distance approximately 2 mm below the sinus floor (Fig. 51-33a). In cases of soft type IV bone and a residual bone height of 5–6 mm, there is usually no need to use the pilot drills. It is sufficient to perforate the cortical bone at the alveolar crest with the round burs.
7. The first osteotome used in the implant site is tapered and has a small diameter (Fig. 51-34). With light malleting, the osteotome is pushed towards the compact bone of the sinus floor (Fig. 51-33b). After reaching the sinus floor, the osteotome is pushed about 1 mm further with light malleting in order to create a "greenstick" fracture on the compact bone of the sinus floor. A tapered osteotome of small diameter is chosen to minimize the force needed to fracture the compact bone.
8. The second tapered osteotome, with a diameter slightly larger then the first one, is used to increase the fracture area of the sinus floor (Fig. 51-35). It is applied to the same distance as the first one.
9. The third osteotome used is straight and has a diameter about 1–1.5 mm smaller than the implant to be placed (Fig. 51-36). Instead of using the osteotomes to fracture the sinus floor, piezoelectric surgery can be used. The advantage of the latter technique is that the perforation of the sinus floor may be achieved in a more controlled way than with osteotomes, and the risk of membrane perforation is thus reduced (Sohn *et al.* 2009). Moreover, this technique could reduce the risk of benign paroxysmal positional vertigo. The main disadvantage of this technique is that it is more time consuming than malleting, especially when the cortical bone at the sinus floor is relatively thick.

From this point onwards, the technique utilized in the surgical procedure depends on whether or not bone grafts or bone substitutes are to be placed.

Implant placement without grafting material

1. Without applying grafting material, the straight osteotome with a diameter about 1–1.5 mm smaller than that of the implant is pushed further into the sinus cavity until it penetrates the sinus floor.

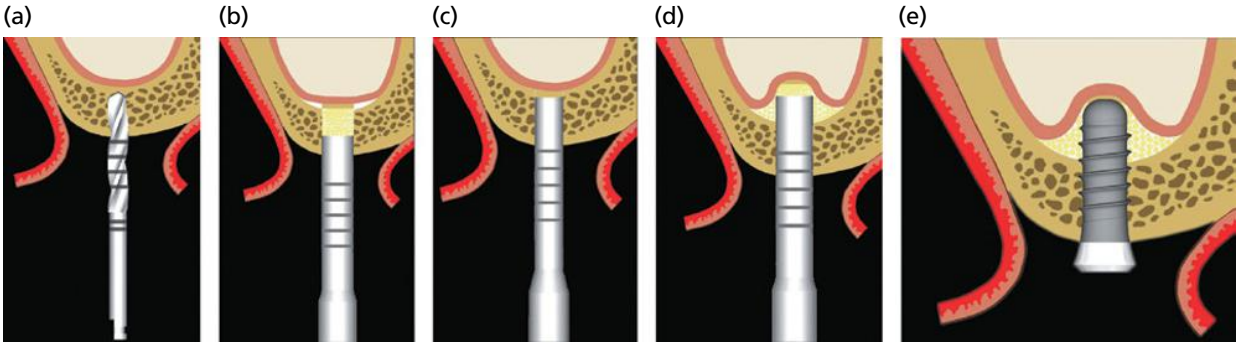

Fig. 51-33 (a) Implant site is prepared to a distance of approximately 2 mm below the sinus floor with a small diameter pilot drill. (b) After reaching the sinus floor, the osteotome is pushed approximately 1 mm further with light malleting in order to create a "greenstick" fracture on the compact bone of the sinus floor. (c) Grafting material is slowly pushed into the sinus cavity with a straight osteotome. This procedure is repeated several times. (d) Tip of the osteotome is only supposed to enter the sinus cavity after some grafting material has been pushed through the preparation site to elevate the sinus membrane. (e) Inserted implant and the grafting material maintain space below the sinus membrane.

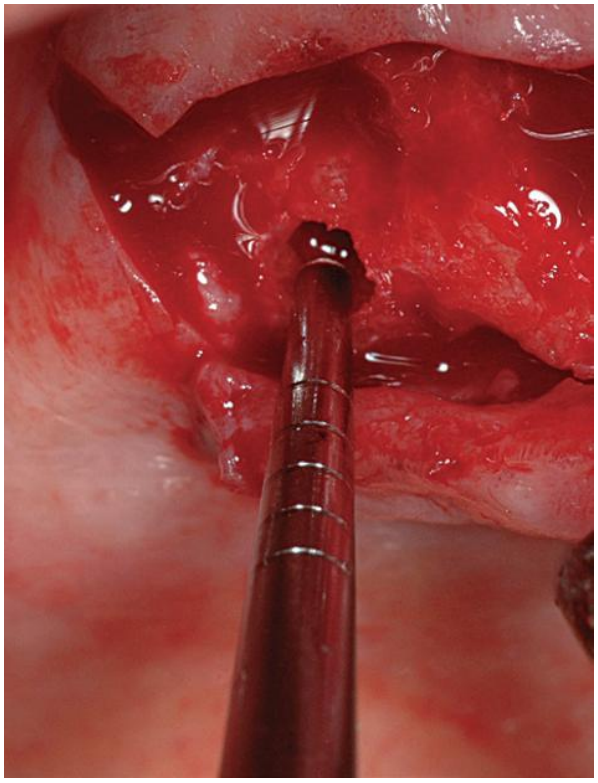

Fig. 51-34 First osteotome used in the implant site is a small-diameter tapered osteotome. Such an osteotome is chosen to minimize the force needed to fracture the compact bone.

2. The last osteotome to be used must have a form and diameter that are suitable for the implant to be placed. For example, for a cylindrical implant with a diameter of 4.1 mm, the last osteotome should be a straight osteotome with a diameter about 0.5 mm smaller than the implant diameter (3.5 mm). It is important that the last osteotome only enters the preparation site once (Fig. 51-37). If several attempts have to be made in sites with soft bone (type III or IV), there is a risk of increasing the diameter of the preparation and this may jeopardize achieving good primary stability. On the other hand, if the last osteotome diameter is too small compared to the implant diameter, too much force

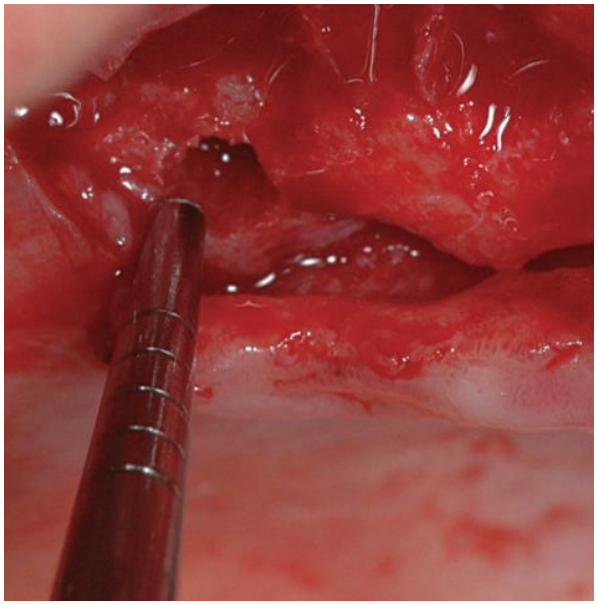

Fig. 51-35 Second osteotome, which is also tapered, but with a diameter slightly larger then the first one, is used to increase the fractured area of the sinus floor.

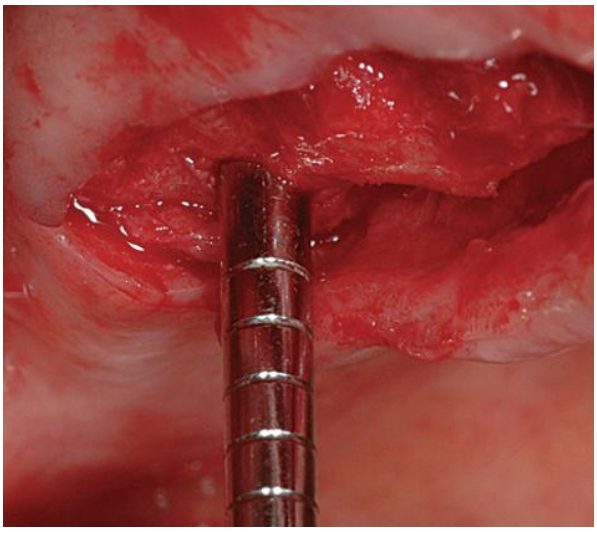

Fig. 51-36 Third osteotome used is a straight osteotome with a diameter about 1–1.5 mm smaller than that of the implant to be placed.

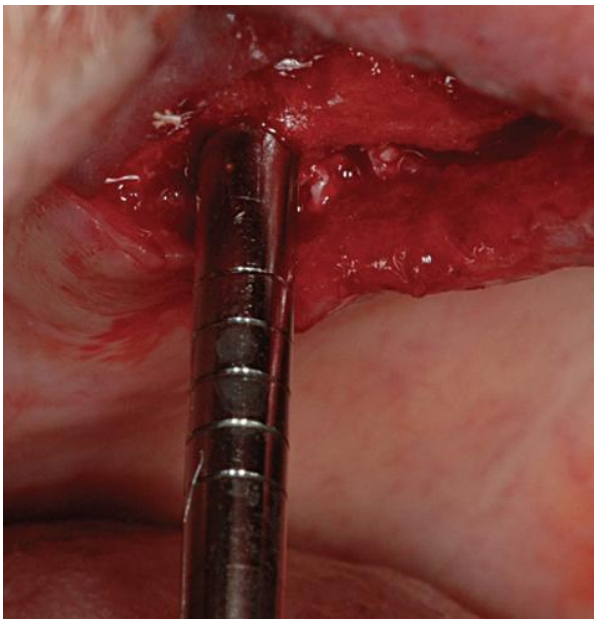

Fig. 51-37 Last osteotome used must have a form and diameter that are suitable for the implant to be placed. It is important that the last osteotome is allowed to enter the preparation site only once.

must be used to insert the implant. By squeezing the bone, more bone trauma and, hence, greater bone resorption will occur, delaying the osseointegration process (Abrahamsson *et al*. 2004). It is thus important, especially when placing implants in sites with reduced bone volume, that the fine balance between good primary stability and traumatizing the bone is respected.

3. During the entire preparation, it is crucial to maintain precise control over the penetration length. Regular osteotomes have sharp cutting edges; thus, their entry into the sinus cavity increases the risk of membrane perforation. The final step before placing the implant is to check that the preparation is patent to the planned insertion depth. An osteotome with a rounded tip or a depth gauge is pushed to a depth that is relevant for the implant diameter (Fig. 51-38).

Implant placement with grafting materials

1. When performing the osteotome technique with grafting materials, the osteotomes are not supposed to enter the sinus cavity *per se*. Repositioned bone particles, grafting materials, and the trapped fluid will create a hydraulic effect that moves the fractured sinus floor and sinus membrane upwards. The sinus membrane is less likely to tear under this kind of pressure.
2. After pushing the third osteotome up to the sinus floor and before placement of any grafting material, the sinus membrane must by tested for any perforations. This is done with the Valsalva maneuver (nose blowing). The patient compresses his/her nostrils (Fig. 51-39), and then blows his/her nose. If air leaks out of the implant site, the sinus membrane is perforated, and no grafting material should be placed into the sinus cavity.
3. If the sinus membrane is judged to be intact, the preparation is filled with grafting material (Fig. 51-40). The grafting material is then slowly pushed into the sinus cavity with the same straight third osteotome (Fig. 51-41). This procedure is repeated

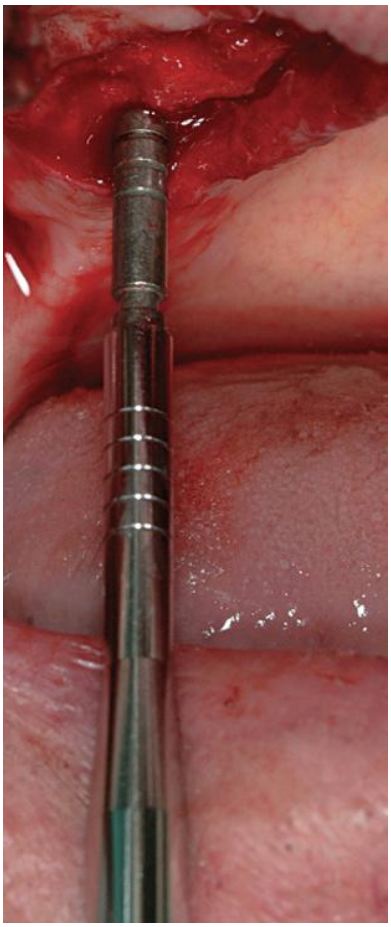

Fig. 51-38 Final step before placing the implant is to check that the preparation is patent to the planned insertion depth. An osteotome with a rounded tip or a depth gauge is pushed to a depth that is relevant for the diameter of the implant.

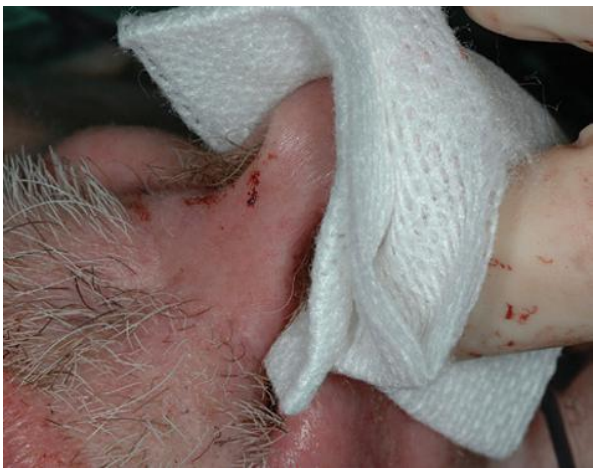

Fig. 51-39 Testing the sinus membrane for perforation.

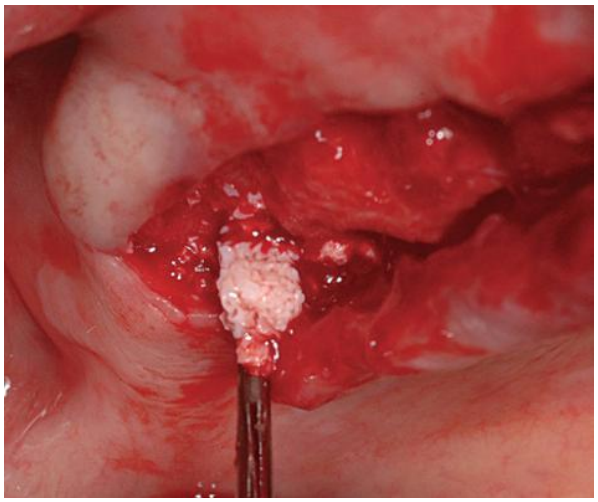

Fig. 51-40 Preparation site is filled four to five times with grafting material.

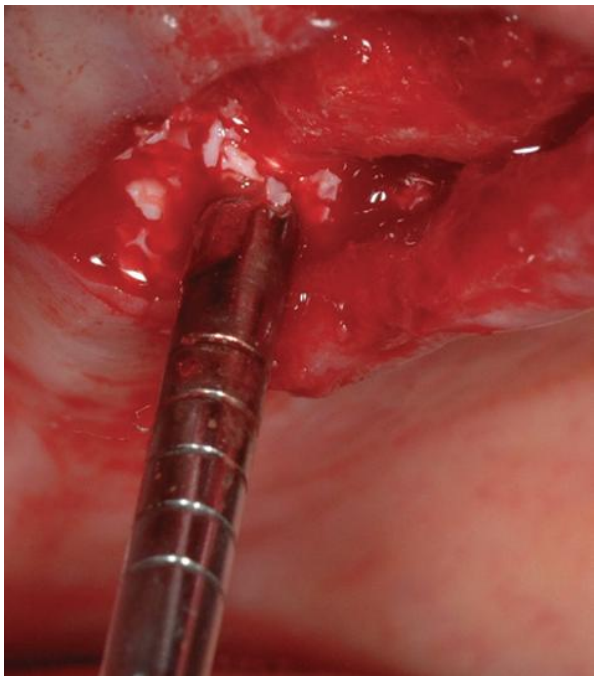

Fig. 51-41 Grafting material is then slowly pushed into the sinus cavity with a straight osteotome with a diameter about 1–1.5 mm smaller than that of the intended implant.

four to five times (see Fig. 51-33c) until about 0.2–0.3 g of grafting material has been pushed into the sinus cavity below the sinus membrane (Fig. 51-42). On the fourth and fifth time of applying grafting material, the tip of the osteotome may enter the maxillary sinus cavity by about 1 mm to test if there is resistance in the preparation site (see Fig. 51-31d).

4. Finally, before implant placement (Fig. 51-43), the preparation is checked for patency by repeating the Valsalva maneuver.

To achieve good primary stability in the soft trabecular bone on the posterior maxilla, implants with a slightly tapered configuration or implants with a

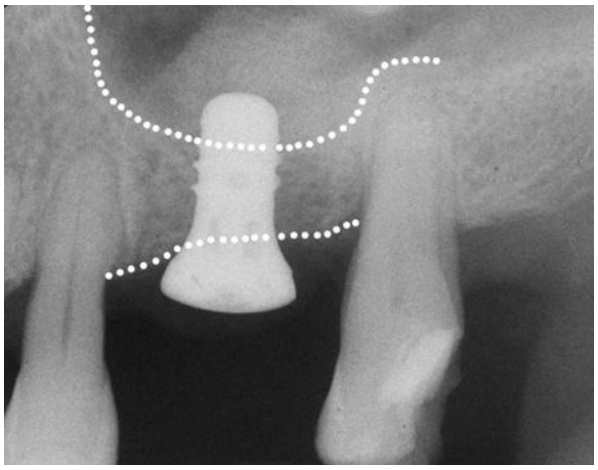

Fig. 51-42 Radiograph, taken after implant placement, showing a dome-shaped configuration of the graft. 0.25 g of grafting material (xenograft) was used to elevate the sinus membrane (dotted lines represent the outlines of the residual bone).

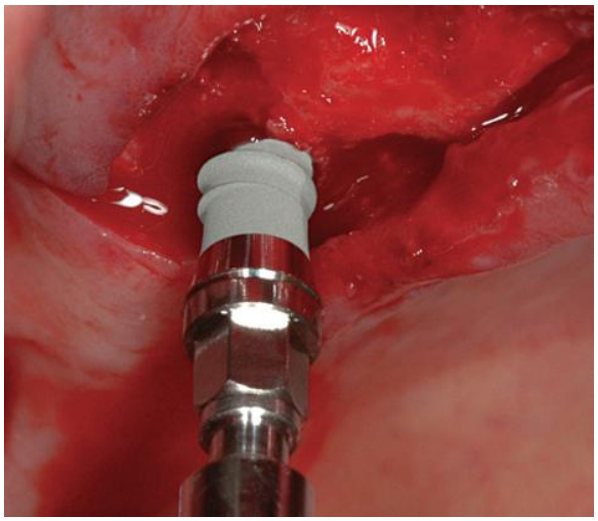

Fig. 51-43 Rough-textured implant was installed after preparing the implant site with the osteotome technique. Good primary stability was achieved.

tulip-shaped neck are recommended. However, it must always be kept in mind that applying too much force on the bone will result in greater bone resorption, delaying the osseointegration process (Abrahamsson *et al*. 2004).

Post-surgical care

The post-surgical care after placing implants with the osteotome technique is similar to that after standard implant placement. In addition to the standard oral home care, antiseptic rinsing with 0.1–0.2% chlorhexidine twice daily for the first 3 weeks after surgery is highly recommended. Although there have been no studies comparing post-surgical care with and without the use of prophylactic antibiotics, antibiotic prophylaxis for 1 week has been recommended in cases where bone substitutes are used.

Complications

Just as with the lateral approach, when performing transalveolar sinus floor elevation, the risk of complications must be considered and their appropriate treatment foreseen.

Again, the most common intraoperative complication is perforation of the sinus membrane. The bone grafts are placed blindly into the space below the sinus membrane and as a result there is the possibility of perforation of the sinus membrane. The presence of maxillary sinus septa and root apices penetrating into the sinus may increase the risk of membrane perforation. In a recent systematic review addressing the transalveolar sinus floor elevation in eight studies with 1621 implants, the incidence of perforation of the Schneiderian membrane varied between 0% and 21.4%, with a mean of 3.8% (Tan *et al.* 2008). Smaller perforations may be closed through the transalveolar preparation using tissue fibrin glue. In cases of larger perforations, access to close the window must be achieved through a lateral window. If the perforation occurs before any grafting material is inserted, the procedure should be aborted or shorter implants used.

Postoperative infections after transalveolar sinus floor elevation are rare complications (0–2.5%, mean 0.8%) (Tan *et al.* 2008). Other reported complications include postoperative hemorrhage, nasal bleeding, blocked nose, hematomas, and loosening of cover screws resulting in suppuration and benign paroxysmal positional vertigo (BPPV). BPPV may cause the patient substantial stress if not correctly identified and properly managed (Vernamonte *et al.* 2011). No air embolism was reported in the study using hydraulic sinus condensation (Chen & Cha 2005).

Pjetursson *et al.* (2009a) evaluated patient-centered outcomes after implant placement using the transalveolar approach. Of the 163 patients included in this study, 23% found the surgical experience unpleasant. When asked about other post-surgical complications, 5% of the patients felt their head was tilted too far back during the surgery, and 5% experienced vertigo, nausea and felt disoriented after the surgical procedure. Never the less, 90% of the patients would be willing to undergo implant therapy again if necessary and dentally indicated.

Grafting material

As discussed above for the lateral approach, there is still controversy with regards to the necessity of using grafting material to maintain the space for new bone formation after elevating the sinus membrane utilizing the osteotome technique.

In the original publication describing the transalveolar approach, Tatum (1986) did not use any grafting material to increase and maintain the volume of the elevated area. Later, Summers (1994) introduced the BAOSFE and a multicenter retrospective study of eight centers was initiated. Evaluation was carried out for 174 implants placed in 101 patients, with the type of grafting material used decided by the individual clinician. Autografts, allografts, and xenografts were used, alone or in combinations. The authors concluded that the type of grafting material did not influence implant survival (Rosen *et al*. 1999).

Of 19 studies included in a recent systematic review (Tan *et al*. 2008), 15 used grafting material, in three the procedure was performed without graft placement, and one did not report whether or not grafting material was used.

A recent clinical study (Nedir *et al.* 2010) reported on 25 10-mm dental implants inserted using the transalveolar approach without grafting material. The implants protruded on average 4.9 mm into the sinus cavity after surgery. After a follow-up of 5 years, the implant protrusion was reduced to 1.5 mm. Hence, 3.4 mm (70%) of the penetrating part of the implants showed spontaneous bone formation. In another clinical study, sinus floor remodeling after implant insertion using a modified transalveolar technique without grafting material was assessed radiographically (Schmidlin *et al.* 2008). The implant survival rate in the 24 patients available for follow-up was 100%. Bone filling around the implants was measured and compared with baseline digital radiographs. The mean height of the newly formed bone was 2.2 mm mesially and 2.5 mm distally, or 86.3% and 89.7% of new bone formation, respectively.

In a prospective study, 252 implants were inserted using the transalveolar sinus floor elevation technique with or without grafting material (Pjetursson *et al*. 2009b). For 35% of these implants, deproteinized bovine bone mineral with a particle size of 0.25–1 mm was used as grafting material, but for the remaining 164 implants, no grafting material was utilized. The mean radiographic bone gain using the transalveolar technique with grafting material was significantly more (4.1 mm, SD 2.4 mm) than that when no grafting material was used (1.7 mm, SD 2.0 mm). When grafting material is used, a cloudy dome-shaped structure with a hazy demarcation may be visible after implant placement. The size of this dome is usually reduced after remodeling but still increases the bone volume compared to the preoperative situation (Pjetursson *et al*. 2009b) (Fig. 51-44).

Brägger *et al.* (2004) investigated the patterns of tissue remodeling after placement of 25 implants in 19 patients using the osteotome technique with composite xenografts and autografts. Intraoral radiographs were obtained presurgically and post-surgically at 3 and 12 months. The mean height of the new bone apical and mesial to the implants was 1.52 mm at surgery, but this was reduced significantly to 1.24 mm at 3 months and 0.29 mm after 12 months (Fig. 51-45). It was concluded that the grafted area apical to the implants underwent shrinkage and remodeling (Fig. 51-46), and the original outline of the sinus was eventually consolidated and replaced by a new cortical plate.

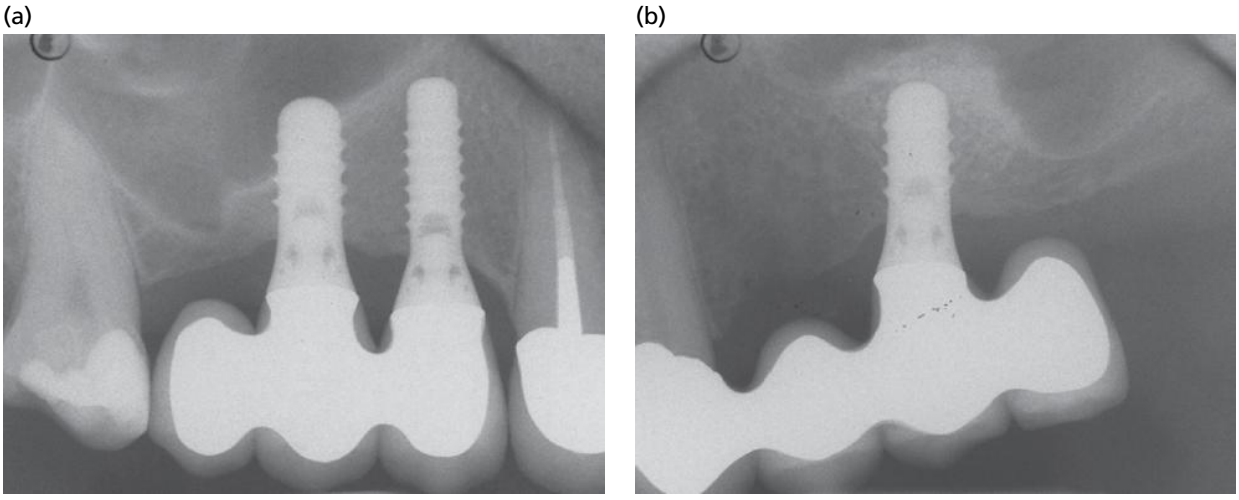

Fig. 51-44 (a) Radiograph taken at the 5-year follow-up visit of an implant placed in the first quadrant utilizing the osteotome technique without grafting material. A new cortical bony plate at the inferior border of the maxillary sinus is clearly visible, but no bony structure can be detected apical to the implant. (b) Radiograph (same patient) taken after 5 years in function of an implant placed in the second quadrant utilizing the osteotome technique with xenograft grafting material. A dome-shaped structure is clearly visible, documenting a definite increase in bone volume compared to the initial situation. The "dome" is surrounded by a new cortical bony plate.

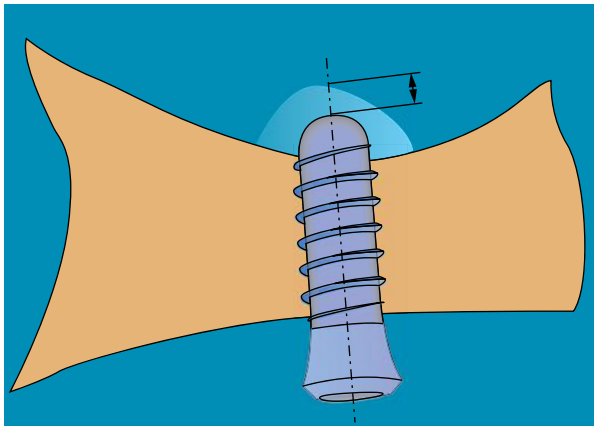

Fig. 51-45 Grafted area apical to the implants undergoes shrinkage and remodeling and the original border of the sinus is eventually consolidated and replaced by a new cortical plate. (Source: Brägger *et al*. 2004. Reproduced with permission from John Wiley & Sons.)

Success and implant survival

In a multicenter retrospective study evaluating the Summers technique applied to the placement of 174 implants in 101 patients, the implant survival rate was 96% when residual bone height was 5 mm or more, but dropped to 85.7% when residual bone height was 4 mm or less (Fig. 51-47) (Rosen *et al*. 1999). Similar results were reported in a recent prospective study in which 20% of the implants were placed in sites with residual bone height of <5 mm (Pjetursson *et al*. 2009a), which tested the limits of the osteotome technique. The survival rates were 91.3% for implant sites with ≤4 mm of residual bone height and 90% for sites with a residual bone height between 4 and 5 mm, compared with 100% for sites with a residual bone height of >5 mm. Moreover, for short 6-mm implants, the survival rate was only 48%. This clearly demonstrated that the transalveolar sinus floor elevation technique was most predictable when the residual alveolar bone height was ≥5 mm and with implants of ≥8 mm. This in turn indicates that the limit of the osteotome technique has been tested.

A recent systematic review (Tan *et al*. 2008) analyzed the survival and complication rates of implants inserted in combination with transalveolar sinus floor elevation. Meta-analysis of the 19 included studies indicated an estimated annual failure rate of 2.48%, which translates to an estimated survival rate of 92.8% (95% CI 87.4–96.0%) for implants placed in transalveolarly augmented sinuses after 3 years in function. Furthermore, subject-based analysis revealed an annual failure of 3.71%, which translates to implant loss in 10.5% of the subjects over 3 years.

Short implants

In the light of sinus floor elevation techniques being indicated to facilitate the installation of dental implants in the maxillary posterior region without adequate bone volume, these treatment alternatives have to be discussed with the patient (see Chapter 32). However, since patient-centered outcomes and morbidity associated with these procedures have not been addressed so far, it has to be anticipated that a great number of patients may not choose sinus floor elevation for their treatment. Hence, shortened dental arches (Käyser 1981) may have to be considered in treatment planning.

A variation to conventional implant installation in the posterior maxilla is the choice of short implants to avoid penetration into the sinus cavity. Jemt and Lekholm (1995) reported that implant failure in edentulous maxilla correlated significantly with bone quality, especially for short (7 mm) implants. Other

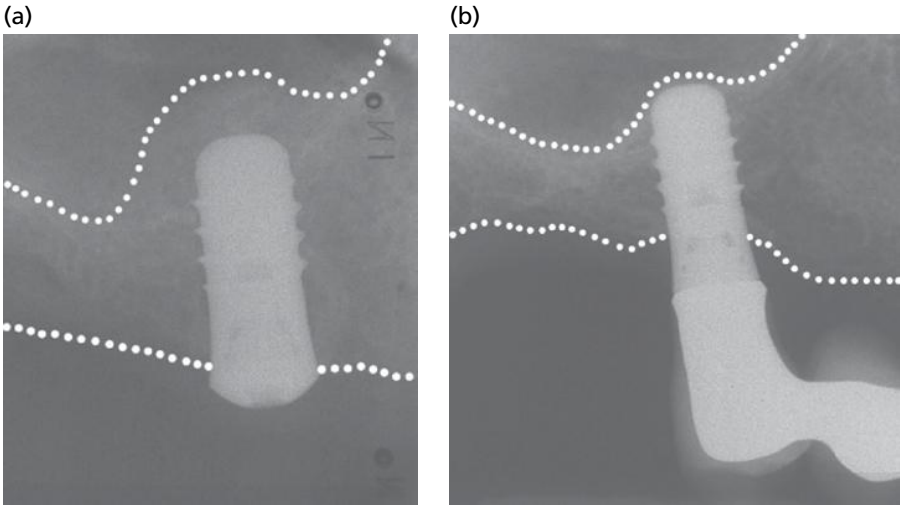

Fig. 51-46 (a) Radiograph taken immediately after implant insertion with the osteotome technique and grafting material, showing a cloudy dome-shaped structure extending 2–3 mm apical to the implant. (b) Radiograph of the same implant taken 1 year later showing significant reduction of the size of the "dome", but the new bony structure is clearly visible apical to the implant (dotted lines represent the outlines of the grafting material and the residual bone).

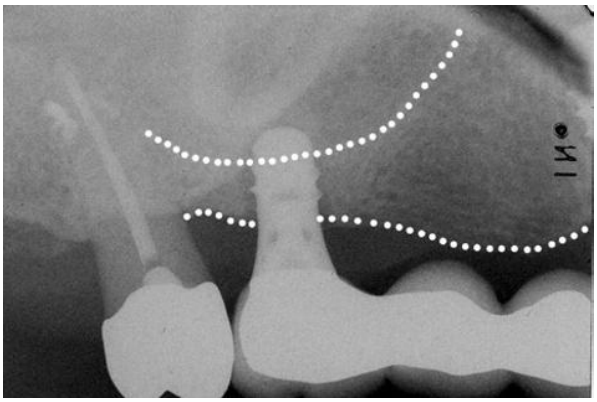

Fig. 51-47 Radiograph of a 6-mm implant that was inserted utilizing the osteotome technique without grafting material. The residual bone height was only 3 mm. After 6 months of functional loading, the implant became loose and had to be removed. After a healing time of 2 months, the maxillary sinus floor was elevated with the lateral approach and two new implants were placed simultaneously (dotted lines represent the outlines of the residual bone).

studies (Friberg *et al*. 1991; Jaffin & Berman 1991) have also reported low survival rates of short implants. However, it must be kept in mind that all these studies reported on implants with machined-surface geometries. Based on these studies and others, the clinical "dogma" has been followed that, generally, only long implants should be inserted in type IV "poor-quality" bone in the posterior maxilla.

A targeted review of study outcomes with short (7 mm) implants placed in partially edentulous patients concluded that machined-surface implants experienced greater failure rates than rough-surface implants (Hagi *et al*. 2004). The implant surface geometry appeared to be a major determinant of the performance of these short implants.

In a multicenter study evaluating 6-mm non-submerged rough-surface dental implants, only one of 208 short implants placed in the mandible was lost compared to six of 45 short implants placed in the maxilla (ten Bruggenkate *et al*. 1998). Four of the implants were lost during the healing phase, with three remaining in function. The survival rates were 99.5% and 86.7%, respectively, after a follow-up of up to 7 years.

In contrast, clinical studies on short implants with rough surfaces, designed for high initial stability, reported survival rates of about 95% (Fugazzotto *et al*. 2004; Renouard & Nisand 2005), which correlates with the survival rate reported for implants after 5 years in a systematic review (Berglundh *et al*. 2002). Two multicenter studies on rough-surface implants (Buser *et al*. 1997; Brocard *et al*. 2000) analyzed the survival and success rates of implants of different lengths. No significant differences were found between 8-, 10-, and 12-mm implants with rough-surface geometry after up to 8 years of follow-up.

The most recent review prepared for the Consensus Meeting of the European Association of Osseointegration (EAO) (Renouard & Nisand 2006) concluded on the basis of 12 studies on machined-surface implants and 22 studies on rough-textured implants meeting the inclusion criteria, that the survival and success rates of short (<10 mm) implants were comparable to those obtained with longer implants, provided that surgical preparation was related to bone density, rough-textured implants were employed, and operators' surgical skills were developed.

The use of short implants may be considered in sites thought unfavorable for implant placement, such as those associated with bone resorption or previous injury and trauma. While in these situations implant failure rates may be increased, outcomes should be compared with those associated with advanced surgical procedures such as bone grafting and sinus floor elevation.

Conclusion and clinical suggestions

In the posterior maxilla, implants with a morphometry designed to achieve high initial stability and a rough surface geometry giving high bone-to-implant contact during the initial healing phase (Abrahamsson *et al*. 2004) are preferred. Implants with slightly conical morphometry or implants with a wider implant neck tend to give better primary stability in cases of reduced residual bone height and soft bone geometry.

The clinical decision on which method (short implants, transalveolar approach or lateral approach) should be chosen, depends on the residual bone height of the alveolar crest and the surgeon's' preference. The following are suggested recommendations:

- Residual bone height of ≥8 mm and a flat sinus floor: standard implant placement (Fig. 51-48).
- Residual bone height of ≥8 mm and an oblique sinus floor: standard implant placement using a short implant or elevation of the maxillary sinus floor using the osteotome technique without grafting material (Fig. 51-49).
- Residual bone height of 5–7 mm and a relatively flat sinus floor: elevation of the maxillary sinus floor using the osteotome technique with grafting material that is resistant to resorption (Fig. 51-50).
- Residual bone height of 5–7 mm and an oblique sinus floor: elevation of the maxillary sinus floor using the lateral approach with grafting material, and simultaneous implant placement (one-stage) (Fig. 51-51).
- Residual bone height of 3–4 mm and a flat or oblique sinus floor: elevation of the maxillary sinus floor using the lateral approach with grafting

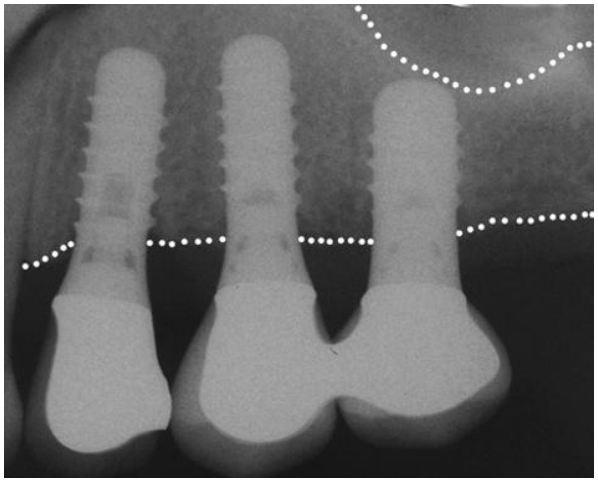

Fig. 51-48 Radiograph of a short (8 mm) implant in the posterior maxilla (dotted lines represent the outlines of the residual bone).

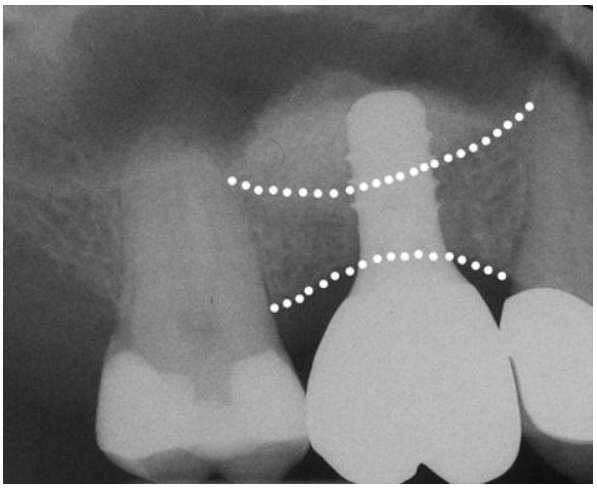

Fig. 51-50 Radiograph of an implant inserted in the posterior maxilla with a flat sinus floor and a residual bone height of 5–6 mm. The osteotome technique with grafting material was used. The radiograph shows a dome-shaped formation covering the entire apex of the implant (dotted lines represent the outlines of the residual bone).

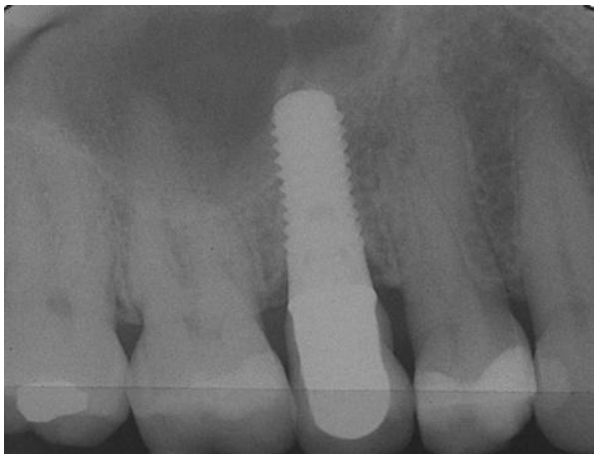

Fig. 51-49 Radiograph of an implant inserted in the posterior maxilla with an oblique sinus floor and a residual bone height of 8–10 mm. The osteotome technique without grafting material was used. The distal aspect of the apex of the implant extends into the sinus cavity, but the mesial aspect is covered with residual bone.

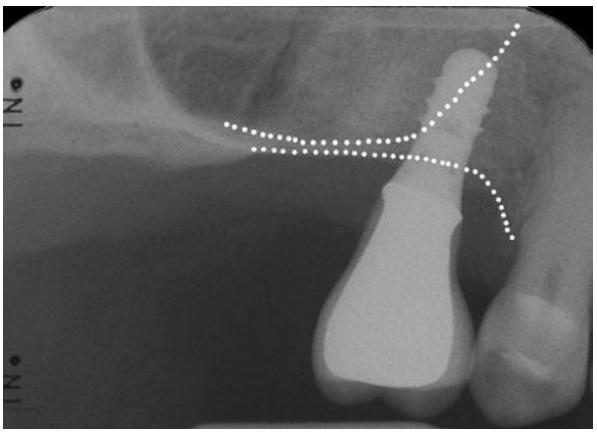

Fig. 51-51 Radiograph of an implant inserted in the posterior maxilla with an oblique sinus floor and a residual bone height between 2 and 8 mm. The maxillary sinus floor was elevated using the lateral approach and one implant was inserted simultaneously (dotted lines represent the outlines of the residual bone).

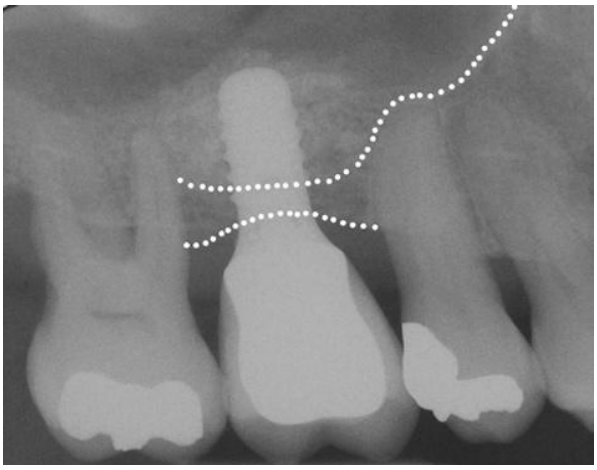

Fig. 51-52 Radiograph of an implant inserted in the posterior maxilla with a flat sinus floor and a residual bone height between 2 and 3 mm. The maxillary sinus floor was elevated using the lateral approach, and one implant was inserted simultaneously (dotted lines represent the outlines of the residual bone).

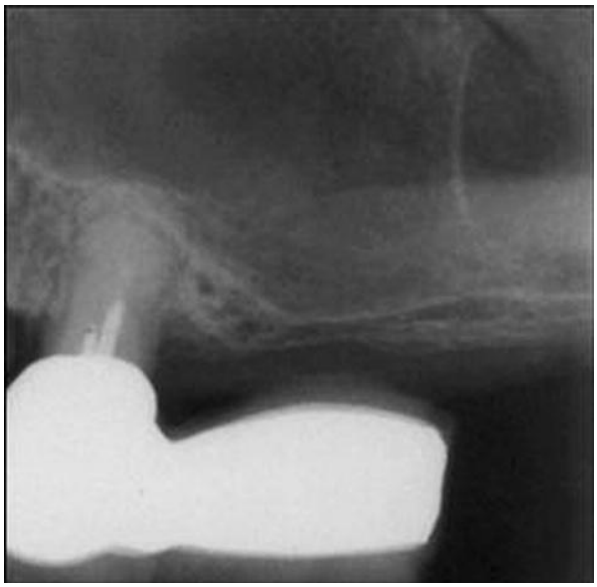

Fig. 51-53 Radiograph showing a large pneumatized maxillary sinus, where a two-stage sinus floor elevation with a delayed implant insertion has had to be used.

material, and simultaneous implant placement (one-stage) (Fig. 51-52).

- Residual bone height of 1–2 mm and a flat or oblique sinus floor: elevation of the maxillary sinus floor using the lateral approach with grafting material and delayed implant placement 4–8 months later (two-stage) (Fig. 51-53).

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Part 16: Occlusal and Prosthetic Therapy

Chapter 52

Tooth-Supported Fixed Dental Prostheses

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Clinical symptoms of trauma from occlusion

Angular bony defects

It has been claimed that *angular bony defects* and *increased tooth mobility* are important symptoms of trauma from occlusion (Glickman 1965, 1967). The validity of this suggestion has, however, been questioned (see Chapter 14). Thus, angular bony defects have been found at teeth affected by *trauma from occlusion* as well as at teeth with normal occlusal function (Waerhaug 1979). This means that the presence of angular bony defects *cannot per se* be regarded as an exclusive symptom of trauma from occlusion.

Increased tooth mobility

Increased tooth mobility, determined clinically, is expressed in terms of amplitude of displacement of the crown of the tooth. Increased tooth mobility can, indeed, be observed in conjunction with *trauma from occlusion*. It may, however, also be the result of a reduction of the height of the alveolar bone with or without an accompanying angular bony defect caused by plaque-associated periodontal disease (see Chapter 16). Increased tooth mobility resulting from occlusal interferences may further indicate that the periodontal structures have adapted to an altered functional demand, that is a widened periodontal ligament with a normal tissue composition has become the end result of a previous phase of progressive tooth mobility (see Chapter 16) associated with trauma from occlusion.

Progressive (increasing) tooth mobility

In Chapter 16, it was concluded that the diagnosis of trauma from occlusion should be used solely in situations where a progressive mobility could be observed. Progressive tooth mobility can be identified only through a series of repeated tooth mobility measurements carried out over a period of several days or weeks.

Tooth mobility crown excursion/root displacement

Initial and secondary tooth mobility

A tooth which is surrounded by a normal periodontium may be moved (displaced) in horizontal and vertical directions, and may also be forced to perform limited rotational movements. Clinically, tooth

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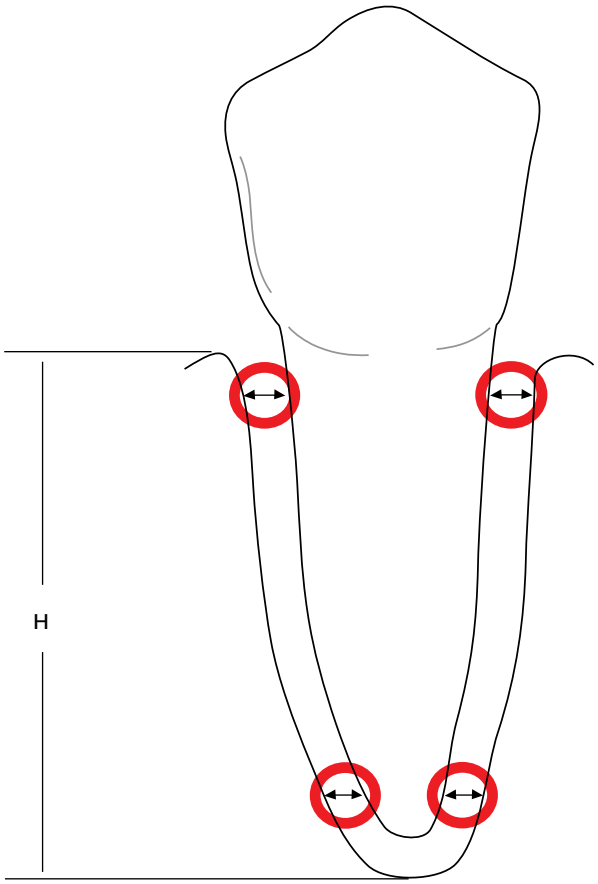

Fig. 52-1 Mobility of a tooth in a horizontal direction is dependent on the height of the alveolar bone (H), width of the periodontal ligament (encircled arrows), and shape and number of roots.

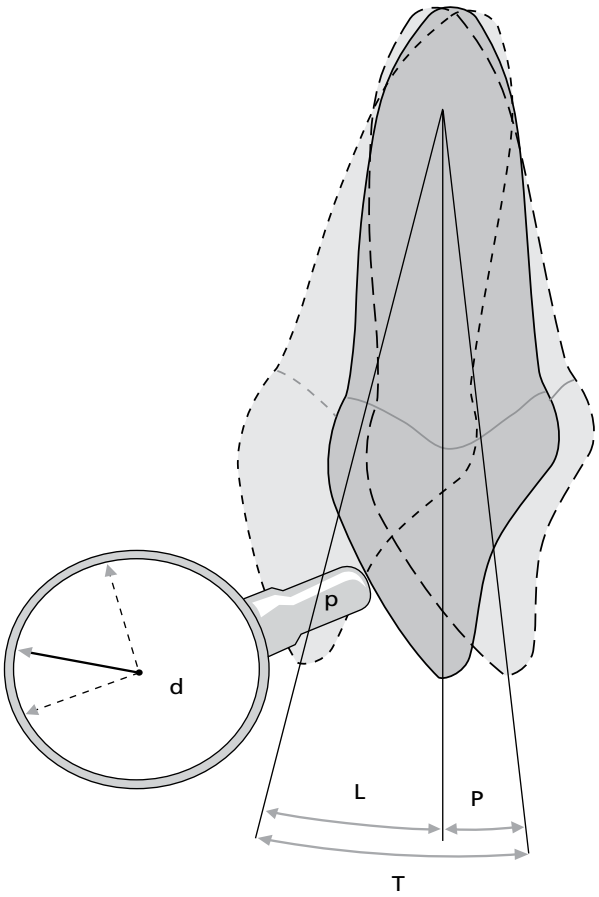

Fig. 52-2 Tooth mobility measurements by means of the Periodontometer. T = L + P = total excursion of the crown. (d, dial indicator; p, pointer; L, labial excursion of the crown; P, palatal excursion of the crown.)

mobility is usually assessed by exposing the crown of the tooth to a certain force and determining the distance the crown can be displaced in the buccal and/or lingual direction. The mobility (= movability) of a tooth in a horizontal direction is highly dependent on the height of the surrounding supporting bone, the width of the periodontal ligament, and the shape and number of roots present (Fig. 52-1).

The mechanism of tooth mobility was studied in detail by Mühlemann (1954, 1960) who described a standardized method for measuring even minor tooth displacements. Using the "Periodontometer", a small force [~45 kg (100 lb)] is applied to the crown of a tooth (Fig. 52-2). The crown starts to tip in the direction of the force. The resistance of the tooth-supporting structures against displacement of the root is low in the initial phase of force application and the crown is moved only 5/100–10/100 mm. This movement of the tooth was called "*initial tooth mobility*" (ITM) by Mühlemann (1954) and is the result of an *intra-alveolar* displacement of the root (Fig. 52-3). In the pressure zone (see Chapter 16), there is a 10% reduction in the width of the periodontal ligament and in the tension zone there is a corresponding increase. Mühlemann and Zander (1954) stated that "there are good reasons to assume that the initial displacement of the root (ITM)

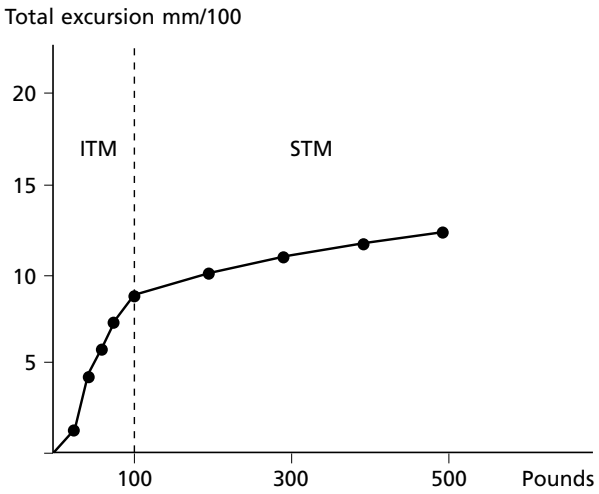

Fig. 52-3 Initial tooth mobility (ITM) is the excursion of the crown of a tooth when a force of 100 lb is applied to the crown. Secondary tooth mobility (STM) is the excursion of the crown of the tooth when a force of 500 lb is applied.

corresponds to a reorientation of the periodontal membrane fibers into a position of functional readiness towards tensile strength". The magnitude of the ITM varies from individual to individual, and from tooth to tooth, and is mainly dependent on the structure and organization of the periodontal

ligament. The ITM value of ankylosed teeth is therefore zero.

When a larger force [~225 kg (500 lb)] is applied to the crown, the fiber bundles on the tension side cannot offer sufficient resistance to further root displacement. The additional displacement of the crown that is observed in "*secondary tooth mobility*" (STM) (Fig. 52-3) occurs as a result of distortion and compression of the periodontium on the pressure side. According to Mühlemann (1960), the magnitude of STM, that is the excursion of the crown of the tooth when a force of 500 lb is applied, (1) varies between different types of teeth (e.g. incisors 10–12/100 mm, canines 5–9/100 mm, premolars 8–10/100 mm, and molars 4–8/100 mm); (2) is larger in children than in adults; and (3) is larger in females than males and increases during, for example, pregnancy. Furthermore, tooth mobility seems to vary during the course of the day; the lowest value is found in the evening and the largest in the morning.

A new method for determining tooth mobility was presented by Schulte and co-workers (Schulte 1987; Schulte *et al*. 1992) when the Periotest® (SiemensAG, Bensheim, Germany) system was introduced. This system measures the reaction of the periodontium to a defined percussion force which is applied to the tooth and delivered by a tapping instrument. A metal rod is accelerated to a speed of 0.2 m/s by the device and maintained at a constant velocity. Upon impact, the tooth is deflected and the rod decelerated. The contact time between the tapping head and the tooth varies between 0.3 and 2 ms and is shorter for stable than mobile teeth. The Periotest® scale (the Periotest values) ranges from −8 to +50 and the following ranges should be considered:

- −8 to +9: clinically firm teeth
- 10–19: first distinguishable sign of movement
- 20–29: crown deviates within 1 mm of its normal position
- 30–50: mobility is readily observed.

The Periotest® values correlate well with (1) tooth mobility assessed with a metric system, and (2) degree of periodontal disease and alveolar bone loss. Hence, this device is commonly used in the "every day" clinic and in various research settings

Clinical assessment of tooth mobility (physiologic and pathologic tooth mobility)

If, in the traditional clinical measurement of tooth mobility, a comparatively large force is exerted on the crown of a tooth which is surrounded by a normal periodontium, the tooth will tip within its alveolus until a closer contact has been established between the root and the marginal (or apical) bone tissue. The magnitude of this tipping movement, which is normally assessed using the tip of the crown as a reference point, is referred to as the "*physiologic*" tooth mobility. The term "*physiologic*" implies that "*pathologic*" tooth mobility may also occur. What, then, is "pathologic" tooth mobility?

1. If a similar force is applied to a tooth which is surrounded by a periodontal ligament with an increased width, the excursion of the crown in the horizontal direction will increase; the clinical measurement consequently demonstrates that the tooth has an increased mobility. Should this increased mobility be regarded as "pathologic"?
2. An increased tooth mobility, that is an increased displacement of the crown of the tooth after force application, can also be found in situations where the height of the alveolar bone has been reduced, but the remaining periodontal ligament has a normal width. At sites where this type of bone loss is extensive, the degree of tooth mobility (i.e. excursion of the crown) may be pronounced. Should this increased tooth mobility be regarded as "pathologic"?

   Figure 52-4b shows a tooth which is surrounded by alveolar bone of reduced height. The width of the remaining periodontal ligament, however, is within normal limits. A horizontally directed force applied to the crown of the tooth in this case will result in a larger excursion of the crown than if a similar force is applied to a tooth with normal

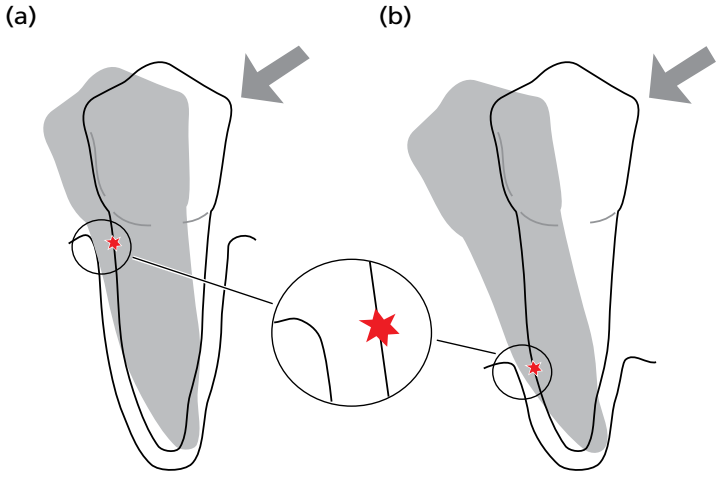

Fig. 52-4 (a) Normal "physiologic" mobility of a tooth with normal height of the alveolar bone and normal width of the periodontal ligament. (b) Mobility of a tooth with reduced height of the alveolar bone. The distance of the horizontal displacement of the reference point (*) on the roots is the same in the two situations (a, b).

height of the alveolar bone and normal width of the periodontal ligament (Fig. 52-4a). There are reasons to suggest that the so-called *increased mobility* measured in the case shown in Fig. 52-4b is, indeed, *physiologic*. The validity of this statement can easily be demonstrated if the displacement of the two teeth is assessed not from the crown, but from a point on the root at the level of the bone crest. If a horizontal force is directed to the teeth in Fig. 52-4, the reference points (*) on the root surfaces will be displaced a similar distance in both instances. Obviously, it is not the length of the excursive movement of the crown that is important from a biologic point of view, but the *displacement of the root* within its remaining periodontal ligament.

In plaque-associated periodontal disease, bone loss is a prominent feature. Another so-called classical symptom of periodontitis is "increased tooth mobility". It is important to realize, however, that in many situations with even or "horizontal" bone loss patterns, the increased crown displacement (tooth mobility) assessed by clinical measurements should, according to the above discussion, also be regarded as physiologic; the movement of the root within the space of its remaining "normal" periodontal ligament is normal.

3. Increased crown displacement (tooth mobility) may also be detected by clinical measurement where a "horizontal" force is applied to teeth with angular bony defects and/or increased width of the periodontal ligament. If this mobility does not increase gradually – from one observation interval to the next – the root is surrounded by a periodontal ligament of increased width but normal composition. This mobility should also be considered *physiologic* since the movement is a function of the height of the alveolar bone and the width of the periodontal ligament.
4. Only *progressively increasing tooth mobility*, which may occur in conjunction with trauma from occlusion, is characterized by active bone resorption (see Chapter 16) and which indicates the presence of inflammatory alterations within the periodontal ligament tissue, may be considered *pathologic*.

Treatment of increased tooth mobility

A number of situations will be described which may call for treatment aimed at reducing an increased tooth mobility.

Situation 1

Increased mobility of a tooth with increased width of the periodontal ligament but normal height of the alveolar bone

If a tooth (e.g. a maxillary premolar) is fitted with an improper filling or crown restoration, occlusal interferences develop and the surrounding periodontal tissues become the seat of inflammatory reactions, that is trauma from occlusion (Fig. 52-5). If the restoration is designed such that the crown of the tooth in occlusion is subjected to undue forces directed in a buccal direction, bone resorption phenomena develop in the buccomarginal and linguoapical pressure zones with a resulting increase of the width of the periodontal ligament in these zones. The tooth becomes hypermobile or moves away from the "traumatizing" position. Since such traumatizing forces in teeth with normal periodontium or overt gingivitis cannot result in pocket formation or loss of connective tissue attachment, the resulting increased mobility of the tooth should be regarded as a physiologic adaptation of the periodontal tissues to the altered functional demands. A proper correction of the anatomy of the occlusal surface of such a tooth, that is occlusal adjustment, will normalize the relationship between the antagonizing teeth in occlusion, thereby

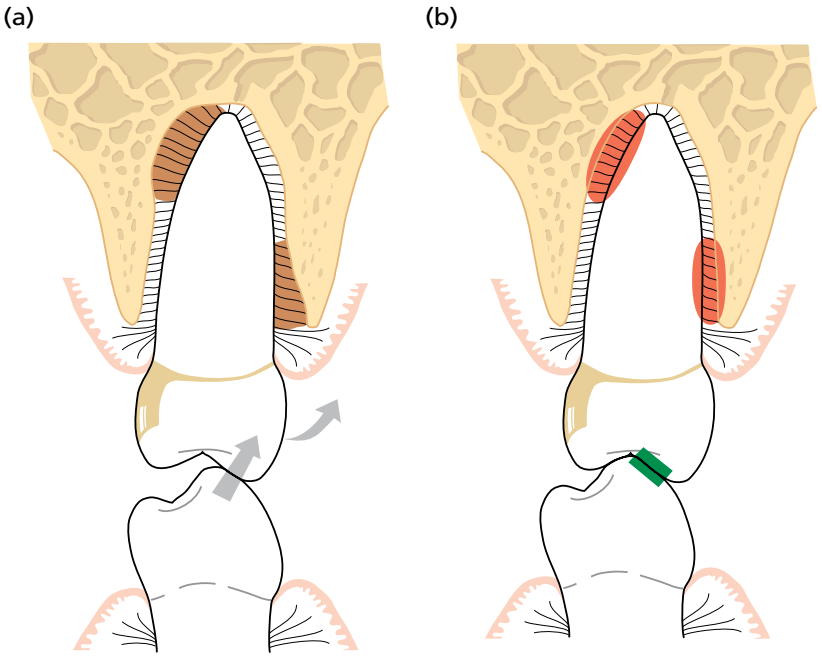

Fig. 52-5 (a) Contact relationship between a mandibular and a maxillary premolar in occlusion. The maxillary premolar is fitted with an artificial restoration with an improperly designed occlusal surface. Occlusion results in horizontally directed forces (arrows) which may produce an undue stress concentration within the "brown" areas of the periodontium of the maxillary tooth. Resorption of the alveolar bone occurs in these areas. A widening of the periodontal ligament can be detected as well as increased mobility of the tooth. (b) Following adjustment of the occlusion, the horizontal forces are reduced. This results in bone apposition ("red areas") and a normalization of the tooth mobility.

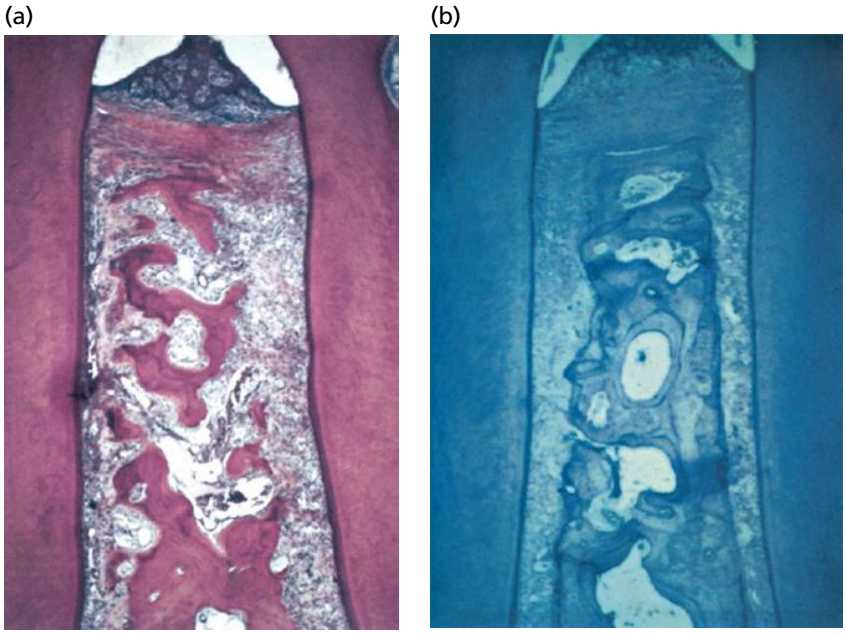

Fig. 52-6 Photomicrographs illustrating the interdental area between two mandibular premolars in the monkey. (a) Two premolars are exposed to jiggling forces. Note the reduction of alveolar bone in the area and the location of the bone crest. Ten weeks after the elimination of the jiggling forces, (b) a considerable regeneration of bone has occurred. Note the increase of the height of the interdental bone and the normalization of the width of the periodontal ligaments. The apical end of the junctional epithelium is located at the cemento-enamel junction. (Source: Polson *et al*. 1976a. Reproduced with permission from John Wiley & Sons.)

eliminating the excessive forces. As a result, apposition of bone will occur in the zones previously exposed to resorption, the width of the periodontal ligament will become normalized and the tooth stabilized, that is it reassumes its normal mobility (Fig. 52-5). In other words, resorption of alveolar bone which is caused by trauma from occlusion is a reversible process which can be treated by the elimination of occlusal interferences.

The capacity for bone regeneration after resorption following trauma from occlusion has been documented in a number of animal experiments (Waerhaug & Randers-Hansen 1966; Polson *et al*. 1976a; Karring *et al*. 1982; Nyman *et al*. 1982). In such experiments, the induced bone resorption not only involved the bone within the alveolus but also the alveolar bone crest. When the traumatizing forces were removed, bone tissue was deposited not only on the walls of the alveolus, thereby normalizing the width of the periodontal ligament, but also on the bone crest area, whereby the height of the alveolar bone was normalized (Fig. 52-6) (Polson *et al*. 1976a). In the presence of an untreated, plaque-associated lesion in the soft tissue, however, substantial bone regrowth did not always occur (Fig. 52-7) (Polson *et al*. 1976b).

Situation 2

Increased mobility of a tooth with increased width of the periodontal ligament and reduced height of the alveolar bone

When a dentition has been properly treated for moderate-to-advanced periodontal disease, gingival health is established in areas of the dentition where teeth are surrounded by periodontal structures of reduced height. If a tooth with a reduced periodontal tissue support is exposed to excessive horizontal forces (trauma from occlusion), inflammatory reactions develop in the pressure zones of the periodontal ligament with accompanying bone resorption. These alterations are similar to those which occur around a tooth with supporting structures of a normal height; the alveolar bone is resorbed, the width of the periodontal ligament is increased in the pressure/tension zones, and the tooth becomes hypermobile (Fig. 52-8a). If the excessive forces are reduced or eliminated by occlusal adjustment, bone apposition to the "pre-trauma" level will occur, the periodontal ligament will regain its normal width and the tooth will become stabilized (Fig. 52-8b).

Conclusion (situations 1 and 2): Occlusal adjustment is an effective therapy against increased tooth mobility when such mobility is caused by an *increased width* of the periodontal ligament.

Situation 3

Increased mobility of a tooth with reduced height of the alveolar bone and normal width of the periodontal ligament

The increased tooth mobility which is the result of a reduction in height of the alveolar bone without a concomitant increase in width of the periodontal membrane cannot be reduced or eliminated by occlusal adjustment. In teeth with normal width of the periodontal ligament, no further bone apposition

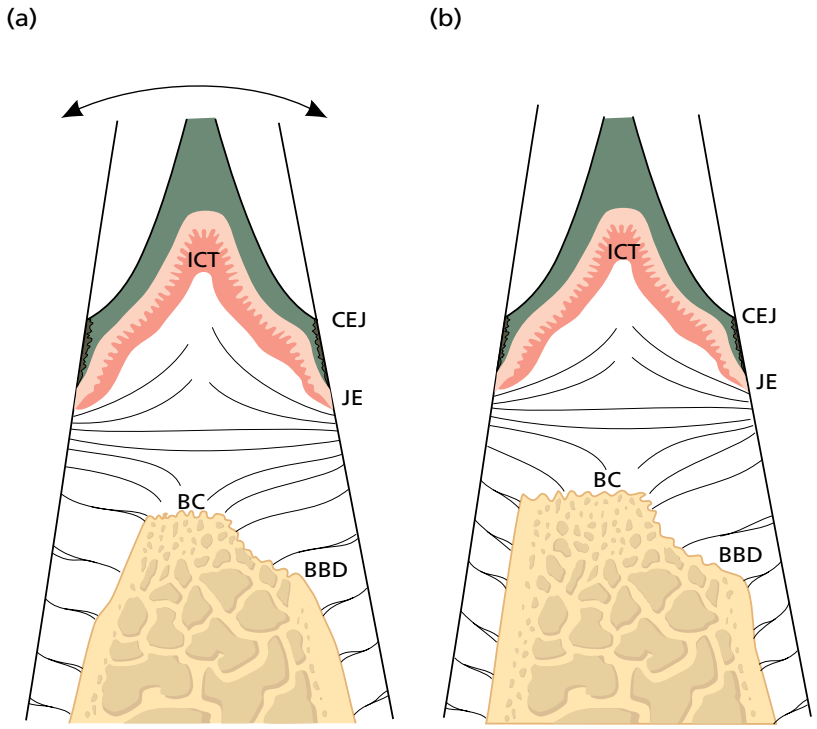

Fig. 52-7 In the presence of an existing marginal inflammation, alveolar bone lost by jiggling trauma (a), will not always regenerate following elimination of the traumatic forces (b). (ICT, infiltrated connective tissue; CEJ, cementoenamel junction; JE, apical end of junctional epithelium; BC, alveolar bone crest; BBD, bottom of angular bony defect.) (Source: Polson *et al*. 1976b. Reproduced with permission from John Wiley & Sons.)

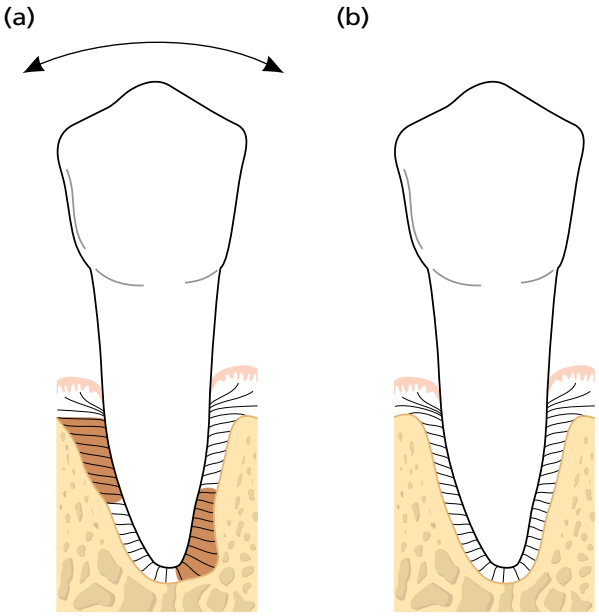

Fig. 52-8 If a tooth with reduced periodontal tissue support (a) has been exposed to excessive horizontal forces, a widened periodontal ligament space ("brown" areas) and increased mobility (arrow) result. (b) Following reduction or elimination of such forces, bone apposition will occur and the tooth will become stabilized.

on the walls of the alveoli can occur. If such an increased tooth mobility does not interfere with the patient's chewing function or comfort, no treatment is required. If the patient experiences the tooth mobility as disturbing, however, the mobility can only be reduced in this situation by splinting, that is by joining the mobile tooth/teeth together with other teeth in the jaw into a fixed unit – a splint.

A splint is "an appliance designed to stabilize mobile teeth" and may be fabricated in the form of joined composite fillings, fixed bridges, removable partial prostheses, etc.

Example: Case A, 64-year-old male

The periodontal condition of this patient is illustrated by the radiographs from the initial examination (Fig. 52-9). Periodontal disease has progressed to a level where, around the maxillary teeth, only the apical third or less of the roots is invested in supporting alveolar bone. The following discussion relates to the treatment of the maxillary dentition.

In the treatment planning of this case, it was decided that the first premolars (teeth 14 and 24) had to be extracted due to advanced periodontal disease and furcation involvement of degree III. For the same reasons, teeth 17 and 27 were scheduled for extraction. Teeth 16 and 26 were also found to have advanced loss of periodontal tissue support in combination with deep furcation involvements. The most likely *definitive* treatment should include periodontal and adjunctive therapy in the following parts of the dentition: 15 and 25, and 13, 12, 11, 21, 22, 23. For functional and esthetic reasons, teeth 14 and 24 obviously had to be replaced. The question now arose as to whether these two premolars should be replaced by two separate unilateral bridges, using 13, 15 and 23, 25 as abutment teeth, or if the increased mobility of these teeth and also of the anterior teeth (12, 11, 21, 22) (Fig. 52-9) called for a bridge of cross-arch design, with the extension 15–25, to obtain a splinting effect. If teeth 14 and 24 were replaced by two unilateral bridges, each one of these three-unit bridges would

(a)

Periodontal chart

Tooth	Pocket depth M	B	D	L	Furcation involvement	Tooth mobility
~~18~~						
17	6	6	8	8	b2, m2, d1	
16	6	6	8	8	m1, d2	2
15	8	8	6	7		2
14	7	7	7	4	3	2
13	8	4	8	4		2
12	8	4	8	4		2
11	6	4	7	4		1
21	6	4	6	4		1
22	6	5	7			2
23	6		6	4		2
24	7		8		3	2
25	6	8	8	4		2
26	8		6		b2, m2, d2	
27	6	6	10	8	b2, d2	1
~~28~~						
~~48~~						
~~47~~						
46	8	6	6	7	b1, l2	
45	6		7	4		1
44	6		6	4		
43	7	7	6	4		
42	4		4	4		1
41	6	4				1
31	6					1
32	4		6	4		1
33	6		6	6		2
34	4		7	4		
35	7		4	6		2
~~36~~						
37	8	5	6	4	b2, l2	3
~~38~~						

(b)

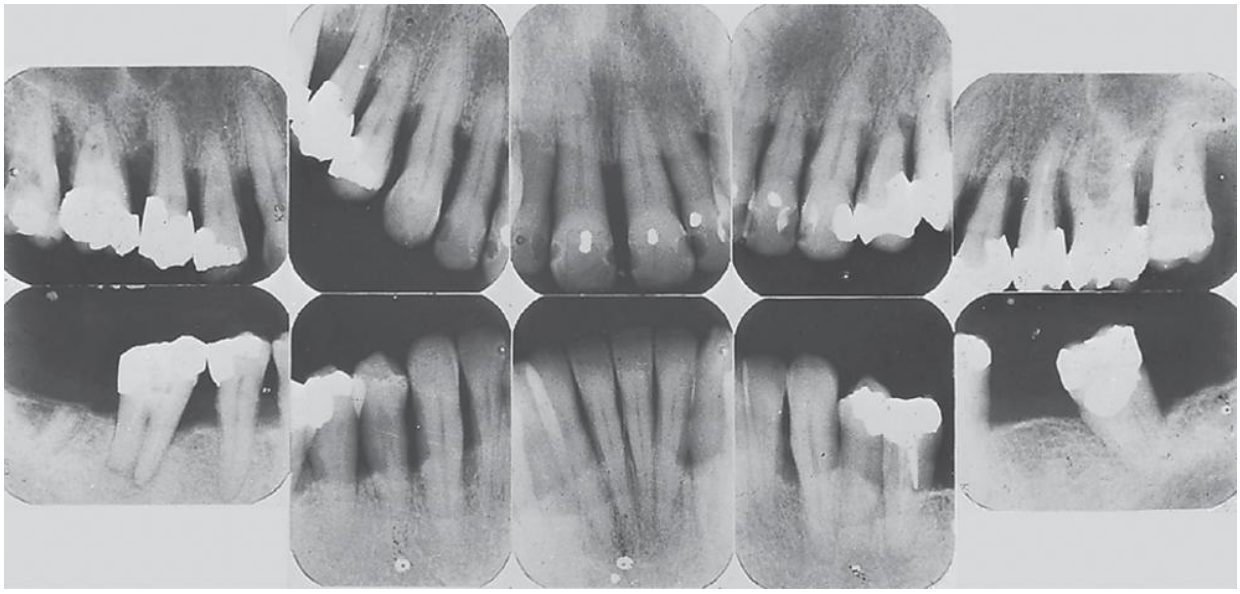

Fig. 52-9 Case A, 64-year-old male. Radiographs prior to therapy.

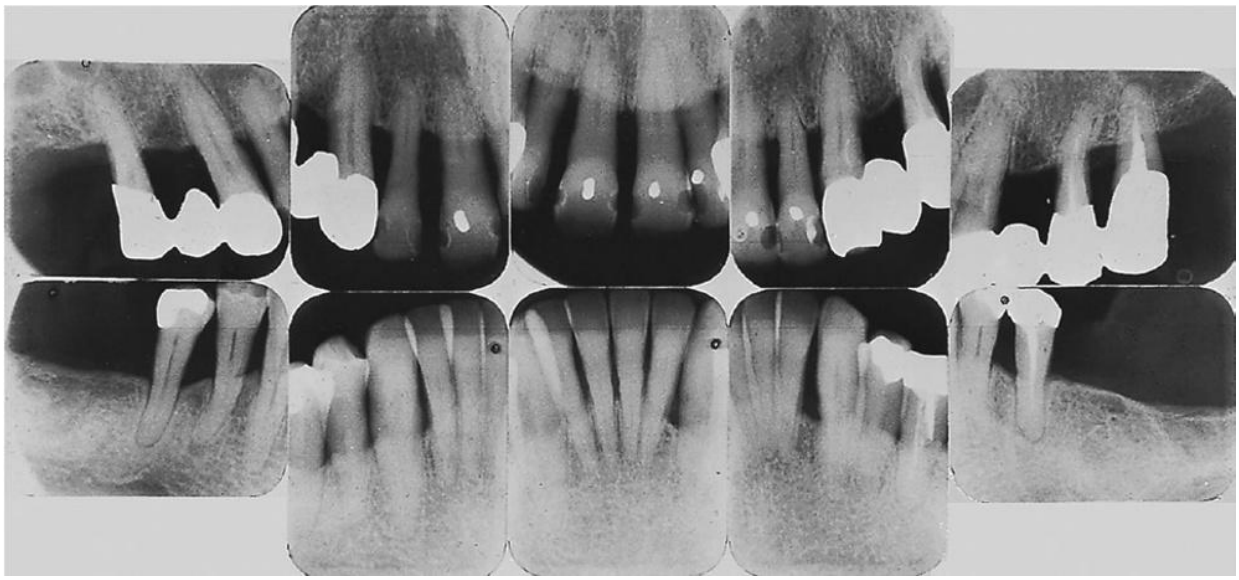

Fig. 52-10 Case A. Radiographs obtained 10 years after periodontal therapy and installation of two unilateral bridges in the maxilla.

exhibit the same degree of mobility in a buccolingual direction as the individual abutment teeth (degree 2) (Fig. 52-9), since a unilateral straight bridge would not have a stabilizing effect on the abutment teeth in this force direction.

From the radiographs it can be seen that the increased mobility observed in the maxillary teeth of this patient is associated mainly with reduced height of the alveolar bone and not with increased width of the periodontal ligaments. This means that the mobility of the individual teeth should be regarded as normal or "physiologic" for teeth with such a reduced height of the supporting tissues. This in turn implies that the increased tooth mobility in the present case does not call for treatment unless it interferes with the chewing comfort or jeopardizes the position of the front teeth. This particular patient had not recognized any functional problems related to the increased mobility of his maxillary teeth. Consequently, there was no reason to install a cross-arch bridge in order to splint the teeth, that is to reduce tooth mobility.

Following proper treatment of the plaque-associated periodontal lesions, two separate provisional bridges of unilateral design were produced (15, 14, 13; 23, 24, 25, 26 palatal root). The provisional acrylic bridges were used for 6 months during which time the occlusion, the mobility of the two bridges, and the position of the front teeth were all carefully monitored. After 6 months, no change of position of the lateral and central incisors and no increase of the mobility of the two provisional bridges had occurred, and the definitive restorative therapy was performed.

Figure 52-10 shows the radiographs obtained 10 years after initial therapy. The position of the front teeth and the mobility of the incisors and the two bridges had not changed during the course of the maintenance period. There had been no further loss of periodontal tissue support during the 10 years of observation, no further spread of the front teeth, and no widening of the periodontal ligaments around the individual teeth, including the abutment teeth for the bridgework.

Conclusion: Increased tooth mobility (or bridge mobility) as a result of reduced height of the alveolar bone can be accepted and splinting avoided, provided the occlusion is stable (no further migration or increasing mobility of individual teeth) and the degree of existing mobility does not disturb the patient's chewing ability or comfort. Consequently, splinting is indicated when the mobility of a tooth or a group of teeth is so increased that chewing ability and/or comfort are disturbed.

Situation 4

Progressive (increasing) mobility of a tooth (teeth) as a result of gradually increasing width of the reduced periodontal ligament

Often in cases of advanced periodontal disease the tissue destruction may have reached a level where extraction of one or several teeth cannot be avoided. In such a dentition, teeth which are still available for periodontal treatment may, after therapy, exhibit such a high degree of mobility, or even signs of progressively increasing mobility, that there is an obvious risk that the forces elicited during function may mechanically disrupt the remaining periodontal ligament components and result in the loss of the teeth.

It will only be possible to maintain such teeth by means of a splint. In such cases, a fixed splint has two objectives: (1) to stabilize hypermobile teeth and (2) to replace missing teeth.

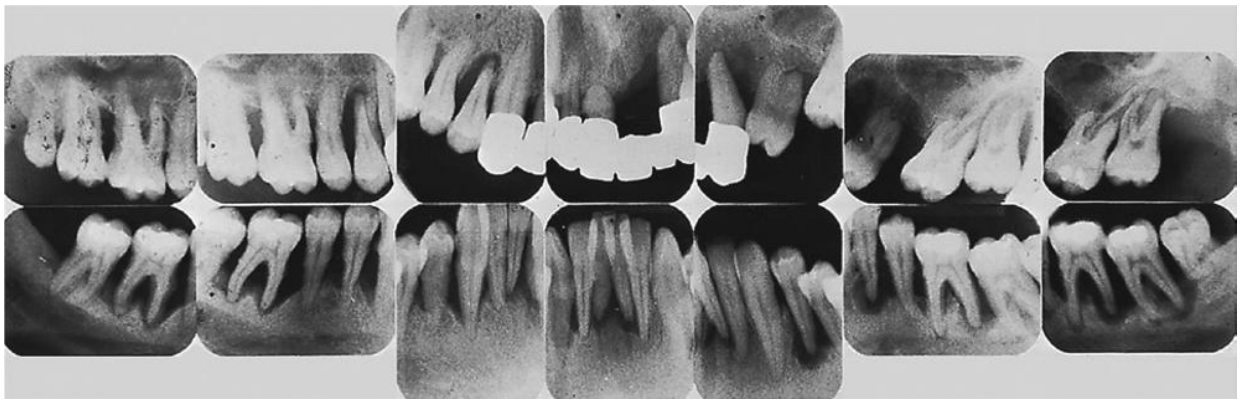

Fig. 52-11 Case B, 26-year-old male. Radiographs showing the periodontal conditions prior to therapy.

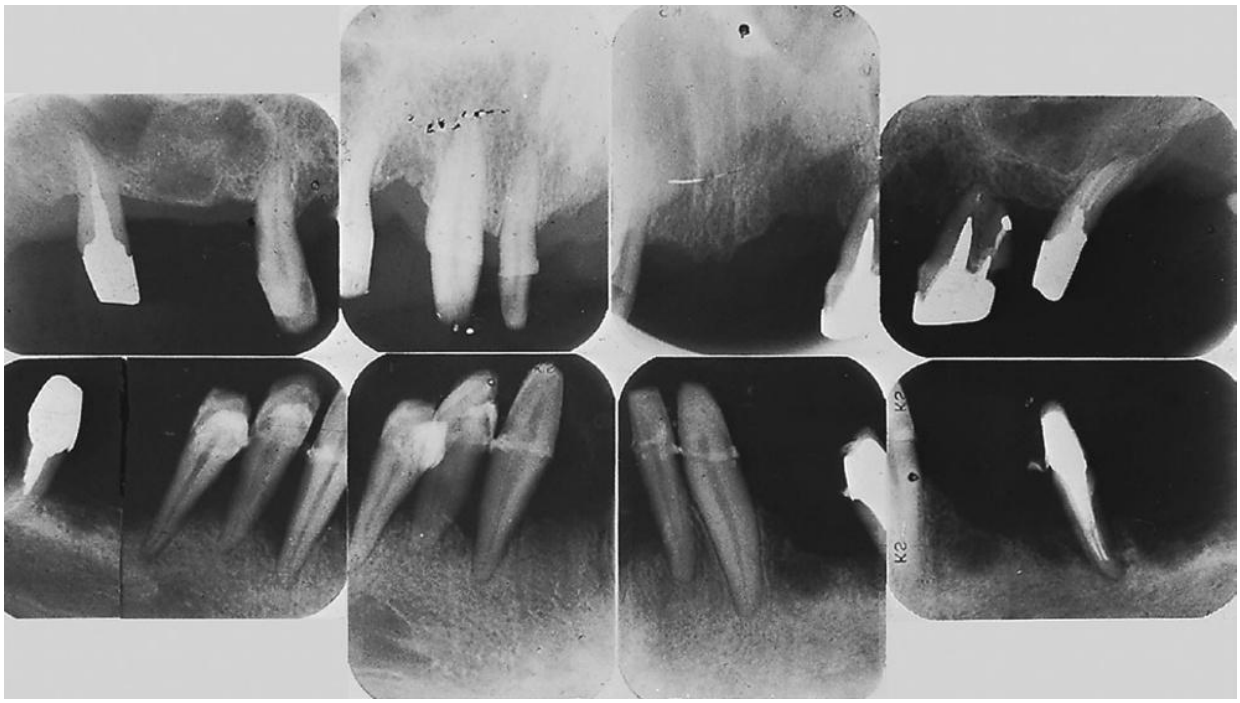

Fig. 52-12 Case B. Radiographs obtained after periodontal treatment and preparation of the abutment teeth for two fixed splints.

Example: Case B, 26-year-old male

Figure 52-11 shows the radiographs taken prior to therapy and Fig. 52-12 those obtained after periodontal treatment and preparation of the remaining teeth as abutments for two fixed splints. All teeth except 13, 12, and 33 have lost around 75% or more of the alveolar bone and widened periodontal ligaments are a frequent finding. The four distal abutments for the two splints are root-separated molars, the maintained roots being the following: the palatal root of tooth 17, the mesiobuccal root of tooth 26, and the mesial roots of teeth 36 and 47. It should be observed that tooth 24 is root-separated and the palatal root maintained with only minute amounts of periodontium left.

Immediately prior to insertion of the two splints, all teeth except 13, 12, and 33 displayed a mobility varying between degrees 1 and 3. From the radiographs in Fig. 52-12 it can be noted that there is an obvious risk of loss of a number of teeth such as 24, 26, 47, 45, 44, 43, and 36 if the patient is allowed to bite with a normal chewing force without the splints in position.

Despite the high degree of mobility of the individual teeth, the splints were entirely stable after insertion, and maintained their stability during a maintenance period of >12 years. Figure 52-13 shows the clinical status and Fig. 52-14 the radiographs obtained 10 years after therapy. From these radiographs it can be observed (compare with Fig. 52-12) that during the maintenance period there had been no further loss of alveolar bone or widening of the various periodontal ligament spaces.

Conclusion: Splinting is indicated when the periodontal support is so reduced that the mobility of the teeth is progressively increasing, that is when a tooth or a group of teeth are exposed to extraction forces during function.

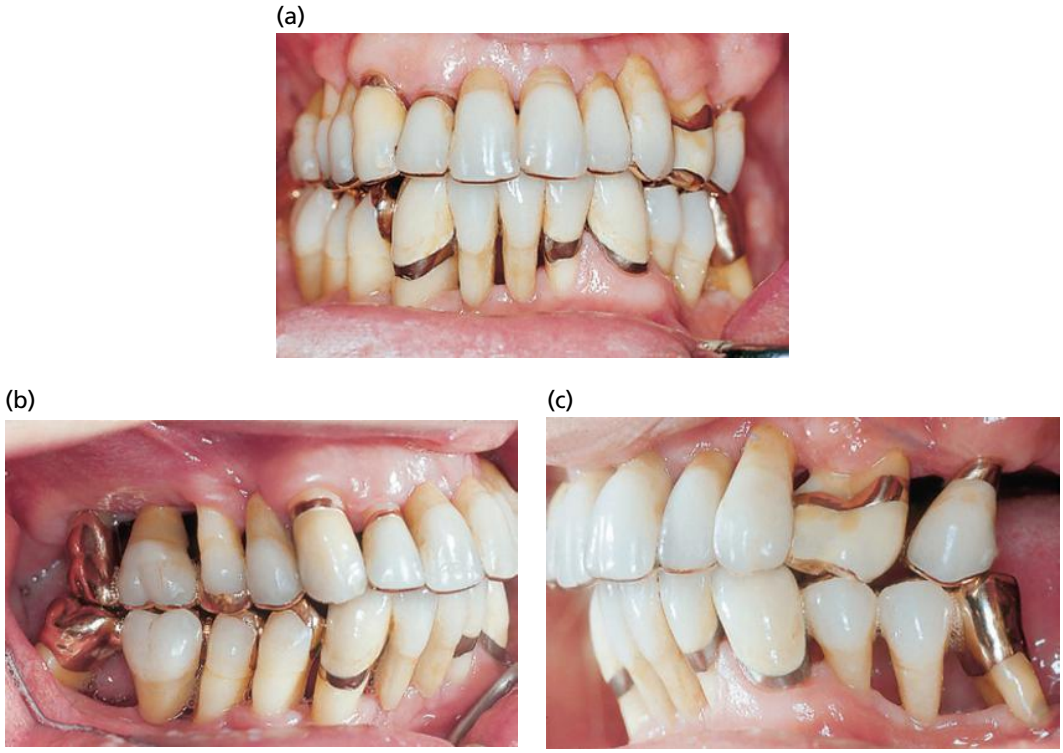

Fig. 52-13 (a–c) Case B. Clinical status 9 years after therapy.

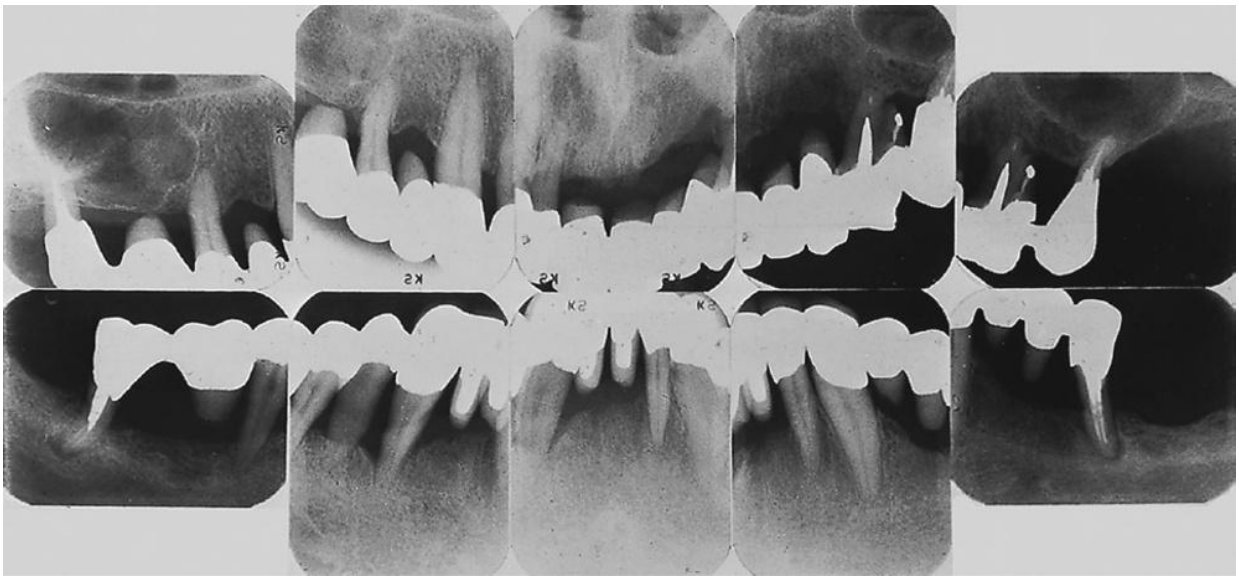

Fig. 52-14 Case B. Radiographs obtained 10 years after therapy.

Situation 5

Increased bridge mobility despite splinting

In patients with advanced periodontal disease, it can often be observed that the destruction of the periodontium has progressed to varying levels around different teeth and tooth surfaces in the dentition. Proper treatment of the plaque-associated lesions often includes multiple extractions. The remaining teeth may display an extreme reduction of the supporting tissues concomitant with increased or progressive tooth mobility. They may also be distributed in the jaw in such a way as to make it difficult, or impossible, to obtain a proper splinting effect even by means of a cross-arch bridge. The entire bridge/splint may exhibit mobility in frontal and/or lateral directions.

It was stated above (situation 3) that a certain mobility of a tooth or a bridge of unilateral design can be accepted provided this mobility does not interfere with the patient's chewing ability or comfort. This is also valid for a cross-arch bridge/splint. From a biologic point of view, there is no difference between increased tooth mobility on the one hand and increased bridge mobility on the other. However, neither progressive tooth mobility nor progressive bridge mobility are acceptable. In cases of extremely advanced periodontal disease, a cross-arch splint with an increased mobility may be regarded as an acceptable

result of rehabilitation. The maintenance of the status quo of the bridge/splint mobility and the prevention of tipping or orthodontic displacement of the total splint, however, requires particular attention regarding the design of the occlusion. Case C is an interesting illustration of this particular clinical problem.

Example: Case C, 52-year-old female

Figure 52-15 shows radiographs obtained at the initial examination. A 12-unit maxillary bridge was installed 10–15 years prior to the present examination using teeth 18, 15, 14, 13, 12, 11, 21, 22, 23, and 24 as abutments. After a detailed clinical examination it was obvious that teeth 15, 14, 22, and 24 could not be maintained because of severe symptoms of caries and periodontal disease. The remaining teeth were subjected to periodontal therapy and maintained as abutments for a new bridge/splint in the maxilla, extending from tooth 18 to the region of tooth 26, that is a cross-arch splint was installed which carried three cantilever units, namely 24, 25, and 26. The mobility of the individual abutment teeth immediately prior to insertion of the splint was the following: degree 1 (tooth 18), degree 0 (tooth 13), degree 2 (teeth 12 and 11), degree 3 (tooth 21), and degree 2 (tooth 23).

Radiographs obtained 5 years after therapy are shown in Fig. 52-16. The bridge/splint had a mobility of degree 1 immediately after its insertion and this mobility was unchanged 5 years later. The radiographs demonstrate that no further widening of the periodontal ligament had occurred around the individual teeth during the maintenance period.

When a cross-arch bridge/splint exhibits increased mobility, the center (fulcrum) of the movement must be identified. In order to prevent further increase in the mobility and/or to prevent displacement of the

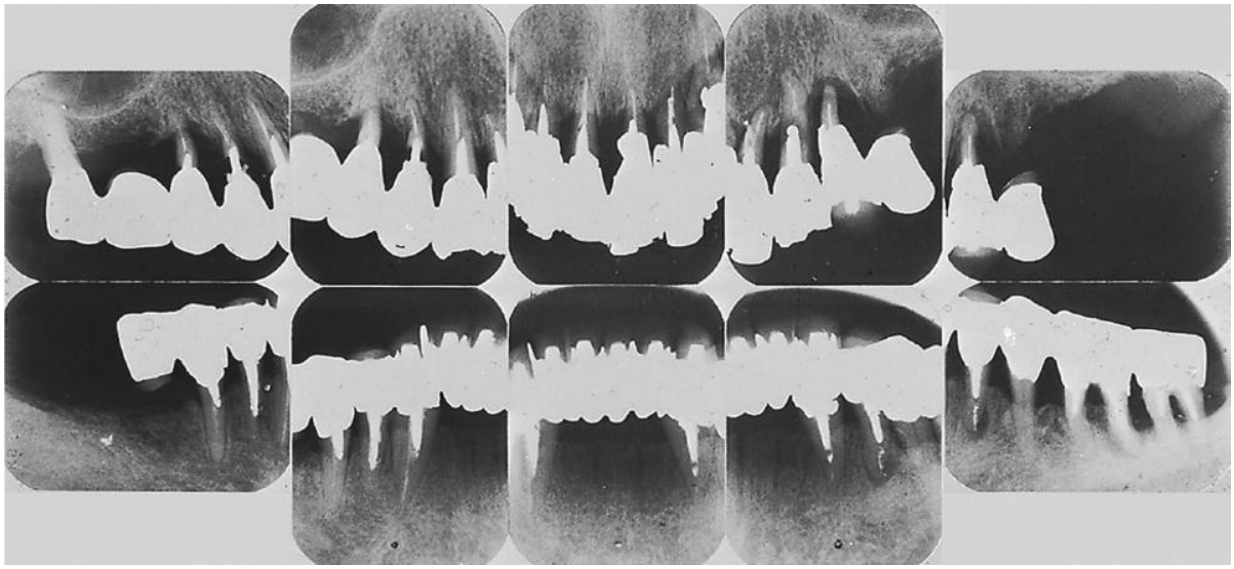

Fig. 52-15 Case C, 52-year-old female. Radiographs obtained at the initial examination.

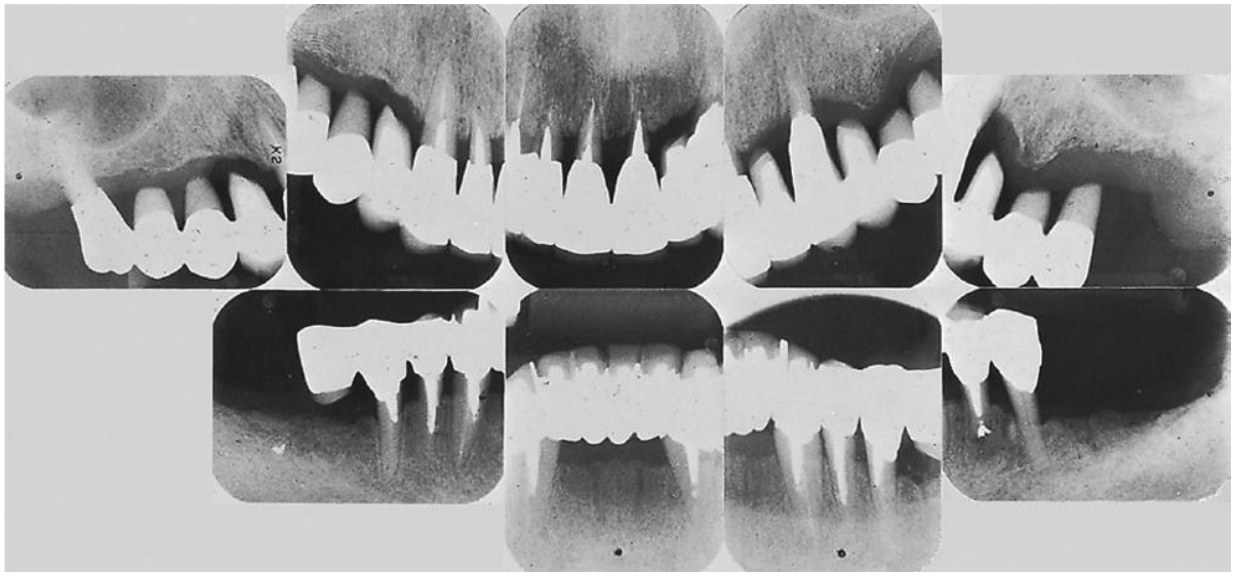

Fig. 52-16 Case C. Radiographs obtained 5 years after therapy.

bridge, it is essential to design the occlusion in such a way that when the bridge/splint is in contact with the teeth of the opposing jaw, it is subjected to a balanced load, that is equal force on each side of the fulcrum. If this can be achieved, the force to which the bridge is exposed in occlusion can be used to retain the fixed prosthesis in proper balance (thereby preventing a further increase of mobility).

Balanced loading of a mobile bridge/splint has to be established not only in the intercuspal position (IP) and centric occlusion (CP), but also in frontal and lateral excursive movements of the mandible if the bridge shows mobility or a tendency for tipping in the direction of such movements. In other words, a force which tends to displace the bridge in a certain direction has to be counteracted by the introduction of a balancing force on the opposite side of the fulcrum of the movement. If, for instance, a cross-arch splint in the maxilla exhibits mobility in the frontal direction in conjunction with protrusive movements of the mandible, the load applied to the bridge in the frontal region has to be counterbalanced by a load in the distal portions of the splint; this means that there must be a simultaneous and equal contact relationship between the occluding teeth in both the frontal and the posterior regions of the splint. If the splint is mobile in a lateral direction, the force acting on the working side of the jaw must be counteracted by a force established by the introduction of balancing contacts in the non-working side of the jaw. The principle for establishing stability of a *mobile* cross-arch splint is consequently the same as that used to obtain stability in a complete denture. In situations where distal abutment teeth are missing in a cross-arch bridge/splint with increased mobility, balance and functional stability may be obtained by means of cantilever units. It is important in this context to point out that balancing contacts on the non-working side should not be introduced in a bridge/splint in which no increased mobility can be observed.

The maxillary splint in Case C exhibited increased mobility in a frontal direction. Considering the small amount of periodontal support left around the anterior teeth, it is obvious that there would have been a risk of frontal displacement of the total bridge had the bridge terminated at the last abutment tooth (23) on the left side of the jaw. The installation of cantilever units in the 24 and 25 region prevented such a displacement of the bridge/splint by the introduction of a force counteracting the frontally directed forces during protrusive movements of the mandible (Fig. 52-17). In addition, the cantilever units provided bilateral contact relationship towards the mandibular teeth in the intercuspal position, that is bilateral stability of the bridge.

Fig. 52-17 Case C. Cantilever section including teeth 24, 25, and 26.

In cases similar to Case C, cantilever units can thus be used to prevent increasing mobility or displacement of a bridge/splint. It should, however, be pointed out that the insertion of cantilever units increases the risk of failures of a technical and biophysical character (fracture of the metal frame, fracture of abutment teeth, loss of retention, etc.).

In cases of severely advanced periodontal disease, it is often impossible to anticipate in the planning phase whether a bridge/splint will show signs of instability and increasing (progressive) mobility after insertion. In such cases, a provisional splint should always be inserted. Any alterations of the mobility of the bridge/splint can be observed over a prolonged period of time and the occlusion continuously adjusted until, after 4–6 months, it is known whether stability (i.e. no further increase of the mobility) can be achieved. The design of the occlusion of the provisional acrylic bridge is then reproduced in the permanent bridge construction. If, on the other hand, stability cannot be obtained, the rehabilitation of the case cannot be achieved with a fixed splint. The alternative treatment then is a complete denture or an implant-supported restoration.

Conclusion: An increased mobility of a cross-arch bridge/splint can be accepted provided the mobility does not disturb chewing ability or comfort and the mobility of the splint is not progressively increasing.

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Chapter 53

Implants in Restorative Dentistry

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Introduction

Ever since oral titanium implants were shown to yield high predictability (97–98%) for incorporation (Berglundh *et al*. 2002; Pjetursson *et al*. 2007, 2012) and satisfactory longevity [survival rates of 95.6% (95% CI 94.4–96.6%) after 5 years and approximately 93.1% (95% CI 90.5–95.0%) after 10 years of service] (Pjetursson *et al*. 2012), the choice of oral implants as abutments for reconstructing the dentition has revolutionized restorative dentistry. Without adequate evidence, some clinicians trust an implant abutment even more than a natural tooth (Lang-Hua *et al*. 2013), and there is an erroneous belief that oral implants now solve most prosthetic problems with a lot more ease and less risks than traditional reconstructive dentistry (Esfandiari *et al*. 2011).

Even though there is an increasing body of evidence documenting that implant-supported reconstructions have a three times higher incidence of technical complications compared to tooth-supported reconstructions (Lang *et al*. 2004; Pjetursson *et al*. 2004a, b; Tan *et al*. 2004; Pjetursson *et al*. 2012) and that the incidence of biologic complications remains approximately the same for the two alternatives, the trend in dentistry – unfortunately – is to prefer the implant over the tooth abutment (Esfandiari *et al*. 2011; Lang-Hua *et al*. 2013).

In this context, it has to be clearly stated that the decision to maintain and treat or to extract a compromised tooth has to precede the decision regarding the need for and the modalities of tooth replacement. In this sense, "*implants are here to replace missing teeth, they are not supposed to replace teeth.*"

If properly evaluated, the indication for oral implants as abutments in restorative dentistry is complementary to traditional approaches and in many instances, facilitates treatment planning.

Treatment concepts

When reconstructing a mutilated dentition, it has to be realized the two most common causes of tooth loss are caries and periodontitis. Only a small proportion of teeth are lost due to trauma or are not present due to agenesis. Hence, the vast majority of patients in need of reconstructions present with an oral biofilm infection of various severity and extent. It is evident that such patients need to be treated with a cause-related approach, that is systematic periodontal therapy has to precede any type of reconstructive therapy. It is of utmost importance that oral biofilm infections are controlled prior to the placement of oral implants, since residual periodontal pockets or untreated ecologic niches within the oral cavity may serve as a

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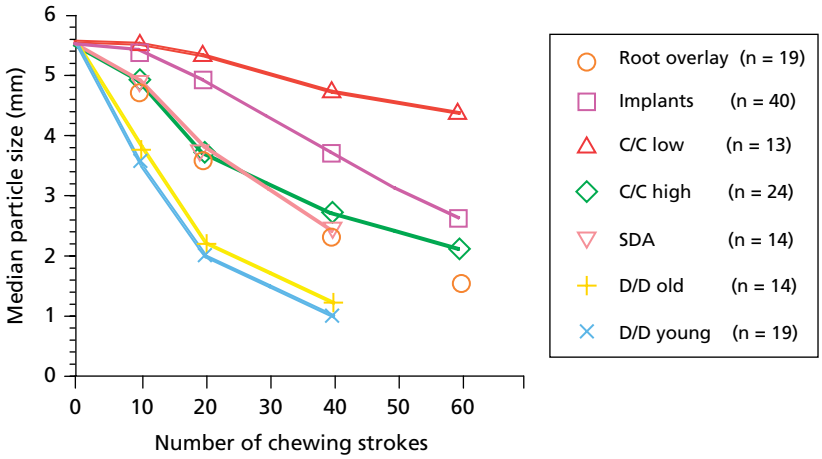

Fig. 53-1 Masticatory chewing efficiency. Number of chewing strokes needed to reach respective particle sizes of the same test food. (Source: Fontijn-Tekamp *et al*. 2000. Reproduced with permission from SAGE Publications.)

source of infection and jeopardize the health of the peri-implant region (Mombelli *et al*. 1995). Hence, implant installation and prosthetic reconstruction is generally not a treatment in itself, but belongs to a systematic approach of comprehensively establishing esthetic and functional demands under healthy conditions (see Chapter 34).

It is obvious that chewing function is affected both by tooth loss and the type of prosthetic reconstruction chosen to replace missing teeth. A quantitative comparison of chewing function by measuring bite force and chewing efficiency with identical methods in subjects with overdentures, complete full dentures, and natural dentitions was performed (Fontijn-Tekamp *et al*. 2000). In the latter group, chewing efficiency was significantly greater than that of patients with full dentures, irrespective of the nature of their mandibular ridge. By installing implants, bite force and chewing efficiency could be significantly improved, although the levels in dentate patients were not reached. Shortened dental arch patients exerted bite forces similar to those of patients with a complete natural dentition, but their chewing efficiency was slightly limited due to the reduced occlusal area. This, in turn, meant that patients with a shortened dental arch will have to perform approximately twice as many chewing strokes to reach the same efficiency as the fully dentate patient (Fig. 53-1.)

Limited treatment goals

Generally, efforts are made to completely reconstruct a partially edentulous dentition. The question arises whether or not missing teeth have to be replaced at all and to the full extent. Usually, single teeth are replaced because of predominantly esthetic demands, while multiple missing teeth may also affect functionality and chewing capacity and hence, are replaced to improve these aspects. However, it is evident from a number of cross-sectional and longitudinal studies (Käyser 1981; Battistuzzi *et al*. 1987; Witter *et al*. 1988, 1990a, b, 1991, 1994) that not all lost teeth are replaced. The loss of one or more molars especially has been thoroughly studied by the Nijmegen group of clinical researchers. No clinically significant differences were found in these studies between subjects with a complete dentition and those with reduced dental arches regarding masticatory capacity, signs and symptoms of temporomandibular disorders, migration of remaining teeth, periodontal support, and oral comfort.

Shortened dental arch concept

Studies on shortened dental arches (SDAs) have shown that dentitions comprising anterior and premolar teeth in general fulfil the requirements of a functional dentition, including patient-assessed oral comfort and chewing ability. A review of the literature on SDAs concluded that the concept deserves serious consideration in treatment planning for partially edentulous patients. However, with ongoing changes, for example in dental health and economy, the concept requires continuing research, evaluation, and discussion (Kanno & Carlsson 2006; Scheuber *et al*. 2012).

Special attention has to be given to the patient's own needs and desires for increased chewing capacity when considering the SDA as a limited treatment goal. Clinical observations as well as research findings indicate that elderly patients can function at an acceptable level with a reduced dentition consisting of 10 or even fewer occluding pairs of teeth (Käyser 1990). The World Health Organization (WHO) goal for the year 2020, namely to maintain a natural dentition of no less than 20 teeth throughout life, is also substantiated by a literature review that proposed dentition will assure oral function (Gotfredsen & Walls 2007).

The choice of implants as abutments to fulfil individual needs may, therefore, become a welcome treatment option within the concept of a shortened dental arch.

Indications for implants

Three major indications can be defined for the use of oral implants:

- To increase subjective chewing comfort
- To preserve natural tooth substance and adequate, existing reconstructions
- To replace strategically important missing teeth.

Increase of subjective chewing comfort

Studies have demonstrated that the installation of a small number of mandibular implants (two to four) may dramatically improve chewing function, especially if the edentulous mandibular ridge shows severe resorption (Fontijn-Tekamp *et al*. 2000, 2004a, b). Hence, it is evident that the completely edentulous patient will benefit from as few as two oral implants installed in the mandibular canine region (Fig. 53-2).

Likewise, subjective chewing comfort may be improved by supplementing single premolar chewing units in the posterior region in order to fulfil individual demands for more chewing capacity under a shortened dental arch concept (Fig. 53-3). It is imperative that the implants be placed in the prosthetically correct location, leaving enough space for an interdental (interimplant) space and observing the dimensions of a premolar width (7 mm).

Instead of adding chewing comfort in premolar units, implant systems with wider necks or platforms may be installed in order to truly mimic the replacement of the missing molars. In these instances, an interimplant distance of 8 mm has to be observed in order to create enough space for the molars and the interimplant space (Fig. 53-4).

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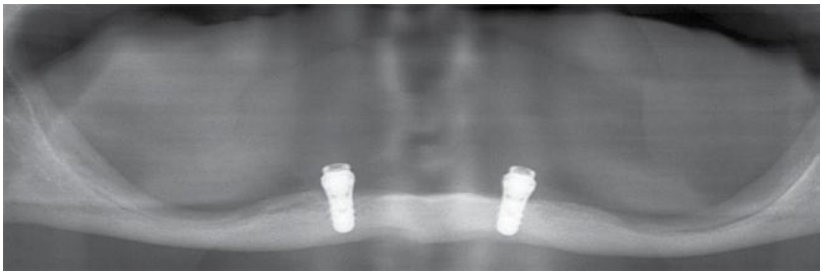

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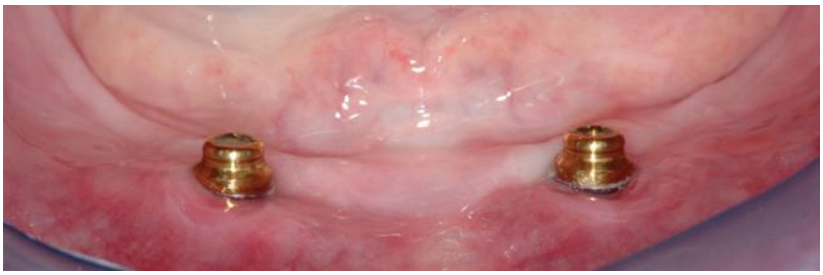
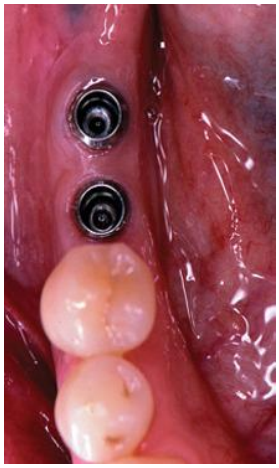


Fig. 53-2 Increasing subjective chewing comfort for a completely edentulous patients. (a, b) Just two implants in the canine region with a retention element (Locator®) without a bar can dramatically improve masticatory ability and efficacy.

(a)



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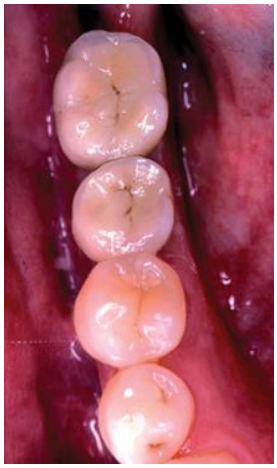

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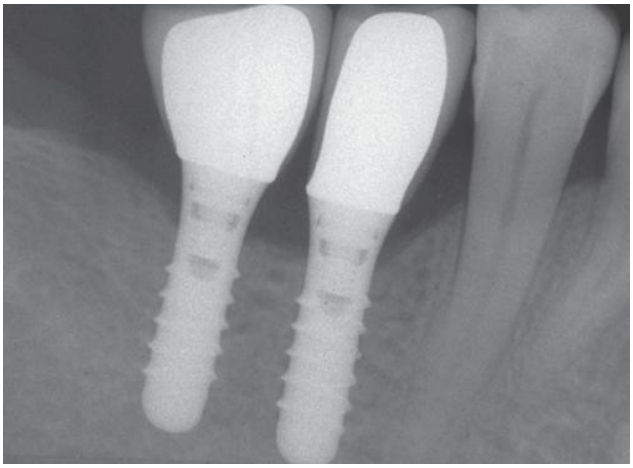

Fig. 53-3 Increasing subjective chewing comfort by replacing missing teeth in a free-end edentulous situation. (a) Installation of two standard size (4.1 mm diameter) Straumann® implants (10 mm) 5 and 11 mm distal of the distal aspect of tooth 45. (b) Chewing units are replaced as a premolar on implant in position 46 and a molar in position 46/47. (c) Radiographic control 5 years after the reconstruction.

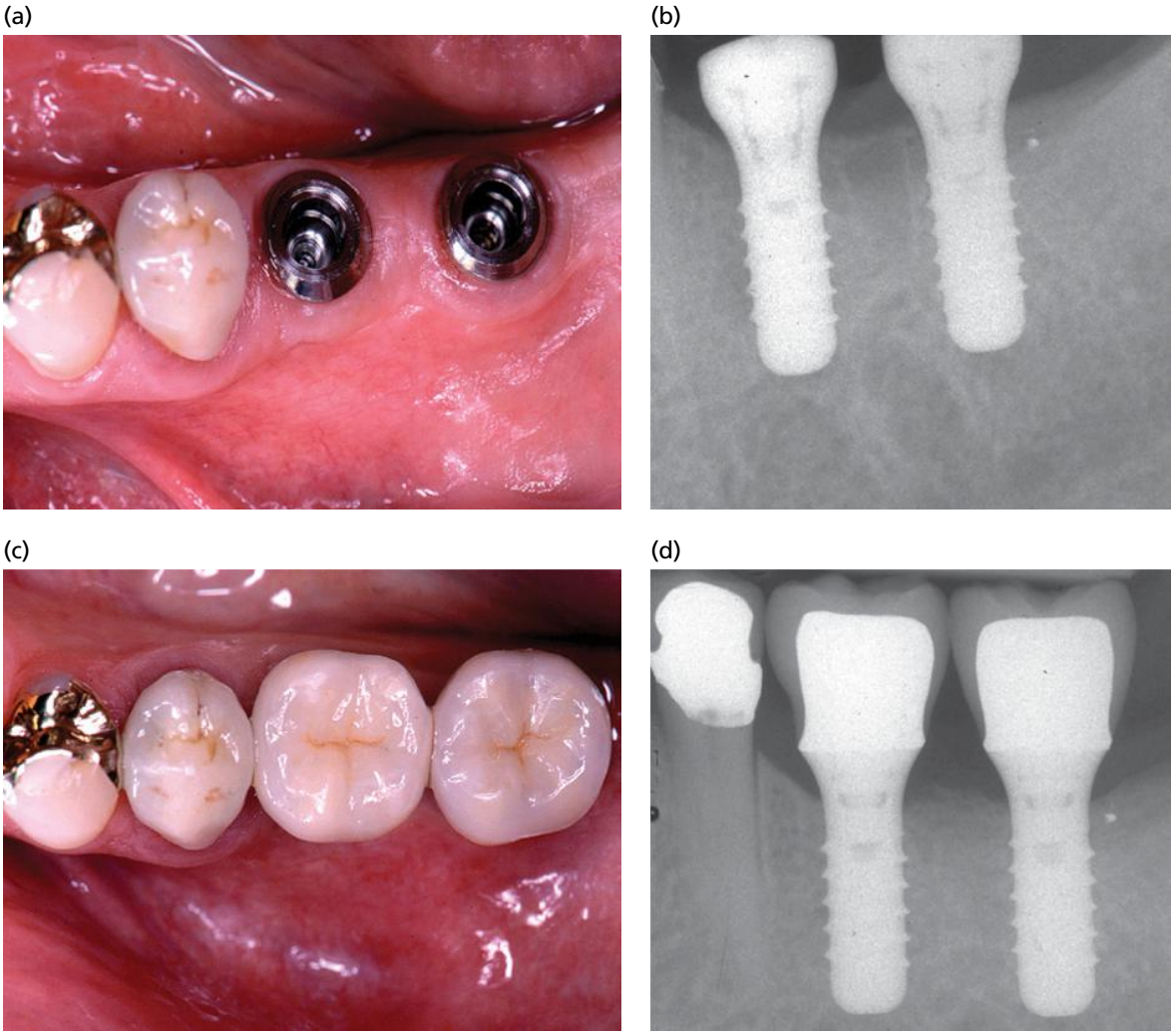

Fig. 53-4 Increasing subjective chewing comfort by replacing missing molars in a mandibular free-end situation. (a) Installation of two standard (4.1 mm diameter) Straumann® implants (8 mm) 6 and 14 mm distal of the distal aspect of tooth 35. (b) Radiographic control at the time of implant installation. (c) Two molar crowns on implants in positions 36 and 37, 8 years after installation. (d) Radiographic documentation, 8 years after loading of the implants.

Preservation of intact teeth or reconstructions

Considering the dimensions of premolars (7 mm) and molars (8 mm) and adequate space for the interdental/interimplant space (4–5 mm), edentulous ridges between existing teeth may be reconstructed and chewing comfort increased without involving adjacent teeth (Fig. 53-5). Obviously, risks can be minimized by reducing the length of bridge spans.

In combined molar and premolar reconstructions (Fig. 53-6), the surgical positioning of the implants has to be calculated in detail and restoration-driven stents may have to be used in order to create adequate conditions for prosthetic reconstruction.

Preservation of natural tooth substance and existing functional and satisfactory reconstructions

Oral implants are ideal abutments if natural tooth substance can be preserved. The preparation of a tooth to serve as an abutment for a crown or a bridge anchor opens about 40 000–70 000 dentinal tubules/mm^2. This, in turn, means that the integrity of a vital tooth is severely compromised. Even though a small proportion of abutment teeth will lose their vitality immediately as a sequela of the preparation procedure, it has been documented that approximately 10% of all vital abutments will have lost vitality after 10 years (Bergenholtz & Nyman 1984; Pjetursson *et al*. 2004a; Tan *et al*. 2004). Hence, it is obvious that an implant installation avoiding tooth preparation represents the most biologic way of replacing a missing tooth (Fig. 53-7).

In areas of esthetic priority, the replacement of a missing tooth with a single implant may – beyond doubt – provide the best and most esthetic treatment option (Fig. 53-8). This is especially true in a periodontally healthy dentition and in situations where the papillae towards the adjacent teeth are still present. By placing the implant in a slightly (1–2 mm) submucosal location, an optimal emergence profile can be achieved.

Instead of preserving natural tooth substance, the clinician may choose to save existing, still satisfactory

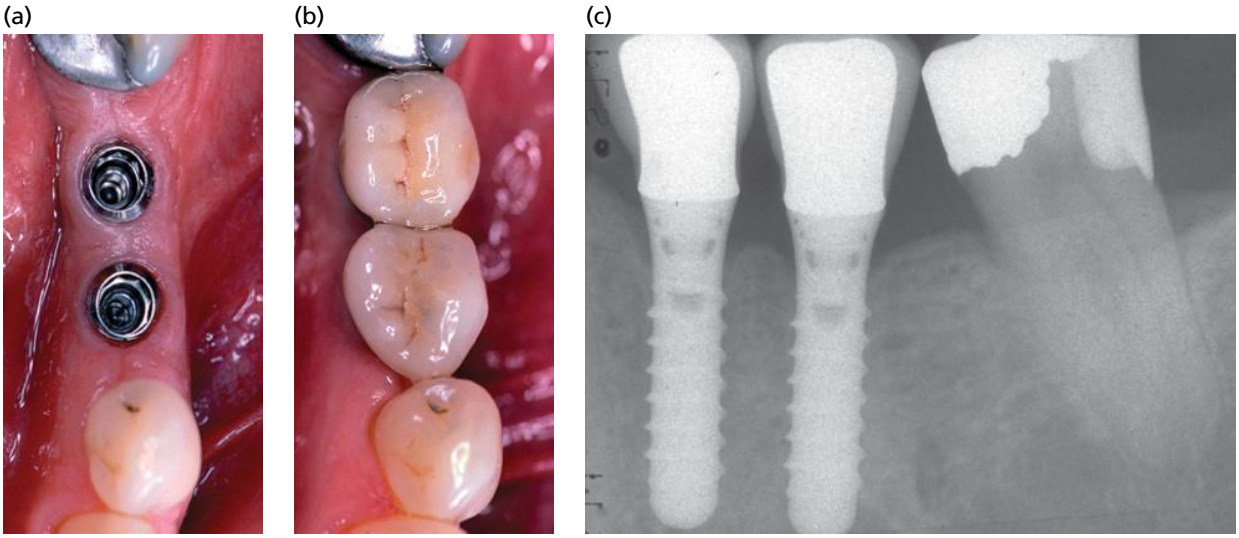

Fig. 53-5 Increasing subjective chewing comfort by closing a mandibular gap. (a) Installation of two standard (4.1 mm diameter) Straumann® implants (10 mm) 5 mm distal of the distal aspect of tooth 34 and 12 mm distal of tooth 34 (= 6 mm mesial of tooth 37). Total extension of the gap: 18 mm. (b) Reconstruction of the implants in premolar units to fit the size of the gap. (c) Radiographic documentation, 6 years after loading. The filling on tooth 37 was satisfactory and did not need replacement.

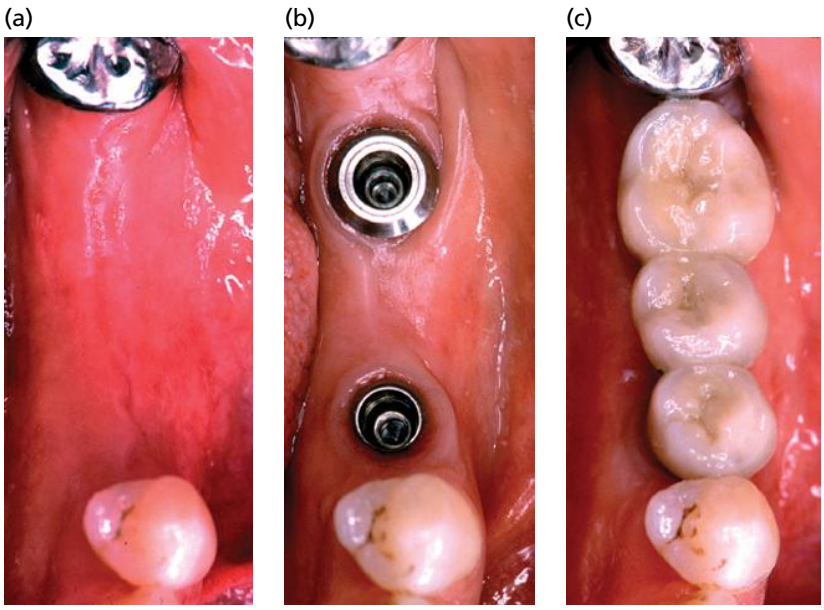

Fig. 53-6 Increasing subjective chewing comfort by filling a large mandibular gap. (a) Edentulous ridge between teeth 34 and 38: 28 mm. (b) Installation of a standard (4.1 mm diameter) Straumann® implant 5 mm distal of the distal aspect of tooth 34 and a wide body (4.8 mm diameter), wide neck Straumann® implant 20 mm distal of the distal aspect of tooth 34 and 8 mm mesial of the mesial aspect of tooth 38. (c) Three-unit implant-supported fixed prosthesis filling the gap.

reconstructions, thereby simplifying the restoration of a mutilated dentition (Fig. 53-9). Occasionally, the reconstruction may have a smaller extent and hence, there is a reduced chance of encountering technical complications during the years of service.

Replacement of strategically important missing teeth

The loss of a strategically important tooth often creates a chain reaction of therapeutic measures that need to be taken. Treatment planning may become highly involved and extensive reconstructions may result from the loss of such a tooth. Especially in dentitions that have received multiple reconstructions, the loss of one strategic abutment may lead to a time-consuming and costly therapy (Fig. 53-10). Oral implants provide valuable and today indispensable treatment alternatives to the need to redo existing reconstructions. By installing oral implants in the strategically correct locations, partial reconstruction of a dentition may become possible. Obviously, installation of such implants has to be restoration driven. In cases with bone dehiscences or lack of

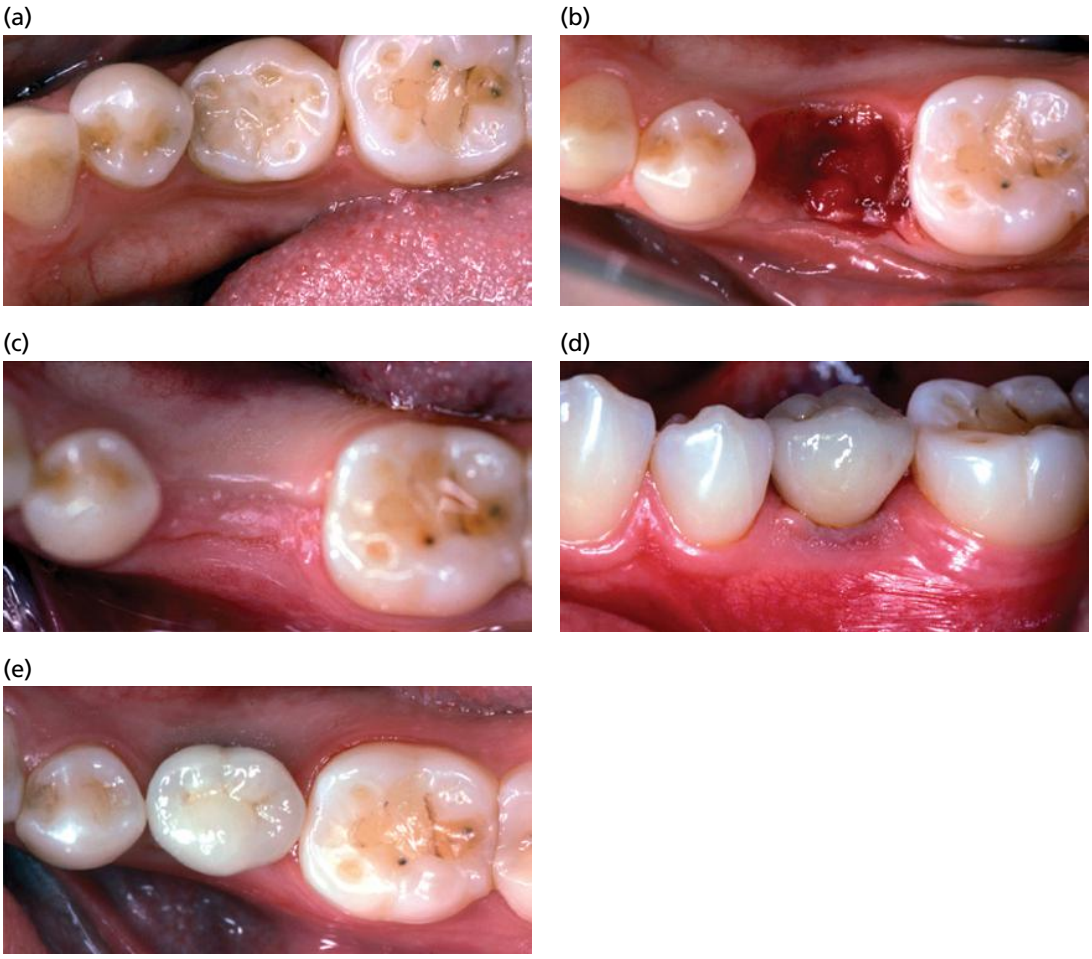

Fig. 53-7 Preservation of natural tooth substance. (a) Deciduous molar 75 has to be replaced owing to the advanced root resorption. (b) Following extraction of tooth 75, the site is ideal for replacing the missing tooth with a three-unit bridge or a single implant. (c) Single implant is chosen to avoid jeopardizing the integrity and vitality of the two adjacent teeth 34 and 36. Cutting preparations for full coverage of the crowns will result in 10% of the prepared teeth losing vitality after 10 years. (d) Single tooth replacement of tooth 75, 5 years after reconstruction. (e) Occlusal view of the single implant-supported crown to replace a deciduous molar, 5 years after reconstruction. The adjacent teeth remain unsevered.

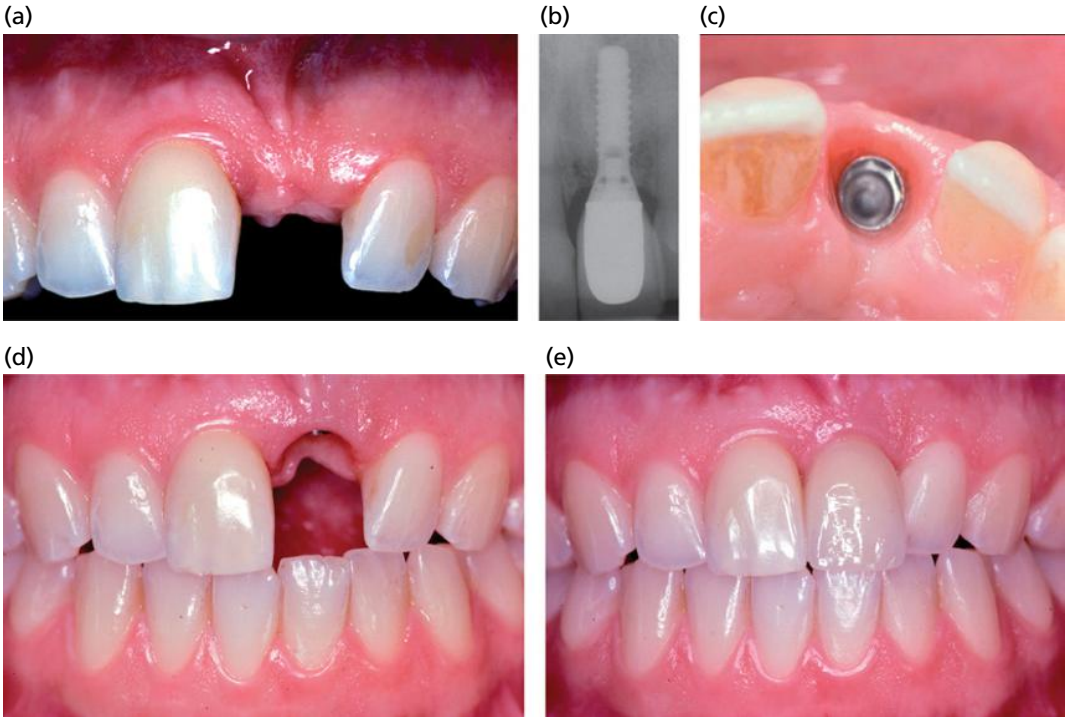

Fig. 53-8 Preservation of intact tooth substance. Single tooth replacement of a missing central incisor 21. (a) Teeth 11 and 22 adjacent to the edentulous space 21 are intact teeth with no fillings and periodontally healthy conditions. Both mesial and distal papillae are intact and reach coronally to the contact area in this juvenile patient. (b) Following the installation of a Standard Plus (4.1 mm diameter) Straumann® implant with a length of 12 mm, the mucosal tissue is conditioned to achieve a perfect emergence profile. (c) Radiographic documentation 2 years after the prosthetic reconstruction of the implant. (d) Tissue conditioning due to a more apical insertion of the implant for esthetic sites. (e) Implant-supported single tooth replacement 21, 2 years after reconstruction.

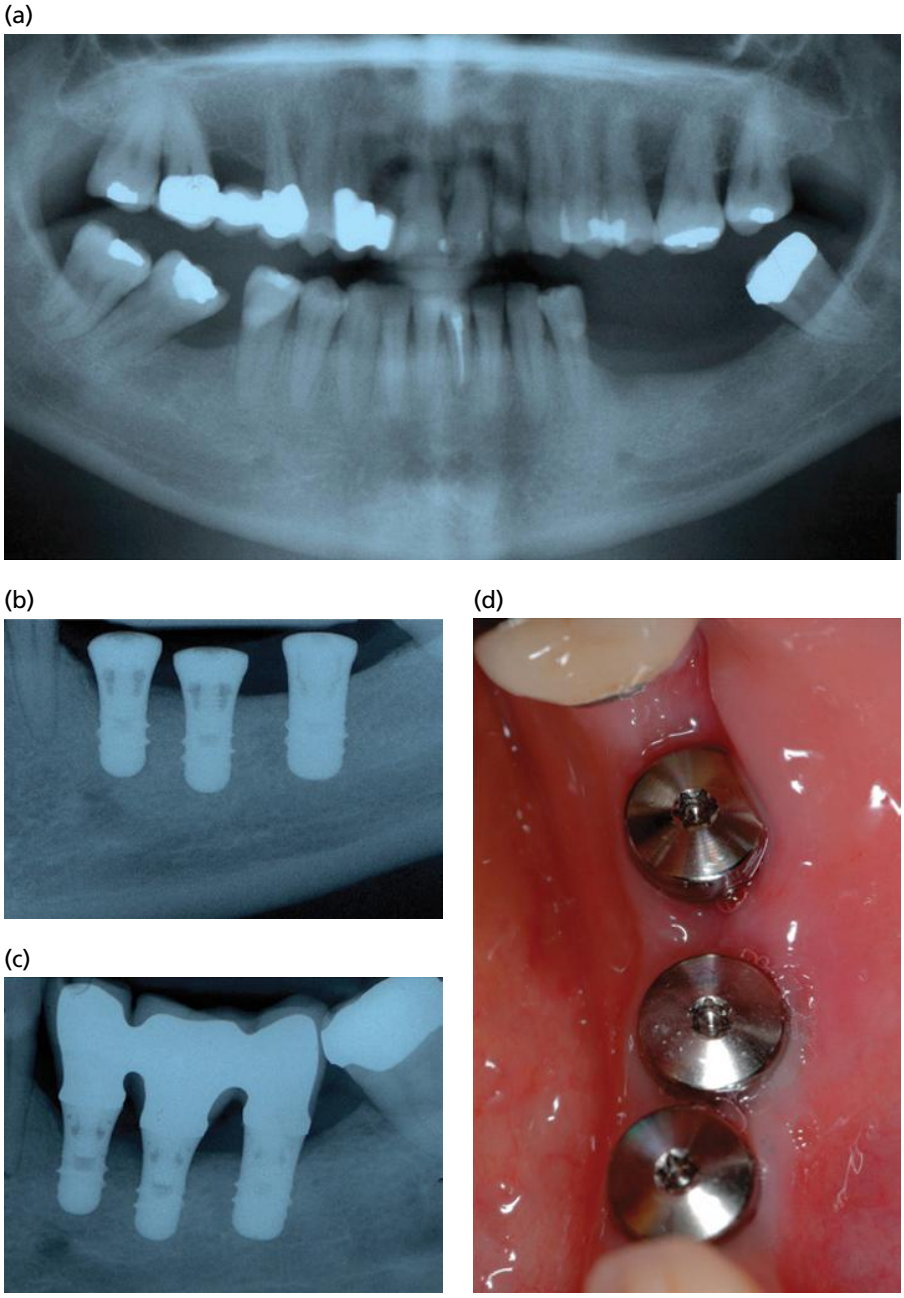

Fig. 53-9 Mandibular edentulous area after the extraction of teeth 35, 36, and 37. (a) Orthopantomogram revealing the neighboring anatomic structures (inferior mandibular nerve) and intact reconstructions on the teeth adjacent to the edentulous ridge. (b) Installation of two standard (4.1 mm diameter) and one wide body (4.8 mm diameter) Straumann® implants at a distance of 5 mm, 11 mm, and 20 mm, respectively, distal to the distal aspect of tooth 34. (c) Transmucosal implant installation for two premolar and one molar unit. Implants covered with healing caps. The intact crown on tooth 38 is visible. (d) Radiographic documentation after 5 years. Implant crowns are splinted because of the short (6 mm) implants (near the inferior mandibular nerve).

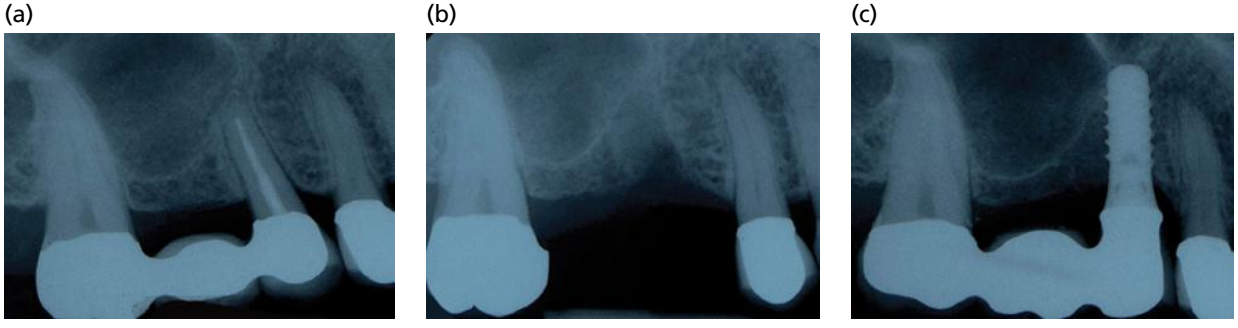

Fig. 53-10 Replacing strategically important teeth. (a) Fixed dental prosthesis is seated on abutment teeth 17 and 15. Tooth 15 was root canal treated and suffered from a root fracture which jeopardized the integrity of the entire reconstruction. (b) Bridge is separated between tooth 17 and pontic 16. (c) New fixed dental prosthesis was seated on the implant 15 and soldered to the existing, still satisfactory, crown 17. In this manner, the implant helped to avoid a costly and extensive reconstruction.

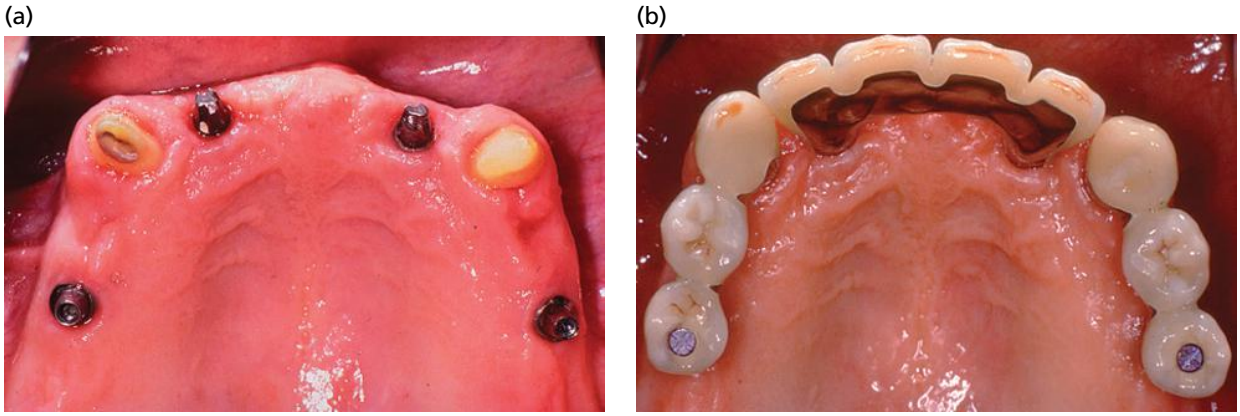

Fig. 53-11 Replacing strategically important abutments. (a) Only the two periodontally healthy maxillary canines 13 and 23 remain. To reconstruct this maxilla with a fixed dental prosthesis requires the installation of oral implants in strategically correct locations. An implant-supported maxillary front reconstruction and two mixed tooth–implant-supported reconstructions in the posterior segments were planned. (b) Eight years following implant installation. The maxillary front reconstruction is cemented on solid abutments that have been installed in the positions of teeth 12 and 22, that is 5 mm mesial of the mesial aspects of the canines. The posterior segment reconstructions are cemented on the canines and screw retained on two implants in the positions of teeth 15 and 25, that is the implants are placed 11 mm distal of the distal aspects of the canines, which allows the placement of three-unit reconstructions with minimal risks. A shortened dental arch as a limited treatment goal provides satisfactory chewing function.

adequate bone volumes, bone augmentation procedures may have to be performed (Fig. 53-11).

Conclusion

Oral implants are best used as abutments in restorative dentistry if the subjective chewing comfort has to be increased, natural tooth substance or existing satisfactory reconstructions have to be preserved, or strategically important missing teeth have to be replaced.

Hence, oral implants have become valuable, indispensable, and welcome treatment alternatives to traditional dental reconstructions. Obviously, oral implants should only be incorporated in oral cavities with healthy conditions, that is a thorough periodontal treatment has to precede restorative therapy.

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Chapter 54

Implants in the Zone of Esthetic Priority

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Introduction

Importance of esthetics in implantology and its impact on patient quality of life

Esthetics has become an increasingly important topic in modern society. It is not only important in itself, but also relates to other more general concepts of well-being (Samorodnitzky-Naveh *et al.* 2007). The loss of one or more teeth in the zone of esthetic priority may impair the esthetic appearance of the patient and therefore, any treatment modality for reconstruction of the lost tissues must address both functional *and* esthetic outcomes.

The structural components of an implant anchored in the bone and covered by soft tissues differ in several aspects from those of a tooth with its periodontium (Berglundh *et al.* 1991; Abrahamsson *et al.* 1996; Lindhe & Berglundh 1998; Welander *et al.* 2008). The lack of root cementum on the implant surface influences the fiber orientation and attachment (Traini *et al.* 2005a, b; Tetè *et al.* 2009), which, in turn, may impair the natural morphology and surface characteristics of the soft tissues. An irregular mucosal arrangement and/or missing papillae, despite being healthy, may strike a discordant note, and be the main reason for an esthetically displeasing result (Garber & Salama 1996).

Several studies have confirmed an altered esthetic outcome after placement of implant-supported reconstructions in the upper anterior area (Chang *et al.* 1999a; Evans & Chen 2008; Schropp & Isidor 2008). In general, implant-supported clinical crowns have been evaluated to be longer than the non-restored contralateral teeth, and factors such as "topography

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of the surrounding soft tissues", "form of the crown", and "contact point position" were found to have a statistically significant influence on the clinicians' determination of the overall satisfaction with appearance (Chang *et al*. 1999b).

The commonly used methodology to investigate patients' esthetic perception is ranking of clinical photographs according to esthetic discrepancies (Dong *et al*. 1999; Kokich *et al*. 1999; Van der Geld *et al*. 2007). However, the expert evaluation of patients' esthetic appearance is often biased and as a consequence, patient self-assessment of dentofacial esthetics through use of questionnaires has become a widely used approach. Surprisingly, patients' judgment of the esthetic result often revealed a higher degree of satisfaction than that judged by professionals (Kokich *et al*.1999; Flores-Mir et al. 2004), and the factors most strongly influencing satisfaction with appearance were age, gender, and tooth shade (Neumann *et al*. 1989; Dunn *et al*. 1996). A recent study by Mehl *et al*. (2009) evaluating the Oral Health Impact Profile (OHIP) (Slade & Spencer 1994), a scale assessing satisfaction with one's own dental appearance and commonly used for capturing dental esthetics, found that this did not evaluate patients' appearance adequately. One of the common problems is that the discriminatory power of most measures is low (Meijering *et al*. 1997) and often minimizes the assessment of specific esthetic concerns as compared with their psychosocial consequences (Larsson *et al*. 2010a). The Orofacial Esthetic Scale (OES) (Larsson *et al*. 2010b), developed especially for prosthodontic patients, is a brief questionnaire based on eight representative items that assess orofacial esthetic impacts and exhibit a good score reliability and validity.

A study by Wolfart *et al*. (2006) on prosthodontic patients evaluated general well-being with self-assessment of their dental appearance, and measured distinct esthetic concerns and psychosocial consequences of esthetic impairment. The orofacial appearance is a conceptual component which has a psychosocial impact on a patient's well-being and influences oral health-related quality of life (John *et al*. 2004). It is therefore important not only to evaluate the esthetic outcome with expert-based assessments, but also to include patient-based approaches (Ekfeldt *et al*. 1994; Avivi-Arber & Zarb 1996; Lamb & Ellis 1996). For profound evaluation, the patient's own assessment of his/her dentofacial esthetics should be captured by appropriate instruments and be included as a component when evaluating future implant success rates.

Decision-making process and informed consent

The long-term success and survival rates of implants inserted to replace missing teeth have been documented in several prospective studies and systematic reviews (Jung *et al*. 2012; Lang & Zitzmann 2012; Pjetursson *et al*. 2012). Although favorable long-term results of implant therapy have been reported, infections and esthetic adverse outcomes do occur. It is possible that some infections around implants, accompanied by esthetic problems, develop slowly. The results of a long-term follow-up study concluded that 9–12 years after implant installation, implant survival rates are high and implant loss seems to cluster within patients. In contrast, after the same period of observation, peri-implant lesions seem to be a common clinical entity (Roos-Jansåker 2007). These results necessitate critical patient evaluation before recommending implant-supported reconstruction, especially in young adult patients and those with a history of periodontal disease. In addition, patients need to understand their options and the likely benefits and potential side effects of each option. Unfortunately, when coming to a decision on treatment, clinicians often unwittingly invest too much confidence in their diagnostic accuracy (Berner & Graber 2008). This finding is not only valid for experts, but also for laypeople. The psychological literature has documented that people are not good at assessing what they know and generally tend to be overconfident in their judgments (Griffin & Tversky 1992; Kruger & Dunning 1999). This, in turn, means that patients have considerable knowledge gaps about treatment and outcomes even if they feel well informed. A recent cross-sectional survey concluded that there is a need to improve assessments of how informed patients are. More decision-specific items have to be created for each situation as they provide more details about what patients know and what potential information gaps they have (Sepucha *et al*. 2010). Using generic items such as patients' perceptions to assess the extent to which participants are informed is problematic. Interestingly, there was a positive relationship ($P = 0.07$) between knowledge scores and a patient's perception of being extremely well informed regarding surgical decisions, but not for medication and screening. A possible explanation for this finding is that surgery is a more significant decision that receives increased attention and involvement, which in turn raises a patient's awareness of his/her knowledge. In the multivariate regression analysis, only trust in the provider was significantly associated with perceptions of feeling extremely well informed.

Basically, trust in one's own surgeon is a fundamental requirement for accepting a treatment plan based on implant placement in the zone of esthetic importance. On the other hand, such trust may not actually correlate with whether or not the clinician has actually provided adequate information to allow the patient to make an informed decision. However, if a patient trusts his/her surgeon, he/she may be less likely to seek other sources of information or to be critical of what he/she is told.

In order to promote quality of care in implantology, informed patient choice has to be emphasized. It

is a key responsibility of clinicians to determine the extent to which patients are actually informed and whether or not they understand the planned treatment solution, the options, and the outcomes, including risks, for any major medical decision they face.

Preoperative diagnostics and risk analysis

Clinical measurements

An implant reconstruction in the area of esthetic importance should resemble a healthy, unrestored tooth in all aspects. For this, an initial, precise evaluation of the edentulous area and the periodontal condition of the neighboring teeth is of utmost importance. As the periodontal status of the residual dentition may influence the survival and success rates of the prospective implants (Mombelli *et al*. 1987; Pontoriero *et al.* 1994; Zitzmann *et al.* 2002), independently of the implant position in the dental arch, some parameters have to be evaluated routinely before starting treatment and while monitoring implant reconstructions over a lifetime, including assessment of oral hygiene habits by quantifying plaque accumulation using the original Plaque Index introduced by Silness and Löe (1964). A modified version of this index has been published to assess biofilm formation in the marginal area of implants (Mombelli *et al*. 1987). The presence of bleeding on probing (notated in records as BoP^+) has been shown to detect an inflammatory lesion in the gingiva around teeth. On the other hand, absence of BoP has been reported to represent periodontal health with a high negative predictive value (Lang *et al*. 1986, 1990). To be confident of acceptable presurgical hygiene conditions, it is recommended that the full-mouth bleeding scores are <20% (Lang *et al*. 1996; Tonetti *et al*. 1998). It has been shown that lipopolysaccharides from a variety of Gram-negative bacteria can inhibit gingival fibroblast proliferation, which, in turn, is responsible for the delayed healing of inflamed sites (Bartold *et al*. 1992). Additionally, an inflamed mucosa cannot be manipulated with the same precision as a healthy one, and primary wound closures are more difficult to achieve as inflamed soft tissues are ambiguous and at higher risk for soft tissue dehiscences during the early healing phases.

The periodontal probing depth today is still one of the most reliable and sensitive diagnostic investigations for the evaluation of the periodontal condition, even if some shortcomings have to be considered (Lang *et al*. 1994). The probing depth around teeth adjacent to an edentulous area is not only an indicator for periodontal treatment needs, but also an important prognostic value for the esthetic result. The presence of an interproximal papilla with a natural appearance between a tooth and an implant mainly depends on the level of the attachment at the neighboring tooth surfaces. For this reason, a preoperative precise recording of the probing pocket depth and the soft tissue level adjacent to an edentulous area, measured from the cementoenamel junction (CEJ) to the gingival margin (mucosal recession), is of utmost importance for the prediction of the post-surgical papillary morphology (Kan *et al*. 2003).

Another factor that influences the esthetic success of an implant reconstruction in the anterior area is the soft tissue biotype (Lee *et al*. 2011). Two periodontal biotypes have been described around teeth (Seibert & Lindhe 1989): (1) a thick flat one associated with quadratic teeth and a wide zone of keratinized mucosa, and (2) a thin, highly scalloped one with slender teeth. Numerous studies on humans show that the first of these is the preferred biotype for optimal surgical and prosthetic outcomes (Henriksson & Jemt 2004; Linkevicius *et al*. 2009; Bressan *et al.* 2010; Linkevicius *et al*. 2010). A thin tissue biotype is more friable, less vascularized, and accompanied by thinner underlying bone (Kois 2001), and seems to be more susceptible to mucosal dehiscences. Extrapolating from the observations of the soft tissue behavior around teeth, the peri-implant soft tissue can also be classified into thin and thick biotypes, with a range of transitional categories in between.

There is a lack of consensus concerning the methods used to measure the mucosal biotype. Some authors consider the soft tissues thin when the transparency of a periodontal probe in the sulcular area can be seen shining through the tissue (Kan *et al.* 2003; Evans & Chen 2008). Others have measured the tissue thickness with a periodontal probe or an endodontic file (Linkevicius *et al*. 2009), or an ultrasonic device (Müller *et al*. 2000), or have just recorded the width of the masticatory mucosa (Chen *et al.* 2009). In a recent study of 100 patients, experienced clinicians were able to visually recognize the thick flat biotype in >70% of the cases, but were unable to identify almost 50% of the thin scalloped biotypes (Linkevicius *et al*. 2009). These cases that were overlooked are precisely those that are susceptible to increased esthetic compromise, which clearly emphasizes the limitations of visual inspection alone and calls for the assessment of mucosal thickness.

Besides the clinical records of the residual dentition, especially around the teeth adjacent to the prospective implant sites, including their restorative condition (e.g. overhangs of fillings, precision and vertical location of crown margins), the inspection of the edentulous area is also important as it strongly influences the prognosis of the esthetic outcome and the additional therapies that are required. The extent of an edentulous space in the arch can be described based on the number of missing teeth. Several authors have tried to classify these areas regarding their morphologic characteristics (Allen *et al*. 1985; Seibert 1983; Wang & Al-Shammari 2002), dividing them into a horizontal and a vertical defect component. Depending on their extent, vertical hard and soft tissue defects show a much better prognosis for

augmentation than horizontal ones. In the latter, the attachment level at the teeth neighboring the defect limits the prognosis and therefore the prospective esthetic result.

Image-guided diagnostics

To ensure a proper planning of the implant position, which is a fundamental requirement in the zone of esthetic priority, the required information can be obtained from the aforementioned clinical examinations and additional appropriate image-guided diagnostics. In investigating an implant site in the anterior upper jaw, a clinician requires information on bone volume and quality, topography, and the relationship to important anatomic structures, such as the roots of neighboring teeth, nasal floor, vessels, and nerves (Harris *et al.* 2002). In the last decade, a rapid adoption of conventional computed tomography (CT) and more recently of cone-beam computed tomography (CBCT) can be observed in implant planning. There is legitimate concern from experts in the clinical and radiology fields that these technical developments will lead to a significant increase in the radiation exposure of patients without a proper risk–benefit analysis. For this reason, guidelines for the use of diagnostic imaging in implant dentistry have been published, based on a consensus workshop of the European Association for Osseointegration (EAO) (Harris *et al*. 2012).

In the upper anterior maxilla, the recommended standard radiographic technique consists of an intraoral radiograph before replacing a missing single tooth, and an additional panoramic image in partially dentate and edentulous patients. The need for cross-sectional imaging has to be carefully evaluated for a sufficient net benefit, weighing the total potential diagnostic or therapeutic benefit against the detrimental effects the exposure might have for the individual. The latter effects can be divided in two categories: (1) tissue reactions which are proportional to the dose and occur in all individuals when the dose is large enough, and (2) stochastic effects which are believed to have no threshold and can be considered as "chance" reactions. The ranges of effective dose for conventional radiography are small and <0.002 mSv for an intraoral single radiograph. The corresponding values for a panoramic image are 0.003–0.024 mSv and 0.019–0.674 mSv for a CBCT. In contrast, the dose of a conventional CT ranges from 0.280 to 1.410 mSv, which makes its value questionable in the therapeutic planning of an implant reconstruction in the upper anterior segment (Harris *et al*. 2012).

A cross-sectional image (CBCT) can be indicated in clinical situations where (1) clinical examinations or conventional radiography have failed to adequately identify the relevant anatomic boundaries or the absence of pathology; (2) such an image can provide additional information and help to minimize the risk of damage to important anatomic structures; (3) these are judged to be clinically borderline, with limited bone, and the surgeon considers that the morphology of the defect requires a more extensive augmentation procedure; and (4) implant positioning can be improved so that esthetic results are optimized. This information can be enhanced by using radiographic templates and surgical guides which help to translate the information from the radiographic evaluation into the clinical procedure. These surgical guides may be a prerequisite when multiple teeth are missing and a fixed reconstruction with implant-supported crowns and bridges is planned.

Visualization of prospective results for diagnostics and to inform patients

When treating the anterior zone of a patient's upper jaw, the wishes and expectations of each individual patient concerning the esthetic result have to be respected. Very often the patient's and the clinician's views of what constitutes an ideal esthetic outcome differ widely (Eagly *et al*. 1991; Langlois *et al*. 2000). While the patient is influenced by his/her self-perception, the social environment, the media, his/her own dental history, and many other factors, the clinician bases his/his choice of a certain clinical strategy on the current dental knowledge, the empirical experience, and, possibly, on available medical checklists. The latter especially carry a risk of standardizing the prospective results and disregarding the individuality and personality of each patient. To address this, the contact and communication with the patient in the diagnostic phase, but also during the following treatment stages, requires special attention as patients are often unable to articulate their wishes and concerns. This personal relationship cannot be replaced with scoring answers to a digital checklist of questions. Additionally, the translation of a digital analysis with the help of computer imaging software idealizes the prospective results, which may not reflect the actual situation. Especially in edentulous areas where a considerable amount of vertical tissue volume is missing, it can be difficult to reconstruct the tissue loss with surgical interventions alone, and clinicians must take care with what they promise patients regarding outcomes. Against this background, each treatment plan for a reconstruction in the zone of esthetic importance should be based on the interaction between all participating persons and must include the patient's opinions and desires.

All the rules that have been learned about tooth form, geometry, and harmony to recreate an esthetically pleasing smile can only be viewed as a general guide. Otherwise, all treatment goals would be the same for all patients and the facial physiognomy and uniqueness of each individual would be neglected.

To facilitate the communication within the treatment team (dentists, other physicians, and dental

technicians) and to include the patient in the decision-making process, the so-called Patient-supported Esthetic Protocol (PEP) (Gebhard 2013) has been developed. It is based on an iPad application (Apple Inc., Cupertino, CA, USA) which can record the patient's wishes and desired changes concerning his/her orofacial appearance, as well as all the diagnostic steps. It is not a checklist or an analysis of existing esthetic shortcomings. Checklists can be helpful to clinicians in identifying problems, but they have a tendency to overlook patient individuality and usually follow a set pattern that ends with a standardization of the procedure. The patient-supported esthetic protocol helps to visualize and develop the treatment goals over the course of the diagnostic steps: a diagnostic wax-up, its transformation into a mock-up for try-in, the provisionals, a full wax-up, the try-in of the first bake, and the final reconstruction (Fig. 54-1).

All the patient's wishes are noted, even those that appear unimportant (e.g. important treatment steps only when there is a full moon), before the clinician or technician starts to describe the individual physiognomy of the face and to define a certain position and form of the teeth. This becomes more crucial when several anterior teeth have to be replaced or restored (Fig. 54-2a). The position of the incisal edges are given by the lower lips. In an ideal set-up, the incisal edges should be slightly depressed at the junction between the lip vermillion and the oral mucosa when vocalizing the F sound (i.e. saying something like "frog" or "fifty five"). Based on this landmark, the form of the teeth and their tooth-to-tooth position can now be built up and transferred to a diagnostic wax-up and mock-up. The visualization of the prospective result is the decisive tool in the diagnostic phase and pictures are taken from the inserted mock-up to document the development of the treatment goals and to use in discussion of further adjustments with the patient. Proposals for changes are marked in red while the comments of the patient are noted in another color (in this case blue) (Fig. 54-2b, c). Once the shape and the arrangement of the teeth are ideal, the new findings are transferred to a provisional, which also serves as a diagnostic aid for the patient. Further adjustment and detail can be incorporated in the final ceramic reconstruction (Fig. 54-2d).

PEP forces clinicians and dental technicians to take the time necessary to deal with the patient's esthetic expectations, to communicate these to the treatment team, and to make notes on each individual step in the development of the prospective esthetic outcome. Additionally, it can be archived in the clinical records and be used for quality assurance.

Checklists and risk assessment (indications and contraindications)

Prior to selecting an implant-based solution, one should carefully review all possible treatment alternatives that have the potential to solve a given problem. Additionally, the advantages and disadvantages of the solutions should be comprehensively pondered, not only in light of long-term survival but also with respect to the esthetic outcome and its stability over time. The therapeutic modalities that can be used to replace a tooth in the zone of esthetic priority, without placing implants, are listed in Table 54-1. In cases with unrestored neighboring teeth, adhesive restorations have been shown to reliably replace single missing teeth in the anterior upper jaw with almost no preparations needed at the anchor teeth (Rosentritt *et al*. 2009).

In young adults especially, a prosthetic solution can be chosen that is documented to have an inferior survival rate in the literature but shows a better clinical predictability regarding the esthetic appearance. This solution gives time for new achievements and technologies in implantology to emerge that may facilitate the reconstruction at a later date (Fig. 54-3).

In comprehensive esthetic treatment planning, attention should be directed not only to implant alternatives but also to strategies aimed at improving the implant sites prior to placing the implant or even at improving a tooth's prognosis such that implant reconstruction can be postponed or even avoided. Based on our personal experience, orthodontic pretreatments especially can improve the clinical situation in many cases and provide a better esthetic prognosis for therapy. These pretreatments include forced eruptions (Giachetti *et al*. 2010) to increase the retention for placement of a conventional crown (Juloski *et al*. 2012) or to condition the site for later implant placement (Amato *et al*. 2012). Another orthodontic treatment option consists of changing the distribution pattern of the edentulous spaces by turning a neighboring two-unit space into two one-unit spaces (Fig. 54-4a). As previously mentioned, the latter situation has a much better predictability regarding the development of papillary-like structures, an important issue for a natural appearance. As shown in Fig. 54-4b, a palatally placed implant offers an absolute anchorage for orthodontic tooth movements without risk of negatively influencing the present occlusion. Additionally, the temporary implant may serve as an ideal anchor in many situations to firmly fix a provisional without any visible attachments on the anterior incisors and canines (Fig. 54-4c) until the implants can be loaded with provisional crowns (Fig. 54-4d).

In patients with open interdental spaces and one or more missing teeth to be replaced, a conventional fixed approach will be critical as a single diastema cannot be closed for symmetry reasons and thus, an implant-supported reconstruction becomes the treatment of choice. Besides diastemata, other situations which favor the inclusion of implants in the treatment plan are: (1) unrestored, healthy neighboring teeth; (2) compromised, risky abutments; (3) extended

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Patient-supported esthetic protocol

Patient:_____ Date:_____2:_____3:_____4:_____5:_____

Patient wishes: _____

_____

_____

Clinical evaluation: _____

_____

_____

Overbite: _____Overjet:_____Vertical dimension (in articulator):_____Photos:_____Bleaching:_____

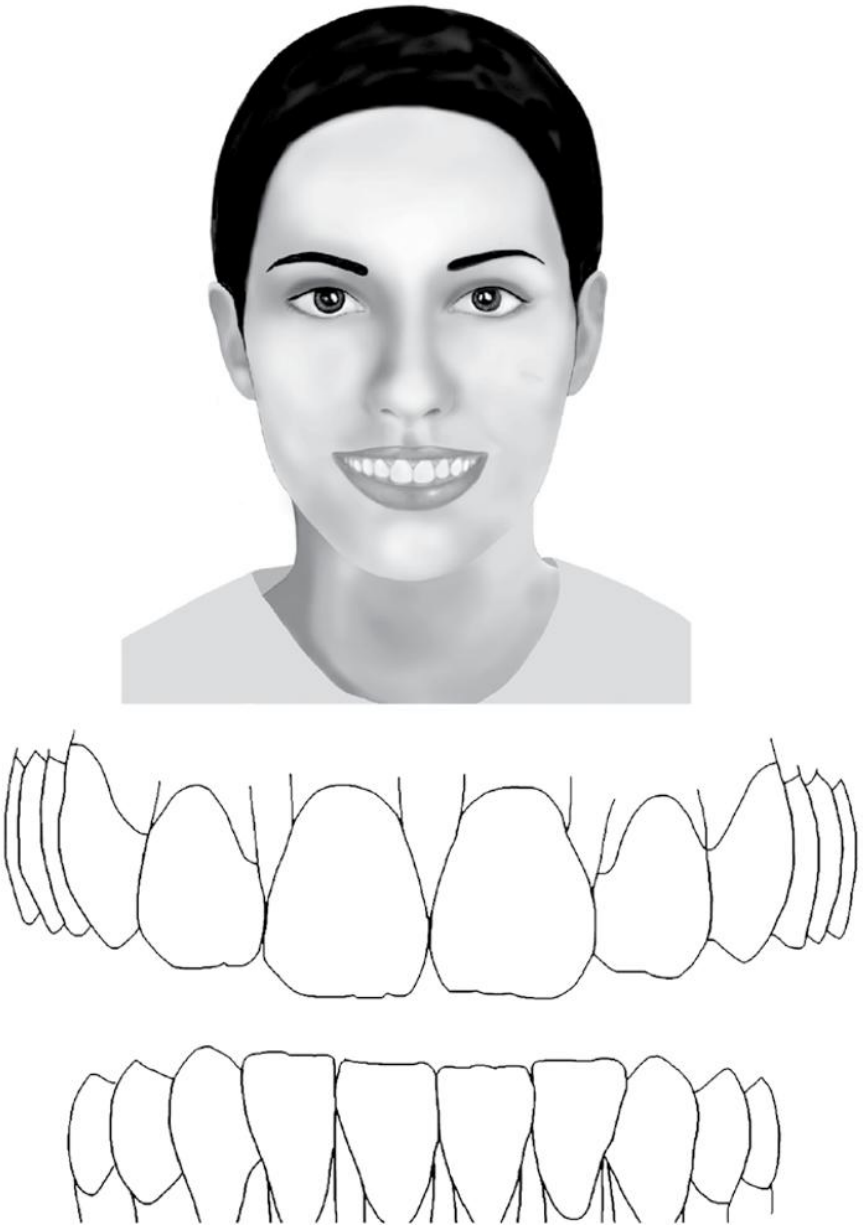
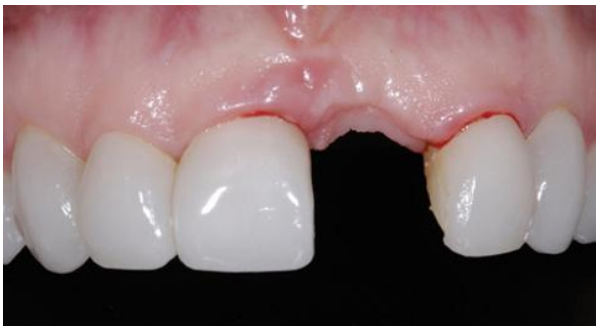


Fig. 54-1 Patient-supported Esthetic Protocol (PEP). Empty form to note the important aspects of the patient's dentofacial appearance. Note that no checklists are included.

(a)



(b)

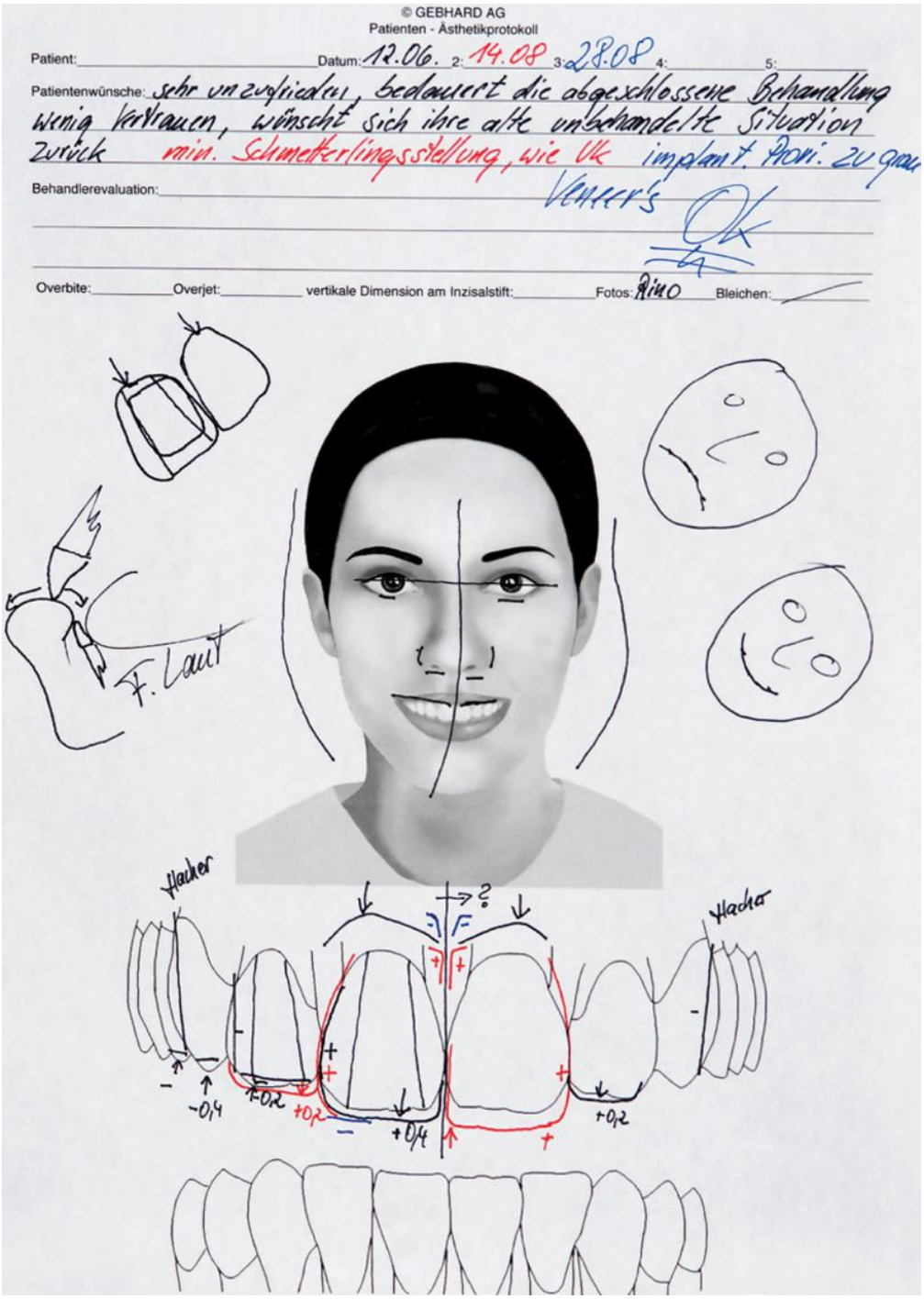


Fig. 54-2 (a) Patient's situation at first visit: missing left central incisor and esthetically insufficient veneers. (b) Completed PEP form. Analysis steps are noted in black, the incorporated changes agreed with the patient in red, and the patient's wishes in blue. In this way, the whole diagnostic sequences can be traced back.

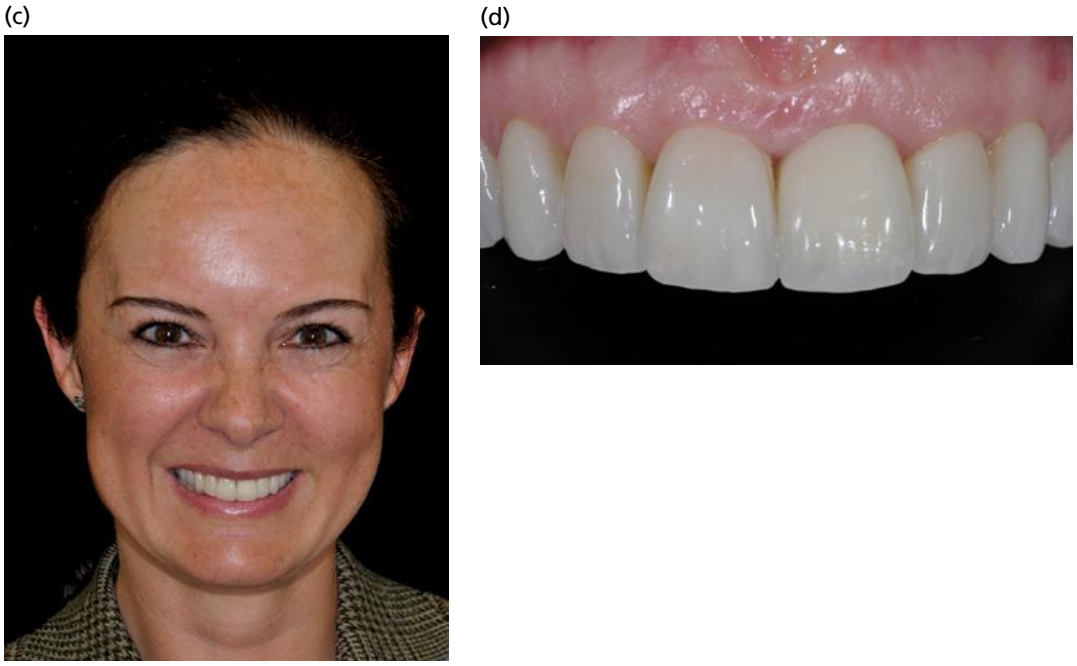


Fig 54-2 (*Continued*). (c) Full-face photograph with new reconstruction in the anterior upper jaw. (d) Final reconstruction with new veneers and implant-supported crown on left central incisor.

Table 54-1 Therapeutic modalities for tooth replacement in the zone of esthetic priority.

• Conventional fixed partial dentures comprising cantilever units
• Adhesive, resin-bonded (cantilever) bridges
• Conventional removable partial dentures
• Tooth-supported overdentures
• Orthodontic therapy (closure of edentulous spaces)
• Implant-supported prostheses (fixed, retrievable or removable suprastructures)
• Combinations of the above

edentulous areas; and (4) missing strategically important abutment teeth. The fulfillment of one or more of these criteria does not necessarily mean that the inclusion of implants in the treatment strategy is a given. Other risk factors related to the bone, soft tissue, and tooth (clinical crown) level have to be carefully evaluated and considered in the decision-making process (Table 54-2).

Provisional restorations and timing of the treatment sequences

In the anterior zone, provisional restorations have a variety of important functions. Provisional restorations should be used to evaluate esthetic, phonetic, and occlusal function prior to delivery of the final implant restorations, while preserving and/or enhancing the condition of the peri-implant mucosal tissues (Santosa 2007). An implant treatment approach in the edentulous anterior zone has three provisional phases:

Phase 1: from provisionalization immediately after tooth extraction to implant placement
Phase 2: from implant placement to abutment connection, prior to loading
Phase 3: from abutment connection to final crown/bridge placement, with loading of the implant and the development of the emergence and mucosa profile.

Phase 1: From tooth extraction to implant placement

After tooth extraction in the zone of esthetic priority, several options are available today to immediately replace the missing tooth/teeth with provisional restorations. These provisional restorations can be in the form of removable or fixed prostheses. It is of great importance for the patient to discuss the options as well as their advantages and disadvantages prior to the therapy. When a patient is going to lose one or more teeth in the anterior area of the upper jaw, an adequate provisional restoration will help give him/her back confidence.

Removable partial acrylic dentures have commonly been used after tooth extraction and possibly also throughout the entire implant therapy (Fig. 54-5). They are simple to construct, relatively inexpensive, and easy to adjust and fit. They can be easily modified in cases undergoing additional extractions by adding provisional teeth to their existing removable dentures at minimal cost. Care must be taken with the gingival portion of the provisional partial denture in order not to apply too much pressure to the healing site. Immediately after tooth extraction, the provisional restoration can be placed with ovate pontics

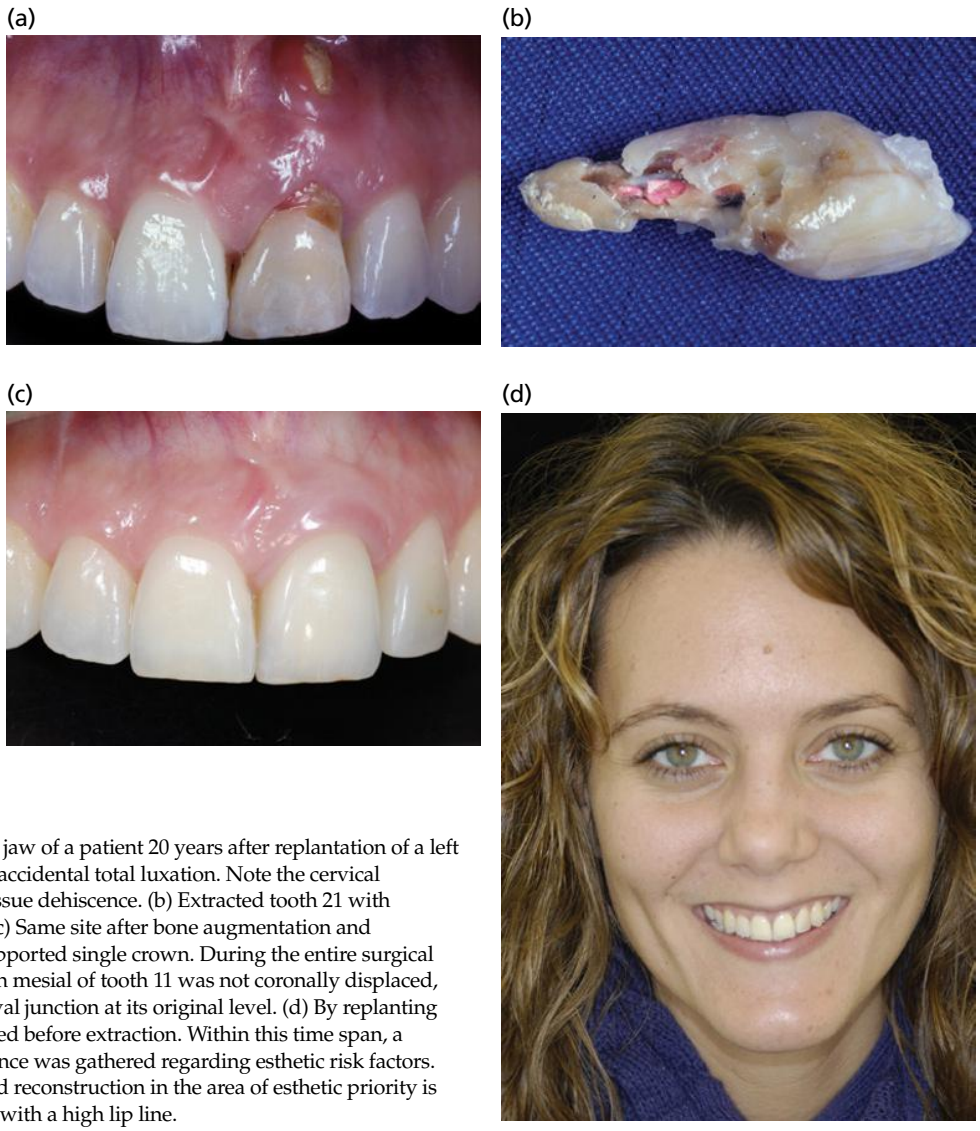


Fig. 54-3 (a) Anterior upper jaw of a patient 20 years after replantation of a left central incisor following an accidental total luxation. Note the cervical resorption and apical soft tissue dehiscence. (b) Extracted tooth 21 with extended root resorptions. (c) Same site after bone augmentation and placement of an implant-supported single crown. During the entire surgical treatment, the scar formation mesial of tooth 11 was not coronally displaced, maintaining the mucogingival junction at its original level. (d) By replanting tooth 21, 20 years were gained before extraction. Within this time span, a substantial amount of evidence was gathered regarding esthetic risk factors. Today, an implant-supported reconstruction in the area of esthetic priority is predictable even in patients with a high lip line.

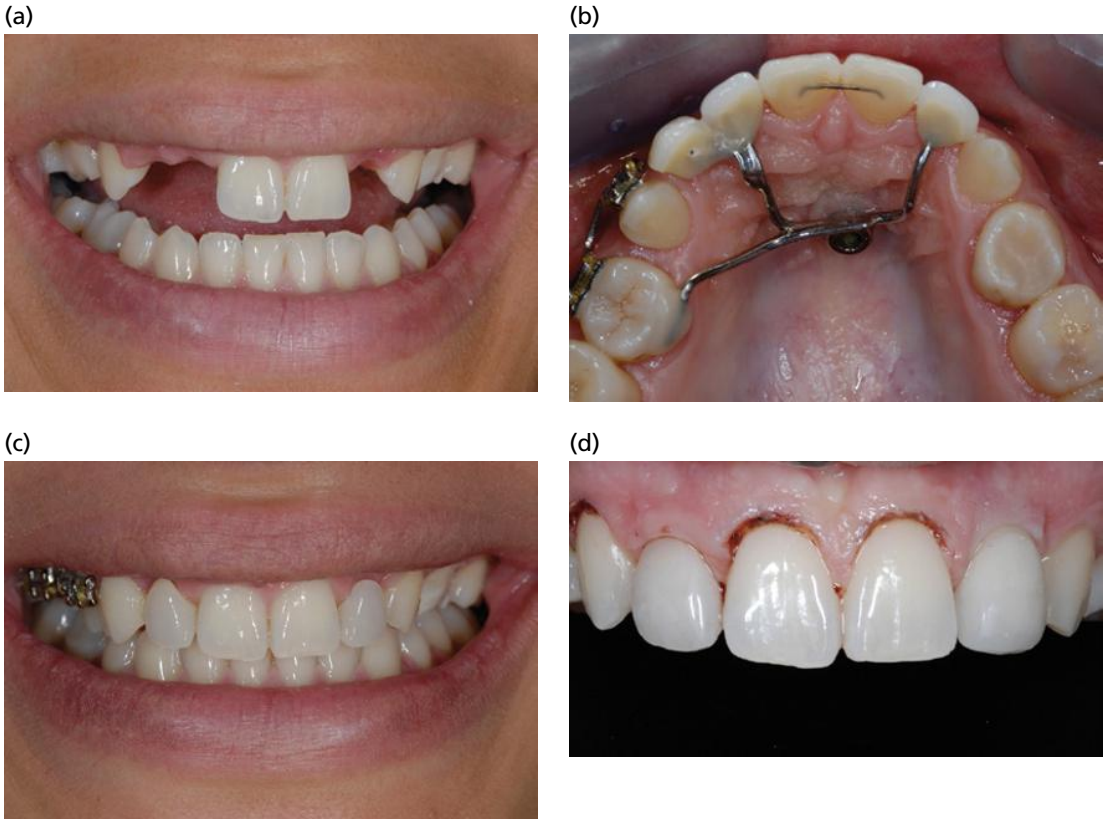


Fig. 54-4 (a) Patient with missing left lateral incisor and missing lateral incisor and first premolar in the right upper jaw. (b) Palatal implant for absolute anchorage and orthodontic movement of the right upper canine mesially. Additionally, the palatal implant serves as an ideal screw fixation for the provisional restoration which is shortened stepwise while moving the canine. (c) Provisionals in the area of teeth 13, 12, and 22, anchored on palatal implant. (d) Clinical picture after orthodontic treatment: three single-unit provisionals fixed on implants in the area of teeth 12 and 22.

Table 54-2 Risk factors for implant placement in the zone of esthetic importance.

	Low risk	Medium risk	High risk
Patient factors			
General health	Systemically healthy		Reduced defense
Smoking status	Non smoker	Occasional smoker	Smoker, heavy smoker
Compliance	Good		Poor
Esthetic expectations	Within normal limits		Very high
Lip line	Low	Medium	High
Dental/facial symmetries	Symmetric		Visible asymmetries
Interarch relationship	Normal situation		Deep bite situation
Hard and soft tissue factors			
Attachment level of neighboring teeth	Intact		Reduced
Periodontal and endodontic health	Healthy		Compromised
Distance contact area to bone level at neighboring teeth	<5 mm	5 mm	>5 mm
Ridge deficiencies	Intact alveolus	Lateral defect	Vertical or combined defect
Mesiodistal gap distance	One tooth (>7 mm)	One tooth (<7 mm)	Two neighboring units
Mucosal biotype	Low scalloped, thick	Medium	High scalloped, thin
Soft tissue surfaces	Intact		Texture irregularities, scar formations
Mucosal scalloping	Regular		Irregular
Tooth factors			
Crown forms	Squared shape		Triangular shape
Structural integrity	Intact, healthy	Sufficiently restored	Decayed, insufficiently restored
Line of incisal edges	Following lower lip		Irregular

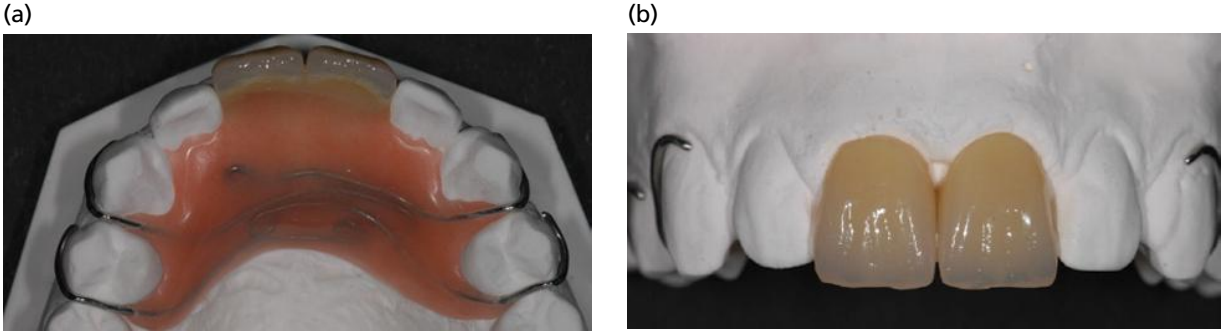


Fig. 54-5 (a) Occlusal view of a removable partial acrylic denture on the cast with wires retained to teeth 14, 13, 23, and 24. (b) Buccal view of a removable partial acrylic denture replacing missing teeth 11 and 21.

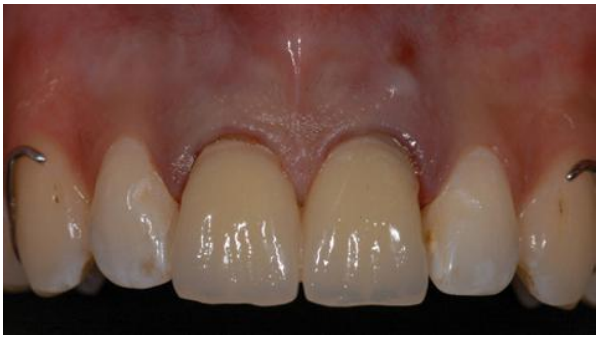


Fig. 54-6 Clinical view of a removable partial acrylic denture replacing extracted teeth 11 and 21, immediately after tooth extraction.

extending into the extraction sockets to partially preserve the pre-extraction soft tissue morphology (Fig. 54-6). These removable partial acrylic dentures are not particularly comfortable because they have a certain resilience and cover part of the palate. There are alternatives to these tissue-borne provisional restorations. An Essix provisional (Fig. 54-7) may be used as a removable prosthesis in these cases, as well as in cases of limited interocclusal space or deep anterior overbite (Moskowitz *et al*. 1997; Santosa 2007). This prosthesis is made from acrylic teeth bonded to a clear vacuform material on a cast of the diagnostic wax up. The prosthesis provides protection to the underlying soft tissue and implant during the healing phase. Limitations of this provisional restoration include its inability to mold the surrounding soft tissue, and lack of patient compliance can cause rapid occlusal wear

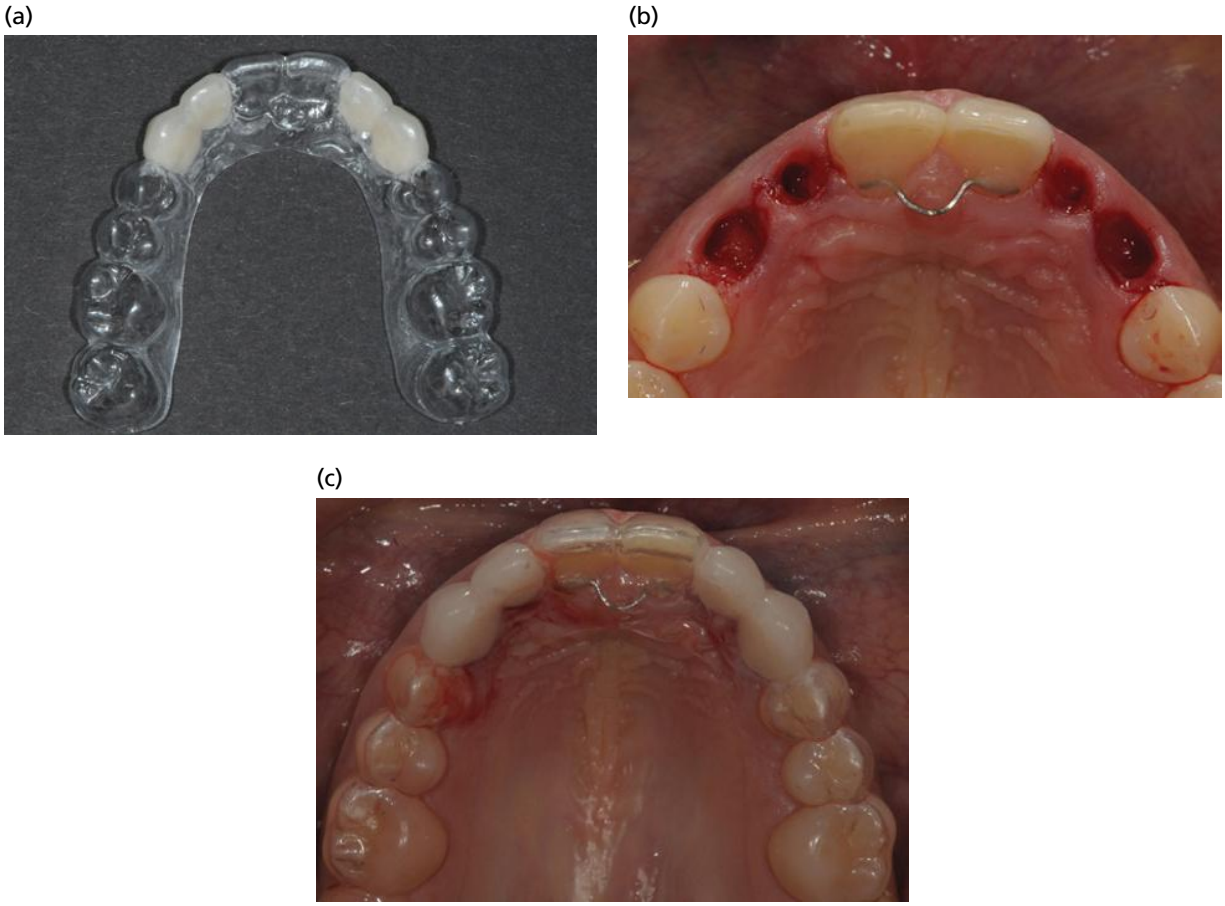


Fig. 54-7 (a) Occlusal view of an Essix provisional made from acrylic teeth bonded to a clear vacuform material. (b) Clinical occlusal view immediately after tooth extraction of the remaining deciduous teeth and before inserting the provisional restoration. (c) Clinical occlusal view of an Essix provisional after teeth extractions in the upper jaw.

from the vacuform material (Santosa 2007). However, some patients may not like wearing, or are unable to tolerate, a removable provisional prosthesis; thus, fixed provisional prosthesis are sometimes necessary.

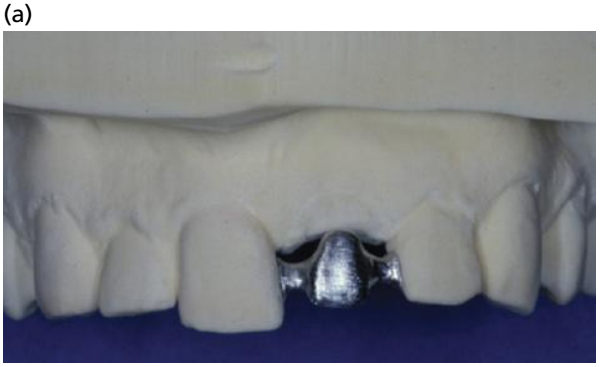
Fixed tooth-supported provisional restorations in the anterior region are mainly resin-bonded pontics or bridges. The pontic can be an acrylic or porcelain tooth, or a decoronated extracted tooth. The resin-bonded acrylic tooth may be reinforced with composite resin and/or fiberglass. These types of provisional restorations are much more comfortable from a functional and phonetic view, and are more esthetic. However, their removal and rebonding after the surgical intervention requires more time and work from the dentist.

If a provisional restoration is needed for a longer time and more stability is required, a resin-bonded, cast metal framework prosthesis such as a Maryland Bridge is indicated (Fig. 54-8a, b). These are cemented to the neighboring teeth by means of acid etching (Fig. 54-8c) and the use of composites (Fig. 54-8d, e). They can be detached by removing the composite within the palatal perforations and using forceps interdentally and a hammer (Fig. 54-8f). This type of fixed provisional restorations also allows more than one missing tooth to be replaced (Fig. 54-8g). However, the relatively high laboratory costs of these resin-bonded, cast metal framework prostheses have to be taken into consideration.

Phase 2: From implant placement to abutment connection

During the period from implant placement to abutment connection, the same provisional restoration options are available as after tooth extraction. However, after implant placement, especially with the use of guided bone replacement (GBR) techniques, a significant swelling of the tissues must be anticipated. Soft tissue-borne prostheses used during this healing period may cause uncontrolled soft tissue pressure, defined as "transmucosal loading", leading to implant exposure, marginal bone loss, and/or failed integration (Cho *et al*. 2007; Santosa 2007). In order to avoid too much contact with the healing soft tissue, the provisional dentures need to be adjusted to give a distance of approximately 2–3 mm to the tissue after surgical interventions. In this context, Essix provisionals have advantages because they are vertically stabilized through the neighboring teeth and, therefore, cause less pressure on the tissue in cases of swelling.

(a)



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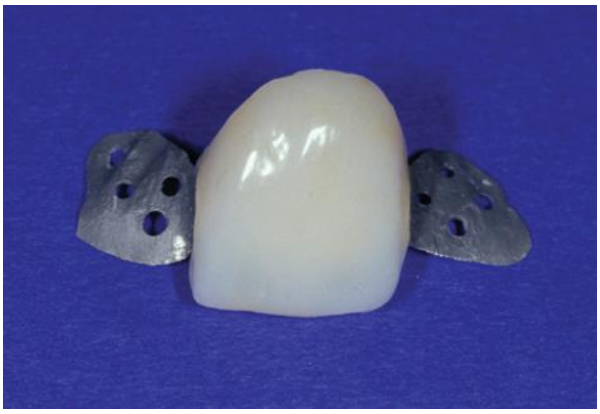

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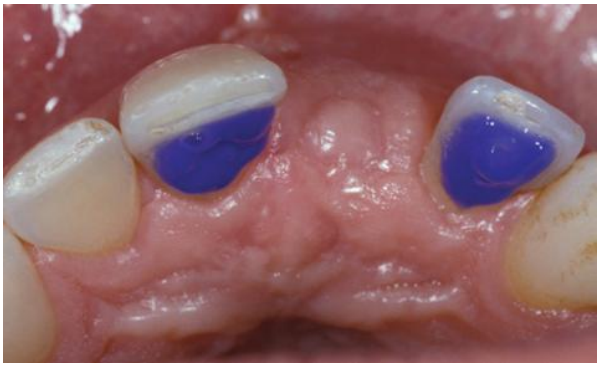

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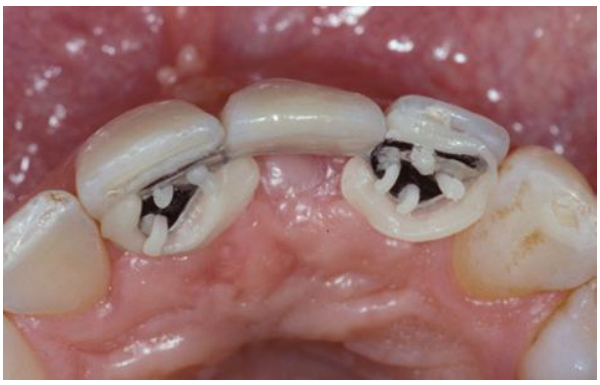

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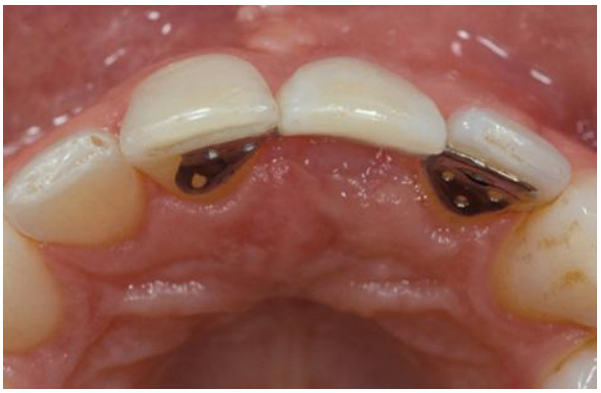

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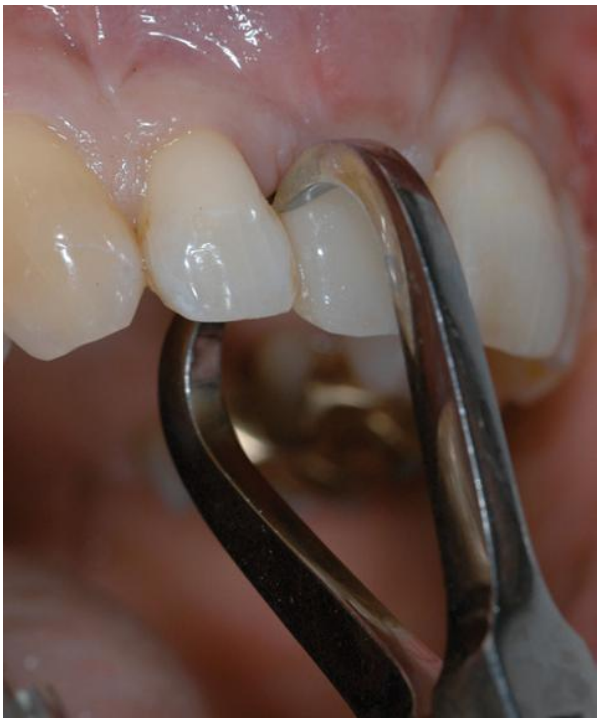

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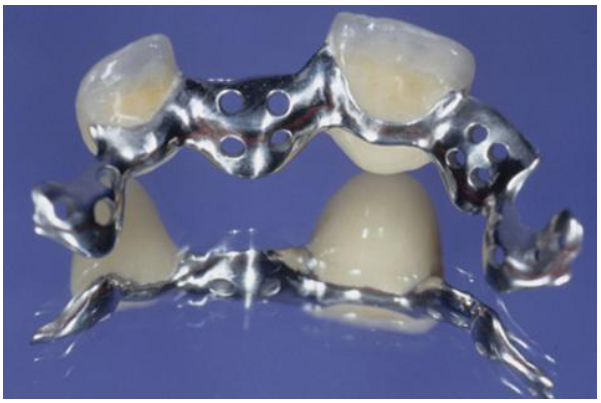


Fig. 54-8 (a) Metal framework before veneering with resin material on a master cast. (b) Cast metal framework Maryland Bridge prosthesis before cementing. (c) Acid etching of both neighboring teeth with 10% phosphoric acid. (d) Placing of the provisional adhesive bridge with filling composite before removing the excess material. (e) Provisional adhesive bridge replacing missing tooth 21 after cementing. (f) Removing the provisional adhesive bridge using forceps interdentally and a hammer. (g) Provisional adhesive bridge replacing missing teeth 12 and 21.

Phase 3: From abutment connection to final crown/bridge placement

According to the preoperative risk assessment, it has to be decided whether an implant will heal best with a submucosal or transmucosal approach. In highly demanding cases with a high lip line, thin biotype and tissue deficiency, a submucosal approach is generally chosen in order to create soft tissue extra volume. In less demanding cases with thick biotypes, sufficient tissue, and possible soft tissue excess, a transmucosal approach with healing abutments or provisional reconstructions can be selected. Hence, the preoperative risk assessment and the intraoperative information (i.e. primary implant stability, bone defects, soft tissue quantity and quality) will determine the timing of the treatment sequences. In cases with lower risks and sufficient tissue, a more straightforward approach without abutment connection can be chosen (Fig. 54-9a). In contrast, higher risk cases demand another treatment sequence with a more complex approach, including abutment connections with or without soft tissue management (Fig. 54-9b). In both situations, a healing abutment is in place at this stage of the treatment and the clinician has to decide whether or not to use an implant-retained provisional reconstruction. In a clinical comparative study of 63 single-tooth implants in the anterior region in 55 patients, the test group received a provisional implant crown and the control group received a healing abutment (Jemt 1999). The results after 2 years revealed that the papilla volume and the marginal bone loss were not significantly different between the treatment groups. However, the results indicated that the use of provisional crowns restored soft tissue contour faster than healing abutments alone (Jemt 1999). Hence, implant-retained provisional reconstructions are mainly beneficial during the diagnostic phase and can be used to evaluate esthetics, phonetics, and function. Furthermore, they can serve as a communication tool between clinicians, laboratory technicians, and patients.

One of the most important functions of an implant-retained provisional restoration is to develop the desired soft tissue emergence profile. Dental implants differ from teeth in size and shape at the crestal bone and mucosa levels. After removal of healing caps, the geometry of the tissue profile is circular and does not match the corresponding one around teeth (Fig. 54-10). The tissue profile created by the emergence profile and form of the teeth has a more triangular shape, especially for incisors. Therefore, the peri-implant soft tissue profile has to be converted into a tissue profile that is in harmony with the neighboring dentition (Wittneben *et al*. 2013). This transition can either be performed through individualized healing abutments or implant-retained provisional restorations. These implant-retained provisional restorations can either be fabricated in an ideal contour (Fig. 54-11a) or with a reduced emergence profile (Fig. 54-11b). For the provisional with an ideal profile, the clinician works in a subtractive way by selectively reducing the diameter before inserting the provisional restoration. In contrast, for the provisional with a reduced

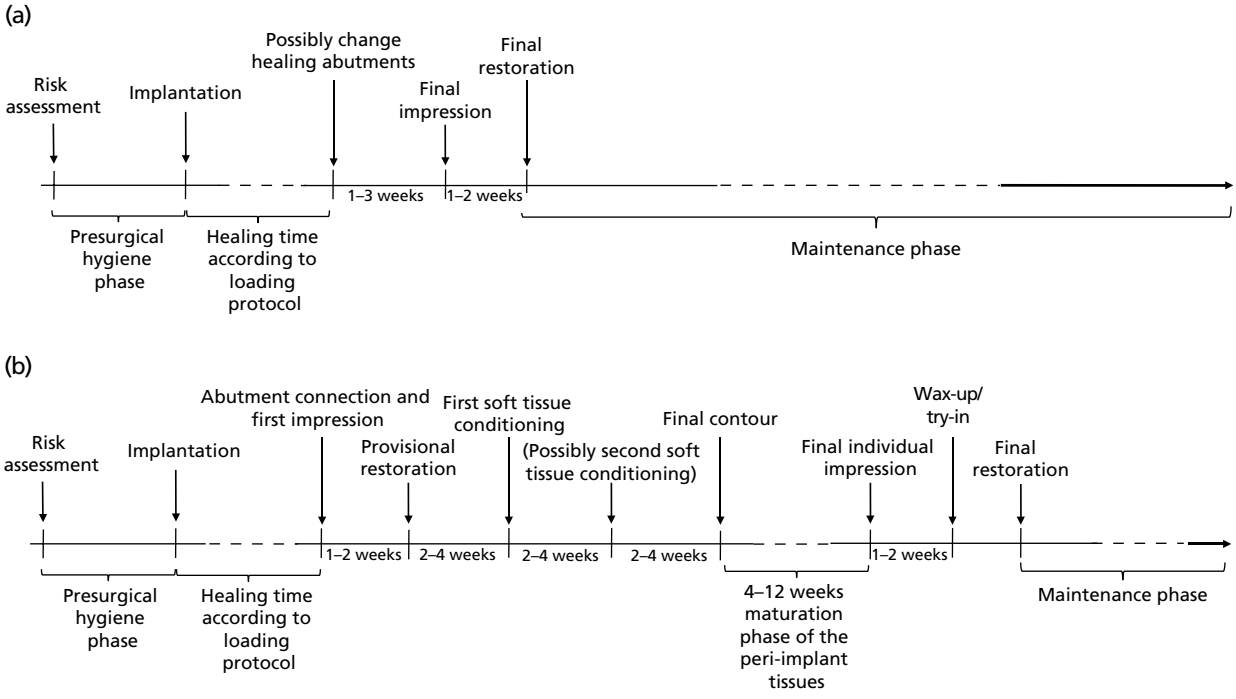


Fig. 54-9 (a) Timeline for a straightforward case without abutment connection and provisional implant-retained restorations. (b) Timeline for an advanced/complex case with abutment connection and provisional implant-retained restorations in order to condition the soft tissues.

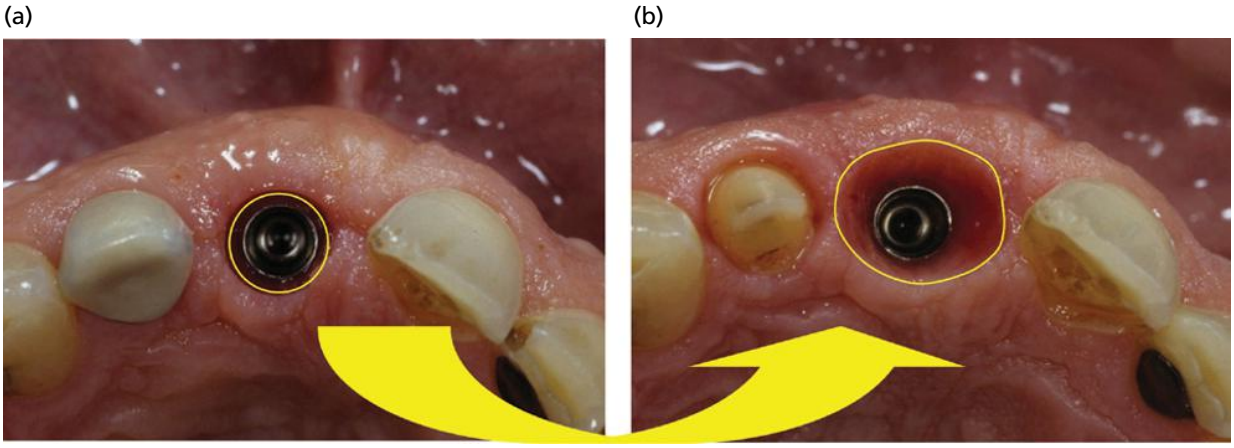


Fig. 54-10 (a) Transition of a circular soft tissue profile immediately after removing the healing abutment and (b) 8 weeks later after soft tissue conditioning with a screw-retained provisional implant restoration.

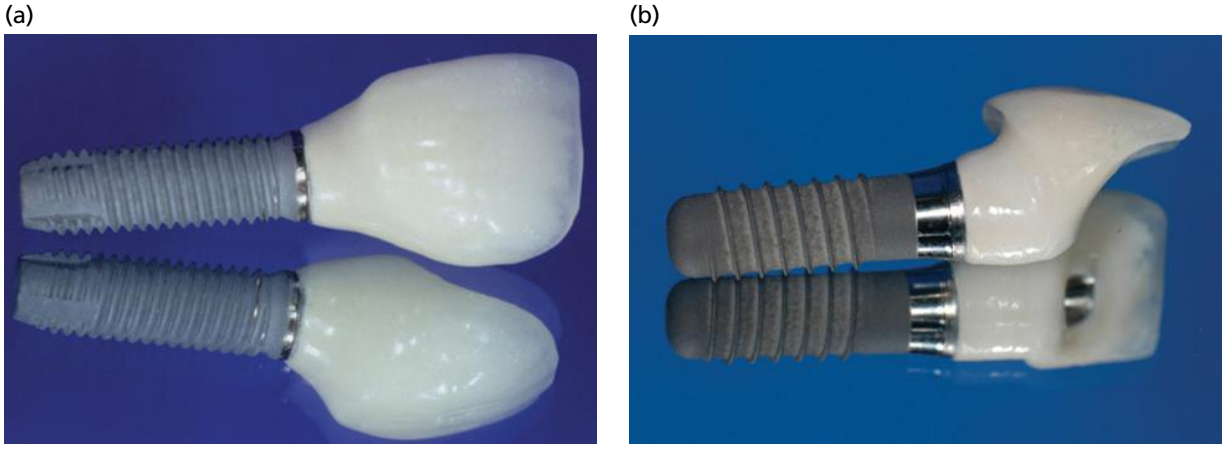


Fig. 54-11 (a) Provisional screw-retained reconstruction with an ideal emergence profile which needs to be individually reduced before insertion. (b) Provisional screw-retained reconstruction with a reduced emergence profile which needs to be individually adjusted by adding resin material before insertion.

emergence profile, the clinician works in an additive way by selectively adding resin material before inserting the provisional.

Provisional restorations can either be cemented or screw-retained. The decision to cement or screw-retain a provisional or final implant restoration depends on the clinical situations (i.e. angulations of the implant and implant position) and the clinician's preference regarding method of fixation. For proper soft tissue conditioning, a screw-retained provisional is preferred as it can be easily removed to allow volume to be added or removed for guiding the soft tissue in the desired direction.

Fixed implant-supported provisionals can be fabricated either in the laboratory or chair-side. In order to improve the soft tissue contour, the provisional reconstruction is inserted in order to apply slight pressure to form the mucosa. The pressure applied to the mucosa at insertion causes an ischemic reaction, a so-called "blanching" of the peri-implant soft tissue (Fig. 54-12), which should only be moderate and disappear within

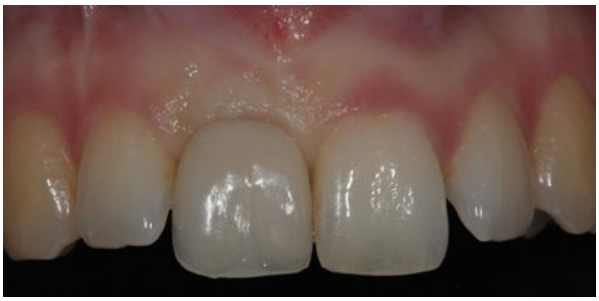


Fig. 54-12 Screw-retained provisional reconstruction immediately after adjusting the emergence profile which causes an ischemic reaction in the surrounding tissue.

15 minutes (Cooper 2008). By customizing the shape and the contour of the provisional restoration, the peri-implant contour is improved and the emergence profile formed. This soft tissue conditioning process is performed over a period of 8–12 weeks by selectively adding flowable composite material or light-cured acrylic resin to the provisional reconstruction

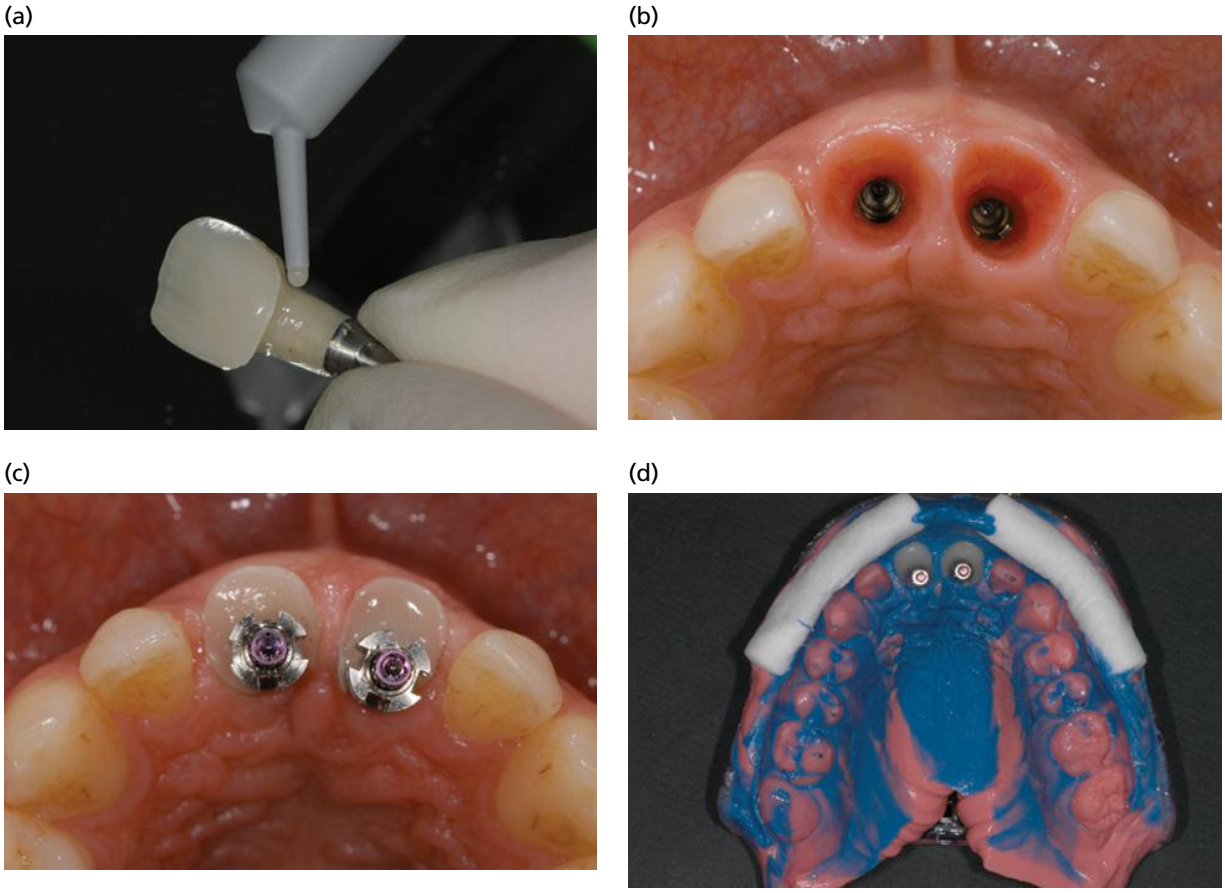


Fig. 54-13 (a) Applying flowable light-curing composite material to the provisional reconstruction after activating the surface. (b) Occlusal view after reaching the final emergence profile of the missing central incisors 11 and 2. (c) Individualized impression copings in place before impression taking. (d) Final impression capturing the information of the emergence profile created by the provisional restorations.

(Fig. 54-13a). After achieving the final emergence profile, it is important to transfer the created soft tissue profile to the final master cast (Fig. 54-13b). This can be achieved with an individualized impression coping that has the same tissue profile as the clinically approved provisional restoration (Fig. 54-13c, d). As the majority of soft tissue recession takes place within the first 3–6 months (Grunder 2000; Oates *et al*. 2002), it can be assumed that the soft tissue margin after the conditioning process will be stable and the final reconstruction can be fabricated.

Surgical considerations when dealing with implants in the zone of esthetic priority

Surgical aspects for an undisturbed wound healing

In general, denuded bone and exposed root surfaces as a result of the surgical intervention must be covered by the soft tissue flap if optimal outcomes are to be achieved. However, in implant surgery, inherent challenges may complicate the procedures. When dealing with implants in the zone of esthetic priority, clinicians are confronted with a variety of anatomic structures, such as hard and soft tissues adjacent to each other, resulting in wounds which are constituted of several interfaces of tissues that fundamentally differ in composition. Furthermore, flap stability and healing outcomes may be hampered during the postoperative phase as the oral cavity is an aqueous environment in which biofilm forms on non-shedding surfaces like teeth and implants and their prosthetic components. Consequently, bacterial colonization may jeopardize uneventful healing (Bartold *et al.* 1992). Also, the negative effect on wound stability and healing outcomes of the mechanical influences of continuous masticatory and other functions of the dentition should not be underestimated (Moore & Hill 1996).

Wound healing primarily depends on early formation and organization of the blood clot and the establishment of an attachment of the clot that is resistant to mechanical forces acting on the flap and opposing surfaces participating in the wound closure (Wikesjö *et al.* 1991b). Impaired clot adhesion may weaken the tensile strength of the wound during early healing events and leave the implant–mucosal flap interface susceptible to tearing, compared to physiologic tensile forces on wound margins (Wikesjö & Nilvéus 1990). Tensile forces vary depending on the stability of the blood clot and subsequently on the biochemical and mechanical properties of the wound bed

(Werfully *et al.* 2002). Hence, healing of peri-implant defects following flap surgery involves conceptually more complex processes than wound healing in most other sites of the body.

Most models investigating the tensile forces on wound margins have considered the interfaces in recession coverings (Wikesjö *et al.* 1991a; Pini-Prato *et al.* 2000). In only one study has the role of flap tension in primary wound closure been investigated in humans (Burkhardt & Lang 2010). In that study, 60 patients scheduled for single implant installation were recruited. Before suturing, the tensile forces on the flaps were recorded with an electronic device. After 1 week the wounds were inspected with regards to complete closure. While flaps under minimal tension of 0.01–0.1 N resulted in only a few (10%) wound dehiscences, flaps with higher closing forces (>0.1 N) yielded significantly increased percentages of wound dehiscences (>40%). This study also revealed that flaps with a thickness of >1 mm demonstrated significantly lower proportions of flap dehiscences at higher closing forces (>15 g) than thinner flaps (≤1 mm). The results of this study indicated a need to control the closing forces at the wound margins. In order to minimize tissue trauma, finer suture diameters may be helpful owing to the fact that thinner sutures (6-0, 7-0) lead to thread breakage rather than tissue tear and breakage (Burkhardt *et al.* 2008b).

It is evident that flap design, flap advancement, and suturing should receive greater attention in situations where mucoperiosteal and/or mucosal flaps are positioned to cover large peri-implant defects. Owing to the fact that the peri-implant wound is constituted of the connective tissue surface of the flap and an avascular surface such as titanium, ceramic or another alloplastic material, peri-implant defects require careful tissue management and stable flap adaptation, especially in the anterior zone of the upper jaw where the mucosal morphology and topography play an important role for the esthetic result.

Incisions and flap designs

Flaps can be classified according to their form (e.g. semilunar, triangular), the direction of the intraoperative advancement (e.g. rotating, apically or coronally advanced) or the composition of the contributing tissues (e.g. full thickness, split thickness). In contrast to connective tissue grafts, which receive their early nutrition by plasmatic diffusion, flaps are characterized by a still functioning network of vessels which provide the injured tissues with blood. Thus, it is evident that when planning the flap outline, attention should focus on the importance of maintaining a good blood supply from vessels entering at the base of a pedicle. To assure a good blood supply, it was recommended that two aspects are noted before starting with the first incision: (1) a broad flap base which allows many nutrient vessels to enter the flap and (2) a flap length-to-width ratio that should not exceed 2:1. These principles seemed to make sense because increasing the flap's width at its base increases the blood supply and supports a greater flap length. However, with a deeper insight into the biologic contexts and processes (Kleinheinz *et al.* 2005), these recommendations now appear rather too simplistic and have been proven to be a fallacy (Milton 1970). It cannot be assumed that major vessels enter the base of mucosal flaps at regular intervals. Additionally, Jeffcoat *et al.* (1982) showed in an animal experiment that the mandibular vasculature is also characterized by arterial vessels traversing somewhat obliquely in a general posterior to anterior direction. Most conclusions from studies focusing on vascular impairment are based on histologic examination of specimens after vascular perfusion and suggest that blood vessels remain intact and patent following surgery. Alternative techniques like fluorescein angiography (Mörmann *et al.* 1975; Mörmann & Ciancio 1977) and laser-Doppler flowmetry (Patiño-Marín *et al.* 2005; Retzepi *et al.* 2007a, b) are more reliable in qualitatively and quantitatively evaluating the vascularity and blood supply of an injured mucosal area.

Following horizontal incisions along the mucogingival junction, the blood supply of the gingiva was displayed with a fluorescent dye (Mörmann & Ciancio 1977). One day after the injury, the gingiva coronal to the incision line showed a severe anemia, which was more pronounced in the interdental and papillary area than in the tooth prominences. The authors explained the differences as the result of the influence of the collateral vessels coming from the ligament and contributing to the marginal vascularity.

These results have been confirmed in another angiographic dog study (McLean *et al.* 1995) comparing two different suture techniques for closing a mucoperiosteal flap. After flap adaptation, primary wound closure was achieved by either horizontal mattress suturing or interrupted single suturing. The flaps reached from $_2P_2$ to $_1M_1$ and were divided into three interproximal and two mid-buccal sites for analysis of intercapillary and vascular diffusion extent. It was realized that the sole act of flap elevation initiated substantial and significant vascular trauma. Significant reduction in flap circulation in relation to the presurgical baseline lasted for at least 3 days in the mid-buccal sites, but persisted for 7 days at the interproximal sites, independent of the applied suture techniques. This is an important finding and might have an impact on the decision regarding the ideal flap outline when dealing with implant placements or retreatments in the upper anterior zone where there is no collateral vascularity from the periodontal ligament.

Another factor influencing the vascularity of a flap is its length, especially when the flap is replaced on an avascular surface like a root or the alloplastic material of an implant or its components. Several studies confirm a decrease of the flap vascularity with increasing flap length (Mörmann & Ciancio

1977; McLean *et al*. 1995). Interestingly, in studies of the early healing stages, significantly greater portions of the flaps took up fluorescence from extravascular diffusion compared to from intracapillary circulation. While it is certainly prudent to avoid long pedicle flaps in implant surgery, other flap properties like thickness and alternate vascular sources deserve recognition.

Based on reliable knowledge of the distribution pattern and architecture of the arterial vascular system of the human oral mucosa, recommendations for ideal flap preparation and releasing incisions can be given (Kleinheinz *et al*. 2005): (1) avoid releasing incisions in the zone of esthetic priority; (2) place mid-crestal incisions in edentulous areas; (3) incise in the sulcular area around teeth and avoid marginal and paramarginal incisions; (4) if a releasing incision is required, cut the flap as short as possible and carry it out at the anterior border of the incision line (Fig. 54-14). The releasing incisions should not be placed on the buccal root prominences as there the mucosa is thicker between two teeth (Müller *et al*. 2000). Incision lines in the concavity between two teeth facilitate a firm flap adaptation and provide a better vascular network within the pedicle flap.

Implant placement in the zone of esthetic priority is often combined with GBR procedures and soft tissue augmentations to compensate for the lost tissue volumes and to restore the morphology of the implant housing in all three dimensions. To achieve a healing on primary intention, the soft tissue flaps must be mobilized to completely cover the augmented sites. Such flap advancement is limited and also has some adverse effects. The common method of flap lengthening consists of a periosteal incision at the base of the buccal flap. This technique releases the flap tension as the connective tissues of the lining mucosa contain elastic fibers. After cutting the dense collagen fibers of the periosteum, lining mucosa can be stretched, whereas the masticatory mucosa is almost inelastic. The extent of flap lengthening depends on the outline of the flap and has been evaluated in a recent cohort study (Park *et al*. 2012). Simply by placing one vertical releasing incision and pulling with a tension of 5 g, the flap could be mobilized by 1.1 ± 0.6 mm, which corresponds to 113.4% of its original length. These values increased to 1.9 ± 1.0 mm (124.2%) when a second vertical incision was made at the opposite end of the horizontal incision and became statistically highly significant after combining the two vertical releasing incisions with a periosteal releasing incision, yielding a flap advancement of 5.5 ± 1.5 mm (171.3%).

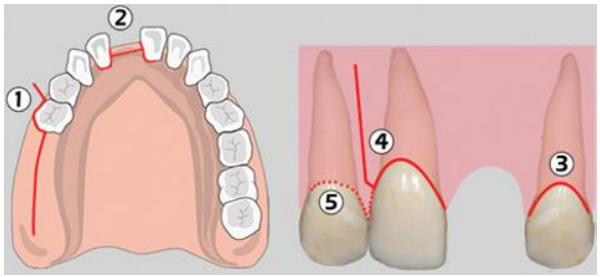


Fig. 54-14 Incision designs: 1, buccal releasing incisions just when needed, as long as necessary and as short as possible; 2, avoid releasing incisions in the zone of esthetic importance, open flap by crestal incisions; 3, incise sulcularly and precisely follow the soft tissue contour; 4, when using releasing incisions, place them besides the root prominences and start right-angled to the soft tissue margins (without coronal displacement); 5, for coronal advancements (dotted line), prepare a full papilla flap and not a papilla preservation flap.

The above-mentioned surgical technique facilitates primary wound closure but also has disadvantages. The masticatory mucosa will be coronally displaced to the crest and leave the buccal area of the implant covered by a zone of mobile, much thinner lining mucosa, which is more prone to soft tissue dehiscence formation (Bengazi *et al.* 1996). Additionally, the irregularity of the mucogingival junction can cause an esthetic problem in high lip line cases when a broad zone of soft tissues is displayed apical of the mucosal margin. In these cases, alternative surgical modalities have to be considered when flap advancement is required for primary wound closure.

As an optional surgical procedure, a free connective tissue graft may be placed on the crest at the reunion of the flap margins. If primary wound closure cannot be achieved, the graft will heal at secondary intention and protect the underlying bone or augmented area (Kan *et al.* 2009; Stimmelmayr *et al*. 2010), although there is only limited weak evidence in the literature that soft tissue grafts are effective in increasing mucosal thickness and improving the esthetic outcome (Esposito *et al*. 2012).

The soft tissue covering of the hard palate consists of masticatory mucosa which is rich in collagen fibers and, therefore, cannot be mobilized with just a U-shaped flap. More sophisticated flap designs are required, such as laterally positioned flaps (Nemcovsky *et al*. 1999; Peñarrocha *et al*. 2005) that are prepared in vertical layers such that the deeper portion, pedicled at the base, can be rotated to cover the denuded area. Similar plastic surgical procedures, based on horizontal flap advancement, are likewise appropriate for primary soft tissue closure in the esthetic zone without displacement of the mucogingival junction (Tinti & Parma-Benfenati 1995; Triaca *et al*. 2001).

Dealing with implants in the esthetic zone is considered to be an advanced or even complex procedure in dentistry and there are many different aspects to the pretreatment planning phase as well as the surgical and prosthetic execution (Devigus 2006). One often neglected aspect is scar formation. Compared to the healing of skin wounds, the oral mucosa is less prone to scar formation due to its different inflammatory cell infiltrate with lower levels of macrophages, neutrophils, T-cell infiltration, and the profibrotic cytokine transforming growth factor-beta 1 (TGF-β1) (Coleman *et al*. 1998; Szpaderska *et al*.

2003). Nevertheless, other factors such as flap tension and the precision of flap margin adaptation influence the extent of scar formation (Burgess *et al*. 1990; Nedelec *et al*. 2000) and each incision in the buccal mucosa of the anterior area of the upper jaw will increase the risk for an adverse esthetic outcome. The importance of masticatory mucosa around implants has raised controversy in the literature and there is only a low level of evidence that a lack of masticatory mucosa has a negative effect on the success rates and esthetic results of implant restorations (Cairo *et al*. 2008; Wennström & Derks 2012). Subjective observations by the authors and feedback from treated patients have suggested that it is beneficial to have a sufficient zone of masticatory mucosa around the implants to sculpt and form a scalloped marginal contour of the soft tissues, with a natural appearing surface texture and morphology, which also influence patient perception (Chang *et al.* 1999b). In a recent systematic review searching for evidence for the best surgical techniques to augment the masticatory mucosa around implants, the vestibuloplasty and apically repositioned flap ranked highest (Thoma *et al*. 2009). However, caution needs to be exercised in adopting this approach because an increase of the width of the masticatory mucosa does not guarantee an improvement of the esthetic result, and as an apically positioned flap always requires releasing incisions, scar formation and unfavorable mucosal textures may hamper the esthetic appearance. Therefore, from the start of implant treatment, the aim should be preservation of the masticatory mucosa and careful evaluation of all the surgical options based on the relevant factors which influence the biologic, functional, and esthetic outcome.

Clinical concepts for a single missing tooth

Before each implant placement in the anterior area of the upper jaw, a comprehensive presurgical risk analysis of a given maxillary anterior single-tooth gap has to be carried out. An increasing body of evidence indicates that the best parameter for achieving an esthetic single-tooth restoration is the interproximal bone height at the level of the teeth confining the edentulous gap (Tarnow *et al*. 1992; Choquet *et al*. 2001). The related bone should be within a physiologic distance (i.e. approximately 2 mm) of the CEJ and thus provide the essential support for the overlying soft tissue compartments. Consequently, preoperative diagnosis will include interproximal radiographic bone height assessment and periodontal probing of the soft tissue attachment level. If a case presents missing interproximal bone (Fig. 54-15a, b), alternative conventional prosthetic solutions need to be taken into consideration. In this particular case of a 38-year-old woman, a zirconia adhesive bridge was inserted after alveolar ridge augmentation procedures (Fig. 54-15c, d).

Sites with no or minor tissue deficiencies

If the risk analysis confirms a favorable vertical level of both soft tissue and underlying alveolar bone at the interproximal aspect of the two adjacent teeth on the one hand, and no major vestibular bone deficiencies on the other hand, the site can be considered appropriate for a straightforward implant surgical protocol. In order to ensure the best chance of a successful and long-lasting esthetic treatment outcome, the implant placement has to be carried out meticulously with attention to the key parameters such as low-trauma surgical principles in general and precise three-dimensional ("restoration-driven") implant positioning in particular (Fig. 54-16).

Sites with extended or severe tissue deficiencies

The risk analysis of a 23-year-old woman revealed a demanding clinical situation with missing buccal bone and a buccal probing pocket depth of 11 mm at the left central incisor (Fig. 54-17a, b). The radiographic analysis demonstrated intact mesial and distal crestal bone levels (Fig. 54-17c). This is an important prerequisite to maintaining the interdental soft tissue level. Based on the clinical and radiographic findings, the diagnosis was a vertical root fracture of tooth 21. After the patient had been informed of the diagnosis and the therapeutic options discussed, it was decided to extract the tooth and to replace it with an implant-supported single crown.

Due to the extended buccal bone defect, it was decided to perform a socket preservation technique to improve the soft tissue quality and quantity before implant placement and bone augmentation procedure (Fig. 54-18).

In this case of extended horizontal alveolar bone crest deficiencies, a simultaneous implant placement and lateral bone augmentation procedure is technically more difficult and less predictable, as the ultimate goal remains optimal "restoration-driven" implant positioning. Therefore, the feasibility of combining implant placement with a simultaneous bone regeneration procedure was evaluated by performing preoperative diagnostics and a CBCT scan. The CBCT revealed an extended buccal bone defect with a minimal amount of apical bone to stabilize the implant (Fig. 54-19).

After three-dimensional computer-assisted implant planning, a computer-guided template was fabricated within the dental laboratory. After a healing period of 6 weeks following tooth extraction, a mucoperiostal flap was elevated. This was achieved with a palatal crestal incision followed by sulcular incisions and a vertical releasing incision distal 22 (Fig. 54-20a). With the help of the computer-guided stent, it was possible to place the implant in the proper prosthetic position (Fig. 54-20b–f). Due to the complete loss of the buccal bone, a volume of stable

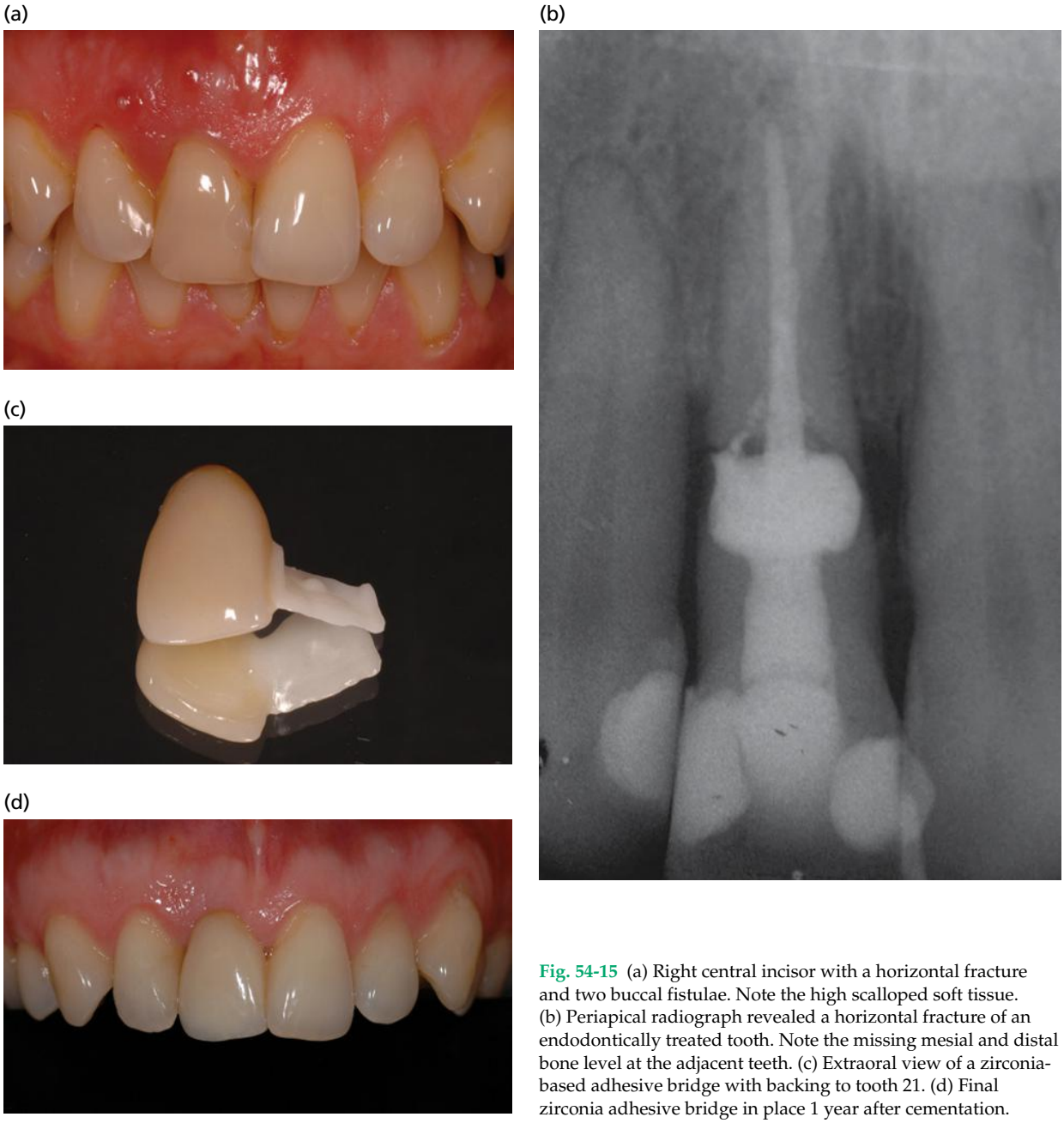


Fig. 54-15 (a) Right central incisor with a horizontal fracture and two buccal fistulae. Note the high scalloped soft tissue. (b) Periapical radiograph revealed a horizontal fracture of an endodontically treated tooth. Note the missing mesial and distal bone level at the adjacent teeth. (c) Extraoral view of a zirconia-based adhesive bridge with backing to tooth 21. (d) Final zirconia adhesive bridge in place 1 year after cementation.

non-bioresorbable membrane was chosen. After grafting the site with autogenous bone particles and demineralized bovine bone mineral (DBBM), a titanium-reinforced expanded polytetrafluoroethylene (ePTFE) membrane was applied to the defect morphology and adapted with titanium pins (Fig. 54-20g–i). Subsequently, the periosteum was released to achieve a completely passive soft tissue closure (Fig. 54-20j). After a healing period of 6 months, a full-thickness flap was elevated again in order to remove the non-bioresorbable membrane and the titanium pins (Fig. 54-20k–m). In addition, a connective tissue graft harvested from the palate was placed underneath the flap in order to increase the soft tissue volume (Fig. 54-20n). Six weeks later, a minimally invasive abutment connection was performed using a U-form incision and rotation of this flap to the buccal site (Fig. 54-20o–r). At the same time as the abutment connection, an impression was taken on the level of the implant shoulder (Fig. 54-20s). The screw-retained implant-borne provisional crown was used for diagnostic purposes and to form the emergence profile. After reaching the final soft tissue contour, a definitive individual impression was taken in order to capture the information from the temporary restoration (Fig. 54-21t, u). In this way, the clinical situation was transferred to the master cast, which contains a replica (analog) of the implant. This master cast was subsequently scanned in order to produce an individual zirconia abutment by means of a CAD/CAM procedure (Fig. 54-20v). By directly veneering this zirconia abutment, it was possible to provide the patient with a natural looking screw-retained all-ceramic crown (Fig. 54-20w, x).

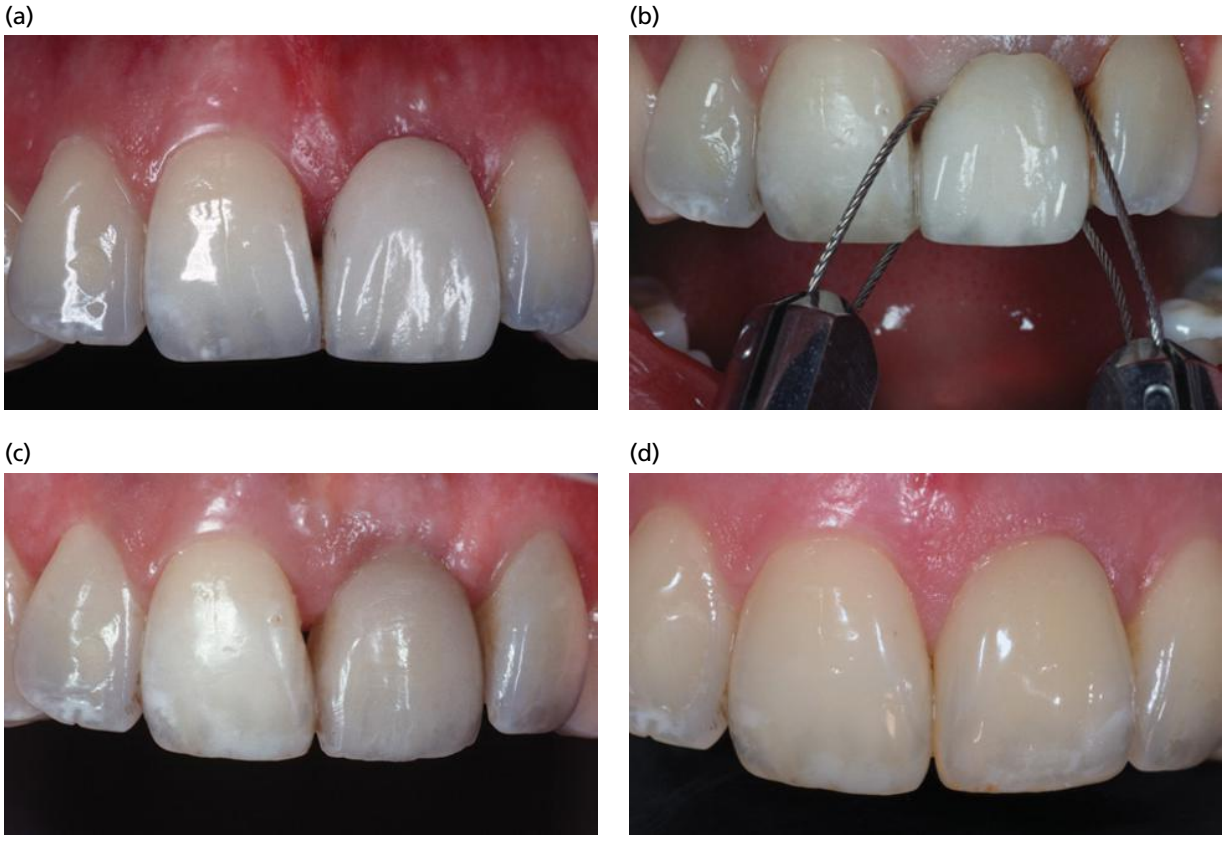


Fig. 54-16 (a) Adhesive bridge, fixed on both neighboring teeth, repeatedly lost its retention on tooth 22 after 7 years of loading. (b) Removal of the bridge after grinding the palatal attachment on tooth 11. (c) Intact, healed ridge without volume deficiencies allowed implant placement in a prosthetically correct position. Situation after provisionalization. (d) Final full-ceramic crown on a zirconia abutment and composite adjustments on a contralateral central incisor.

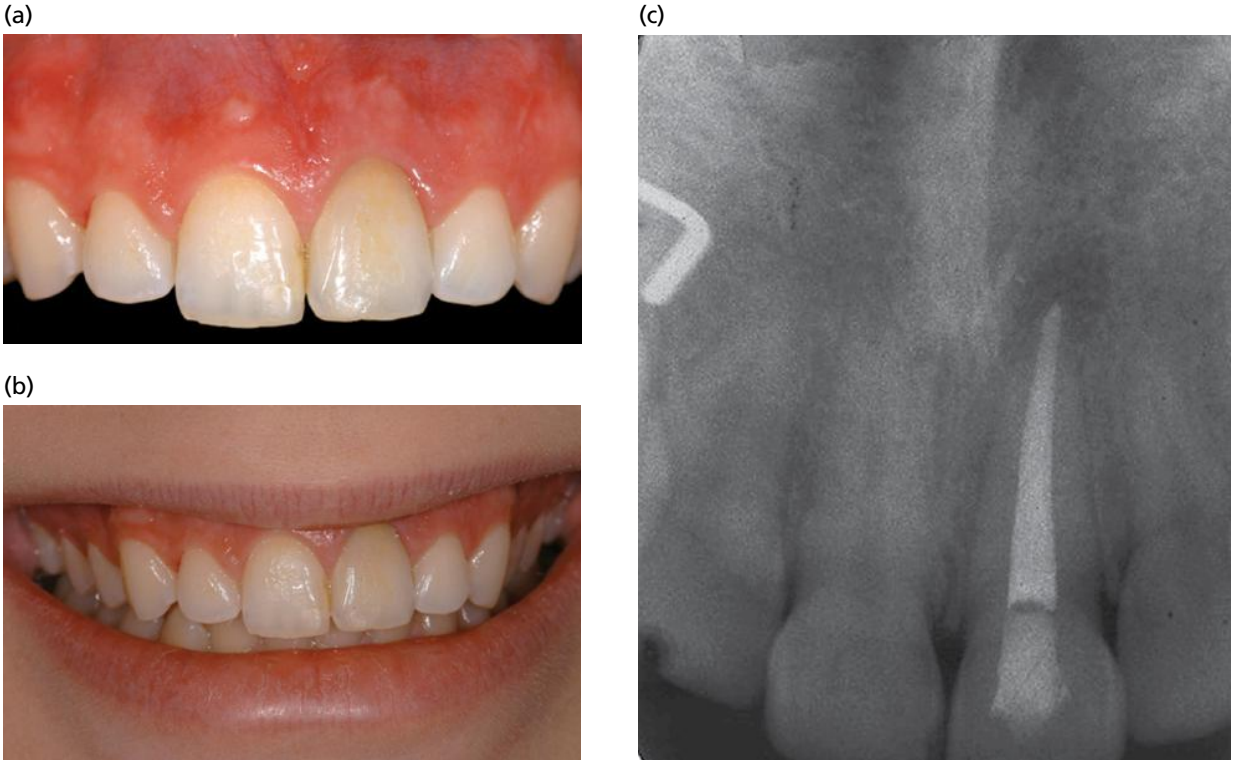


Fig. 54-17 (a) Preoperative view of a 23-year-old woman. Left central incisor shows slight discoloration and apical migration of the gingival margin. (b) Smile line was considered to be high and also the patient had high esthetic expectations. (c) Radiographic analysis revealed an endodontically treated incisor and an apical radiolucency. Mesial and distal bone levels were intact.

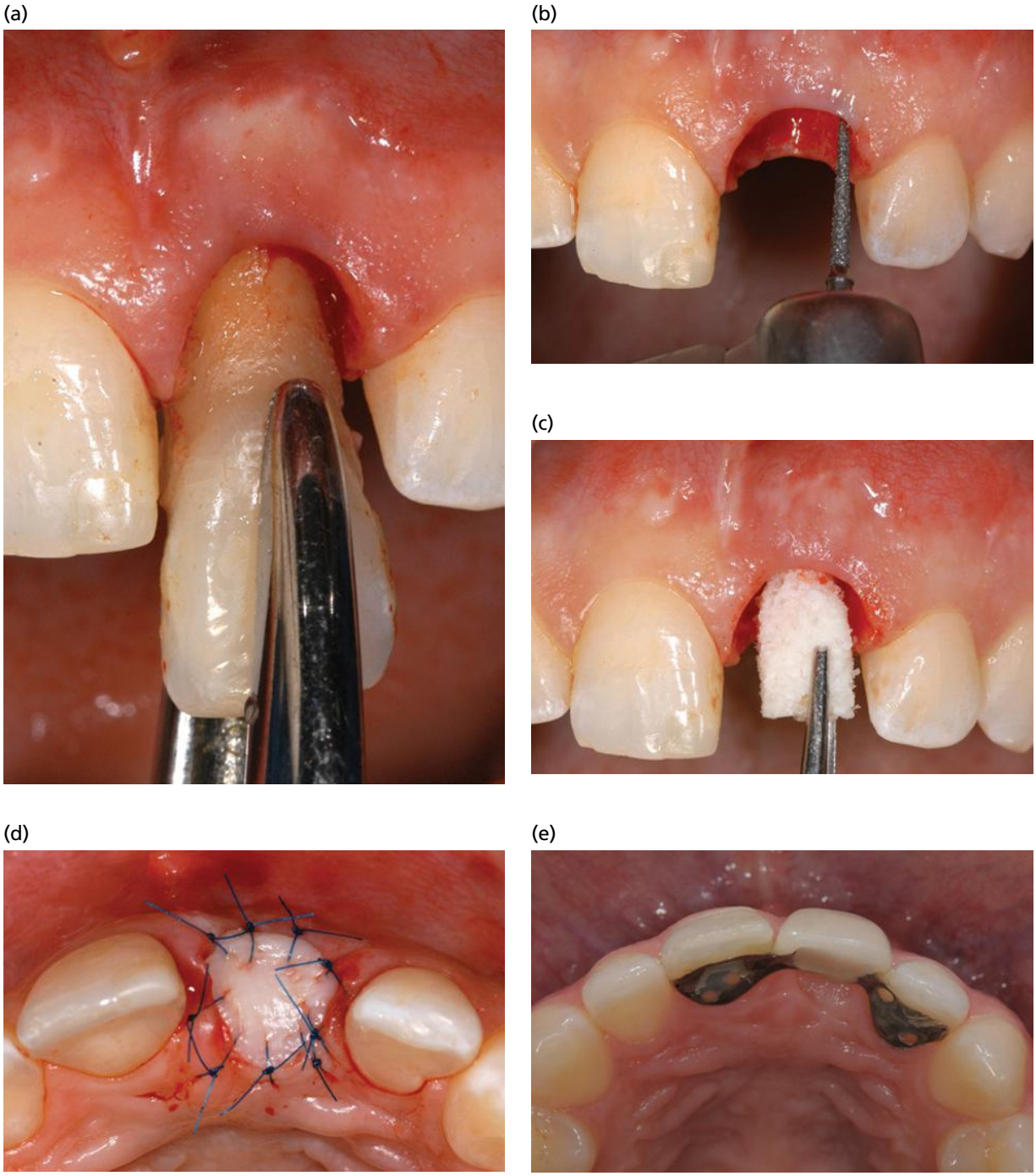


Fig. 54-18 Same patient as in Fig. 54-17. (a) Flapless and minimally-traumatic extraction was performed and followed by a socket preservation technique using deproteinized bovine bone mineral with 10% of collagen (DBBM-Coll) and a free mucosal graft. The main objective of this technique was to maintain soft tissue contour. (b) Internal epithelium of the socket was carefully removed using a diamond bur to promote bleeding and improve graft healing. (c) DBBM-Coll was shaped according to the root anatomy and placed into the socket. (d) After harvesting a free mucosal graft from the palate using a biopsy punch, the graft was carefully sutured and stabilized with 7/0 monofilament sutures. (e) Provisionalization with a temporary adhesive bridge (Maryland type).

Clinical concepts for multiple missing teeth

The normal consequence following the loss of two or more adjacent upper anterior teeth is a flattening of the edentulous segment. In particular, the disappearance, in an apical direction, of the crestal bone originally located between the incisor teeth can be observed. This phenomenon is not, or only minimally, present at the interproximal aspect of the remaining anterior teeth and thus explains the fundamental difference between a maxillary anterior single-tooth gap and a multiunit edentulous segment.

If two standard screw-type titanium implants are inserted to replace two missing maxillary central incisors (Fig. 54-21), an additional peri-implant bone remodeling process will take place. In the frontal plane, two different characteristic processes, one between the tooth and implant and the other between the two implants, can be distinguished. At the site

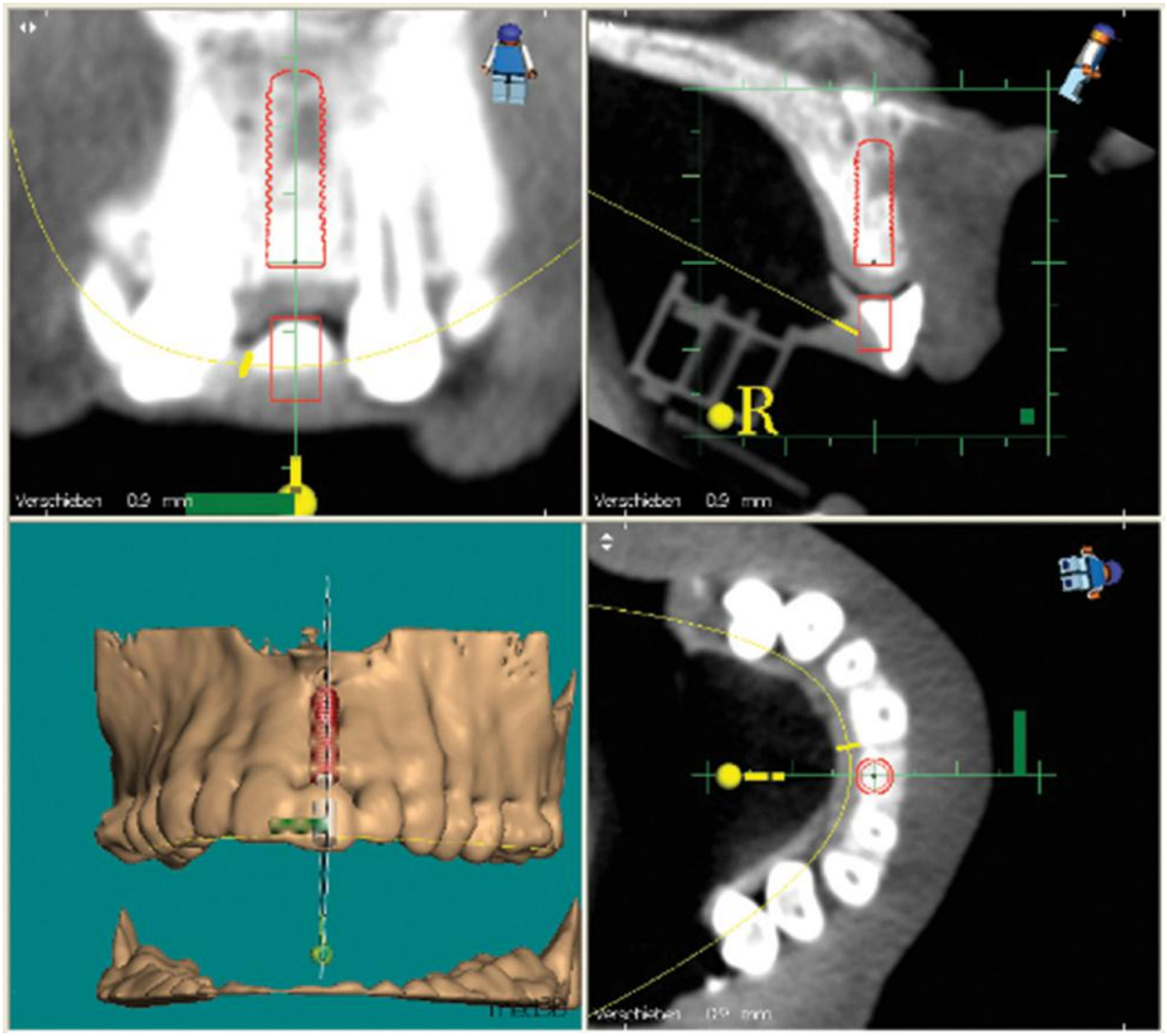


Fig. 54-19 Same patient as in Figs. 54-17 and 54-18. CBCT was obtained using a scanning template with barium sulfate ($BaSO_4$) teeth according to the previously performed wax-up. The ideal implant position was established using a 3D planning software and a surgical guide was fabricated.

between the tooth and implant, the tooth-sided interproximal bone height should theoretically remain at its original location, that is within 2 mm of the CEJ, from where the implant-sided interproximal bone height drops in an oblique manner towards the first implant-to-bone contact, normally located approximately 2 mm apical of the junction ("microgap") between the implant shoulder and the abutment or suprastructure. This phenomenon has been referred to in the literature as the establishment of a "biologic width" (Hermann *et al*. 1997, 2000, 2001a, 2001b). In contrast, the interimplant bone height normally decreases further in an apical direction, once the respective abutments or suprastructures are connected to the implant shoulder. This process is mostly accompanied by a loss of interimplant soft tissue height and hence may lead to unsightly, so-called "black interdental triangles". The schematic close-up views comparing the original dentate situation with the status after integration of two adjacent implant restorations, clearly demonstrate the negative consequences on the course of the marginal soft tissue line in a case of multiple adjacent maxillary anterior implants (Fig. 54-22).

For all of the above-mentioned reasons, the implant position and distribution in cases with multiple missing teeth in the area of esthetic priority are of great importance. With two missing central incisors, two implants will need to be placed with sufficient space between them. In cases of a missing central and a missing lateral incisor, it is preferable that only one implant at the position of the central incisor is placed, with a cantilever replacing the lateral incisor. Due to the small diameter of a lateral incisor, the mesiodistal dimension often does not allow two implants to be placed with sufficient interimplant distances. In the clinical situation of three missing incisors, including teeth 11, 21, and 22, it is recommended to place two implants. One option is to place two implants at positions 11 and 22 in order to have sufficient space

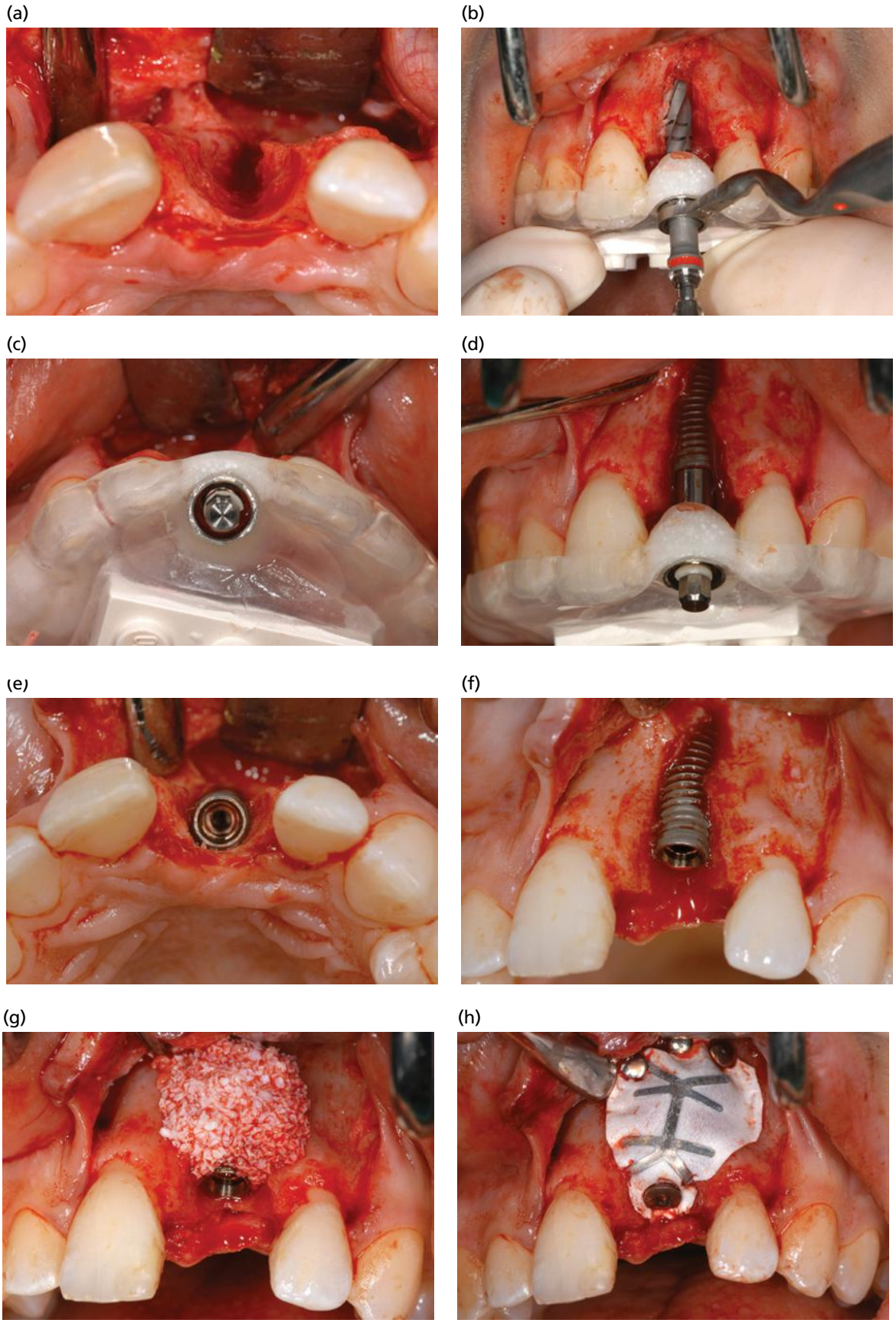


Fig. 54-20 Same patient as in Figs. 54-17, 54-18, and 54-19. (a) Six weeks after tooth extraction, a mucoperiosteal flap was elevated with distal vertical releasing incisions. The graft material that had been used to stabilize the soft tissue contour was removed before implant placement and further guided bone regeneration (GBR) procedures. Note the horizontal defect with a complete loss of the buccal wall. (b) Guided implant drilling was performed based on the CBCT and implant planning software helped to stabilize the drills during the preparation process. (c) Guided implant placement led to an ideal prosthetic implant position. (d) Ideal vertical position was achieved by placing the implant shoulder of a bone level type of implant approximately 3 mm below the mucosal margin of the prospective restoration. Note the expected dehiscence defect along the buccal wall. (e) Occlusal view of the implant in place. Note the non–self-containing buccal osseous defect, which limits the GBR options. (f) Buccal view of the bone level implant in place. Note the expected buccal dehiscence affecting almost the entire length of the implant. Primary stability was achieved thanks to the apical and palatal anchorage. (g) After placement of autogenous bone particles, harvested from the neighboring area, an additional layer of deproteinized bovine bone mineral (DBBM) was added on top of the implant in order to recreate the missing contour. (h) Due to the non–self-containing osseous defect, a volume of stable non-bioresorbable titanium-reinforced e-PTFE membrane was used in combination with titanium fixation pins. Additionally, the implant cover screw was used to stabilize the membrane.

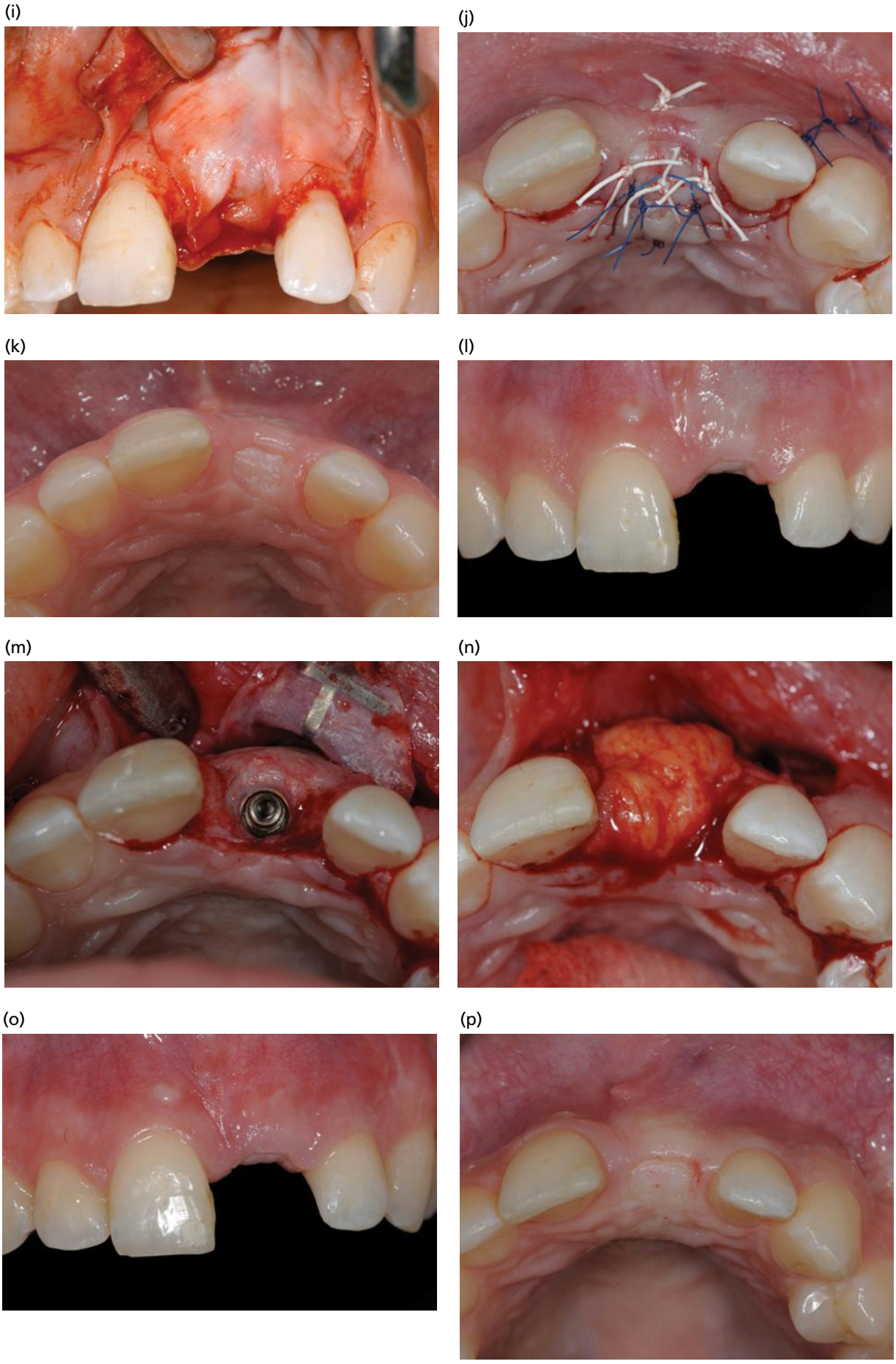


Fig. 54-20 (*Continued*) (i) Primary healing is crucial for GBR success. Accordingly, a collagen bioresorbable membrane was used to cover the e-PTFE non-bioresorbable membrane and decrease the risk of membrane exposure. (j) After a periosteal releasing incision, horizontal mattress sutures (5/0 e-PTFE) were used to approximate the wound borders and decrease flap tension. Further single interrupted sutures were used to close the wound. (k, l) Occlusal and buccal views after a healing period of 6 months. Note the maintained buccal ridge contour. (m) Full thickness flap was raised in order to remove the volume of stable e-PTFE non-bioresorbable membrane. The implant was completely covered by bone and the buccal contour was recreated. (n) Additionally, a connective tissue graft, harvested from the palate, was placed to augment both the occlusal and buccal aspects of the ridge. It was first sutured to the palate and then mobilized to the buccal site. (o, p) Occlusal and buccal views 6 weeks after completion of healing.

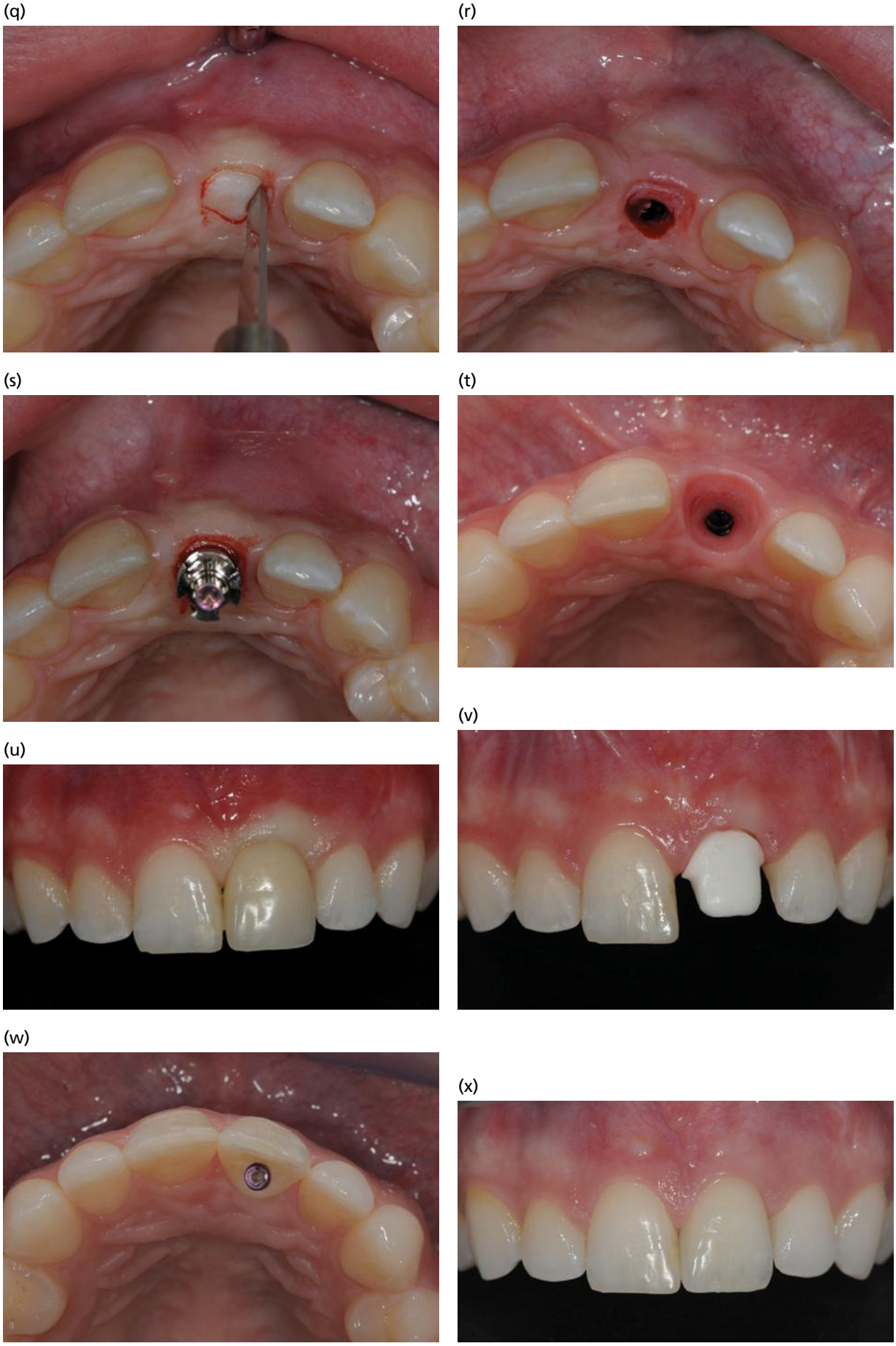


Fig. 54-20 (*Continued*) (q) Minimally invasive abutment connection was performed using a U-form incision technique. (r) Flap was then rotated to the buccal site. (s) Simultaneously, an impression was taken at the level of the implant shoulder and sent to the laboratory to fabricate a screw-retained acrylic provisional. (t) Progressive modifications of the provisional led to a buccal displacement of the soft tissues, and adequate emergence profile and gingival margins. (u) Wax-up try-in. (v) An individualized CAD/CAM zirconia abutment was designed. (w) Occlusal view of the final screw-retained restoration. Note the ideal position of the access hole for the prosthetic screw. (x) Final restoration was fabricated by direct ceramic veneering of the zirconia abutment. Note the symmetry between the soft tissue margin and contour, compared to the right central incisor.

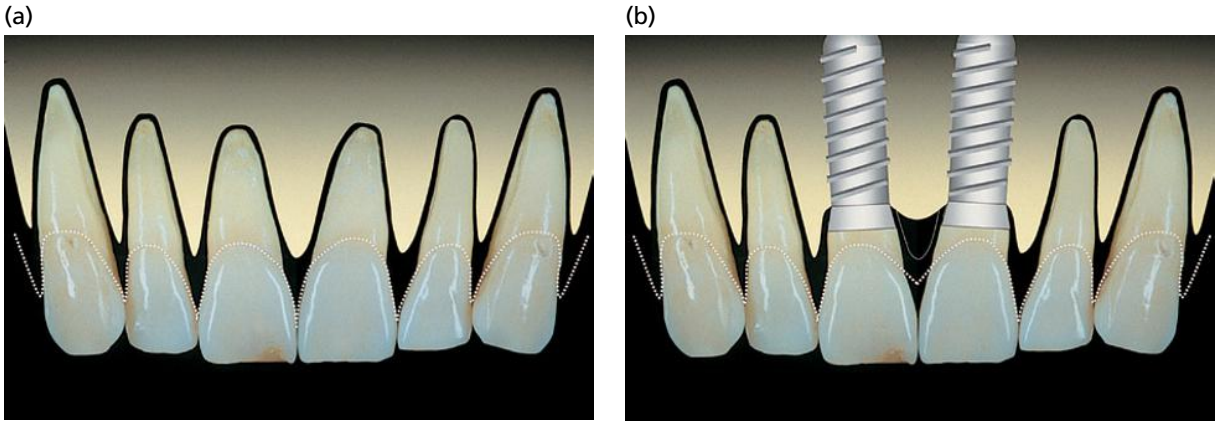


Fig. 54-21 (a) Schematic representation of the six maxillary anterior teeth, including their bony support and the course of the marginal soft tissue, corresponding ideally approximately to the cementoenamel junction (dotted line). (b) Loss of the two central incisors and their subsequent replacement by implant restorations normally leads to well-defined bone loss ("micro-gap", establishment of a "biologic width") around the implant sites. The main consequence from an esthetic point of view is vertical soft tissue deficiencies, namely between the adjacent implants (dotted lines).

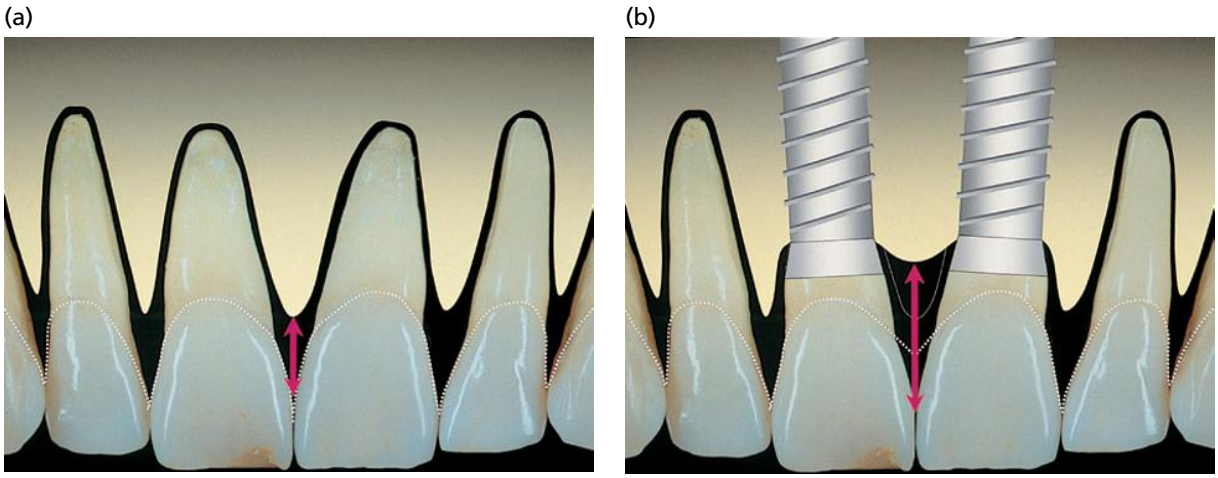


Fig. 54-22 (a) Schematic close-up view of the relationship between the cementoenamel junction, alveolar bone, and gingiva in the maxillary incisor area. (b) Same area after implant therapy. The arrow represents the distance between the interimplant bone crest and the interdental contact point. The lack of bony support for the interdental soft tissue often causes the appearance of black triangles, compromising the esthetic treatment outcome.

between the implants. The drawback of this option is the difficulty with creating a similar appearance of the emergence profile of an implant restoration (implant 11) and a pontic at position 21 with a prosthesis. Alternatively, if there is a sufficient mesiodistal dimension in the area of the two missing central incisors, one implant can be placed at position 11 and the other at position 21 with a cantilever to replace tooth 22. With this second option, two identical emergence profiles can be created, but has the drawback of having two implants next to each other. When all four incisors are lost, generally two implants are placed at the position of the two lateral incisors. This concept might also apply to the use of reduced diameter implants at positions 12 and 22.

Sites with minor tissue deficiencies

In cases with minor tissue deficiencies, the previously described shortcomings are also inherent in multiple adjacent implant restorations. Therefore, some restorative "tricks", including peri-implant soft tissue conditioning and a particular interproximal crown design, need to be implemented to predictably achieve an acceptable esthetic compromise.

The initial prosthetic planning, the implant surgery, and the prosthetic reconstruction for a 54-year-old man who in an accident had lost three incisors and one pontic at the position of tooth 21 are shown in Figs. 54-23, 54-24, and 54-25, respectively.

Sites with extended tissue deficiencies

A 55-year-old female patient presented a left central and a lateral incisor with periapical pathologies and insufficient tooth substance to maintain these teeth as abutments for conventional crowns. After careful evaluation from an endodontic and a prosthetic point of view, both teeth were judged to be hopeless and were scheduled for extraction. A missing central and

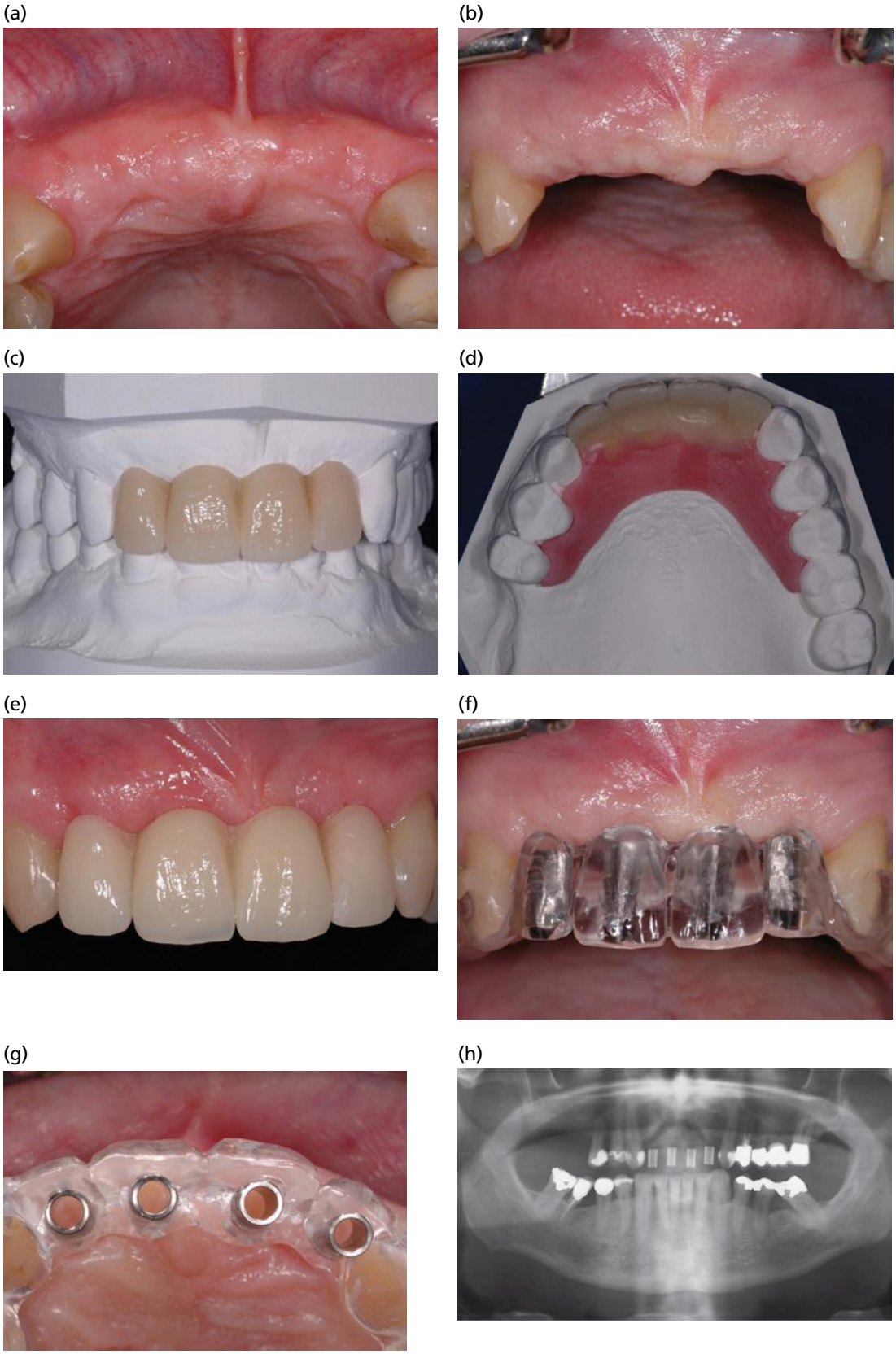


Fig. 54-23 (a) Initial occlusal view of four missing incisors revealing minor contour deficiencies. The 54-year-old male patient was referred after an accident, to restore these four missing teeth with a fixed dental prostheses. (b) Buccal view of the initial clinical presentation demonstrated a flat alveolar ridge with sufficient keratinized mucosa. A risk analysis was performed and the patient was informed about the treatment with implants. (c) Before starting implant therapy, the prosthesis was planned with the four missing teeth set up on a master cast. (d) Set-up was fabricated in a way that it could be used as a try-in within the oral cavity. (e) After placing the set-up within the patient's mouth, the functional, phonetic, and esthetic outcomes were assessed. Note the long contact areas in between the teeth that compensate for the lack of scalloping. (f) Based on the set-up, a radiographic and surgical template was fabricated with transparent PMMA material. (g) Occlusal view of the radiographic and surgical template with four titanium cylinders indicating the four possible implant positions. (h) Initial panoramic X-ray with the radiographic template in place. According to the available bone and the ideal implant distribution, two implants at positions 12 and 22 were planned.

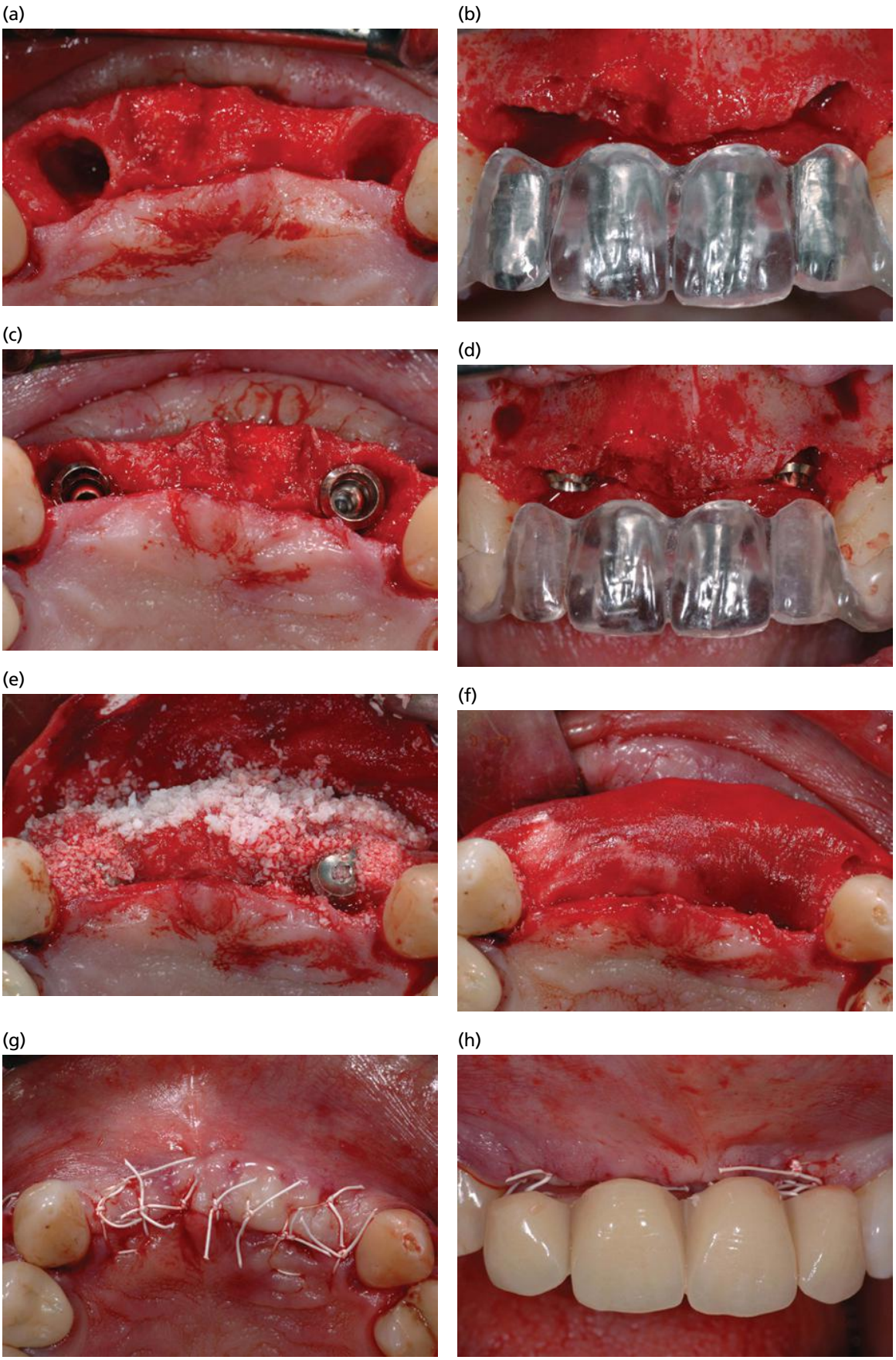


Fig. 54-24 Same patient as in Fig. 54-23. (a) Occlusal view of the edentulous alveolar ridge 8 weeks after extraction of the fractured anterior teeth. The former sockets were still visible. (b) Buccal view of the edentulous alveolar ridge with the surgical template in place indicating the ideal implant positions in relation to the horizontal and vertical dimensions. Note that the former radiographic template has been adapted to serve as a surgical template. (c) Two implants were placed at positions 12 and 22 according to the prosthetic plan. (d) The surgical template indicated the proper vertical implant position to be approximately 2 mm apical to the future implant crown margin with this type of soft tissue level implant. (e) A slowly resorbing bovine graft material was chosen to fill the gap between the implant and the buccal bone plate and to further augment the buccal bone contour. (f) Collagen membrane was used to cover the grafted area before soft tissue closure. (g) After periosteal releasing incisions were made, the mucoperiosteal flap was closed without tension using horizontal mattress and single interrupted sutures. (h) The removable temporary reconstruction was released to give a distance of 2–3 mm to the mucosa in order to compensate for the post-surgical swelling.

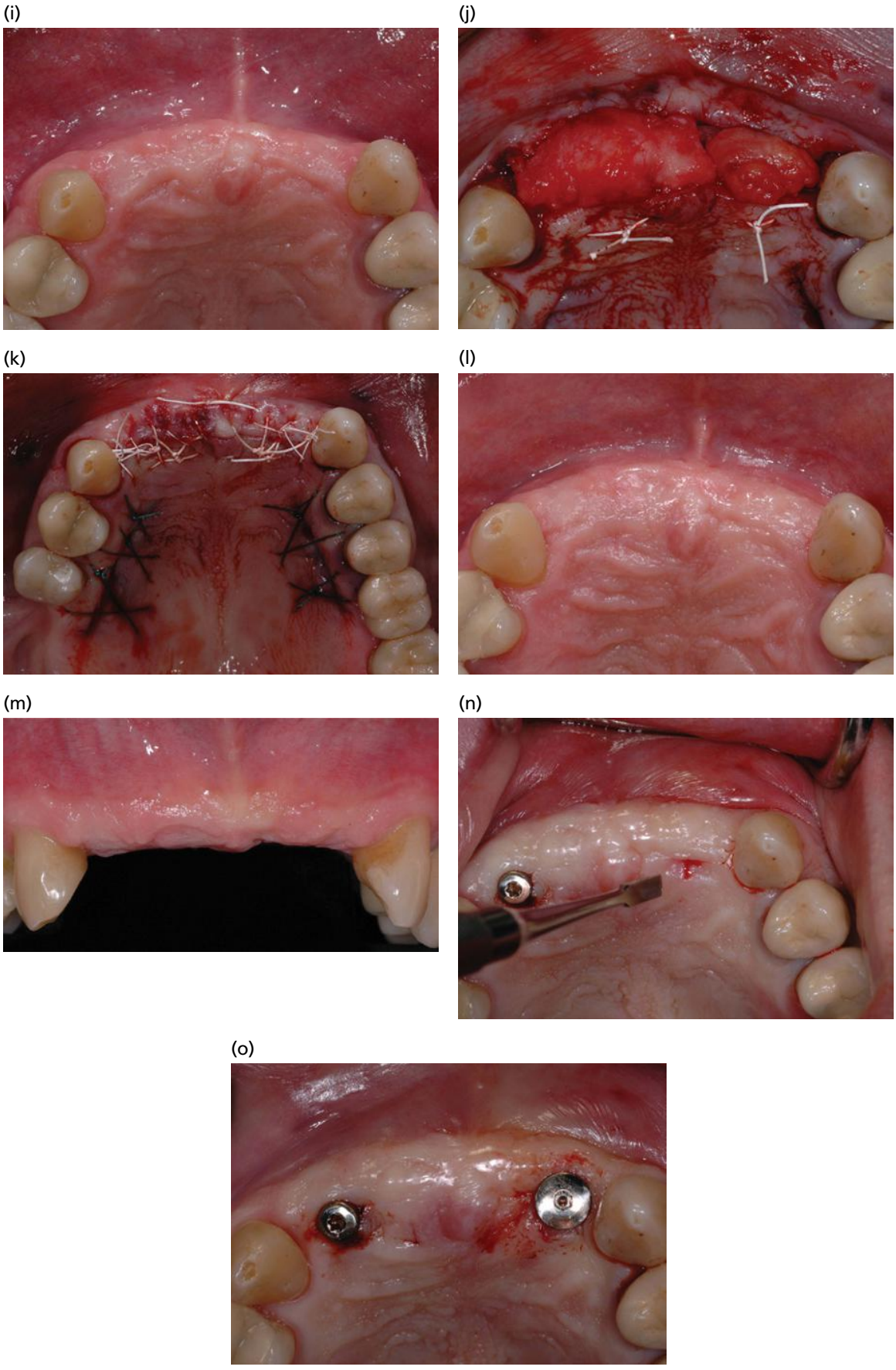


Fig. 54-24 (*continued*). (i) Three months after implant placement, re-evaluation of the alveolar contour revealed a slight horizontal discrepancy at the level of the soft tissues. In consultation with the patient, it was decided to perform an additional soft tissue grafting procedure in order to increase the buccal contour. (j) Two connective tissue grafts were harvested from both sites of the palate and placed in the area of the missing incisors. (k) Occlusal view after suturing of the recipient and the harvesting sites. (l) After soft tissue grafting, an ideal bucco-oral contour was achieved. (m) Buccal view revealed healthy soft tissues with sufficient keratinized width. (n) A minimally-invasive abutment connection with a "T-shape" incision was performed for both implant sites. (o) Titanium healing abutments were chosen and placed in such a way as to avoid overlap with the level of the neighboring soft tissue.

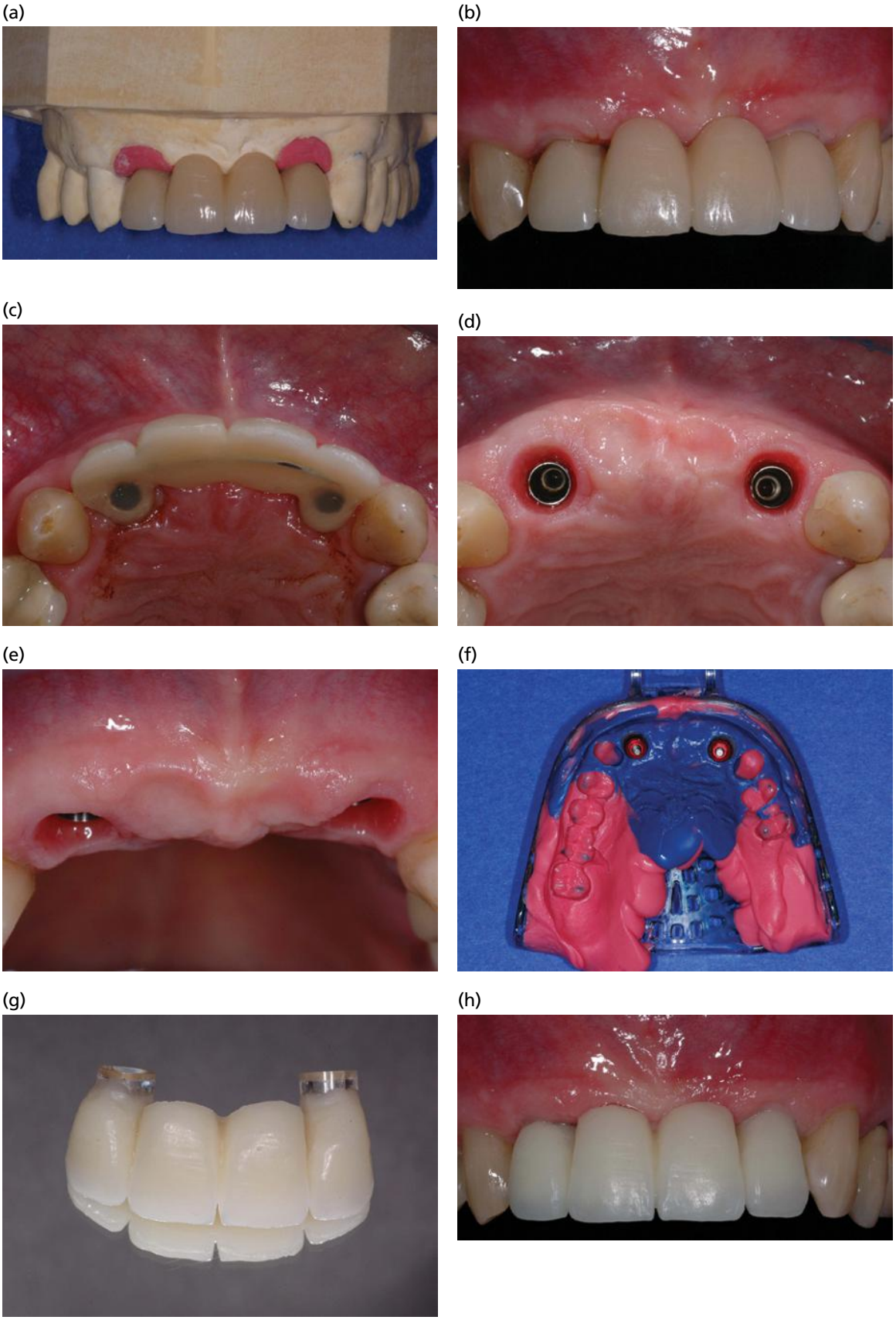


Fig. 54-25 Same patient as in Figs. 54-23 and 54-24. (a) After an impression was taken at the level of the implants, a temporary reconstruction made of resin was fabricated. (b) Screw-retained temporary resin reconstruction was inserted within the patient's mouths in order to start the soft tissue conditioning process, with flowable composite material subsequently added to the submucosal part of the temporary reconstruction. (c) Occlusal view of the screw-retained temporary reconstruction. (d) Occlusal view after completing the soft tissue conditioning process. Note the shape of the pontics for the two missing central incisors. (e) Buccal view of the soft tissue contour with a slight scalloping of the mucosa in between the pontics. (f) With the help of two individualized impression copings, a final impression was made using a polyether impression material. (g) A wax-up for try-in was fabricated on the master cast. (h) Wax-up within the patient's mouth, checking again for function, phonetics, and esthetics.

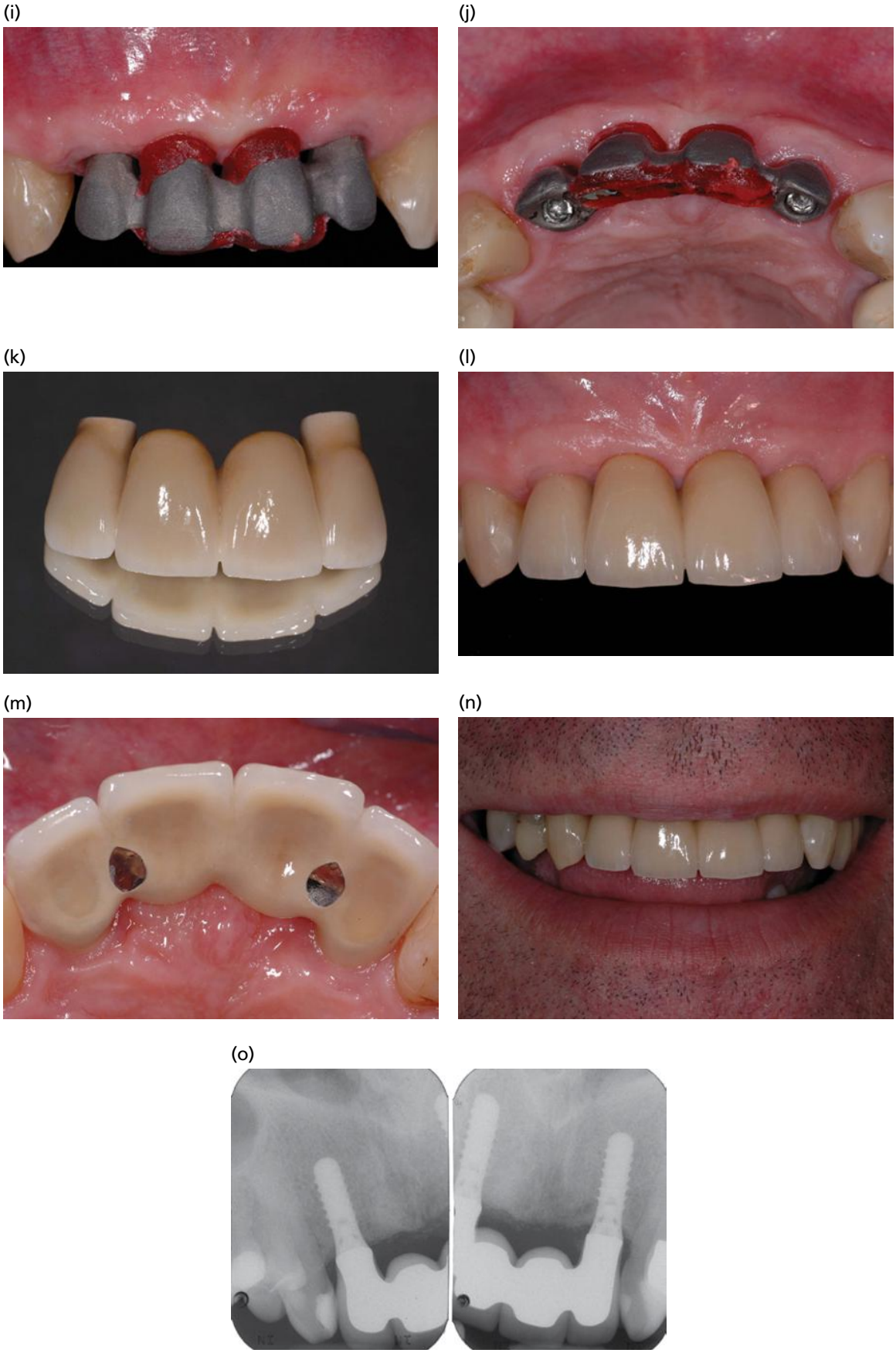


Fig 54-25 (*Continued*). (i) Buccal view of the metal framework. A PMMA material was used to capture the pontic areas. (j) Occlusal view of the metal framework demonstrating the ideal implant positions for a screw-retained reconstruction. (k) Extraoral view of the final screw-retained porcelain-to-metal reconstruction. (l) Buccal view of the final reconstruction in place. Note the slight papilla in between the two central incisors, but almost no papilla between the implant sites and the central incisors. (m) Occlusal view of the porcelain-fused-to-metal (PFM) reconstruction after covering the screw-access hole with composite material. (n) Final lip line of the patient without visible mucosal aspects apical to the implant-supported crowns and pontics. (o) Periapical X-rays 2 years after insertion of the final reconstruction, showing stable bone levels.

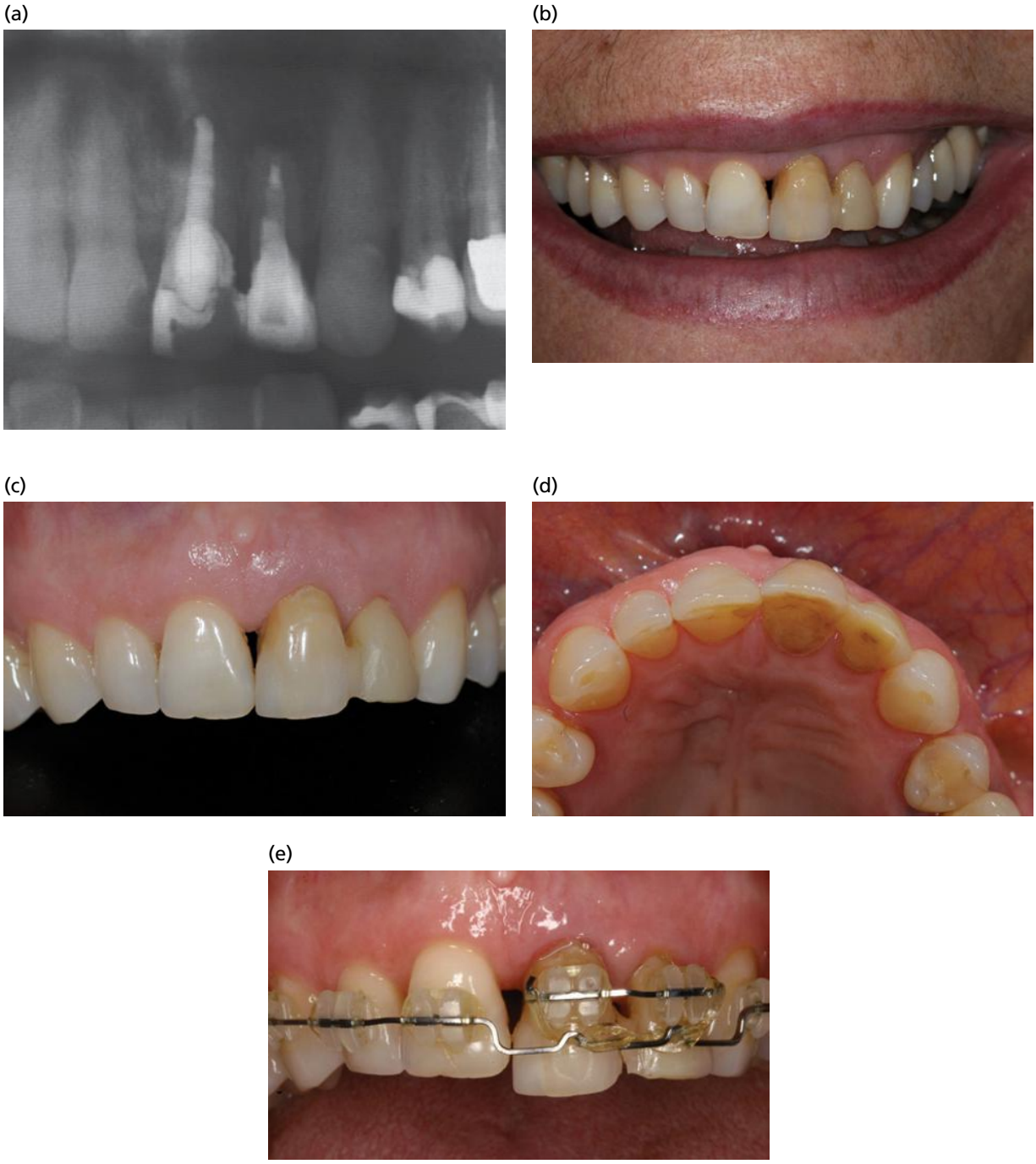


Fig. 54-26 (a) Initial radiograph of a 55-year-old female patient with a left central and a lateral incisor with periapical pathologies and insufficient tooth substance to maintain these teeth as abutments for conventional crowns. In addition, tooth 21 had a buccal fracture of the root. From an endodontic and a prosthetic point of view, both teeth are considered to be hopeless and were scheduled for extraction. (b, c) Esthetic analysis revealed a high lip line, a black triangle between the central incisors, and irregular gingival margins for the left central and lateral incisors compared to the contralateral tooth. Left central and lateral incisors were yellowish in color due to loss of tooth vitality. (d) Occlusal view of the initial clinical situation. Left central and lateral incisors were splinted due to their increased mobility. (e) After an extensive esthetic and functional analysis and diagnosis phase, the planned treatment was presented to and was discussed with the patient. Due to the irregular gingival margins, orthodontic tooth extrusion before extraction was preferred in order to coronally displace soft tissues. Only one implant in position 21 with an extension for position 22 planned. In order to correct the black triangle, a ceramic veneer for position 11 was planned.

lateral incisor is considered a very challenging situation because implants have to symmetrically match the contralateral incisors. This clinical case is shown in Figs. 54-26, 54-27, 54-28, 54-29, and 54-30 and represents a situation with more extended soft and hard tissue deficiencies.

Sites with severe tissue deficiencies

In a 25-year-old patient with severe soft and hard tissue deficiencies, due to an accident at the age of 12 years, the left central incisor had ankylosed very early with the result that there was a large soft tissue

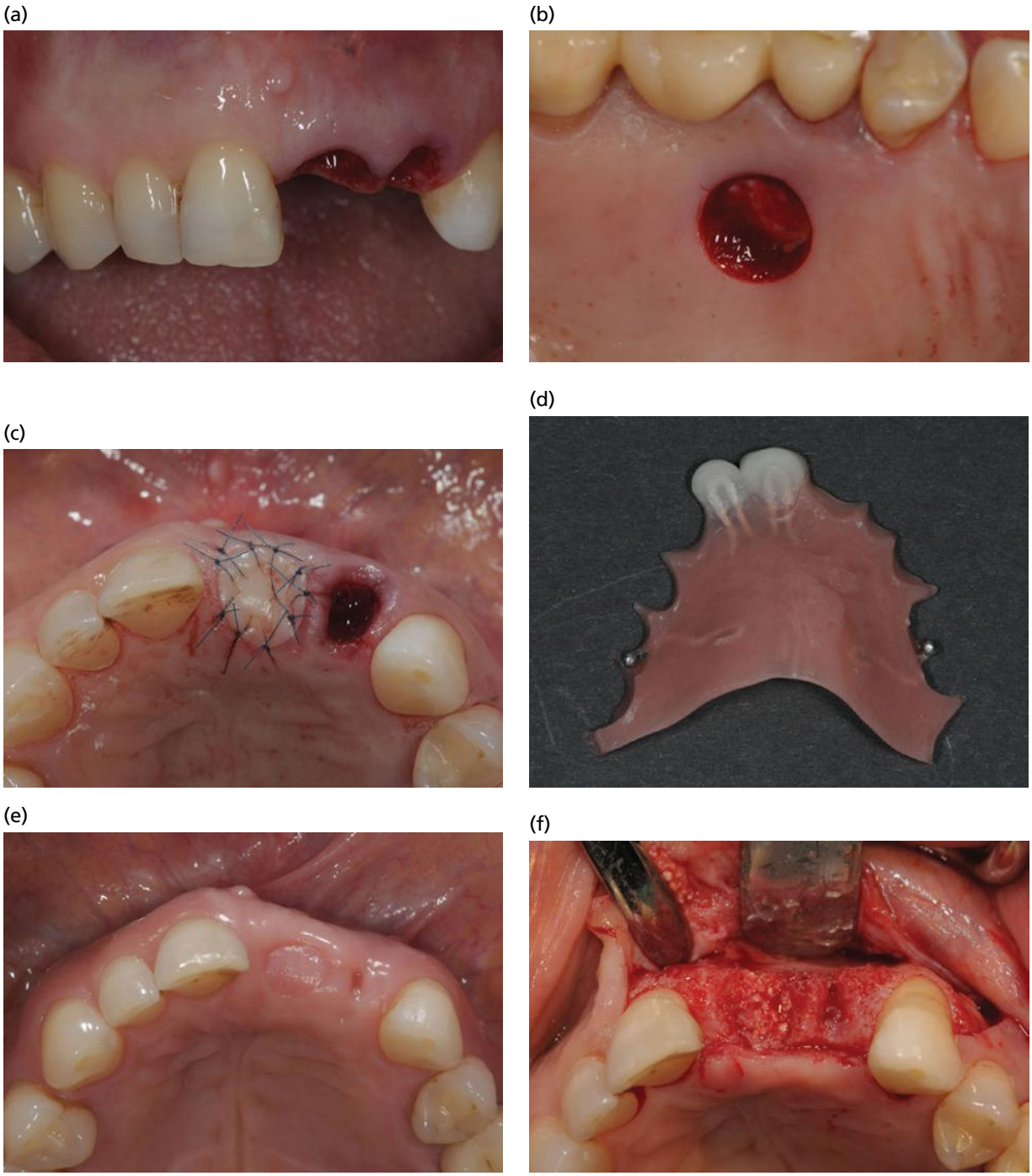


Fig. 54-27 Same patient as in Fig. 54-26. (a) After 2 months of active orthodontic movement and 4 months of retention, teeth 21 and 22 were extracted with minimum trauma. In order to maintain the alveolar ridge dimensions after tooth extraction, the socket of the central incisor was then filled with demineralized bovine bone mineral (DBBM) with 10% collagen. (b) Subsequently, a biopsy punch was used to obtain a free mucosal graft from the palate. The area between the first molar and second premolar is generally preferred for this. (c) Free mucosal graft was placed on top of the DBBM-Collagen and sutured with 6/0 monofilament. Careful adaption is crucial for survival and success. Special attention should be paid to the adaptation of the interproximal areas. (d) A removable provisional acrylic restoration was prepared and placed after the extractions. (e) Eight weeks after extraction, the soft tissues had completely healed and ridge volume was maintained. (f) A mucoperiosteal flap with a vertical releasing incision distal to the canine was elevated. Note the presence of the DBBM particles in the extraction socket.

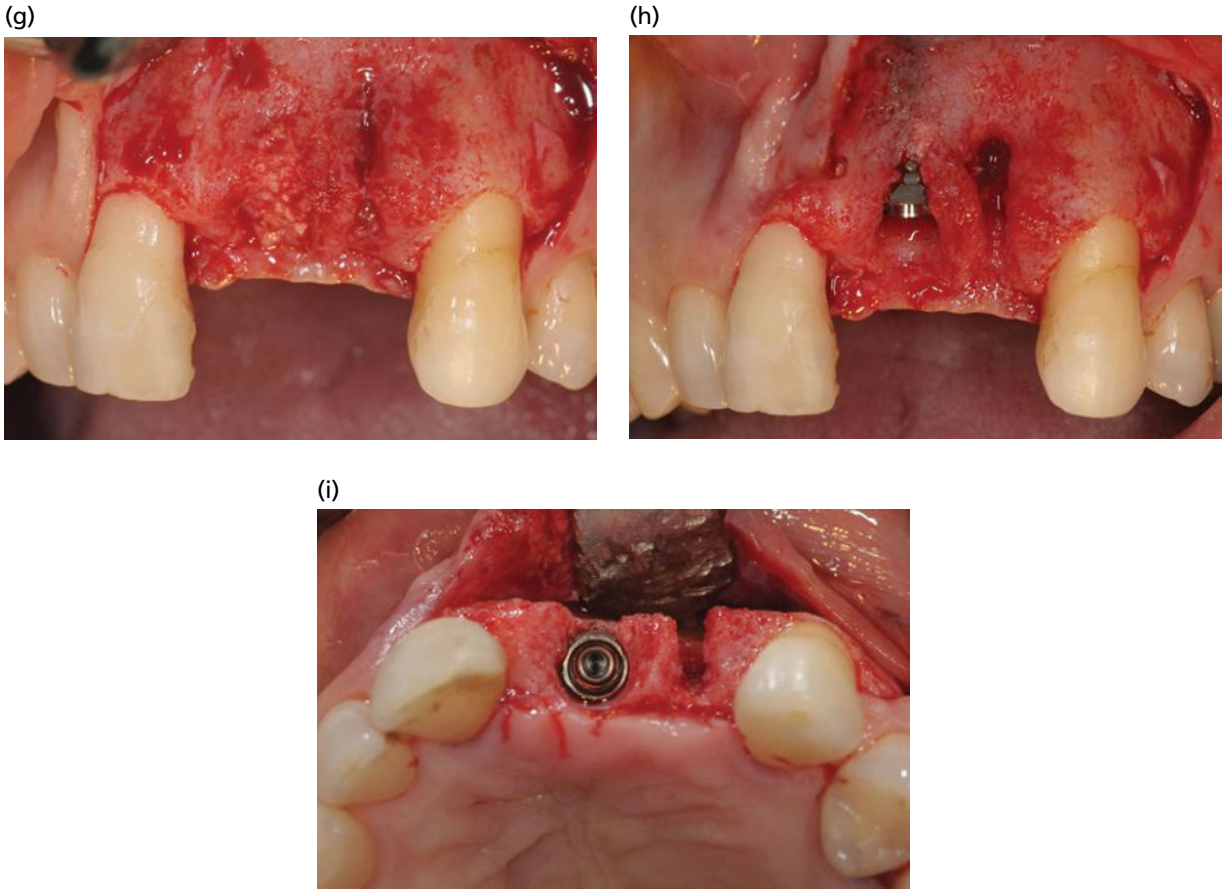


Fig. 54-27 (*Continued*) (g) Buccal view after flap elevation. Note the difference between the central incisor socket and lateral incisor socket, which was left empty. (h) A bone level implant was placed according to the prospective restoration and gingival margins. Vertical position was 3–4 mm apical of the prospective gingival margin. Note the buccal dehiscence of 3 mm. (i) Occlusal view revealed an ideal implant position and a self-containing defect affecting the buccal aspect of the implant. Guided bone regeneration with DBBM and bioresorbable collagen membrane was indicated.

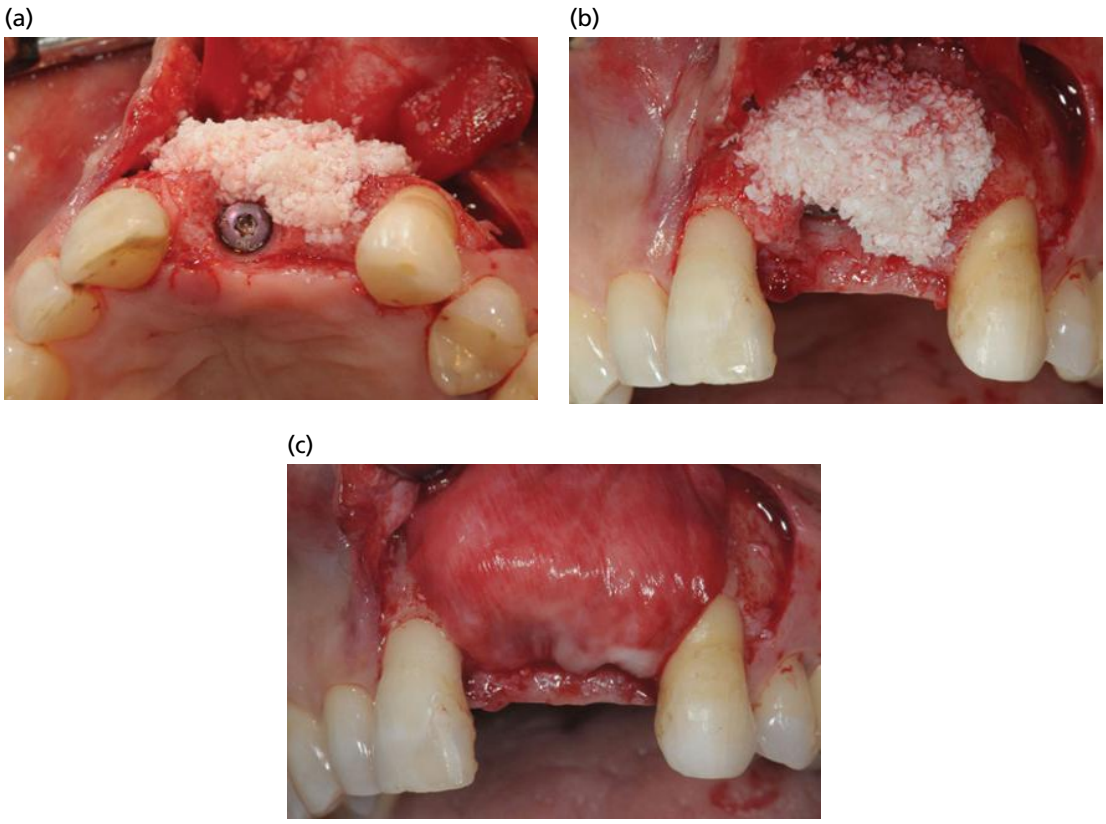


Fig. 54-28 Same patient as in Figs. 54-26 and 54-27. (a, b) For the guided bone regeneration (GBR) procedure, autogenous bone particles from the surrounding area were placed on top of the implant surface and then covered by a deproteinized bovine bone substitute. Overcorrection of the defect was performed to compensate for further material displacement during membrane placement and suturing. (c) A bioresorbable collagen membrane was shaped in order to adapt it to the defect, and it was fixed apically with two bioresorbable pins.

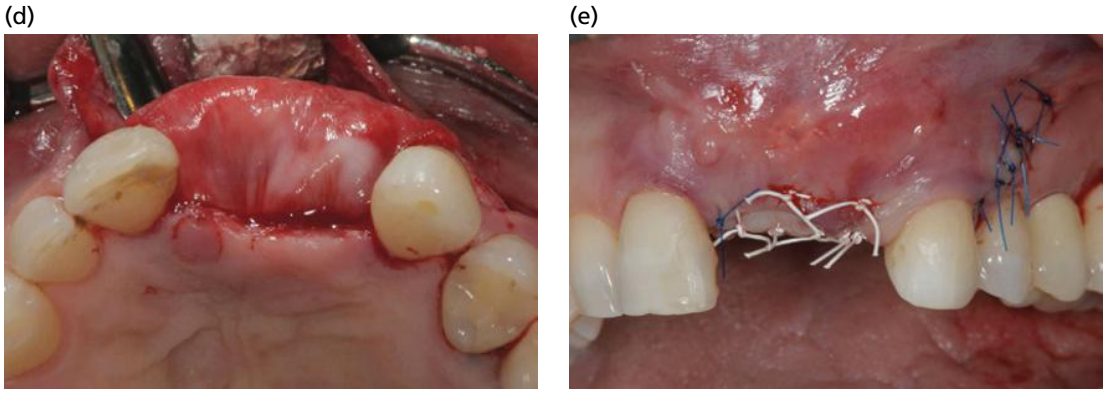


Fig. 54-28 (*Continued*) (d) Occlusal view shows the overcorrection of the defect in order to compensate for further material displacement and resorption. (e) Tension-free soft tissue closure is a critical issue when GBR is performed. Horizontal releasing incisions in the periosteum were executed prior to suturing to ensure relaxation of the flap. Then, horizontal mattress sutures were placed to approximate wound margins and reduce flap tension. Finally, an e-PTFE membrane and monofilament 5/0 sutures were placed in the crestal and vertical incisions without tension to ensure flap adaptation.

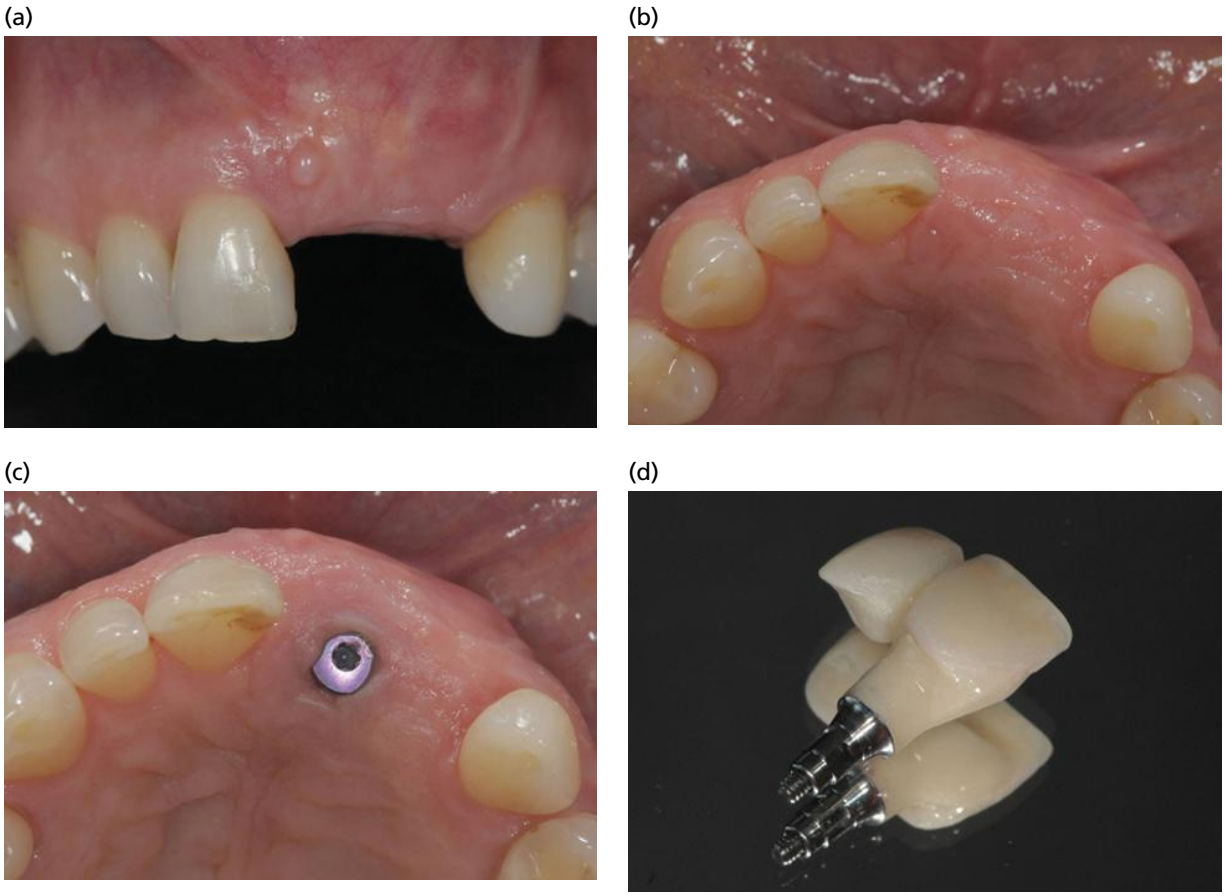


Fig. 54-29 Same patient as in Figs. 54-26, 54-27, and 54-28. (a) Three months after implant placement, soft tissues were completely healed and healthy. (b) At that time, a connective tissue graft was performed 4 weeks prior to second-stage surgery. The aim of the connective tissue graft was to increase the soft tissue thickness at the occlusobuccal aspect of the ridge. (c) Minimally-invasive second-stage surgery was performed with just a small palatal incision and displacement of soft tissues slightly buccally. Direct impression technique with an open tray was used and a healing abutment was placed. (d) Two weeks later, a provisional screw-retained restoration was placed. The provisional restoration was designed to give the ideal buccal size and shape, but the technician left the inner part empty. This empty space was then progressively filled in the clinic by the dentist in order to compress and displace the soft tissues in the desired direction.

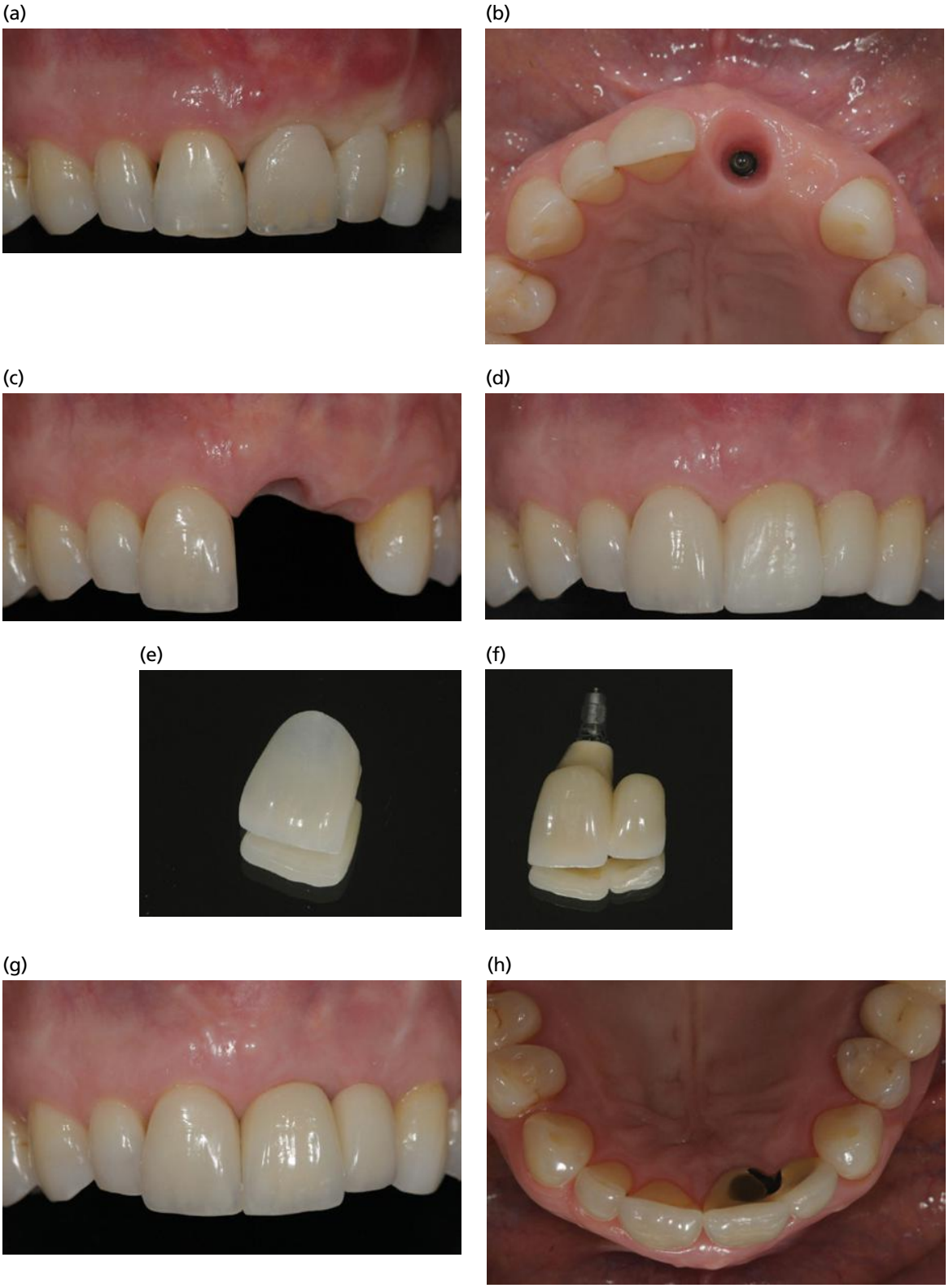
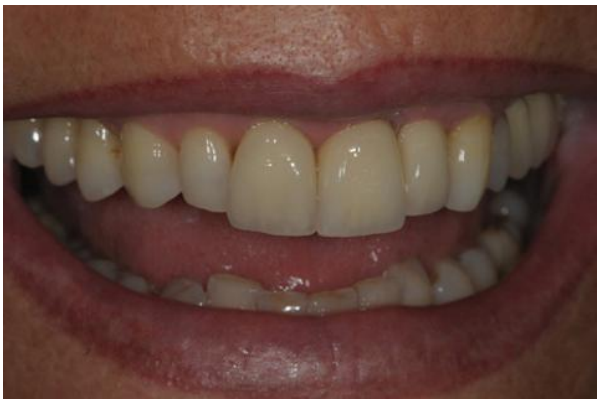


Fig. 54-30 Same patient as in Fig. 54-26, 54-27, 54-28 and 54-29. (a) Provisional restoration in place. Note the pressure on the soft tissues. Ideally, whitish mucosa should recover a normal pink color after some minutes. (b) Occlusal view after the soft tissue conditioning process with the temporary reconstruction. (c) Buccal view of the finally shaped soft tissue margins before crown placement. (d) Wax-up and veneer try-in revealed that the progressive modifications of the provisional had led to a buccal displacement of the soft tissues and adequate mucosal margins. (e) To improve the final esthetic result and achieve symmetry, a facial veneer was prepared for the right central incisor. A slight change in the original shape of the central incisors and an apical contact point lead to closure of the black triangle. (f) Final screw-retained porcelain-fused-to-metal (PFM) restoration with a distal cantilever replacing 22. (g) Final screw-retained restoration (21 with extension 22) and all-ceramic veneer (11) in place. Note the perfect integration with the soft tissues and the aligned gingival margins. (h) Occlusal view of the final reconstruction. Due to the limited interocclusal distance, the connector to the extension was left in metal. The screw access hole was still covered with a provisional resin material which was to be replaced with a permanent composite material.

(i)



(j)

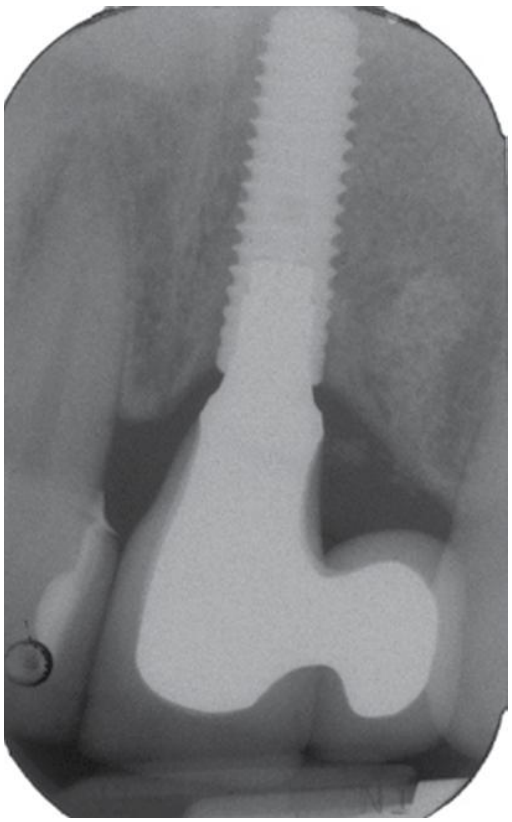


Fig 54-30 (*Continued*). (i) Smile line revealed an esthetically pleasing result with the reconstruction perfectly integrated within the rest of the dentition and the soft tissues. (j) Final result 1 year after insertion of the screw-retained PFM reconstruction on position 21 with a cantilever to position 22.

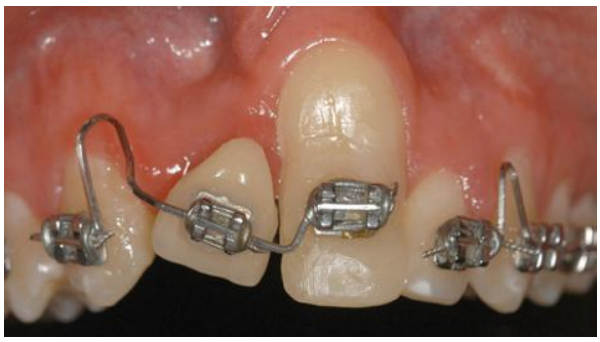


Fig. 54-31 A 25-year-old male patient presented with a missing right central and lateral incisor and a very early ankylosed left central incisor due to a ski accident at the age of 12 years.

dehiscence on the buccal aspect of tooth 21. The risk analysis and treatment plan were presented to and discussed with the patient. The treatment plan included the extraction of ankylosed tooth 21 with a soft tissue graft in order to restore the soft tissues before further surgical interventions. The further treatment plan comprised a primary bone augmentation procedure with an autogenous bone block, two implants with two implant-supported crowns, and prosthetic modifications of 13 into 12 and 14 into 13 using either composite or veneers. The clinical steps are shown in Figs. 54-31, 54-32, 54-33, 54-34, and 54-35.

Prosthetic reconstruction in the zone of esthetic priority

Prosthetic reconstruction in the anterior area of the upper jaw is of upmost importance. As high implant survival and success rates have been reported, the esthetic outcome of the reconstruction has become the main focus of interest in these sensitive areas. The prosthetic reconstruction should imitate the appearance of the healthy teeth as closely as possible. When deciding the final prosthetic reconstruction, three major questions need to be addressed: (1) screw-retained reconstruction or cemented reconstruction?; (2) standardized prefabricated or customized abutments?; (3) porcelain-fused-to-metal (PFM) or all-ceramic reconstructions?

Screw-retained versus cemented reconstructions

Before an abutment can be selected, the first decision that needs to be made is whether a screw-retained or a cemented reconstruction is to be used. This important decision process is discussed in detail in Chapter 55. In brief, screw-retained reconstructions allow a better retrievability and facilitate the replacement and the maintenance of a reconstruction. In addition, it is easier to shape the emergence profile with screw-retained implant provisionals and to transfer the contour to the master cast. However, screw-retained restorations usually involve more

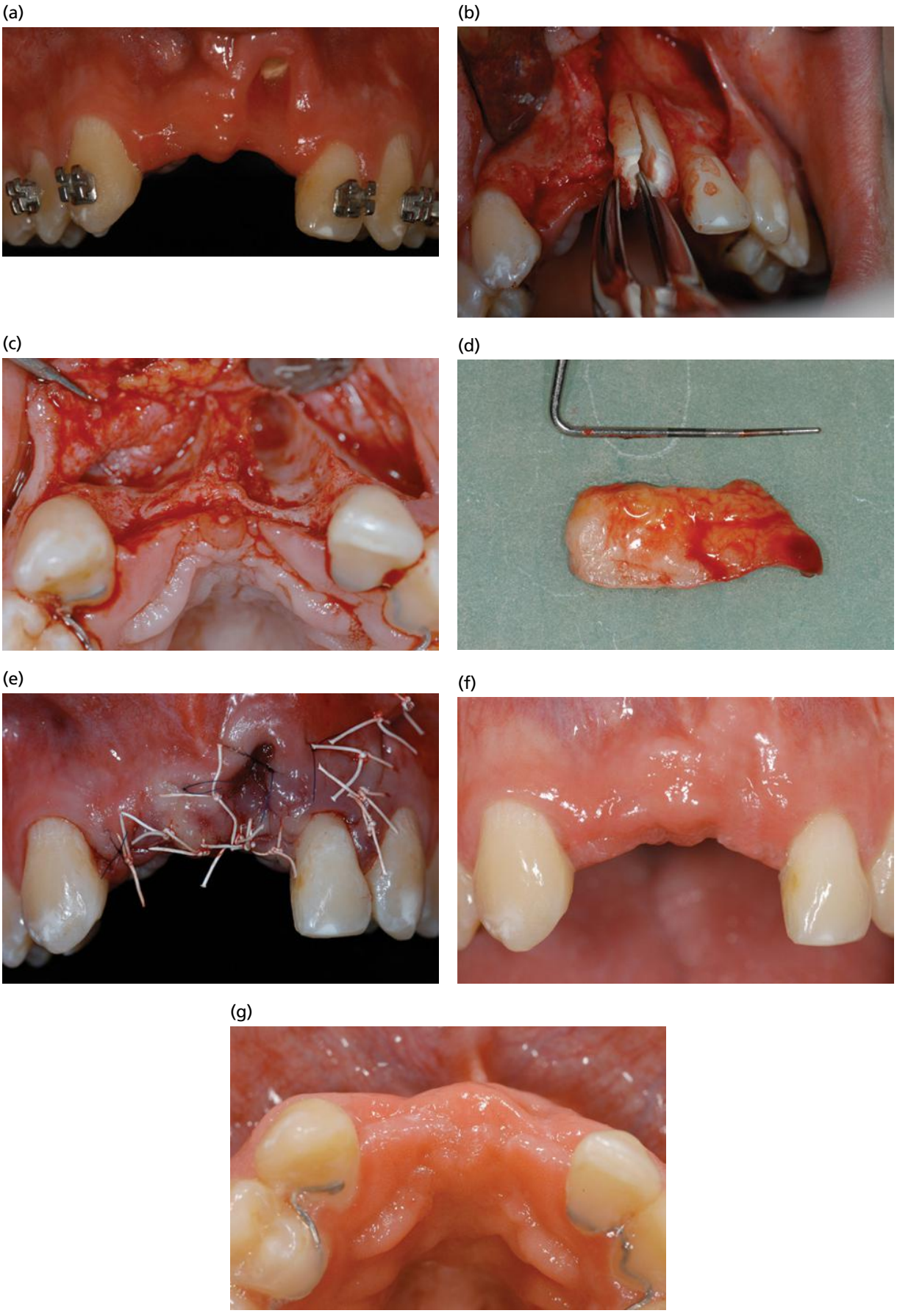


Fig. 54-32 Same patient as in Fig. 54-31. (a) Four weeks after cutting tooth 21 at the bone level in order to allow the soft tissue to partially regenerate the large soft tissue deficiency. (b) Mucoperiosteal flap was elevated to expose the root for extraction after dissecting the remaining root. (c) Occlusal view of the defect after the extraction. Bone level was maintained at the right canine but there was a horizontal defect all around the edentulous area and a vertical defect affecting the mesial aspect of tooth 22. (d) Connective tissue graft was harvested from the palate to cover the soft tissue defect. (e) Connective tissue graft was sutured in the area of the extraction socket in order to improve quantity and quality of the soft tissues for further procedures. (f) Three months after extraction, the buccal view revealed that the healing of the soft tissues was complete and the mucosal architecture restored. (g) Occlusal view 3 months after tooth extraction showed sufficient keratinized tissue for bone augmentation.

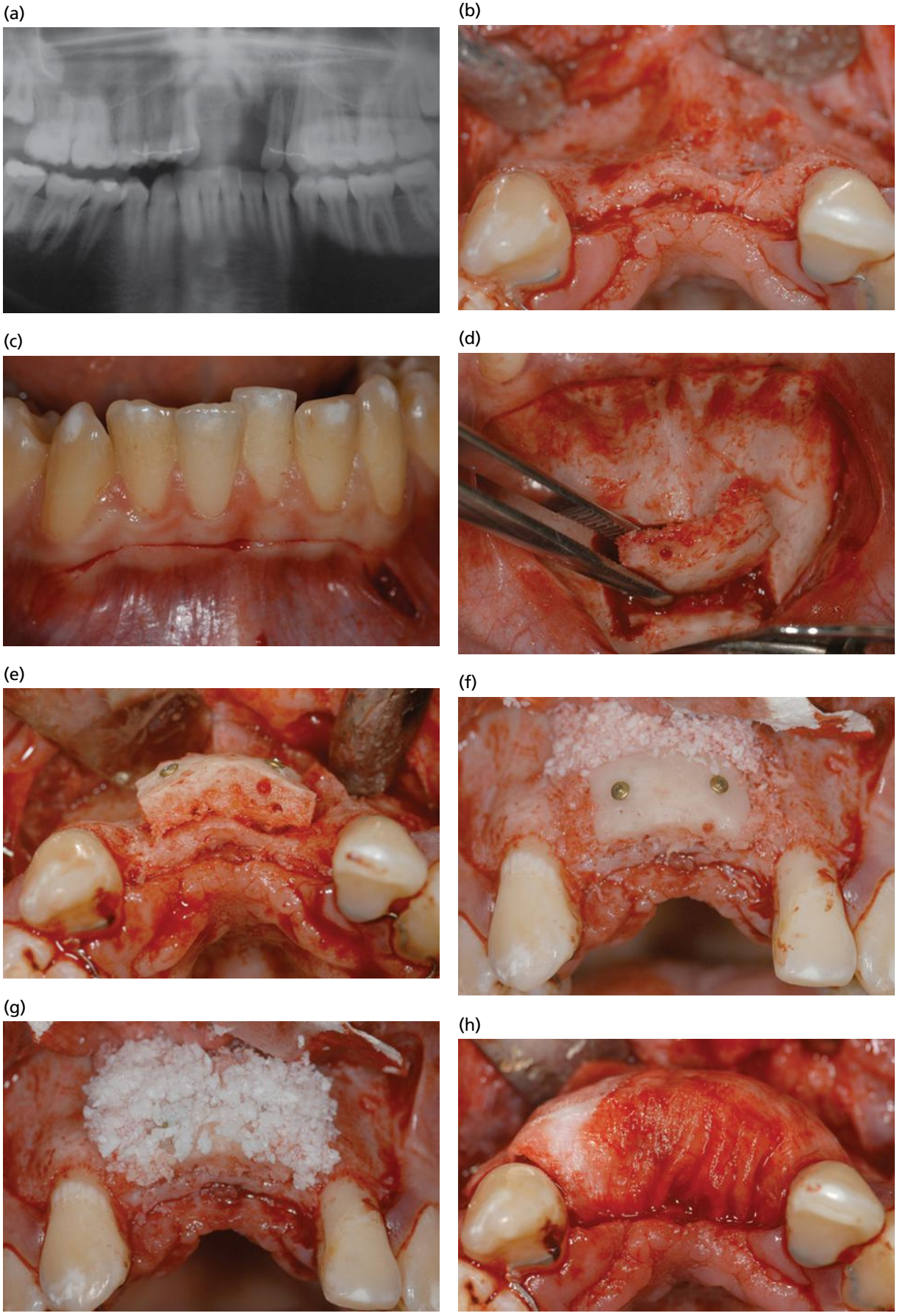


Fig. 54-33 Same patient as in Figs. 54-31 and 54-32. (a) Panoramic X-ray before bone augmentation procedures. (b) A mucoperiosteal flap was elevated with a slightly palatal crestal incision and two releasing incisions distal to tooth 13 and distal to tooth 22. Due to the horizontal defect, the implant could not be placed and a previous autogenous bone block was indicated. (c) In the chin area, a horizontal incision 1 mm above the mucogingival margin was performed from canine to canine with small distal apical releasing incisions. (d) Precise graft harvesting was done with an ultrasonic device, for which a minimum distance of 5 mm from the tooth apex, mental foramina, and chin base had to be respected. Finally, bone chips were obtained with a bone scraper. (e) Bone block was fixed in the desired position with two screws. (f) Empty spaces were filled with bone chips and deproteinized bovine bone mineral (DBBM). (g) A layer of DBBM was placed on top of the bone block to compensate for bone resorption during healing. (h) Finally, the augmented area was covered by a bioresorbable collagen membrane, which was stabilized apically with two bioresorbable pins. Subsequently, after making proper periosteal releasing incisions, the mucoperiosteal flap was closed.

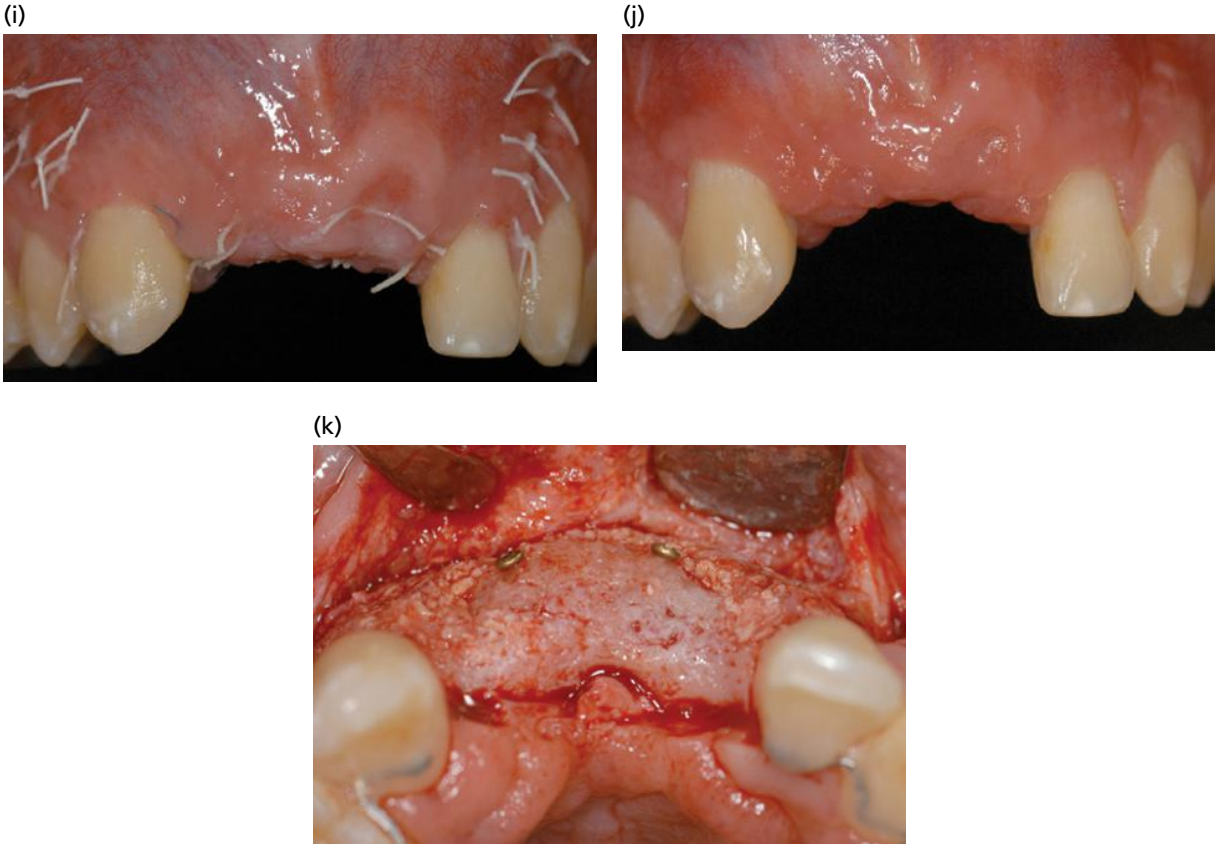


Fig. 54-33 (*Continued*). (i) Ten days after bone augmentation the healing process was uneventful and sutures could removed. (j) Buccal view of the soft tissue after 5 months of healing before implant surgery was performed. Ideally, implant placement should be performed between 4 and 6 months after a bone block graft in order to ensure integration and stability, but also to avoid too much bone resorption. (k) After elevation of a mucoperiostal flap, the occlusal view demonstrated a well-integrated autogenous bone block with minimal resorption.

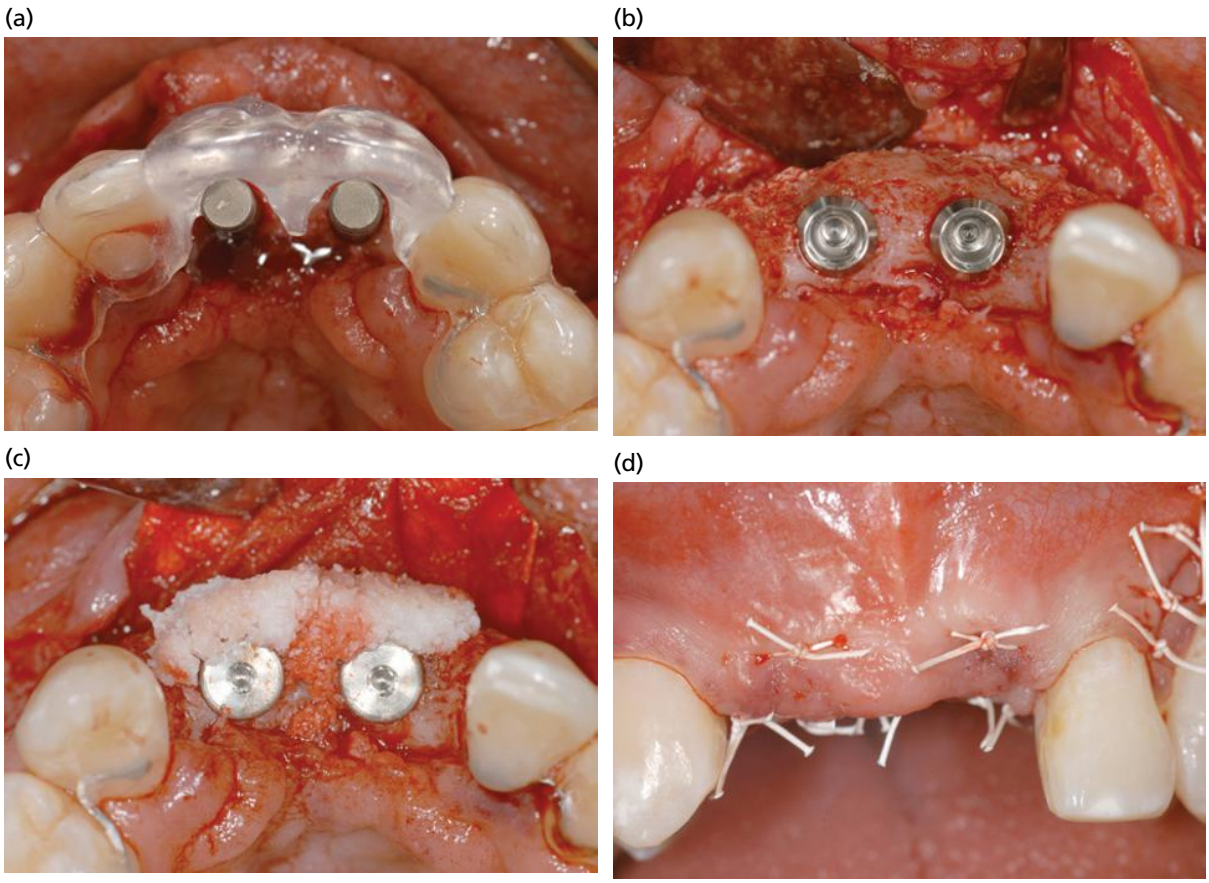


Fig. 54-34 (a) Same patient as in Figs. 54-30, 54-31, 54-32, and 54-3. (a) Conventional surgical splint based on previous wax-up facilitated the ideal prosthetic position for the implants. (b) Two soft tissue-level implants were placed at the ideal prosthetic position without any bone defects. (c) To prevent future bone resorption and to maintain buccal bone volume, additional guided bone regeneration (GBR) was performed with DBBM and a bioresorbable collagen membrane. (d) Flap closure was accomplished with two horizontal mattress sutures and single interrupted sutures.

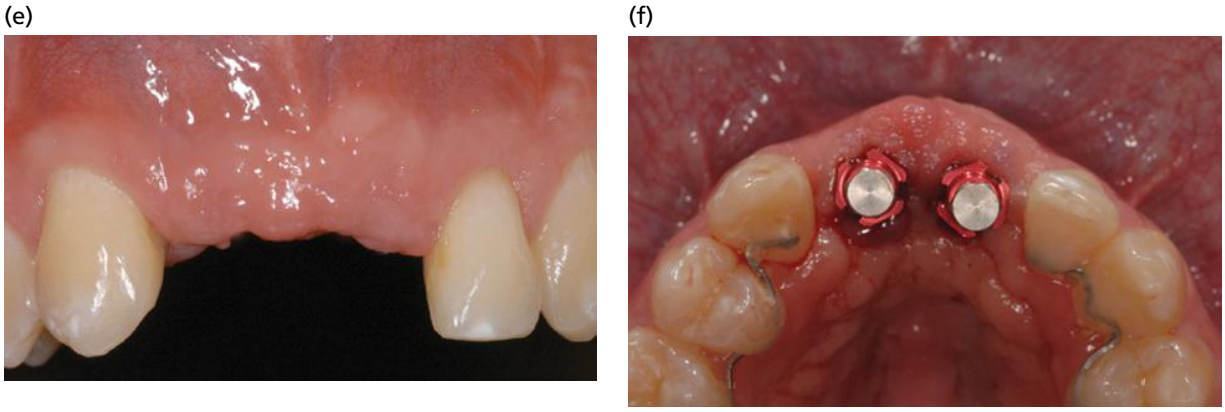


Fig. 54-34 (*Continued*). (e) Buccal view after 3 months of implant healing right before abutment connection. (f) Occlusal view with impression copings in place after second-stage surgery.

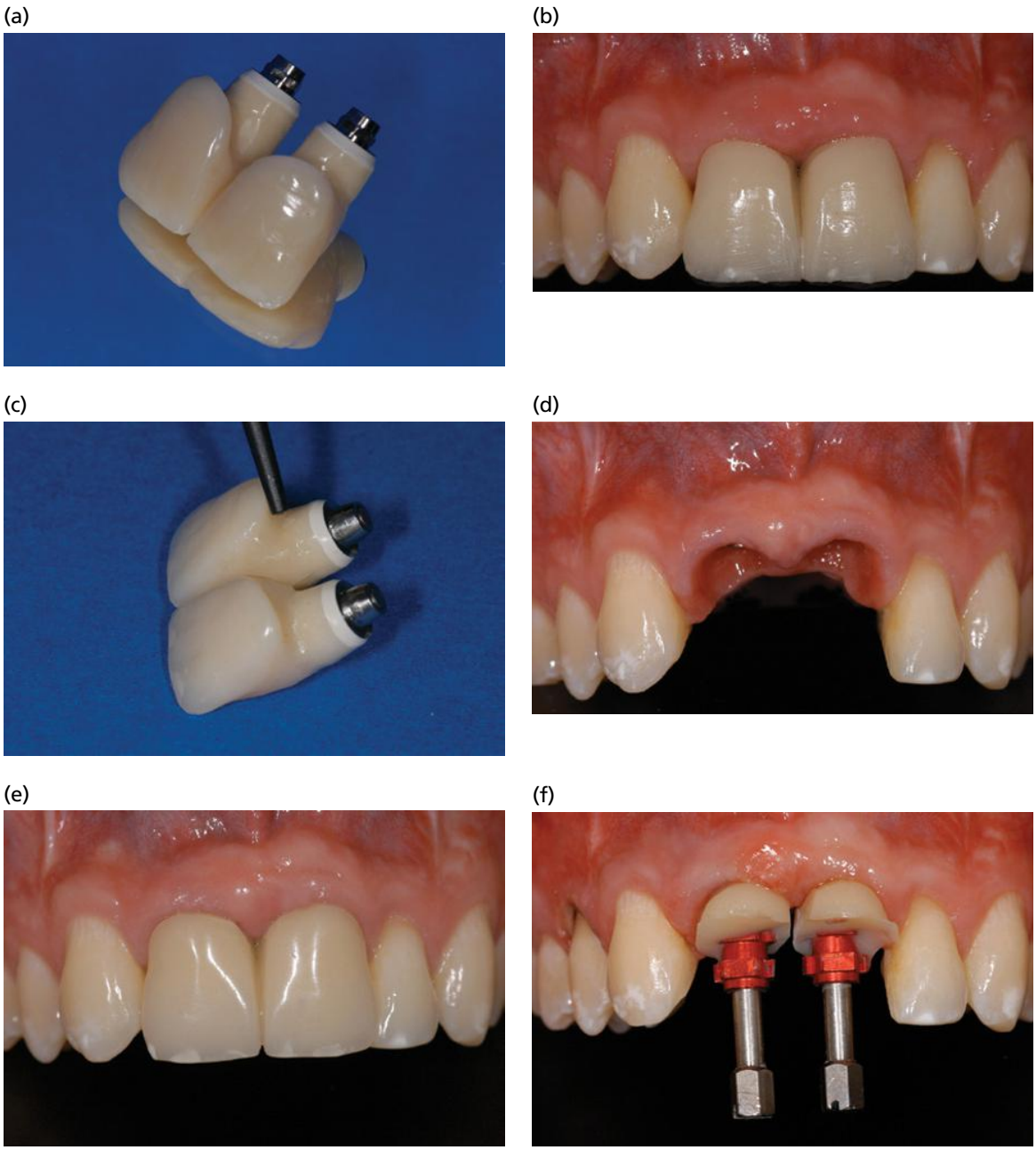


Fig. 54-35 Same patient as in Figs. 54-31, 54-32, 54-33, and 54-34. (a) The dental technician fabricated provisional acrylic restorations on top of a plastic abutment. The buccal aspect of the crown was designed according to the ideal shape based on the wax-up. The apical part of the provisional was removed to leave enough space for the soft tissues. (b) Buccal view of the screw-retained provisional restoration. The acrylic provisional restoration was used to improve the emergence profile of the two implants. (c) Flowable composite was used to progressively fill the concavity in order to push the soft tissues buccally and create an adequate emergence profile. (d) Progressive light and controlled pressure applied to the buccal soft tissues created the adequate emergence profile. (e) Provisional restoration after 6 months. Adequate emergence profile and soft tissue contour were achieved. (f) Buccal view of two individualized impression copings to capture the emergence profile for a precise transfer to the cast. Note the correction of scar tissue buccomesial of tooth 11 with a diamond bur and the crown lengthening of tooth 14 in order to better mimic a canine.

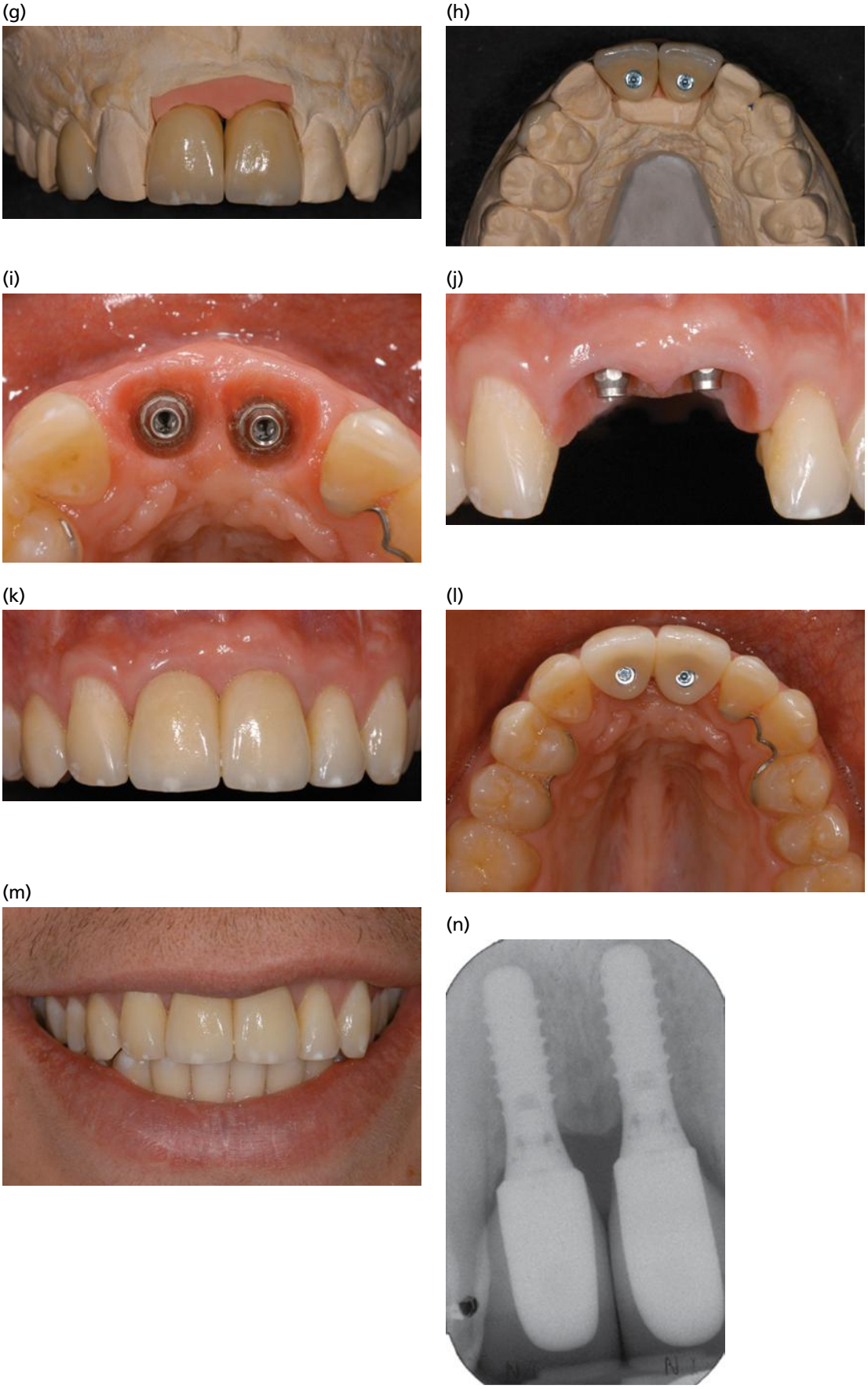


Fig. 54-35 (*Continued*). (g) Buccal view of two all-ceramic restorations and a veneer on tooth 14. A single tooth implant-supported solution was chosen. In order to compensate for the missing interimplant tissue, a long contact area was created. (h) Occlusal view of the screw-retained single-unit restorations and the veneer on tooth 14 on the master cast. (i) Occlusal view of the implants before final insertion of the two crowns. Note the thickness of the buccal soft tissue and the customized emergence profile that has been created during the provisional phase. (j) Buccal view of the soft tissue situation immediately before crown placement. Long-term provisional restoration and successive modifications led to pleasing mucosal margins and the creation of a minimal papilla. Tooth 13 had been shaped and adapted with composite to mimic a lateral incisor. (k) Final restoration in place. The right first premolar was modified with slight preparation and a ceramic veneer to look like a canine. Characterization with some white spots in the incisal edge and lines in the area of the neck created the look of a natural dentition. (l) Occlusal view of the final reconstruction in place. The ideal implant position allowed the screw access hole to be in the right place. (m) After a long treatment of close to 2 years, an esthetically pleasing result was achieved based on the integration of the restoration within the rest of the structures of the mouth and the face. (n) Final periapical X-ray demonstrating two bone level implants 3 years after loading.

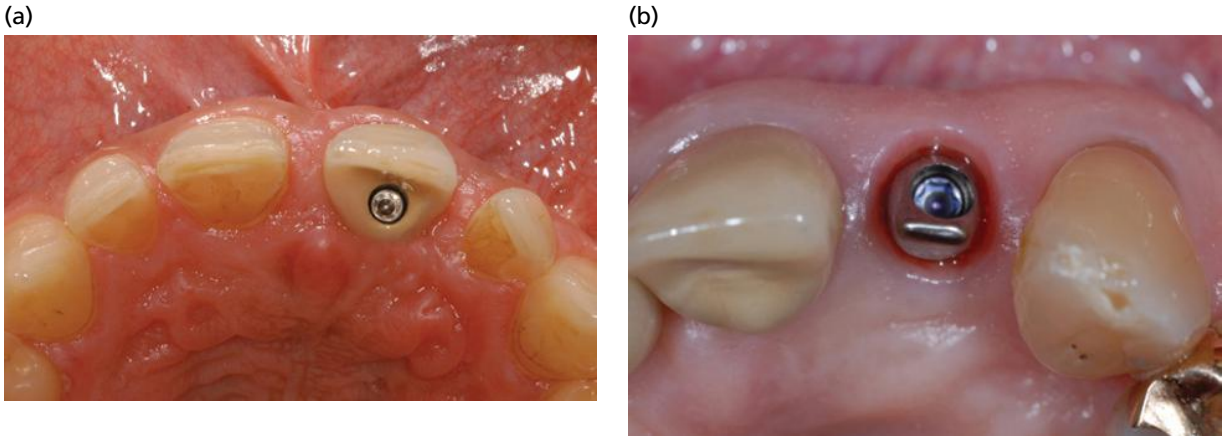


Fig. 54-36 (a) For a screw-retained restoration, an ideal implant position and axis is of great importance for a proper position of the screw-access hole. (b) A cemented restoration with an individualized abutment can compensate for a too buccally tilted implant position.

complex and more expensive laboratory procedures and can suffer from inherent mechanical complications such as screw loosening and fractures (McGlumphy *et al*. 1998; Pietrabissa *et al*. 2000). In contrast to the screw-retained restorations (Fig. 54-36a, where the ideal implant axis is a prerequisite, the cemented restoration offers the option to better compensate for a suboptimal implant position (Fig. 54-36b). Cement-retained implant reconstructions offer excellent esthetics due to the absence of the screw access hole, and incur lower technical costs than screw-retained restorations due to the reduced number of implant components and fewer technical steps that are needed (Taylor & Agar 2002). A variety of disadvantages of cemented reconstructions have been reported: difficulty of cement removal, more complex retrievability, and the possibility of crown loosening due to loss of retention (Breeding *et al*. 1992; Agar *et al*. 1997; Kent *et al*. 1997; Chee *et al*. 1999; Michalakis *et al*. 2003). These disadvantages can be minimized by choosing the correct abutment design and type.

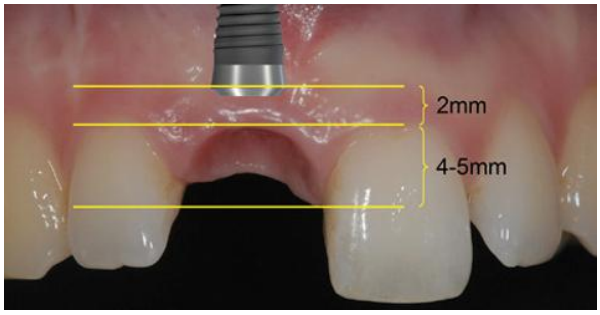


Fig. 54-37 Depth of an implant shoulder in a normally scalloped anterior site.

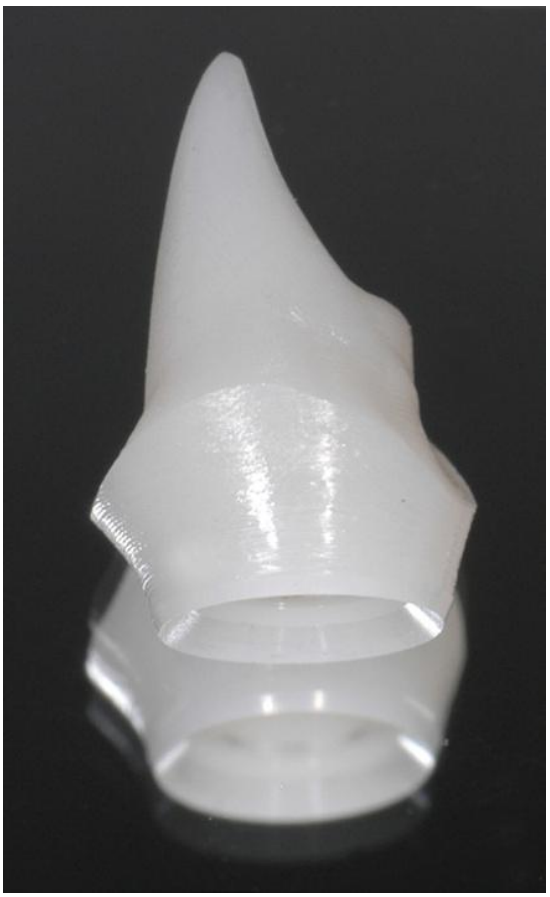


Fig. 54-38 CAD/CAM fabricated zirconia abutment.

Standardized prefabricated versus customized abutments

Each patient should be individually analyzed in order to decide whether to use a standardized prefabricated abutment or a customized abutment when esthetics play an important role. A thorough assessment includes the following factors: (1) soft tissue morphology, including soft tissue scalloping and vertical implant position; (2) discrepancy between the cross-sections of implant and tooth; (3) clinical and dental technical handling; (4) costs.

Anterior implant sites are often characterized by a high scalloped mucosal margin (Fig. 54-37). Implant shoulders, which are positioned 2–3 mm apical to the buccal mucosal margin have a proximal depths of up to 7–8 mm depending on the individual scalloping of the soft tissue (Fig. 54-38). If a standardized abutment that does not follow the soft tissue margin is used, removal of the excess cement is difficult, especially in the mesial and distal areas. The influence of the remaining cement on the health of the peri-implant

tissue has been recently investigated (Wilson 2009). It was demonstrated that excess dental cement was associated with signs of peri-implant disease in the majority (81%) of cemented single-unit fixed dental prostheses with mainly standardized abutments. Clinical and endoscopic signs of peri-implant disease were absent in 74% of the implants after removal of the excess cement. Hence, it seems that meticulous removal of cement is an important prerequisite for peri-implant health. An *in vitro* study evaluated the efficiency of cement removal from restorations luted to titanium abutments with simulated subgingival margins (Agar *et al.* 1997). It was concluded, that in each case there was remaining cement. It seems that, even under standardized conditions, it was not possible to completely remove composite, glass–ionomer or zinc–phosphate cement from a clinical analog model with crown margins located 1.5–3 mm submucosally. Therefore, in clinical situations with high scalloped soft tissue morphologies and deep vertical implant positions, customized abutments are recommended. These abutments allow an individual emergence profile of the reconstruction to be obtained directly by the abutment (Figs. 54-39, 54.40a). Hence, the crown margin can be located no >1.5 mm below the soft tissue margin and following the scalloping of the mucosa (Figs. 54-40b).

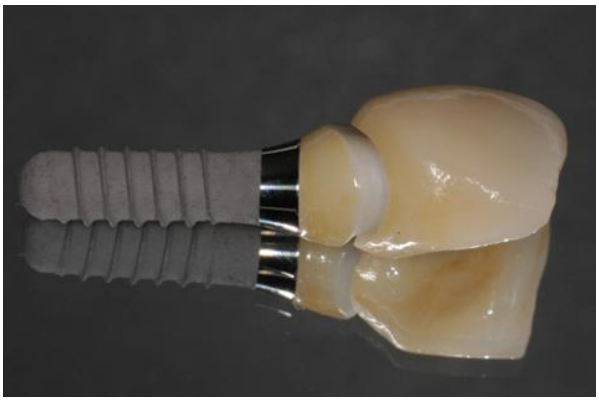


Fig. 54-39 Individualizing the CAD/CAM abutment in order to better match the color of the all-ceramic crown.

Customized abutments can be fabricated either by copy-milling techniques or by means of computer-guided (CAD/CAM) systems. For both manufacturing procedures, a resin or wax model of the desired abutment is designed on a master cast by the dental technician. This prospective abutment can be used as a guide to individually shape an ingot with a copy-milling machine (Glauser *et al.* 2004). In computer-aided manufacturing, these abutments can be scanned, digitized, and the data sent to a central production facility via the internet (Kucey & Fraser 2000). Today more and more customized CAD/CAM abutments are being virtually designed without previous fabrication of a pro-abutment.

This procedure allows many options for individualizing the abutment to the clinical situation. However, from a clinical and technical handling perspective, it is more time consuming and slightly more expensive compared to the manufacture of standardized prefabricated abutments. Therefore, in clinical situations with flat gingival morphologies, shallowly placed implants, and minor discrepancy between the cross-sections of the implant and tooth, standardized prefabricated abutments are the therapy of choice (Fig. 54-41). After the decision about a standardized prefabricated and customized abutment, it is important to choose the material of the abutment and the reconstruction.

Porcelain-fused-to-metal versus all-ceramic abutments

In the anterior zone of the upper jaw, the choice of abutment material is mainly influenced by the soft tissue architecture, the esthetic expectations of the patient, and the esthetic goal to be achieved with the reconstruction, that is the value and color of the neighboring teeth. The gray color of titanium abutments needs to be masked with metal–ceramic reconstructions. Due to refinements of the veneering ceramics for metallic frameworks, excellent esthetic results can be achieved with this kind of reconstructions. However, many authors have reported that the grayish color of

(a) (b)

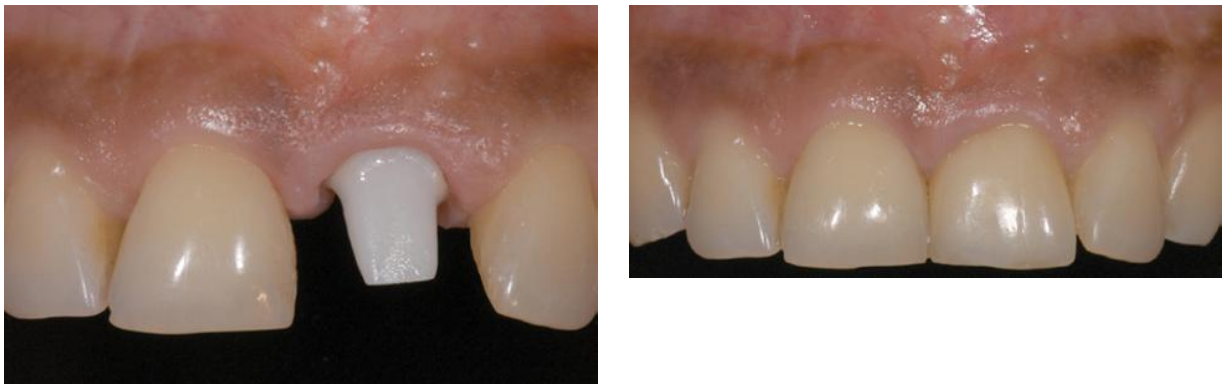


Fig. 54-40 (a) Customized zirconia abutment following the gingival morphology before cementing the all-ceramic crown. (b) Final clinical result after cementing the all-ceramic crown 21.

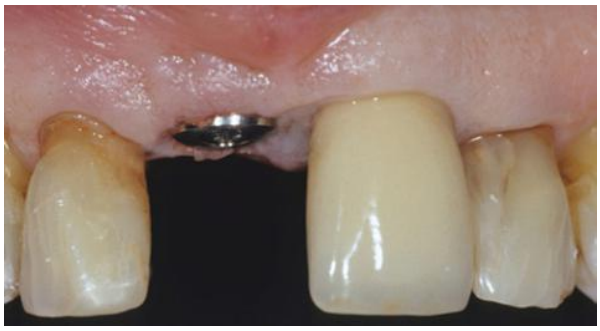


Fig. 54-41 Flat gingival morphology in an elderly patient where a standard abutment is indicated.

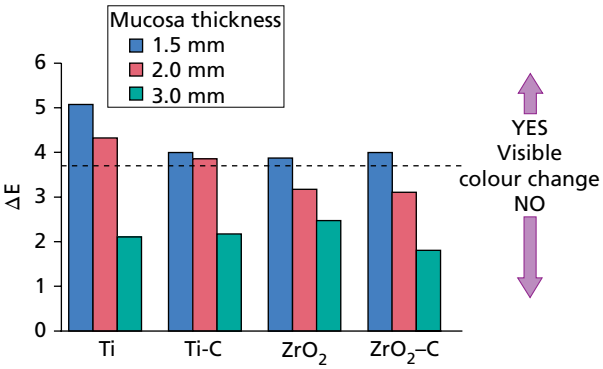


Fig. 54-42 Bar chart illustrating the ΔE values for the different materials evaluated under different mucosal thicknesses. The line at ΔE = 3.7 represents the critical ΔE threshold for intraoral color distinction as perceived by the naked eye. (Ti, titanium; Ti-C, veneered titanium; ZrO_2, zirconia; ZrO_2-C, veneered zirconia.)

the abutments impairs the esthetic result due to a discoloration of the peri-implant soft tissues (McCartney *et al.* 1993; Sadoun & Perelmuter 1997; Yildirim *et al.* 2000; Henriksson & Jemt 2003). It is often reported that ceramic abutments are esthetically advantageous as their color is similar to that of natural teeth. Different clinical and preclinical studies have been performed to evaluate the color change effect of all-ceramic restorations compared to PFM restorations on the marginal peri-implant soft tissue (Jung *et al.* 2008). In a randomized controlled clinical trial, 30 patients were divided into two groups of 15 subjects each. The all-ceramic group received all-ceramic crowns on Al_2O_3-based abutments, while the PFM group received PFM crowns on titanium or gold abutments (Jung *et al.* 2008). A reflectance spectrophotometer was used to measure the color difference between the mid-facial peri-implant mucosa after insertion of the restoration and that of the gingival margin of the corresponding neighboring tooth. It was demonstrated that all-ceramic restorations revealed a significantly better color match compared to the unrestored teeth than PFM restorations. It was also shown that increasing the thickness of the soft tissue by using connective tissue grafts reduced the risk for soft tissue discoloration independent of the reconstruction material. This is important clinical information; however, it would be of great interest to know the critical thickness of the mucosa that is needed to mask the grayish color of titanium abutments.

In order to evaluate this critical thickness, an *in vitro* study analyzed the influence of mucosal thickness on color changes caused by different abutment materials: titanium, veneered titanium, zirconia, and veneered zirconia (Jung *et al.* 2007). It was demonstrated that all restorative materials induced an overall color change, which decreased with increase in soft-tissue thickness. Titanium induced the most pronounced color change of all materials tested. Zirconia, however, did not induce a visible color change at mucosal thicknesses of 2 and 3 mm, irrespective of whether or not it had been veneered. The human eye could not distinguish a color change for any test specimen at a mucosal thickness of 3 mm. It can, therefore, be concluded that 2 mm is the critical mucosal thickness and the following clinical recommendations might be given: (1) with a mucosal thickness of >2–3 mm, PFM or all-ceramic reconstructions can be recommended, and (2) with a thin gingiva of ≤2 mm, either a soft tissue graft or an all-ceramic reconstruction is indicated (Jung *et al.* 2007; Fig 54-42).

In addition to the esthetic evaluation, the decision whether or not to use an all-ceramic or a metal abutment should also be based on the clinical performance and the mechanical properties. A recent systematic review of the performance of ceramic and metal implant abutments supporting fixed implant reconstructions included a total of 29 clinical studies (Sailer *et al.* 2009). The estimated 5-year failure rates for ceramic and metal abutments appeared to be similar, with no evidence for differences in the technical and biologic outcomes of ceramic and metal abutments. However, for ceramic abutments, only a limited number of studies and abutments were analyzed, and the follow-up time was also limited.

Esthetic failures

All treatment modalities in any dentoalveolar segment that are visible upon full smile and which include the placement of one or more implants, must be classified as an advanced or even complex procedure. For that reason, esthetic failures do occur, most often due to the lack of proper preoperative planning. Compared to conventional approaches with crowns on teeth, the risk for buccal soft tissue dehiscences is more pronounced around implant-supported reconstructions (Bengazi *et al.* 1996; Oates *et al.* 2002; Zigdon & Machtei 2008) and these are the major cause of adverse esthetic effects at implant sites. Follow-up studies document that most of the soft tissue changes happen within the first 6 months after prosthetic loading (Bengazi *et al.* 1996; Schropp *et al.* 2003; Cosyn *et al.* 2012; Pieri *et al.* 2013). Another frequently observed esthetic impairment is the lack of papillary-like structures between tooth and implant or between two implants (Schropp *et al.* 2005; Chow & Wang 2010;

Chang *et al*. 2012; Perez *et al*. 2012). Regarding this aspect, the esthetic appearance seems to improve over time, mainly dependent on the attachment level of the adjacent teeth (Finne *et al.* 2012). The lack of papillae not only influences the patient's satisfaction with the esthetic appearance, but also his/her phonetic speech (Suphanantachat *et al*. 2012).

Only one case report (Hidaka & Ueno 2012) and two prospective studies have been published regarding the treatment of such complications (Burkhardt *et al*. 2008a; Zucchelli *et al*. 2012). The results clearly indicate the difficulty in classifying soft tissue defects around implants in order to give a reliable prognosis for the treatment outcome.

Classification of esthetic failures

A classification of soft tissue inadequacies around implants should allow the severity of the lesion to be diagnosed and the prognosis of the treatment evaluated. Murphy (1997) has described the desirable characteristics of such a classification of defects. It should be (1) useful, (2) exhaustive, (3) disjointed (no particular case should fall into more than one class), and (4) simple. It is obvious that many local factors influence the therapeutic outcome of surgical retreatments: hard and soft tissue characteristics (e.g. volume, thickness, surface textures, scar formations), vertical and horizontal position of the implant, neighboring structures (tooth/implant), and presence or absence of inflammation. As a consequence, the prediction of a certain result is a complex process that should consider data from reliable studies and cannot be drawn from theoretical considerations. Additionally, other recognized patient- and technique-related prognostic factors and the operator's skill can decisively influence the outcome and make a relevant classification system almost impossible.

Nevertheless, based on our personal experience, some guidelines can be given. Before planning to surgically rebuild the architecture of the soft tissues in the anterior upper jaw for esthetic reasons, the tissues should be free from mucositis and/or peri-implantitis and the patient must be compliant. Thus, first interventions might aim to eliminate inflammatory reactions and improve the soft tissue conditions. Once the conditions are favorable for a further intervention, the surgical limits should be well balanced with the patient's wishes and expectations. Depending on the above-mentioned variables, good results can be achieved concerning the coverage of buccal mucosal dehiscences, while the anatomic prerequisites of the approximal soft tissues do not allow a prognosis which justifies a surgical intervention to augment the volume of these structures. In a prospective cohort study (Burkhardt *et al*. 2008a), ten consecutively treated patients each with one buccal soft tissue dehiscence at an implant site were evaluated postoperatively concerning the amount of coverage up to 6 months. A substantial amount of soft tissue coverage was achieved immediately following the intervention (coronally advanced flap combined with a connective tissue graft), with a mean percentage coverage of 99.3%. After 3 months of healing, however, a clinically and statistically significant soft tissue shrinkage was noted at each treated site, which continued for up to 6 months, at which time the mean coverage was 66%.

In another study, 20 patients each with a single soft tissue dehiscence in the zone of esthetic importance were enrolled (Zucchelli *et al.* 2012). The treatment consisted of crown removal, preparation of the underlying abutment, a coronally advanced flap combined with a connective tissue graft, and placement of a new reconstruction. One year after treatment, the mean coverage of the previously denuded implant areas was still 96.3%, and 75% of the treated cases showed complete coverage of the defects. These results are promising, but we must not ignore the fact that the preoperative defect characteristics in this patient cohort were not ideal for coverage. Additionally, the prosthetic crowns had been rebuilt, which further increased the treatment effort and costs.

The CEJ to height of the interdental papillae dimension has been demonstrated to influence the outcome of recession coverage around teeth (Zucchelli *et al*. 2006). It is obvious that this dimension cannot directly be extrapolated to the implant site as the level of the CEJ can only be approximated from the contralateral teeth if these are present and have not undergone any restoration at all. In order to estimate the result of mucosal defect coverage at implant sites, the prospective level of the CEJ has to be related to the height of the papillary structure and bony support mesial and distal of the dehiscence defect.

Recommendations for retreatment of esthetic failures

Based on the above-mentioned criteria, it can be concluded that in cases with a flattened or even no papillary morphology, the prognosis for a surgical treatment to improve the soft tissue appearance is poor, and the treatment modalities must focus on prosthetic adjustments only or placement of an epithesis to mask the defect (Fig. 54-43).

In situations with favorable conditions regarding coverage of the dehiscence defect, a surgical approach can be considered (Fig. 54-44). Basically, the combined approach of a coronally advanced flap with an underlying connective tissue graft seems to stabilize the wound and provides a better prognosis.

A bucco-oral position of implants has been shown to be one of the main reasons for post-prosthetic soft tissue shrinkage at implant sites (Evans & Chen 2008). If the implant has been placed in a too labial position, beyond an imaginary tangent drawn between the buccal CEJ of the adjacent teeth, a dehiscence coverage alone would not change the causative factors and the result later on would be a similar

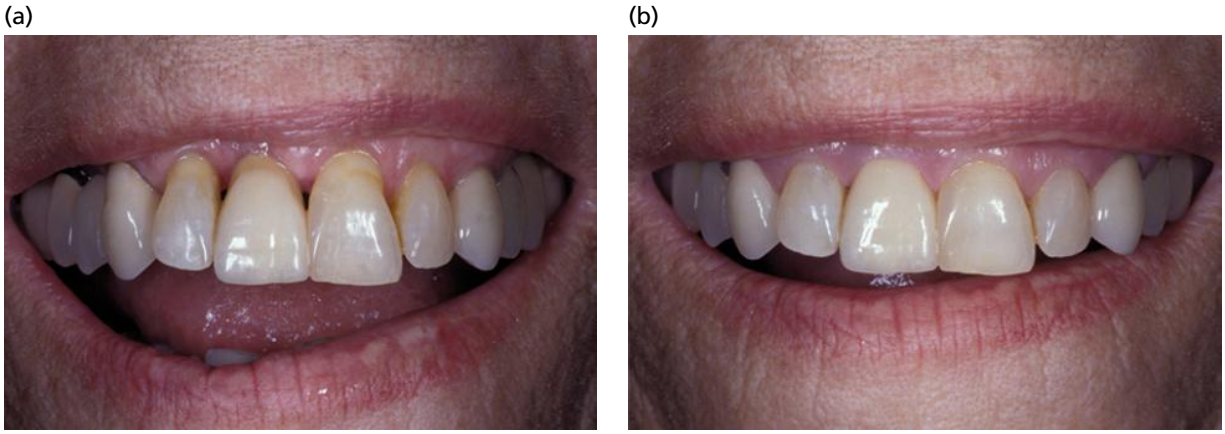


Fig. 54-43 (a) Implant-supported crown with open triangles between the crowns. (b) Correction of such an impairment cannot be achieved with a surgical intervention. An epithesis made of silicon improved the esthetic appearance.

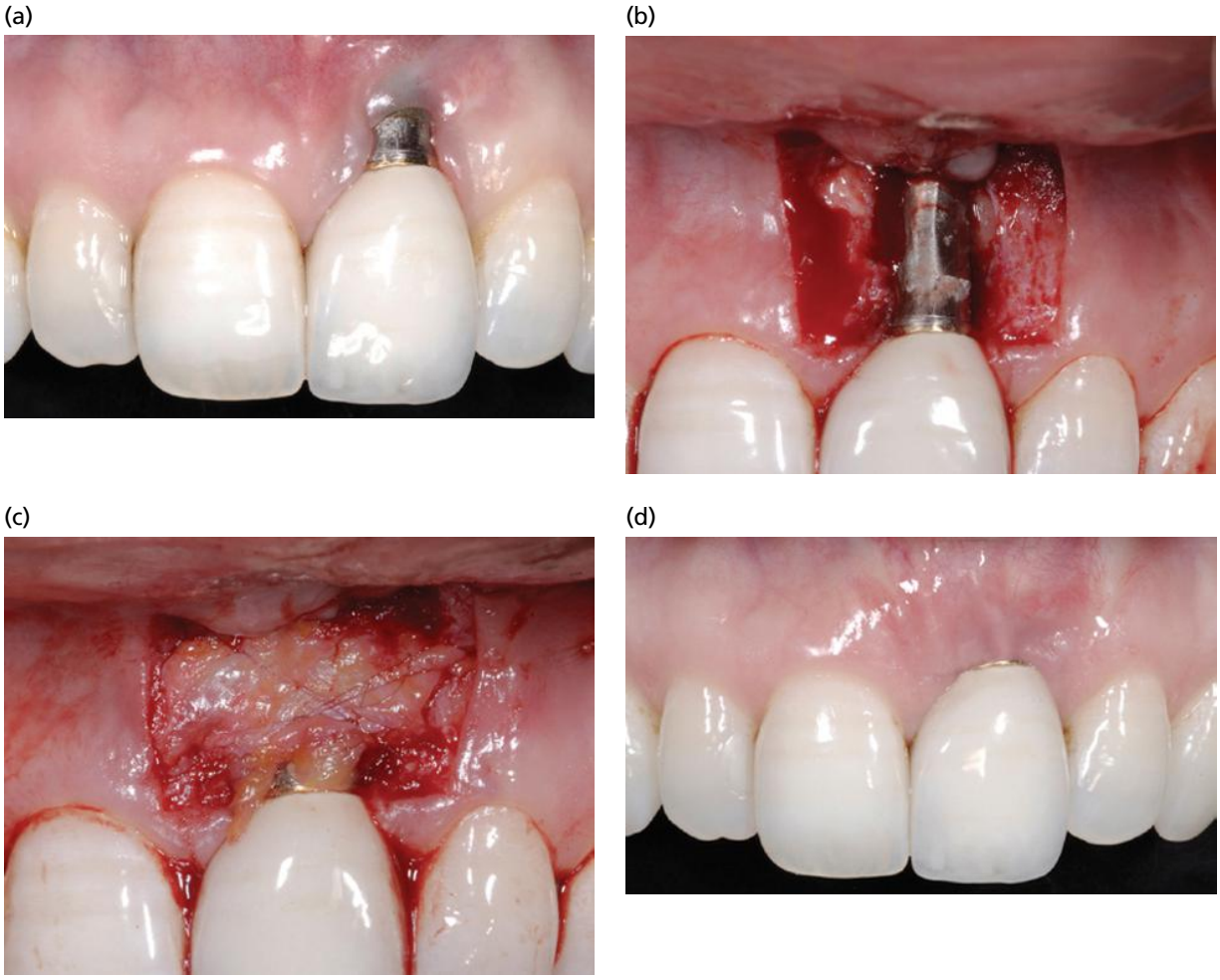


Fig. 54-44 (a) Buccally placed implant covered by a thin mucosa, resulting in a soft tissue dehiscence. (b) To augment the keratinized mucosa, a double pedicle papilla flap was prepared after smoothing out the implant surface. (c) For thickening the marginal mucosa, a connective tissue graft was placed underneath the flap. (d) Almost complete coverage of the mucosal dehiscence could be achieved combined with a functional improvement (mucosal thickening).

situation. In such circumstances, the soft tissues have to be augmented and in most cases a new reconstruction is indicated. To facilitate the surgical procedure and improve the prognosis, the implant has to be resubmerged (Fig. 54-45).

In cases with a completely malpositioned implant, the only promising solution is removal of the implant. However, this treatment option has to be carefully evaluated as the removal of a fully osseointegrated implant is a demanding surgical procedure that carries the potential risk of further impairment of the esthetic result. Furthermore, the reconstruction in such a situation is often time consuming as it requires several treatment steps

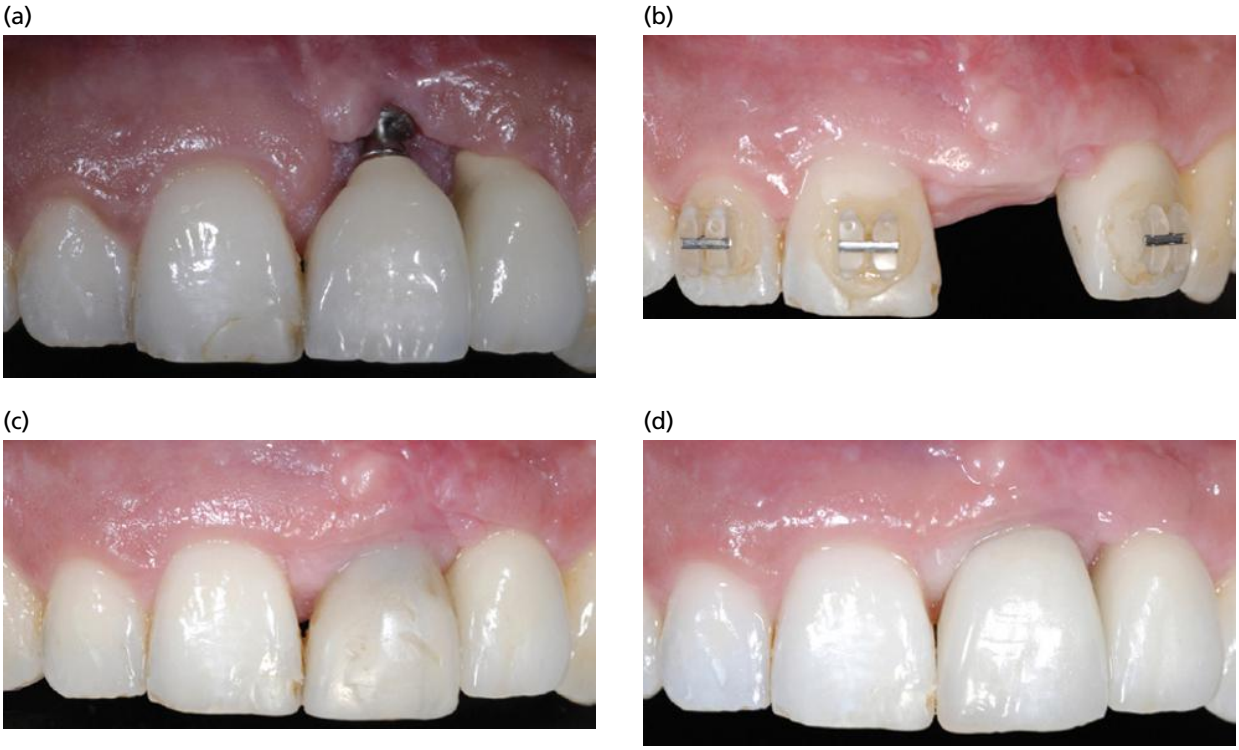


Fig. 54-45 (a) Status a few years after the accident with loss of central and lateral incisors and subsequent implant reconstruction of the missing teeth. Note the scar formation and mucosal dehiscence around the implant-supported crown 21. (b) Implant has been resubmerged and primarily covered by a palatally-pedicled flap and two connective tissue grafts underneath. (c) Three months after healing, the abutment connection was performed and a provisional crown was placed. This crown was left *in situ* for >1 year. (d) Final crown was completely custom-made and fabricated to compensate for the buccal implant position. The soft tissue margin remained stable over the following years.

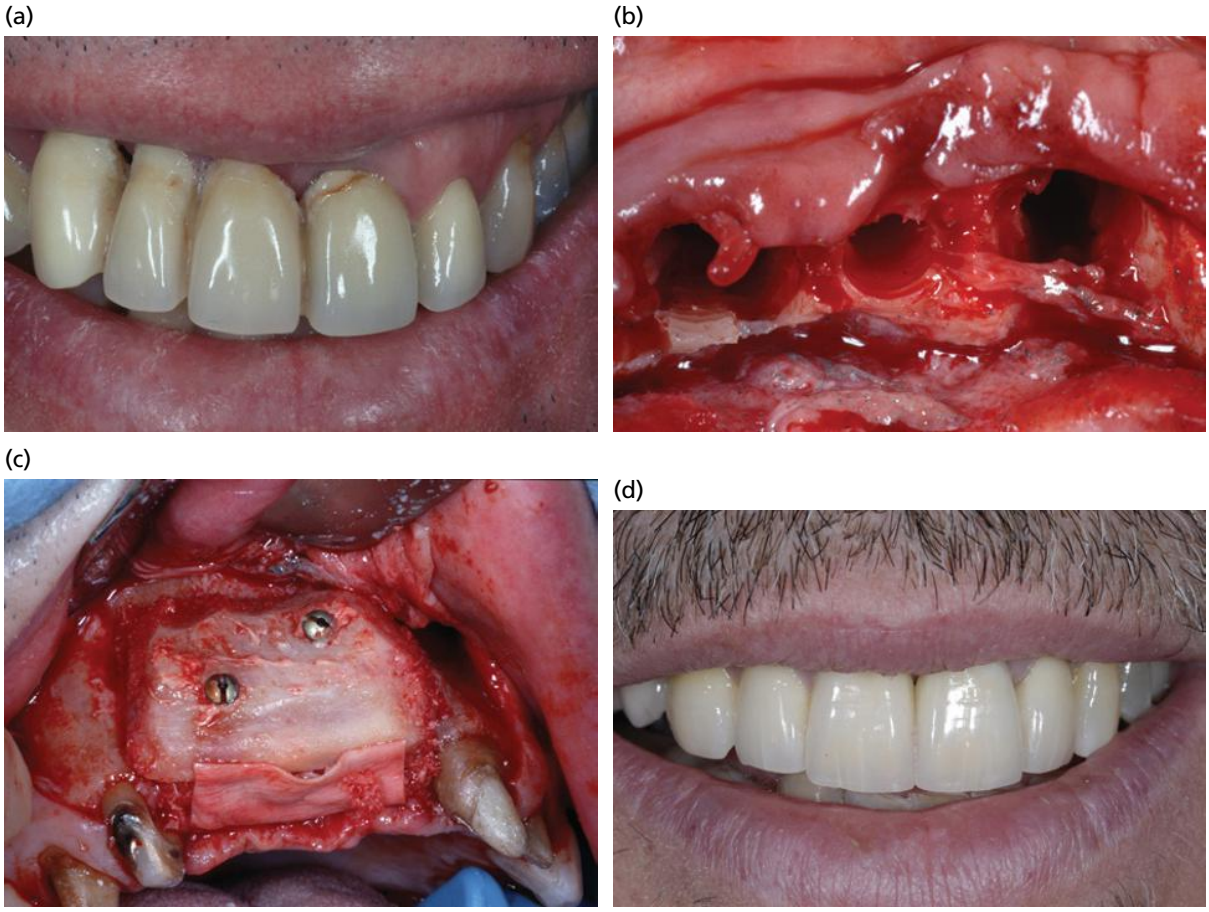


Fig. 54-46 (a) Case of malpositioned implants in the areas 13, 12 and 11, placed far too apically. (b) Fully osseointegrated implants (machined surfaces) could be unscrewed. (c) Extended bone augmentation compensated for the vertical and horizontal volume deficiency. (d) Several additional soft tissue augmentations were indicated to increase the tissue volume of the papilla-like structures with a natural appearance.

(Fig. 54-46) and is costly for the patient. To date, there are no reliable recommendations in the literature for how to remove an implant without causing a substantial amount of bone loss. It can be speculated that an implant with a modern rough surface cannot just be unscrewed by applying a reverse torque. The force required to remove a short implant with a rough surface is >100 Ncm and increases with increasing implant length. In contrast, the required reverse torque to unscrew a fully osseointegrated implant with a machined surface has been measured to be in the range of 35 Ncm and it is not proportional to the implant length (Bernard *et al*. 2003). Applying torque forces >100 Ncm on an implant risks breaking the alveolar structure.

Based on the proverb "a stitch in the time saves nine", it must be emphasized that the surgical correction of esthetic complications is a demanding intervention in most respects and to date, there are no generally recommended treatment options in the literature offering a good prognosis based on literature data. Thus, the clinician's attention should be directed to the alternative treatment modalities before choosing an implant-supported reconstruction. This would help to prevent severe esthetic failures.

Concluding remarks and perspectives

Within the last two decades the concepts and therapeutic modalities have been developed to solve most of the problems of partial edentulism in the zone of esthetic priority. Additionally, the majority of these concepts have been proven in the published literature data and the decisive risk factors are well known.

Nevertheless, each implant-based restoration in a zone which is visible upon full smile, requires special attention and represents a demanding procedure even if the prerequisites for a good outcome appear to be fulfilled at first glance. As implant placement is a non-reversible act, careful presurgical planning is mandatory and special attention must be paid to the alternative options with all their benefits and side effects. It is a duty of clinicians to make sure that patients have understood the planned treatment solution, including the risks this carries for a possible adverse esthetic outcome.

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Chapter 55

Implants in the Posterior Dentition

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Introduction

The overall favorable long-term survival and success rates reported in the literature for osseointegrated implants in the treatment of various types of edentulism (Brånemark *et al.* 1995; Jemt *et al.* 1996; Lindquist *et al.* 1996; Buser *et al.* 1997; Andersson *et al.* 1998a; Buser *et al.* 1998a; Eckert & Wollan 1998; Lindh *et al.* 1998; Mericske-Stern 1998; ten Bruggenkate *et al.* 1998; Wyatt & Zarb 1998; Gunne *et al.* 1999; Lekholm *et al.* 1999; Van Steenberghe *et al.* 1999; Wismeijer *et al.* 1999; Behneke *et al.* 2000; Hosny *et al.* 2000; Hultin *et al.* 2000; Weber *et al.* 2000; Boioli *et al.* 2001; Gomez-Roman *et al.* 2001; Kiener *et al.* 2001; Mengel *et al.* 2001; Oetterli *et al.* 2001; Zitzmann *et al.* 2001; Bernard & Belser 2002; Buser *et al.* 2002; Haas *et al.* 2002; Leonhardt *et al.* 2002; Romeo *et al.* 2002; Esposito *et al.* 2009; Bragger *et al.* 2011) permit consideration of dental implants as one of the reliable therapeutic modalities during the establishment of any prosthetic treatment plan. In numerous clinical situations, implants can clearly contribute to a notable simplification of therapy, frequently enabling removable prostheses to be avoided, keeping it less invasive with respect to remaining tooth structure, or rendering the treatment both more elegant and versatile as well as more predictable (Belser *et al.* 2000).

Beyond any doubt, the advent of osseointegration has had a fundamental impact on the therapeutic approach and strategies implemented today in the field of prosthetic rehabilitation of the compromised posterior dentition. The implant statistics of the University of Geneva School of Dental Medicine, for example, reveal that from April 1989 until December 2011 > 8700 implants of 6–12 mm in length were

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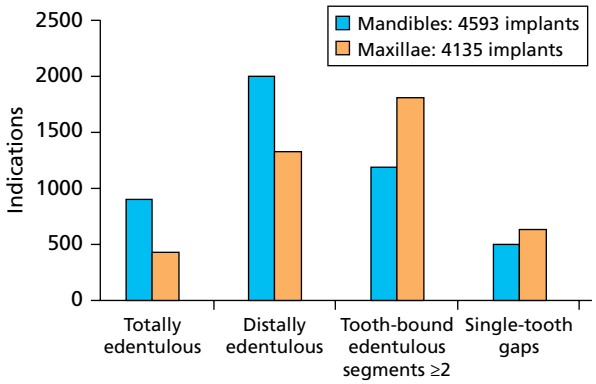

Fig. 55-1 Implant statistics from the University of Geneva, 1989–2011: Indications.

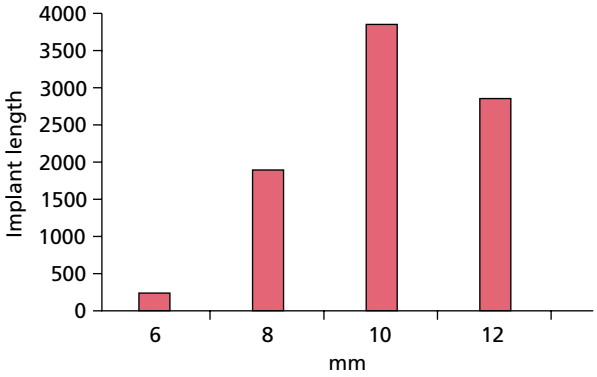

Fig. 55-2 Implant statistics from the University of Geneva, 1989–2011: Implant length distribution.

inserted in about 3250 patients presenting with different types of edentulism (Figs. 55-1, 55-2). This treatment modality is increasingly applied worldwide and has had a tremendous influence on traditional prosthodontic attitudes (Beumer *et al.* 1993; Zarb & Schmitt 1995; Tarnow *et al.* 1997; Zitzmann & Marinello 1999; Belser *et al.* 2000; Schwartz-Arad & Dolev 2000; Bragger *et al.* 2001; Deporter *et al.* 2001; Zitzmann & Marinello 2002). Since most of the established dental implant systems today comprise a wide range of mostly screw-type implants with different diameters and dimensions to replace missing premolars and molars (Fig. 55-3), the versatility of implant therapy in the load-carrying part of the dentition of partially edentulous patients has been significantly enhanced. As part of a textbook focusing essentially on clinical periodontology, this chapter addresses implant therapy performed in the posterior segments of partially dentate patients. In this context, the use of implants may often significantly reduce the inherent risk of "borderline" conventional tooth-borne fixed dental prostheses (FDPs) (e.g. prostheses based on compromised abutment teeth, long-span FDPs, cantilevers) by implementing the principle of segmentation. It is currently widely accepted that – in comparison with extended splinted prosthetic segments – small ones are preferable as they are easier to fabricate, generally provide improved "passive fit" and marginal fidelity, offer better access for the patient's oral hygiene, and

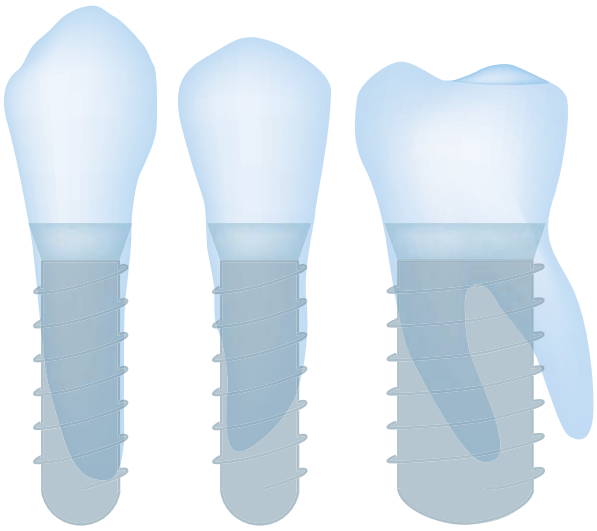

Fig. 55-3 Different implant diameters are available for the replacement of posterior teeth.

ultimately are less complicated to handle where there is need for re-intervention.

It is the aim of this chapter to present clinically-oriented guidelines and procedures for implant therapy of various types of edentulism located in the load-carrying part of the dentition, addressing the partially dentate patient and focusing on implant-supported FDPs.

Indications for implants in the posterior dentition

When it comes to partial edentulism in the posterior segments of the jaws, implants are increasingly used either to preserve sound mineralized tooth structure or to avoid partial removable dental prostheses (RDPs) and high-risk conventional FDPs. This includes situations with missing teeth in otherwise intact dentitions (Fig. 55-4), the distally shortened dental arch (Fig. 55-5), extended edentulous segments, missing "strategic" tooth abutments, and structurally, endodontically or periodontally compromised potential abutment teeth (Table 55-1).

Numerous other indications have been added to the so-called classical indications for the use of implants – severely atrophied edentulous jaws, missing teeth in otherwise intact dentitions (congenitally missing tooth/teeth loss due to trauma or to a localized endodontic/restorative/periodontal complication or failure), and the distally shortened dental arch (particularly when premolars are missing). Among these other indications, one should also mention all the strategies aimed at either reducing the prosthodontic risk in general or rendering the treatment simpler and more cost-effective. Virtually no limits on the placement of implants seem to exist any more owing, for example, to advanced bone augmentation techniques, comprising anterior sinus floor elevation and distraction osteogenesis (Buser *et al.* 1993, 1995, 1996, 1998b; Chiapasco *et al.* 1999; Buser & von Arx

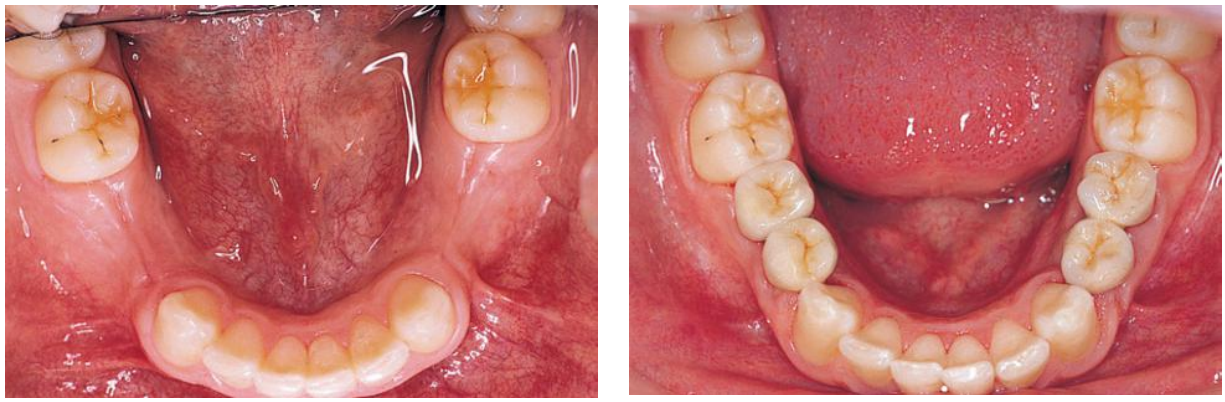

Fig. 55-4 (a) Occlusal view of the mandible of a 22-year-old male patient. All premolars are congenitally missing; the remainder of the dentition is intact. (b) Final view after insertion of four implants, restored with cemented metal–ceramic suprastructures.

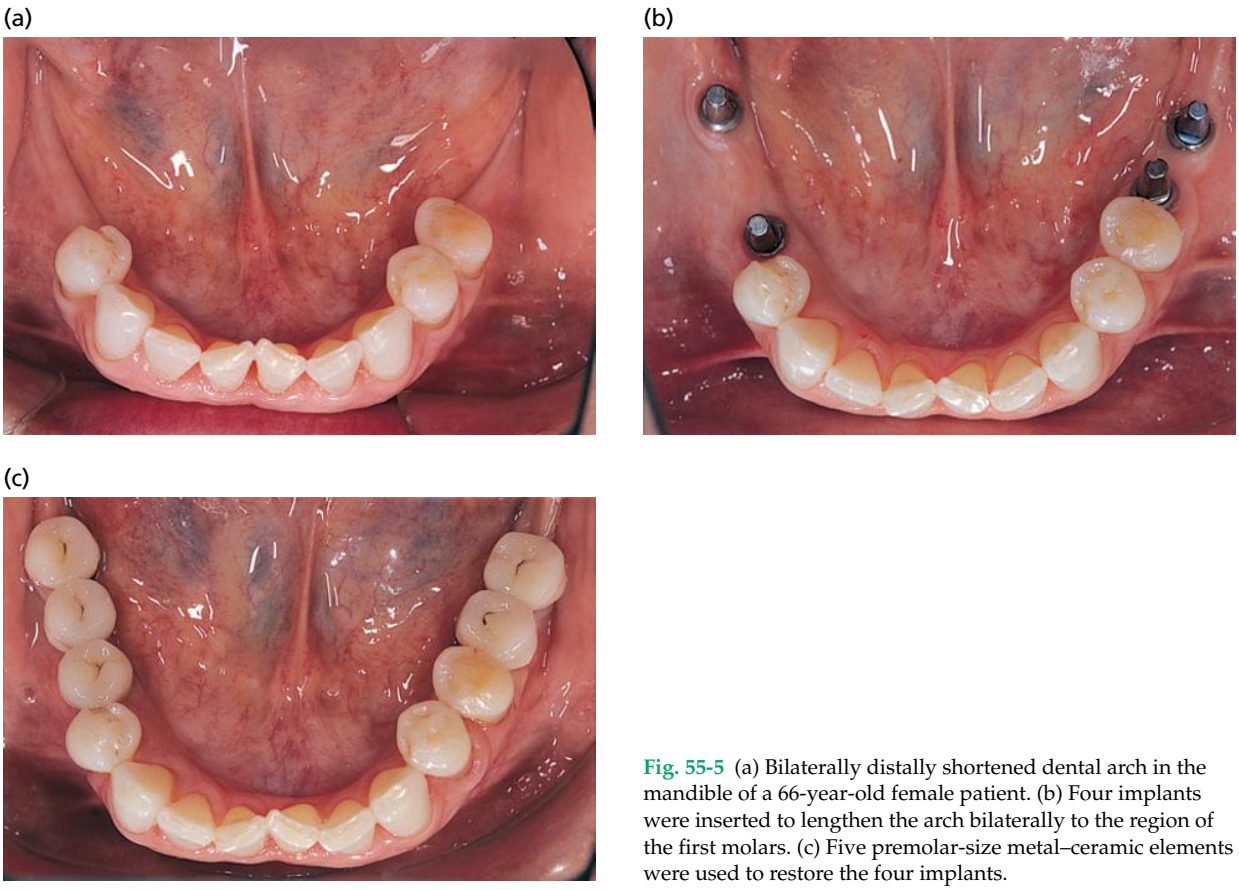

Fig. 55-5 (a) Bilaterally distally shortened dental arch in the mandible of a 66-year-old female patient. (b) Four implants were inserted to lengthen the arch bilaterally to the region of the first molars. (c) Five premolar-size metal–ceramic elements were used to restore the four implants.

Table 55-1 Indications for posterior implants.

- Replacement of missing teeth in intact dentitions (e.g. congenitally missing premolars), that is preservation of tooth structure
- Avoidance of removable partial dentures (RDPs)
- Increase of the number of abutments:
  - Reduction of the prosthetic risk
  - Application of the principle of segmenting
  - Ease of eventual re-interventions
- Maintenance of pre-existing crowns and fixed dental prostheses (FDPs)
- Following prosthetic complications and failures

2000; Chiapasco *et al.* 2001; Simion *et al.* 2001; von Arx *et al.* 2001a, b; Buser *et al.* 2002).

The rapid advance in terms of the broad utilization of dental implants is not exclusively based on the associated favorable long-term reports for this treatment modality. Other parameters such as purely "mechanical" advantages and the availability of prefabricated components and auxiliary parts, which in turn contribute notably to the simplification of the treatment, also have had a significant impact on current concepts and strategies (Table 55-2). Furthermore, clinical decision-making based on

Table 55-2 Impact of dental implants related to the treatment of posterior partial edentulism.

- Favorable overall long-term results
- Preservation of mineralized tooth structure
- "Mechanical" advantages:
  - Commercially pure (c.p.) titanium (biocompatibility, mechanical properties, no risk for caries)
  - Reproducible, prefabricated ("machined") primary, secondary, and tertiary components and auxiliary parts
- Simplified clinical and laboratory protocols

Table 55-3 "High-risk" conventional fixed partial dentures.

- Long-span fixed partial bridges
- Cantilever units (mainly distal extensions)
- Missing "strategic" tooth abutments
- Structurally-/periodontally-/endodontically-compromised tooth abutments
- Reduced interarch distance
- Presence of occlusal parafunctions/bruxism

Table 55-4 Controversial issues related to posterior implant restorations.

- Adequate number, size (length/diameter), design, and distribution of implants
- Cemented versus screw-retained (transocclusal/transverse screw retention)
- Single units versus splinted adjacent implant restorations
- Longest possible versus shorter implants
- Impact of implant axis
- Optimal implant shoulder sink depth
- Minimum ratio between implant length and suprastructure height
- Combination of natural teeth and implants in the same restoration
- Design of the optimal abutment-to-implant connection
- Implant-specific occlusal concepts, including occluding restorative materials, non-axial loading, type of guidance during mandibular excursions
- Healing times prior to functional loading (immediate/early/delayed)
- Significance of offset/staggered implant positioning

prosthetically-oriented risk assessment (Table 55-3) frequently leads to the need for an increased number of abutments. The objective is to reduce the overall risk associated with a given prosthetic solution on the one hand, and to implement the principle of segmenting on the other.

Controversial issues

Despite the ever-growing body of scientific evidence indicating that implant therapy in the partially edentulous patient is an overall highly predictable treatment modality, several conceptual issues remain controversial (Table 55-4). These controversial issues include open questions addressing adequate number, size, and distribution of implants for optimal therapy of a given type and configuration of partial edentulism, as well as parameters related to occlusion and occlusal materials, to implant axis, to the minimal acceptable ratio between suprastructure height and implant length, and – last but not least – to questions focusing more specifically on the mechanical aspects and requirements of posterior implant prosthodontics. Among these, the kinds of connection between implant and abutment in particular have to be mentioned. Most of these questions will be discussed in the remainder of this chapter, at length where possible and appropriate, or more superficially where solid information is missing or where the topic is more adequately covered by other authors of this textbook.

General considerations and decision-making for implants in the posterior dentition

Decision-making between implant-supported reconstruction and tooth-supported fixed dental prostheses

When it comes to the decision-making process between implant-supported reconstruction and tooth-supported FDPs, the related decision criteria should be derived essentially from scientific evidence and objective prosthetically-oriented risk assessments, as well as patient-related factors, including cost effectiveness and quality of life.

In the clinical situation of a hopeless tooth in the posterior dentition, the therapeutic options are a conventional bridge or an implant-supported single crown (Fig. 55-6). In terms of a hierarchy of decisions, the most important question is whether or not the prognosis of an implant-supported reconstruction is similar to that of a tooth-supported FDP. A systematic review of implant-supported single crowns reported an estimated survival rate of 96.8% after 5 years and 89.8% after 10 years (Jung *et al.* 2008). These results were similar to the data reported for tooth-supported FDPs, revealing a survival rate of 93.8% after 5 years and of 89.1% after 10 years (Pjetursson *et al.* 2004). From a prognosis point of view, neither of the two treatment modalities appears to be superior to the other. However, it has to be considered that the type of complications seems to be different with each modality. Conventional tooth-supported bridges reveal more biologic complications like caries and loss of abutment vitality, whereas implant-supported single crowns show more technical complications like abutment or occlusal screw loosening. This has an impact on the severity and the invasiveness of the therapeutic intervention during the maintenance phase.

At the next level in the hierarchy for the decision-making process is the clinical assessment and the patient's expectations. The clinical analysis comprises the comprehensive evaluation of the

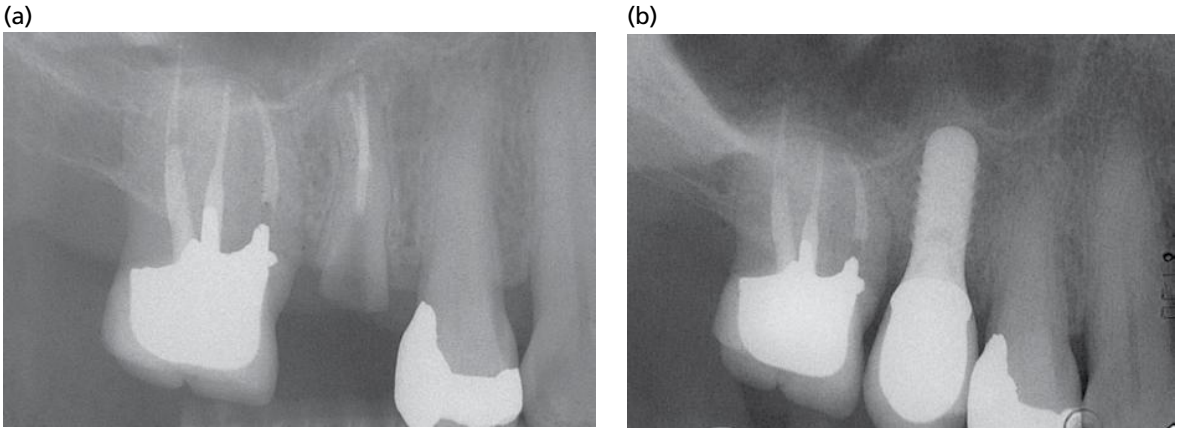

Fig. 55-6 (a) *Ad hoc* radiograph of the upper right posterior sextant. Note the presence of a structurally greatly compromised second premolar with a periapical pathology. Based on the clinical and radiographic assessment, tooth 15 was considered hopeless. (b) Postoperative radiograph shows that the root of the second premolar was replaced by a single-tooth implant restoration. In particular, the pre-existing metal–ceramic crown on the first molar could be maintained with this approach.

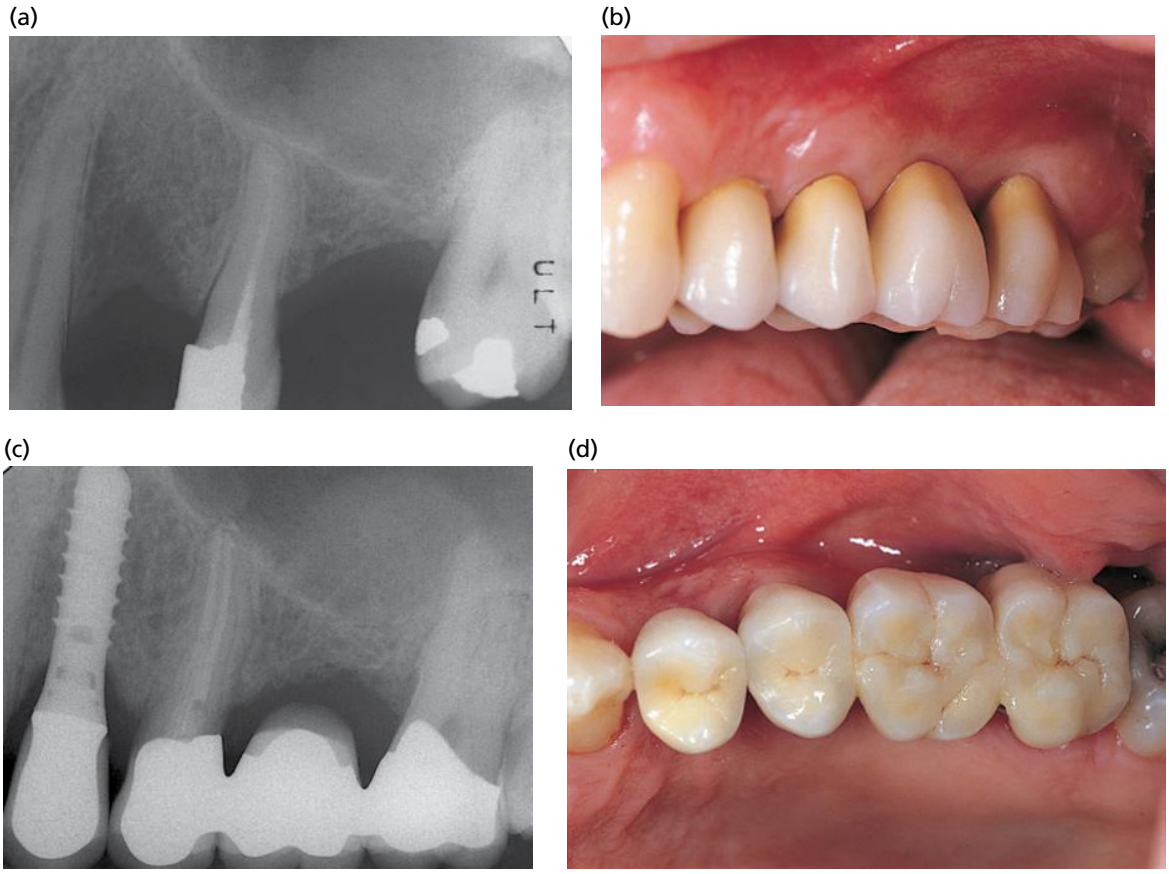

Fig. 55-7 (a) Preoperative radiograph of the left maxilla, revealing two missing dental elements. Note in particular an intact canine, a structurally reduced second premolar, and an extended recessus of the sinus in the area of the missing first molar. (b) Vestibular view of the prosthetic rehabilitation of the maxillary left quadrant: an implant-supported single-tooth restoration on the site of the first premolar, and a three-unit tooth-borne FDP to replace the missing first molar. (c) Postoperative radiograph documents that an endodontic revision has been performed on the second premolar prior to its restoration with an adhesive carbon-fiber, post-based build-up and a metal–ceramic crown. (d) An identical prosthetic design has been applied for both the implant-supported and the tooth-supported restoration.

neighboring natural abutment teeth, including their structural, restorative, periodontal, and endodontic status. This objective evaluation is of primary importance and represents an ever increasing challenge to the clinician. This is illustrated by a maxillary posterior segment where both the first premolar and the first molar were missing (Fig. 55-7). The insertion of a five-unit tooth-borne FDP was considered too invasive given the intact canine, and also not suitable because of a slightly questionable status of

the endodontically-treated second premolar in view of its eventual use as a so-called "peer-abutment". Finally, an implant had been placed at the site of the missing first premolar and subsequently restored with a single-unit restoration. As the proximity of the maxillary sinus at the location of the missing first molar would have required a grafting procedure to make an implant installation possible, a three-unit tooth-supported FPD was ultimately chosen, after having duly discussed the relevant advantages and shortcomings with the patient. Having attributed a "strategic value" to the moderately compromised second premolar by using it as an abutment for a short-span bridge, there was still a difficulty in consistently establishing clinical treatment plans that were fully based on scientific evidence.

Finally, the patient's expectations and requests are very important in the decision-making process. Besides the prognosis and the invasiveness of the reconstruction, the patient will want to know the cost difference and the treatment time difference between implant-supported reconstructions and tooth-supported FDPs. In a retrospective clinical study performed in private practice, 37 patients received 41 conventional FDPs and 52 patients received 59 implant-supported single crowns (Bragger *et al.* 2005b). The aim was to assess and compare the economic aspects by recording the number of visits, chair-side time, treatment costs, and costs for implant components and laboratory work. It was reported that the implant treatment required more visits than FDP treatment; however, the total treatment time was similar. Regarding the costs, the laboratory costs and the total treatment costs were higher for FDPs than for implant-supported single crowns. Even when considering opportunity costs for each visit, the implant solution was less expensive. It was stated that over a short observation period of 1–4 years, the implant reconstruction demonstrated a more favorable cost-to-effectiveness ratio. Especially in clinical situations with either non- or minimally restored teeth and sufficient bone, the implant reconstruction is to be recommended from an economic point of view (Bragger *et al.* 2005a).

Conclusion: The decision-making process between implant-supported reconstruction and tooth-supported FDPs should be based on the prognosis and the complication rate, the clinical assessment of the neighboring teeth and the anatomic condition of the edentulous area, and the patient's expectations.

Implant restorations with cantilever units

There is strong evidence in the dental literature that cantilever units – in particular distal extensions – of conventional tooth-borne FDPs are associated with a significantly higher 10-year complication/failure rate when compared to FDPs featuring a mesial and a distal abutment and a central pontic (Pjetursson *et al.* 2004, 2007). Failures could be attributed to decisive factors such as non-vital abutment teeth as well as specific occlusal conditions such as a reduced interarch distance and/or occlusal parafunctions (Glantz & Nilner 1998). In a more recent prospective cohort study on partially dentate patients treated with implant-supported cantilever FDPs (Romeo *et al.* 2009), the authors reported highly favorable long-term success rates and concluded that the risk of mechanical failures was lower with cantilevered implant-borne reconstructions than with comparable conventional fixed situations. Risks, however, do exist. As loss of retention, one of the frequent complications encountered with conventional cantilevered prostheses, can easily be prevented with implant-supported restorations of this type, the latter seem to be a viable alternative in cases where the local alveolar bone crest conditions do not allow the insertion of an implant at the most favorable location (Wennström *et al.* 2004; Bragger *et al.* 2005a; Halg *et al.* 2008; Zurdo *et al.* 2009; Aglietta *et al.* 2012). In such situations, the clinician has to ponder whether a bone augmentation procedure (simultaneous or staged) can be objectively justified in order to allow the insertion of an implant at the optimal position, or if the risk for complications of a more simple, straightforward approach, that is implant insertion requiring a cantilever restoration, can be considered low. In this context, a recent study retrospectively compared posterior maxillary and mandibular implant-supported single crowns comprising a cantilever extension with posterior FDPs supported by two implants and similarly featuring a cantilever extension (Aglietta *et al.* 2012). No implant loss was registered in either group, yielding a 100% survival rate. Mean marginal bone levels and probing pocket depths were not statistically different between the groups at baseline and at the follow-up examination. The authors concluded that the presence of one mesial or distal cantilever extension in the posterior part of the jaws does not jeopardize either the survival or marginal bone levels of implants supporting single crowns or short-span FDP after an observation period of at least 5 years. From a treatment planning point of view, these data may permit consideration of short-span implant-supported FDPs as a valid treatment option for the replacement of missing posterior teeth that avoids the more complex surgical bone augmentation procedures that are necessary for placement of an implant in a traditionally optimal position from a prosthodontic point of view. Hence, one may speak of a minor change of paradigms. It has to be underlined in this context, however, that basic prosthodontic design principles, such as increased dimensions of the connectors, have to be respected to avoid mechanical complications.

The 16-year clinical and radiographic follow-up of a posterior mandibular three-unit FDP featuring a premolar-size mesial cantilever extension is shown in Fig. 55-8.

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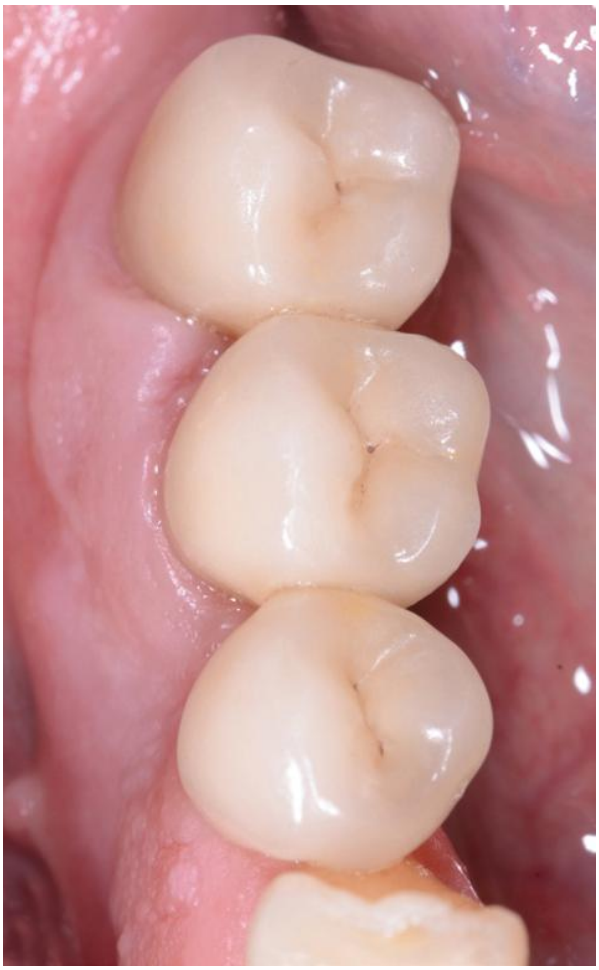

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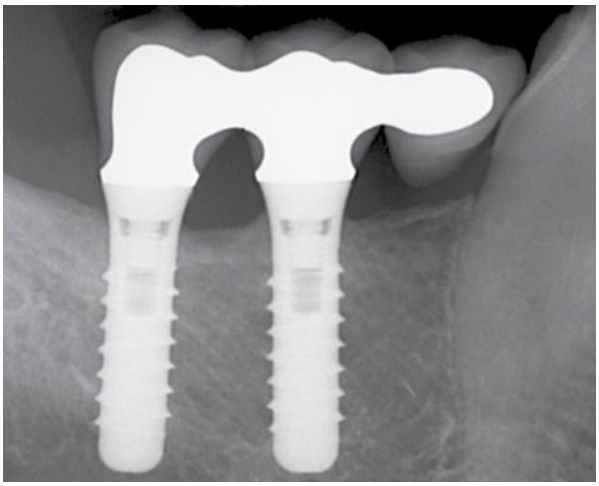
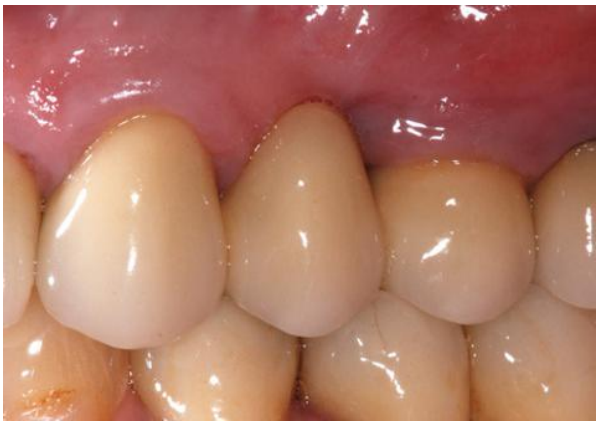


Fig. 55-8 16-year clinical follow-up of a posterior mandibular three-unit FDP featuring a premolar-size mesial cantilever extension. (b) Periapical radiograph of an FDP with mesial cantilever extension 16 years after insertion.

Combination of implant and natural tooth support

Combined tooth- and implant-supported FDPs are a treatment option in clinical situations where bone deficiencies only allow the placement of one implant

(a)



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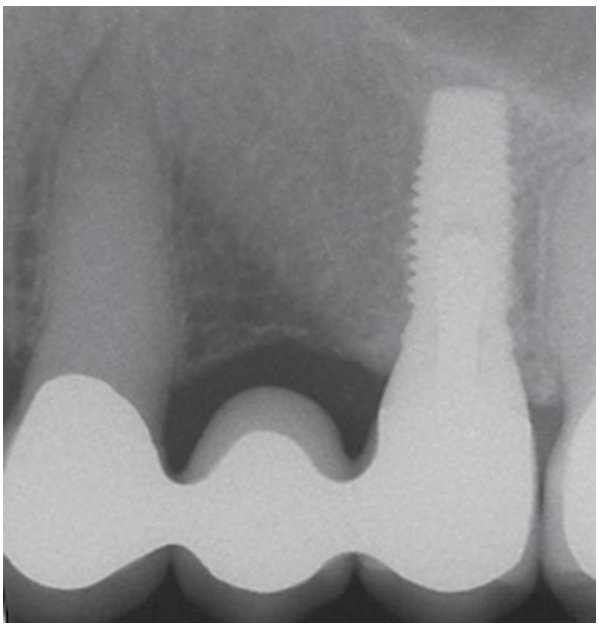


Fig. 55-9 (a) Clinical view and (b) radiograph of a combined tooth- and implant-supported FDP after 5 years of function. This therapy was chosen due to limited bone volume in the area of 24 in order to avoid horizontal bone augmentation procedure.

(e.g. posterior sites) or for patients with limited finances. The potential advantages of combined FDPs are lower patient morbidity and lower treatment cost (Fig. 55-9). From a biomechanical point of view, the splinting of teeth and implants is a challenge due to the different mobility of a tooth in comparison to an osseointegrated implant (Weinberg 1993). In order to overcome this problem, rigid and non-rigid connectors have been proposed. The effects of the two connection types have been analyzed with finite element analysis or other simulation models (Nishimura *et al.* 1999; Menicucci *et al.* 2002; Lin *et al.* 2008; Srinivasan & Padmanabhan 2008; Burak Ozcelik *et al.* 2011), and by means of *in vitro* (Rangert *et al.* 1991; Breeding *et al.* 1995) and *in vivo* (Naert *et al.* 2001a, b; Block *et al.* 2002; Nickenig *et al.* 2006, 2008) studies. The issue remains controversial, but overall it seems that the use of a rigid

connector results in a better clinical outcome (Chee & Mordohai 2010).

From a clinical perspective, the most important issue is the survival and complication rates of combined FDPs in comparison with FDPs supported by implants only. The survival rates of combined FDPs have been analyzed in a number of clinical studies (Gunne *et al.* 1999; Hosny *et al.* 2000; Kindberg *et al.* 2001; Lindh *et al.* 2001; Naert *et al.* 2001a; Block *et al.* 2002; Mau *et al.* 2002; Tangerud *et al.* 2002; Nickenig *et al.* 2006; Akca & Cehreli 2008; Nickenig *et al.* 2008; Bragger *et al.* 2011). Systematic reviews on combined FDPs reported a 5-year FDP survival rate of 90.1% (Lang *et al.* 2004) to 94.7% (Mamalis *et al.* 2012). At 10 years, the survival rates ranged from 77.8% (Mamalis *et al.* 2012) to 82.1% (Lang *et al.* 2004), which are significantly lower than the 10-year survival rates of FDPs supported by implants only (Pjetursson *et al.* 2004). An important factor leading to the loss of the combined FDPs was a relatively high rate of abutment tooth loss (10.6%) and implant loss (15.6%) (Lang *et al.* 2004). A particular biologic complication for combined FDPs is the intrusion of the abutment teeth, which was reported to occur in 5.2% of all teeth. Intrusion appears to be more frequent with the use of a non-rigid connection between teeth and implants (Block *et al.* 2002).

Conclusion: The indications for combined tooth- and implant-supported FDPs are limited due to their relatively low survival rates. If a combined FDP is to be inserted, a rigid connector should be chosen.

Splinted versus single-unit restorations of multiple adjacent posterior implants

In situations with multiple adjacent implants, the dentist faces the decision between fabricating either splinted or unsplinted implant crowns. The rationale for splinting implants is to evenly distribute loading forces on all the implants in order to minimize the stress on the marginal bone, implants, and prosthetic components. Dentists usually give the following reasons for splinting adjacent implants:

- Poor bone quality or major bone augmentation procedures (e.g. sinus floor elevation (Figs. 55-10, 55-11)
- Short implants or reduced diameter implants
- Anticipation of high occlusal forces (e.g. bruxism)
- Easier handling for the dentist (no adjustment of interproximal contacts is necessary).

The main arguments against splinting are:

- Perfect framework fit is more difficult to achieve with a multiunit FDP
- Interproximal hygiene is more demanding (if the use of interdental brushes or floss is hampered by the connector)

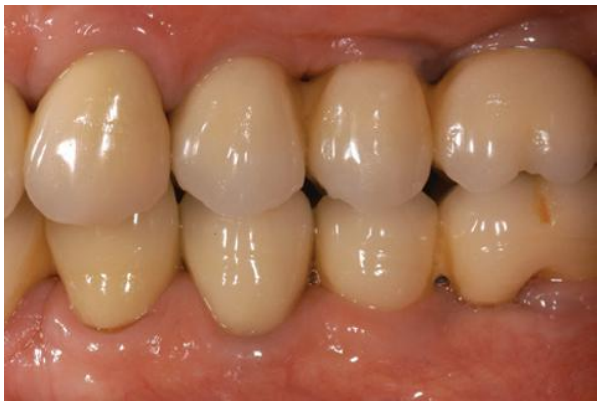


Fig. 55-10 Clinical image of a posterior reconstruction with splinted implants.

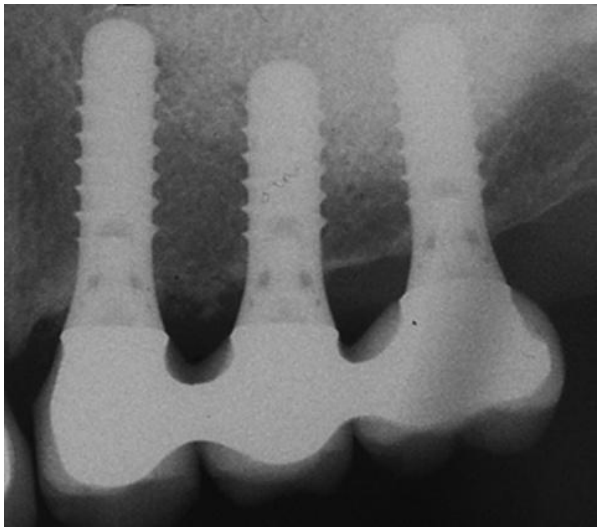


Fig. 55-11 Radiograph of three splinted implants placed after sinus floor elevation.

- Re-intervention is more complicated for multi- than single-unit FDPs (especially for cemented FDPs).

In the literature, the issue of splinting adjacent implants is controversial (Grossmann *et al.* 2005). *In vitro* studies measured the stress resulting from non-axial forces in splinted and unsplinted restorations at two different points: at the implants and in the marginal bone. Splinting did not reduce the stress in the cervical region of the implants in an *in vitro* study (Guichet *et al.* 2002; Wang *et al.* 2002; Nissan *et al.* 2010), but it reduced the stress on the peri-implant bone in a finite element analysis (Wang *et al.* 2002). A photoelastic study showed that splinted restorations distributed the stresses more evenly between the implants (Guichet *et al.* 2002). It remains unclear which one of these findings is clinically relevant. The few clinical studies directly addressing the issue reported no difference in survival rate or marginal bone loss between splinted and unsplinted implants (Naert *et al.* 2002; Vigolo & Zaccaria 2010). The concept of splinting adjacent implants is also challenged

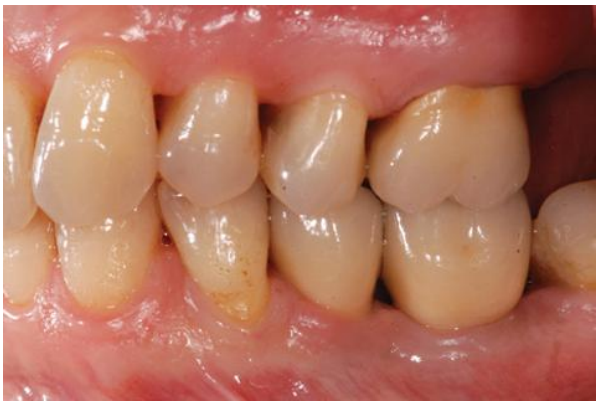


Fig. 55-12 Clinical image of unsplinted implants in bone of good quality.

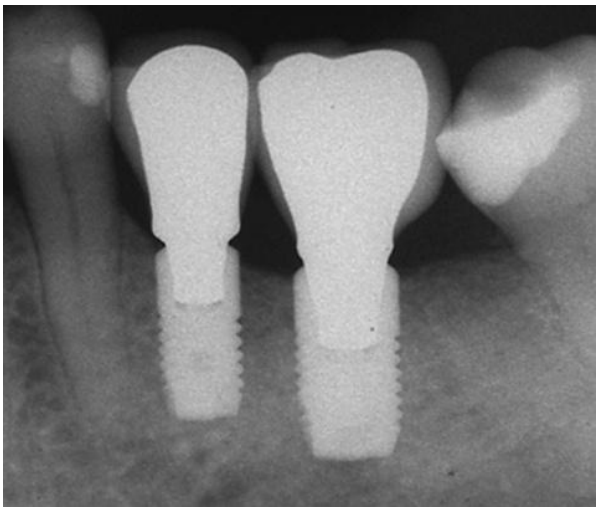


Fig. 55-13 Radiograph of two unsplinted single-tooth implants.

by the evidence for high survival and success rates of unsplinted short implants (Fugazzotto 2008). In general, there is no evidence that overloading of osseointegrated implants is a phenomenon that occurs under standard clinical conditions. Thus, there is probably no need to distribute loading forces over several implants and no need to splint implants of standard diameter and length in sufficient bone quality and in patients without parafunctional habits (Figs. 55-12, 55-13).

Longest possible versus shorter implants, including impact of crown-to-implant ratio

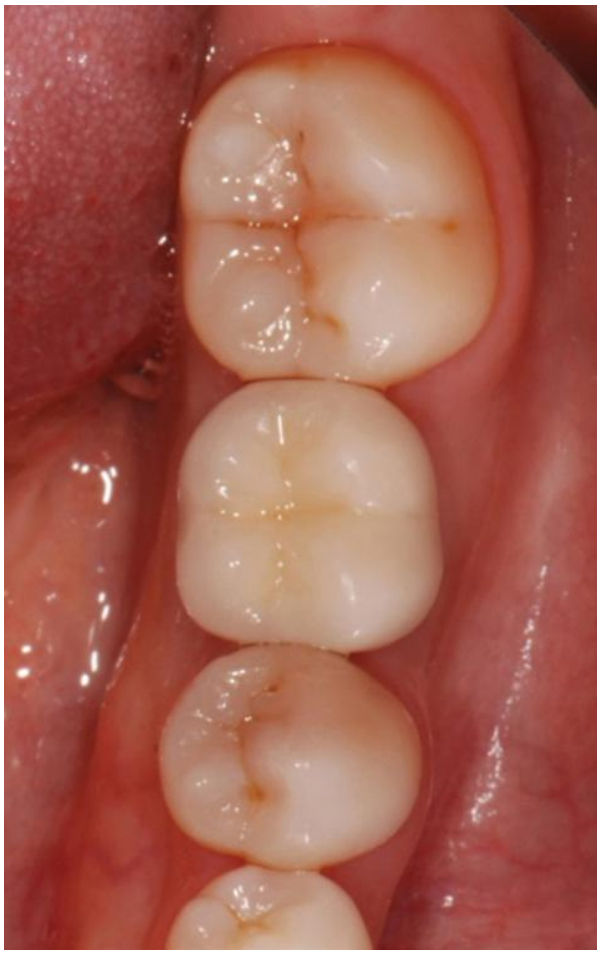
Clinicians are quite frequently confronted with posterior edentulous jaw segments that present all of the major prerequisites for successful implant therapy listed earlier in this chapter, with the exception of sufficient vertical bone height for the insertion of one or several implants featuring what is broadly accepted as an adequate length of the implants *per se* and also in relation to the prospective height of the suprastructures. The question that arises is whether there is a minimal implant length required in the context of posterior single-unit restorations and whether the ratio between implant length and suprastructure height has an influence on crestal bone resorption and ultimately on the longevity of the entire implant–suprastructure complex.

Standard-length implants (≥10 mm) have been universally recommended for many years, as it was widely accepted that this length was reasonable for a predictable success; the functional forces exerted on the implant were assumed to be distributed over a large surface area throughout the entire length of the implant. Another factor, which may have undermined the use of shorter implants, was the hypothesized elastic deformation of such implants under load. This intrabony deformation occurring under short-duration loading (e.g. chewing cycles) was reported to be considerably superior to that of standard-length implants, especially when subjected to lateral force vectors resulting in greater bending moments and thus inducing an increased stress on the crestal bone. However, later experimental studies concluded that this stress might not be minimized if the length of the implant is increased. Hence, it has been claimed that the generated interface stresses are, in fact, concentrated on the crestal bone and not redistributed over the entire length of the implant, and that shorter implants may even be more favorable in terms of peri-implant bone stimulation and resulting bone density (Renouard & Nisand 2006).

Currently, implants that are <8 mm long are broadly considered as "short implants", whereas early descriptions of "standard-length implants" refer to implants with intrabony lengths of ≥10 mm. Short dental implants were engineered to avoid interferences with vital anatomic structures (e.g. mandibular nerve canal, maxillary sinus), to reduce surgical trauma and associated risks, to decrease the morbidity involved with advanced grafting/bone augmentation procedures, and to foster "prosthetically-driven" implant positioning. As a result, these short dental implants may directly increase patient comfort and compliance, as well as minimize the amount of radiologic investigation and the number of visits, chairside time, and costs involved.

The analysis of the implant data collected at the University of Geneva School of Dental Medicine in the frame of a prospective multicenter study from 1989 to 2011, permitted the conclusion that shorter implants (6–8 mm) did not show higher average crestal bone resorption than longer implants (10–12 mm), and that a so-called unfavorable ratio between implant length and suprastructure height did not lead to more pronounced crestal bone resorption (Bernard *et al.* 1995; Bernard & Belser 2002; Blanes *et al.* 2007a, b). These data are corroborated by other reports (ten Bruggenkate *et al.* 1998; Bischof *et al.* 2001; Deporter *et al.* 2001; Heitz-Mayfield *et al.* 2004; Nedir *et al.* 2004; Bischof *et al.* 2006; Fugazzotto 2008; Birdi *et al.* 2010; Rossi *et al.* 2010; Esposito *et al.* 2011).

(a)



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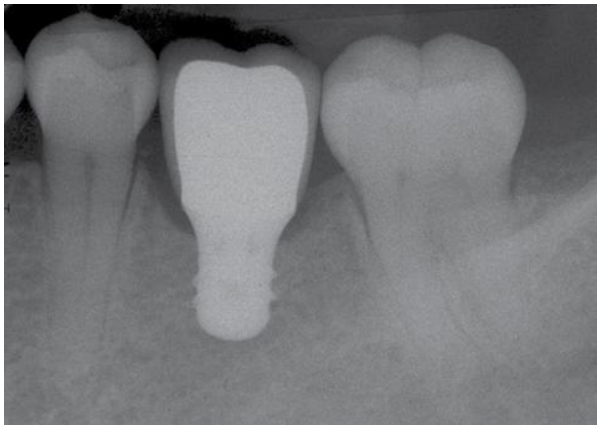


Fig. 55-14 (a) Occlusal view of a single tooth implant crown on a short 6-mm implant in the area of 36. (b) Radiograph of this single tooth crown after 2 years of function.

A representative clinical example of a posterior single-tooth FDPs, featuring so-called unfavorable implant length-to-suprastructure height ratios, is shown in Fig. 55-14.

A recent literature review based on 53 clinical studies involving a total of 4778 short implants (<8 mm, observation time up to 14 years), reported a cumulative survival rate of 90.4% (Srinivasan *et al.* 2012). Of the 4778 implants, the 1608 with a micro-rough surface revealed a cumulative survival rate of 97.2% (observation time up to 9 years), whereas an overall survival rate of 88.6% (observation time up to 14 years) was calculated for the 7-mm short implants with machined surfaces. The overall cumulative survival rates, that is regardless of the surface type, reported for either the maxilla or mandible were 83.3% and 92.6%, respectively, based on a total of 2709 implants placed in an identified location. Hence, it was concluded that short implants with micro-rough surfaces have similar survival and success rates to those reported for standard-length implants (10–12 mm). Based on a shorter observation time and involving a limited number of implants and studies, it would appear that even 4-mm implants may lead to similarly favorable survival rates. However, clinical common sense and manufacturing limitations on the one hand, and concerns relative to peri-implantitis (Quirynen *et al.* 2002) and technical complications (fatigue) related to implant components (screws, abutments) on the other hand, may lead to the conclusion that the use of such "ultra-short" implants should be limited to particular clinical situations. Clearly, prospective clinical trials with standardized protocols and well-defined study parameters are still needed to further assess treatment outcomes and predictability relative to short implants.

Implants in sites with extended vertical bone volume deficiencies

It is quite common that distally shortened dental arches do not feature an adequate local bone volume at the prospective implant sites. This may refer to bone height, bone width, alveolar bone crest axis or to the vicinity of noble structures such as the mandibular alveolar nerve canal or the anterior part of the maxillary sinus. Often, a combination of several of the mentioned limitations is encountered. Implant insertion is clearly a three-dimensional surgical and restorative procedure and a "restoration-driven" rather than "bone-driven" implant placement is widely recommended. Therefore, a meticulous presurgical site analysis – based on the envisioned treatment objective – is of primary importance. In order to keep the treatment as easy and cost-effective as possible, one should evaluate comprehensively all available treatment options. Among the options to be considered are: (1) primary or simultaneous bone augmentation procedures in combination with standard-length implants; (2) use of shorter implants and therefore avoiding extensive bone regenerative procedures; and (3) even a minor deviation from the ideal implant position without accepting the risk that this treatment adversely affects predictability, longevity, and/or subjective comfort (Ilizarov 1989a, b; Raghoebar *et al.* 1996; Howell *et al.* 1997; Simion *et al.* 2006; Pjetursson *et al.* 2008, 2009b; Esposito *et al.* 2011).

Maxilla: sinus floor elevation versus short implants

In the posterior regions of the maxilla, the clinician is often confronted with a reduced bone height due to a close relationship to the maxillary sinus. In these cases, different options exist: (1) primary sinus elevation and subsequent implant placement; (2) implant placement with simultaneous sinus elevation (transalveolar approach or lateral window technique); (3) use of shorter implants to avoid extensive bone augmentation procedures; and (4) installation of angulated zygoma implants (Chen *et al.* 2007; Davo *et al.* 2007; Pjetursson *et al.* 2009b; Esposito *et al.* 2011). The last of these options is mostly performed in edentulous cases by experienced maxillofacial surgeons, and has only been documented in a few case reports (Davo 2009; Bedrossian 2010).

Primary sinus augmentation procedures are indicated in cases with insufficient implant stability, which are often encountered when the vertical ridge height is <4 mm (Pjetursson *et al.* 2008). This procedure is well documented, predictable, and can lead to high implant survival rates, provided that rough surface implants are used (Wallace & Froum 2003; Pjetursson *et al.* 2008). (Fig. 55-15). However, the overall treatment time is maximized since a healing time of several months (3–12 months depending on the graft material used) is required before implant placement can be performed. In some cases, primary implant stability can be achieved (ridge height 3–6 mm) (Fig. 55-16) when standard-length implants are placed simultaneously with either one of the two sinus elevation procedures (transalveolar or lateral window approach) (Summers 1994; Rosen *et al.* 1999; Pjetursson *et al.* 2009a, b). Simultaneous bone augmentation and implant placement can reduce the overall treatment time and costs, and limit the number of surgical interventions. Implant survival rates are reported to be similar for all three sinus elevation procedures (transalveolar approach, lateral window one-stage or two-stage approach) with estimated implant survival rates over 3 years ranging between 88.5% and 98.3% (Pjetursson *et al.* 2008; Tan *et al.* 2008). However, the transalveolar procedure offers benefits in being less invasive and less time-consuming (Fontana *et al.* 2008).

Over the years, implant designs, surfaces, lengths, and diameters have changed significantly. Previously, implants were bicortically anchored in the jaw to assure stability. Thus, the longest possible implant length was used depending on the existing jaw height. This concept was overruled when it was demonstrated that bicortical implant anchorage may not be advantageous over monocortical anchorage (Ivanoff *et al.* 2000; Attard & Zarb 2004). Nowadays, available implant lengths have decreased continuously due to advances in implant surfaces and design. Currently, implants with an infrabony part >8 mm are considered to be standard-length implants with clinically reported high success and survival rates (Hobkirk & Wiskott 2006). Nevertheless, the existing ridge height is often below 8 mm in posterior segments of the jaw and therefore does not allow placement of a standard-length implant. In order to overcome limitations associated with extensive bone augmentation procedures and to simplify the clinical procedures, shorter implants were developed, but rarely used in clinical studies. This was mainly due to speculations of a mechanical nature. The use of shorter implants potentially implies drawbacks such as an unfavorable crown-to-implant ratio and risk of loss of osseointegration due to mechanical overload. However, neither loss of osseointegration due to mechanical overload nor high crown-to-implant ratios have proven to be of clinical relevance based on preclinical and clinical data (Gotfredsen *et al.* 2001a, b, c; Blanes *et al.* 2007a, b; Schneider *et al.* 2012). In addition, more recent systematic reviews failed to demonstrate statistically significant differences with respect to the survival rates of short rough surface implants versus longer implants, or to find a relationship between implant length and failure rate (Kotsovilis *et al.* 2009; Telleman *et al.* 2011; Neldam & Pinholt 2012;). Compared to standard-length implants in combination with extensive bone grafting procedures, the use of shorter implants potentially provides a variety of benefits: lower risk of damage to adjacent structures (roots, nerves, vessels, sinus), fewer complications, less invasiveness, fewer diagnostic procedures necessary, less diagnostic and surgical skill necessary, shorter treatment time, easier removal in case of failure, and less patient morbidity (Renouard & Nisand 2005). In order to demonstrate that the use of short implants may result in similar survival rates to those for longer implants with sinus elevation procedures, various studies have been conducted and others are ongoing. In a recent randomized controlled clinical trial, short implants (5 mm) were compared to long implants (10 mm) placed in augmented sinuses (Esposito *et al.* 2011). At 1-year post loading, the results demonstrated similar survival rates for both implant lengths and treatments. However, the use of short implants was associated with a faster and cheaper treatment and less patient morbidity (Esposito *et al.* 2011). Even though only short-term results are available, these indicate that the use of short implants in the posterior maxilla may be considered a valuable treatment option (Felice *et al.* 2009a) (Fig. 55-17).

Mandible: vertical ridge augmentation versus short implants

In cases with a reduced ridge height in the mandible, three options exist: primary vertical ridge augmentation and subsequent implant installation; simultaneous implant placement with vertical ridge augmentation; and the use of short implants (Simion *et al.* 2001, 2007; Rocchietta *et al.* 2008; Felice *et al.*

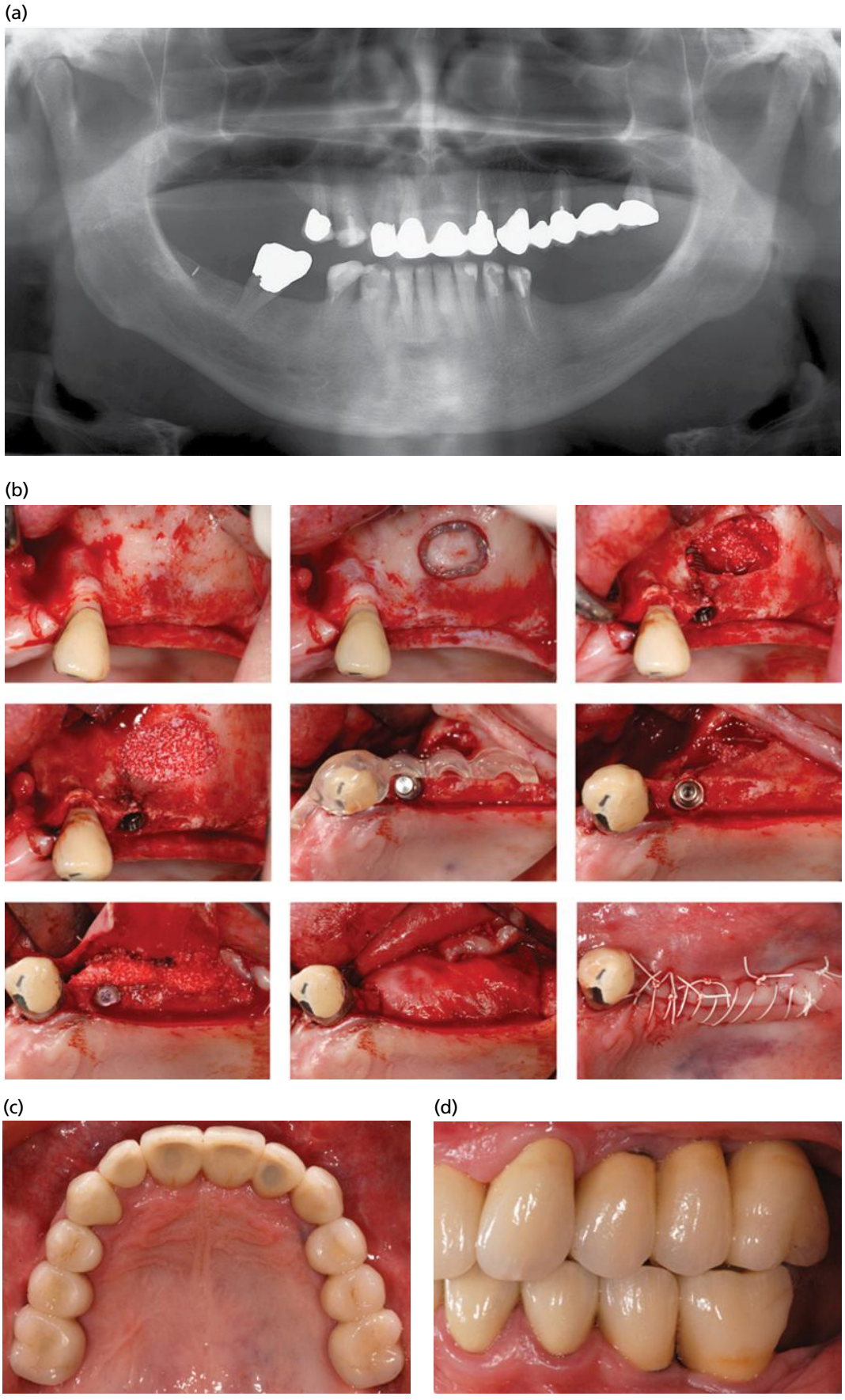


Fig. 55-15 (a) Panoramic radiograph revealed an extended vertical ridge deficiency in the upper left and right jaw. Teeth 25 and 27 are hopeless. A two-stage sinus elevation procedure was performed in region 16 and 26. One-stage sinus elevation was performed in region 24. (b) Sinus elevation procedure performed with the lateral window approach. Two-stage sinus elevation procedure was performed in region 26. One-stage sinus elevation with lateral bone regeneration was performed in areas 24 and 25. (c) Final reconstruction in place (FDP 24 × 26) occlusal view after 1 year in function. (d) Final reconstruction in place (FDP 24 × 26) buccal view after 1 year in function.

(e)

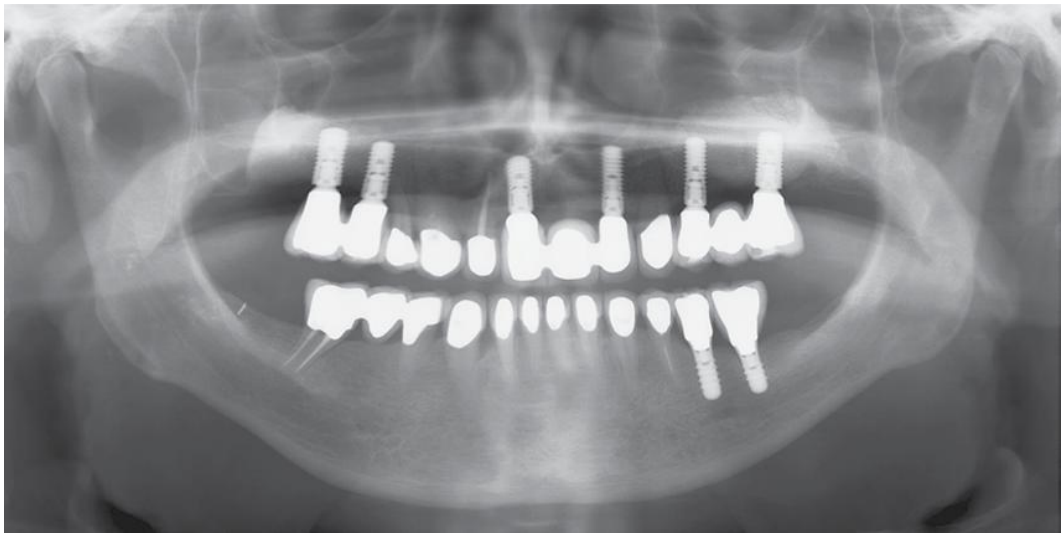
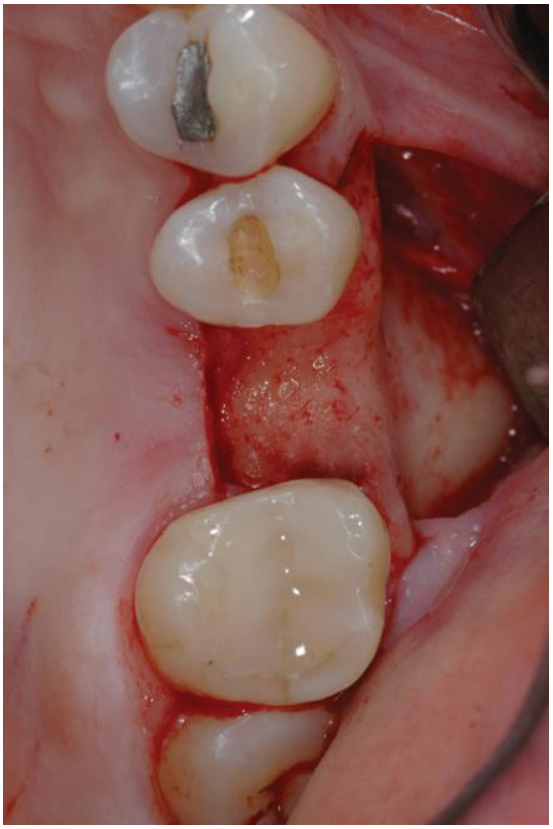


Fig 55-15 (*Continued*) (e) Panoramic radiograph 1 year after insertion of the final reconstruction.

(a)



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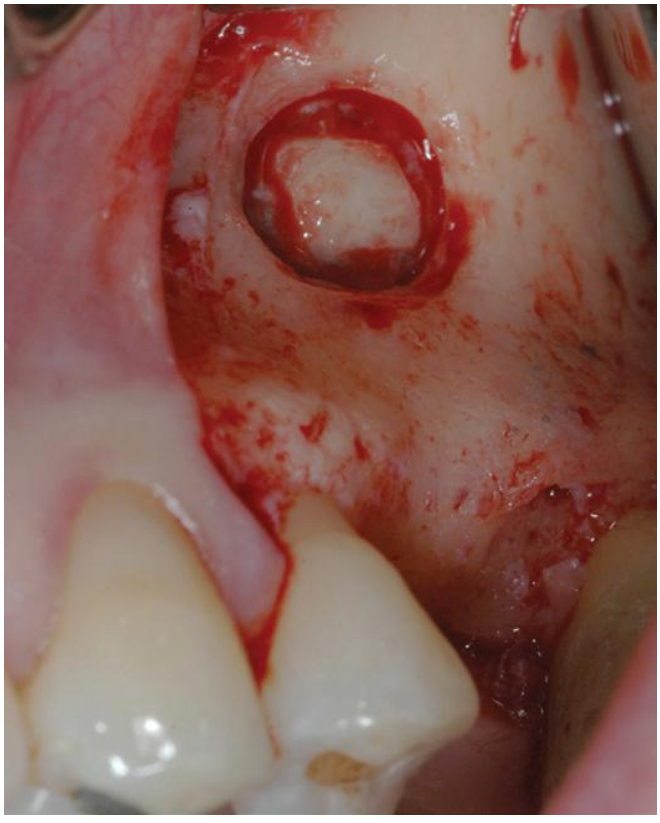
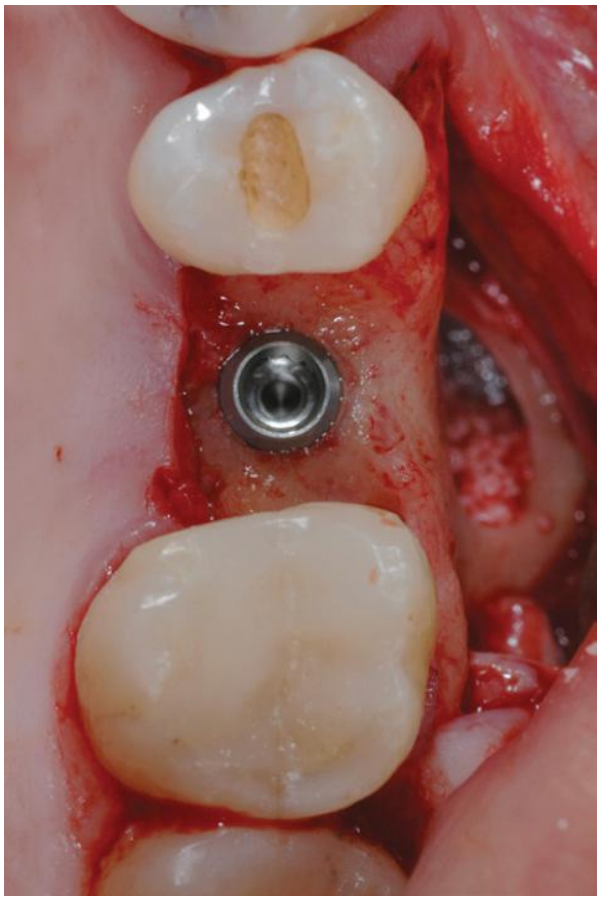


Fig. 55-16 (a) Preoperative occlusal view of a single-tooth gap 26. (b) Simultaneous sinus elevation with lateral window approach and implant placement in region 26.

2009a). Primary ridge augmentation procedures that allow the placement of standard-length implants have been proposed to result in smaller crown-to-implant ratios, better esthetics, and better cleanability of the prosthetic reconstruction (Mecall & Rosenfeld 1991). An array of different techniques (Ilizarov 1989a, b; Chiapasco *et al.* 2007; Merli *et al.* 2007, 2010) have been described for primary bone augmentation, including guided bone regeneration (GBR), distraction osteogenesis (DO), and onlay bone grafting (OB). The success rates of these techniques vary quite extensively. In addition, only a limited number of publications are available and these are from a confined number of surgeons who are able to perform these treatments successfully. Their general use has therefore not been recommended based on the outcomes of a systematic review (Rocchietta *et al.* 2008). The main reasons

(c)



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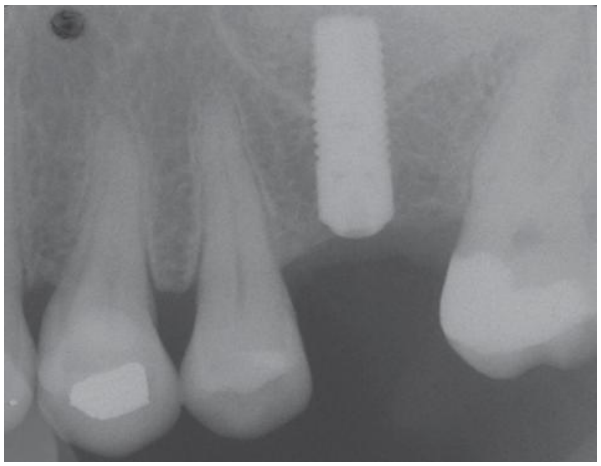

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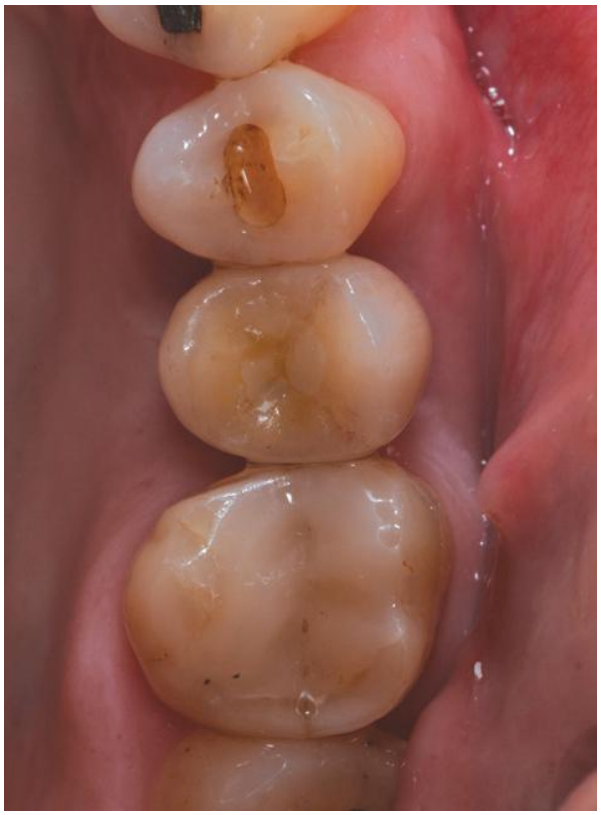

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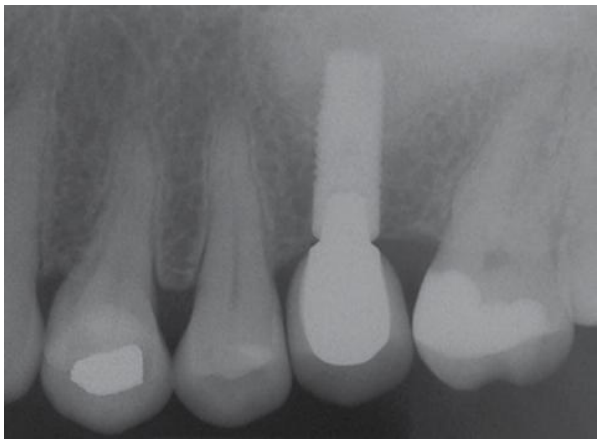
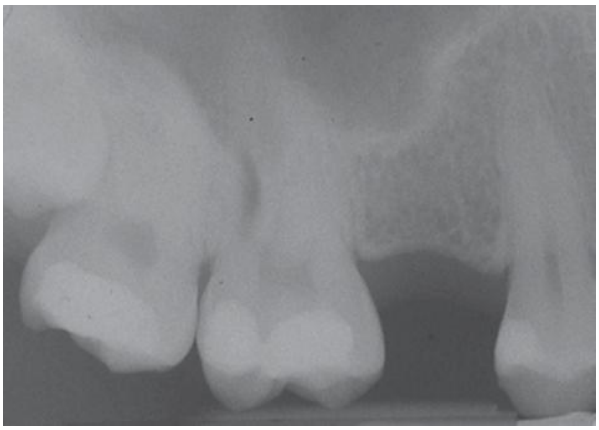


Fig. 55-16 (*Continued*) (c) Occlusal view after implant installation and sinus elevation procedure. (d) Postoperative radiograph of a 13-mm implant. (e) Occlusal view of the final screw-retained crown after 1 year in function. (f) Periapical radiograph 1 year after insertion of the final reconstruction.

(a)



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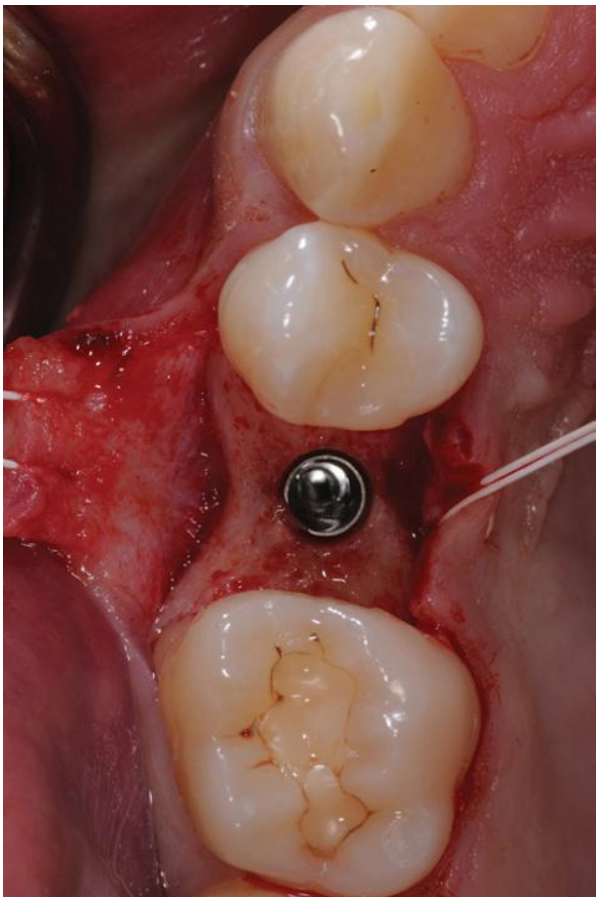

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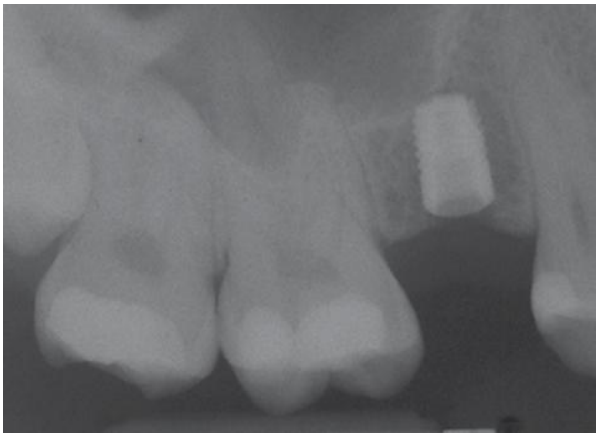

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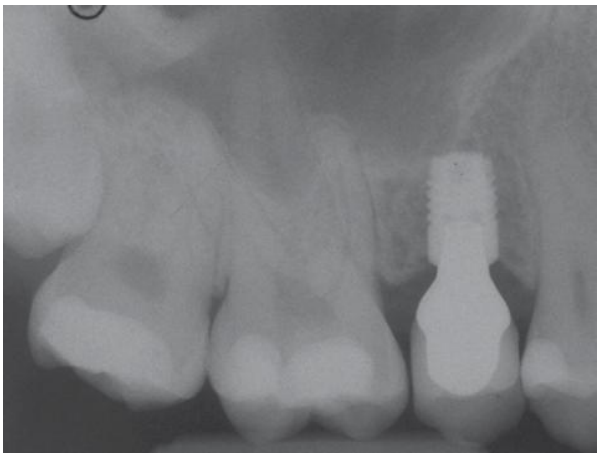

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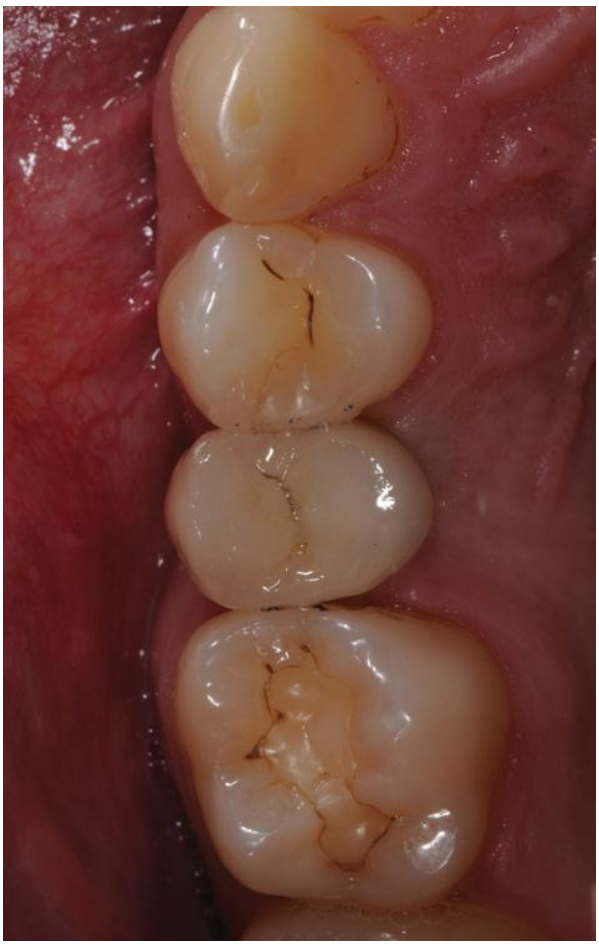


Fig. 55-17 (a) Preoperative radiograph demonstrates a reduced alveolar ridge height (6 mm) in region 15. (b) Occlusal view after implant installation without an additional sinus elevation procedure. (c) Radiograph after implant placement with a 6-mm short implant. (d) Periapical radiograph 1 year after insertion of the final reconstruction. (e) Occlusal view of the final porcelain-fused-to-metal crown after 1 year in function.

for this lack of recommendation included great variability in outcomes, a high rate of complications (extending up to 75%), and operator sensitivity (Rocchietta *et al.* 2008). In contrast, the use of shorter implants may avoid extensive bone regenerative procedures in cases with a ridge height exceeding 6 mm. Comparative clinical studies demonstrated fewer implant failures and fewer wound dehiscences associated with short implants compared to primary ridge augmentation and longer implants (Felice *et al.* 2009a, b; Esposito *et al.* 2011). Similarly to in the maxilla, both patients and clinicians may benefit from the use of short implants. However, more comparative clinical studies with documented long-term data need to be provided.

Preoperative diagnostics and provisional reconstructions in the posterior dentition

Preoperative prosthetic diagnostics

Dental implants are placed to support reconstructions (Esposito *et al.* 1998), and therefore, prosthetically-driven implant placement is a prerequisite for the achievement of an ideal biomechanical, functional, and esthetic treatment result. Together with site evaluation and risk assessment, the preoperative prosthetic diagnostics are essential for correct treatment planning in implant dentistry. The larger the span and higher the complexity of the planned reconstruction, the more important are the preoperative diagnostics.

Prosthetic diagnostics are conventionally performed by means of a diagnostic set-up manufactured on plaster models (Fig. 55-18). Over the past years, several systems for computer-assisted design of reconstructions based on the data obtained from optical scans have been developed (Mormann *et al.* 1987; Syrek *et al.* 2010) (Fig. 55-19).

The three-dimensional space available for the reconstruction will have a significant impact on the prosthetic planning. In cases with reduced or excessive mesiodistal or vertical (distance from the prospective restorative margin to the opposing occlusion) space, adjunctive therapy may be necessary to adjust the space to that needed for the planned reconstruction (Fig. 55-20). This may involve orthodontic, surgical, reconstructive or endodontic treatment procedures. Therefore, such clinical situations will result in an increased complexity of the treatment with dental implants.

Prior to the selection of implant type and three-dimensional (3D) planning, the following prosthetic elements have to be defined:

- Reconstruction design
- Prospective mucosal margin
- Retention type
- Occlusal schema.

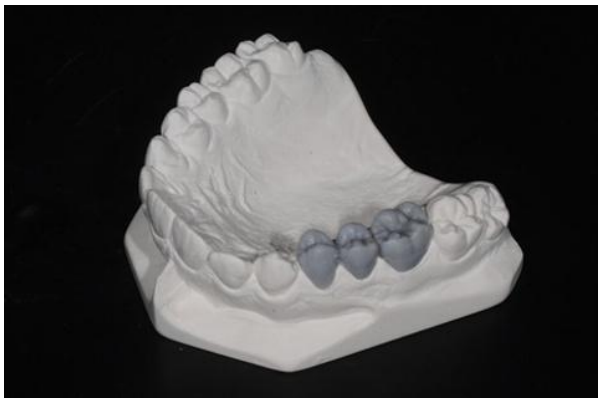


Fig. 55-18 Conventional wax-up on a cast.

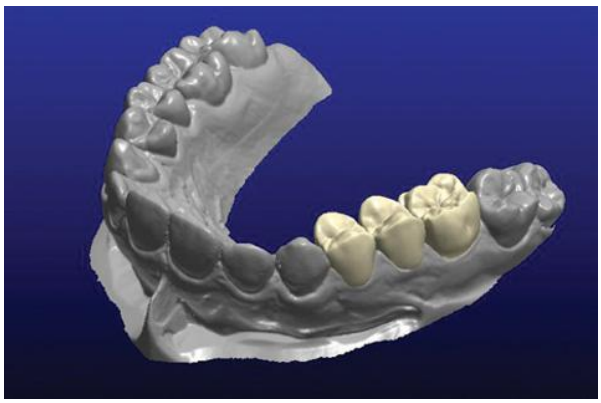


Fig. 55-19 Digital set-up as a screen view.

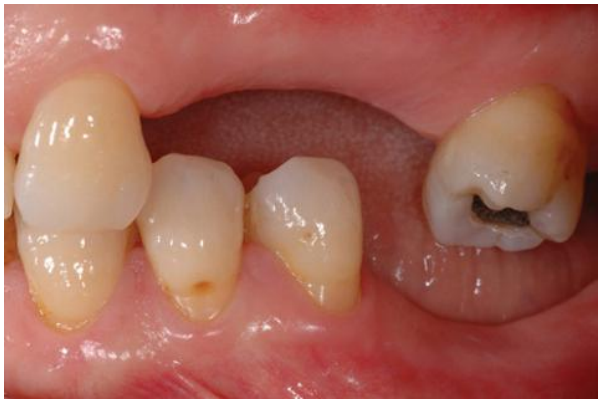


Fig. 55-20 Reduced vertical amount of space in the area of missing teeth 24, 25, and 26 due to elongation of antagonist teeth.

Three-dimensional radiographic diagnostics and planning

The introduction of cone-beam computed tomography (CBCT) has allowed the acquisition of 3D images with an adequate quality for dentomaxillofacial examinations (Suomalainen *et al.* 2009; Fatemitabar & Nikgoo 2010) at reduced radiation doses compared to conventional multislice computed tomography (CT) (Rustemeyer *et al.* 2004; Ludlow *et al.* 2006; Ludlow & Ivanovic 2008). The radiation burden of CBCT is, however, considerably higher in comparison

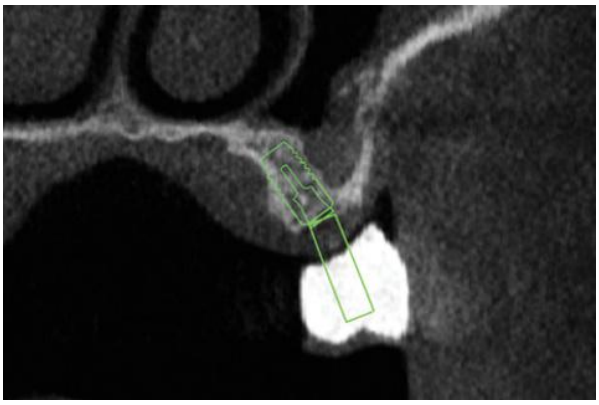


Fig. 55-21 Implant planning aimed at avoiding sinus floor elevation.

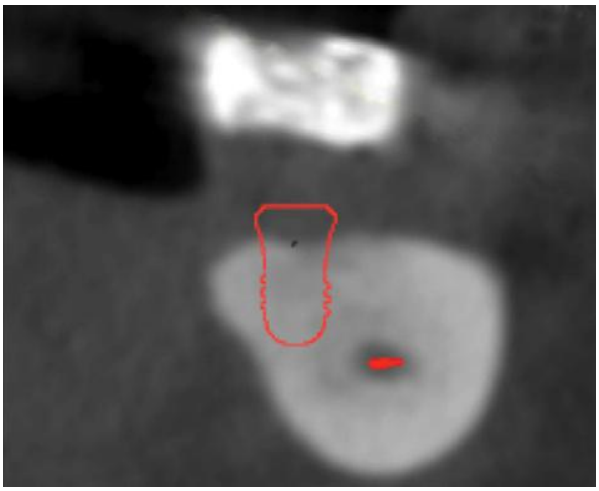


Fig. 55-22 Implant position planning lingual to the inferior alveolar nerve canal.

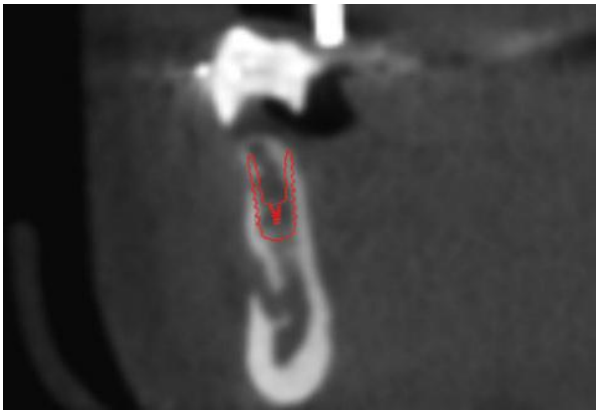


Fig. 55-23 Three-dimensional implant planning in a site with limited bone width.

to conventional two-dimensional (2D) radiography. Therefore, cross-sectional imaging should only be undertaken when it gives a justifiable benefit to the patient (Harris *et al.* 2002).

Several software programs for computer-assisted implant planning based on the data from CT scans have been recently developed (Jung *et al.* 2009a; Schneider *et al.* 2009). A prerequisite for optimal implant planning when using such systems is the combination of the information on bone anatomy with the 3D image of the previously planned prosthetic reconstruction. This can be achieved by means of radio-opaque prosthetic templates or by superimposing a digital set-up on the CT image. To transfer the preoperatively planned implant position to the surgical site, intraoperative (static) guidance or (dynamic) navigation is required (Hämmerle *et al.* 2009). Due to the limitation of computer-assisted implant planning and placement regarding accuracy (Jung *et al.* 2009a; Schneider *et al.* 2009), the clinician should always allow an adequate safety margin for the relevant anatomic structures (Harris *et al.* 2002).

The following clinical situations may benefit from 3D radiographic diagnostics and planning:

- 2D radiographs have failed to identify relevant anatomic structures
- Due to the proximity of the maxillary sinus or inferior alveolar nerve canal, there appears to be a need for sinus floor elevation or vertical bone augmentation (Figs. 55-21, 55-22)
- In sites with limited bone width where there appears to be a need for lateral bone augmentation (Fig. 55-23).

Provisional reconstructions

The period of time between the beginning of therapy and implant loading in implant dentistry may amount to several months. Due to the functional and esthetic impairments during this period, it might be necessary to intermediately restore the edentulous region by means of a provisional reconstruction. Additionally, the provisional reconstruction may be indicated in order to test the ideal design of the final reconstruction and patient's adaptation to the planned reconstruction.

The selection of provisional type has to be based on the patient's requirements, conditions of the edentulous site, prosthetic requirements of the adjacent teeth, duration of the provisional phase, and financial considerations. The following types of temporary reconstruction are available:

- Removable partial denture (Fig. 55-24)
- Removable thermoplastic sheet containing pontics of missing teeth (Essix provisional) (Fig. 55-25)
- Fixed partial denture (if full coverage of the adjacent teeth is required).

Resin-bonded partial dentures are generally unfavorable for the provisionalization of posterior dentition due to the risk of debonding and fractures.

A correctly designed provisional should include the ability to accommodate changes of the underlying soft tissue and avoid uncontrolled pressure on healing implants and augmented regions.

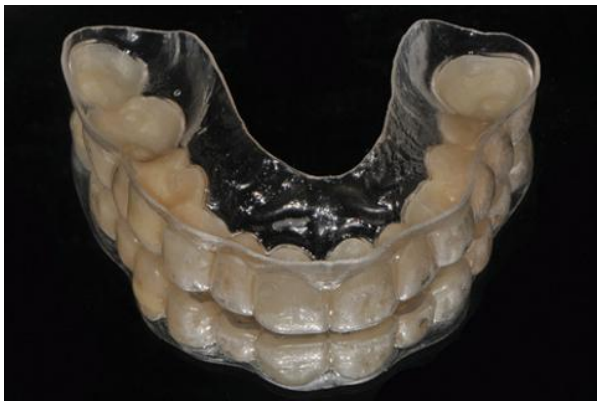


Fig. 55-24 Provisional removable partial denture.

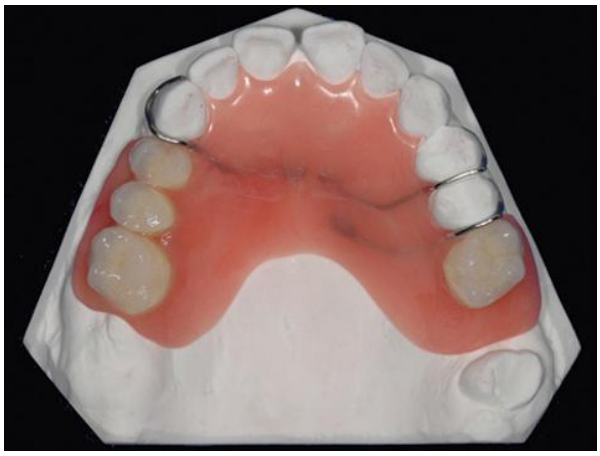


Fig. 55-25 Clear thermoplastic sheet containing pontics of the missing teeth.

Clinical concepts for the restoration of free-end situations with fixed implant-supported prostheses

Free-end situations in the posterior dentition represent a frequent indication for the use of dental implants. Whenever possible, the adopted treatment strategy consists of restoring the shortened dental arch to the region of the first molars. Occasionally, implant therapy is restricted to the premolar area, according to the principles of the well-established premolar occlusion concept, or extended to the second molar area if an antagonistic contact has to be established for an opposing natural second molar.

Number, size, and distribution of implants

It is still unclear to date how many implants of which dimension and at which location are required to optimally rehabilitate a given edentulous segment in the load-carrying part of the dentition. Several different recommendations and related strategies are currently in use, mostly derived from traditional prosthodontic experience and attitudes, and based on so-called clinical experience and common sense rather than on solid scientific evidence. In defense of this situation, one should be aware, however, that it is often difficult to design and carry out randomized clinical trials evaluating exclusively and without interference one specific parameter of conceptual relevance.

In a situation where the canine is the most distal remaining tooth of a dental arch, at least five different options can be considered if it is planned that the missing teeth up to the first molar area are to be replaced): (1) replacement of each missing occlusal unit by one implant (Fig. 55-26a); (2) a mesial and a distal implant to support a three-unit FDP with a central pontic (Fig. 55-26b); (3) two distal implants to permit the insertion of a three-unit FDP with a mesial cantilever (Fig. 55-26c); (4) two mesial implants to sustain a three-unit FDP with a distal cantilever (55-26d); and (5) only one distally inserted implant in view of a four-unit FDP combining implant and natural tooth support (Fig. 55-26c).

As far as the recommendation to use premolar-size units for implant-borne posterior FDPs is concerned, it has proven its practical validity in >10 years of clinical experience (Buser *et al.* 1997; Bernard & Belser 2002). In fact, a crown featuring a mesiodistal diameter of 7–8 mm at its occlusal surface allows the optimal generation of a harmonious axial profile, gradually emerging from the standard-implant shoulder (diameter 4–5 mm on average) to the maximum circumference. In addition, the width of the occlusal table is confined, thereby limiting the risk for unfavorable bending moments to the implant–abutment–suprastructure complex (Belser *et al.* 2000).

Based on an increasing body of scientific evidence, most clinicians' first choice is the mesial and distal implant and the FDP with the central pontic (Fig. 55-27). Prospective long-term data (Buser *et al.* 1997; Bernard & Belser 2002) have confirmed the efficacy and predictability of this specific modality. In fact, it permits the defined treatment objective to be reached with a minimum number of implants and associated costs. Although formal evidence at the level of prospectively documented, randomized clinical trials is still lacking, it appears from clinical experience that the use of two implants to support a four-unit FPD with two central pontics (Fig. 55-28) may be adequate in certain clinical situations. Clinicians tend to use this approach in the presence of favorable bone conditions, permitting standard-size or wide diameter implants of appropriate length (i.e. ≥8 mm).

If the alveolar bone crest dimension is also sufficient in an orofacial direction, the utilization of wide diameter/wide platform implants is preferred (Bischof *et al.* 2006). Due to their increased dimensions, a better adapted suprastructure volume and improved axial emergence profile of the implant restoration – when compared to a so-called premolar unit – can be achieved in the molar area (Fig. 55-29). In this way, the intercuspation with an opposing natural molar is also facilitated.

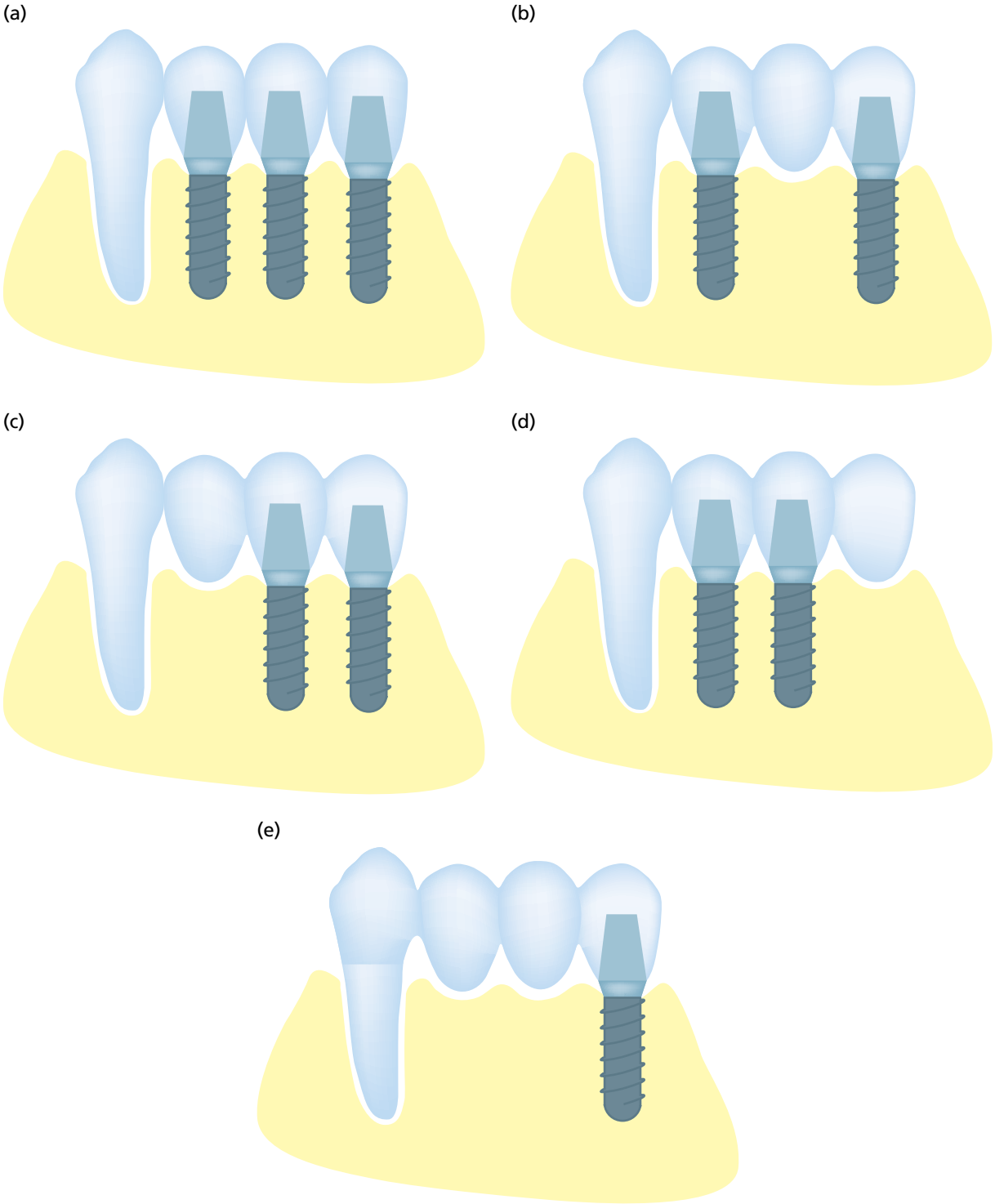


Fig. 55-26 Schematic representation of the distally shortened dental arch. (a) One therapeutic option consists of replacing each missing occlusal unit up to the first molar area with an implant. (b) An alternative option would be the replacement of the three missing occlusal units with two implants to support a three-unit suprastructure with a central pontic. (c) In a case of an inadequate bone volume in the area of the missing first premolar, the placement of two distal implants may be considered, leading to a three-unit suprastructure with a mesial cantilever. (d) In a case of an inadequate bone volume in the area of the missing first molar, the placement of two mesial implants may be considered, leading to a three-unit suprastructure with a distal cantilever. (e) In a case of inadequate bone volume in the area of the two missing premolars, the placement of a distal implant may be considered, leading to a four-unit suprastructure with a mixed (tooth and implant) support.

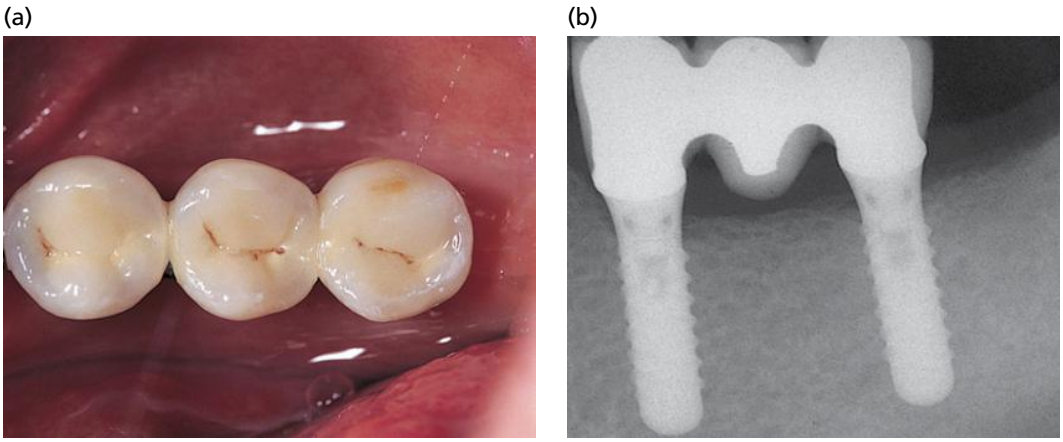


Fig. 55-27 (a) Occlusal view of a cemented three-unit metal–ceramic FPD, supported by a mesial and a distal implant. (b) Corresponding 3-year follow-up radiograph confirms stable conditions at the implant–bone interface of the two 12-mm solid screw implants.

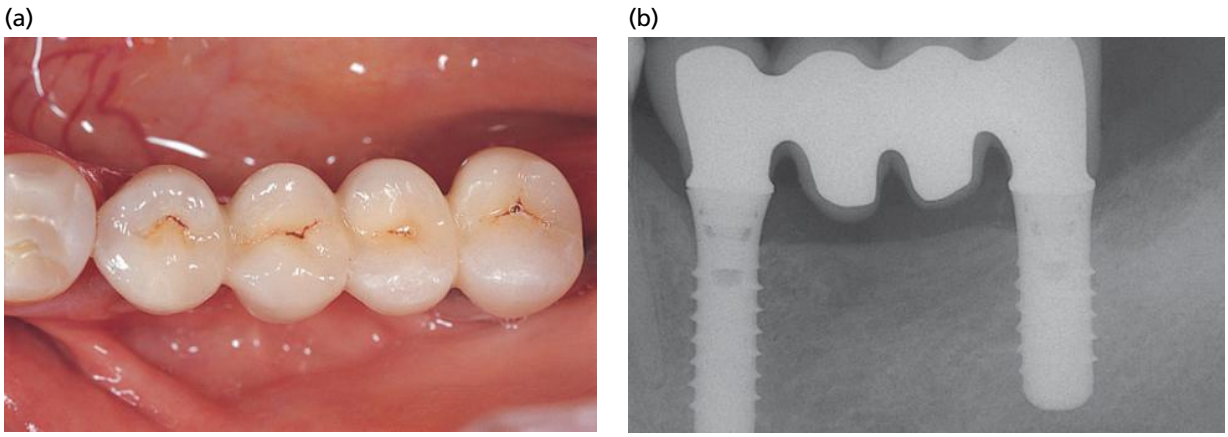


Fig. 55-28 (a) Occlusal view of a cemented four-unit metal–ceramic FPD supported by a mesial and a distal implant. (b) Corresponding 2-year follow-up radiograph documents that at the distal site a 10-mm solid screw implant with an increased diameter ("wide-body implant") has been used.

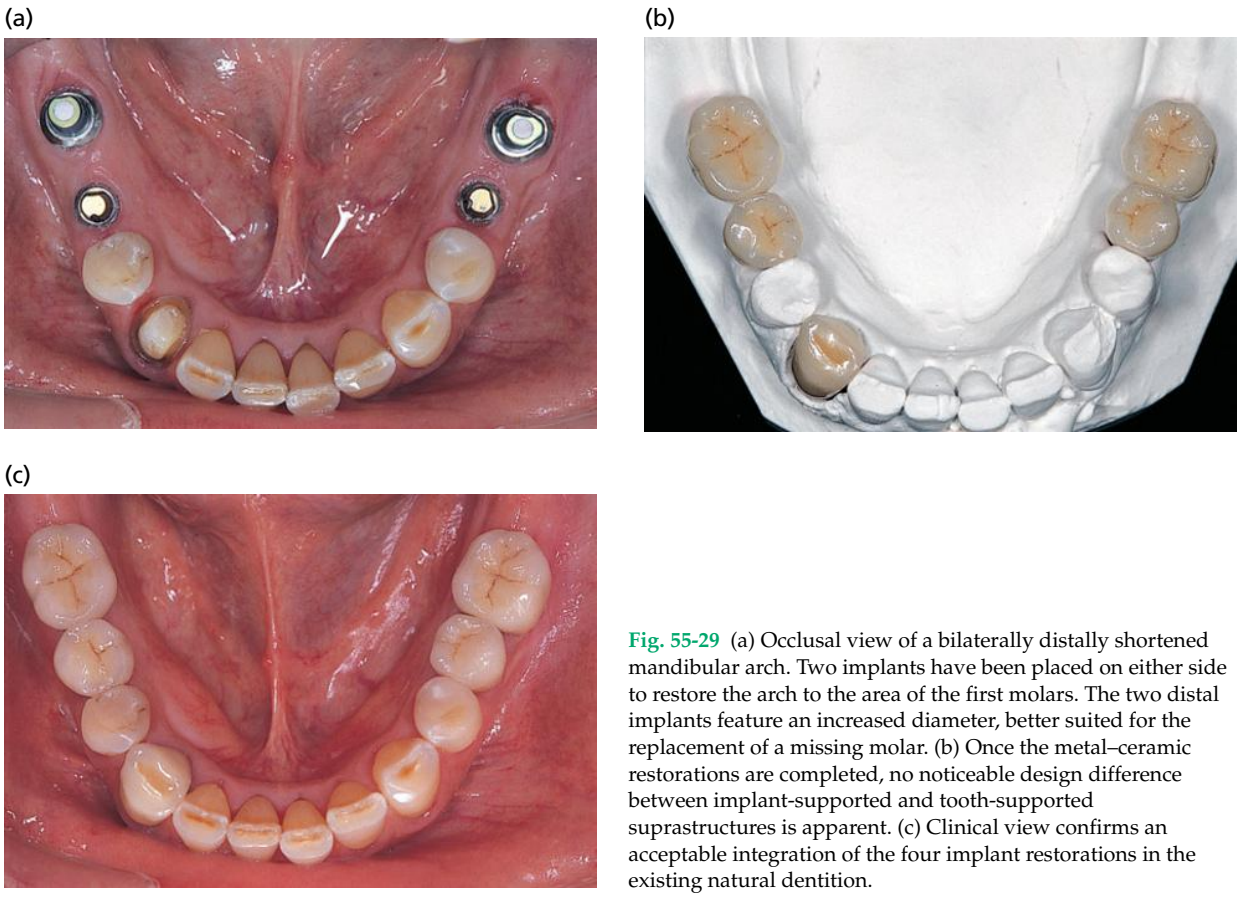


Fig. 55-29 (a) Occlusal view of a bilaterally distally shortened mandibular arch. Two implants have been placed on either side to restore the arch to the area of the first molars. The two distal implants feature an increased diameter, better suited for the replacement of a missing molar. (b) Once the metal–ceramic restorations are completed, no noticeable design difference between implant-supported and tooth-supported suprastructures is apparent. (c) Clinical view confirms an acceptable integration of the four implant restorations in the existing natural dentition.

Clinical concepts for multiunit tooth-bound posterior implant restorations

Number, size, and distribution of implants

When it comes to implant therapy in extended posterior edentulous segments confined mesially and distally by the remaining teeth, the question about optimal number, size, and distribution of implants has to be raised again. Among the key parameters to be addressed during the decision-making process are the mesiodistal dimension of the edentulous segment, the precise alveolar bone crest volume (including bone height and crest width in an orofacial direction), the opposing dentition (premolars or molars), interarch distance, and specific occlusal parameters, as well as the periodontal, endodontic, and structural conditions of the neighboring teeth.

One feasible approach consists of segmenting the edentulous space in premolar-size units of approximately 7 mm in mesiodistal diameter at the level of the occlusal plane, and of approximately 5 mm at the prospective implant shoulder. At posterior locations, clinicians increasingly prefer a rather superficial implant shoulder location or in many instances even a supramucosal one, so measurements can be carried out at the crest level of study casts. It is important during this process to anticipate a minimal distance between implant shoulders of approximately 2 mm, and between a natural tooth and an implant of about 1.5 mm (to be measured at the interproximal soft tissue level). Again, the treatment objective – a long-lasting implant-supported FDP – should be predictably reached (1) with optimal efficacy and (2) with minimum invasiveness and cost. The remaining controversy of whether each missing occlusal unit should be replaced by one implant or whether a minimal number of implants should be used, has already been addressed earlier in this chapter.

In the case of three missing occlusal units and no other particular restrictive conditions such as limited local bone volume, the authors recommend the insertion of a mesial and a distal implant to support a three-unit FDP with a central pontic (Fig. 55-30). This approach permits the fabrication of three metal–ceramic elements with a mesiodistal diameter of about 7 mm each. Based on an average implant shoulder dimension of approximately 5 mm, one can anticipate a gradually increasing, harmonious emergence profile from the implant shoulder to the occlusal surface. In order to satisfy the remaining important dimensional conditions, that is respecting the minimal distance between adjacent implants and in between teeth and implants, one needs to dispose of a minimal total mesiodistal gap of 21–22 mm.

In the case of two missing occlusal units, one should try as a general rule to select the largest possible implant diameters with respect to the total mesiodistal distance of the given tooth-bound edentulous segment. Decisive parameters are again interimplant distance and space between implants and adjacent teeth, as well as the orofacial crest width at the two prospective implant sites. For a total gap diameter of about 14–15 mm, two standard-size implants are most suitable (Fig. 55-31), while for one of 17–18 mm the combination of one standard and one wide diameter/wide platform implant is considered adequate (Fig. 55-32). It goes without saying that the latter choice also requires the appropriate orofacial bone volume.

These are just the frequently encountered clinical examples, and for the function of other morphology and dimensions of edentulous tooth-bound segments, additional approaches and implant combinations may be envisioned (Fig. 55-33). Such a

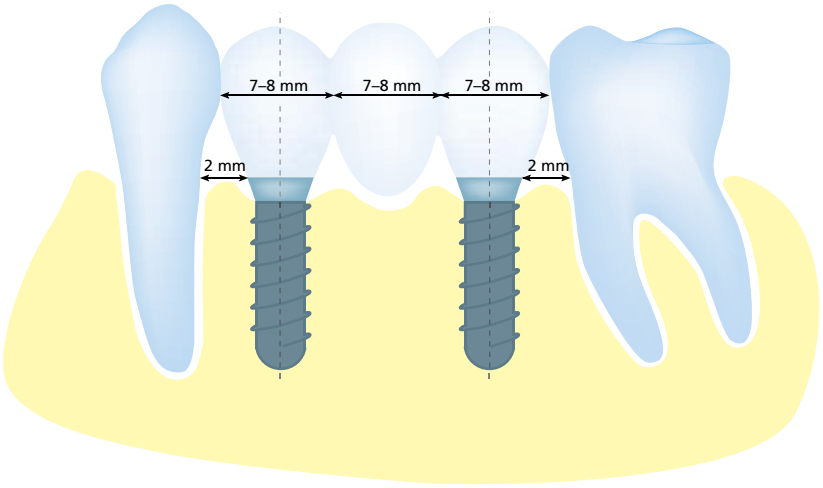


Fig. 55-30 In a case of three missing occlusal units, an implant-supported FDP with a centric pontic (approximately 7 mm in width) might be the therapy of choice.

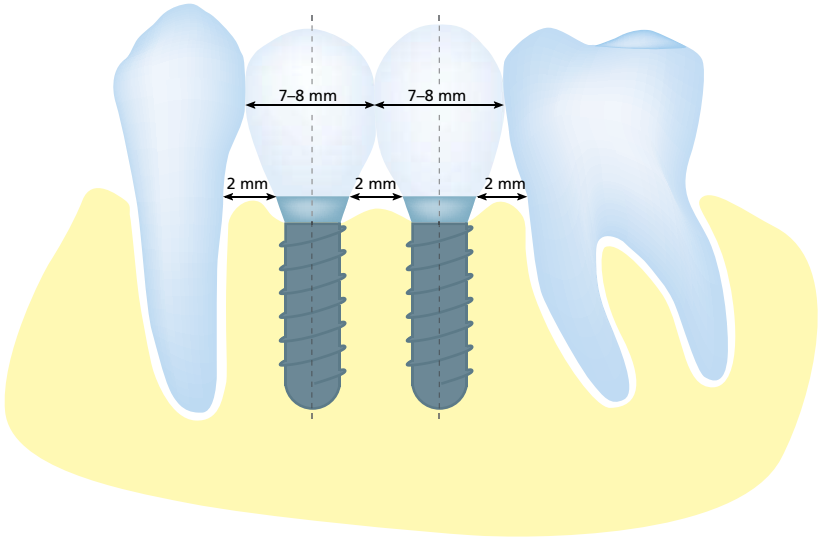


Fig. 55-31 If a given tooth-bound edentulous space only permits the insertion of two adjacent implants, a minimal interimplant distance of 2 mm and a minimal implant-to-tooth distance of 2 mm should be respected.

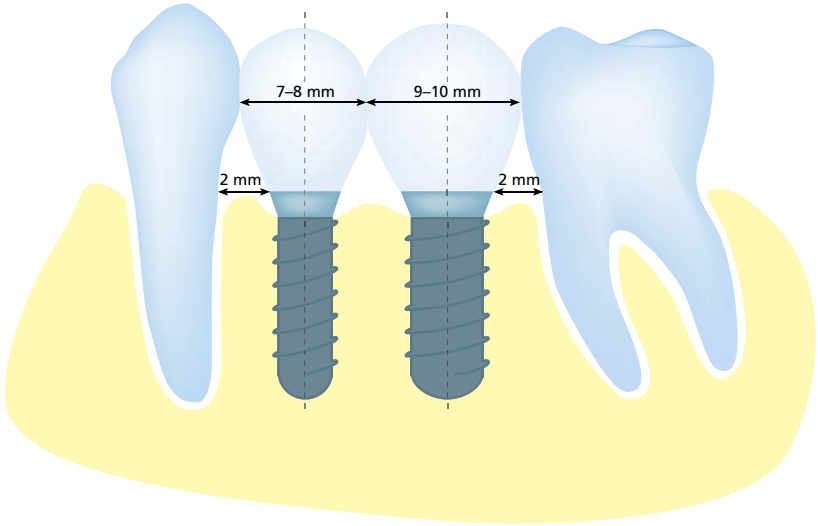


Fig. 55-32 In the presence of a mesiodistal gap width of approximately 17 mm, the combination of a standard and an increased-diameter implant may be considered. The same minimal interimplant and implant-to-tooth distances have to be respected.

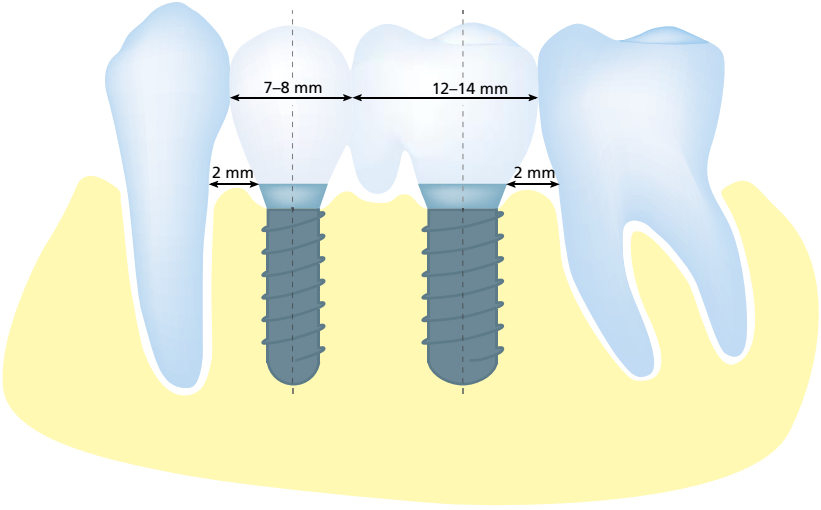


Fig. 55-33 If a posterior mesiodistal gap has a width of approximately 20 mm, a small central pontic should be considered to simplify the cleaning process.

clinical situation is shown in Fig. 55-34. The gap diameter required the two adjacent implants to be spaced wider than the normally advocated interproximal 2 mm. The laboratory technician compensated for this excess of space with a root-imitation pontic, which in turn provided an excellent guide facilitating the use of an interdental brush (Fig. 55-34a).

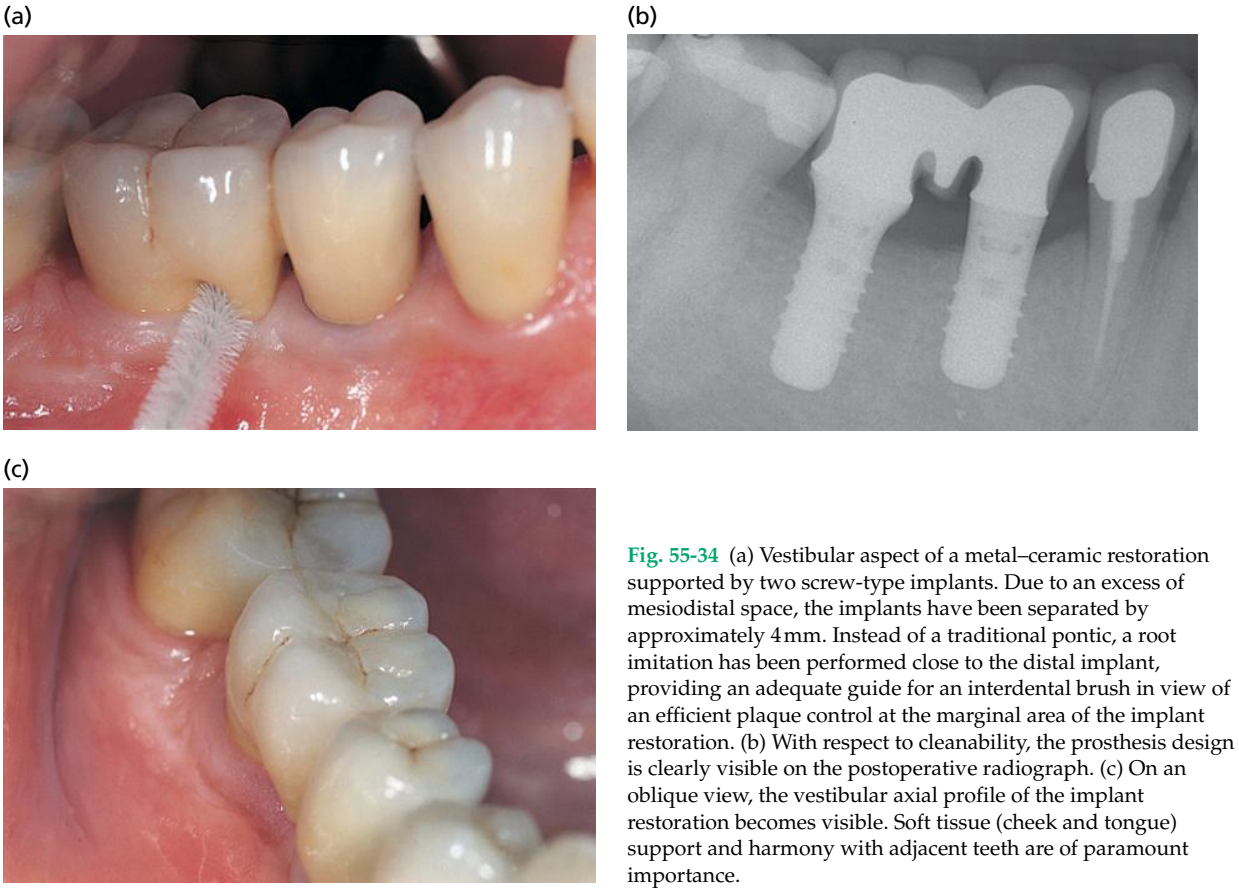


Fig. 55-34 (a) Vestibular aspect of a metal–ceramic restoration supported by two screw-type implants. Due to an excess of mesiodistal space, the implants have been separated by approximately 4 mm. Instead of a traditional pontic, a root imitation has been performed close to the distal implant, providing an adequate guide for an interdental brush in view of an efficient plaque control at the marginal area of the implant restoration. (b) With respect to cleanability, the prosthesis design is clearly visible on the postoperative radiograph. (c) On an oblique view, the vestibular axial profile of the implant restoration becomes visible. Soft tissue (cheek and tongue) support and harmony with adjacent teeth are of paramount importance.

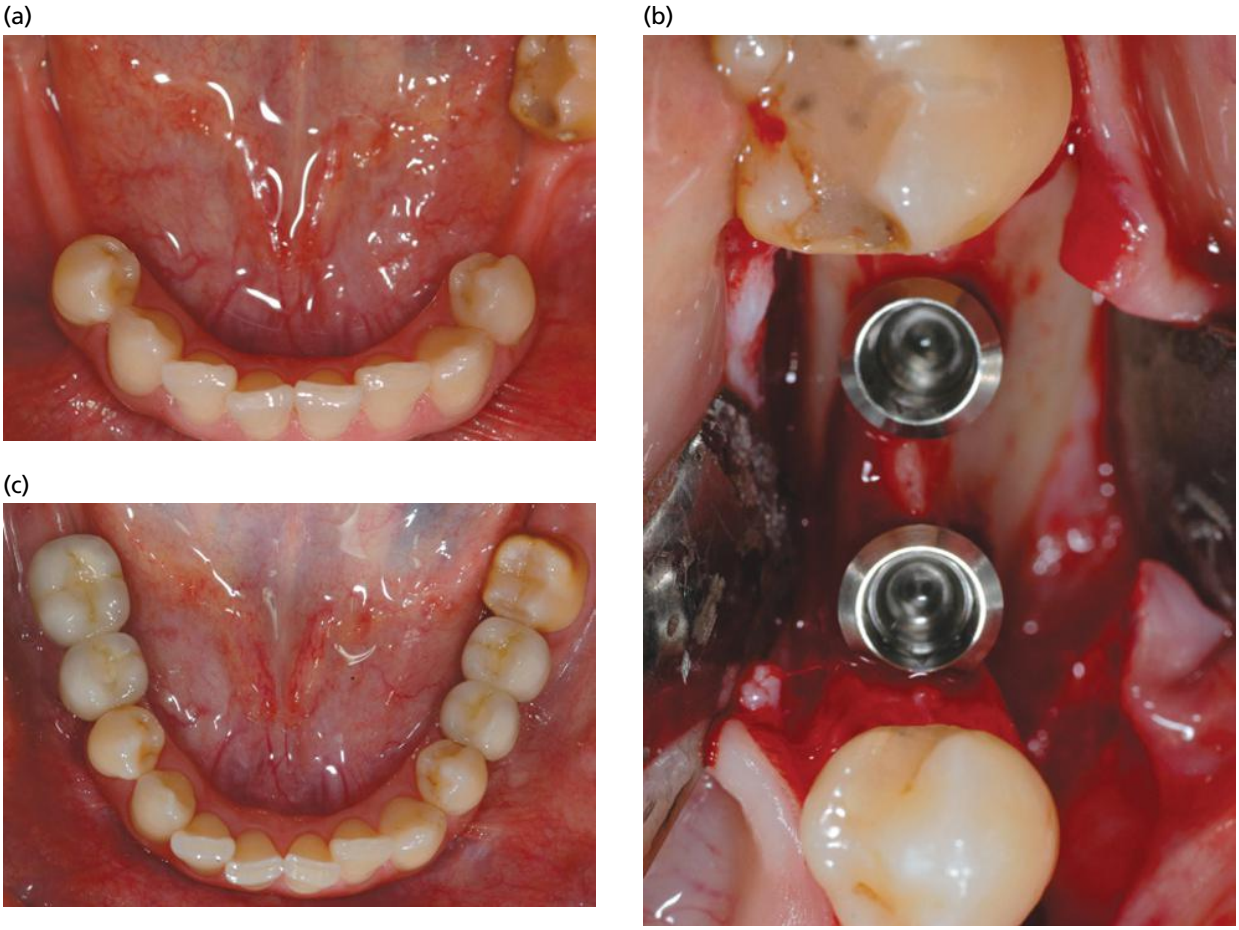


Fig. 55-35 (a) Occlusal view of a tooth-bound edentulous gap with missing teeth 35 and 36. (b) Mesiodistal gap dimensions allowed to two standard-diameter implants to be placed a the required distances in between the implants and next to the neighboring teeth. (c) Occlusal view of the final reconstructions after 1 year in function.

(d)

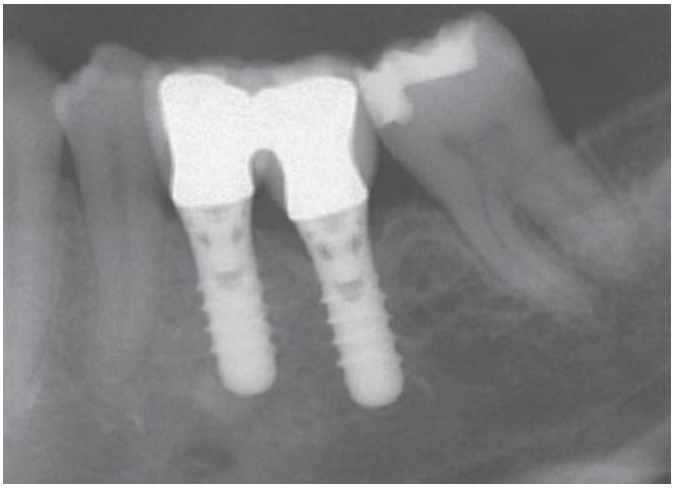
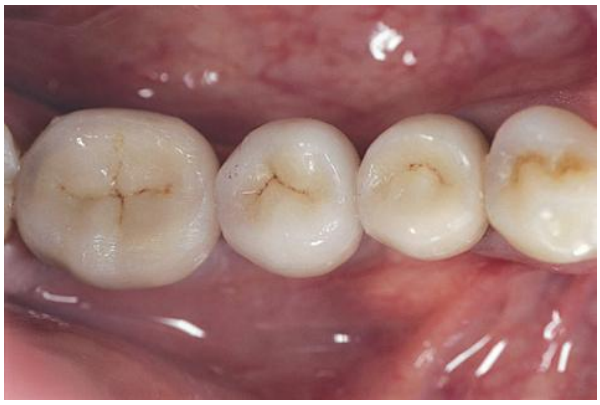


Fig. 55-35 (*Continued*) (d) Radiograph of the two splinted implants after 1 year in function.

(a)



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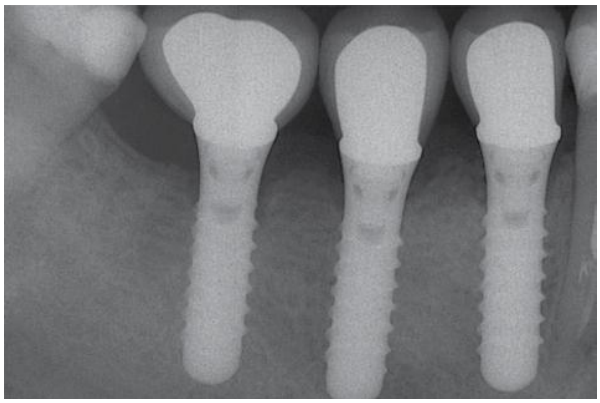

Fig. 55-36 (a) Occlusal view of three independent, implant-supported fixed metal–ceramic restorations in the right posterior mandible. (b) As confirmed by the follow-up radiograph, an increased (more molar-like) dimension was given to the most distal restoration, despite the fact that a standard-size implant had to be used for restricted bone volume reasons.

Further clinical examples with different mesiodistal gap widths are shown in Figs. 55-35 and 55-36.

Clinical concepts for posterior single-tooth replacement

At the time when most implant systems had basically only one "standard" dimension at disposition, this corresponded to approximately 4–5 mm at the implant shoulder and thus was optimally suited for premolar-size restorations, with a continuously increasing (in the coronal direction) flat axial emergence profile and a mesiodistal diameter of about 7–8 mm at the occlusal surface. However, clinicians were not infrequently faced with posterior single-tooth sites that did not comply with these dimensions, for example in cases of missing first molars or after the loss of persisting deciduous (primary) second molars. As a consequence, the resulting implant restorations featured either unfavorable excessive interproximal overcontour or wide open embrasures. The first situation was difficult to clean, while the second led to undesired food retention (impaction). Nowadays, most of the leading implant manufacturers offer wide body/wide platform implants designed for the replacement of multirooted teeth.

Premolar-size single-tooth restorations

When it comes to posterior single-tooth gaps that correspond dimensionally to an average premolar, standard-size screw-form implants are well suited. The implant dimensions, which include both the intrabony part and the implant shoulder, offer the additional advantage of being mostly compatible with a limited bone volume in an orofacial direction. Whenever feasible, a straightforward low-maintenance restorative design is advocated, which normally consists of a cementable porcelain-fused-to-metal (PFM) crown with vestibular and oral axial contours that are in harmony with the adjacent teeth and thus provide adequate guidance for the cheek and tongue (Fig. 55-37).

As one increasingly strives for the best possible biologic, functional, and esthetic integration of a given implant restoration in the pre-existing dentition, 3D preoperative site analysis is of paramount importance. It is not infrequent that this subsequently calls for a multidisciplinary approach, which may

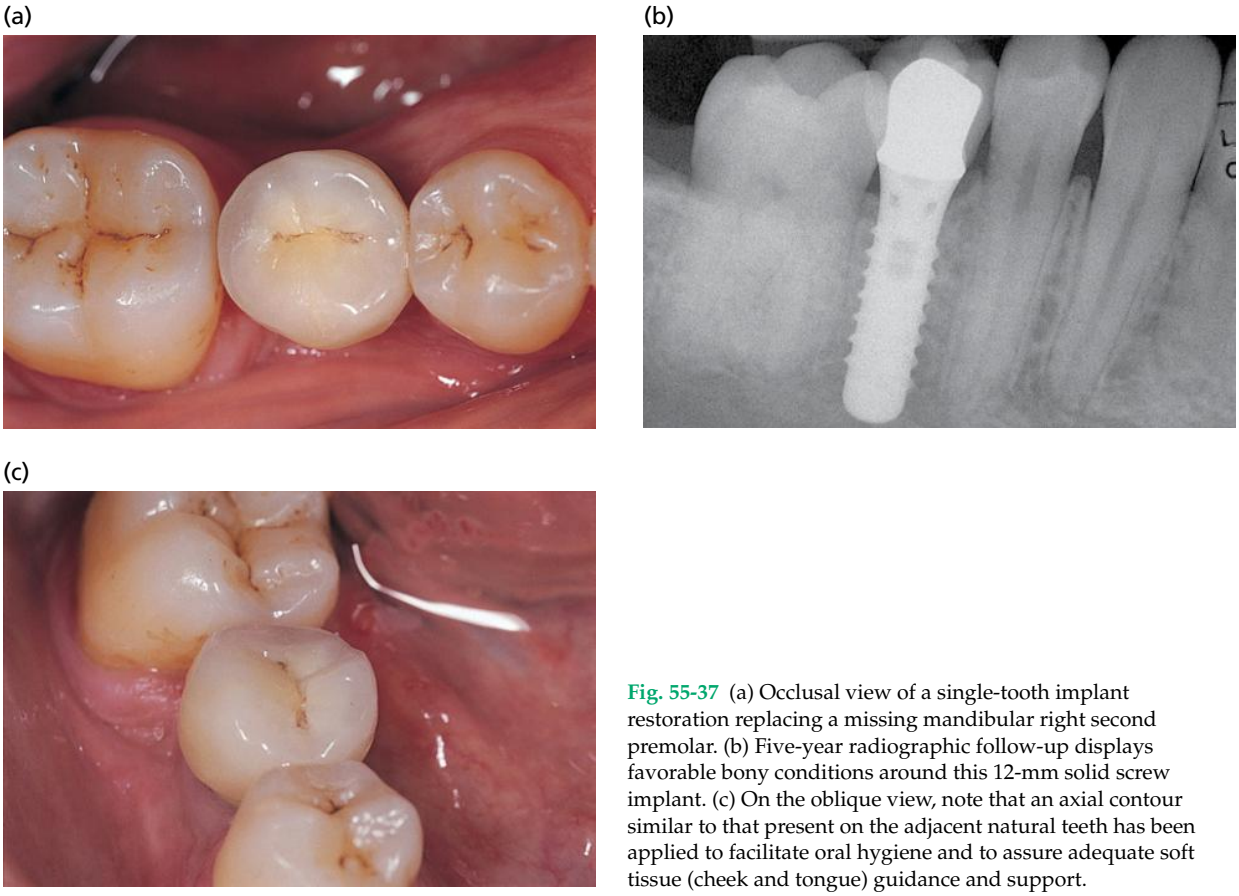

Fig. 55-37 (a) Occlusal view of a single-tooth implant restoration replacing a missing mandibular right second premolar. (b) Five-year radiographic follow-up displays favorable bony conditions around this 12-mm solid screw implant. (c) On the oblique view, note that an axial contour similar to that present on the adjacent natural teeth has been applied to facilitate oral hygiene and to assure adequate soft tissue (cheek and tongue) guidance and support.

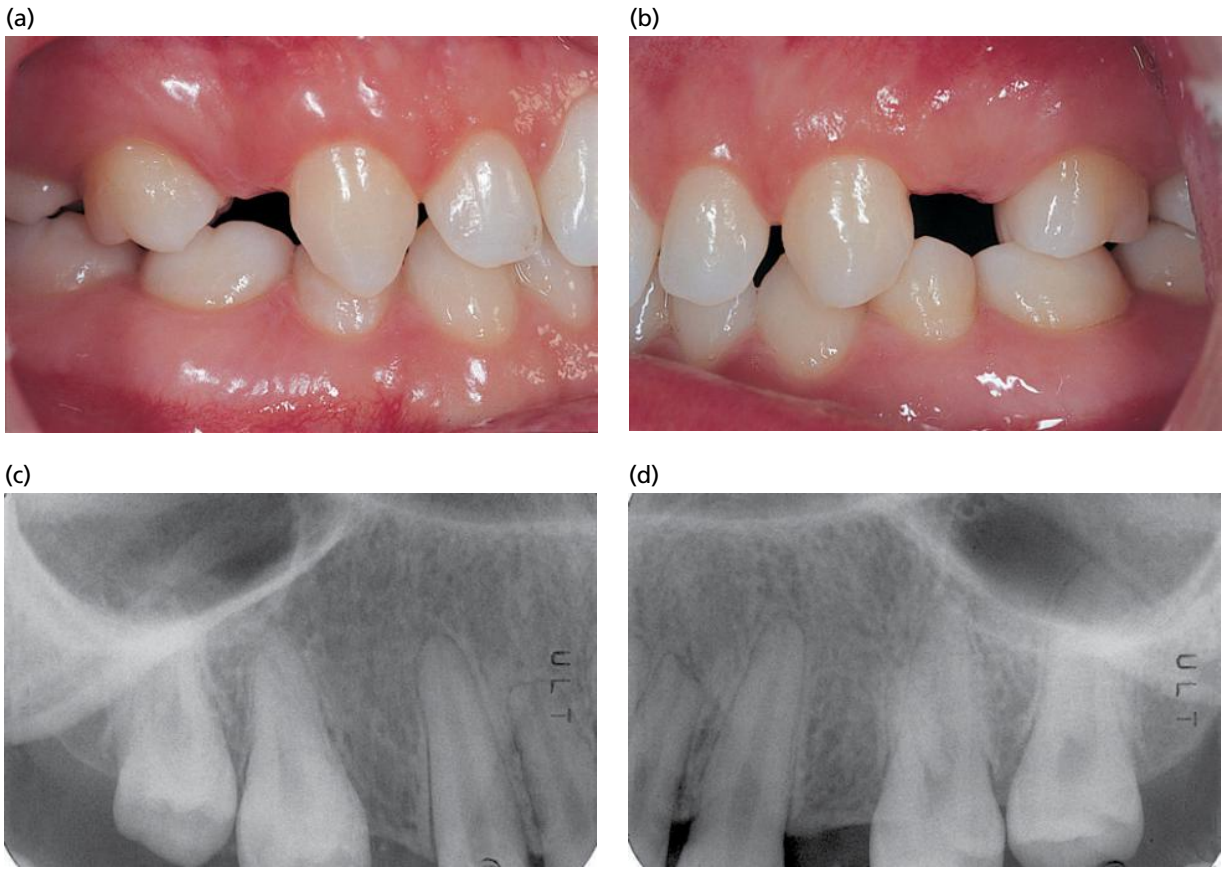

Fig. 55-38 (a) Right lateral view of a 19-year-old female patient, congenitally missing all four permanent maxillary premolars. Note both an inadequate mesiodistal gap width and a reduced interarch distance. (b) Similar situation regarding the interarch distance is present on the patient's left side. (c) Corresponding radiograph underlines the need for additional orthodontic therapy prior to the insertion of an implant in order to optimize the gap width and the inter-radicular distance. (d) Although to a lesser degree, presurgical orthodontic therapy is also indicated for the maxillary left posterior segment.

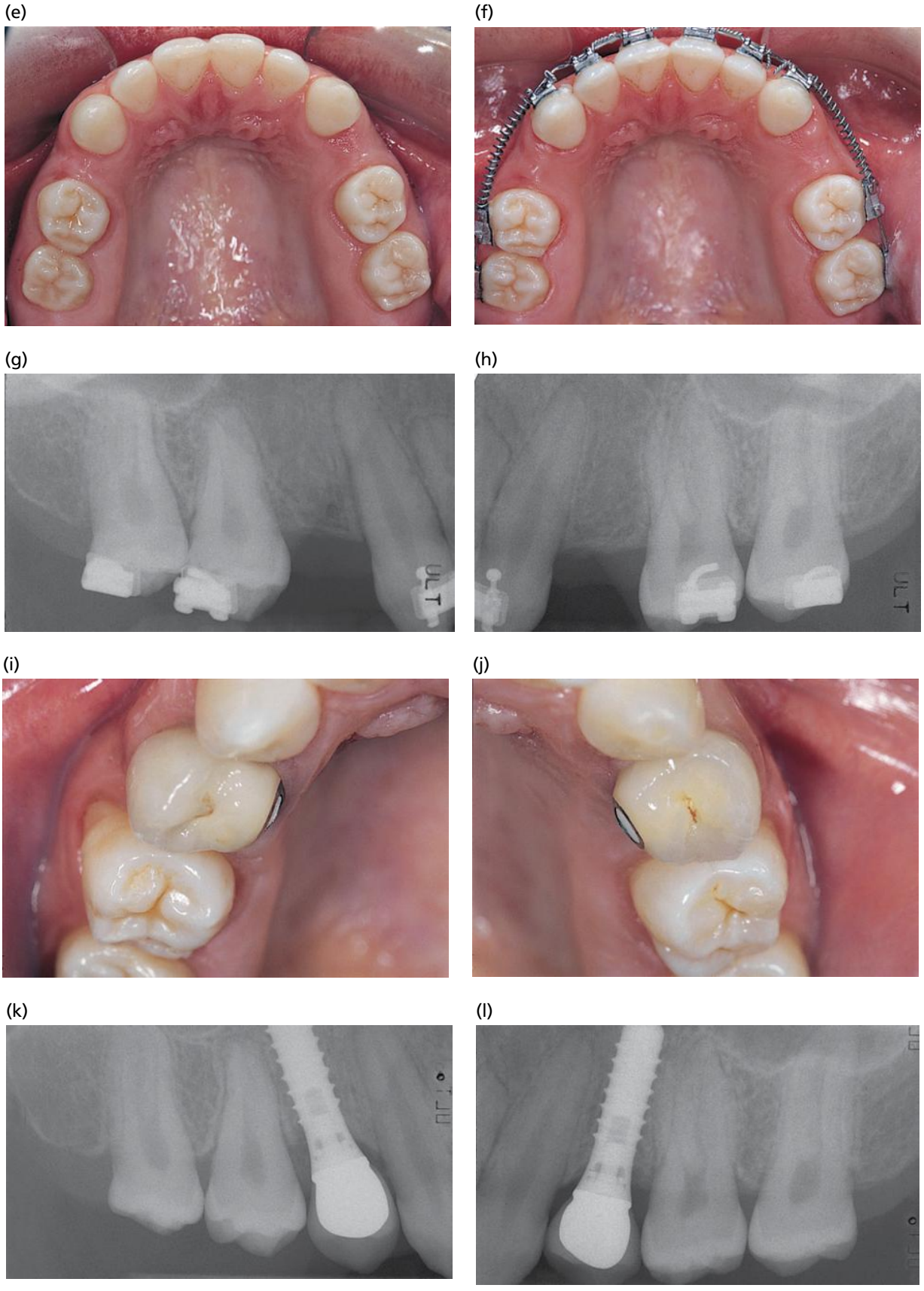

Fig. 55-38 (*Continued*) (e) Clinical occlusal view displays the bilateral edentulous spaces in the premolar area. Despite previously performed orthodontic therapy, aimed at reducing the edentulous spaces to the size of one premolar, the mesiodistal gap width on the right side is insufficient for the insertion of an implant. (f) After 6 months of additional orthodontic treatment using an upper fixed full-arch appliance, the dimensions of the two prospective implant sites appear compatible with this kind of therapy. (g) Corresponding radiograph confirms adequate space in the upper right premolar region for the placement of a standard single-tooth implant. (h) Similar presurgical situation is radiographically confirmed for the upper left premolar site. (i) Right oblique occlusal view of the implant restoration clearly demonstrates the advantage of the transverse screw-retention design: no occlusal screw access channel interfering with the functional occlusal morphology and esthetics or with structural requirements inherent to the metal–ceramic technology. (j) As described for the patient's right side, the left maxillary fixed single-tooth implant restoration integrates appropriately with the existing natural dentition. (k) Follow-up radiograph taken 1 year after the insertion of the 12-mm solid screw implant shows adequate marginal fidelity and stable conditions at the bone–implant interface. (l) Similar findings are present in the corresponding left-sided follow-up radiograph.

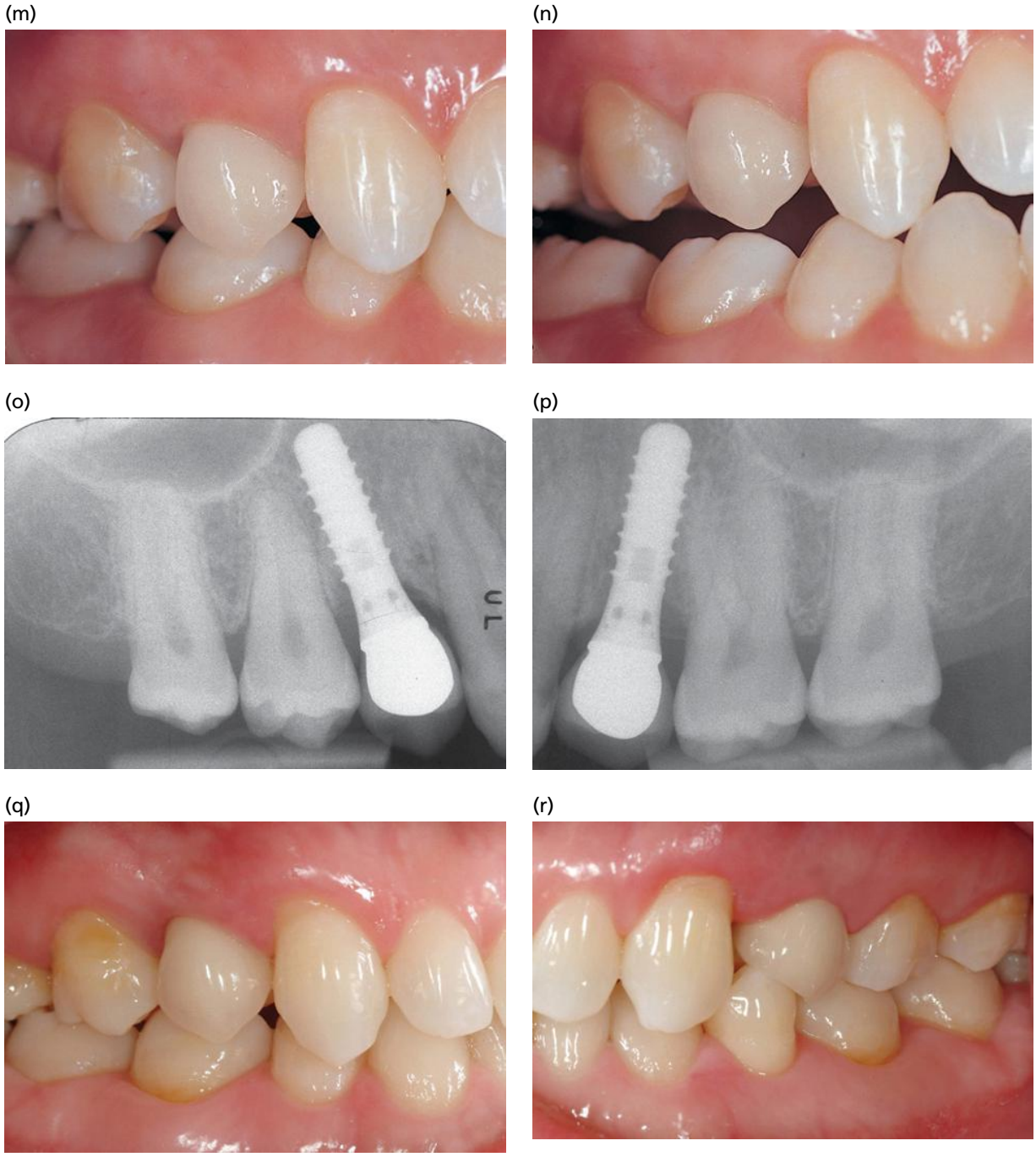

Fig. 55-38 (*Continued*) (m) Final right lateral view in centric occlusion shows acceptable general interarch conditions and related intercuspation. (n) During the right lateral excursion of the mandible (working-side movement), a canine guidance could be established. (o) Periapical X-ray after 13 years of loading shows stable crestal bone levels at the upper right premolar. (p) At the upper left side, the periapical radiograph shows very stable bone-to-implant conditions 13 years after crown insertion. (q) Buccal clinical view at the right side shows the implant crown after 13 years of loading. The soft tissue around the implant remained very stable. However, a recession was detected at the neighboring tooth 13. (r) Clinical view of the left side also reveals very stable soft tissue conditions 13 years after implant crown insertion. The soft tissue is slightly inflamed.

also include presurgical orthodontic therapy (Fig. 55-38). The objective is clearly to create local conditions that are best suited for the type of therapy chosen. If implants are to be involved, the local bone and soft tissue anatomy, as well as the mesiodistal and orofacial distances of a given edentulous segment, have to comply optimally with the most appropriate implant dimensions. Quite often, the mesiodistal gap dimensions have to be optimized orthodontically and neighboring roots aligned, so that they will not interfere with "restoration-driven" implant positioning. The case shown in Fig. 55-38 demonstrates a preoperative situation which does not allow posterior implants to be placed without a preoperative orthodontic therapy.

Molar-size single-tooth restorations

If a given posterior single-tooth gap instead corresponds to the mesiodistal dimension of a molar, it is recommended, for the reasons given in the previous

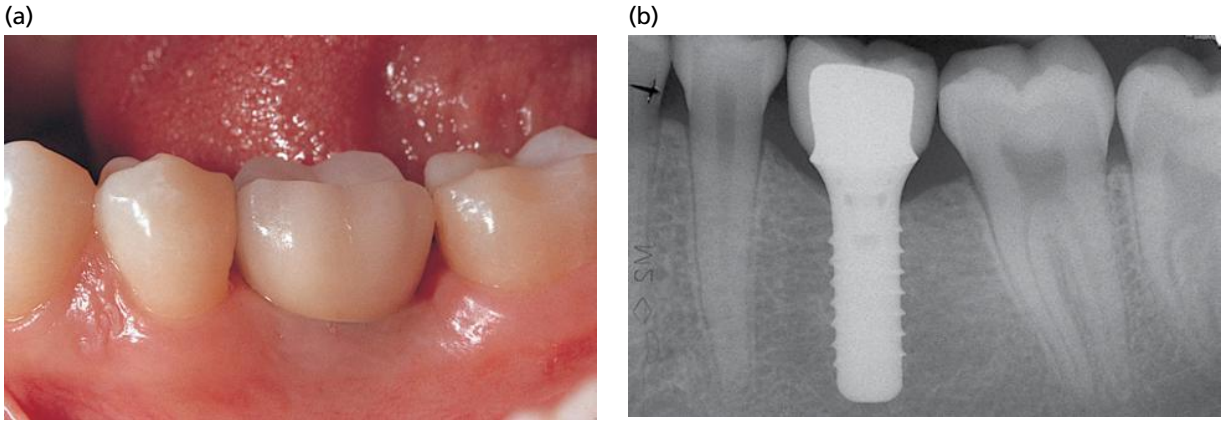

Fig. 55-39 (a) In a case of the replacement of a single missing molar, the use of an implant with corresponding dimensions is recommended to permit a restoration featuring optimal subjective comfort and cleanability. (b) On the 1-year radiographic follow-up, a diameter- increased implant can be noted, which is essential for a suprastructure design without extremely open interdental embrasures, which would be prone to food retention and oral parafunctions.

paragraph, that the insertion of a wide-neck implant is planned (Bahat & Handelsman 1996). This approach, however, also requires the appropriate bone volume in an orofacial direction. If this is not the case, presurgical site analysis, eventually in the form of a bone mapping, should identify whether it is possible to combine an implant placement with a lateral bone augmentation procedure using a simultaneous approach. If the local bone anatomy requires bone augmentation according to a staged protocol, one has to carefully ponder and discuss with the patient if this additional effort, risk, and ultimately also cost can be justified by an anticipated implant restoration featuring close-to-ideal axial contours and embrasures.

A clinical example demonstrating the potential of increased diameter implants for the optimal replacement of a single missing mandibular molar is given in Fig. 55-39.

Prosthetic reconstructions in the posterior dentition

Loading concepts for the posterior dentition

Loading concepts in implant dentistry have been widely discussed in the literature. Initially, healing phases of 3 months in the mandible and 6 months in the maxilla were recommended (Brånemark *et al.* 1977). To meet the patient's expectations for earlier prosthetic rehabilitation, shortened healing periods between implant installation and loading have been introduced. A variety of influencing factors, like initial implant stability, implant surface characteristics, bone quantity, bone healing, interim prosthesis design, and occlusal pattern during the healing phase, have been identified for successful osseointegration with modified loading protocols (Chiapasco 2004). Developments of the implant design especially, including structured and chemically modified surfaces, have led to the accelerated osseointegration of implants (Abrahamsson *et al.* 2004; Buser *et al.* 2004; Bornstein *et al.* 2008). With these improvements and increased knowledge of patient- and site-related risk factors allowing more comprehensive patient selection, earlier loading of implants has become possible.

So far no consensus has been found in the terminology for timing of loading. Depending on the reference, "immediate" loading is defined as a restoration within 48 hours (Weber *et al.* 2009) or within 7 days (Esposito *et al.* 2007) after implant placement; "early" loading between 48 hours and 3 months (Weber *et al.* 2009) or 7 days to 2 months (Esposito *et al.* 2007); "conventional" loading between 3 and 6 months (Weber *et al.* 2009) or later than 2 months (Esposito *et al.* 2007); and "delayed" loading as later than this (Weber *et al.* 2009) (Table 55-5).

Loading concepts for fully edentulous patients

In fully edentulous patients, immediate or early loading in the maxilla using removable prostheses is scarcely documented. Survival rates of 87–96% after only 2 years have been reported (Gallucci *et al.* 2009). Immediately or early loaded implants supporting fixed reconstructions show superior survival rates in the maxilla and mandible over removable prostheses. The degree of scientific documentation and the implant survival rate after immediate or early loading are generally higher in the mandible than in the maxilla (Table 55-6).

Loading concepts for partially edentulous patients

In patients with partially edentulous posterior segments, various studies have confirmed high implant survival of immediately or early loaded implants, ranging from 93% to 100% after 1–7 years (Cordaro *et al.* 2009; Roccuzzo *et al.* 2009). Overall, immediate loading seems to be inferior in terms of implant survival compared to early loading. Implants placed in the mandible perform better than in the maxilla, which is attributed to differences in bone quality. Conventional loading should be the procedure of choice for partially edentulous posterior sites (maxilla and

Table 55-5 Terminology of loading times.

	Immediate	Early	Conventional	Delayed
Esposito *et al.* (2007) Cochrane systematic review	<7 days	7 days to 2 months	>2 months	
Weber *et al.*(2009) 4th ITI Consensus Conference, Stuttgart 2008	<48 hours	48 hours to- 3 months	3–6 months	>3–6 months

Table 55-6 Loading concepts for fully edentulous patients.

	Removable						Fixed					
	Maxilla			Mandible			Maxilla			Mandible		
	No. of studies	Follow-up (years)	Implant survival rate (%)	No. of studies	Follow-up (years)	Implant survival rate (%)	No. of studies	Follow-up (years)	Implant survival rate (%)	No. of studies	Follow-up (years)	Implant survival rate (%)
Conventional	3	1–10	94.8–97.7	10	1–10	97.1–100	4	3–10 y	95.5–97.9	4	3–10	97.2–98.7
Early	2	1–2	87.2–95.6	4	1–2	97.1–100	3	1–3 y	93.4–99	3	1–3 y	98.6–100
Immediate	1	1	96	7	1–13	96–100	6	1–3 y	95.4–100	7	1–3 y	98–100
Immediate/ immediate	–	–	–	–	–	–	4	2– 5	87.5–98.4	2	1.5–2	97.7–100

Table 55-7 Loading concepts for patients with partially edentulous posterior segment.

	Maxilla			Mandible		
	No. of studies	Follow-up (years)	Implant survival rate (%)	No. of studies	Follow-up (years)	Implant survival rate (%)
Conventional (3–6 months)	–	–	–	–	–	–
Early (48 hours to 3 months)	12	1–7	95.2–100	8	1–5	96–100
Immediate (<48 hours)	6	1–3	88–100	9	1–2	91–100

Table 55-8 Loading concepts for single tooth replacements (single crowns, posterior segment).

	Maxilla + mandible			Mandible		
	No. of studies	Follow-up	Implant survival rate (%)	No. of studies	Follow-up	Implant survival rate (%)
Immediate restoration	1	1 year	91	1	2 years	100
Immediate loading	–	–	-	5	6 months to 3 years	91.7–100

mandible) in cases of low implant stability, extensive bone augmentation or patient-related risk factors (e.g. parafunction) (Weber *et al.* 2009) (Table 55-7).

Loading concepts for single-tooth replacements

Based on a systematic review including seven clinical studies with a total of 188 implants, mainly placed in the mandible, it was documented that implants restored with single crowns in the molar region showed survival rates of 91–100% after 6 months to 3 years if loaded immediately (Atieh *et al.* 2010) (Table 55-8).

It is important to point out that the scientific documentation is almost exclusively based on studies with implants placed in sites with sufficient bone and without concomitant bone augmentation techniques. Therefore, little scientific documentation exists on outcomes of implants placed with simultaneous GBR procedures. Depending on the size of the bone defect, it might be advisable to allow for longer healing periods after implant placement in conjunction with GBR procedures (Zembic *et al.* 2010). Human histologic data show a marked increase of bone in grafted sites between 6 and 8 months after augmentation (Fugazzotto 2003). In clinical practice, loading of implants 3–6 months after placement together with GBR procedures has been documented to be a successful concept after 3–5 years of observation (Jung *et al.* 2009b; Truninger *et al.* 2011).

In general, immediate or early loading can be considered in patients with a high primary implant stability and without systemic risk factors or

significant peri-implant bone defects. Splinted fixed reconstructions are favored over removable or single crown reconstructions in the posterior segments. If possible, immediate or early reconstructions should be free from occlusal load (Cordaro *et al.* 2009; Gallucci *et al.* 2009; Roccuzzo *et al.* 2009; Weber *et al.* 2009).

Screw-retained versus cemented reconstructions

When it comes to the prosthetic reconstruction of implants in the posterior region, the clinician has to decide whether to attach the suprastructure by means of screw-retention or cementation to the abutment or the implant. The decision is based on both general and clinical considerations.

General considerations

The major advantages of screw-retained prostheses include retrievability and accessibility, facilitating replacement and maintenance of the reconstruction (Chee *et al.* 1999; Michalakis *et al.* 2003). In addition, it is easier to shape the emergence profile with screw-retained implant provisionals and to transfer the contour to the master cast. Screw-retained restorations usually involve more complex and more expensive laboratory procedures and can suffer from inherent mechanical complications such as screw loosening and fractures (McGlumphy *et al.* 1998; Pietrabissa *et al.* 2000). Furthermore, the presence of a screw access hole may impede the occlusal morphology and thus, interfere with the occlusion (Hebel & Gajjar 1997). The ceramic layer is thereby discontinued, which could have an impact on the stability of the ceramics in the long-term. This assumption is supported by several *in vitro* studies, which found a higher fracture resistance and fewer chip on the veneered ceramics of cemented metal–ceramic crowns than of screw-retained implant crowns (Torrado *et al.* 2004; Karl *et al.* 2007; Zarone *et al.* 2007; Al-Omari *et al.* 2010; Shadid *et al.* 2011). These findings should be interpreted with caution however, since any clinical relevance supported by long-term clinical studies is lacking. Further clinical complications include the loss of the screw access hole restoration. This is reported to be the second most common technical complication based on a systematic review focusing on implant-supported FDPs (Lang *et al.* 2004) and occurred at a rate of 8.2% in a clinical study (Ortorp & Jemt 1999; Ortorp *et al.* 1999).

In contrast to the screw-retained restorations, where the ideal implant axis is a prerequisite, the cemented restoration offers the option to better compensate for a suboptimal implant position. The restoration of inadequately positioned implants is facilitated through cementation and the esthetics of the restoration can be enhanced since the screw access hole is not visible (Chee *et al.* 1999; Taylor & Agar 2002). One of the major advantages of cement-retained restorations therefore is the absence of a screw opening. As well as the above-mentioned advantageous esthetics, an optimal occlusal morphology and a sound ceramic layer are enabled (Hebel & Gajjar 1997). Cemented restorations incur lower technical costs than screw-retained restorations due to a reduced number of implant components and the fewer technical steps needed (Taylor & Agar 2002). A variety of disadvantages for cemented reconstructions have been reported, including the difficulty of removing cement without increasing the risk of peri-implant disease, a more complex retrievability of the reconstruction, and the possibility of crown loosening due to loss of retention (Breeding *et al.* 1992; Agar *et al.* 1997; Kent *et al.* 1997; Chee *et al.* 1999; Michalakis *et al.* 2003). Loss of retention can amount to 5.5% at 5 years and 16% at 10 years at implant-supported fixed partial dentures and single crowns (Bragger *et al.* 2001; Jung *et al.* 2008).

To assure long-term success of a cemented crown, an adequate retention and resistance form as well as sufficient restorative space is required. In situations with only 4 mm of interocclusal space (distance from the implant surface to the opposing teeth), adequate retention of cemented restorations is unrealistic (Chee & Jivraj 2006). In those cases, screw-retained restorations are the only predictable solution.

Clinical considerations

Clinically, the choice between using screw-retained or cemented reconstructions is controversial and mostly depends on the preference of the clinician (Misch 1995; Hebel & Gajjar 1997; Chee *et al.* 1999; Michalakis *et al.* 2003). Numerous clinical and *in vitro* studies evaluated the outcomes of screw-retained compared to cement-retained restorations: (1) the survival rates of implants and reconstructions, (2) technical parameters, (3) biologic outcomes, (4) esthetics, and (5) economic aspects were considered.

Implant/prosthodontic survival rates

With regard to the survival of implants and restorations, no differences were reported in either a 3-year prospective clinical study or a randomized controlled study with a 4-year follow-up on cemented and screw-retained implant reconstructions (Vigolo *et al.* 2004; Weber *et al.* 2006). These results were confirmed in a systematic review focusing on the comparison of the two treatment modalities (Weber & Sukotjo 2007). Based on the meta-analysis, no statistically significant differences with respect to the survival of implants (98.1% for cemented and 97.7% for screw-retained restorations at 6 years) and reconstructions (93.2% and 83.4%, respectively, at 6 years) were found (Weber & Sukotjo 2007). According to these results, it is not evident that one method of retention is superior to the other for both implants and reconstructions.

Technical considerations

The literature reports conflicting data on the incidence of technical complications at screw-retained and

cemented reconstructions. Additionally, the reported studies have included different numbers of these two fixation types, and only a few are randomized and controlled. Thus, it remains difficult to draw any conclusions relevant to the clinic. Some studies support a higher number of complications for screw-retained restorations (Levine *et al.* 2002; Duncan *et al.* 2003), whereas a more recent study found that cemented FPDs are associated with more complications than screw-retained FPDs (10.4% versus 5.9%) (Nedir *et al.* 2006). In that study, porcelain fractures occurred in 16 cemented reconstructions and two screw-retained ones (Nedir *et al.* 2006). Another study reported no significant differences in technical complications (not considering screw loosening) at screw-retained FPDs compared to cemented FPDs on implants (Bragger *et al.* 2001). Tightening of the screw was necessary in 21 of 45 screw-retained reconstructions, whereas recementation was necessary in 20 of 127 cases (De Boever *et al.* 2006). The higher number of cemented restorations might explain the significantly higher percentage of complications at screw-retained reconstructions compared to cemented reconstructions.

Biologic considerations

From a biologic point of view, no significant differences in probing depth, bleeding on probing, amount of keratinized mucosa, mucosal inflammation, and plaque were observed at 4 years in a randomized prospective study comparing cemented and screw-retained single implant crowns (Vigolo *et al.* 2004). These data are supported by a more recent study, which also found no differences for bleeding on probing between cemented and screw-retained anterior implant crowns (Cutrim *et al.* 2012), while contrary results with a more favorable peri-implant tissue response were reported earlier for screw-retained restorations (Weber *et al.* 2006). Still, it has been stated that the design of the implant–abutment junction may have an impact on the amount of bacterial penetration into the internal part of dental implants and may influence the peri-implant soft and hard tissues (Hermann *et al.* 2001; Piattelli *et al.* 2001). However, there is limited information available with respect to differences in the microbial penetration of the microgap of implants with different connection designs. Furthermore, the clinical relevance of this is questionable.

Esthetic considerations

Deviations from the optimal implant position and angulation can lead to an unesthetic restoration in case of screw-retained implant reconstructions, due to the visible screw access hole which is difficult to cover with composite (Walton & MacEntee 1994). Thus, in these cases, cement-retained restorations are indicated in order to achieve an acceptable esthetic outcome. When comparing the pink esthetic scores of screw-retained and cemented anterior crowns, no significant differences were found in a recent study (Cutrim *et al.* 2012).

Economic considerations

In posterior regions, the clinician has the option to keep the margin of the restoration more superficial than is possible in the anterior regions due to a minor esthetic priority. Thus, the more affordable standardized cemented restorations represent a viable treatment option for the posterior area. In contrast, in the anterior region, esthetics play a major role. In these cases, either screw-retained restorations or cemented individualized abutments and crowns might be the first choice and help to avoid problems associated with removal of cement or remnants, as well as visible crown margins in case of recessions.

Conclusion: On the basis of the existing scientific evidence, the decision to cement or screw-retain an implant restoration can rest on a clinician's personal preference, provided that the implants are placed in a manner that allows both options (implant placement enabling optimal location of the screw access hole at screw-retained restorations). Ideally, the choice should depend on each particular patient situation, including anatomic, economic, and esthetic factors. Figures 55-40, 55-41, and 55-42 show three clinical cases. Proposed indications for the two retention systems are listed in Table 55-9.

Selection criteria for choice of restorative materials (abutments/crowns)

The posterior region of the jaw bears the most load and as such must be mechanically stable. Biocompatible materials are needed for restorations. Today, a large variety of biocompatible materials is available due to the widespread use of CAD/CAM technology. Different factors are crucial to making the right decision between the optimal material and the reconstruction type for the posterior region.

In general, a choice can be made between two kinds of abutments: prefabricated and customized. The decision-making process should be based on a variety of clinical, technical, and biologic factors: For implant reconstructions (irrespective of their location), an adequate emergence profile is a prerequisite for healthy soft and hard tissue integration (biologic width), as well as ease of cleaning for the patient and a natural appearance. In case of low scalloped soft tissues and an appropriate distance between the implant shoulder and the crown margin (i.e. 3 mm), a biologic width can be established and the use of prefabricated abutments is indicated. The formation of a biologic width is reported to occur also in a horizontal direction (approximately 1.5 mm) (Tarnow *et al.* 2000).

In molar areas, a large deviation between implant and crown diameters can be found. In these situations, customized abutments together with the ideal emergence profile allow the crown margin to follow the present mucosal outline (Marchack 1996). Further conditions, like a limited vertical distance between

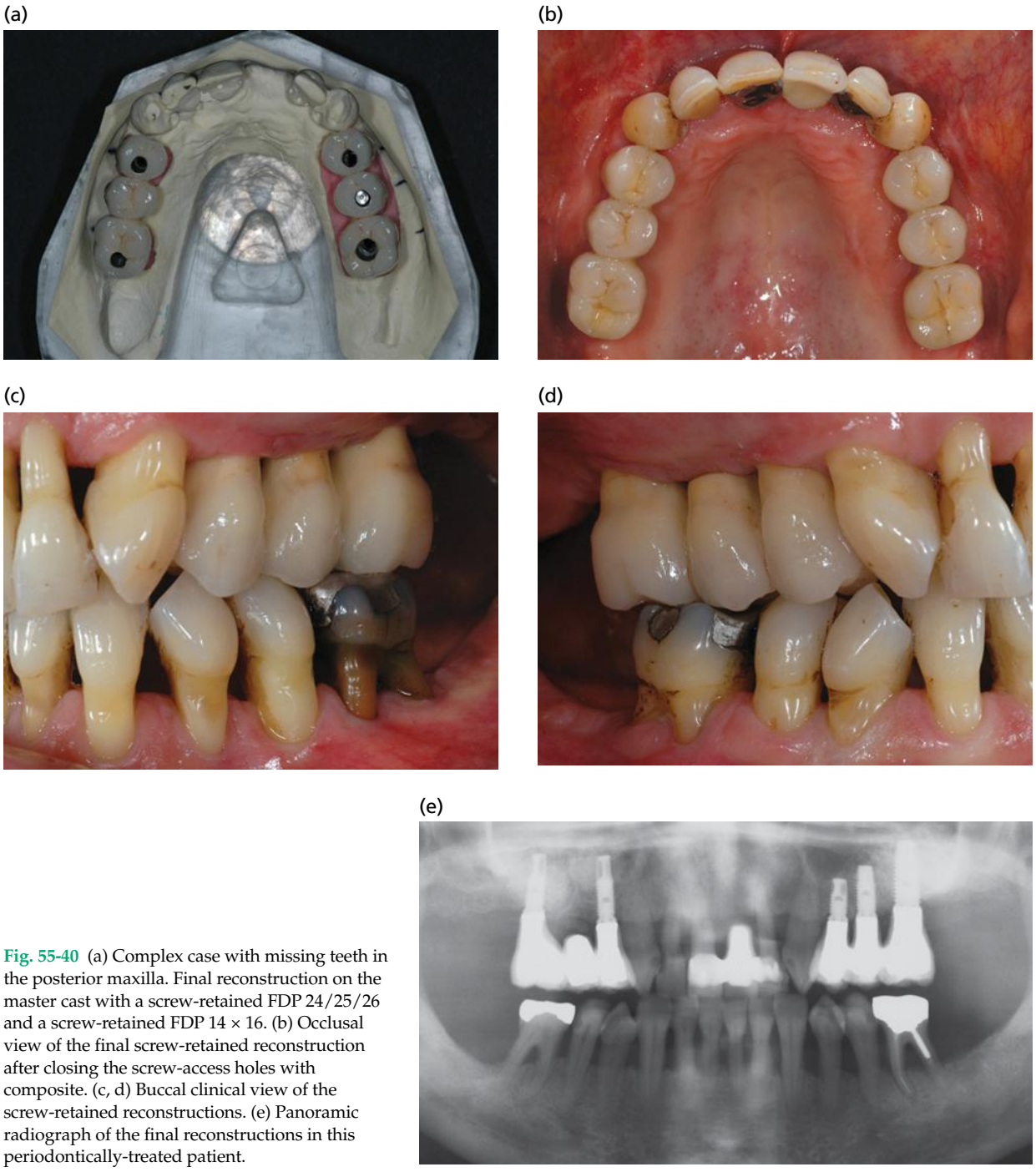

Fig. 55-40 (a) Complex case with missing teeth in the posterior maxilla. Final reconstruction on the master cast with a screw-retained FDP 24/25/26 and a screw-retained FDP 14 × 16. (b) Occlusal view of the final screw-retained reconstruction after closing the screw-access holes with composite. (c, d) Buccal clinical view of the screw-retained reconstructions. (e) Panoramic radiograph of the final reconstructions in this periodontically-treated patient.

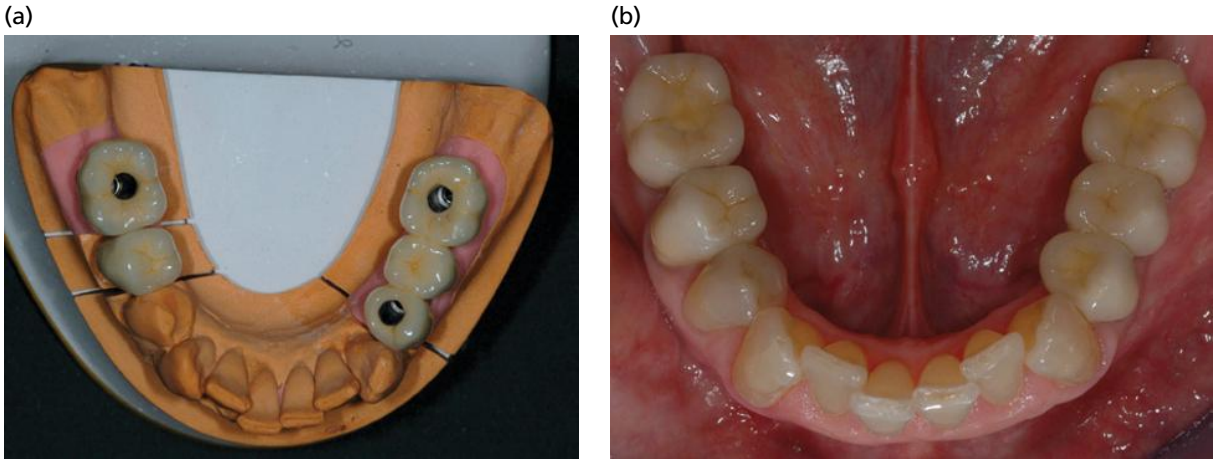

Fig. 55-41 Missing teeth (46, 34, 35, 36) in the posterior mandible. The final screw-retained reconstruction on the master cast. (b) Screw-retained reconstruction with single implant crown (46) and screw-retained FDP (35 × 37) after closing the screw-access holes.

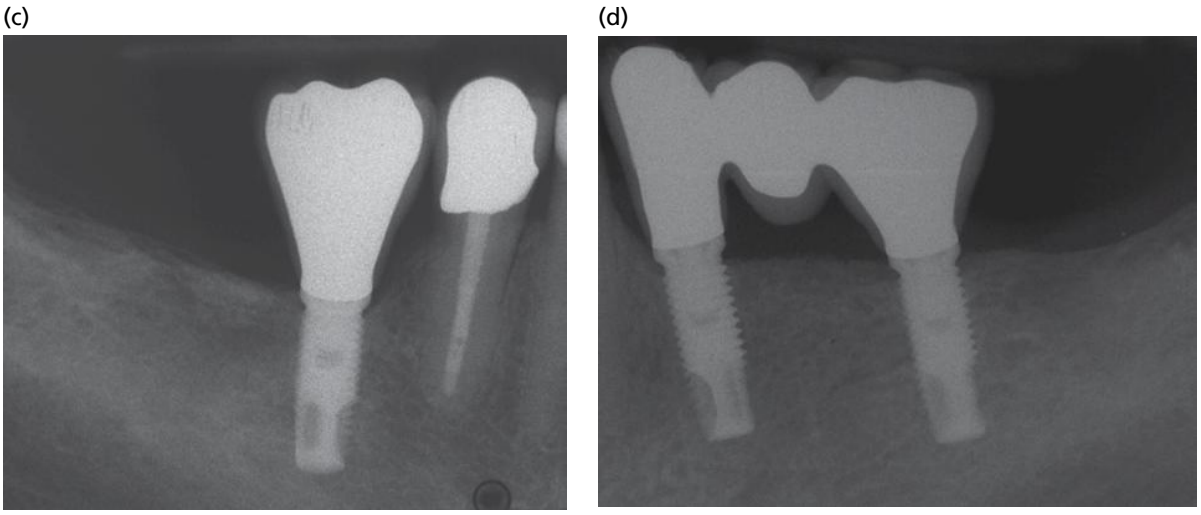

Fig. 55-41 (*Continued*) (c) Periapical X-rays post insertion of single implant crown 46. (d) Periapical X-rays post insertion of FDP 35 × 37.

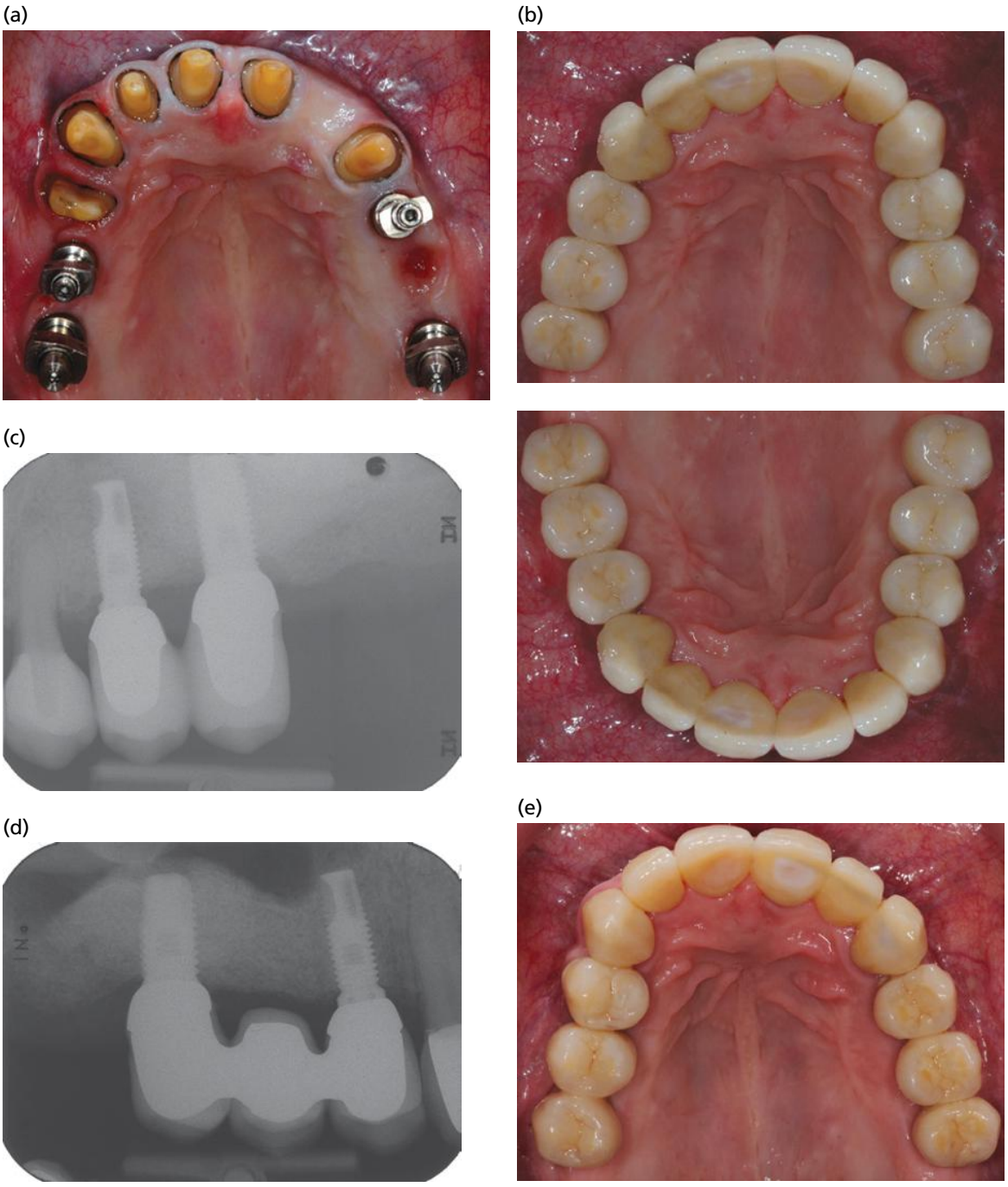

Fig. 55-42 (a) Missing posterior teeth in the maxilla (15, 16, 24, 25, 26) reconstructed with single crowns (15, 16) and an FDP (24 × 26). Status at final impression. (b) Occlusal view post insertion with cemented reconstructions (single tooth crowns 15 and 16; FDP 24 × 26). (c, d) Final periapical radiographs after insertion. (e) Clinical situation at 5 years post insertion, occlusal view.

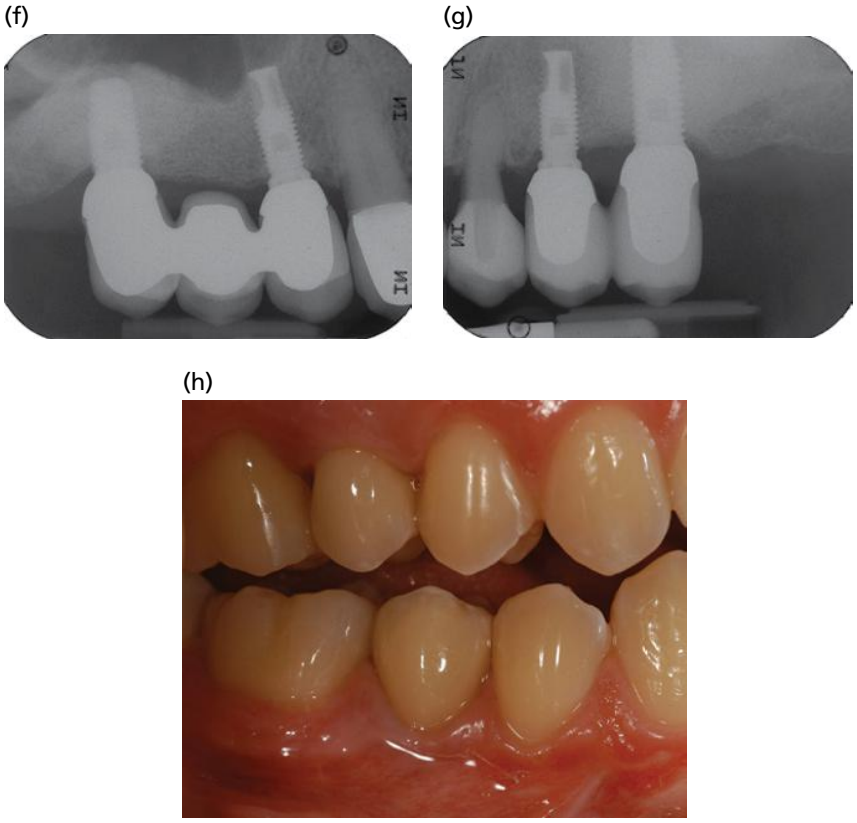

Fig. 55-42 (*Continued*) (f, g) Periapical radiographs of the reconstruction after 5 years of function. (h) Highly scalloped and thin mucosa at implant 45, restored with an individualized zirconia abutment and a cemented all-ceramic crown.

Table 55-9 Proposed indications for the two retention systems.

Parameter	Screw-retained	Cement-retained
Crown margin >2 mm submucosal	x	
Crown margin ≤2 mm		x
Reduced interocclusal distance <5 mm	x	
Interocclusal distance ≥5 mm	x	x
Re-intervention desired	x	
Multiple implants/high level of complexity	x	x
Immediate loading/restoration of single and multiple implants	x	
Conditioning of the emergence profile	x	
Divergent or unfavorable implant position		x
Costs		x

the crown and the surrounding bone, a prosthetically inadequate implant position, and a thin highly scalloped mucosa, require customization of abutments even in posterior regions (Fig. 55-42f).

A large variety of materials is available both for prefabricated and customized abutments (gold, titanium, alumina, and zirconia). Metal abutments offer excellent material stability and exhibit very good clinical outcomes (Sailer *et al.* 2009a). For a long time, they were considered to be the "gold standard" in posterior regions of the jaws (Henry *et al.* 1996; Andersson *et al.* 1998b; Scheller *et al.* 1998). Today, high strength ceramics are competing with the well-documented metal materials. However, it remains controversial whether or not use of the former in posterior regions is acceptable.

Alumina abutments, the first generation of high-strength ceramic abutments, showed fracture rates ranging from 1.9% to 7% (Andersson *et al.* 2001, 2003). Zirconia, the subsequently developed high-strength ceramic, exhibits twice the bending strength and fracture toughness of alumina (Rieger 1989; Tinschert *et al.* 2001) and was, therefore, considered an alternative material for posterior sites.

Satisfactory clinical outcomes and survival rates were reported for zirconia abutments at premolar and molar sites (Canullo 2007; Zembic *et al.* 2009; Nakamura *et al.* 2010; Nothdurft & Pospiech 2010). Although these results are promising, zirconia abutment fractures have been described (Villa *et al.* 2010; Ekfeldt *et al.* 2011; Roe *et al.* 2011). It is thus still necessary to prove that zirconia abutments represent a safe treatment option for posterior implant restorations (Nakamura *et al.* 2010). Hence, for now metal abutments remain the "gold standard" for molar regions.

Besides mechanical stability, the biocompatibility of the implant abutment is decisive. Titanium abutments led to the development of stable peri-implant soft tissues, consisting of a junctional epithelium and underlying connective tissue firmly adhering to the abutment surface (Abrahamsson *et al.* 1998). Alumina and zirconia both exhibited equal or even better

biologic outcomes compared to titanium (Abrahamsson *et al.* 1998; Nakamura *et al.* 2010). Furthermore, less plaque accumulation was found at zirconia as compared to titanium (Rimondini *et al.* 2002; Scarano *et al.* 2004; Degidi *et al.* 2006). Thus, from a biologic point of view, alumina, zirconia, and titanium are equivalent. In contrast, gold abutments led to peri-implant soft tissue inflammation and bone resorption in animal experiments (Abrahamsson *et al.* 1998; Welander *et al.* 2008).

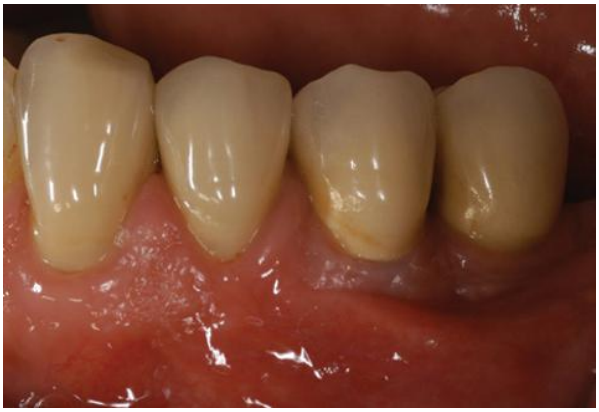

Fig. 55-43 Similar esthetic appearance of implant crowns 35 and 36 restored with different materials (35: metal–ceramic crown cemented on an individualized titanium abutment; 36: all-ceramic crown cemented on an individualized zirconia abutment). The choice of the abutment and crown material was based on a randomization protocol of a randomized controlled clinical trial. (Source: Sailer *et al.* 2009b. Reproduced with permission from John Wiley & Sons.)

Even though esthetics is of minimal importance in the posterior region of the jaw, it still has a certain influence on the decision-making process. The dark color of metals was reported to cause esthetic problems, raising the need for more esthetic solutions also in posterior regions (Sailer *et al.* 2009b). Both titanium and zirconia abutments induced a similar amount of mucosal discoloration compared to natural teeth (Sailer *et al.* 2009b; Zembic *et al.* 2009) (Fig. 55-43). The mucosal thickness was around 2 mm for both abutment materials (Sailer *et al.* 2009b; Zembic *et al.* 2009). With an increased soft tissue thickness (>2 mm), it can be expected that the abutment material will have less influence on the soft tissue color (Jung *et al.* 2007, 2008). Thus, in these cases, both titanium and zirconia abutments are suitable. In cases with a mucosal thickness of <2 mm, zirconia abutments might be preferable also in posterior sites from an esthetic point of view.

All-ceramic (Fig. 55-44) and metal–ceramic (Fig. 55-45) single-implant crowns exhibited excellent survival rates in recent systematic reviews, ranging from 99.8% to

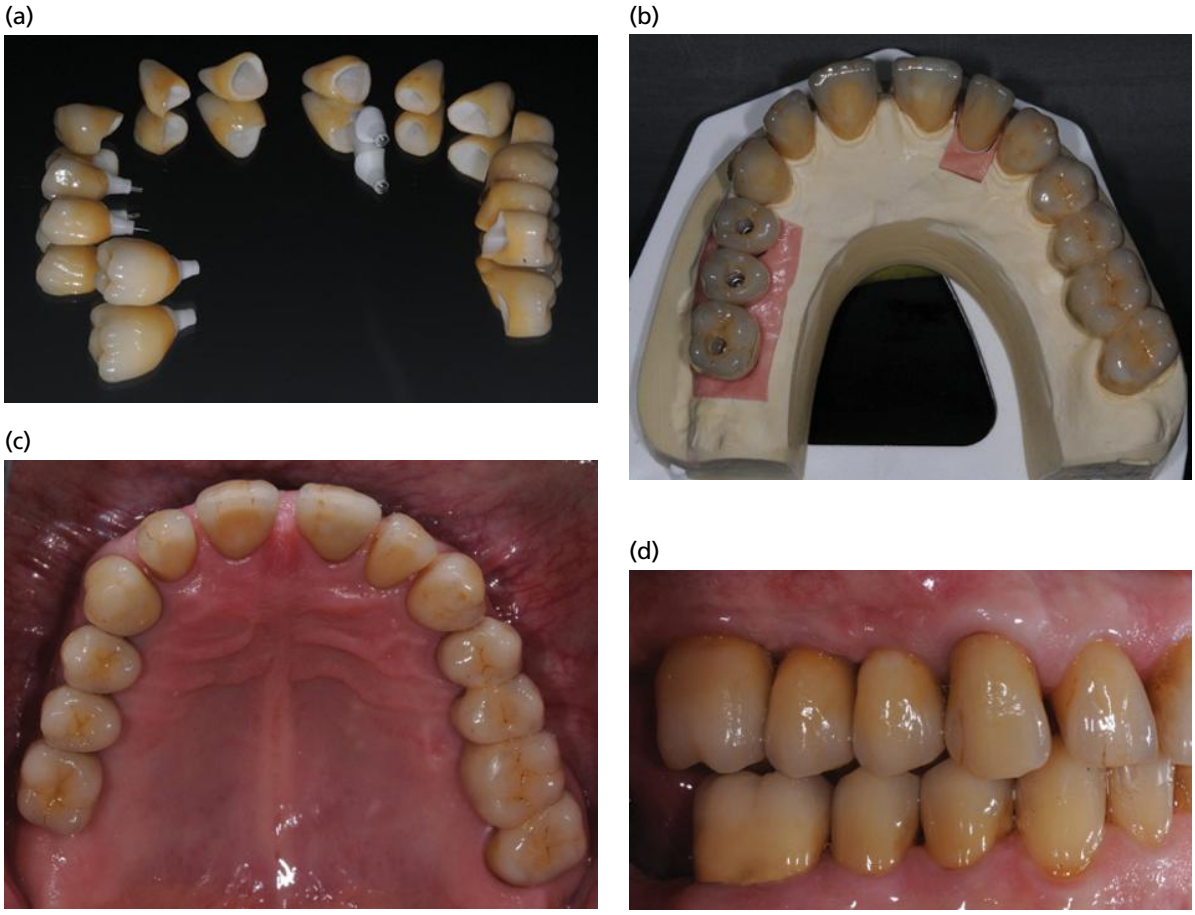

Fig. 55-44 (a) Example of a complete rehabilitation of the maxilla with zirconia-based reconstructions including posterior implant-supported screw-retained zirconia crowns. (b) Final zirconia-based reconstruction on the master cast before insertion. (c) Occlusal view of the zirconia-based reconstruction after insertion and closing the screw-access holes with composite in the upper right maxilla. (d) Buccal clinical view of the single-unit zirconia-based screw-retained implant reconstructions 14, 15, and 16.

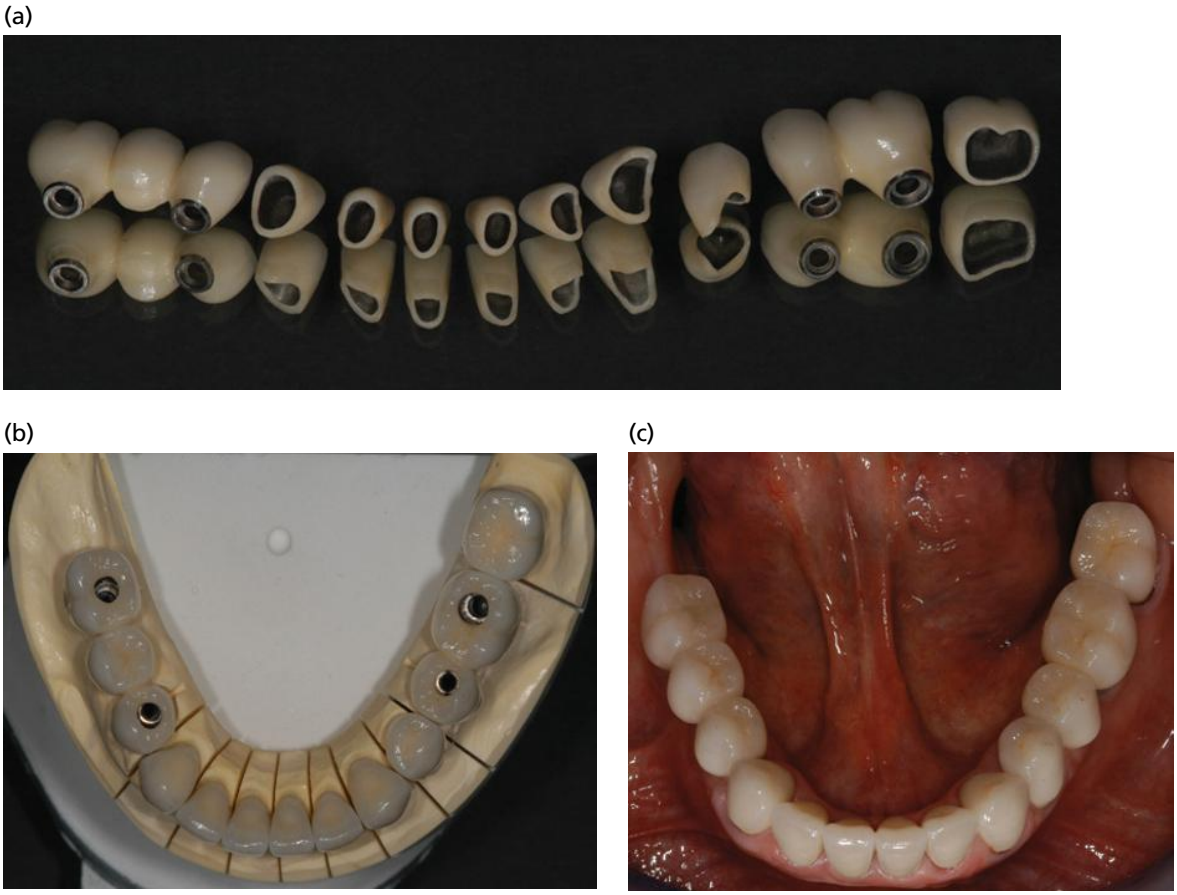

Fig. 55-45 (a) Example of a complete rehabilitation of the mandible with metal–ceramic reconstructions including posterior implant-supported screw-retained bridges. (b) Final porcelain-fused-to-metal reconstruction (PFM) on the master cast. (c) Occlusal view of the PFM reconstruction 35, 36, and 44 × 46 after insertion and closing the screw-access holes with composite.

100% at 5 years (Jung *et al.* 2008; Sailer *et al.* 2009a). Hence, both types of reconstructions may be considered as treatment options. It should be considered that the abutment material may have an influence on the stability of all-ceramic crowns. It was recommended that all-ceramic crowns should be used in combination with ceramic abutments in order to reduce the risk for fracture and esthetic failure (Sailer *et al.* 2009a). In a randomized controlled trial of all-ceramic and metal–ceramic single-implant crowns in posterior regions, no differences in the survival rates were found at 3 years of function (Zembic *et al.* 2009). Minor chipping of the veneering ceramic was the only technical complication (Zembic *et al.* 2009).

Interestingly, all-ceramic implant FDPs with zirconia frameworks also showed good clinical survival rates (Larsson *et al.* 2006; Larsson & Vult von Steyern 2010). No fractures occurred in the zirconia frameworks. In contrast, high rates of veneering ceramic fractures (Figs. 55-46, 55-47) of up to 70% raised major concern with this type of implant reconstruction (Larsson & Vult von Steyern 2010). Other studies have confirmed the high incidence of chipping at zirconia-based implant-supported reconstructions (Glauser *et al.* 2004; Larsson *et al.* 2006; Canullo 2007; Nothdurft & Pospiech 2010). Numerous factors

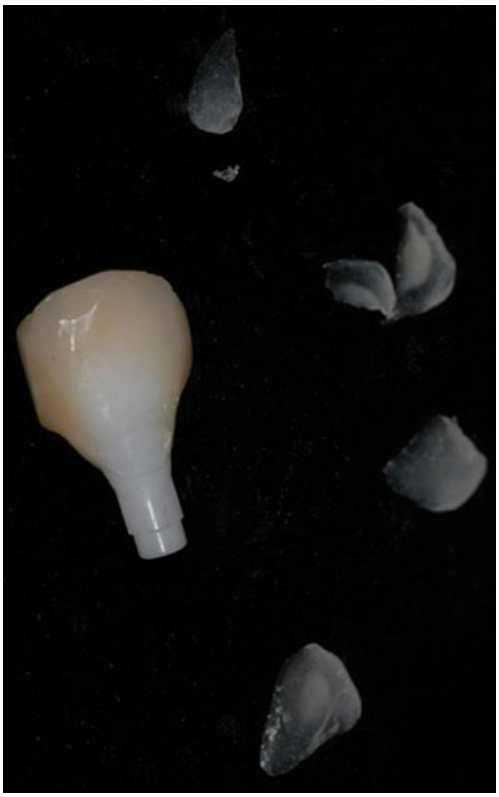

Fig. 55-46 Fractures of the cervical portion of the veneering ceramic (chips) at a posterior single-tooth zirconia-based crown.

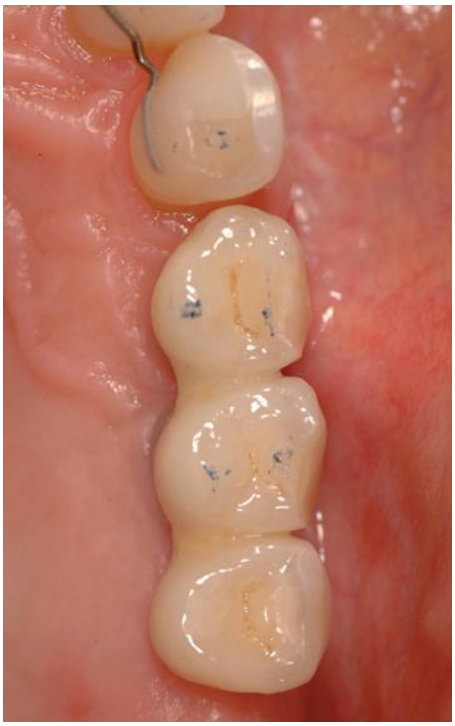

Fig. 55-47 Chipping of the buccal veneering ceramic of an implant-borne zirconia-based cemented FDP 4 years after insertion.

might contribute to this problem and are being analyzed at present; however, the major cause and solution have not been found yet (Al-Dohan *et al.* 2004; Ashkanani *et al.* 2008; Tsalouchou *et al.* 2008; Fischer *et al.* 2009). As a consequence, currently metal–ceramics should be preferred for posterior multiunit FDPs.

Concluding remarks and perspectives

The possibility of performing highly predictable treatments by using dental implants in the load-carrying part of the dentition offers the clinicians a broad range of therapeutic options for any kind of edentulism. In this context, the use of implants may often significantly reduce the inherent risk of "borderline" conventional tooth-borne FDPs (e.g. prostheses based on compromised abutment teeth, long-span FDPs, cantilevers) by implementing the principle of segmentation. This evolution is dynamic and holds promise for further significant developments.

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Chapter 56

Role of Implant–Implant- and Tooth–Implant-Supported Fixed Partial Dentures

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Introduction

The restoration of a partially edentulous situation involves a combination of systematic diagnosis, treatment planning, and careful assessment of the therapy choices and the outcomes. The replacement of a continuous span of teeth creates challenges that involve assessment of anatomy, physiology, cost, time, impact on oral health quality of life, and patient desires. A critical part of modern care is to assure tooth replacement therapy is provided in an economic and expedient manner. Dental implants offer advantages for many clinical situations. In certain situations, the restoration of missing teeth using individual free-standing implant-supported crowns is a logical and satisfactory treatment option. At other times, use of an implant-supported fixed partial denture (FPD) is the most satisfactory approach (Fig. 56-1). Because of functional and esthetic priorities, anterior and posterior multi-tooth implant restorations can present different clinical challenges. This chapter considers implant–implant supported FPDs (bridges) separately from tooth–implant-supported prosthesis since each type of prosthesis is unique and creates its own novel issues. The use of a fixed complete denture (FCD) to replace all of the teeth in an arch can be considered a form of FPD.

Patient assessment

For predictable esthetic and functional outcomes of implant treatment, comprehensive diagnostic and treatment planning is required (Stanford 2005a; Bidra 2011; Drago & Carpentieri 2011). As a member of the implant team, the prosthodontist collaborates with the surgical specialist, laboratory technician, and allied team members such as radiologists, and dental and surgical assistants. The initial assessment of the patient's medical and dental history assists in the determination of the implant system and devices that will meet the patient's therapeutic needs. The patient interview should establish the patient's individual esthetic requirements. The assessment should determine a patient's history of bruxism, periodontal disease (and type of disease), tobacco use, uncontrolled diabetes mellitus, and metabolic diseases of bone (Moy *et al.* 2005; Ahmed *et al.* 2012; Cochran & Nevins 2012; Froum & Rosen 2012; Wadsworth 2013). Implant therapy may have a variable prognosis in patients with advanced chronic periodontitis,

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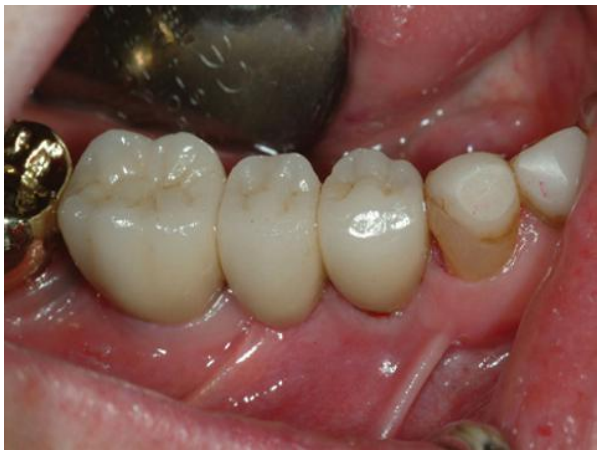
(a)



(b)

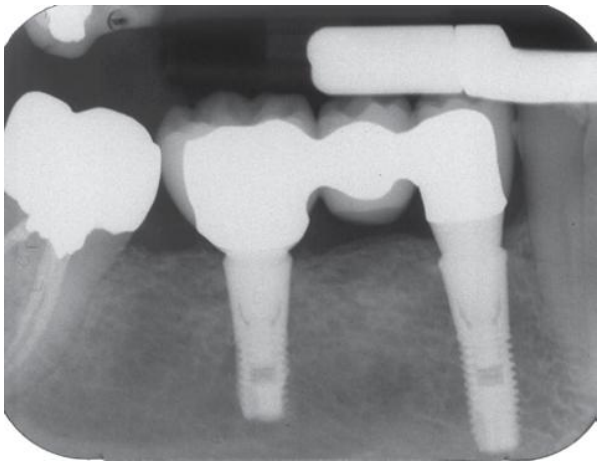


Fig. 56-1 Implant-supported fixed partial denture (FPD). (a) Patient restored with two implants (44 and 46) restored with three united FPDs. (b) Five-year recall radiograph demonstrates stability of the osseous tissues around the implants.

although with maintenance therapy a more predictable outcome can be achieved (Nevins & Langer 1995; Ellegaard *et al*. 1997; Brocard *et al*. 2000; Pjetursson *et al*. 2004; Wennström *et al*. 2004a). Maintenance therapy is vital since longitudinal bone loss around implants may occur and can be observed after many years of asymptomatic clinical service (Hardt *et al*. 2002). In addition, the assessment should educate patients about the etiology of tooth loss, reveal their attitudes towards treatment as well as their ability to tolerate it, and inform them of the estimated therapy costs (Pjetursson *et al*. 2005; Stanford 2005a). Throughout the surgical and prosthetic phases of the implant reconstruction, the dental practitioner should obtain comprehensive written and verbal informed consent to treatment from the patient. The consent form should document the risks and benefits of the proposed treatment plan, as well as the alternative treatments that have been discussed with the patient, including the option of no treatment and its consequences. This initial assessment phase should provide the clinical team with sufficient information

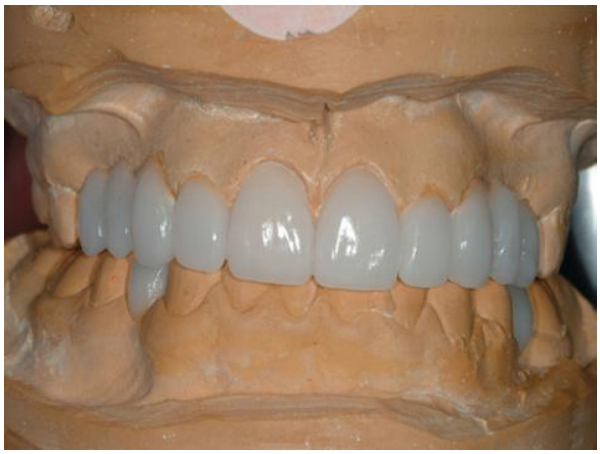


Fig. 56-2 Diagnostic wax-up for implant therapy demonstrating desired contours for the planned definitive restorations.

to characterize the patient-related risk factors influencing the care plan.

To assure that implant location and the number and dimension of implants are congruent with the anticipated prosthesis, it is essential that the dentist designs and composes the proposed prosthesis during the diagnostic phase. Planning will dictate the number and dimension of implants, their position and angulation. The plan will assimilate all clinical, radiographic, and psychological information gathered from the patient interview, clinical examination, and radiographic survey. During the clinical exam, the dentist should carefully evaluate the shape and contour of the residual ridge, and evaluate other sites in the mouth for the potential risk of recession. A careful evaluation of the patient's risk factors for soft and hard tissue changes, whatever final restoration is planned, should be made not only to comply with the informed consent process, but also to encourage realistic patient expectations. However, to move beyond assessing the feasibility of implant treatment, it is essential to utilize articulated diagnostic study casts to fully assess the tissue architecture and relationship of teeth and mucosa with the existing edentulous areas. Thus, the initial clinical examination should conclude only when sufficient materials are available to accurately mount diagnostic casts and interpret the study casts and screening radiographs using recorded clinical information. Based on this diagnostic information, a surgical guide or denture can be fabricated through the process of developing a diagnostic waxing of the planned prostheses and this can direct or indicate the desired implant position and angulation, the probable abutment dimension and angulation, and the possible need for hard/soft tissue augmentation before or during implant placement (Fig. 56-2). The diagnostic wax-up is a key step in the assessment of local risk factors affecting FPD supported by dental implants and is critical to the process of strategically planning implant placement to limit these risks.

Implant treatment planning for the edentulous arch

The mandibular arch can be restored using a FCD, FPD or overdenture. The FCD has either a gold casting or CAD/CAM-milled titanium or chromium cobalt framework, full milled monolithic zirconia or conventional acrylic resin teeth, or teeth veneered with porcelain (Adell *et al*. 1990; Ozkurt & Kazazoglu 2010). An overdenture with an attachment to the implant can be fully supported and retained by the implant(s), or a combination mucosa/implant-borne prosthesis can be used. Clinical studies indicate high patient acceptance of this form of therapy (Feine *et al*. 1994, 2002; Duyck *et al*. 2004; Naert *et al*. 2004a, b; Zitzmann *et al*. 2005)

Prosthesis design and full-arch tooth replacement therapy

If minimal bone resorption exists, restoring the edentulous maxillae with a porcelain-fused-to-metal (PFM) restoration will have a reasonable outcome (Stanford 2005a). The restorative dentist must perform a diagnostic work-up including impressions, jaw relationship records, and an esthetic try-in using prosthetic denture teeth on a trial denture base, a diagnostic wax-up template, or a CAD-milled composite template of a computer-aided esthetic set-up. Lip support and smile line (i.e. anterior and posterior occlusal planes) of the diagnostic denture set-up or "mock-up" should be evaluated intraorally. It is useful to evaluate the patient's lip support with and without the anterior facial denture flange (Lewis *et al*. 1992; Stanford 2002). The amount of tooth exposure at the anterior smile line (relaxed and exaggerated), provides clues about the expected crown length, gingival display, and potential need to use gingival-tone porcelain for appropriate tooth length and esthetics in a full-arch reconstruction. Communication and discussion with the dental laboratory technician is very helpful at this point, prior to finalizing the treatment plan. A fixed maxillary prosthesis has greater incidences of esthetic, phonetic, and oral hygiene problems compared with an overdenture prosthesis, in part associated with excessively long anterior teeth, excessive facial cantilever pontics, and mesiodistal complications with embrasures. Given the clinical and laboratory complexity of these prostheses, a maxillary overdenture on four to six implants may be an alternative (Phillips & Wong 2001; Anon 2003; Naert *et al*. 2004b).

Complete-arch fixed complete dentures

A complete-arch FCD provides excellent function and patient acceptance (Lewis *et al*. 1992; Feine *et al*. 1994). During the diagnostic phases, the advantages and disadvantages of the FCD compared with those of an overdenture should be discussed with the patient. If using a metal–ceramic full-arch fixed reconstruction, consideration should be given to replacing every three teeth with a three-unit FPD on two implants (e.g. 13–11) using the pontic contours to adjust for implant alignment and esthetic demands (Stanford 2002). A fixed maxillary reconstruction entails four, six or eight implants (first molar, first premolar, canine. and central incisor) with four independent FPDs (molar to premolar, canine to central incisor, bilaterally). With care taken to limit loading, up to six implants may be used with distal cantilevers on two FPDs (cantilever pontics limited to one premolar-size tooth). An overdenture should use a sufficient number of implants for long-term stability, typically four in the maxilla (canine and second premolar region) and two in the lower canine or first premolar region (Mericske-Stern *et al*. 2000).

Using the denture set-up, a radiographic guide is fabricated with radio-opaque markers (e.g. gutta percha or bur shanks) within the denture at the sites of interest. An alternative approach involves duplicating the denture set-up with teeth made from 5% medical-grade barium sulfate mixed with clear autopolymerizing resin or the use of temporary cement painted on the outside of the teeth on an all-acrylic resin partial or complete denture (and on the intaglio side) as a reference marker for contours to be identified on a cone-beam computed tomography (CBCT) scan. This approach allows easy visualization of tooth size, angle, and position in the CT-aided treatment planning. In the mandible, the trial set-up evaluates the height and position of the prosthetic teeth relative to the symphyseal cross-sectional anatomy. A conventional FCD with acrylic teeth bonded to a titanium alloy framework requires a minimum of 15 mm between the alveolar bony crest to the planned incisal edge (Stanford 2005a). If the vertical dimension of occlusion and jaw anatomy is insufficient, one alternative is to perform an aggressive alveoectomy or to rehabilitate with metal–ceramic restorations (along with treatment planning for the additional cost).

Radiographic information and diagnostic set-up will help determine the type of definitive prosthesis design. Skeletal class I and II relationships with minimal resorption may allow normal contours and lip support with an FCD. A prognathic class III relationship can increase prosthetic problems, especially if implants cannot be placed distal to the mental foramens, limiting the anteroposterior spread of the implants and consequent biomechanical challenges. In such cases, an overdenture approach yields a more predictable result (Naert *et al*. 1997) or a tilted implant approach can be used in which the distal implants are placed at 30° toward the back of the mouth and angled abutments upright the implant relationship to the occlusal plane (Cavalli *et al*. 2012; Grandi *et al*. 2012; Patzelt *et al*. 2013).

Prosthesis design and partially edentulous tooth replacement therapy

Clinician or patient preferences for the use of implants for restoration of partial edentulism using FPDs must be carefully weighed against the potential limitations associated with this therapy. Technical complications related to implant components and suprastructures are more frequently reported than complications related to peri-implant tissues (Berglundh *et al.* 2002). Also, complications with implant-supported FPDs are together more frequent than implant loss or implant fracture. For example, Bragger *et al.* (2001) reported that over a 10-year follow-up period the percentage of reconstructions without any biologic or technical failures/complications was 66.5% for single crown-implant restorations, 54.4% for implant-supported FPDs, and 50% for tooth–implant-supported FPDs. Importantly, the authors concluded that prostheses with a history of complications were at greater risk of implant failure. It may be possible to infer that complications reflect the functional features of the prosthesis or the patient and, furthermore, that some of these complications are due to limitations in implant and prosthesis planning, placement, or

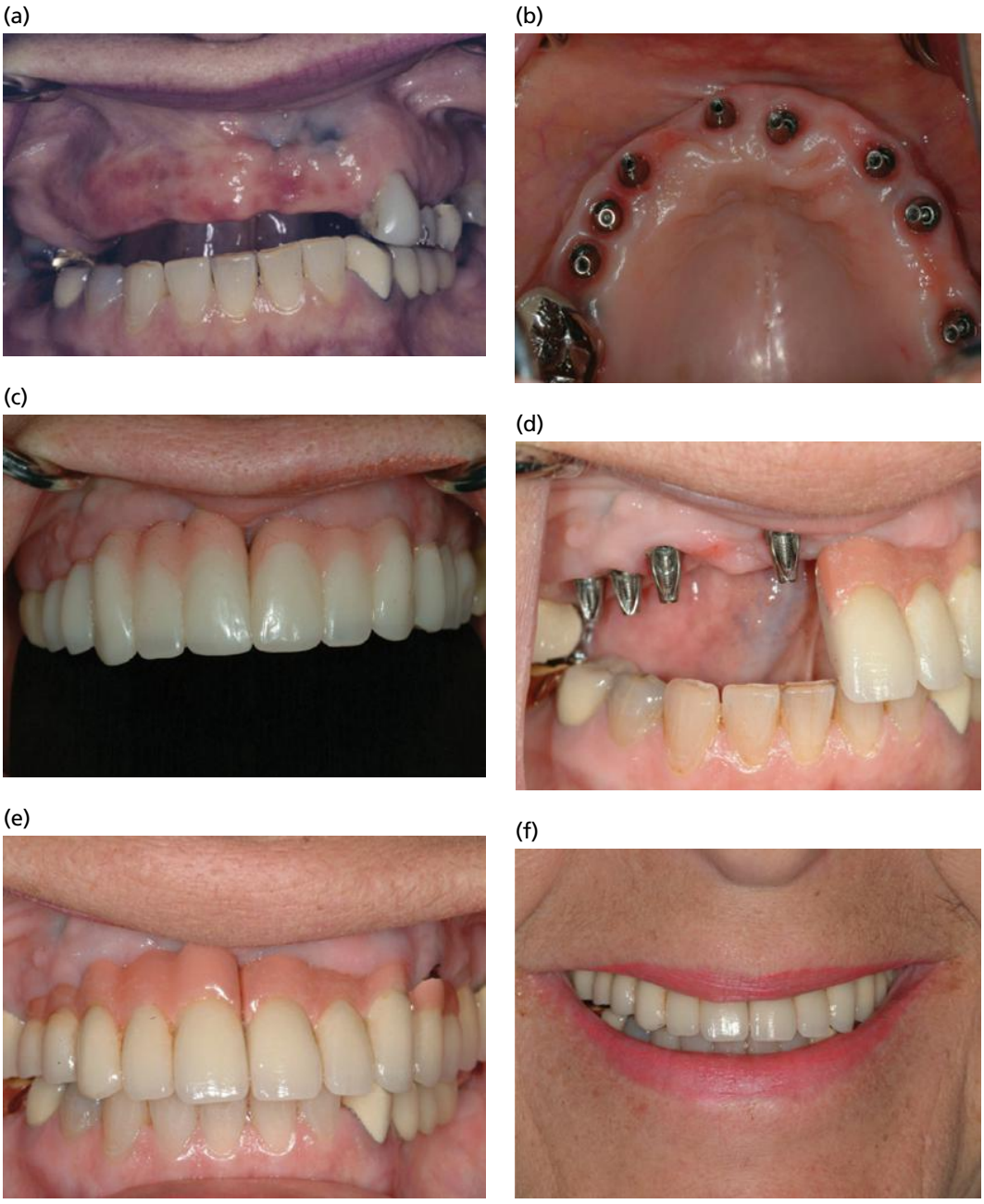


Fig. 56-3 Use of fixed partial dentures to restore missing hard and soft tissue. (a) Patient presented with a 40-year history of an edentulous space in the maxilla. Following placement of eight implants (b), a long-term acrylic resin provisional was fabricated simulating the desired tooth and soft tissue dimensions (c). (d) Based on the long-term provisional, metal–ceramic fixed prostheses were fabricated using mucosa-colored ceramic materials on a metal framework. (e, f) Five-year recall demonstrating fixed prosthetic outcomes and anterior esthetics.

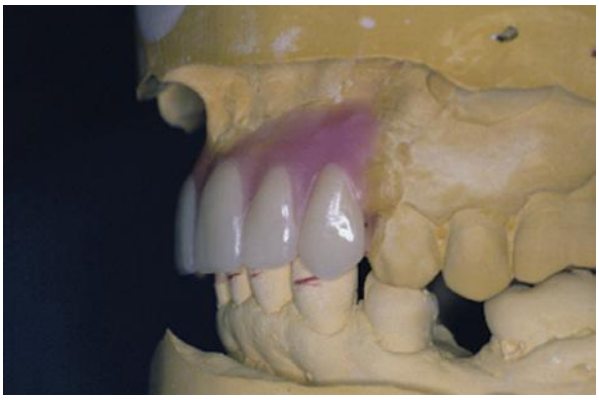
construction, or the innate limitations of implant components. Complications most frequently observed for FPDs include veneer fracture, opposing restoration fracture, bridge screw loosening or fracture, abutment screw loosening or fracture, and metal framework fracture (Goodacre *et al.* 2003a). The considerations for treatment planning of implant-supported FPDs must include features that affect not only implant success, but also abutment and bridge screw performance, prosthesis esthetics, and longevity (Fig. 56-3).

Primary among clinical considerations for any implant prostheses is some estimation of the potential forces that will be exerted during function. It is well recognized that masticatory forces increase as the point of interaction moves posterior in the arch. Additionally, damaging bending moments are increased with the acting lever arm length. Greater concern is warranted when implants are planned to support prostheses with large occlusogingival dimension (extensive resorption) or for prostheses with extensive mesial, buccal or lingual cantilevers or any substantial distal cantilever (discussed below). Additional immediate considerations typically address the esthetic potential of the prosthesis. These are clearly most relevant for anterior FPDs. Tooth-like restorations are dependent on proper dimensions and, again, greater concern is raised with increasing residual ridge resorption. However, basic features of implant placement such as avoiding encroachment of embrasures are critically important for anterior FPDs. These features are revealed by evaluating the diagnostic wax-up and conveying this information to the surgical guide (Fig. 56-4).

The current absence of discrete rules that govern the precise number and dimension of implants (or a particular implant) needed to support any given masticatory function is acknowledged. Renouard and Rangert (2008) proposed that support factors can be attributed to implants and that relative risk can be assigned to various clinical scenarios. This approach of recognizing relative risk factors and modifying the clinical approach to therapy – even in a subjective way—merits consideration. At the very least, each clinical scenario should be considered in terms of prosthetic and implant risk both biologically and biomechanically, and treatment should be adapted to recognize these risks if possible. Obvious examples include the use of additional or larger implants to support molar function as opposed to premolar function, and the avoidance of distal cantilevers in patients with bruxism.

A simple strategy for reducing the biomechanical risks to implants and prostheses of implant-supported FPDs is to use treatment planning procedures to assure that the abutment–crown interfaces are located beneath the cervical aspect of the terminal mesial and distal crowns of all prostheses whenever possible. This approach reduces the length of bending moments, irrespective of the imposed load, and assures that the implant and abutment do not encroach on the embrasures to limit oral hygiene or esthetic potential of the restoration (see Fig. 56-1).

(a)



(b)

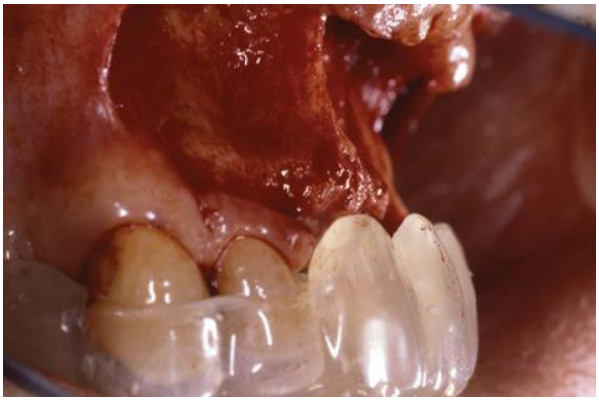


Fig. 56-4 (a) Diagnostic wax-up demonstrating desired tooth position and wax used to demonstrate the amount of planned augmentation needed. (b) At the time of site development, the surgical guide demonstrates the difference between the desired tooth position and the residual ridge.

When multiple implants are placed in an edentulous span, careful treatment planning will indicate the mesial and distal widths of the desired restorative teeth. This plan will in turn indicate proposed sites where implants (e.g. every other tooth) may be placed for stability of the prosthesis. Choice of implant location (and angle of placement) depends on available osseous tissues, soft tissue thickness, esthetics, phonetics, and need for ridge development.

When having a dialog with patients about the desired tooth replacement therapy, clinicians often recommend an implant-per-tooth approach. When this approach is done with individual free-standing crowns, it provides the potential for a natural tooth-by-tooth replacement. However, a significant issue for the prosthetic restoration can be created if the implants are not placed in exactly the desired location. Therefore, the use of short-span FPDs has certain general advantages. First, the use of two implants to replace three teeth enables the technician to judiciously use the pontic contours to alter the shape and contour of the prosthesis to compensate for implants that are not optimally positioned. For instance,

implants that emerge at the desired interproximal area can be compensated for with the use of angled abutments or customized CAD/CAM abutments that facilitate use of connector dimensions that give an illusion of natural teeth. Another advantage cited by some is the establishment of interproximal contacts between the prosthesis and adjacent teeth.

In order to assess the predictability of these types of restorations, clinical research studies need to be assessed. Randomized controlled clinical trials of partially edentulous patients with a history of periodontal bone loss were evaluated in a 5-year trial by Wennström *et al.* (2004a). This study reported on 149 self-tapping implants (AstraTech AB, Mölndal, Sweden) placed in maxillae (n = 83) and mandibles (n = 66) in the premolar and molar area. Each patient received two implants (machined surface versus grit blasted with TiO_2) that were allowed to heal for 6 months prior to loading. Screw-retained FPDs were completed and maintenance therapy provided following the CIST program (Lang *et al*. 2004a). Implant loss was 5.9% at the subject level. FPDs demonstrated a total 5-year bone loss from implant placement of 0.41 ± 0.78 mm (subject level) (Wennström *et al*. 2004a). There was a statistical difference in the frequency of bone loss between implants placed in the upper versus those placed in the lower jaw: 38% of the maxillary implants demonstrated >1-mm bone loss, while 9% of the FPDs in the lower arch had >1 mm bone loss at 5 years. Previous studies evaluating bone loss with the implant system used in this study in a variety of research protocols have reported mean marginal bone loss from implant placement to be an average of −0.46 ± 0.38 mm (Olsson *et al*. 1995; Yusuf & Ratra 1996; Karlsson *et al*. 1997; Makkonen *et al*. 1997; Norton 1997; Arvidson *et al*. 1998; Karlsson *et al*. 1998; Astrand *et al*. 1999; Cooper *et al*. 1999; Palmer *et al*. 2000; Puchades-Roman *et al*. 2000; van Steenberghe *et al*. 2000; Cooper *et al*. 2001; Gotfredsen & Karlsson 2001; Norton 2001; Steveling *et al*. 2001; Weibrich *et al*. 2001; Engquist *et al*. 2002; Wennström *et al*. 2004a, b; Palmer *et al*. 2005; Rasmusson *et al*. 2005; Wennström *et al*. 2005). When implants were placed in the posterior maxilla with the indirect sinus lift technique and restored with FPDs at 6 weeks using a fluoride-modified implant, outcomes demonstrated bone loss of −0.19 to −0.4 mm (SD = 0.73) from implant placement, with a 98.3% cumulative implant survival rate (CISR) (Stanford 2006). These data support the concept that partially edentulous patients can be restored with FPDs (Gotfredsen & Karlsson 2001). However, post-insertion maintenance is critical. Hardt *et al.* (2002) observed in a population with a history of bone loss associated with periodontitis, that poor oral hygiene and compliance with maintenance therapy resulted in an elevated failure rate of 8% at 5 years, and 62% of the implants in patients susceptible to periodontitis versus 44% in the non-perio groups demonstrated >2 mm of bone loss (Hardt *et al*. 2002). This emphasizes the need for ongoing supportive care for patients undergoing tooth replacement therapy (Lang *et al*. 2004a; Schou *et al*. 2004).

Cantilever pontics

In managing tooth replacement therapy, often a mesial or distal extension is needed off the retainer. The use of cantilever extensions increases the mechanical angular moment on the prosthesis and the potential for early fatigue and prosthetic complications (Brunski 2003). The use of cantilever extensions was first advocated as a routine prosthetic approach in the Toronto mandibular FCD for the edentulous arch (Zarb 1988; Zarb & Schmitt 1990a, b, 1991). Clinical studies on the use of cantilever extensions suggest greater complications with extensions longer than 15 mm, although there are many opinion-based recommendations that range from 10 to 20 mm (Shackleton *et al*. 1994) Cantilever extensions do increase the angular moment on the most distal implant and abutment connection, and complications such as loosening screws, fractured components, etc. are related to a combination of factors including cantilever design, composition, occlusion, jaw relationships, and implant/abutment design (Brunski *et al*. 1986). In an analysis of survival over 80 months of FCDs with an acrylic resin tooth replacement and of the external hex Brånemark system, Shackleton *et al.* (1994) observed a 100% survival rate for cantilever extensions of <15 mm but of <30% for extensions of >15 mm.

In the anterior quadrant where esthetics are desired, there are often missing lateral incisors that leave only minimal mesiodistal space for implant placement. One option may be to use narrow diameter implants in such sites, but control of occlusion is important (Stanford 2005b). An alternative, especially when there are missing adjacent teeth, is to use cantilever pontics of minimal dimension to replace the missing teeth (Fig. 56-5). This has the potential for more predictable esthetics without requiring excessive site development, expense, and time. The use of cantilever pontics in the posterior quadrants is more controversial. Cantilever pontics in metal–ceramic FPDs create larger moment arms on the prosthesis and have the potential to increase mechanical complications with the implant–abutment stack (Stanford 1999; Brunski 2000; Brunski *et al*. 2000; Gratton *et al*. 2001; Brunski 2003). There are times when posterior cantilever pontics are useful, but the clinician should primarily consider them for esthetics and also for areas of controlled occlusal forces. Further, their use with metal–ceramic FPDs should be limited, with no more than a premolar-sized pontic (~7 mm mesiodistal dimension) and only light centric occlusal contacts on the pontic (Stanford 2005b)

There are ongoing issues regarding cemented relative to screw-retained FPDs. While the choice of prosthesis is dependent on multiple factors (clinician

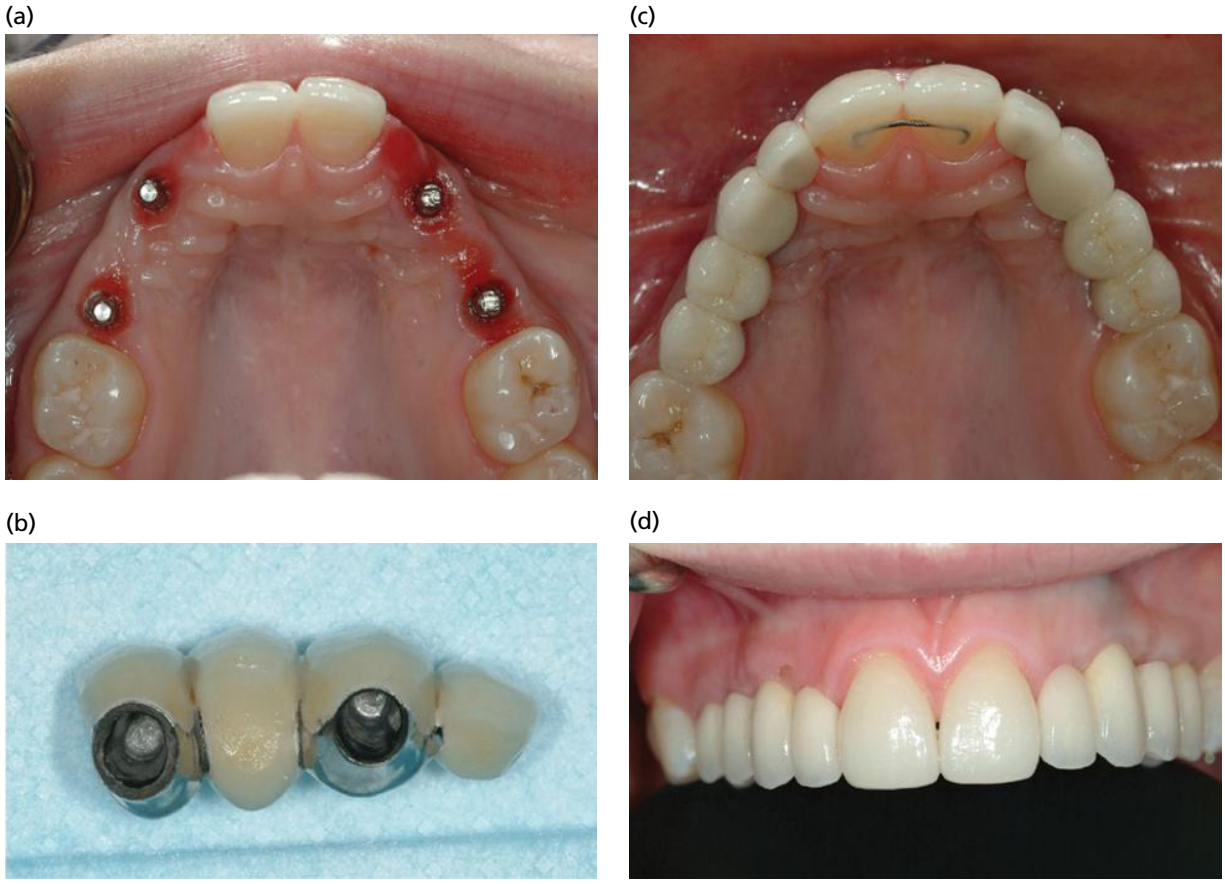


Fig. 56-5 Use of cantilever pontics to replace missing lateral incisors as a part of fixed partial denture (FPD) therapy. (a) Four implants were placed in the maxilla in the second premolar and canine region. (b) A four-unit FPD with cantilever pontics (12 and 22) was fabricated, allowing restoration of eight missing teeth with four implants (c) and establishment of an acceptable esthetic result (d).

preference, flexibility, passivity of fit, cost, etc.), there are times when one or the other approach is preferable. For instance, in situations where the patient has multiple clinical signs of recession (thin tissue biotype, recession, lack of keratinized mucosa, etc.), a screw-retained fixed prosthesis may be preferable (Stanford 2005a), as this approach will allow the clinician to remove the prosthesis at a later point in time and make repairs which may salvage the prosthesis. Patients with a history of implant loss in the area, difficult implant placement or elevated medical risk are other indications to consider a screw-retained fixed prosthesis. Further, if the prosthesis needs to be routinely removed (e.g. in a research protocol) for accurate measurement of pocket probing depths (PPDs) and bleeding on probing (BoP), the clinician may want to choose a screw-retained prosthesis.

There are also indications for fabricating a fixed prosthesis that replaces both hard and soft tissues (Garcia & Verrett 2004). In sites where there has been considerable loss of supporting structures, as is common following trauma or long-term chronic bone loss such as with periodontal disease, it may be necessary to replace both dental and osseous supporting structures (see Fig. 56-3). If this cannot be accomplished with biologic site development, the clinician may need to reconstruct this area with a combination of porcelain teeth developed with the appropriate mesiodistal and incisogingival dimensions to match the adjacent teeth and blend into the esthetic contours of the dentition and face. In doing so, it may become obvious that the gingival tissues need to be replicated in "mucosa"-colored porcelain or acrylic (Fig. 56-6). The development of tissue-matched mucosal shades takes significant laboratory skill and dexterity, and often means the patient needs to be seen directly by both the technician and the restorative dentist (Malament 2000; Malament & Neeser 2004) Customized mucosal shades often need to be developed and matched chair side. While these approaches can be quite time consuming, the end results can be quite satisfactory and surpass what can be accomplished with repeated soft tissue procedures (Fig. 56-6). The restorative dentist needs to carefully assess the patient early in the diagnostic process for implant therapy and determine if he/she is at elevated risk for unpredictable loss of soft tissue. Key factors to assess are thin tissue biotype, previous history of recession, mucosal inflammation, and tooth loss due to trauma or chronic progressive osseous disease (e.g. periodontitis). All of these conditions influence the stability and position of the mucosal tissues following implant tooth replacement therapy.

Fig. 56-6 Soft and hard tissue prosthetic replacement. (a) Patient presented with soft tissue loss in the area of 21 and 22. (b) Missing mucosal and hard tissue contours were replaced with a combination of gingival and tooth-colored ceramic materials, achieving a prosthetic solution to a difficult esthetic situation (c).

Immediate provisionalization

The application of implant FPDs has a unique role, especially in early and immediate loading procedures. While the splinting of implants for long-term osseointegration is not considered routinely necessary, the early splinting of multiple implants during the osseous healing process is considered important (Cooper *et al*. 2002, 2005; Slaets *et al*. 2005; Cooper *et al*. 2006; De Kok *et al*. 2006; Duyck Vandamme *et al*. 2006). Immediate provisionalization procedures have the potential to provide rapid function, esthetics, and patient satisfaction, and the use of implant-supported FPD prosthetic designs plays an intimate role in controlling micromotion and allowing successful outcomes similar to those with conventional loading procedures (De Kok *et al*. 2006; Duyck *et al*. 2006; Hall *et al*. 2006; Peleg *et al*. 2006) .

The immediate provisionalization of implant-supported FPDs has a unique role in the retreatment of failing fixed prostheses. When large fixed prostheses are present with only one or two failing abutments, further tooth-supported restoration often requires extensive restoration. This is particularly true if strategic abutments, such as a canine or terminal abutment tooth, are not salvageable due to caries, fracture or localized periodontitis. In such cases, segmental resection of the failed tooth and supported pontic teeth can be replaced by dental implants. The advantages are obvious in terms of preventing retreatment with a much larger FPD and providing an esthetic and functional treatment option for an anterior restoration.

Disadvantages of implant–implant fixed partial dentures

The disadvantages of FPDs on implants are associated with increased difficulty with cleaning and maintaining the prosthesis, along with the prosthesis complications associated with a conventional tooth-supported FPD. There is the potential that the patient will not be satisfied with the inability to clean between the retainers and pontic contours. FPDs on implants can also be more difficult to fabricate in the laboratory: there may be issues with the path of insertion on the abutments (necessitating customized abutment) or difficulties in obtaining draw and passive fit between multiple abutments. There is also the danger of mechanical wear and material failure with the completed prosthesis, such as abutment loosening, prosthesis fracture or veneer material failure. The use of screw-retained prostheses may be helpful if retrievability is critical, but the screw access hole appears to weaken the strength of the veneering material. Lastly, there is also the danger that if one of the supporting implants is lost or the abutment demonstrates recession, exposing the transmucosal titanium surface, the entire prosthesis may have to be replaced, which increases both the treatment time and expense to the patient.

In assessing the clinical success of implant-supported FPDs, it is often difficult to determine outcomes due to incomplete reporting, yet the primary measure of evidence-based care is the systematic assessment of the clinical question of interest. The literature supporting the use of this type of prosthesis is often retrospective in nature, with different outcome measures, end points, duration of recall, etc. This makes comparisons between studies difficult and limited. In the assessment of prosthodontic mechanical complications, the pattern of defects often will vary in a time-dependent pattern. In implant-supported FPDs, early failures (before loading) are often associated with implant loss (Goodacre *et al.* 2003b). As discussed by Pjetursson *et al.* (2004), implant loss prior to restoration can be expected on average to occur in 2.5% of all placed implants, with an additional 2–3% lost over the first 5 years of function. In this systematic assessment, 21 of the 176 reviewed studies were considered reliable based on inclusion and exclusion criteria. The authors summarized the current literature for five implant systems in 1123 patients (total of 1336 FPDs on 3578 implants) followed for at least 5 years. Implant survival, FPD survival, success, and complications were reported (Table 56-1). While the authors outlined that this type of assessment is limited by the quality of the studies, their duration, number of drop-outs, and reliability, but in this instance, with the limited dataset, they

reported the most common complication to be loss of veneering material (often acrylic facings), followed by other mechanical complications inherent in screw-retained style prosthesis. Biologic complications, such as peri-implantitis (PPD >5 mm) with BoP, were reported in one study to occur in an average 10% of patients (Pjetursson *et al.* 2004). Pjetursson *et al.* (2004) used a random-effects Poisson modeling approach to determine a pooled cumulative rate of 8.6% for biologic complications (95% CI 5.1–14.1%) based on an assessment of nine studies providing sufficient information for analysis.

FPDs supported by two or more implants provide a valuable treatment option. It has a role in providing rehabilitation for patients with challenging implant positions and angulation, lost hard and soft tissues, at reduced cost and may allow avoidance of some grafting procedures (e.g. sinus grafting). The selection of an FPD supported by implants often represents the alternative to selecting a much larger FPD supported by many teeth (Table 56-2). While reviews suggest that there may be little difference in the long-term complication rates for FPDs supported by teeth and implants, it is of practical importance that implant-supported FPDs often are smaller prostheses that are economically efficient over the long term. FPDs also serve a vital role in immediate loading procedures by controlling loading during the healing phase. FPDs do present prosthetic challenges and the final result may not be acceptable to all patients. On balance, however, the use of FPDs plays a valuable role in providing multiple tooth replacement therapy.

Table 56-1 Implant-supported fixed partial dentures (FPDs) after an average of 5 years of follow-up.[a]

	Average	95% Confidence interval
Implant survival (%)	95.6	93.3–97.2
FPD prosthesis survival (%)[b]	95	92.2–96.8
FPD success (%)[c]	61.3	55.3–66.8
Complications (%)	38.7	
Veneer fracture	13.2	8.3–20.6
Lost occlusal restorations	8.2	
Loose screws	5.8	3.8–8.7
Fractured abutments/ occlusal screws	1.5	0.8–2.8
Fractured implants	0.4	0.1–1.2

[a] 90% of the FPDs were screw-retained.
[b] Survival defined as retained in function within the mouth. Prostheses may have had multiple repairs.
[c] Success defined as in function with no clinical complications.
Data from Pjetursson *et al.* (2004).

Tooth–implant fixed partial dentures

The use of dental implants combined with teeth as retainers for FPDs has been advocated by a number of clinicians to restore multiple missing teeth. There are multiple case reports in the literature of prosthesis designs that have either a rigid connection between the natural tooth and implant retainers or a non-rigid connection to ostensibly allow individual movement of the implant(s) relative to the greater mobility of the natural teeth (Stanford & Brand 1999). The difference in mobility can be greater than an order magnitude, with mobility of 50–200 μm for teeth with a healthy periodontal ligament, while an integrated implant will have a mobility of <10 μm (Brunski & Hipp 1984; Brunski 1988a, b; Rangert *et al.* 1997; Brunski 1999, 2003). The use of implant–tooth FPDs has the potential to reduce cost, time, and morbidity, especially if the outcomes provide a service to the patient that is equivalent to those for

Table 56-2 Local features to be considered in risk assessment for implant-supported fixed partial dentures (FPDs).

FPD location	Anterior location has higher esthetic risk Posterior location may have higher functional risk
Length of span	Long span increases complexity of prosthesis Short span may result in abutment crowding and restricts hygiene
Occlusogingival dimension	Increased occlusogingival dimension results in longer bending moments at abutment and bridge screws Reduced occlusogingival dimension (<6 mm) may limit prosthesis construction and integrity
Excessive vertical residual ridge resorption	Excessive vertical residual ridge resorption results in excessive occlusogingival dimension of the restoration
Implant malpositioning	Buccal or lingual malpositioning creates unintended buccal or lingual cantilever of prosthesis Mesial or distal malpositioning encroaches on embrasure and hygiene access; both reduce esthetic potential Excessive deep placement increases bending moment at abutment screws, may create an anaerobic environment, can lead to bone resorption and esthetic complications
Thin mucosal biotype	Risk of mucosal resorption and unesthetic display of abutment material
History of periodontitis	Risk of peri-implantitis if control is absent May need multiple staged procedures for hard and soft tissue augmentation

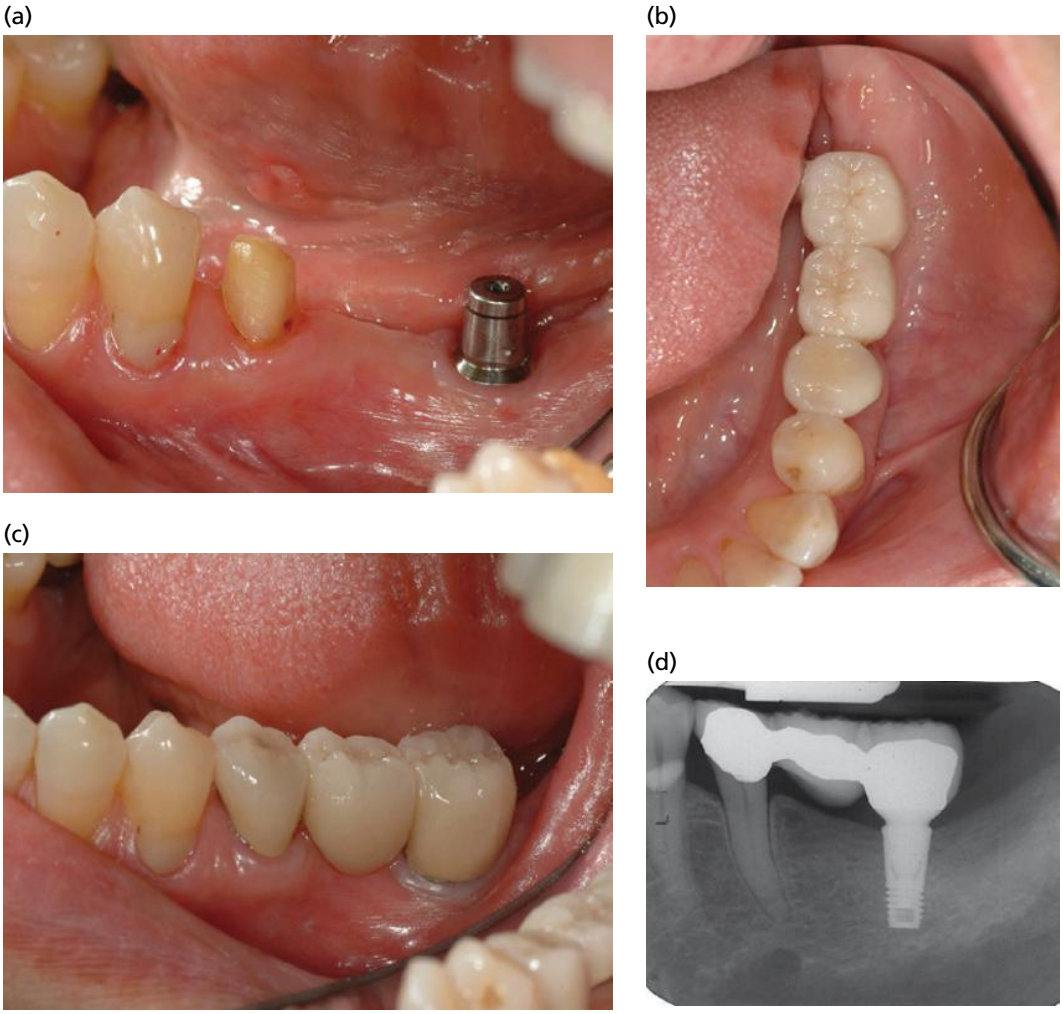


Fig. 56-7 Implant–tooth fixed partial denture (FPD). (a) Use of a rigid FPD framework on a three-unit FPD (35–37). (b) Metal–ceramic prosthesis was cemented and monitored with frequent recall over 5 years (c). (d) Five-year recall radiograph indicates healthy periapical and peri-implant osseous tissues.

implant–implant FPDs or single-tooth implant restorations (Fig. 56-7). The advantages though must be balanced against the potential complication of pathology associated with the dental retainers or the implant(s). The fate of both is tied together. Lang *et al.* (2004b) performed a systematic review of clinical studies evaluating tooth–implant FPDs over at least 5 years and identified 13 studies using the inclusion/exclusion criteria. Of these, nine were prospective and four retrospective, addressing outcomes with five different implant systems in 555 patients (538 FPDs on 1002 implants), the majority (91%) of which were reported to be screw-retained. Of those studies with follow-up of 5–6.5 years, 25 of the 932 implants installed were lost prior to restoration and 65 during the recall period, giving a 5-year implant survival rate of 90.1% (CI 82.4–94.5%) (Lang *et al*. 2004b). In a second group of studies where patients were followed for10 years post implant, implant survival was estimated at 82.1% (CI 55.8–93.6%). Following the same theme, a systematic review of biologic and technical complications (Berglundh *et al*. 2002) indicated that tooth–implant-borne FPDs were at greater risk for implant loss (irrespective of complications leading to abutment tooth loss) than implant–implant FPDs. Prosthesis survival at 5 years was estimated to be 94.1% (CI 90.2–96.5%), and 77.8% (CI 66.4–85.7%) at 10 years. By 5 years, 3.2% of dental abutments had been lost due to fracture, caries, endodontic or periodontal complications (Lang *et al*. 2004b). If the patient has the option to restore the missing teeth with conventional removable partial denture therapy combined with implant-fixed prosthodontics, it is interesting to assess the long-term outcomes. Aquilino *et al*. (2001) evaluated a large insurance dataset to assess outcomes of dental abutments in bounded edentulous spaces. In this study, 10-year Kaplan–Meier estimates indicated dental abutments restored with FPDs had a 97% 5-year and a 92% 10-year survival rate, compared to only 77% at 5 years and 56% at 10 years for removable partial denture abutments.

A number of concerns have been raised concerning connecting teeth to implants with FPDs. Some of these complications are associated with technical complications of the prosthesis. For instance, the prognosis of the FPD can be shortened by veneer fractures and other esthetic issues (Kindberg *et al*.

2001). Loss of retention through fracture of the abutment/prosthetic screws or loss of cement retention is possible. In a systematic review of two studies that assessed lost retention (Hosny *et al*. 2000; Naert *et al*. 2001), Lang *et al.* (2004b) reported an average loss of 6.2% (CI 3.7–10.4%) at 5 years. Endodontic complications on the abutment teeth can also be a significant concern, with 3–28% of teeth needing post-insertion root canal therapy (average of 11%) (Goodacre *et al*. 2003b). Naert *et al*. (2001) reported on complications after a mean period of 6.5 (1.5–15) years in a retrospective comparison study of implant–implant FPDs to tooth–implant FPDs with 123 patients in each group. Complications included a history of chronic apical periodontitis (3.5%), tooth fracture (0.6%) along with a tooth intrusion (3.4%), and cement failure (8%) (Naert *et al*. 2001). An interesting and unusual observation was natural tooth intrusion (Pesun 1997). Earlier use of implants combined with teeth advocated the use of non-rigid attachments within the prosthetic design to allow differential movement between the implant and tooth. In some cases, the natural tooth appears to retract away from the prosthesis. This phenomenon has been suggested to be due to the interplay of disuse atrophy, food impaction, rebound memory of the periodontal ligament, and/or mechanical binding (Rieder & Parel 1993; Schlumberger *et al*. 1998; Cordaro *et al*. 2005; Palmer *et al*. 2005). In a multicenter study, Block *et al*. (2002) assessed posterior FPDs either rigidly connected or non-rigidly connected with one type of attachment. Of the 30 subjects followed over 5 years, there was no difference in bone loss between the two types of connections, but there was a 66% incidence of measurable intrusion in the non-rigid group versus 44% in the rigid group. The authors concluded that tooth–implant FPDs had a higher level of maintenance and postoperative complications. Fugazzotto *et al*. (1999) retrospectively assessed a multigroup practice outcome for 843 patients (1206 implants, 3096 attachments) over a period of 3–14 years, and observed nine instances of intrusion (0.3%) associated with fractured or lost lateral set screws (rigid retention). In a prospective 3-year study, Palmer *et al*. (2005) evaluated 19 subjects with rigid cemented prosthesis between natural teeth and implants. The short-term outcomes at 3 years showed implant bone loss no greater than expected (0.78 ± 0.64 mm), with no signs of intrusion with the rigid tooth–implant FPD designs. These results have led to the clinical recommendation that if the clinician needs to join natural teeth with implants, a rigid connection is used with close monitoring for clinical signs of complications (Naert *et al*. 2001; Palmer *et al*. 2005; Stanford 2005a).

FPDs used to join teeth to implants is a controversial issue. There are times when an assessment of clinical needs, patient desires, costs, time, and risk support the consideration of this treatment option. It is critical that the patient is informed of the relative risks associated with this type of prosthesis, implant, and abutment tooth in the process of informed consent.

Conclusion

FPD therapy for the restoration of multiple missing teeth has a long track record in dental implant care. Connecting two or more implants, or in selective cases teeth with implants, can provide a stable, esthetic, and predictable outcome. All treatment options need to start with a careful assessment of anatomy, clinical parameters, and patient needs and desires. The patient needs to be informed of the assumptions made in treatment planning and the relative costs and benefits that this treatment approach can provide.

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Chapter 57

Complications Related to Implant-Supported Restorations

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Introduction

The quality of dental implants has significantly improved since their introduction and this has been coupled with a steady increase in clinical success and/or survival rate (Cochran 1996; Esposito *et al.* 1998; Lindh *et al.* 1998; Jokstad *et al.* 2003). The biologic aspect particularly, namely osseointegration, has been the target of intensive investigation and there have been conspicuous advances. As a part of these developments, there have been continuous efforts to improve the characteristics, micro/nano topographies, and chemistries of the implant surface. A major change in surface topography can be summarized by the evolution from a machined surface to a production-based moderately roughened surface. Superior biologic response, or osseointegration, to roughened implant surfaces has been widely documented in the literature (Astrand *et al*. 1999; Rocci *et al*. 2003; Schneider *et al*. 2003). The cumulative effect of all this effort is reflected in the extremely high biologic success rate of dental implants. However, complications do occur and can be related to both biologic and prosthetic issues. This chapter discusses potential complications of dental implant-supported restorations, focusing particularly on complications related to the prosthetic aspects of therapy.

Clinical complications in conventional fixed restorations

Implant dentistry shares many of the long-term mechanical complications of conventional dental restorative therapy. Goodacre *et al.* (2003a, b) presented data regarding the incidence of clinical complications associated with conventional fixed dental restorations/prostheses, including single crowns (all-metal, metal–ceramic, resin-veneered metal) and fixed partial dentures (FPDs) (all-metal, metal–ceramic, resin-veneered metal); all-ceramic crowns; resin-bonded prostheses; and posts and cores. This study still holds significant relevance. Regarding single crowns, the most common complication was post-cementation endodontic therapy (3%), followed by porcelain fracture (3%), loss of retention (2%), periodontal disease (0.6%), and caries (0.4%). Regarding FPDs though, the most common complications were caries (18% abutments; 8% prostheses), need for endodontic treatment (11% abutments; 7% prostheses), loss of retention (7%),

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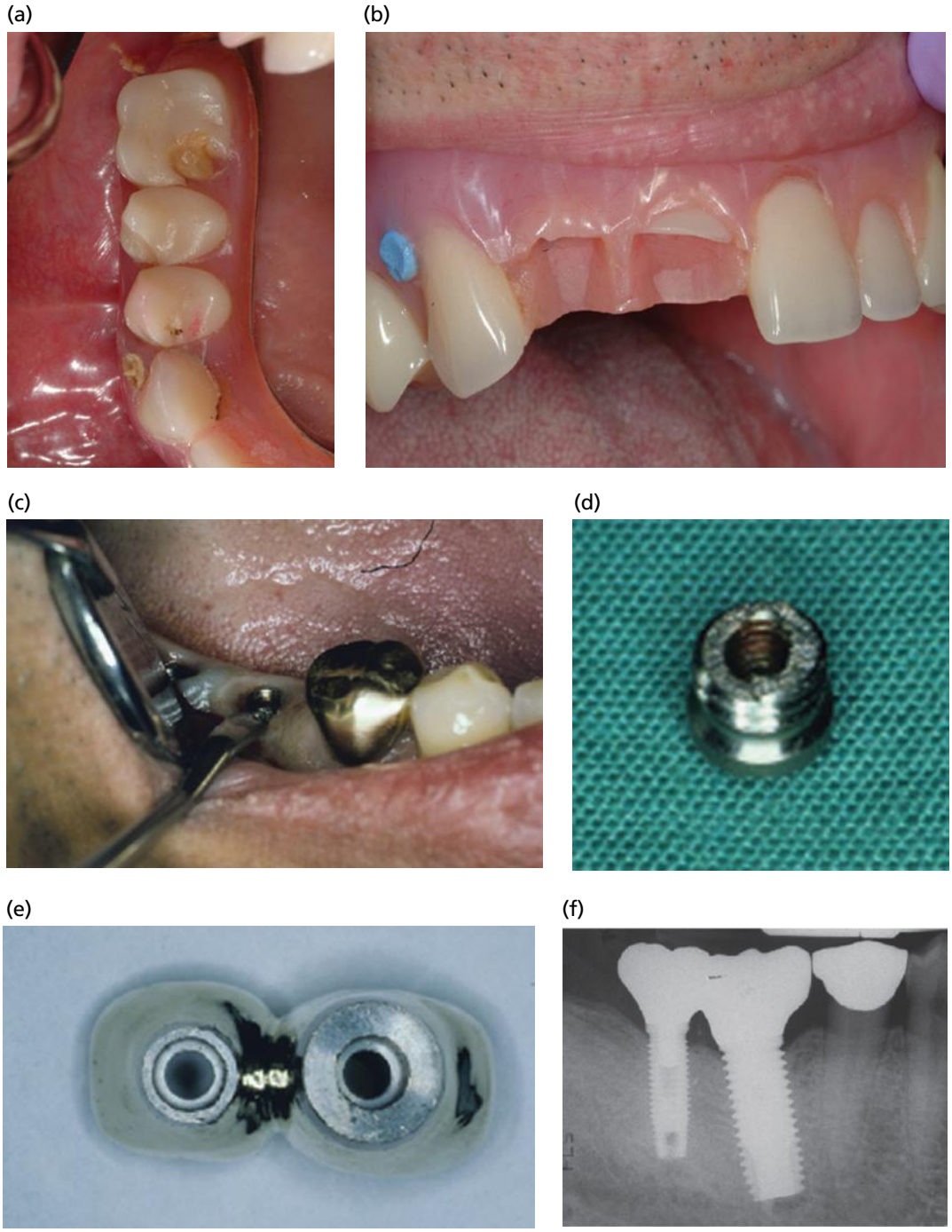

Fig. 57-1 Prosthetic challenges related to wear and component fracture. Wear, fracture, and change in esthetics are common with acrylic resin teeth (a), as are fractures of acrylic resin prosthetic teeth on fixed complete dentures (b). While implant fractures are rare, the consequences are challenging. (c) Case example of implant that was mobile 2 years after delivery; the prosthesis was removed and the head of the implant was found to be fractured (d). (e) Implant was replaced with a wide diameter implant in order to increase the wall thickness and provide a greater abutment–implant interface. (f) Recall at 10 years.

esthetics (6%), periodontal disease (4%), tooth fracture (3%), prosthesis fracture (2%), and porcelain veneer fracture (2%). In this narrative review, the authors concluded that complication incidence with conventional FPDs was significantly higher than that for single crowns. In addressing issues related to implant restorations, material failure and wear is a common occurrence with both dental and implant-supported restorations (Fig. 57-1). It is likely that the higher biomechanical complexity of the design of the prosthesis contributes to higher complication incidence. Among the complications, pulpal complications, periodontal disease, and caries will apply to only tooth-supported restorations (Goodacre *et al.* 2003a, b).

Tan *et al.* (2004) assessed the long-term success/survival rate of conventional FPDs in a systematic review and evaluated the failure rates of FPDs due to specific biologic and technical complications. The meta-analysis indicated a 10-year survival rate (retention with or without intervention during the recall period) for FPDs of 89.1%, but a 10-year success rate

(no intervention needed over the recall period) of 71.1%. In general, the mean 10-year survival rate of conventional FPDs was 90% and mean success rate was 80% in the literature. In this study, the most common reasons for dental FPD failure included periodontal disease and secondary caries. Regarding the complications related to caries, the 10-year risk for decay on abutments was 9.5%, but only 2.6% of FPDs were lost as a result of this disease process. In this study, it was clear that loss of vitality of abutment teeth occurred at a date that was later than could be attributed to the trauma from the preparation of the teeth. This may either indicate a slow progressive tissue degeneration induced by the procedure or reflect the increased susceptibility of pulpal infection by dentinal tubules in advanced periodontitis (Bergenholtz & Nyman 1984). The presence of cast post and dowels and non-vital abutments, especially distal abutments, has been shown to be associated with increased loss of retention and fracture of teeth and cores. This cautions against over dependence on non-vital teeth as strategic abutments. The 10-year risk of loss of FPDs due to recurrent periodontitis was only 0.5%. Overall, there seemed to be no adverse changes in FPDs incorporated into periodontally well-maintained teeth/patients, even in those patients who presented with a history of advanced periodontal disease. Where the recall or maintenance is less stringent, periodontal breakdown may occur, and may be more pronounced when margins are subgingivally located (Valderhaug & Karlsen 1976). Secondary use of the bridge for removable prosthesis has a detrimental effect on the gingival tissue (Libby *et al.* 1997). The 10-year risk for technical complications such as loss of retention, loss due to abutment fracture, and material complications were also calculated in this study. An issue in any of these studies is the multifactorial nature of the causes of failure. The highest 10-year risk was for loss of retention (6.4%). Far lower was the 10-year risk for the loss of FPDs due to abutment tooth fracture (3.2% for fractures of the framework, veneers, and/or cores) and relatively low 10-year risks were obtained for material complications. A comparison of the difference in survival between FPDs with acrylic facings and metal–ceramic FPDs showed that over an 18-year period, 38% of FPDs with acrylic facings and 4% of metal–ceramic FPDs were replaced (Sundh & Odman 1997). Reasons cited for the higher failures in the former were the greater incidence of discoloration and fracture after extensive wear of the older acrylic resin material.

Clinical complications in implant-supported restorations

Biologic complications

Surgical complications

Surgical complications directly related to implant placement are generally rare. However, due to the surgical nature of implant therapy, it is impossible to avoid surgical sequelae. Surgical methods excluding tissue flap openings (so-called "flapless approaches") seek to minimize surgical trauma but carry their own risks. Goodacre *et al.* (2003b) provided data regarding the types of complications that have been reported in conjunction with endosseous root-form implants. The most common surgical complications associated with implant surgery were hemorrhage-related complications (24%), neurosensory disturbance (7%), and mandibular fracture (0.3%).

Implant loss

There is no known single factor that can cause implant loss. Some of the factors generally accepted to be involved in the etiology include infection and/or contamination, patients' physical status, trauma from surgical procedures, excessive and/or premature occlusal loading, cement retention, etc. Most surgery-related implant losses can be managed by maintaining a strict infection control protocol, meticulous patient screening prior to the surgery, and reducing the surgical time/trauma. Occlusal loading is a more challenging factor since the operator has more limited control over it. Premature occlusal loading can be detrimental to osseointegration when it is combined with excessive load and/or off-axis force. This can happen during the stage of early or immediate provisionalization and indicates that the patient should be closely monitored during this initial healing period. In the literature, it has been stated that overloading at any stage of osseointegration can lead to bone loss or even complete disintegration of the implant (Isidor 1996, 1997; Brunski *et al*. 2000; Steigenga *et al*. 2003). However, the concept of implant "overload" has been questioned as a series of studies indicated bone is highly responsive to dynamic loads and is resistant to bone loss even at high levels of occlusal function (Stanford & Brand 1999; Duyck *et al.* 2000, 2001; Stanford 2005b). The primary concern regarding mechanical forces (occlusion) and implant outcomes should focus more on mechanical breakdown of materials rather than a loss of the biologic interface.

According to the literature, implant loss ranges from a high of 19% with maxillary overdentures to a low of 3% with both mandibular fixed complete dentures (FCDs) and single crowns (Goodacre *et al*. 2003a). Implant loss has conventionally been greater with implants of 10 mm or less in length compared with implants of >10 mm long (ten Bruggenkate *et al*. 1998; Lekholm *et al*. 1999; Friberg *et al*. 2000; Palmer *et al*. 2000), but with the improved implant systems now available, this may longer be true (Atieh *et al*. 2012). Implant loss is more likely to occur in the presence of type IV bone compared with more favorably typed bones (Stanford 1999; Stanford & Brand 1999; Stanford 2005b). Other risk factors that have been suggested include smoking, and prior history of

periodontal disease or radiation therapy (Moy *et al.* 2005; Ahmed *et al*. 2012; Cochran & Nevins 2012; Esposito *et al*. 2012; Pjetursson *et al*. 2012; Wadsworth 2013). If loss of implant occurred, approximately half or more of the lost implants were lost prior to functional loading. This result is in agreement with the result from an earlier systematic review (Berglundh *et al*. 2002).

Peri-implant complications

Possible peri-implant complications include marginal bone loss, peri-implant mucosal inflammation/proliferation, soft/hard tissue fenestration/dehiscence, fistula, etc. It is widely accepted that continuous marginal bone loss around established implants over time jeopardizes the potential success and/or survival of the implant therapy. Factors that potentially induce marginal bone loss include surgical trauma during implant placement, trauma during repeated abutment insertions and removal, functional load transfer and concentration, micro-motion at the implant–abutment junction, and peri-implant gingival inflammation, potentially induced by a range of prosthodontic factors. According to the literature, the mean bone loss over the first year post implant is 0.9–1.5 mm, and the subsequent loss per year is around 0.1 mm (Albrektsson *et al*. 1986). More recently, bone loss of <0.5 mm has been proposed as a common standard (Albrektsson *et al*. 2013).

Peri-implant inflammation and its role in bone loss have recently gained significant attention. In part, this inflammation can be represented by conventional measures such as bleeding on probing (BoP), purulence, and local hyperemia (Fig. 57-2). The presence of such a mucositis in the absence of bone loss is referred to as "peri-mucositis", in contrast to the same set of presenting signs and symptoms but with the addition of progressive mesial and distal bone loss, referred to as "peri-implantitis" (Mombelli & Decaillet 2011). Peri-implantitis is defined as an inflammatory reaction associated with the vertical loss of supporting bone in the tissues around a functioning implant (Albrektsson *et al*. 1994) (Fig. 57-3). Note that this diagnosis does not denote any causative reason for the inflammatory etiology and in fact, a combination of host factors (genetic and epigenetic, such as the risk factors associated with aggressive periodontitis), environmental factors (e.g. smoking), microbial biofilm (flora, virulence, microbial genetic/epigenetic, and environmental responses), in addition to prosthodontic etiologic factors (e.g. crown/FPD contours, loose retainers, retained cement, etc.) are probably involved (Stanford 2010). Clinically, peri-implantitis can be detected with the formation of vertical bony defects and increasing probing depth. Radiographically, a saucer-shaped vertical radiolucent lesion may be observed to form around the implant over a period of time (typically years in service) (Fig. 57-3). This should be differentiated from short-term formation of the same radiographic appearance, which often represents fracture of an oral implant.

From a prosthetic perspective, the onset of peri-mucositis or peri-implantitis (associated with bone loss) can lead to soft tissue recession and unesthetic show of abutment or prosthetic components. Recent epidemiologic cross-sectional data suggest this occurs in 10% of implants or 20% of patients after about 10 years of service (Mombelli & Decaillet 2011). There has been considerable discussion about the significant number of cases of peri-implantitis that are related to retained dental cement (especially resin-based cement) on the transmucosal portion of the implant abutment. The retained cement allows elevated retention of a biofilm and this acts as an idiopathic cause for early implant loss (Wadhwani *et al.* 2012).

Marginal defects on the facial aspect of the implant complex are not only esthetically compromising, but can jeopardize the stability and long-term success of the implant. These defects, dehiscence or fenestration, are typically caused by the resorption of the buccal/labial plate of the alveolar bone. This is especially a concern when immediately placing implants upon

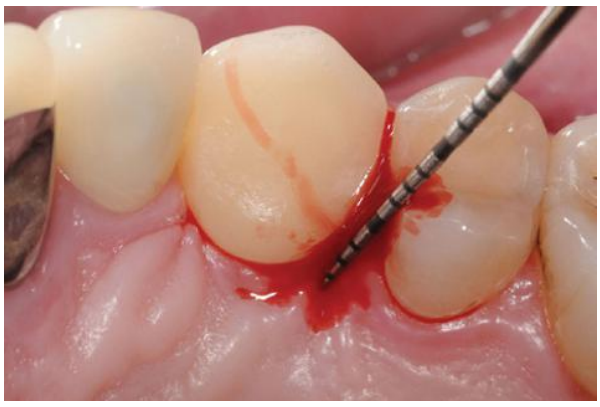

Fig. 57-2 Peri-implant disease can be assessed by presence of bleeding on probing, purulence, and increasing probing depths over time.

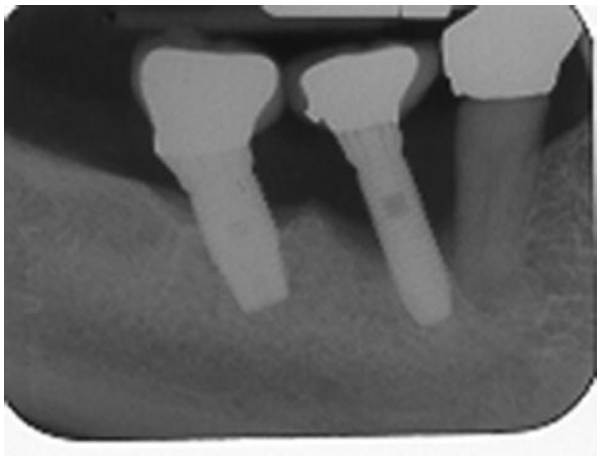

Fig. 57-3 Peri-implantitis is observed radiographically as vertical crater-like defects around the implants.

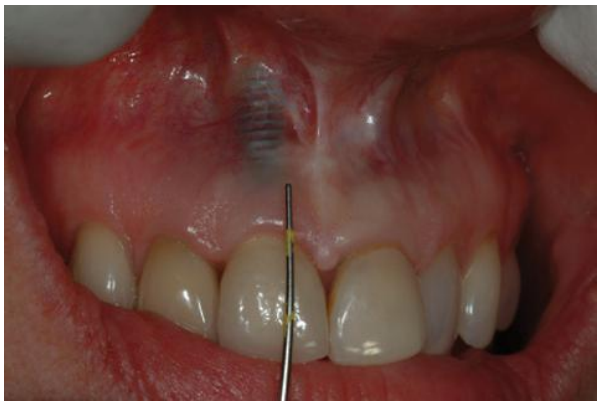

Fig. 57-4 Immediate implant placement into extraction sockets can lead to facial wall dehiscence and bone loss since the implant body will not prevent loss of the bundle bone on the socket wall.

extraction of a tooth (Fig. 57-4) (Araújo & Lindhe 2011; Januario *et al.* 2011; Sanz *et al*. 2014). In order to prevent this type of defect, it is important to maintain a minimum of 1-mm thickness of buccal/labial plate (Stanford 2005a). However, in certain areas, this may be difficult to achieve. To reduce the risks of facial marginal defects, one can utilize bone augmentation procedures, mainly autogenous, around the marginal alveolar bone in order to maintain the thickness around the implants. Autogenous bone particles derived from the drilling of the osteotomy may be enough for the purpose. In terms of the timing of implant placement after tooth extraction, it is generally accepted that immediate placement has a greater risk of facial marginal defects compared to delayed placement (Nemcovsky *et al*. 2002).

Malpositioned implants

A "malpositioned implant" is defined as an implant placed in a position that creates restorative and biomechanical challenges. A malpositioned implant can be caused by numerous factors. The most common is the deficiency of the osseous housing around the proposed implant site. Bone resorption is observed in osseous remodeling following tooth loss, osteoporosis, orthopedic revisions, craniofacial defects, or post oral cancer ablation associated with surgery/radiation. For the best biologic, biomechanical, and esthetic result of implant rehabilitations, proper implant placement is essential. The placement of an implant into a defective osseous site not only prevents adequate positioning of the final prosthetic restoration, but also results in compromised integration and subsequently a poor prognosis for the therapeutic outcome. In order to place an implant in the optimal prosthetic position for a restoration, augmentation procedures are often necessary. Current approaches in bone reconstruction use biomaterials, autografts or allografts, although restrictions on all these techniques exist. Restrictions include donor site morbidity and donor shortage for autografts (Damien & Parson 1991), as well as immunologic barriers for allografts and the risk, albeit low, of transmitting infectious diseases (Meyer *et al.* 2004). Numerous artificial bone substitutes containing metals, ceramics, and polymers have been introduced to maintain bone function.

If the status of the existing, deficient bone is addressed prior to the surgery and the restorative dentist/prosthodontist confirms it will be possible to fabricate the final prosthesis with the implant(s) in the proposed location, generally implant placement can be a straight forward procedure. The implant team and the patient are faced with a significant complication when the implants are placed only in the available bone, ignoring the optimal desired prosthetic position (Fig. 57-5). Communication between the surgical and restorative teams is vital. The best way of communicating between the two parties is through the use of comprehensive treatment planning, diagnostic wax-up on mounted casts, and fabrication of a surgical guide. The standard protocol for placing implants will start with a treatment plan developed by the restorative dentist. The surgical guide represents the ideal position and angle of the implant determined by a series of diagnostic procedures. It should ideally indicate the three dimensions of the proposed implant position – horizontal position, vertical position, and angle (Fig. 57-6). Horizontally, the surgical guide should clearly indicate the buccolingual and mesiodistal location of the proposed site. In most cases, this is determined from the morphology and location of the diagnostic wax-up of the missing tooth. Vertically, the surgical guide should indicate how deep the surgeon should place the implant relative to the planned cementoenamel junction (CEJ). This is particularly important for implants placed in the esthetic zone. As a general rule, the restorative margin for an implant-supported restoration should be located at the vertical height, slightly deeper than that of the CEJ of the adjacent teeth. Thus, with an implant system in which the head of the implant represents the restorative margin, the implant should be placed 3 mm below the planned CEJ or occasionally on a line connecting the CEJ of adjacent teeth and the facial aspect of the implant body placed 2 mm to the palatal aspect of the same CEJ reference point (the "3 × 2 rule") (Cooper & Pin-Harry 2013) When an implant system is capable of adjusting the height of the restorative margin through a separate abutment(s), the placement depth of the implant may be more flexible (Fig. 57-7). Whichever system is used, the surgical guide should include a component that notifies the surgeon of the proposed depth of the implant. The angle of the implant should also be correct to prevent facial or lingual fenestration of the implant, as well as implant penetration into the radicular portions of adjacent teeth or other structures. The angle should be correct for the prosthesis as well. Should the angle of the implant be too facial, the restorative dentist could face significant esthetic challenges, for example screw

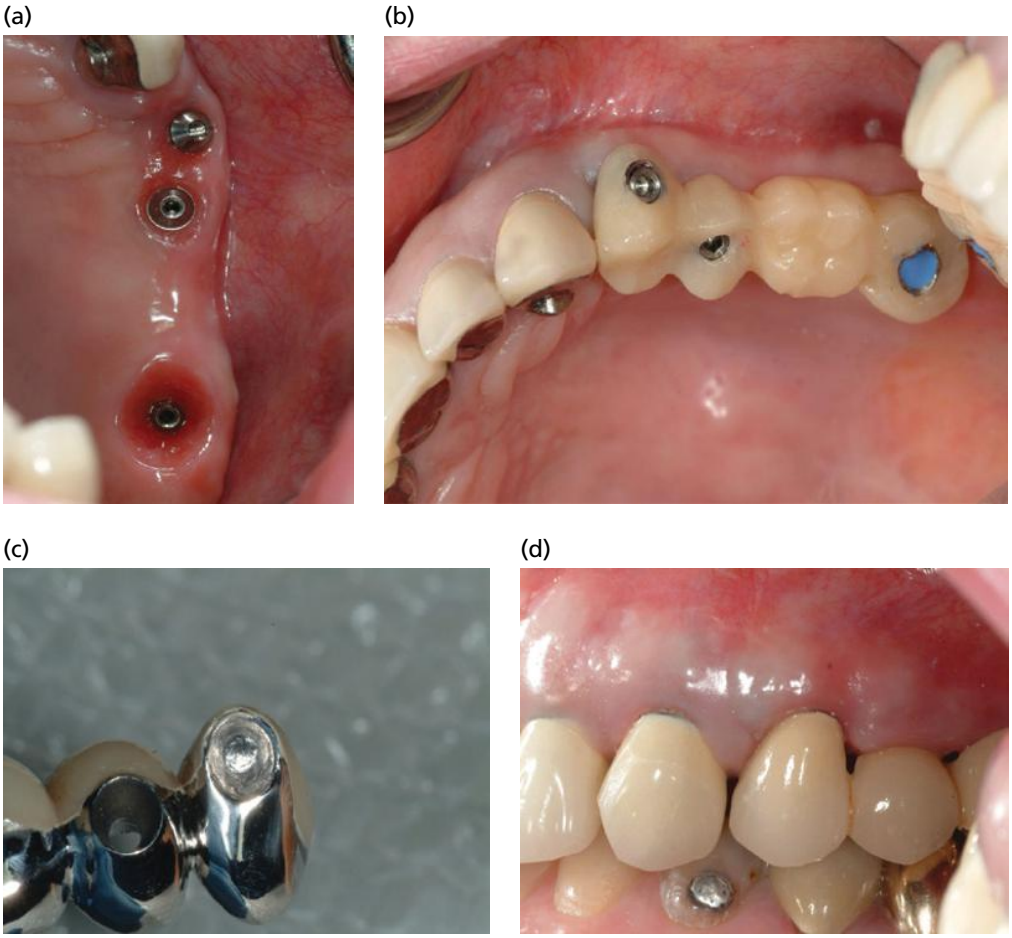

Fig. 57-5 Prosthetic complications with malpositioned implants. (a) Patient had an implant placed in the area of 24 with facial angulation. (b) Provisional fixed bridge demonstrated the facial position. Due to the depth and position of the implant, a fixed prosthesis was made that rested on the implant abutment (c), allowing a satisfactory esthetic and functional restoration (d).

Fig. 57-6 Surgical guides for implant placement. Using a guide with a restrictive channel allows for evaluation in diagnostic imaging studies and during the surgical placement phase.

Fig. 57-7 Restorative margin may be the head of the implant with certain implant designs, necessitating the surgeon having a clear idea of where the final margin will be when placing the implant. Other systems use an abutment for cemented restorations that allows variation in the vertical position of the restorative margin.

access hole position, necessity of using angled abutments, CAD/CAM customized abutments, etc. (Fig. 57-8).

Mechanical complications

Overdenture complications

Numerous studies indicate that the use of an acrylic-based implant overdenture has the highest number of postoperative complications, where complication is defined as a need for some form of intervention, the degree of which is not necessarily defined. Complications include loss of overdenture attachment retention or fracture of the attachment system, fracture of components of the denture, prosthesis-related adjustments, etc.

Goodacre *et al.* (2003a) suggested the most common complication in this category was the need for adjustments due to loss of retention and/or attachment system fracture. O-ring systems, Hader-bar and clip-, IMZ-, Ceka-, ERA-, ZAAG, and, more recently, Locator-attachments, all use various forms of plastic components within the anchorage system. Over time, the plastic component tends to wear and distort, which is actually a good thing, since this motivates

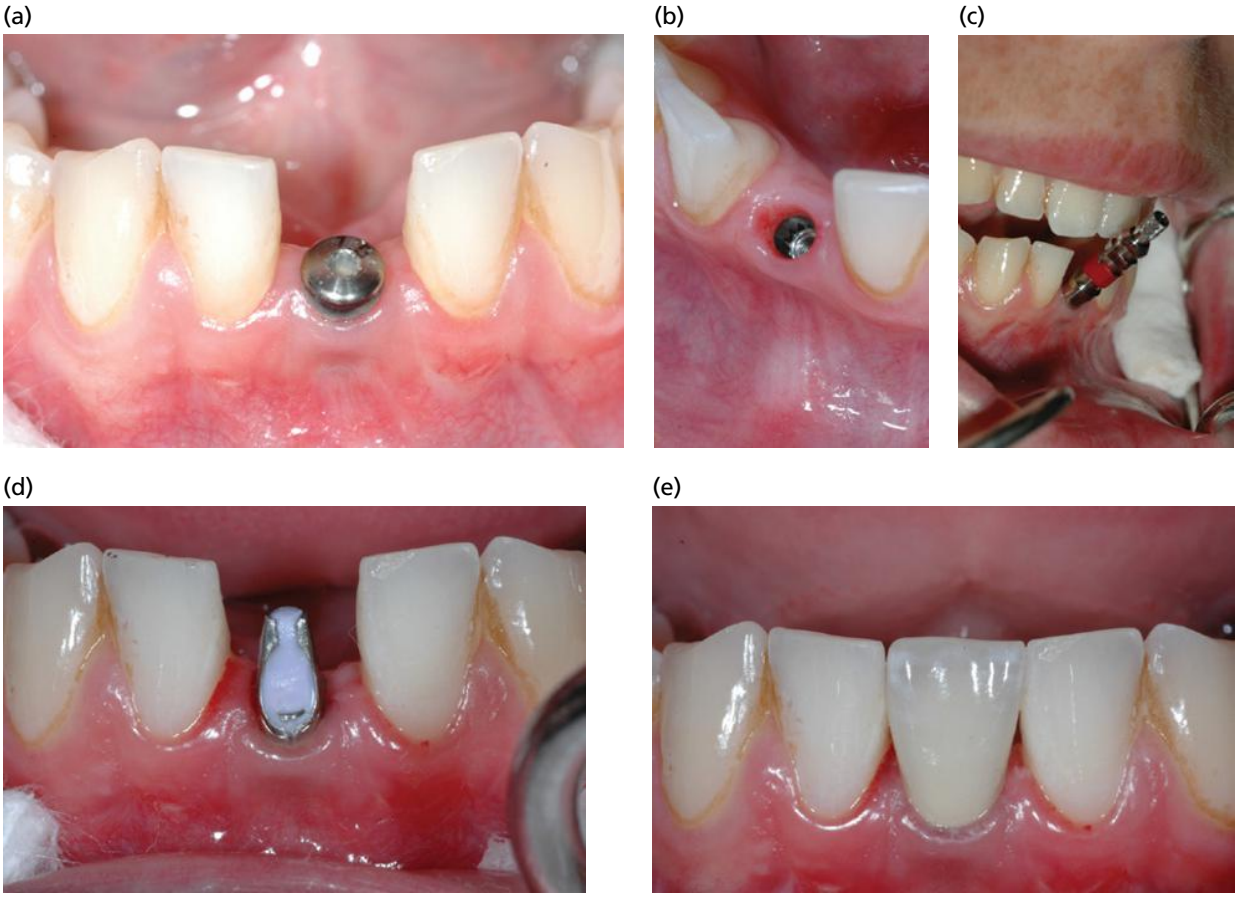

Fig. 57-8 Innovative use of abutments. (a) Patient presented with a healing abutment indicating placement within the residual ridge. Soft tissue health (b) was adequate, though the final impression coping (c) indicates an angled position relative to the remaining teeth. (d, e) Patient was restored with a cement-retained restoration, but using a low profile abutment.

patients to return for recall appointments. Traditional ball attachment systems utilize metal spring matrices and these tend to deform and lose retention with time. Studies that have assessed the difference in frequency of maintenance requirement between bar/clip systems and individual attachment systems indicate that individual attachment systems require more frequent adjustments due to loss of retention of the matrix or patrix (van Kampen *et al*. 2003; Walton 2003; MacEntee *et al*. 2005). However, the simplicity and ease of the repair procedure in some individual attachment systems may reduce frequent complications and have led to the increasing popularity of these abutment designs (e.g. the Locator System in North America). Systems with exchangeable plastic components especially have become popular due to easy maintenance procedures. Further, the conversion of a complete denture patient who rarely returns for maintenance therapy into a routine recall patient (valuable for early caries detection, oral cancer exams, etc.) who is motivated to have his/her attachment system serviced provides a valuable ethical service for the patient.

Because of the housing and attachment components, overdentures typically have a reduced thickness of acrylic resin base in certain areas compared to conventional dentures. It is these thin areas that have a higher risk of fracture. In addition, patients with implant-supported overdentures have a tendency to generate higher masticatory force compared to patients with conventional dentures. The incidence of acrylic base fracture may increase depending on the opposing occlusion. For example, an overdenture opposing an implant-supported FCD will be at a greater risk of fracture, accelerated wear or prosthetic tooth fracture than one opposing a conventional denture. Overdenture fracture is a relatively common problem according to some studies, and could be as high as 7% of all the mechanical complications related to implant-supported restorations (Carlson & Carlsson 1994; Goodacre *et al*. 2003a).

Prosthesis-related adjustments include reline/rebase of the overdenture, occlusal adjustments, and with denture adjustment due to soft tissue complications. Normally, the hard and soft tissue under the overdenture will remodel with time. Additionally, overdentures, based on their design, allow limited rotational movements between the abutment and the anchorage system. This means there will be positive vertical and horizontal load on the edentulous ridge, in the area away from the anchorage system. Changes in mucosal adaptation of the prostheses will induce subsequent problems like occlusion changes and soft tissue trauma.

Fracture of fixed restoration veneers/fixed restorations

Without the periodontal ligament to provide shock absorption and proprioceptive reflex, dental implants are essentially ankylosed to the surrounding bone. Further, patients tend to generate higher masticatory forces on implant-supported restorations relative to the natural dentition. It has been reported that the maximum bite force generated with conventional dentures is around 50–60 N, whereas a full-arch implant-supported restoration can generate a bite force above 200 N (Carr & Laney 1987; Mericske-Stern *et al*. 1996; Fontijn-Tekamp *et al*. 1998; Morneburg & Proschel 2002; Steigenga *et al*. 2003). As a result, an implant-supported prosthesis is exposed to a risk of higher restorative material failure. Among prosthetic failures, studies suggest fracture of the restorative veneer material is the most common type of mechanical complication (Fig. 57.9). Fracture can occur both of the veneering porcelain and of resin-based prosthetic teeth. Veneer fracture can happen anywhere in the mouth: restorations in areas of heavy functional forces and higher non-axial forces such as the occlusal surfaces of mandibular posterior restorations, facial cusps of maxillary posterior restorations, and maxillary anterior restorations. To reduce or avoid material failure, especially veneer material fracture, the restoration should have sound supporting structures. The framework that supports the restorative veneer should have sufficient strength and stability to safely support the overlying veneer material. It should have minimal flexure even under functional loading – veneer materials usually lack tensile strength and as a result are weak under flexural stress. The framework should be carefully designed so that it will provide maximum support with no areas of the veneer material unsupported (Fig. 57-10), which today often means use of a milled high strength alloy such as zirconia, chromium cobalt, or titanium alloy. Another important approach to reducing complications with veneering materials is control of the occlusion. To reduce or eliminate excessive stress on one particular tooth or restoration, wide distribution of the occlusal force will be better than loads concentrated on a localized area. Also, limiting the main occlusal force on the restoration directly supported by implants may be beneficial; cantilevered restorations may be at higher risk of fracture than those supported by the implant/abutment under identical occlusal loads (Becker 2004; Pjetursson *et al*. 2004).

Implant-borne restorations with occlusal wear are more evident in implant- versus dental-supported restorations. Especially when there is a mismatch of opposing restorative materials, wear can be dramatic. Thus, one must be prudent in not only selecting the material for the occlusal surface of the restoration, but also the status of polishing to avoid serious maintenance issues. It is known that porcelain can be abrasive when opposed with enamel, metal, resin, or even porcelain, especially when this does not have a highly polished surface (Monasky & Taylor 1971). An exposed opaque layer and use of external characterizations with metal oxides all add to the abrasiveness of porcelain and should be used with care.

A rare but possible complication is the fracture of mandibular implant-supported FCDs at the midline (Fig. 57-11). It is speculated that flexure of the edentulous mandible during function can cause this type of complication. With repeated extreme mouth opening, fatigue can accumulate in the metal framework, and once this accumulated fatigue exceeds the fatigue strength of the material, the prosthesis may facture or veneering material delaminate from the framework. Clinically, patients with this type of restoration may feel tightness of the mandible, especially during function, and once the restoration fails, they express "relief" from the tightness. To avoid this problem, fabricating a two-piece fixed restoration has been advocated, although it can generate its own problem: because of the lack of the bracing effect and rigidity of the framework, these restorations may tend to have a higher incidence of retention screw-related problems.

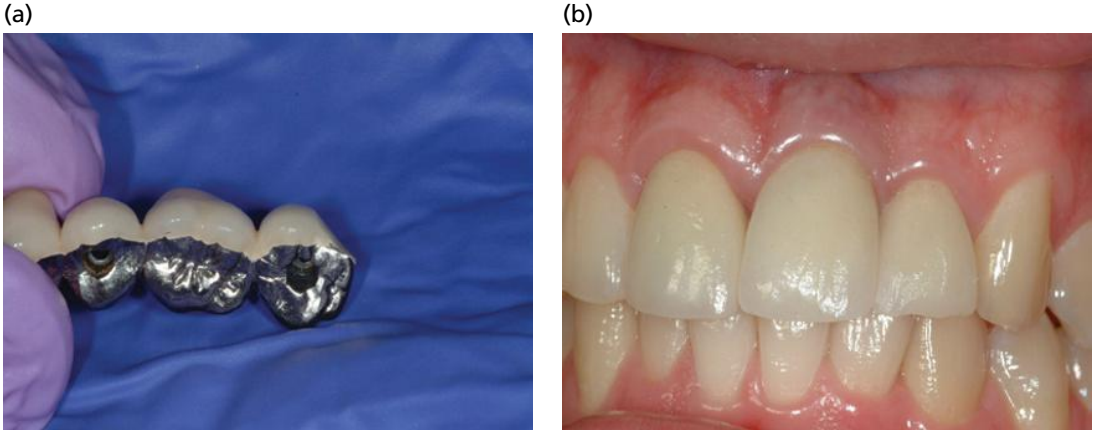

Fig. 57-9 Factures of veneering ceramic material. (a) Facial shear fracture of porcelain on posterior unit. (b) Ceramic shear fracture on facial surface of 22 all-ceramic restoration.

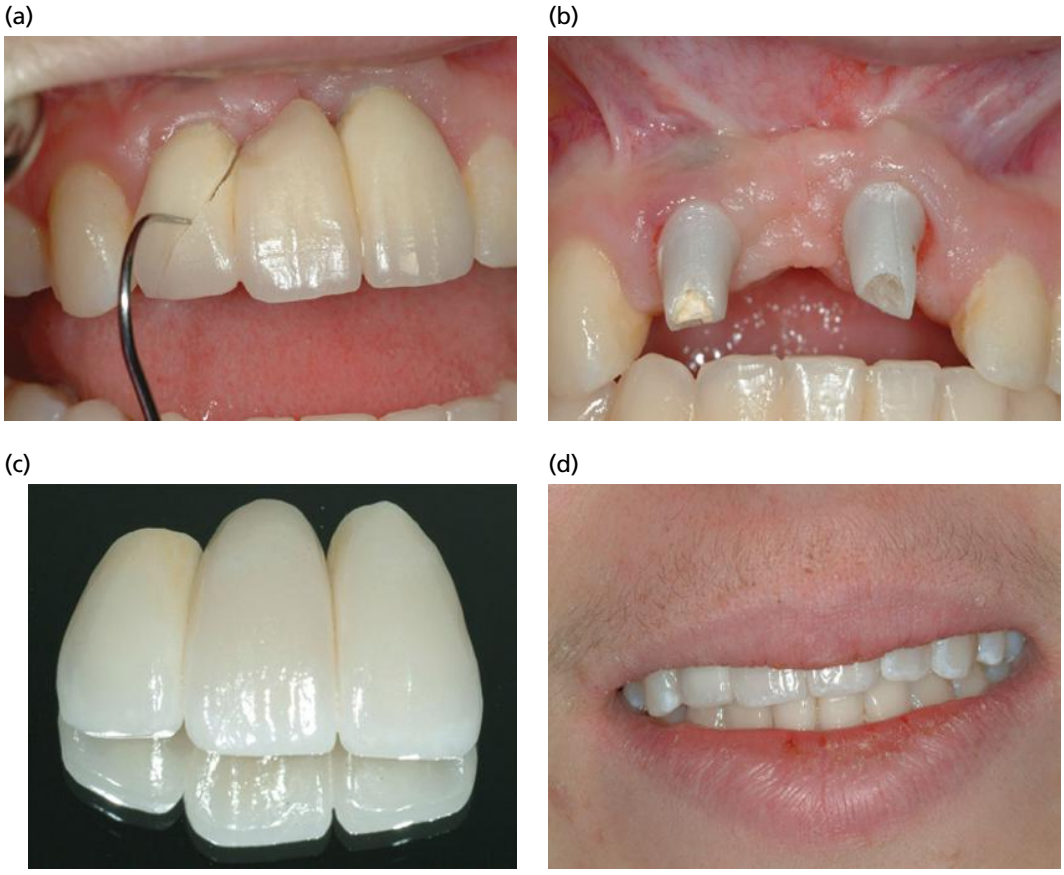

Fig. 57-10 Fractured all-ceramic implant restoration. Patient had a three-unit fixed partial denture with glass-infused ceramic structure. (a) Restoration demonstrated catastrophic rupture 2 years after delivery. Restoration was removed (b), zirconia abutments cleaned and a new zirconia reinforced FPD fabricated for enhanced strength (c). (d) Final esthetic appearance of the FPD.

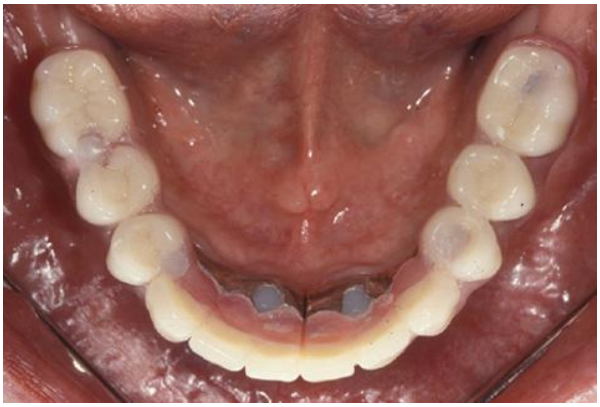

Fig. 57-11 Splitting full-arch metal–ceramic restoration at the midline to reduce impact of mandibular flexure.

Implant screw-related complications

Numerous studies indicate that complications related to the screw components of the implant system are common and require clinical intervention, which could range from simple retightening of the screw(s) to total replacement of the abutment and screw(s). This requires additional time from both dentists and patients and incurs additional cost. Jemt and Linden (1992) observed, with earlier screw abutment designs, screw loosening in 49% of maxillary implant-supported restorations and 21% of prostheses in the mandible. They also observed that 57% of the abutment screw loosening occurred within the first year of service and only 37% remained stable over a 3-year period. Goodacre *et al.* (2003a) observed that the frequency of complications related to implant screws, like screw loosening or fracture, for abutment or prosthetic screws could account for as much as 19% of all the potential mechanical complications in implant restorations. Ding *et al.* (2003) reported that the incidence of screw loosening for an external hex system could be as high as 38%, which suggests one reason for the reduced popularity of this abutment–implant connection. In their systematic review, Pjetursson *et al.* (2004) observed that abutment or occlusal screw loosening/fracture was the third most common technical complication, behind only veneer fracture after restoration and loss of occlusal screw access restoration. Its cumulative incidence after 5 years of follow-up was 7.3% (Pjetursson *et al*. 2004).

Theoretically, the lifespan of an abutment or prosthetic screw in an implant restoration needs to be $>10^8$ cycles of loading or approximately 20 years, assuming the system is accurately constructed and the loading conditions simulate the natural oral environment (Patterson & Johns 1992). However, there are several factors that, if not designed or functioning properly, could drastically reduce the predicted service life, resulting in screw loosening and/or fracture. For example, the abutment–implant

interface geometry, precision of fit and/or passivity of components, and the amount of preload may reduce service life. For the older external hexagonal implant system studies, it was shown that larger implant–abutment contact area provided superior stability of the system and resistance to screw complications, and this was a driving force for the use of wider diameter implant devices (Binon 2000). Additionally, precise antirotational features should be present for the joint components to withstand rotational movements that could potentially cause screw loosening in butt-joint configurations (Khraisat 2005). Precise fit of the abutment to the implant interface is highly important. In a study on machining accuracy of several different external hex implant systems, all systems demonstrated rotational movement in excess of 4° (Binon 1995). The "slip-joint" figures, such as in external hex implant systems, are naturally vulnerable to vibration and micro-motion during functional loading (Schwarz 2000; Hoyer *et al.* 2001). This has led to the popularity of conus or internal abutment to implant systems in the last 10 years. In the absence of passivity between the implant components, it has been shown that screws accumulate internal stress, which eventually results in metal fatigue failure and screw loosening/fracture (Kano *et al.* 2006). The resulting clamping force between the abutment and implant generated by the screw is called *preload*. In an external hex system, the preload, along with the frictional force of the abutment–implant joint wall, is the major force resisting functional loads. In most implant systems, a tightening torque is applied and the preload stress at the interface is increased to what it should be within the elastic range of the screw material. The screw tightening should result in an optimum preload level for the maximum outcome of the implant complex after dynamic loading. The literature indicates that as long as the external loading stress does not exceed the preload stress, the abutment–implant connection can be regarded as safe (Patterson & Johns 1992; Lang *et al.* 2003). Insufficient or excessive preload stress could compromise the lifespan of the abutment–implant connection.

Chronic problems associated with the external hex– or butt–joint interface implant systems have been documented. Because of these inherent problems with the external hex design, investigators have presented new concepts in implant design, which aim to improve support and reduce the complications associated with the external hex design, by means of additional frictional force between the internal wall of the implant and the external wall of a one-piece abutment/abutment screw. ten Bruggenkate *et al.* (1998) proposed an 8° internal-taper connection between the implant and abutment. The original concept of Morse taper comes from engineering, particularly from the area of machine taper. When connecting exchangeable working bits into the work piece, a popular and very effective method is to use frictional forces between the two components, where the pressure of the spindle against the work piece drives the tapered shank tightly into the tapered hole. The friction across the entire interface surface area provides a surprisingly large amount of torque transmission. The abutment–implant junction can be designed such that an internal connection is utilized with minimal taper (2–15°), while the screw base portion of the abutment will be connected into the receiving portion of the implant. There are numerous studies reporting on the higher mechanical and enhanced clinical behavior of these internal connection implants (Binon 2000). Norton (1997, 1999) verified that the internal conical designed systems significantly enhanced the resistance of the connection system against external bending forces. Levine *et al.* (1999) found that the internal connection showed a significantly lower incidence (3.6% to 5.3%) of screw-related complications compared to external hex designed systems. The use of the internal interference fit abutment designs has simplified the prosthetic phase of therapy and increased the long-term stability of the screw–joint connections (Stanford & Brand 1999; Brunski 2000, 2003; Jokstad *et al*. 2003).

Abutment-related complications

In positioning an abutment into the implant, there are potential mechanical complications that can arise. One common issue is incomplete seating of the abutment in the implant body (Fig. 57-12). Depending

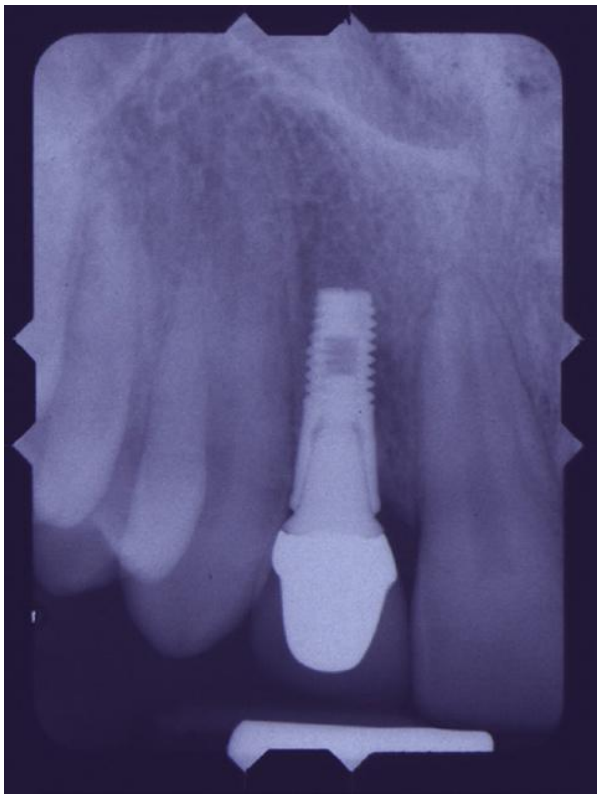

Fig. 57-12 Incomplete seating of abutment in a two-piece implant system. Implant abutment was incompletely seated in the implant due to contact on the adjacent osseous contours.

on the implant position and depth, it is also possible that the peri-implant bone may inhibit complete seating of the abutment (giving the dentist the impression that the abutment is fully seated when in fact it is resting on adjacent bone). This may or may not be evident on a radiograph, depending on the implant–abutment angulation relative to the central beam of the radiographic unit.

Since most prefabricated abutments are produced in standard size and shape, it can be challenging to customize these to individual patients. Modification of a prefabricated abutment may in turn compromise the biomechanical properties of the abutment to achieve an esthetic result. More recently, systems have shifted form a modified "stock" or "prefabricated" titanium abutment to the use of CAD/CAM milling approaches. The latter approach provides industrial tolerance and manufacturing control, and a more predictable long-term abutment–implant solution.

When the head of the implant is placed below the adjacent bone, the bone can develop a sloped architecture, extending from the periodontal ligament support of the adjacent teeth down and across to the implant. This often happens in the maxilla area where implants are generally placed deeper to avoid esthetic issues. Periodically this scalloped osseous architecture necessitates the prosthodontist to assess and then modify the abutment, and occasionally the implant body in this area (Fig. 57-13). In this case, the mucosal transition zone of the abutment is modified to avoid placing pressure on the bone and soft tissues. It is also helpful to develop a flat or even concave emergence profile of the final restoration to maintain soft tissue dimensions around the restoration (Stanford 2005a).

Other issues related to prosthetic complications

Implant angulation and prosthetic complications

The impact of angled implants on clinical outcomes is often of significant concern. As far back as 1995, Clelland *et al.* evaluated the stresses and strains generated by an abutment system capable of three angulations (0°, 15°, and 20°). They observed that peak stresses were located in the cortical bone, and the magnitude of these stresses increased with an increase in the abutment angulation. The maximum stress values were generally within the physiologic parameters described for animals, but in one case, the peak compressive stress for the 20° abutment was slightly above this physiologic zone. Peak tensile strains also increased with abutment angulation, but maximum compressive strain values were the same for all three angles. This study suggested that angled abutments were safely used relative to the bone stability around the implant body (Clelland *et al*. 1995).

One advocated approach has been to use multiple implants and to place a faciolingual offset between

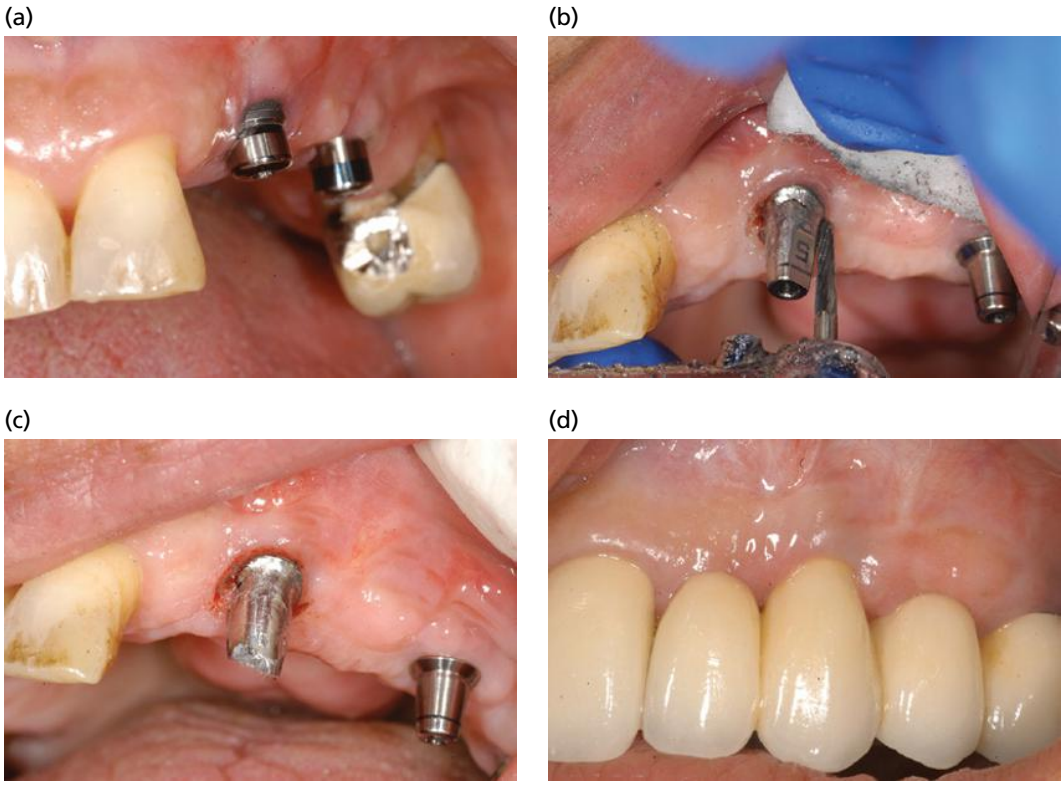

Fig. 57-13 Implant and abutment modification. Patient presented with soft tissue dehiscence in an integrated implant (a), necessitating placement of an abutment and preparation of the abutment and implant body (b). A fixed partial denture was fabricated using the modified abutment (c) that achieved a reasonable esthetic and functional outcome for this compromised situation (d).

them to enhance the mechanical stability of a connected FPD. Sutpideler *et al.* (2004) evaluated the effect of an offset on the transmission of force to bone-supporting implants aligned in either a straight-line configuration or an offset configuration. They also addressed the effect of different prosthesis heights and different directions of force application. They observed that vertical loading of an implant-supported prosthesis produced the lowest stress on the supporting bone, and increasing the angle resulted in greater stress that theoretically simulated surrounding bone. They also observed that reducing the height of the prosthesis from 12 mm to 6 mm (crown-to-implant ratio) or establishing an offset implant location for the middle of three implants may reduce stress, but this reduction did not compensate for the increase in stress found with non-axial loading (Sutpideler *et al*. 2004). This concept has been extended with the recent advocacy for the intentional placement of implants at significant angulation relative to each other (tilted implant position) to avoid vital structures and sinus cavities, and to improve the putative biomechanical position of the implants (Krennmair *et al.* 2005; Esposito *et al.* 2012; Truninger *et al*. 2012).

Chun *et al.* (2006) investigated the effect of three different abutment types (one-piece, internal hex, and external hex) on the stress distribution in bone under vertical and inclined loads by finite element analysis. For one-piece implant designs, they observed the load was transferred evenly into bone as well as within the implant system. However, the maximum stress generated in bone with the one-piece system was always higher than that generated with the internal hex implant, regardless of load angle inclination. In the case of the internal hex implant, the contact condition with friction between abutment and implant in the tapered joints and at the abutment neck reduced the effect of bending caused by the horizontal component of inclined load. The maximum stress in bone was highest for the external hex implants (Chun *et al*. 2006).

Erneklint *et al.* (2006) evaluated the load resistance in a conical implant system with two different screw-retained abutment angled designs (20° and 45°) and three different retaining-screw materials. They observed that the 20° abutment withstood non-axial forces to a greater extent than the 45° abutment, regardless of the retaining-screw material. The 45° abutment failed under oblique loads between 450 and 530 N, while the 20° abutment failed at 1280–1570 N. Differences between the retaining-screw materials were more obvious in the 20° abutment, but also were not insignificant in the 45° abutment. In general, it was concluded that abutment taper angles were more important than retaining-screw material in determining the assembly strength (Erneklint *et al*. 2006).

The angulation of the implants can also influence the outcomes of implant overdenture therapy. Gulizio *et al.* (2005) evaluated the retentive capacity of gold and titanium overdenture attachments placed on implants positioned at 0°, 10°, 20°, and 30° from a vertical reference axis. They observed significant differences in retention of gold matrices when ball abutments were positioned at 20° and 30°, but not at 0° and 10°. Also, they noted significantly higher variance in retention among the titanium matrices, despite the finding that angle was not a factor affecting retention for titanium matrices. In other words, the angle of the implants had an effect on the retention of gold matrices, but not on titanium matrices. This study supports the clinical observation that implant-supported overdentures have higher maintenance needs and may have higher long-term ongoing costs relative to conventional tooth replacement therapies (Naert *et al*. 2004a, b; Krennmair *et al*. 2005; Zitzmann *et al*. 2005; Trakas *et al*. 2006; Visser *et al*. 2006).

Screw-retained versus cement-retained restorations

The method of attachment of the prosthesis to the implant/abutment can cause prosthetic complications. The major advantages of screw-retained implant-supported restorations include their retrievability and freedom from residual cement problems (Wadhwani *et al*. 2012). Thus this type of restoration scheme can be applied when there is a need for future removal, for example for hygiene maintenance or when the prognosis of the restoration is questionable. It could also be applied when the restorative margin is located too deep for removal of excess cement. The same advantage applies to the provisional restorations as well. However, this type of restoration has inherent disadvantages. The required screw access hole may compromise the esthetics and occlusion, and potentially the strength of the restoration due to the lack of material around the screw access shaft through the prosthesis. The presence of the prosthetic screw itself may bring screw complications. Additionally, this type of restoration is more sensitive to the passive fit of the restoration to the supporting implants.

Regarding the clinical performance of each type of restoration, the literature indicates that screw-retained restorations may present more postoperative complications compared to cement-retained restorations (although much of this literature is based on older abutment to implant designs). Duncan *et al.* (2003) reported that patients restored with screw-retained restorations had problems with prosthetic screws and screw access hole filling material, while after 3 years no complications had been encountered by patients restored with cement-retained restorations. Karl *et al.* (2006) found that cement-retained FPDs may result in lower strain levels compared to conventional screw-retained FPDs at the time of either the cementation or screw-tightening procedure. Higher strain level at the time of load delivery may reduce the passivity of the fit of the restoration and

increase potential future complications. This result is in accordance with other *in vitro* studies (Guichet *et al*. 2000; Taylor *et al*. 2000). However, this study tentatively suggests that regardless of the type of restoration, no true passive fit can be achieved. Skalak (1983) theorized that a non-passive fit of the restoration could induce biologic and prosthetic complications. However, Jemt and Book (1996) reported that they could find no direct association between implant prosthesis misfits and marginal bone loss over 5 years. Vigolo *et al.* (2004) found no evidence of difference in the behavior of the peri-implant marginal bone and soft tissue response around screw-retained and cement-retained single-tooth implant restorations.

Overall, there is no consensus on the superiority of one type over the other, and the choice depends on the clinical situation and operator's preference.

Ceramic abutments

Ceramic implant abutments have recently gained in popularity due to their superior esthetic results compared to conventional titanium abutments, especially in thin tissue biotypes (Stanford 2005a; Leutert *et al*. 2012). Because of the strength concerns, reinforced ceramic abutment are currently the first choice, for example alumina (Al_2O_3) or yettria-stabilized zirconia (ZrO_2) (Fig. 57-10). These abutments were introduced during the 1990s and the first consisted of densely sintered aluminum oxide (alumina). Andersson *et al.* (2003) conducted a 5-year multicenter prospective study evaluating the clinical outcome of alumina ceramic abutments. According to this study, the cumulative success rate for alumina ceramic abutments was 98.1% at 5 years compared to 100% for conventional titanium abutments. More recently, zirconia has become popular for ceramic implant abutments. Because ceramic materials are vulnerable to tensile stress, especially around defects or cracks, a ceramic material with higher fracture toughness will be a good material for ceramic abutments. Zirconia is generally known to have a higher range of fracture toughness (K_{IC} ~7–15 $MPam^{-1}$) than alumina (K_{IC} ~4–4.5 $MPam^{-1}$). Its fracture toughness is comparable to that of metal alloys (K_{IC} ≥20 $MPam^{-1}$) (Piconi & Maccauro 1999; Kelly 2004; Marinis *et al*. 2013). Zirconia is known to have the relatively unique property of transformation toughening, where the metastable tetragonal phase can be converted into the monoclinic phase with associated volume expansion (Chevalier 2006). This phenomenon is induced by stress concentration at defective or crack tips: the crack is compressed and its growth retarded. This is the main mechanism for the higher fracture toughness of zirconia, and it could significantly extend the reliability and lifetime of the restoration. However, there is little evidence that the abutment retains this property after being reduced to <1 mm during clinical usage. Further, the hydrolytic properties of water interacting with the material during aging (hydrolytic aging or "low temperature degradation") is still an active area of laboratory investigation (Rekow & Thompson 2005; Denry & Kelly 2008). Depending on the design, an all-ceramic abutment can fail either due to misindexing within the implant (since the abutment is harder than the titanium body) or body fracture, often due to laboratory adjustments to the CAD/CAM abutment (Fig. 57-14). There are outstanding questions relative to the use of this material, including long-term fatigue strength, degree of preparation/wall thickness needed, intraoral sites, clinical long-term prognosis, etc. Due to its relatively recent introduction, few studies have assessed the clinical performance of these abutments (Att *et al*. 2006; Denry & Holloway 2006; Deville *et al*. 2006; Itinoche *et al*. 2006; Studart *et al*. 2006).

Esthetic complications

The most frustrating and challenging complication is unacceptable esthetic outcomes. With a growing population of esthetically concerned patients, esthetic complications are a serious matter even if the implant team has done its best throughout the procedure. This is an important issue that the implant team and the patient need to be aware of and endeavor to find solutions to prevent or overcome. Common esthetic complications include complications due to malposition of oral implants, black interproximal spaces, thin tissue "biotypes", and unfavorable soft tissue responses.

The potential cause and impact of malpositioned implants was described earlier. A very difficult aspect of implant rehabilitation is that sometimes a slight malpositioning can induce dramatic esthetic compromises which only become evident when the technician is working with the case. A facially malpositioned implant can become a major challenge for the restorative team (see Figs 57-5, 57-8, 57-13). In this case, the restorative dentist may have to address a variety of potential problems, including excessive incisogingival dimensions of the crown, exposed head of the implant, unequal gingival margins, etc. Usually, the facially malpositioned implants create greater problems than other malpositioned implants. A position 1 mm lingual to the implant in the maxillary esthetic zone can create a prosthetic challenge in achieving a final restoration that appears even and uniform with the natural dentition. Mesially or distally malpositioned implants can induce improper anatomy of the restoration as the technician attempts to compensate for implant components in the interproximal space (Fig. 57-15).

Unfavorable soft tissue response can also make the treatment very difficult. It is generally accepted that individuals who have relatively thin attached gingiva, or thin tissue biotype, are more vulnerable to gingival/periodontal disease and subsequent

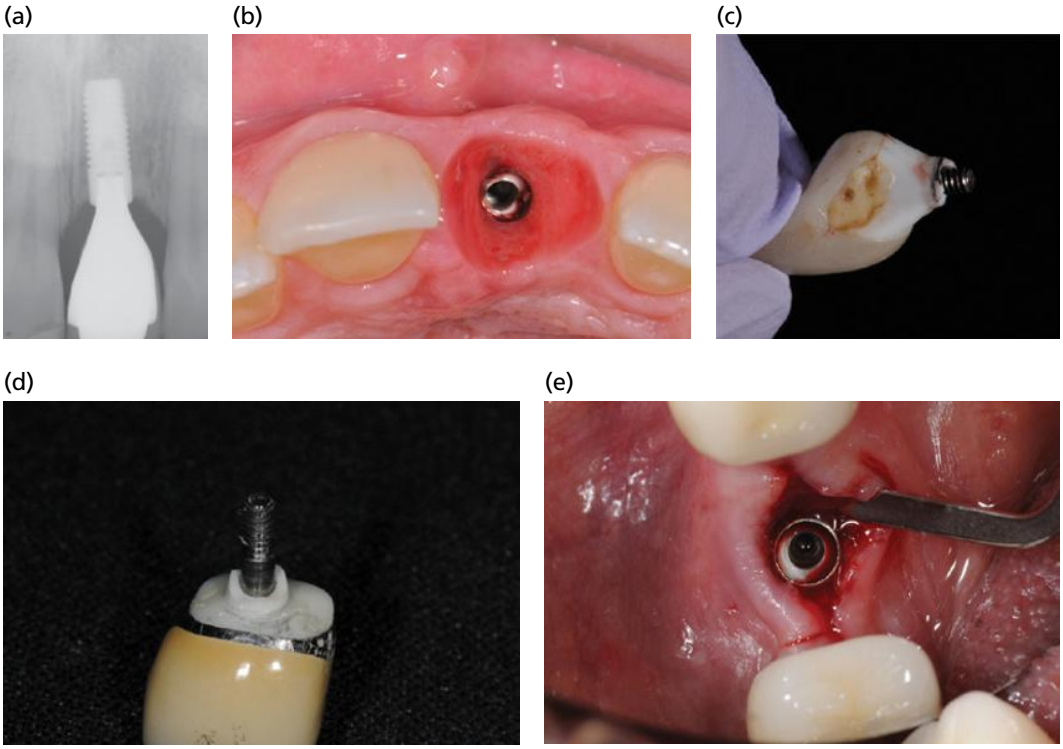

Fig. 57-14 Fracture of all-ceramic abutments. (a) Two years following delivery of the crown and zirconia abutment, the patient had a loose 21. (b) On removal of the crown/abutment, a fractured portion of the index of the abutment was observed within the implant. (c) This type of fracture may be due to misseating of the index within the implant. Note the residual resin cement on the transmucosal aspect of the abutment, yet the lack of this appearance on the radiograph (a). (d) Fractures can also occur with the body of the abutment (commonly due to laboratory adjustment to the ceramic), leading to the need to remove the fractured portion with a surgical microscope. (e) Note the position of the fracture within the body of the abutment.

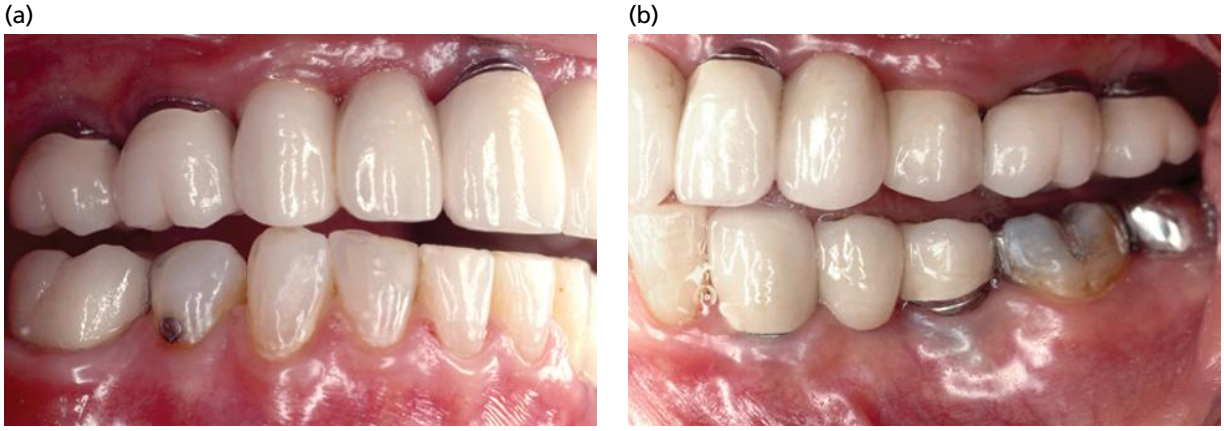

Fig. 57-15 Soft tissue recession on the facial aspect of an implant-supported restoration.

sequelae, including gingival recession (Sailer *et al.* 2007). Similar findings are reported for the tissue response around implant restorations (Kan *et al.* 2003). Thin biotype tissues tend to show a greater recessive response to trauma. Restorative procedures like preparation, impression, repeated abutment/provisional removal or even toothbrushing can sometimes cause enough trauma to these thin biotype tissues to result in significant recession that compromises the treatment outcome. It is very important to identify the tissue type early at the treatment planning stage to prevent unfavorable treatment outcome (Fig. 57-16).

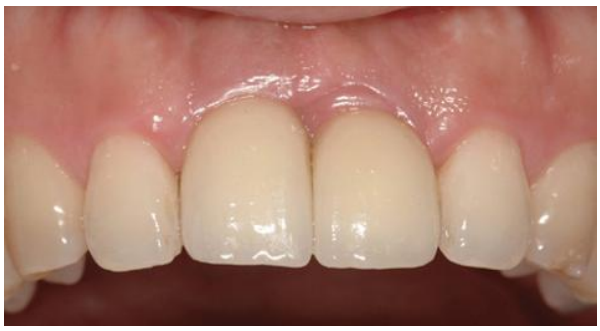

Fig. 57-16 Challenges in creating esthetic outcomes when implants are insufficiently placed. Example demonstrates teeth 11 and 21 with compromised contours due to the close proximity of the implants.

Success/survival rate of implant-supported prostheses

As previously described, the biologic success/survival rate is extremely high and has become more predictable even in areas that were considered to be of high risk (e.g. the maxillary posterior region). It may be beneficial to know what the literature indicates regarding the success/survival rate of restorations fabricated on osseointegrated implants. Pjetursson *et al.* (2004) obtained estimates of the long-term survival/success rates of implant-supported FPDs and of the incidence of technical complications in partially edentulous patients over an observation period of >5 years. In this study, "FPD survival" was defined as "the FPD remaining *in situ* with or without modification for the observation period", as compared to the definition of "FPD success", which was "FPD being free of all complications over the entire observation period". The cumulative FPD survival rate was 95% after 5 years and 86.7% after 10 years. The authors noted the important fact that most of the prosthetic complications occurred after 5 years of clinical service. The underlying issue this illustrates is the problem associated with the rapid rate of manufacturing market changes in implant products and components. By the time the restoration needs repair or replacement, the required components may be difficult, if not impossible, to obtain. Regarding comparison of different implant systems, there is little evidence that any one system is superior to another in terms of mechanical failure. Implant–abutment joint geometry, design of the restoration, and patient factors like parafunctional habits or heavy occlusal forces tend to have more impact on the outcome of implant-supported restorations than implant surface material or topography (Rangert *et al*. 1995; Astrand *et al*. 1999; Naert *et al*. 2002a, b). Some studies indicate that the cumulative complication rate of prosthetic problems can be as high as 43.1% after 5 years (Jemt *et al*. 2003), compared to other studies finding it to be as low as 19.3% after 5 years (Bragger *et al.* 2001; Pjetursson *et al*. 2004). Together these studies indicate that after 5 years one may expect one in four implant-supported restorations to require some type of repair, whether minor, such as screw or abutment tightening, or major, such as entire restoration replacement. This implies that significant chair time may be necessary for the maintenance of these restorations (Pjetursson *et al*. 2004).

Berglundh *et al.* (2002) also noted the higher mechanical/technical complication rate compared to the biologic complication rate. This study observed several interesting aspects: the incidence of implant loss prior to functional loading was three-fold higher when multiple implants were placed for larger restorations like overdentures or fixed complete restorations, compared to single-tooth restorations. Implant loss during function occurred in 2–3% of implants supporting fixed reconstructions, while twice as many implants were lost in overdenture therapy over a 5-year period. In this case, the highest frequency of implant loss during function occurred in the maxilla.

Conclusion

Implant therapy as a form of tooth replacement therapy provides many benefits. As with any form of prosthetic rehabilitation, it has limitations, including wear, material fatigue and fracture, soft tissue recession and subsequent complications, and increased maintenance and costs. The benefits though can be enormous, including enhanced patient quality of life with a definitive replacement of teeth. Patients need to be aware during the treatment planning process that the treatment provided may need to be replaced periodically as normal aging and wear occurs. Specific patient-based risk factors such as parafunctional habits should be discussed and the patient made aware of the risks to the prosthetic reconstructions.

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Part 17: Orthodontics and Periodontics

Chapter 58

Tooth Movement in the Periodontally Compromised Patient

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Introduction: Biologic principles of orthodontic tooth movement

Physiologic tooth movements are those that a tooth makes to attain, and then to maintain, its functional position. They are associated with the processes of tooth growth and eruption, and also occur when external forces are applied. *Orthodontic movements* are those generated by external forces applied in a controlled manner with the purpose of attaining a predetermined tooth movement. In both types of tooth movements, the transmission of mechanical forces from the root to the periodontal ligament (PDL) will elicit biologic reactions between the cells and the extracellular matrix, leading to modeling and remodeling processes in the neighboring alveolar bone housing and, as a result, change of the tooth spatial position.

The application of orthodontic forces causes a physical distortion within the PDL that evokes a series of cell–matrix interactions. These trigger a series of biochemical reaction cascades that change cell physiology through changes in extracellular, cell membrane, and nuclear transduction mechanisms (Masella & Meister 2006). These adaptive responses to applied orthodontic forces are highly sophisticated biologic processes, transforming mechanical forces into controlled cellular activities that are regulated by different neurotransmitters, growth factors, cytokines, and mediators, and hence eliciting a controlled inflammatory response in the absence of pathology (Meikle 2006).

Depending on the amount and direction of the mechanical force applied to a tooth, the resulting tooth movement will vary. A mechanical force perpendicular to the longitudinal axis of a tooth produces wide areas of pressure on one side of the root and corresponding areas of tension on the other. If the force could be placed near the center of resistance of the root, the resulting movement would be a horizontal translation of the tooth or a bodily movement. In this type of movement, there is an even distribution of pressure and tension areas on both sides of the root. This movement, however, is impossible in most clinical situations since the root is invested in bone and the only surface available to apply the orthodontic force is the crown. In orthodontic treatment, therefore, the forces need to be applied against the tooth crown via some kind of system or appliance that ensures a two-point contact to enable the necessary couple that transfers the applied force to the tooth center of rotation. The point of application of such movement will vary depending on the site of the force application, the shape of

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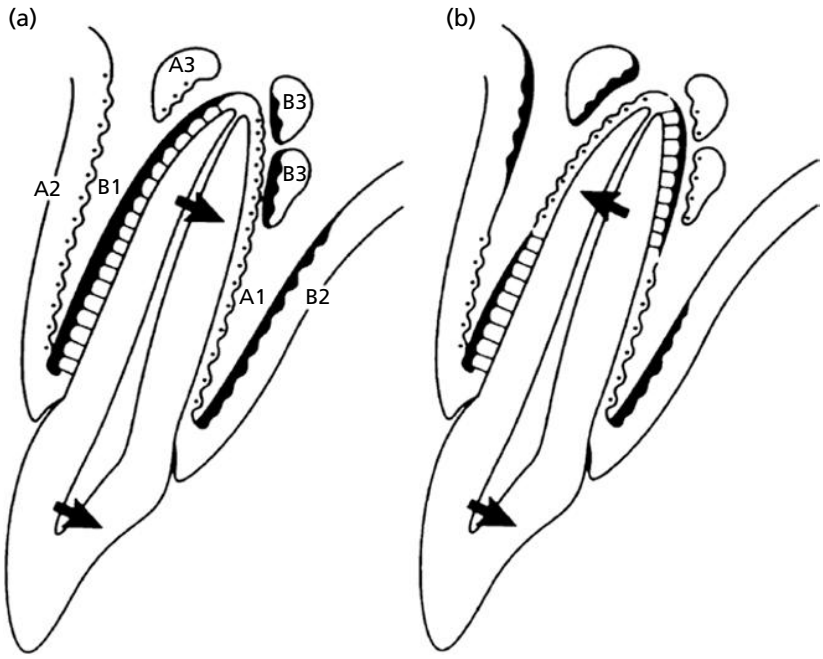


Fig. 58-1 (a) Mechanical force perpendicular to the longitudinal axis of a tooth produces wide areas of pressure on one side of the root and corresponding areas of tension on the other. (b) Point of application of the force varies depending on the site of the force application, shape of the tooth, and architecture of the tooth-supporting system. The resulting movement will be a combination of bodily and tilting movements, leading to pressure and tension forces on either side of the root and a varying distribution of the stress along the periodontal ligament.

the tooth, and the architecture of the tooth-supporting system. The resulting movement will be a combination of bodily and tilting movements leading to pressure and tension forces on either side of the root and a varying distribution of the stress along the PDL (Fig. 58-1). In general, the tension side will make the PDL space wider, hence stretching the fibers and evoking cellular processes leading to bone formation. In contrast, the periodontal space on the pressure side becomes narrower, thus evoking cellular processes leading to bone resorption.

Application of light mechanical forces (approximately 50–100 g/tooth) on the pressure side is associated with "direct bone resorption". In these situations the vessels are patent and the physiology of the cells and tissues is preserved. In contrast, stronger mechanical forces will cause a crushing injury to PDL tissues, with cell death, hyalinization, and the formation of cell-free areas between the PDL and the adjacent alveolar bone, which will interfere with the tooth movement and will slow the biologic processes. Patient variability in the response to similar mechanical forces is common in orthodontic practice and there are many possible reasons for this heterogeneity, such as differences in alveolar bone mineral density, in vascularity, in the number of available bone cells, and in the many inherent cellular and metabolic responses due to differences in the patient's genome that dictate differences in cell recruitment, differentiation, and function, as well as in the expression of the many proteins and regulatory molecules that intervene in bone metabolism.

The objective of orthodontic therapy is to correct malocclusions and altered tooth positions by utilizing orthodontic appliances and techniques that combine compression and tension forces applied on the appropriate tooth surfaces (Wise & King 2008; Meikle 2006; Dolce *et al*. 2002). This therapy has distinctive characteristics when applied to dentitions in growing bone (such as in children and adolescents) compared to dentitions where the bone has stopped growing (in adults). In the first case, the orthodontic therapy combines guidance of the jaw's growth to the adequate intermaxillary relationships with dentoalveolar tooth movements. In adults, orthodontic therapy is limited to dentoalveolar tooth movements and in many instances to teeth with a healthy but reduced PDL as a consequence of periodontal disease. With the increasing esthetic demands of modern society, an increasing number of adult patients are seeking orthodontic treatment to correct common conditions such as anterior tooth diastemata, crowding, uneven gingival margins, or loss of interdental papillae.

In patients suffering from moderate and severe chronic periodontitis, the combination of bone loss, early tooth loss, and primary or secondary tooth trauma causes pathologic tooth migration and frequently severe malocclusions and malpositions, which lead to further deterioration of the patient's dentition. In these situations, orthodontic therapy is a prerequisite to restore the patient's functional dentition. The treatment of these patients requires a close coordination and collaboration between the orthodontist, the periodontist, and the restorative dentist to optimize treatment outcomes. This chapter specifically reviews how orthodontic therapy can be implemented in adults with periodontally affected dentitions.

Periodontal and orthodontic diagnosis

It is a prerequisite in any adult patient seeking orthodontic therapy to achieve periodontal health and therefore, a periodontal diagnosis including oral examination, periodontal charting, and a complete

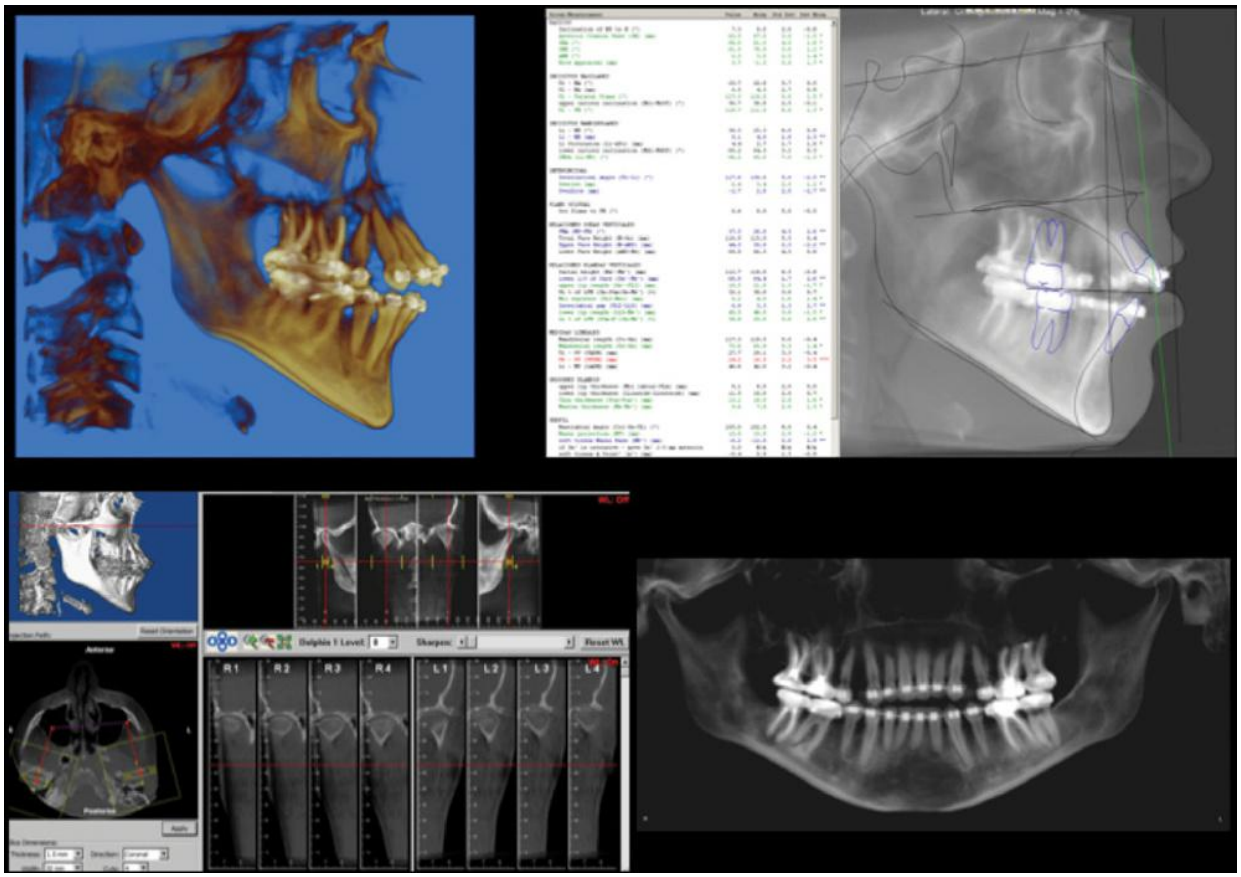


Fig. 58-2 Different diagnostic methods used in orthodontic treatment planning. The classical combination of orthopantomography (OPG) and cranium lateral radiography allows a cephalometric analysis, with cone-beam computed tomography (CBCT) providing further information on the morphologic aspects of the craniofacial complex.

periapical radiographic series should always be carried out before the start of the orthodontic therapy. Periodontal charting should include recording of full-mouth probing pocket depths, presence of gingival recessions, bleeding on probing, and plaque accumulation in four to six sites per tooth, as well as the evaluation of tooth mobility, presence of furcation involvements, and mucogingival defects.

In conjunction with the periodontal examination, it is important to evaluate carefully the status of the remaining dentition with close attention to the presence of undiagnosed caries or presence of periapical pathology which may interfere with the orthodontic therapy. If these pathologies are present, appropriate restorative and/or endodontic therapy should also be carried out before the start of the orthodontic therapy.

In the diagnosis of the patient's malocclusion, the appropriate intraoral and extraoral examination should be conducted with close collaboration between the orthodontist and the periodontist. In the extraoral examination, a full-smile analysis will assess the shape and form of the lips, the tooth, and the gingival exposure, as well as the exposure of the posterior corridors. In the intraoral examination, a static and dynamic occlusal examination should determine the presence of prematurities in maximum intercuspidation, as well as the presence of interferences in protrusive and lateral disclusive movements. The intermaxillar relationships should be studied on the appropriate intraoral and extraoral records. Appropriately mounted intraoral models should reveal the shape of both arches, presence of diastemata, tooth crowding, tooth rotations, anomalies in the size, shape and number of teeth, and their interocclusal relationships. Classically, the combination of orthopantomography (OPG) and cranium lateral radiography will allow a cephalometric analysis leading to the appropriate diagnosis of the patient's malocclusion. Cone-beam computed tomography (CBCT) has broadened the diagnostic opportunities for examining the morphologic aspects of the craniofacial complex, including evaluation of the buccal alveolar bone height and thickness, and assessment of the transverse dimension, presence of ectopic and supernumerary teeth, as well as the position of the soft tissues in relation to the bone envelope (Fig. 58-2).

In the treatment of adult patients it is also important to undertake a detailed medical and drug history. Adult patients often suffer from medical conditions or take several medications that might interfere with the periodontal and/or the orthodontic therapy. To assure the appropriate response to periodontal therapy, patients who smoke should be advised to cease

and patients who are diabetic or prediabetic should achieve appropriate glycemic control.

With regards to orthodontic therapy, it is important to obtain an accurate drug-consumption history, since adults frequently take different drugs, vitamins, and non-steroidal anti-inflammatory drugs (NSAIDs) that may influence the cells targeted by the orthodontic forces during tooth movement. It has been demonstrated that NSIADs not only effectively reduce inflammation and pain, but also affect the sequence of tooth movement by inhibiting, or at least reducing, the associated inflammatory and bone resorptive processes. New-generation anti-inflammatory drugs such as nabumetone have also been shown to reduce the amount of root resorption with intrusive orthodontic forces, without affecting the pace of tooth movement (Krishnan & Davidovitch 2006). Another group of drugs that may affect adult patients under orthodontic care are muscle relaxants, such as cyclobenzaprine, and tricyclic antidepressants, such as amitriptyline and benzodiazepines. The main side effect of the latter is xerostomia, which can negatively affect the proper maintenance of oral hygiene, and hence the proper periodontal health during the orthodontic therapy. Similarly, in patients requiring chronic use of inhalers with steroids, such as those suffering from asthma, oral candidiasis and xerostomia are common. Appropriate measures should be implemented in these patients, such as the use of topical antifungal agents and salivary substitutes before and during the orthodontic treatment.

A condition that frequently affects women in adult age is osteoporosis and most of the current therapies for this disease are antiresorptive (bisphosphonates, selective estrogen receptor modulators, and calcitonin), which may slow the remodeling phase (resorption) of bone turnover and potentially interfere with orthodontic therapies. Similarly, in patients suffering from rheumatoid arthritis or other chronic inflammatory conditions, therapy aims to block the catabolic cytokine production responsible for the damage to soft tissues and bones (TNF or interleukin antagonists). These immune-modulatory agents might also interfere with the orthodontic tooth movement.

Another group of drugs that need special consideration are those associated with gingival hyperplasia, such as phenytoin used for seizure disorders, calcium channel blockers used as antihypertensive drugs, or cyclosporin A used in organ transplant patients. These drugs induce gingival hyperplasia, which might prevent the application of certain orthodontic mechanics, as well as the maintenance of proper oral hygiene and periodontal health.

Tooth movement might also be affected in patients who have recently received chemotherapy with busulfan/cyclophosphamide (<2 years of disease-free life), since these drugs are known to damage the precursor cells involved in bone remodeling processes.

Treatment planning

Once the patient has undertaken the needed dental and periodontal treatment and achieved full oral and periodontal health, an orthodontic and multidisciplinary treatment plan should be designed, taking into account the patient's main concerns and expectations, as well as the functional and esthetic objectives that can realistically be accomplished with the orthodontic therapy.

Periodontal considerations

The effects of orthodontic treatment on the periodontium have been extensively studied. The primary etiologic factor in periodontal tissue inflammation and destruction is infection, and since orthodontic tooth movements must be carried out in the absence of inflammation, the accumulation of dental biofilm during orthodontic treatment must be prevented and closely monitored. This is particularly important since fixed orthodontic appliances facilitate plaque accumulation and hinder the patient's oral hygiene. Moreover, in some patients with poor oral hygiene, the fixed orthodontic appliances may promote gingival hyperplasia, especially in the lower incisor area. In these situations, continuation of the orthodontic therapy requires the resolution of the inflammation and the re-establishment of proper hygienic measures. This is usually accomplished by removal of the orthodontic appliance and the application of appropriate periodontal therapy. Sometimes the appropriate position of the tissues in relation to the clinical crown can only be reached by surgical removal of the excessive gingival tissue (Sanders 1999; Graber & Vanarsdall 1994).

There are contradictory findings in the scientific literature on the impact of malocclusion and orthodontic appliances on periodontal health. Some clinical studies have reported a mean increase in probing depth of about 0.5 mm during orthodontic treatment, which is usually a result of inflammatory changes rather than periodontal attachment loss (Ristic *et al*. 2007; van Gastel *et al*. 2008). A comparative clinical trial has shown that molars with bands exhibit greater gingival inflammation and loss of attachment than bonded molars (Boyd & Baumrind 1992). Other studies, however, have reported the presence of gingival inflammation as a result of the accumulation of subgingival plaque around the bands, but without loss of attachment (Diamanti-Kipioti *et al*. 1987; Huser *et al*. 1990) or without demonstrating significant differences in other clinical periodontal parameters when comparing banding and bonding procedures (van Gastel *et al*. 2008; Sinclair *et al*. 1987). In fact, many clinical studies have clearly shown that with adequate plaque control, the orthodontic treatment of patients with reduced but healthy periodontium achieves the orthodontic objectives without aggravating their periodontal conditions, and the risk of periodontal recurrence in these patients is not increased during orthodontic

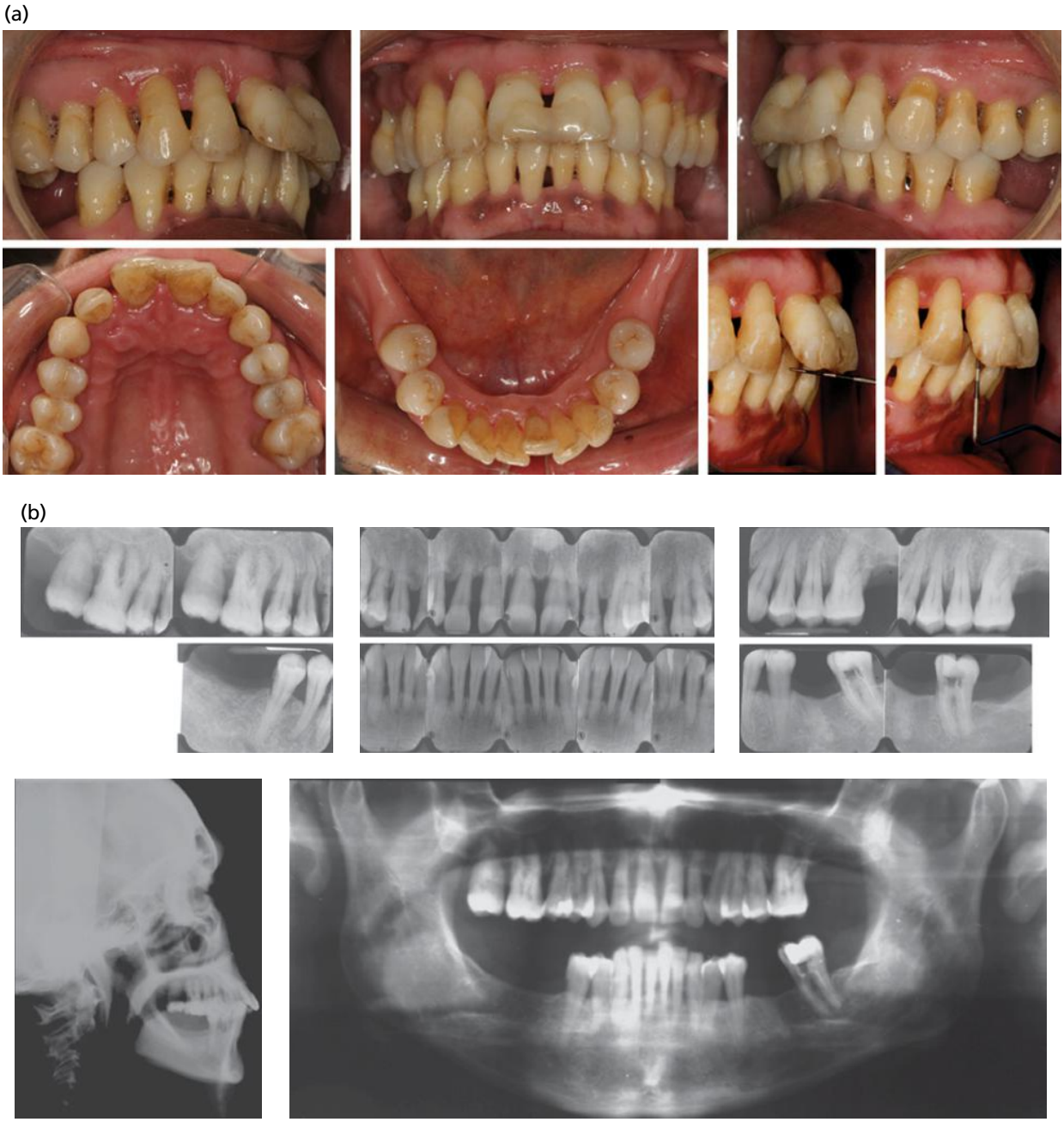


Fig. 58-3 Patient with severe chronic periodontitis, together with pathologic tooth migration, secondary occlusal trauma, and severe esthetic and functional impairment. (a) Intraoral initial clinical pictures. (b) Initial orthopantomogram (OPG), lateral cephalogram, and periapical series.

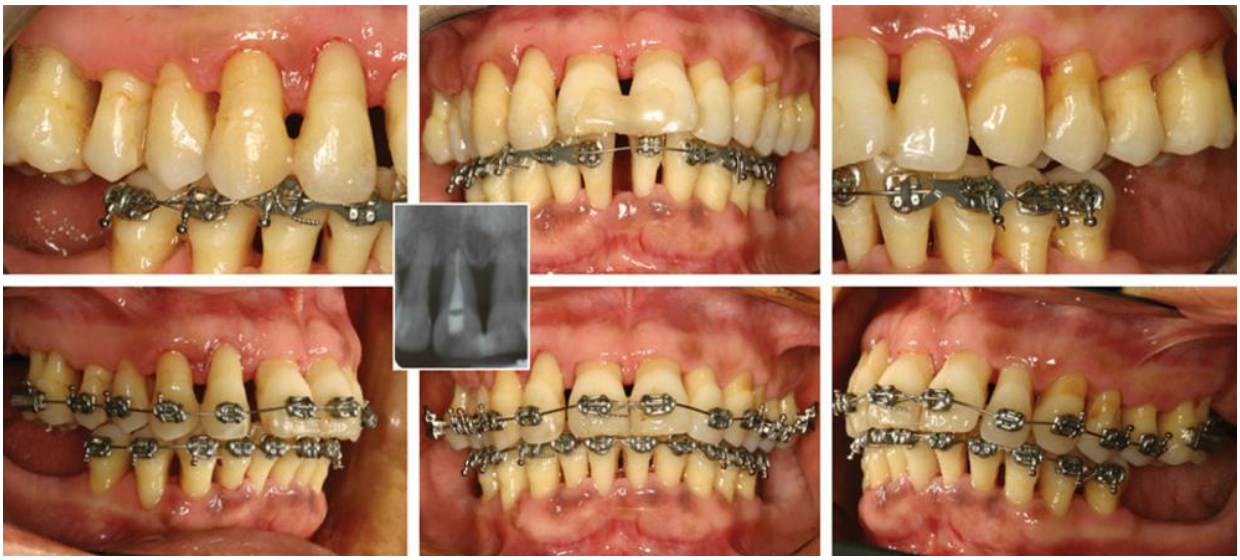
therapy (Re *et al*. 2000). If the periodontal inflammation is not fully controlled during the orthodontic treatment, however, these inflammatory processes can accelerate the progression of periodontal destruction, leading to further loss of attachment (Fig. 58-3).

Before the start of the orthodontic therapy, the patient needs to demonstrate excellent oral hygiene and gingival and periodontal health. If the patient does not demonstrate acceptable levels of oral hygiene, he/she must be adequately motivated until these levels are achieved before the start of the orthodontic treatment, and he/she should be informed that the orthodontic treatment might be terminated if the lack of adequate infection control poses a significant risk of periodontal breakdown. The orthodontic therapy should not start before 6 months after the completion of periodontal therapy, in order to carry out the orthodontic tooth movements in fully healed periodontal tissues. The patient's compliance and the clinical periodontal parameters should be recorded just before starting orthodontic treatment, assuring the presence of only shallow probing pocket depths, minimal plaque accumulation, and no bleeding on probing.

Orthodontic considerations

Orthodontic tooth movement *per se* does not cause attachment loss and gingival recession (Wennström 1996). In areas of thin buccal gingival tissue or when

(c)



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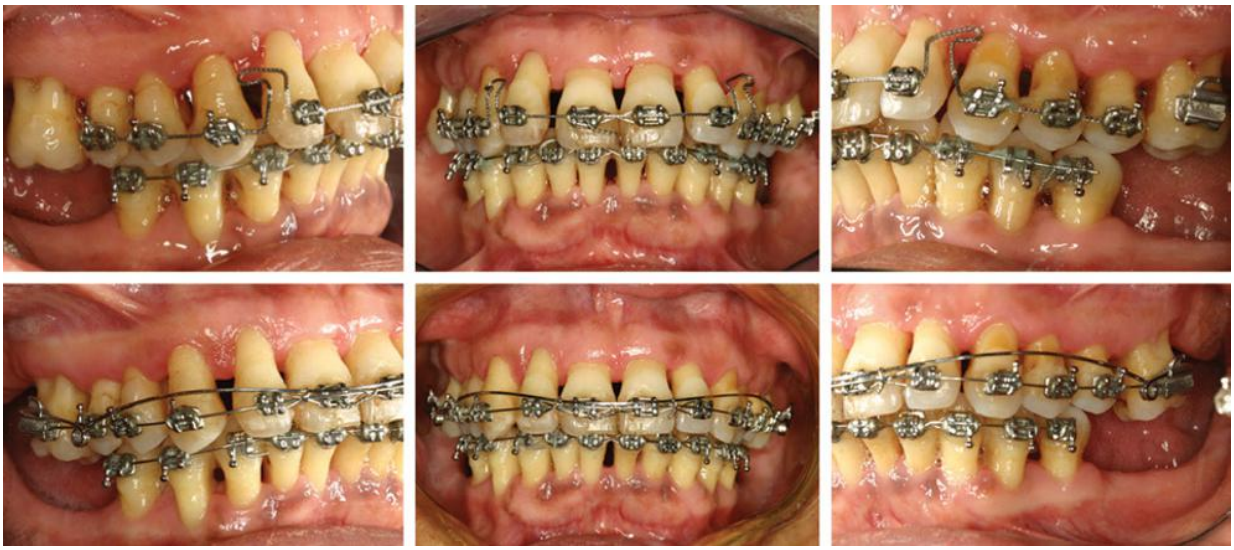

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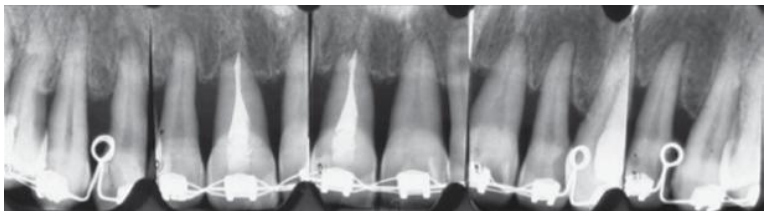


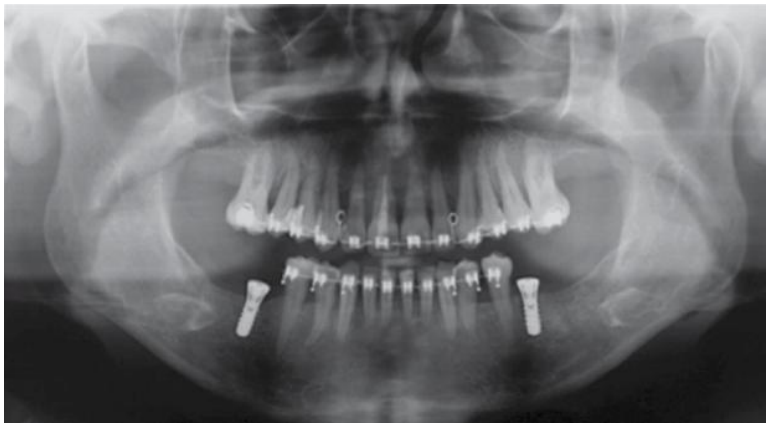


Fig. 58-3 (*Continued*) (c) Orthodontic treatment progress, lower arch appliances first and preventive root canal treatment prior to upper arch appliances. (d) Orthodontic treatment progress. (e) Follow-up periapical series and OPG.

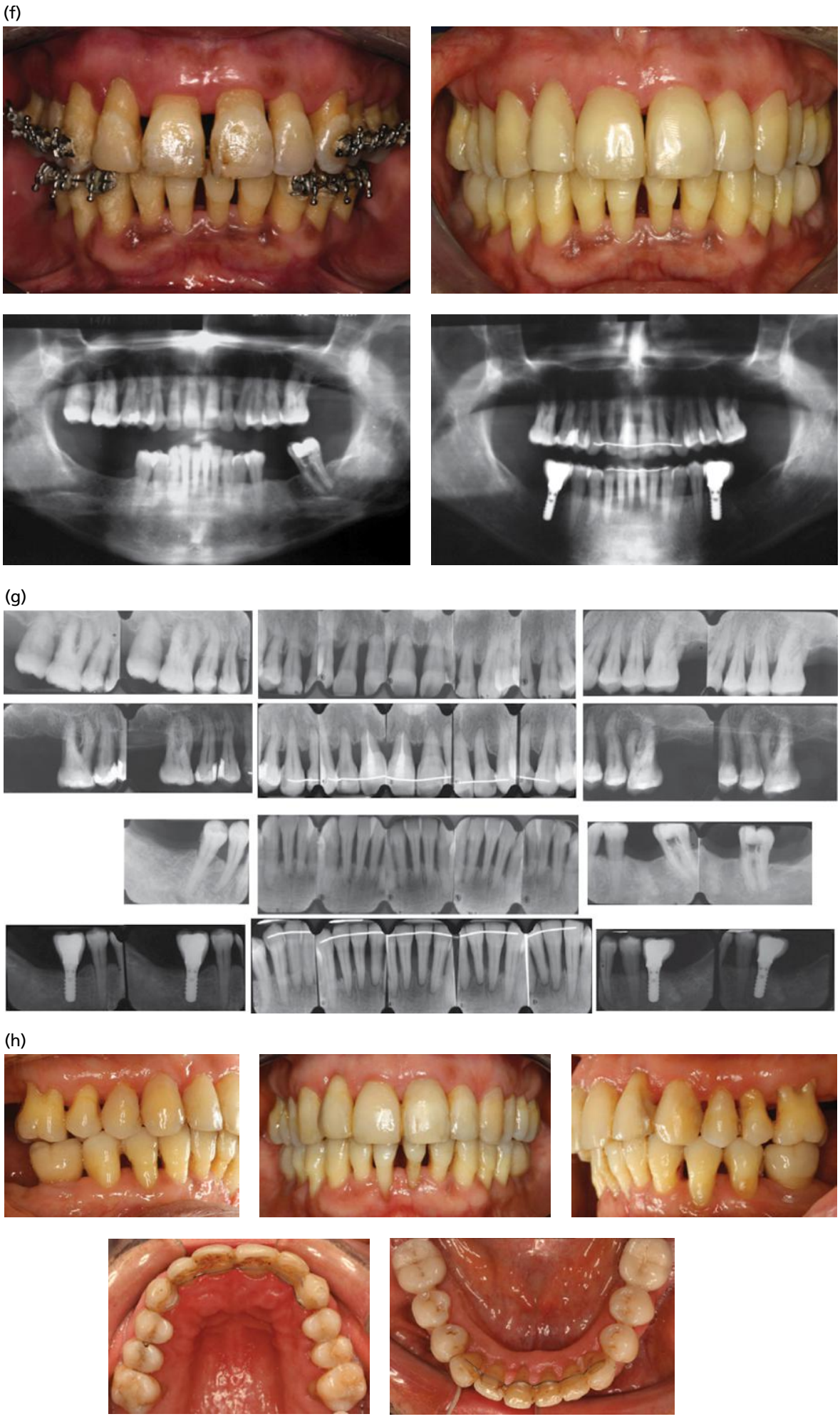


Fig. 58-3 (*Continued*) (f) Composite veneers and initial/final OPG. (g) Initial/final periapical series. (h) Five-year post-retention intraoral clinical photographs.

there is absence of a minimum width of keratinized gingival tissue, however, labial orthodontic tooth movement can result in bone dehiscences, thus creating an environment in which plaque and/or toothbrush trauma may result in attachment loss and localized gingival recessions (Wennström 1996; Artun & Krogstad 1987; Coatoam *et al*. 1981; Maynard 1987). In the presence of a thick gingival tissue, gingival recessions will not occur, even when labial or expansive tooth movements are carried out (Wennström 1996; Artun & Krogstad 1987; Coatoam *et al*. 1981; Maynard 1987). In situations of thin labial gingival tissue or when there is a lack of keratinized gingiva, if the orthodontist plans to move the affected tooth or root labially, the gingival tissue should be augmented with the appropriate mucogingival

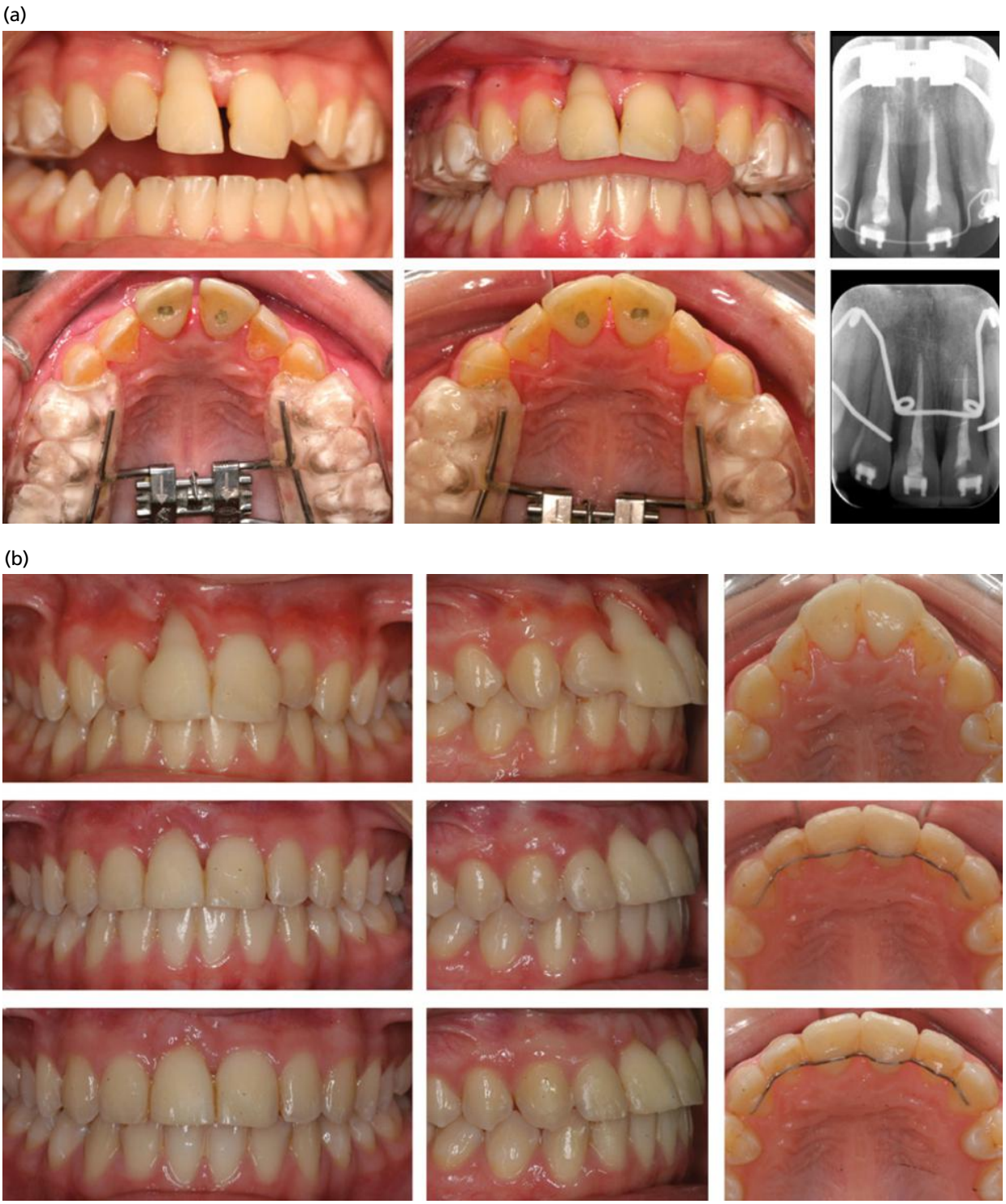


Fig. 58-4 Patient with localized gingival recession and absence of keratinized tissue in a central incisor prior to orthodontic therapy. (a) Orthodontic therapy was initiated by rapid palatal expansion. (b) Prior to expansion and retraction of upper central incisors, an autogenous gingival graft was placed. The final intraoral images demonstrate the root coverage of the recession by a combination of grafting and lingual tooth movements.

surgical techniques before the orthodontic tooth movement is started. In contrast, if a labially positioned tooth is orthodontically moved lingually, the bone dehiscence may disappear and the gingival thickness increase (Steiner *et al*. 1981; Karring *et al*. 1982; Wennström *et al*. 1987). In these situations, the mucogingival conditions should be closely monitored during the orthodontic therapy and the possible indication for a mucogingival surgical procedure should be evaluated during and after the orthodontic treatment (Fig. 58-4).

Some authors have reported the risk of gingival recessions in the area of maxillary premolars and molars when rapid maxillary expansion movements are carried out after mid-palatine suture fusion (after 20 years of age) (Graber & Vanarsdall 1994). Similarly, the movement of teeth into edentulous spaces (areas of reduced buccolingual bone dimension) is often possible with slow, light orthodontic forces, depending on the tooth-to-bone width ratio, although sometimes loss of alveolar bone and the presence of dehiscences have been reported, even under optimal conditions (Stepovich 1979; Hom & Turley 1984; Pontoriero *et al*. 1987; Goldberg & Turley 1989; Fuhrmann *et al*. 1995; Wehrbein *et al*. 1995).

Goldberg and Turley (1989) studied the periodontal changes associated with orthodontic space closure of edentulous maxillary first molar areas in adults. With a space closure averaging 5.3 mm, the resulting vertical bone loss averaged 1.2 mm in the second molar and 0.6 mm in the second premolar, with 60% of the teeth showing ≤1.5 mm of bone loss. Although space closure can be considered a potential solution in the absence of the first permanent molar, attachment loss and space reopening can be common complications.

Orthodontic treatment

Once orthodontic therapy starts, periodontal patients should be closely monitored for any signs of recurrence of periodontal pathology and they should be frequently recalled for professional infection control. These recall visits should be customized according to the severity of the reduced periodontium and the associated patient risk factors (smoking, diabetes, etc.). At each visit, the relapsing pockets and gingival bleeding should be monitored and if necessary, appropriate root instrumentation, together with other concomitant therapy (adjunctive antiseptics, such as chlorhexidine, cetyl pyridinium chloride or phenolic compounds) should be implemented.

In patients with a reduced periodontium, the total surface of the periodontal ligament that receives the orthodontic forces is significantly less and the tooth's center of resistance is displaced apically, which results in the expression of greater moments of force. In these situations the orthodontic treatment should be carefully planned and monitored in order to achieve bodily, instead of tipping, tooth movements (Melsen 1988). In terms of orthodontic appliances, it is always advisable to use the simplest orthodontic system for diminishing plaque accumulation and thus facilitating oral hygiene practices. It has been shown, although only short term, that the design of the bracket may significantly influence bacterial accumulation and gingival inflammation (van Gastel *et al*. 2007). In this context, self-ligating brackets or wire ligatures are considered better than elastomeric ligatures (Turkkahraman *et al*. 2005; Alves de Souza *et al*. 2008).

The presence of reduced periodontal support also implies different anchorage requirements and in many situations, the use of skeletal anchorage devices, such as orthodontic mini-screws, mini-plates or conventional dental implants, is recommended for a better control of three-dimensional tooth movements (Fig. 58-5).

After finishing orthodontic treatment and once the final tooth position has been achieved, a permanent retention is recommended in patients with a reduced periodontium. Retainers bonded to both canines and incisors are usually the chosen retention method, although in some studies these lingual fixed retainers have shown an adverse influence on the periodontal parameters (Pandis *et al*. 2007; Levin *et al*. 2008), while in others no significant long-term periodontal changes were shown (Reitan 1969). In some severe cases, a two-retainer approach is chosen, using a conventional lingual retainer and a segmented retainer in each interdental segment, inserted within the crowns of two adjacent teeth and covered with composite resin. Removable retainers should be avoided in order to prevent pathologic jiggling movements on the periodontally compromised teeth.

Specific orthodontic tooth movements

Extrusion movements

Tooth extrusion is a predictable tooth movement to level bone margins or to lengthen the clinical crown for restorative purposes or in the presence of tooth fractures at the level or below the bone crest. When extruding teeth with a healthy periodontium, a concomitant displacement of the gingival margin and the mucogingival junction occurs in 80% and 52.5% of cases, respectively (Pikdoken *et al*. 2009). Similar results have been reported in experimental studies: the free and attached gingiva followed the tooth movement in 90% and 80% of cases, respectively, while the mucogingival junction remained in the same position (Berglundh *et al*. 1991; Kajiyama *et al*. 1993).

In the presence of intrabony defects, orthodontic extrusive movements will predictably eliminate the angular bony defect, but the periodontal attachment levels will remain unaltered. This treatment option is particularly indicated in the presence of one-wall intrabony defects, since in these lesions periodontal

regenerative techniques do not have a favorable prognosis and the intact connective tissue attachment will be positioned in a more coronal position (Ingber 1974). Simon *et al*. (1980) evaluated histologically and radiographically orthondontic extrusion of endodontically-treated teeth in dogs. At 2 weeks, areas containing immature bone or osteoid were identified histologically in the periodontal ligament of normal width. Radiographically, these areas around the roots appeared radiolucent. By the seventh week, however, both the radiographic image and histologic characteristics were normal.

Orthodontic extrusion of "hopeless" teeth prior to implant placement has been proposed with the objective of displacing the bone coronally and thus improving the bone availability in the alveolar crest, which is an alternative to bone augmentation procedures in areas of deficient bone. Korayem *et al*. (2008) have recently reported a systematic review of this indication. Even though most of the selected

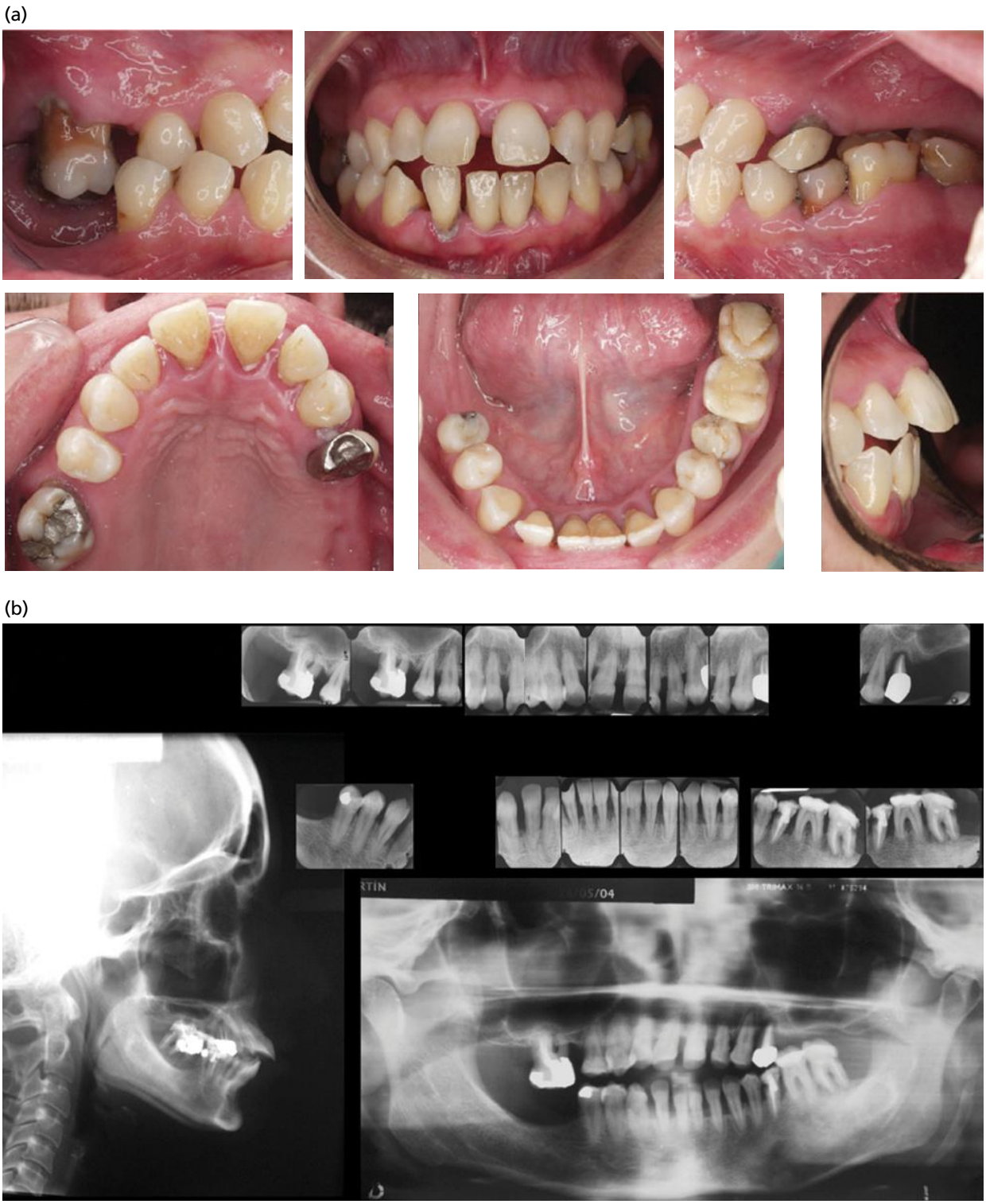


Fig. 58-5 Patient with severe chronic periodontitis, together with pathologic tooth migration, open anterior bite, and posterior bite collapse. (a) Intraoral images before periodontal and orthodontic therapy. (b) Radiographic images demonstrating the severe bone loss and posterior bite collapse.

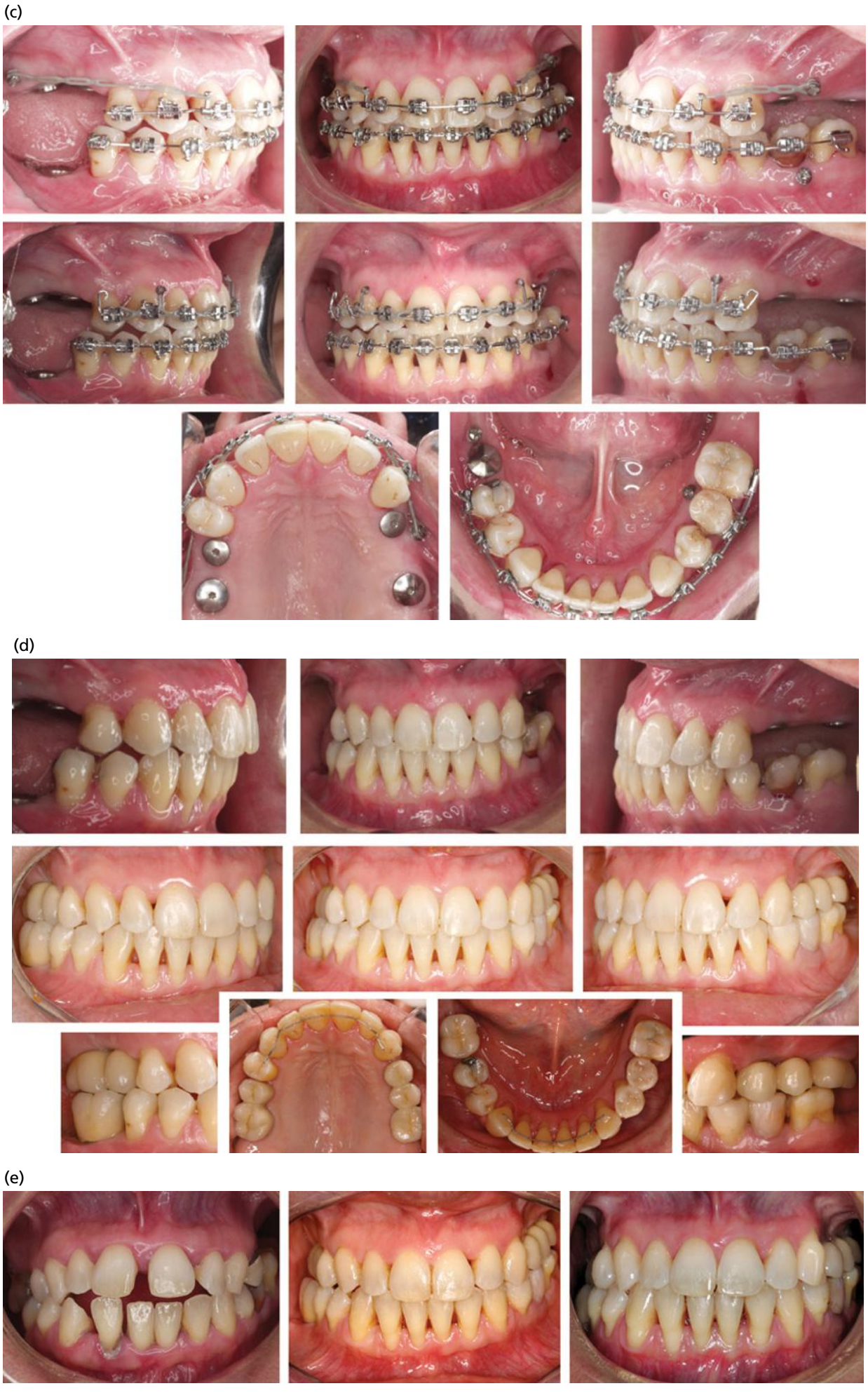


Fig. 58-5 (*Continued*) (c) Orthodontic therapy accomplished by using micro-implants as anchorage. Posterior dentition was restored by dental implants. (d) Final retention and esthetic treatment was accomplished with composite veneers. Posterior function was restored with implant-supported restorations. (e) Patient before treatment, after restorative therapy, and 3 years post retention.

studies were case reports or case series describing orthodontic extrusion of periodontally hopeless maxillary anterior teeth, all of the publications reported improvements in bone availability at the implant recipient site, with qualitative and quantitative gains in alveolar bone and soft tissues. In spite of the heterogeneity of the different orthodontic methods reported in the different studies, the authors developed treatment guidelines recommending: (1) the use of light, constant, extrusive forces of 15 g for the anterior teeth to 50 g for the posterior teeth; (2) the rate of extrusion should be maintained at a slow and steady rate of no >2.0 mm/month; (3) a buccal root torque component may be applied concomitantly to increase the buccolingual bulk of alveolar bone; (4) a retention and stabilization period of no <1 month for every month of active extrusion prior to extraction; and (5) overlay wires (anchorage wires) to reinforce anchorage and avoid tipping of adjacent teeth toward the tooth undergoing active extrusion (Fig. 58-6).

Molar uprighting

The orthodontic uprighting of mesially tilted molars achieves similar outcomes to the extrusive movements in angular bony lesions. In this case, the angular bony lesion only occurs in the mesial aspect of the inclined molar and this lesion will disappear and the bone crest will level, although without modifying the periodontal attachment levels. In these clinical situations, the recommended movement is to displace the tooth away from the defect in a disto-occlusal direction, thus causing tension in the periodontal ligament collagen fibers and making the contour of the alveolar crest shallower (Diedrich 1996). Even though the level of the connective tissue attachment remains unchanged, the new anatomic position of the molar usually translates into an improvement in probing depth levels and crown-to-root ratio (Brown 1973) (Fig. 58-7).

If the mesially tilted molar has a furcation involvement, the orthodontic tooth movement may exacerbate the periodontal lesion, unless strict infection control prevents the development of any periodontal inflammation (Burch *et al*. 1992). A valid alternative in these clinical situations is to treat the furcation lesion with appropriate therapy (hemisection or bysection) and then, before the final restorative therapy, carry out the orthodontic movement in one or both roots until the ideal tooth position is reached (Muller *et al*. 1995).

Orthodontic tooth movements through cortical bone

When the alveolar width between the buccal and lingual cortical plates is not appropriate, orthodontic tooth movement into these areas may cause complications. Tooth movement through cortical bone may retard the rate of the movement and buccal and/or lingual bone dehiscences may develop. To avoid these unwanted consequences, bone augmentation procedures to increase the alveolar bone width before the orthodontic movement have been suggested (Diedrich 1996).

Edentulous ridge contraction is the physiologic consequence of tooth extraction. Most of the buccolingual reduction in the edentulous ridge will occur within the first 3 months after tooth extraction (Schropp *et al.* 2003), although this resorptive process may continue, albeit at a slower rate (Carlsson *et al*. 1967). Several authors have recommended orthodontic tooth movement into recently extracted areas to counteract this resorptive process and thus develop a new edentulous ridge. Ostler and Kokich (1994) demonstrated in a sample of 20 patients that this orthodontic tooth movement developed a new edentulous ridge with <1% of bone contraction at 4 years. Similar results were reported in an experimental study in dogs where the pressure side (towards the socket) showed increased bone height, while on the tension side the bone level remained unaltered (Lindskog-Stokland *et al*. 1993).

In edentulous areas the orthodontic movement of teeth with a reduced but healthy periodontium is usually possible with minimal loss of bone, provided the movement is parallel to the ridge and light orthodontic forces are used (Hom & Turley 1984), although even under the most optimal conditions, loss of attachment and bone support may occur (Goldberg & Turley 1989).

Experimental studies have shown that when bodily movements are carried out through the cortical bone in a labial direction, there is no bone formation in the buccal aspect of the tooth and a dehiscence defect occurs (Steiner *et al.* 1981). The labial root movement *per se* does not cause attachment loss and gingival recession, but results in bone dehiscence and thin soft tissues, which develop a site of low resistance for attachment loss due to inflammation or trauma (Wennström 1996). In contrast, lingual movements of labially displaced teeth showing dehiscence defects will result in new bone formation in the buccal aspect of the root, as well as soft tissue augmentation (Karring *et al*. 1982; Wennström *et al*. 1987). Wennström (1996) recommended the treatment of localized gingival recessions with orthodontic movements whenever the affected tooth was labially displaced and lingual orthodontic movements were possible. Pini Prato *et al.* (2000), however, recommended the placement of a gingival autograft prior to the orthodontic therapy in these situations in order to prevent periodontal attachment loss and the occurrence of recession defects, since pure lingual root movements through cortical bone are difficult and in most cases crown tipping or rotation components will occur, hence moving the root buccally and causing further bone dehiscence and soft tissue loss. Djeu *et al.* (2002) did not find a correlation between orthodontic labial inclination of mandibular central

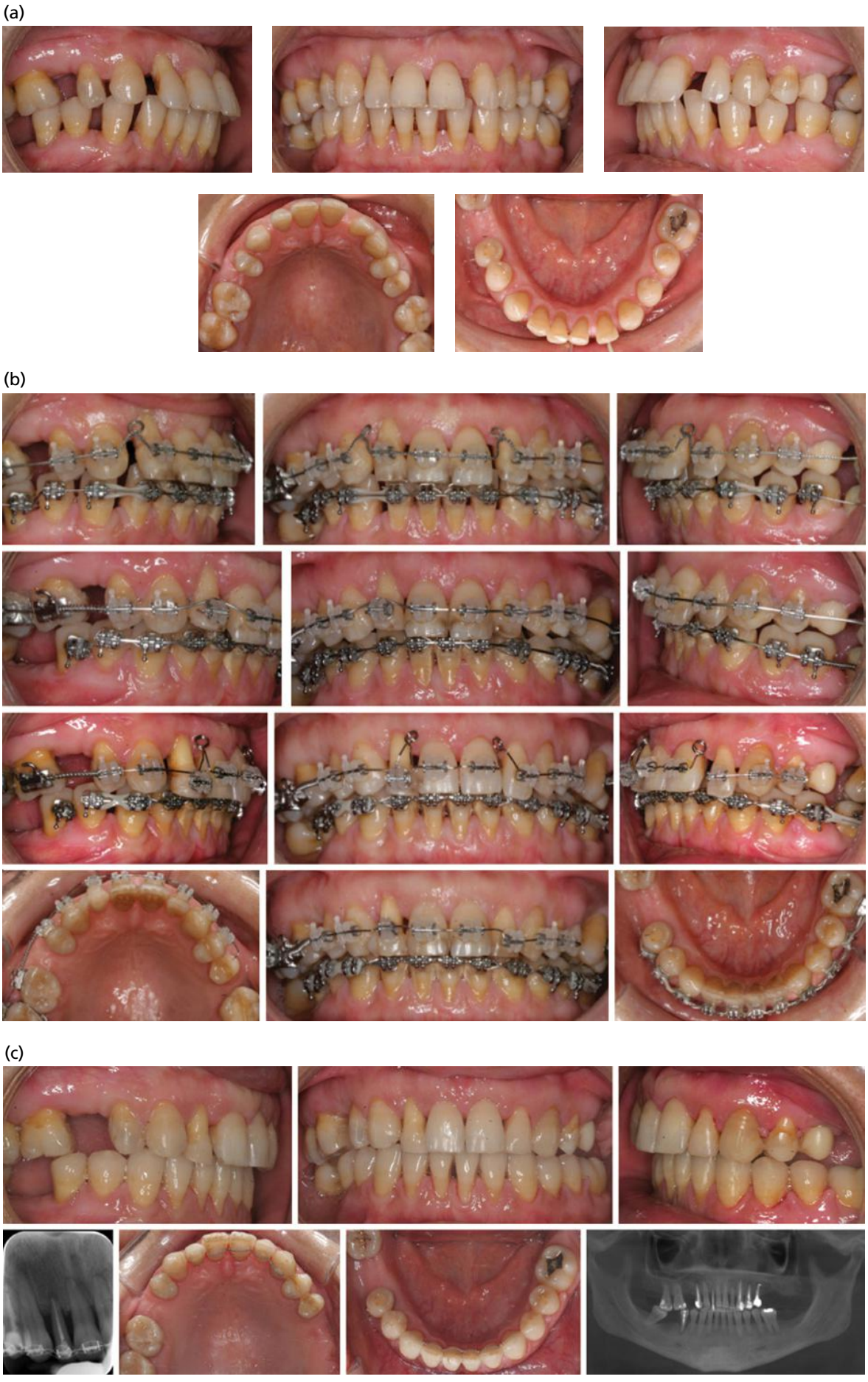


Fig. 58-6 Patient with severe chronic periodontitis, presence of diastemata, and pathologic tooth migration, together with a hopeless prognosis for tooth 12. (a) Intraoral images before orthodontic therapy. (b) Orthodontic therapy was aimed at closing the diastemata, distributing spaces, and controlling forced extrusion of tooth 12 in order to create bone and soft tissue prior to implant placement. (c) End of orthodontic therapy prior to tooth extraction and implant placement. Note the position of the gingival margin in relation to the adjacent teeth.

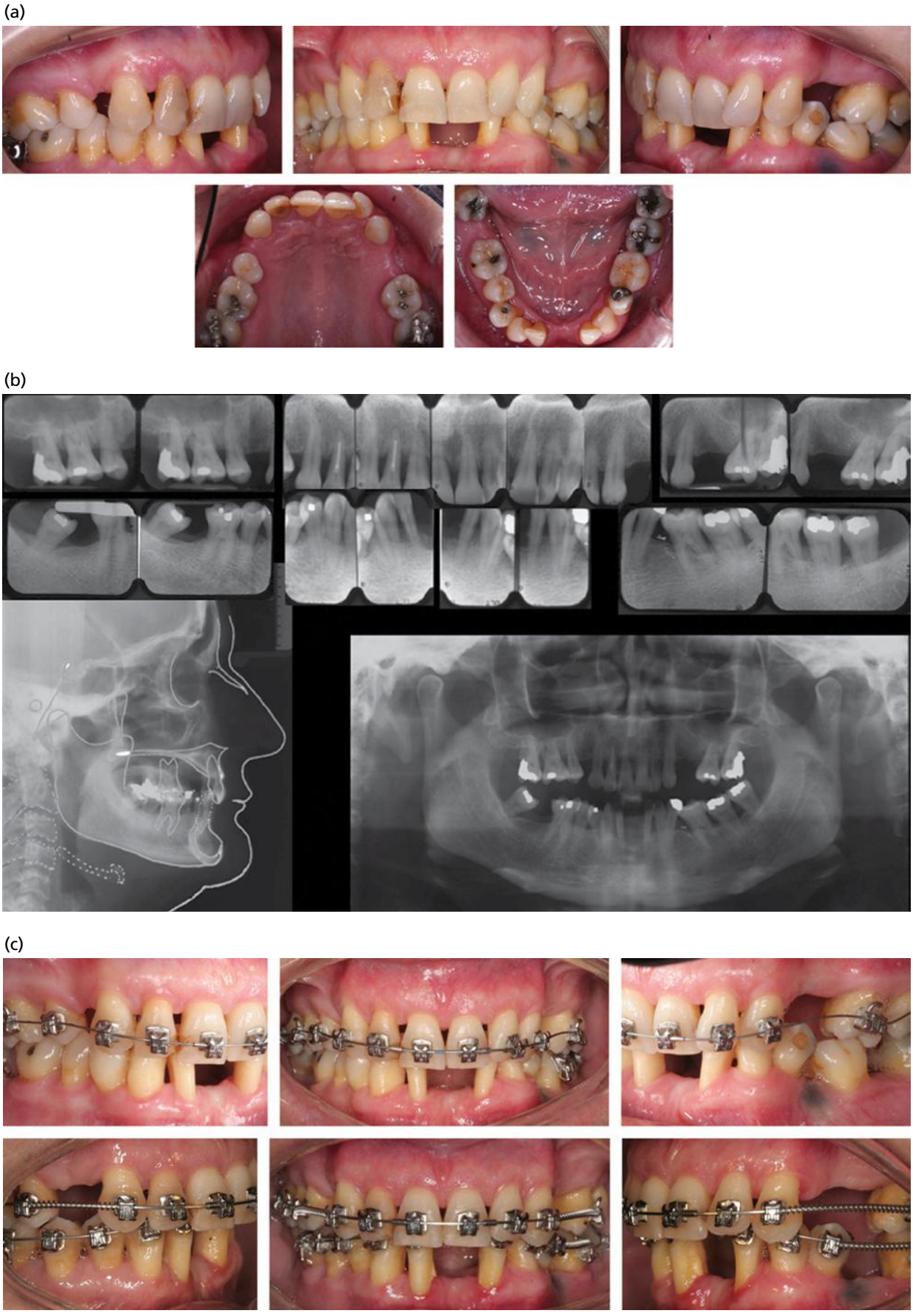


Fig. 58-7 Patient with severe chronic periodontitis, partial edentulism, and collapsed posterior bite. (a) Intraoral images of the patient before orthodontic therapy. (b) Initial panoramic, lateral cephalogram and periapical radiographic series depicting the patient's bone loss and presence of mesially inclined first lower molars. (c) Orthodontic therapy was aimed at uprighting lower molars and distributing the spaces prior to implant therapy to restore lost dentition.

(d)

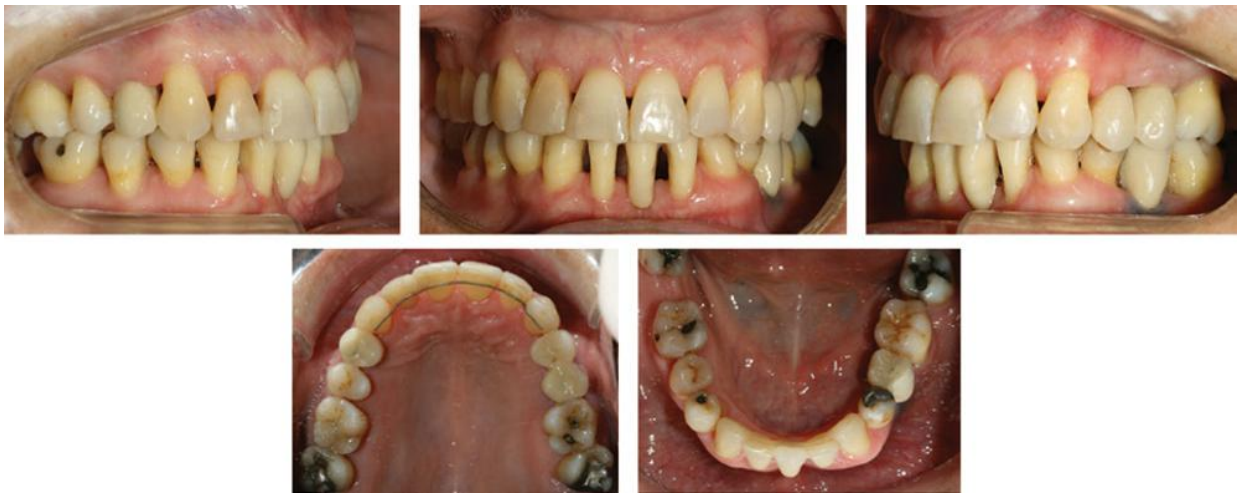


Fig. 58-7 (*Continued*) (d) End of orthodontic therapy with restoration of the posterior occlusal plane and alignment of upper incisors. Note the position of the lower mandibular molars.

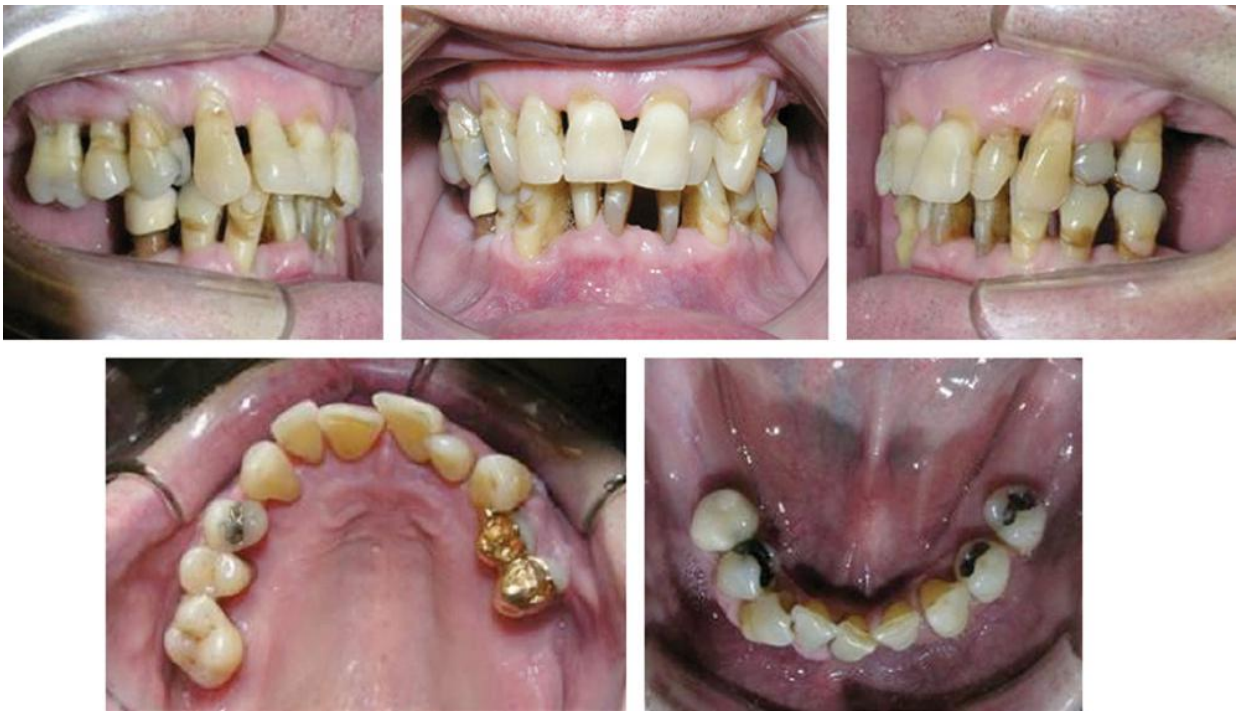
incisors and the development of gingival recessions in a retrospective clinical study. Similar results have been reported by Artun and Grobety (2001) and by Ruf *et al.* (1998) in children. In adults, however, a prospective study showed a significant correlation between the incidence and the severity of recession lesions with excessive proinclination (>10°) of the mandibular incisors (Artun & Krogstad 1987). The main risk factors for developing or aggravating recession lesions after adult orthodontic therapy are the presence of a thin gingival biotype, an insufficient width of keratinized gingiva, gingival inflammation, and the presence of recession lesions before the orthodontic treatment (Melsen & Allais 2005). The final tooth inclination (>95°) and the thickness of the marginal gingiva (<0.5 mm) have been associated with the occurrence of recessions in mandibular central incisors in adults after orthodontic treatment (Yared *et al*. 2006). However, a recent longitudinal study in adults with mandibular prognathism subjected to orthognathic surgery concluded that, in spite of extensive labial tipping, there was no negative outcome for periodontal tissues of the mandibular incisors (Ari-Demirkaya & Ilhan 2008) (Fig. 58-8).

Intrusive tooth movements

Intrusive tooth movements can be attempted even in the situation of reduced periodontal support provided the periodontal tissues do not have any inflammation and the plaque control is excellent. Melsen *et al.* (1989) recommended the use of light forces for these intrusive movements (5–15 g/tooth) in order to avoid root resorption, mainly in teeth with reduced periodontal support with an increased crown-to-root ratio. There is controversy whether this orthodontic tooth movement should be recommended in the presence of angular bony lesions and intrabony defects. Ericsson *et al*. (1977) demonstrated in dogs that intrusive movements in the presence of plaque transform the supragingival plaque into subgingival plaque and periodontal pockets and infrabony defects develop as a result. Polson *et al.* (1984), however, showed that intrabony defects were resolved when teeth are moved bodily into the bony defect, provided there is no inflammation. Healing occurred through the formation of a long junctional epithelium and the periodontal attachment levels did not change. These results were contradicted by Melsen (1988), who in monkeys also demonstrated the resolution of bone defects by intrusive movement whenever a healthy gingival environment was assured, but healing occurred through the formation of a new connective tissue attachment and periodontal regeneration. In humans, several clinical studies have also shown improvements in clinical attachment levels with intrusive tooth movements in the absence of periodontal inflammation (Melsen *et al*. 1989; Cardaropoli *et al.* 2001).

Corrente *et al*. (2003) recommended the treatment of infrabony defects in anterior teeth by combining surgical periodontal therapy with intrusive orthodontic movements, and reported significant attachment gains and radiographic bone fill. Similarly, Re *et al*. (2004) reported a 50% reduction in recession after intrusion of periodontally comprised teeth. These movements, however, are not always predictable and some authors have recommended that intrabony defects are first treated with surgical periodontal regenerative procedures, followed by the intrusive tooth movement (Diedrich 1996; Re *et al*. 2002a). In the presence of circumferential bony lesions, providing they are not deep, orthodontic intrusive movements can resolve the defect. If these defects, however, are deep and wide angular lesions not amenable to periodontal regenerative procedures, orthodontic intrusive movements might also be recommended to improve the defect anatomy before carrying out the regenerative procedure (Rabie *et al*. 2001; Passanezi *et al*. 2007) (Fig. 58-9).

(a)



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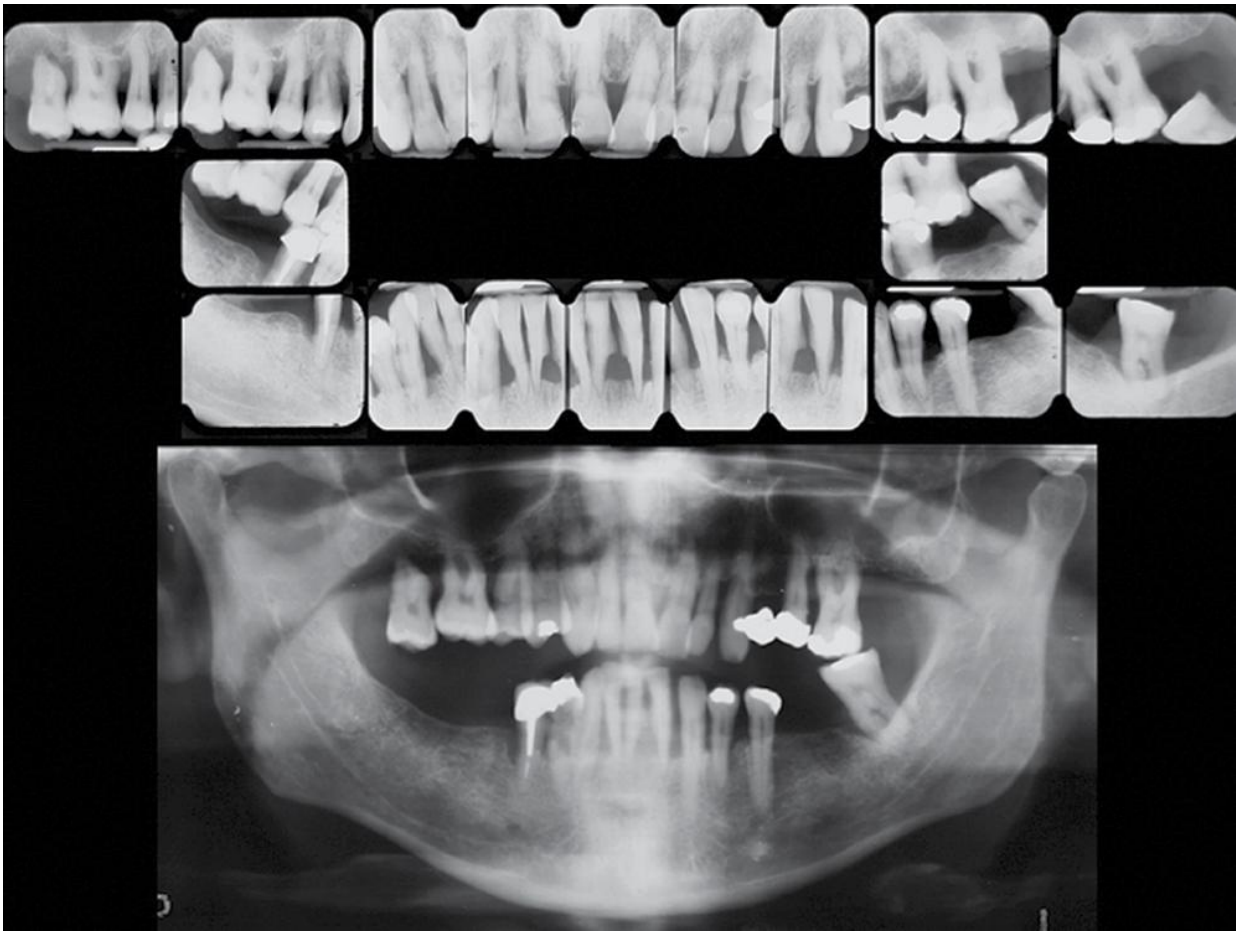


Fig. 58-8 Patient with severe chronic periodontitis, partial edentulism, and severe malocclusion. (a) Intraoral images after periodontal therapy and before orthodontic therapy. (b) Initial panoramic and periapical radiographic series depicting the bone loss and tooth malposition.

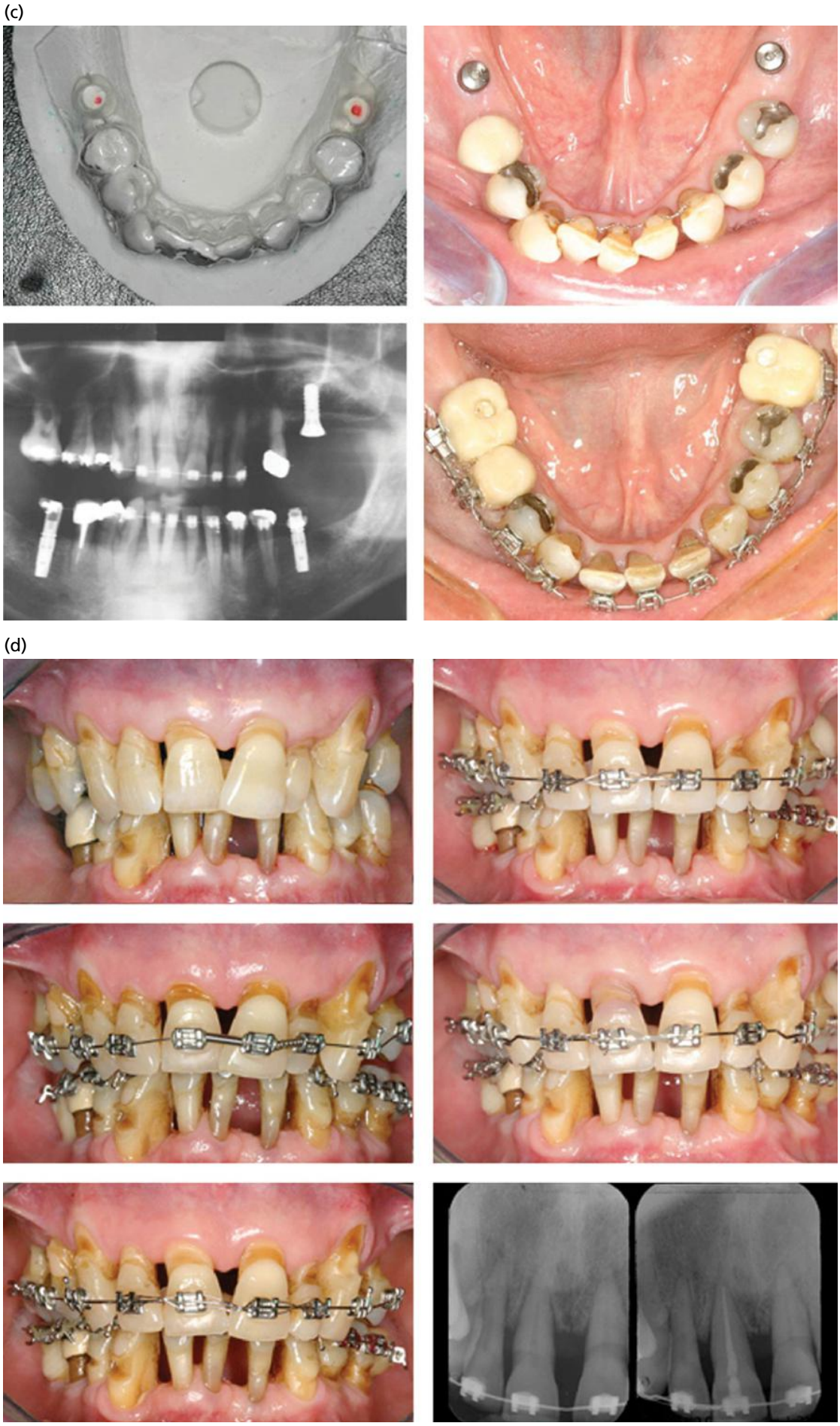
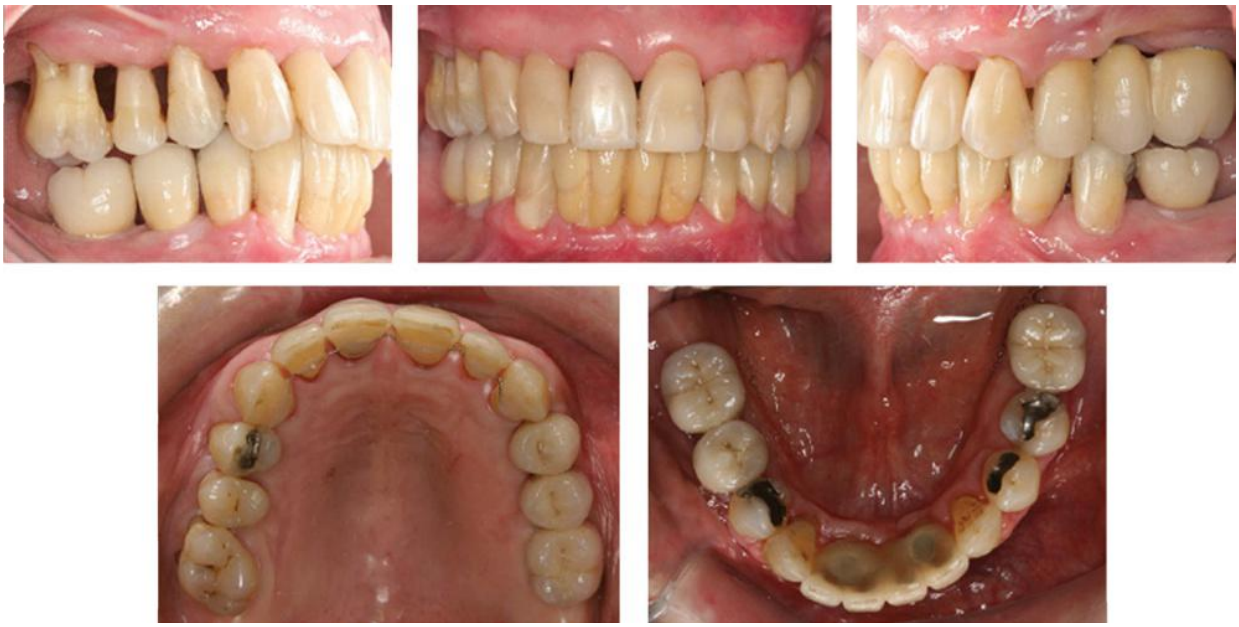


Fig. 58-8 (*Continued*) (c) Dental implants were placed in the posterior mandible before the orthodontic therapy to serve as anchorage for the orthodontic tooth movements. (d) Orthodontic therapy was aimed at aligning the teeth and distributing the spaces prior to implant therapy to restore the lower anterior teeth. Note the gingival recessions and severe abrasion in the upper cuspids.

(e)



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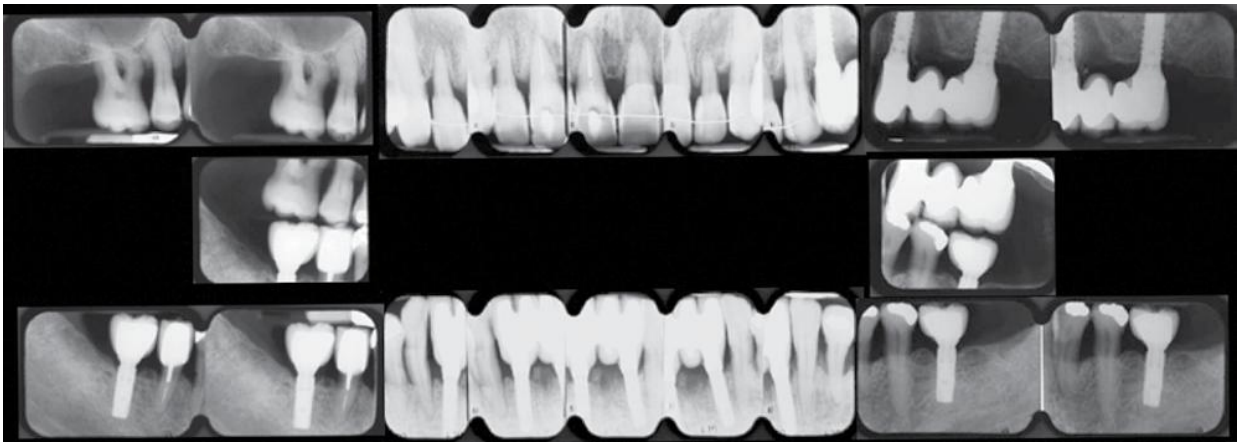


Fig. 58-8 (*Continued*) (e) End of orthodontic therapy with restoration of the posterior occlusal plane and alignment of the upper incisors. Note that the recessions were treated by means of connective tissue autografts and the open papillae have been filled with composite veneers. (f) Final radiographs depicting stable bone levels and restoration of the posterior occlusal plane.

(a)

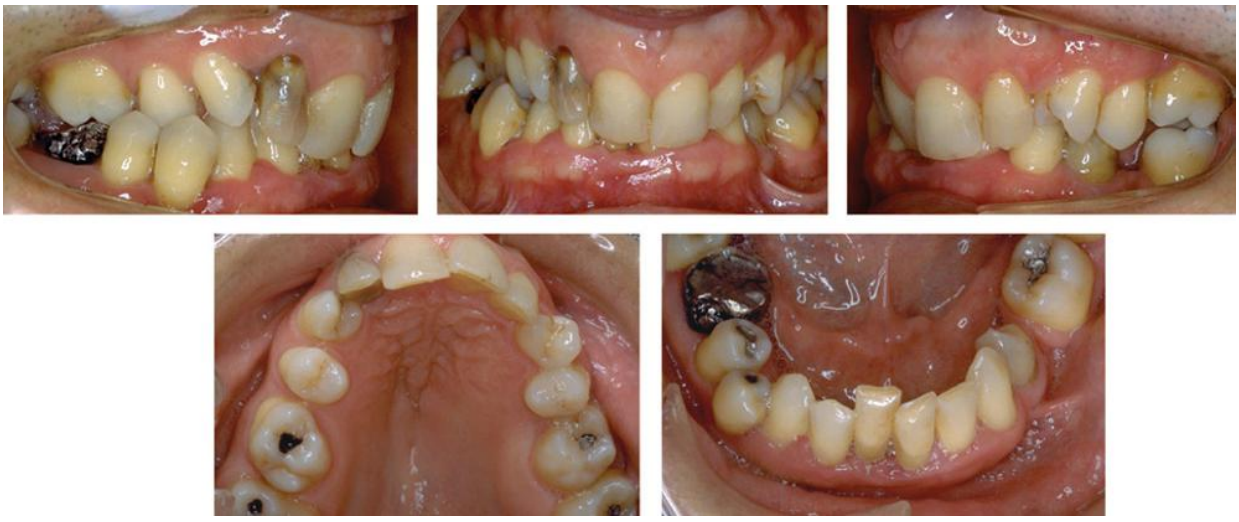
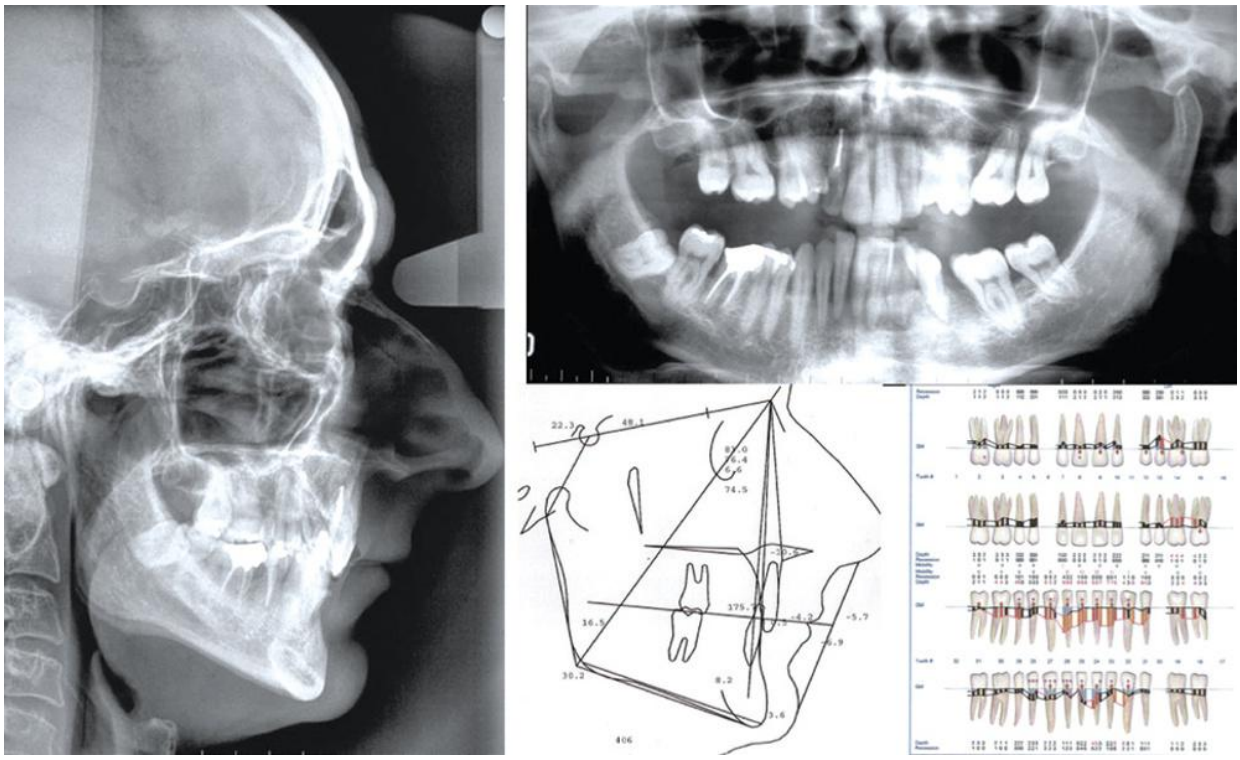


Fig. 58-9 Patient with severe chronic periodontitis and severe overbite. (a) Intraoral images before orthodontic therapy. Note the posterior bite collapse and severe overbite.

(b)



(c)

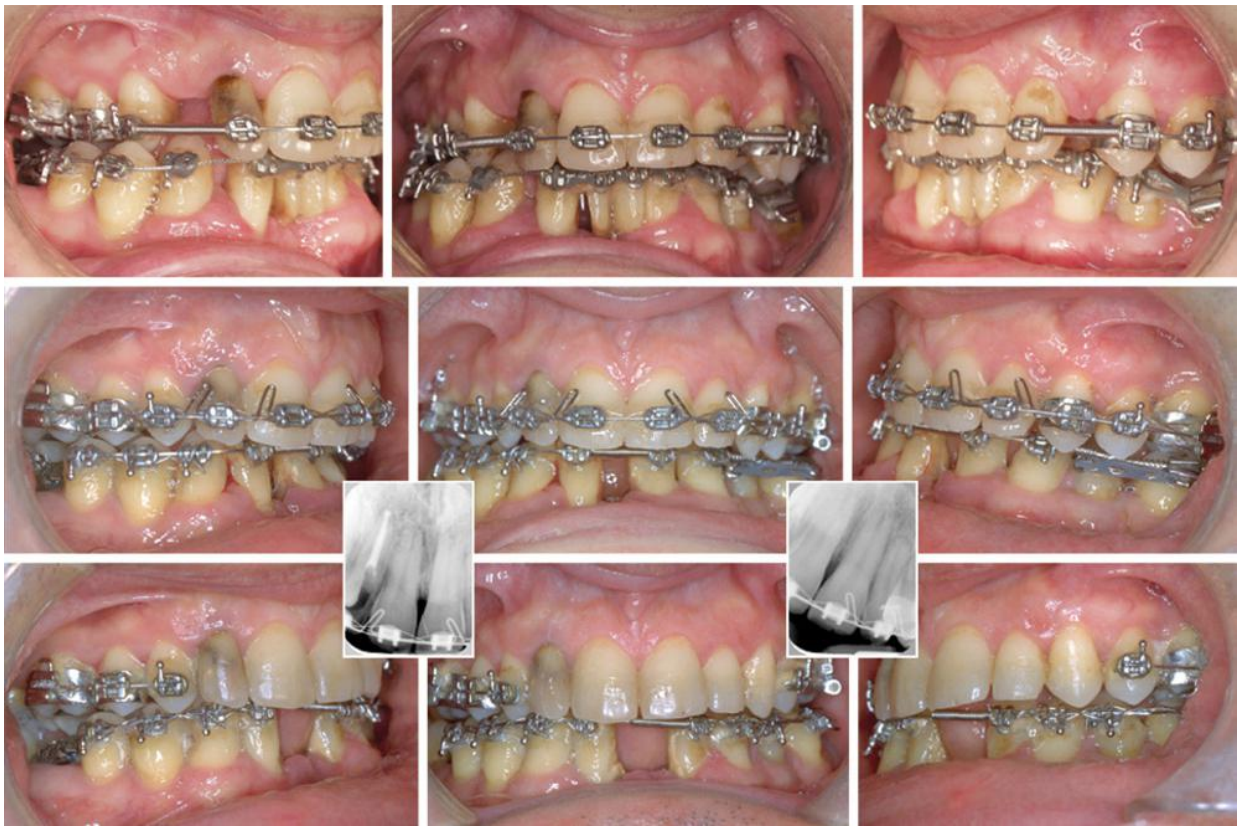


Fig. 58-9 (*Continued*) (b) Initial panoramic and lateral cephalogram depicting the bone loss. The periodontal charting after therapy shows lack of periodontal pockets except in the lower anterior region, with tooth 41 having a hopeless prognosis. (c) Orthodontic therapy was aimed at aligning the teeth by intrusion of maxillary teeth. Note the slight root resorption of the upper laterals after the orthodontic tooth movement.

(d)

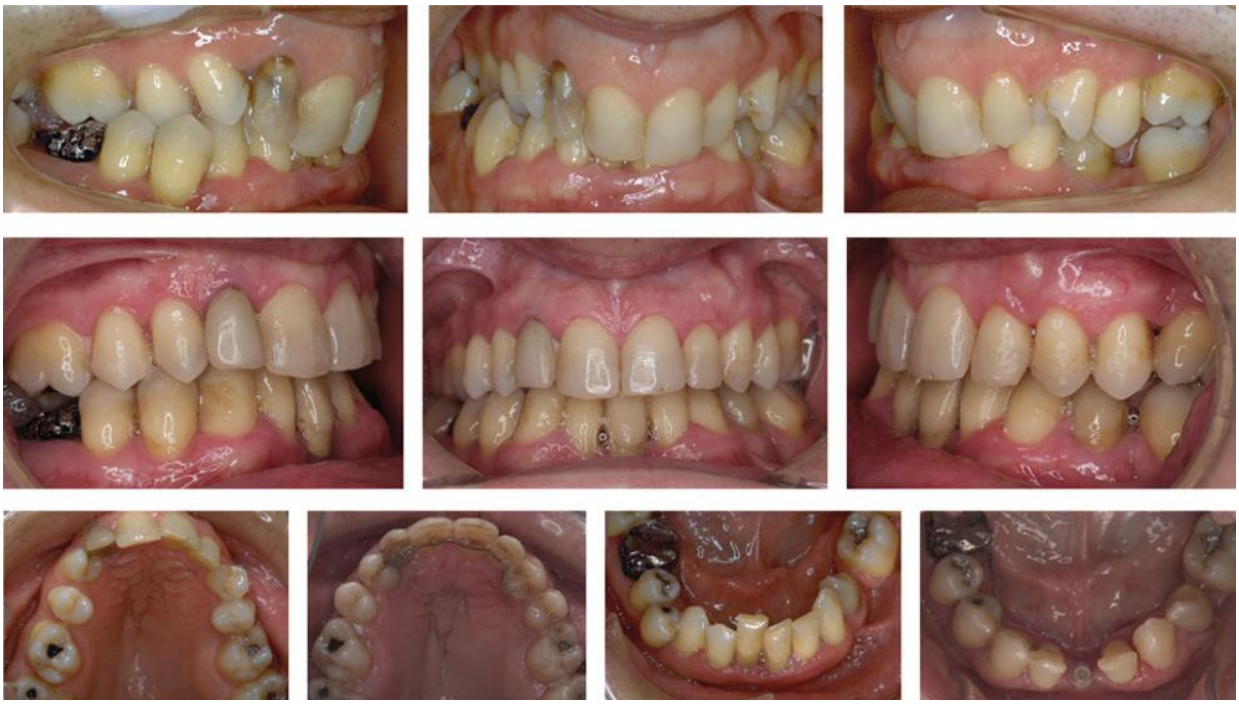


Fig. 58-9 (*Continued*) (d) End of orthodontic therapy with proper alignment of the upper incisors and re-establishment of an occlusal plane. Note the resolution of the deep overbite by orthodontic tooth intrusion.

Orthodontic intrusion movements have also been recommended for leveling gingival margins with the adjacent teeth when treating extruded and malaligned teeth, since the mucogingival junction and the gingival margin will move apically together with the tooth (Erkan *et al.* 2007).

Orthodontic tooth movements and periodontal regeneration

Periodontal regenerative procedures are frequent in the treatment of chronic periodontitis, particularly in the presence of angular bony defects. These surgical techniques aim to establish a new periodontal attachment apparatus to a root surface previously affected by the destructive process of periodontitis. Histologically, periodontal regeneration requires the formation of new cementum on the affected root and the establishment of a new connective tissue attachment between the new cementum and the alveolar bone. Several regenerative technologies have demonstrated these outcomes in experimental studies, such as guided tissue regeneration (GTR), bone graft materials, and enamel matrix derivatives (EMDs), and the evidence on their clinical efficacy has been reported in several recent systematic reviews (see Chapter 45).

When orthodontic tooth movements are indicated in patients for whom periodontal regenerative surgeries have formed part of their periodontal therapy, there has been a debate on whether the quality of tooth movements through the regenerated periodontium might be different or whether these movements might create unwanted effects (root resorption, bone loss, ankylosis, etc.). There has also been controversy on the optimum timing for starting the orthodontic therapy after the regenerative procedure, as well as the necessary stability after moving teeth into regenerated areas. Most of these questions have been answered by experimental studies and further corroborated with clinical human research.

Diedrich *et al.* (1996) conducted a series of experimental studies demonstrating that the use of both resorbable and non-resorbable barrier membranes achieved periodontal regeneration and the subsequent orthodontic treatment did not affect the newly gained periodontal structures. Subsequently, several case reports in humans have corroborated these experimental results, also demonstrating the long-term stability of these periodontal structures when subjected to orthodontic therapy (Stelzel & Flores-de-Jacoby 1995; Efeoglu *et al.* 1997; Stelzel & Flores-de-Jacoby 1998; Aguirre-Zorzano *et al.* 1999).

Barrier membranes has also been utilized on fresh extraction sockets with the aim of preserving the edentulous ridge by preventing the remodeling processes of the socket walls (Tiefengraber *et al.* 2002). When teeth subsequently moved into these regenerated areas, the orthodontic therapy was uneventful and there were no complications. One of the limitations on the use of barrier membranes is the collapse of the barrier into the defect when the anatomy of the defect does not allow for space maintenance. To overcome this limitation, different bone grafts have been used to fill the defect and to support the barrier membrane.

Orthodontic tooth movements through regenerated bone after using xenografts of bovine origin have also been investigated in animal studies (Araújo *et al.* 2001; Kawamoto *et al.* 2002, 2003; da Silva *et al.* 2006; Zhang *et al.* 2006). Araújo *et al.* (2001) showed that orthodontic tooth movement was possible without

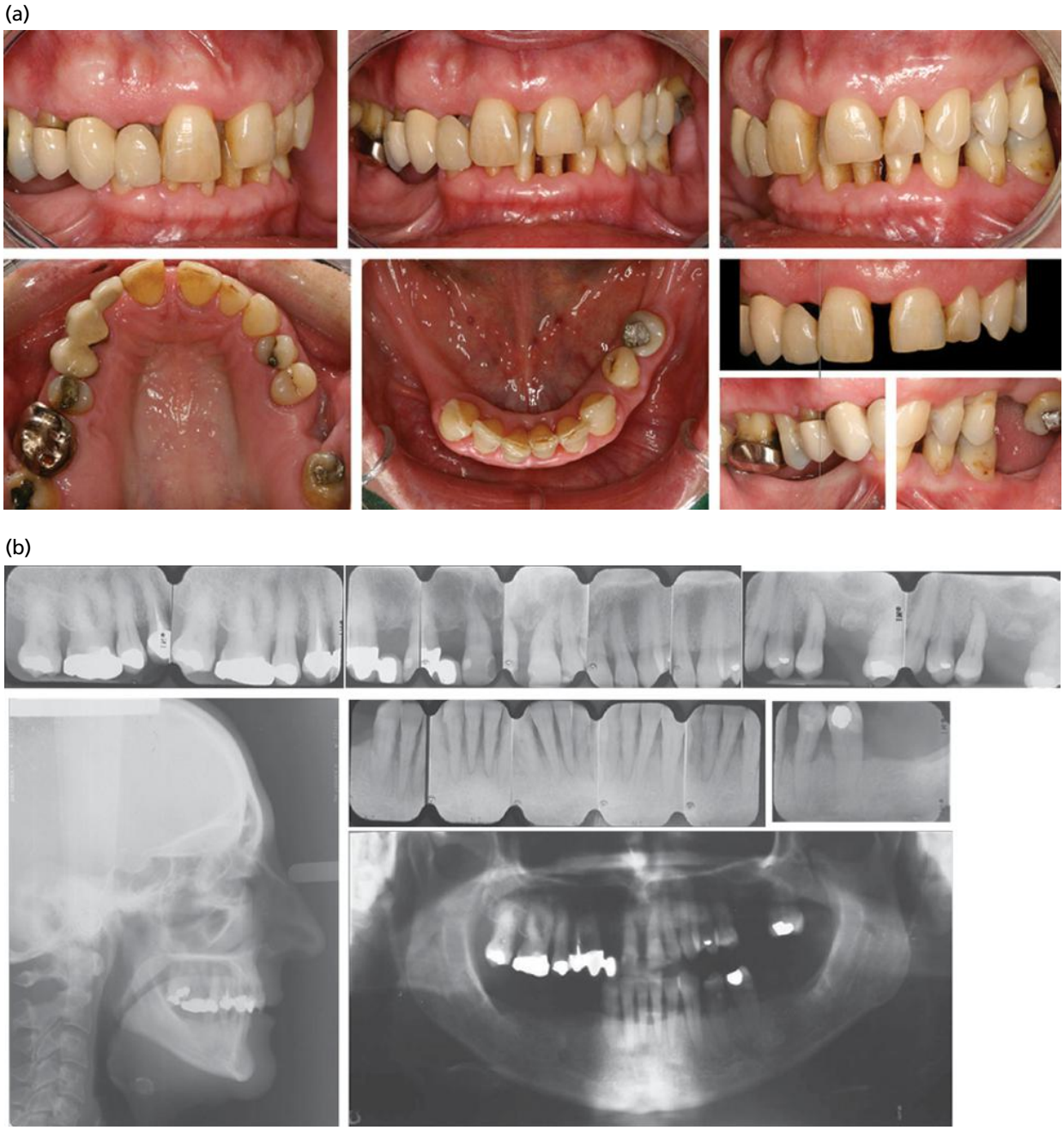


Fig. 58-10 Patient with severe chronic periodontitis, presence of deep intrabony defects in maxillary teeth, and severe malocclusion. (a) Intraoral images before orthodontic therapy. Note the anterior diastema, severe extrusion of maxillary right posterior teeth, and presence of edentulous spaces. (b) Initial panoramic, lateral cephalogram and periapical radiographic series depicting the bone loss and presence of deep intrabony defects in the upper incisors and the upper and lower left premolars.

any complication. The graft material was partially resorbed on the pressure side, while there was no sign of resorption on the tension side. These findings are explained by the enhanced osteoclastic activity with the tooth movement. Similar observations were made by da Silva *et al*. (2006) who implanted xenogeneic grafts into furcation defects. After the healing process, each tooth either underwent orthodontic tooth movement or remained in its initial position. They found no differences in the amount of newly developed bone and no signs of root resorption. Similar results were reported with the use of synthetic biomaterials and bio-glasses in rats (Hossain *et al*. 1996; Kawamoto *et al*. 2002; Zhang *et al*. 2006).

The results from these experimental studies have been corroborated in several clinical case series in humans where orthodontic movements were carried out in teeth previously treated with allogeneic and xenogeneic grafts and collagen barrier membranes. These cases showed stable bone levels 12–18 months after the end of the orthodontic therapy, without any unwanted side effects (Yilmaz *et al.* 2000; Ogihara & Marks 2002; Re *et al.* 2002b; Naaman *et al*. 2004; Maeda *et al.* 2005; Cardaropoli *et al*. 2006; Ogihara & Marks 2006; Pinheiro *et al*. 2006). There are however, no clinical trials comparing the outcome of orthodontic therapy in teeth with and without previous regenerative therapy (Fig. 58-10).

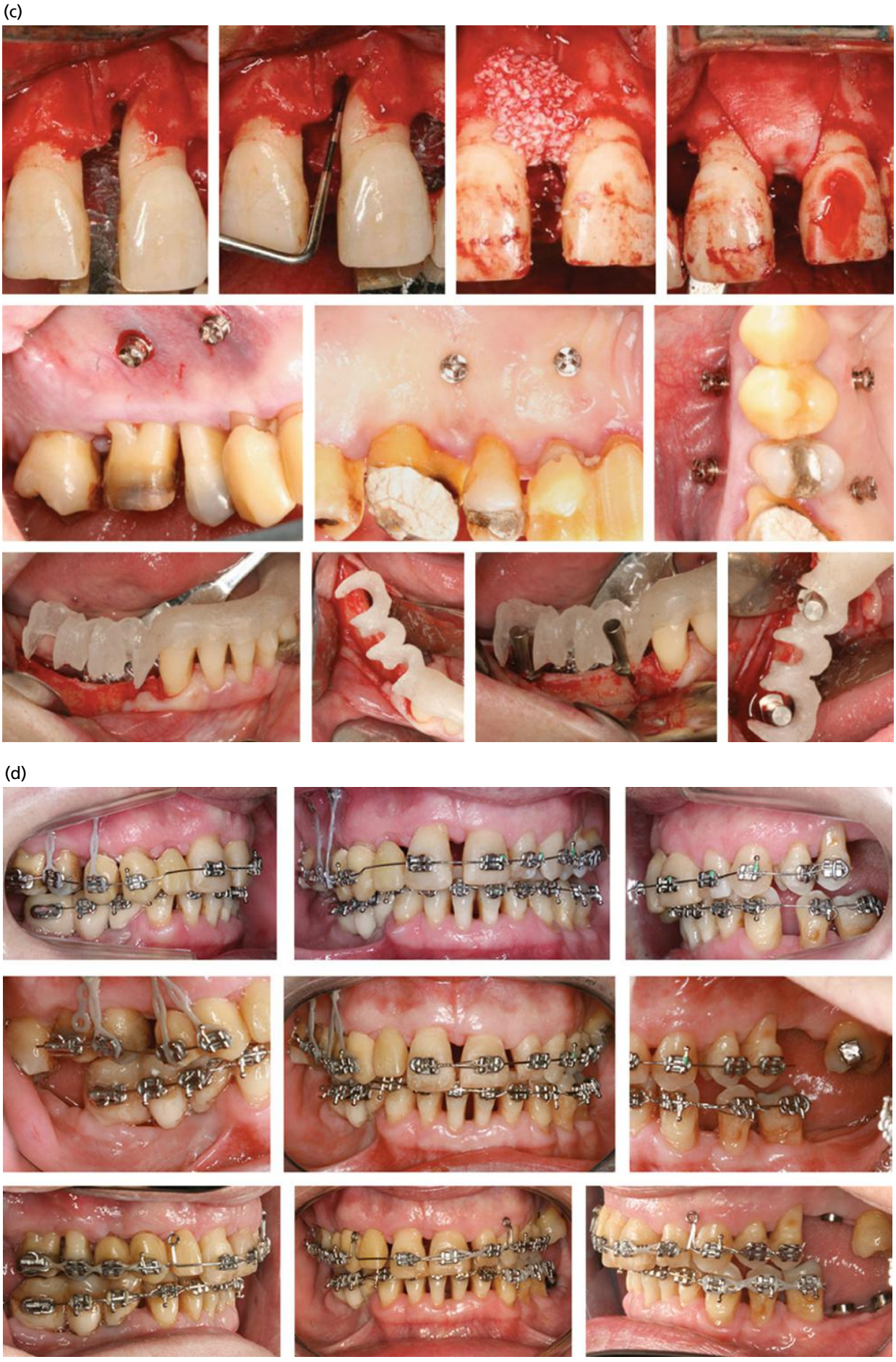
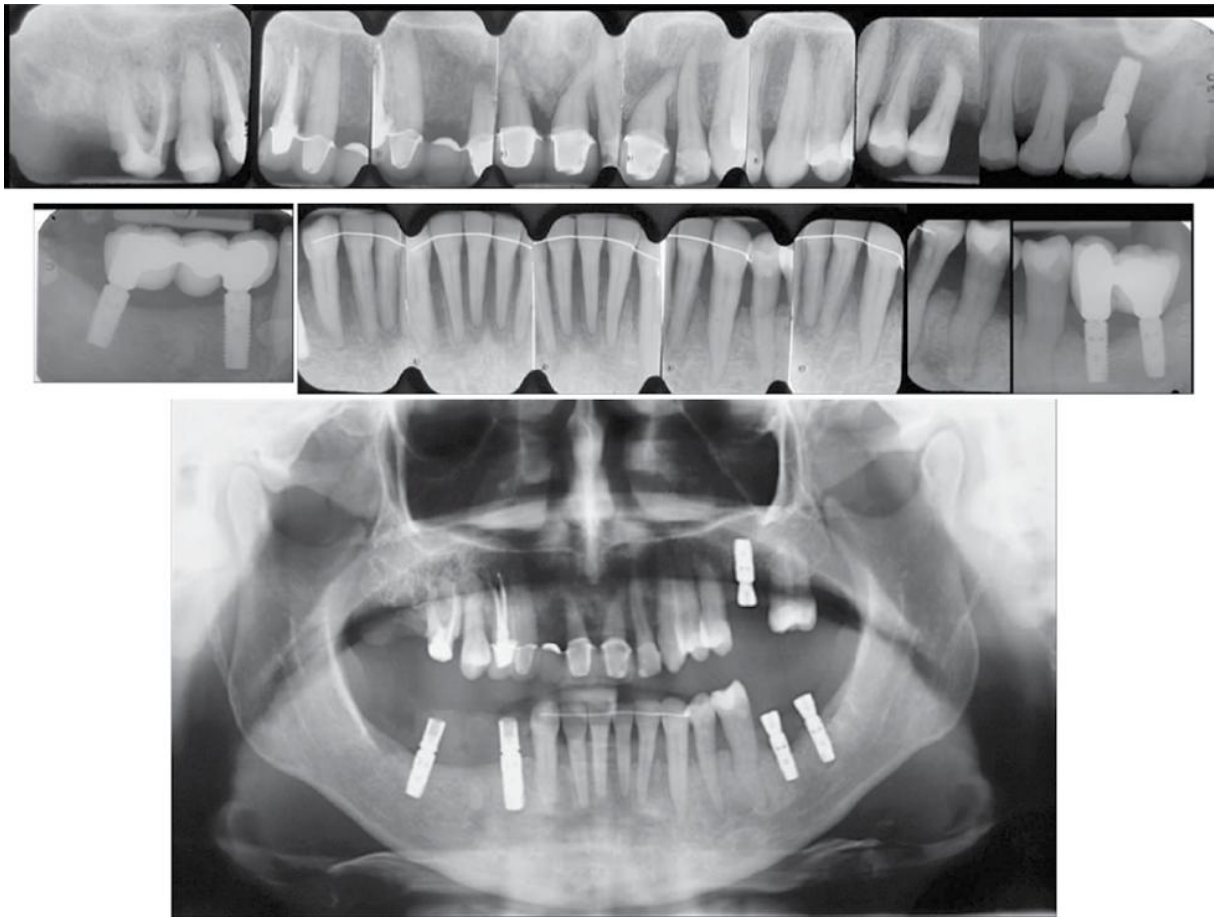


Fig. 58-10 (*Continued*) (c) Regenerative surgical procedure using guided tissue regeneration with a xenogeneic bone graft and a collagen resorbable membrane to treat the deep one-two wall defect in tooth 21. Dental implants were placed in the posterior mandible for anchorage during orthodontic therapy. Similarly, micro-screws were placed in the maxillary right posterior tooth for anchorage for the intrusive movements. (d) Orthodontic therapy was aimed at intruding the upper posterior right segment, aligning the teeth, closing the diastema, and distributing the spaces prior to final implant therapy in the posterior maxilla. The orthodontic tooth movements in the maxilla were carried out 9 months after the periodontal regenerative procedure.

(e)



(f)

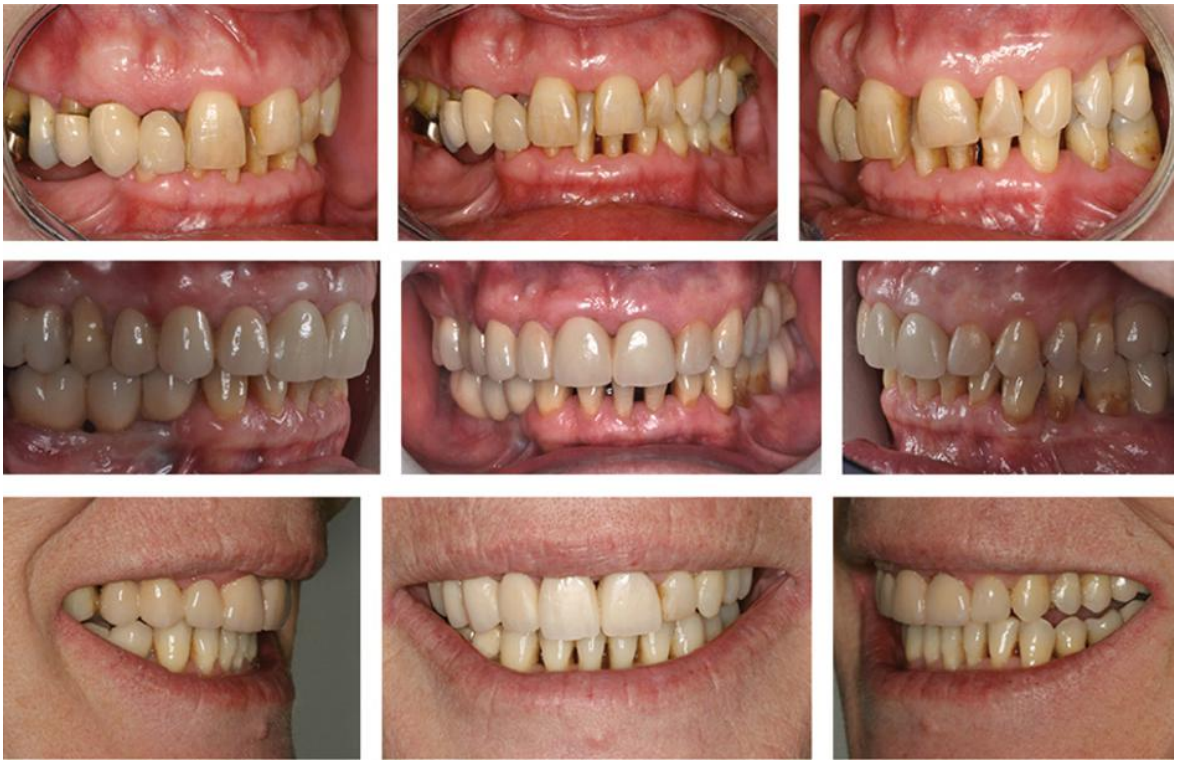


Fig. 58-10 (*Continued*) (e) Final radiographs depicting stable bone levels and resolution of the intrabony defects. (f) End of orthodontic therapy with proper alignment of the upper incisors and re-establishment of an occlusal plane. Final restorations were done using full ceramic crowns.

Uneventful results have also been demonstrated for orthodontic movements in teeth previously treated with EMDs in both experimental studies (Diedrich 1996) as well as in human clinical case reports (Juzanx & Giovannoli 2007).

Pathologic tooth migration

Pathologic tooth migration (PTM) is a common complication of moderate-to-severe periodontitis and is often the motivation for patients to seek orthodontic therapy. It is characterized by significant changes in tooth position as a consequence of the disruption of the forces that maintain teeth in a normal relationship and it usually presents clinically by extrusion and flaring out of the anterior maxillary teeth, resulting in diastemata and increased overbite. Prevalence of PTM among periodontal patients has been reported to range between 30% and 55%. The etiology of PTM appears to be multifactorial, although the destruction of periodontal supporting tissues seems to be a major factor. In these teeth with reduced periodontal support, non-axial occlusive forces might contribute to the abnormal migration of teeth. This is frequent when posterior teeth are lost and the subsequent lack of arch integrity with an anterior component of force leads to a posterior bite collapse with loss of the vertical dimension. The soft tissue forces of the tongue, cheeks, and lips can also play a role in these unwanted tooth migrations, mostly resulting in the extrusion and flaring of the anterior teeth.

Treatment of this complex anatomic and functional condition requires a multidisciplinary approach with complete periodontal therapy to eliminate the infection and the inflammation of the periodontal tissues, followed by orthodontic therapy and restoration of the lost dentition with dental implants and/or prosthetic restorations (Fig. 58-11).

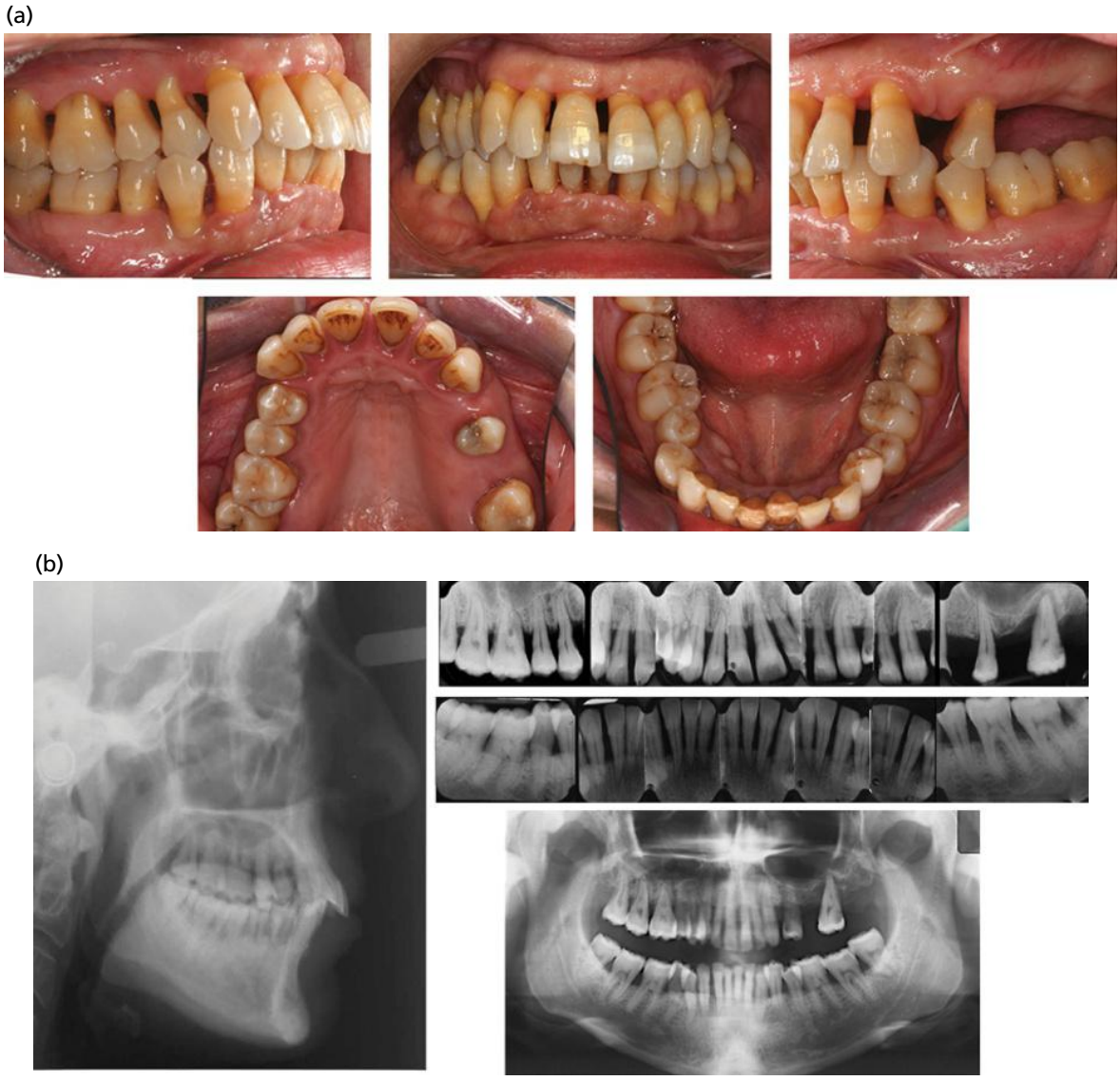


Fig. 58-11 Patient with severe chronic periodontitis, together with pathologic tooth migration, posterior right cross-bite, and posterior bite collapse. (a) Intraoral images after periodontal and before orthodontic therapy. (b) Radiographic images demonstrating the severe bone loss. Note the hopeless prognosis of tooth 26.

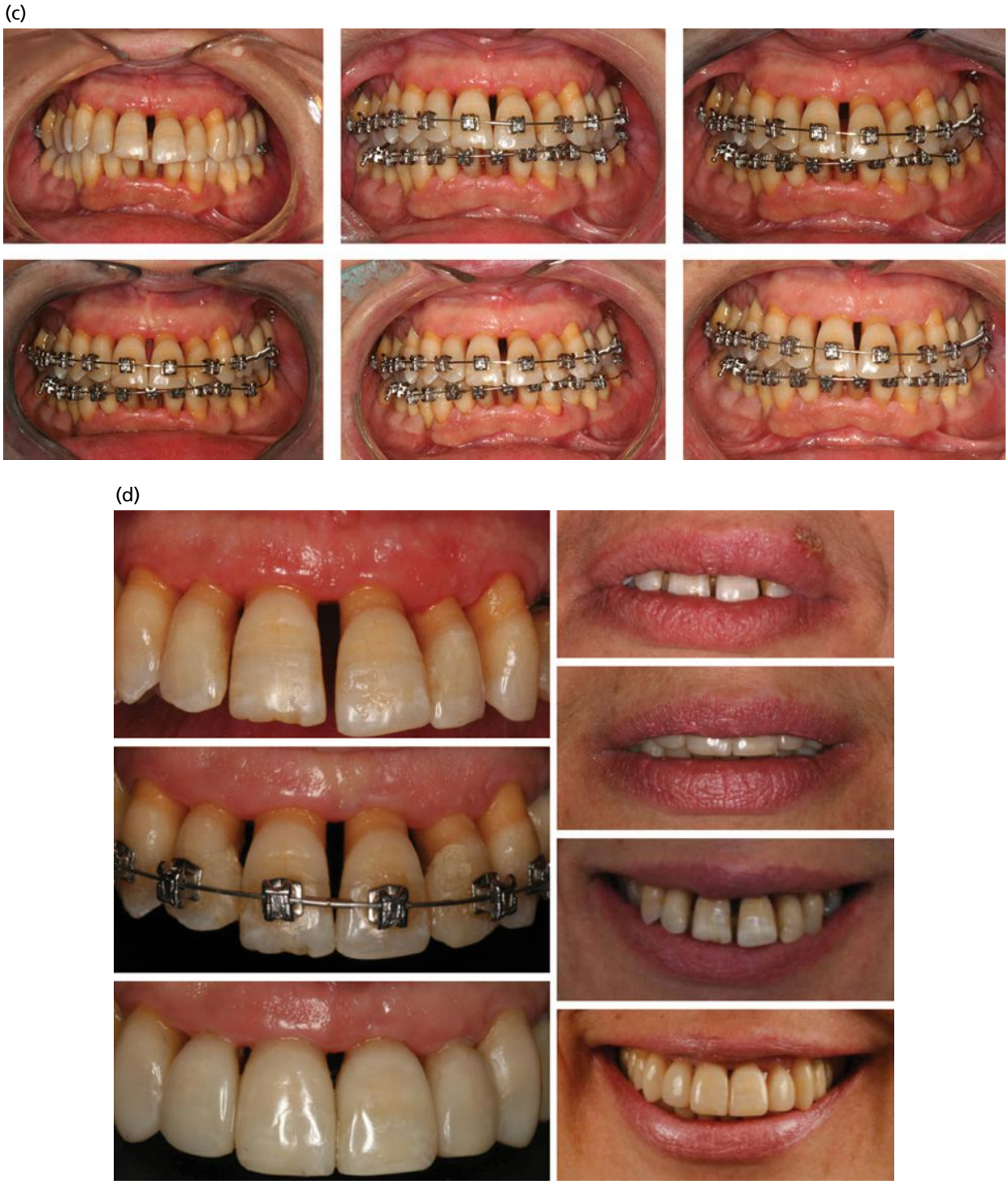


Fig. 58-11 (*Continued*) (c) Orthodontic therapy was aimed at intruding the upper anterior segment, aligning the teeth, and distributing the spaces prior to final implant therapy in the posterior left maxilla. (d) Final retention and esthetic treatment was accomplished with composite veneers. Note the improvement in the esthetic result and the lack of interdental papillae following the restorative work.

Multidisciplinary treatment of esthetic problems

During the course of orthodontic therapy in periodontally affected dentitions, the advent of unesthetic complications is relatively frequent, mainly related to loss of interdental papillae, gingival margin discrepancies or excessive gingival exposure (Kokich 1996; Gkantidis *et al*. 2010). Kurth and Kokich (2001) have reported a 38% prevalence of open gingival embrasures in the region of the maxillary incisors after adult orthodontic treatment. Improper root angulation, divergent or triangular-shaped crown forms, and periodontal bone loss are factors associated with this unwanted effect. Burke *et al*. (1994) correlated the incidence and size of pretreatment tooth overlap with the post-treatment gingival embrasure space between maxillary central incisors

in orthodontic patients. Another important factor in the loss of the interdental papilla is bone loss. Tarnow et al. (1992) correlated the distance from the contact point to the crest of bone with the presence or absence of the interproximal dental papilla. When this distance was ≤5 mm, the papilla was present in almost 100% of cases; when 6 mm, 56%; and when ≥7 mm, 27%. In the clinical situation where there is a combination of severe anterior crowding and periodontal bone loss, orthodontic therapy should be aimed not only at attaining the proper tooth alignment of the teeth, but also reducing the interdental space in order to compress the interdental soft tissues to force the formation of a new papilla. In these situations, the orthodontic tooth movement should be combined with restorative procedures aimed at raising the contact point, thus creating the illusion of a healthy interdental papilla.

The gingival marginal relationships of the upper anterior teeth play an important role in the esthetic appearance of the smile. These gingival marginal contours should mimic the natural anatomy of the tooth cementoenamel junction (CEJ), providing adequate scalloping with thin marginal tissues and papillae filling the interdental spaces. When orthodontic therapy is applied to periodontally affected dentitions, gingival marginal discrepancies are frequent and should be treated orthodontically with minor intrusive or extrusive tooth movements until the correct marginal alignment is reached. In situations with clear presence of localized marginal recessions, the appropriate mucogingival surgical techniques for root coverage should be implemented before the orthodontic tooth movement (see Figs 58-3, 58-5, 58-11).

It is very important to evaluate these gingival marginal discrepancies in relationship to the patient's gingival exposure during smiling and the length of the tooth clinical crowns (Kokich 1996). Depending on these factors, different combinations of periodontal plastic surgical techniques and orthodontic tooth movements will be indicated. In some situations, the indication will be the extrusion of the longer tooth and subsequent grinding of its incisal edge, while in others, it will be intrusion of the shorter tooth with subsequent reconstruction of its incisal edge.

The problem of excessive gingival exposure (a gummy smile) can also be found frequently in adults requiring adult orthodontic treatment. There can be several reasons for this: excessive maxillary growth, tooth extrusion in deep anterior overbites, and delayed apical migration of the gingival margin over the maxillary anterior teeth. Its esthetic correction largely depends on its etiology.

If the cause of the gummy smile is the extrusion of the upper anterior teeth, orthodontic intrusion will solve the problem, hence eliminating the excessive gingival display. In contrast, retardation of the physiologic apical migration of gingival margins will require a mucogingival excisional surgical correction. In situations with a clear skeletal cause, an orthognathic surgical approach is the only corrective solution.

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Chapter 59

Implants Used for Orthodontic Anchorage

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Introduction

Anchorage is one of the limiting factors in orthodontics and its control is essential for successful orthodontic treatment. The term "orthodontic anchorage" was first introduced by Angle (1907) and later defined by Ottofy (1923). Orthodontic anchorage denotes the nature and degree of resistance to displacement of teeth offered by an anatomic unit when used for the purpose of tooth movement. The principle of orthodontic anchorage is implicitly explained in Newton's third law (1687), according to which an applied force can be divided into an *action* component and an equal and opposite *reaction* moment. However, even today, there is no evidence for the exact relation between an applied force and the velocity of the induced tooth movement (Ren *et al*. 2003). Nevertheless, reciprocal effects must be evaluated and controlled in orthodontic treatment.

Orthodontic anchorage is oriented to the quality of the biologic anchorage of the teeth. This is influenced by a number of factors such as the size of the root surfaces available for periodontal attachment, height of the periodontal attachment, density and structure of the alveolar bone, turnover rate of the periodontal tissues, muscular activity, occlusal forces, craniofacial morphology, and nature of the tooth movement planned for the intended correction (Diedrich 1993). Basically, each tooth has its own anchorage potential as well as a tendency to move when force is applied to it. When teeth are used as anchorage, the inappropriate movements of the anchoring units may result in a prolonged treatment time, and unpredictable or less-than-ideal outcomes.

To maximize tooth-related anchorage, techniques such as differential torque (Burstone 1982), moving the roots of the anchor teeth into the buccal cortical bone (Ricketts 1976), and distal inclination of the molars (Tweed 1941; Begg & Kesling 1977) may be used. If the periodontal anchorage is inadequate with respect to the intended treatment goal, additional intraoral and/or extraoral anchorage may be needed to avoid negative effects. Among these, extraoral (Kingsley 1880) and intermaxillary (Stewart *et al.* 1978) anchorage appliances are the most common. While the teeth are the most frequent anatomic units used for anchorage in orthodontic therapy, other structures, such as the gingiva or perioral soft tissues by means of plates or lip bumpers (Nevant *et al*. 1991;

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Osborn *et al.* 1991, Grossen & Ingervall 1995; Ferro *et al*. 2004), the lingual mandibular alveolar bone, the occipital bone, and the neck are also alternative support structures.

However, additional anchorage to provide extraoral and intraoral forces is visible and hence, compliance dependent (Nanda & Kierl 1992), as well as associated with the risk of undesirable effects such as tipping of the occlusal plane, protrusion, gingival recession of mandibular incisors, and extrusion of teeth.

Implants, mini-screws, and ankylosed teeth, do not possess a normal periodontal ligament as they are in direct contact with bone. As a consequence, they do not move when low-to-moderate orthodontic forces are applied (Melsen & Lang 2001; Hsieh *et al.* 2008; Wehrbein & Göllner 2009) and hence, may be used for "absolute anchorage" that is independent of patient compliance.

Evolution of implants for orthodontic anchorage

Skeletal anchorage was first attempted in 1945. Gainsforth and Higley (1945) placed vitallium screws and stainless steel wires into the ramus of dog mandibles and applied elastics that extended from the screw to the hook of a maxillary archwire to distally tip/retract the canine by immediate orthodontic loading (Fig. 59-1). Even though the authors did not describe the development of infection, the failures encountered may be attributed to infection and the lack of antibiotics at that time, as well as the early dynamic loading of the screws. Although minor tooth movement was accomplished using basal bone anchorage in two animals, an effective orthodontic force could not be maintained for >31 days.

Skeletal anchorage systems have since evolved from two directions. One such development originated from orthognatic fixation techniques used in maxillofacial surgery. The pioneers Creekmore and Eklund (1983) used a vitallium bone screw to treat a patient with a deep impinging overbite. The screw was inserted in the anterior nasal spine to intrude and correct the upper incisors using an elastic thread from the screw to the incisors 10 days after the screw had been placed. Subsequently, Kanomi (1997) described a mini-screw specially designed for orthodontic use.

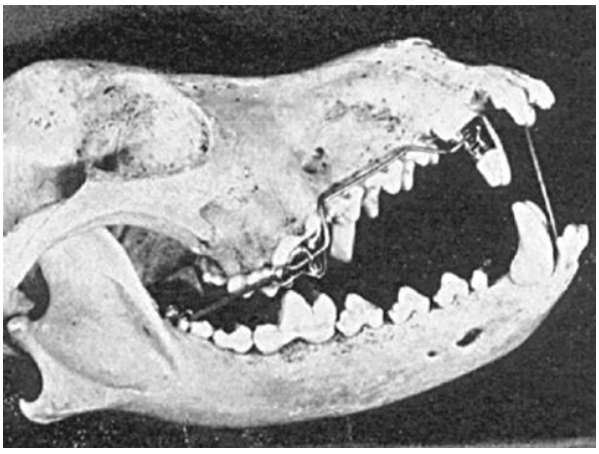


Fig. 59-1 Orthodontic appliance using vitallium screw anchorage. (Source: Gainsforth & Higley 1945. Reproduced with permission from Elsevier.)

The second development originated from applications in implant dentistry. Linkow (1969) used blade implants for rubber band anchorage to retract teeth, but never presented long-term outcomes. Later, endosseous implants for orthodontic anchorage were suggested (Ödman *et al.* 1988; Shapiro & Kokich 1988; Ödman *et al.* 1994). As indicated in various animal studies, osseointegrated titanium implants remained positionally stable under orthodontic loading and thus could be used for orthodontic anchorage (Turley *et al.* 1980; Roberts *et al*. 1984; Turley *et al.* 1988; Roberts *et al.* 1989; Wehrbein & Dietrich 1993; Wehrbein 1994; Wehrbein *et al.* 1998; De Pauw *et al.* 1999; Majzoub *et al.* 1999) (Fig. 59-2). This resulted in the development of specially designed implants in the retromolar area (Roberts *et al.* 1990) and the palatal site of the maxilla (Triaca *et al.* 1992; Wehrbein *et al.* 1996a). Both applications are used for direct or indirect anchorage, as described later.

From a clinical point of view, it is of relevance whether implants are to be used only as temporary anchorage devices (TADs) (Daskalogiannakis 2000) or are subsequently to be used as abutment for supporting prosthetic appliances. These aspects determine insertion sites, implant type and dimensions, as well as type of orthodontic anchorage. Moreover, the fact that these devices may need to be placed in growing patient is of particular importance. In these cases, only TADs are suitable.

Prosthetic implants for orthodontic anchorage

The insertion site of prosthetic implants for orthodontic anchorage is determined by the subsequent use of the implant as a prosthetic abutment. The length and diameter of implants depend on the later prosthetic use. Their positions within the alveolar process and number, however, have to be selected with reference to prospective final tooth position and space after orthodontic treatment.

It may be confusing to determine the location of the prosthetic implants before orthodontic therapy. This is especially true if the teeth are moving towards or away from the implant during orthodontic treatment. In these situations, the presumptive outcomes must be predetermined to achieve the proper implant location and the correct size of the crowns and pontics on the implant-supported prosthesis. In order to use oral implants for both orthodontic anchorage as well as the subsequent restorative therapy, protocols have been developed for determining the accurate placement of dental

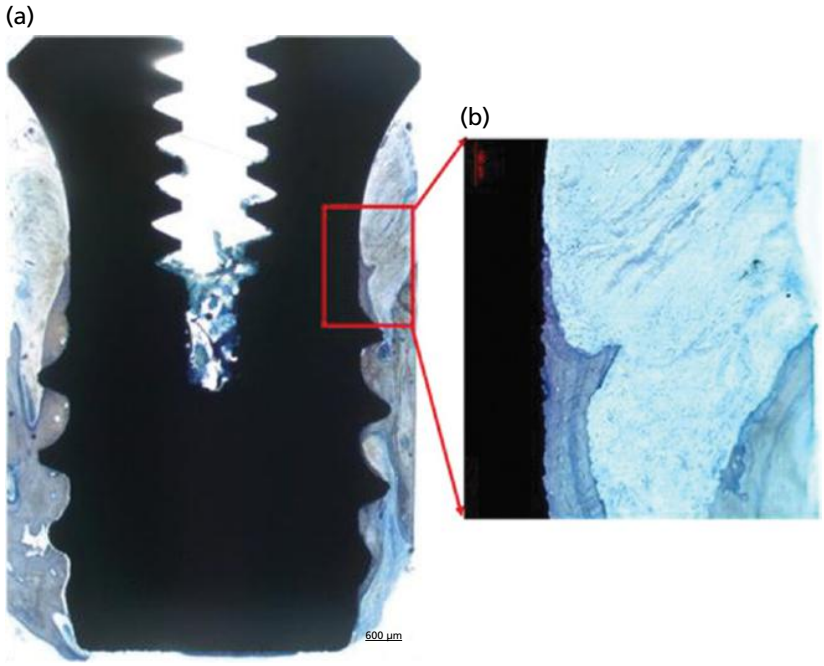


Fig. 59-2 (a) Histologic overview of a second-generation explanted palatal implant (4.1 mm × 4.2 mm; staining: toluidine blue, original magnification × 16). (b) Margin of bone coverage is at the junction (enlargement, staining: toluidine blue, original magnification × 100) between the microretentive SLA surface of the implant body and the smooth machined surface of the transmucosal neck. (Source: Jung *et al.* 2011a. Reproduced with permission from Springer Science and Business Media.)

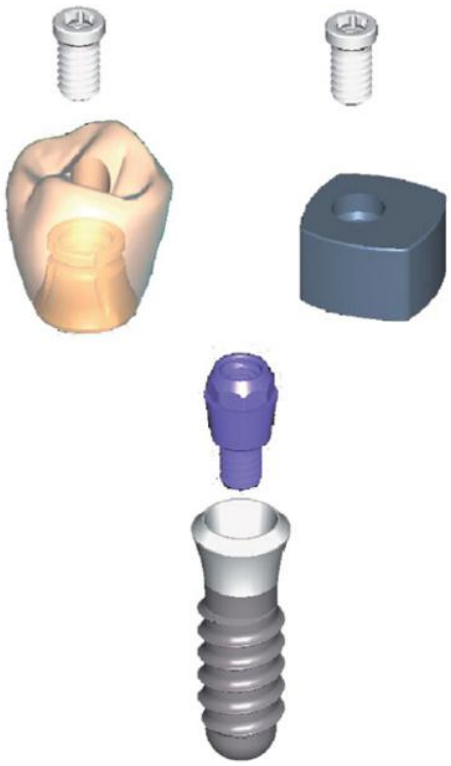


Fig. 59-3 Schematic illustration of the assembly of an orthodontic base on an oral implant intended for prosthetic use after the orthodontic treatment.

implants for prosthetic reconstruction before orthodontic therapy (Smalley 1995; Smalley & Blanco 1995). The clinician determines the proper implant location using a plastic placement guide that is constructed based on information derived from a diagnostic wax-up. Therefore, it is necessary to construct the set-up casts from an exact duplicate of the tooth and base portions of the original dental casts. The bases are used as a reference for the proposed position of the implant.

An orthodontic attachment is then either fixed to the provisional crown or to a prefabricated bonding base (Figs. 59-3, 59-4; see also Fig. 59-7). The orthodontic force acts at the implant suprastructure. The reactive moments and forces are then directly transmitted to the implant and its adjacent bone (direct implant anchorage).

Bone reaction to orthodontic implant loading

Dental implants should not only fulfil prosthetic stability, but also withstand the stress and strain applied during orthodontic treatment. The effect of orthodontic loading to the adjacent bone of the oral implant is of great interest, because the applied forces should not have a negative impact on the peri-implant bone and, therefore, should not impair the long-term prognosis as a prosthetic abutment. However, increased turnover of peri-implant bone is a commonly observed phenomenon with loading (Gotfredsen *et al.* 2001; Melsen 2001; Melsen & Lang 2001; Trisi & Rebaudi 2002). It has been demonstrated that the local strain distribution has a significant impact on the biologic activity of the peri-implant bone tissue. However, there are substantial differences between orthodontic forces and occlusal loading. Orthodontic forces are continuous and horizontal, while occlusal loads are discontinuous and mainly applied in a vertical direction on the implants/teeth.

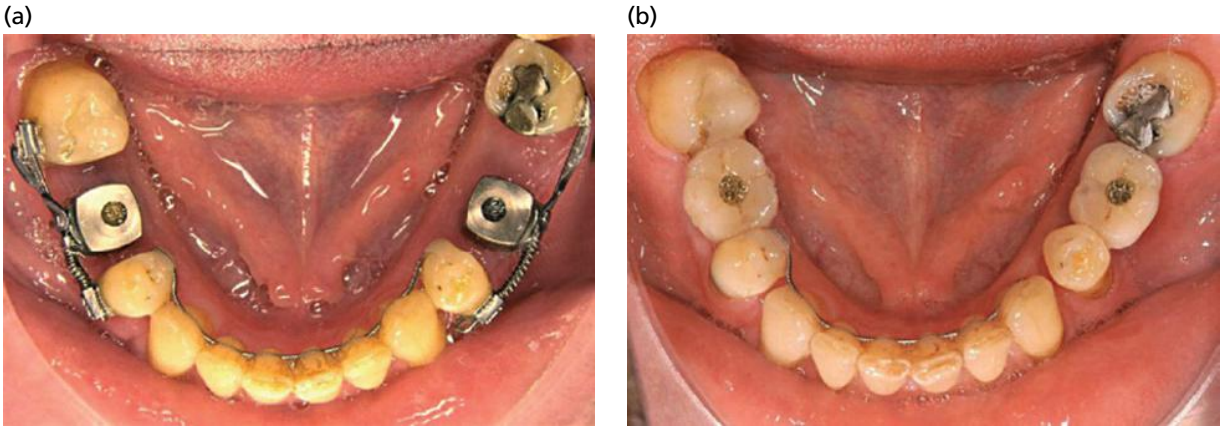


Fig. 59-4 Use of oral implants intended for prosthetic reconstruction as anchorage for orthodontic treatment. (a) Prefabricated orthodontic base as anchorage element. (b) Reconstruction of teeth 35 and 45 on oral implants following orthodontic treatment. (Courtesy P. Göllner and T. Liechti, Berne).

Table 59-1 Bone tissue turnover characteristics of alveolar bone in a relation to the magnitude of strain applied.

Strain values	Bone appositional surface in percentage	Resting bone (homeostatic surface in percentage	Bone resorptive surface in percentage
>6700 µstrain			
Mean	16.4	21.2	51.5
95% confidence interval	11–22	16–26	42–62
3400–6600 µstrain			
Mean	62.7	16.9	5.0
95% confidence interval	56–70	12–22	1–9
<3300 µstrain			
Mean	20.9	61.9	43.5
95% confidence interval	15–29	56–68	34–53

Source: Melsen & Lang (2001).

In monkeys, specially designed oral implants were inserted and subjected to well-defined continuous loading (Melsen & Lang 2001) (Table 59-1). None of the implants had lost osseointegration after 11 weeks of loading, but loading significantly influenced the turnover of the alveolar bone in the vicinity of the implants. Bone apposition was most frequently found when the calculated strain varied between 3400 and 6600 µstrain. Several other studies of applied orthodontic forces confirmed the apposition or increase in bone density rather than loss of bone surrounding an oral implant (Roberts *et al.* 1984; Wehrbein & Diedrich 1993; Asikainen *et al.* 1997; Akin-Nergiz *et al.* 1998).

Finite element analysis, however, indicated that not all force systems might be tolerated on a long-term basis. High strain values (>6700 µstrain) resulted in a negative balance between bone apposition and bone resorption (Melsen & Lang 2001). An study using a monkey model demonstrated that six of eight implants failed under excessive loading in the lateral direction during an 18-month period of observation (Isidor 1996). Similar findings were demonstrated in an experimental dog study (Hsieh *et al.* 2008). All implants loaded with a light continuous orthodontic force (100–200 g) remained stable during the whole study period and showed no displacement up to 6 months. However, tipping movement was observed 3 months after the implants were loaded with a force of >500 g. The extent of movement increased further after 6 months of force loading (Figs. 59-5, 59-6). The displacement occurred without loss of stability. Radiographic examination showed no apparent bone loss at the crestal area and around implant fixtures. The application of a well-controlled continuous force may be a critical factor leading to displacement with continuous bone formation in the surrounding peri-implant tissue.

Tipping of the implants might be a response to structural adaptation to strain (Frost 1987). The response to loading of intense strain may be the formation of woven bone, which possibly represents a physiologic process of microfracture repair (Burr *et al.* 1989; Jee & Li 1990; Melsen 1999). Displacement of implants under a high strain for a long period of time results from the accumulation of trabecular microfractures and adaptative remodeling during the orthodontic force application. Possible fatigue failure of cancellous bone around the loaded fixtures has also been postulated. If the damage exceeds repair on one side of an implant, then it is likely that implant migration will continue and the displacement will become obvious (Hsieh *et al.* 2008).

Even though osseointegrated implants might be considered to be "absolute" under low-to-moderate orthodontic loading over a long time (Turley *et al.* 1980; Roberts *et al.* 1984; Turley *et al.* 1988; Roberts *et al.* 1989; Wehrbein & Dietrich 1993; Wehrbein 1994; Wehrbein *et al.* 1998; De Pauw *et al.* 1999; Majzoub *et al.* 1999), but if the applied force exceeds a certain threshold of physiologic adaptation, the negative balance in the biologic

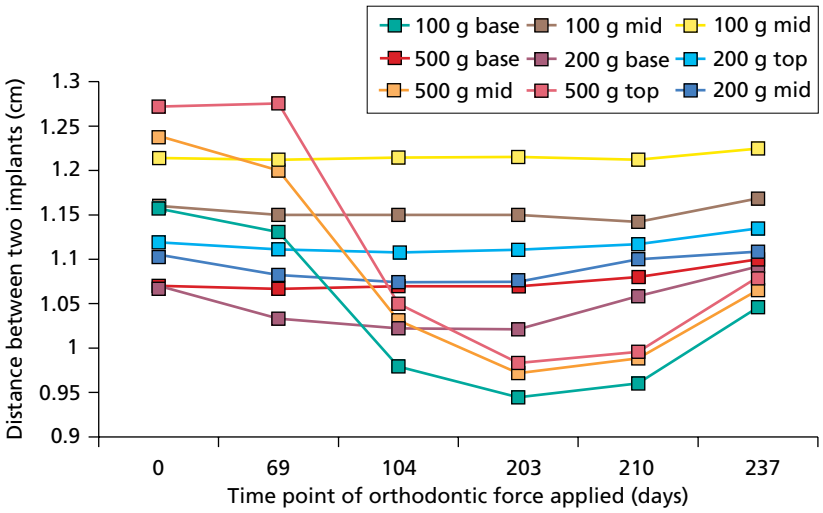


Fig. 59-5 Changes of distance between two implants measured at different levels after various durations of 100, 200, and 500 g force applications. (Source: Hsieh *et al*. 2008. Reproduced with permission from John Wiley & Sons.)

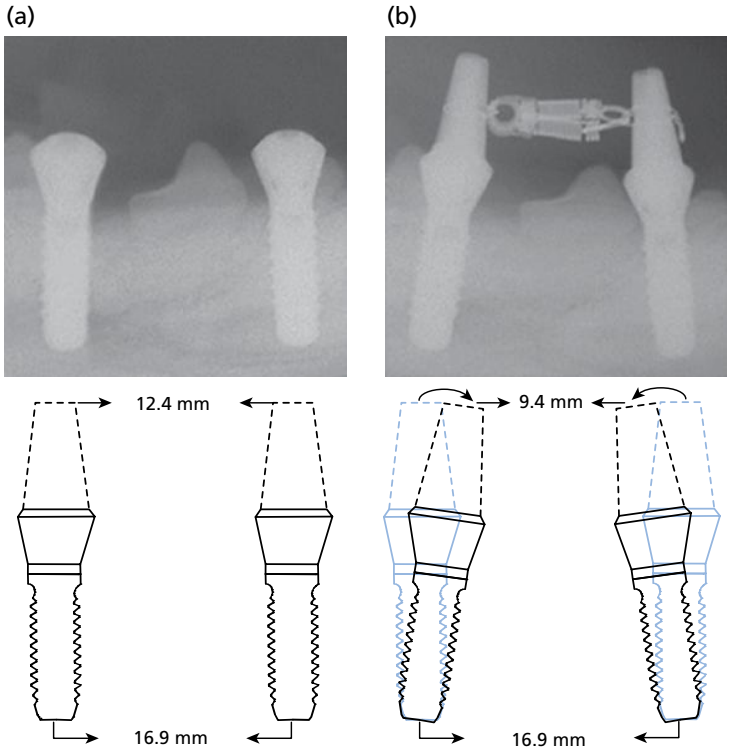


Fig. 59-6 Radiographs and the sketched illustrations showing the change of implant position after 6 months of a 500 g pulling force loading (Source: Hsieh *et al*. 2008. Reproduced with permission from John Wiley & Sons.)

response of peri-implant bone could possibly cause the displacement of the previously uneventful implant without marginal bone loss or complete disintegration. Therefore, endosseous implants may not be considered in all circumstances to be true "solid" or "ankylosed" anchorage, because of the dynamically biologic responses toward the stimuli from the surrounding environment under heavy loading (Isidor 1996; Melsen & Lang 2001; Hsieh *et al*. 2008).

Indications for prosthetic oral implants for orthodontic anchorage

Orthodontic anchorage provided by prosthetic oral implants may be indicated for partially edentulous adult patients with intra-arch malposition of teeth to correct over-eruption, infra-eruption or tipping of teeth; to retract anteriorly displaced frontal teeth and intra-arch protraction of teeth that are positioned distally to reduce a multi-tooth gap; or to improve tooth position in edentulous spaces (Fig. 59-7). Prosthetic oral implants might also be used for the correction of interarch malocclusion of single teeth or the entire dentition.

The most important factor in the entire process is interdisciplinary communication and planning. It is critically important for the orthodontist, periodontist, and restorative dentist to work closely as a team during the planning and treatment to achieve the best possible final result (Kokich 1996).

Prosthetic oral implant anchorage in growing orthodontic patients

The use of prosthetic oral implants in growing individuals has been studied in both clinical (Ödman *et al*. 1988; Thilander *et al*. 1994, 1999) and animal

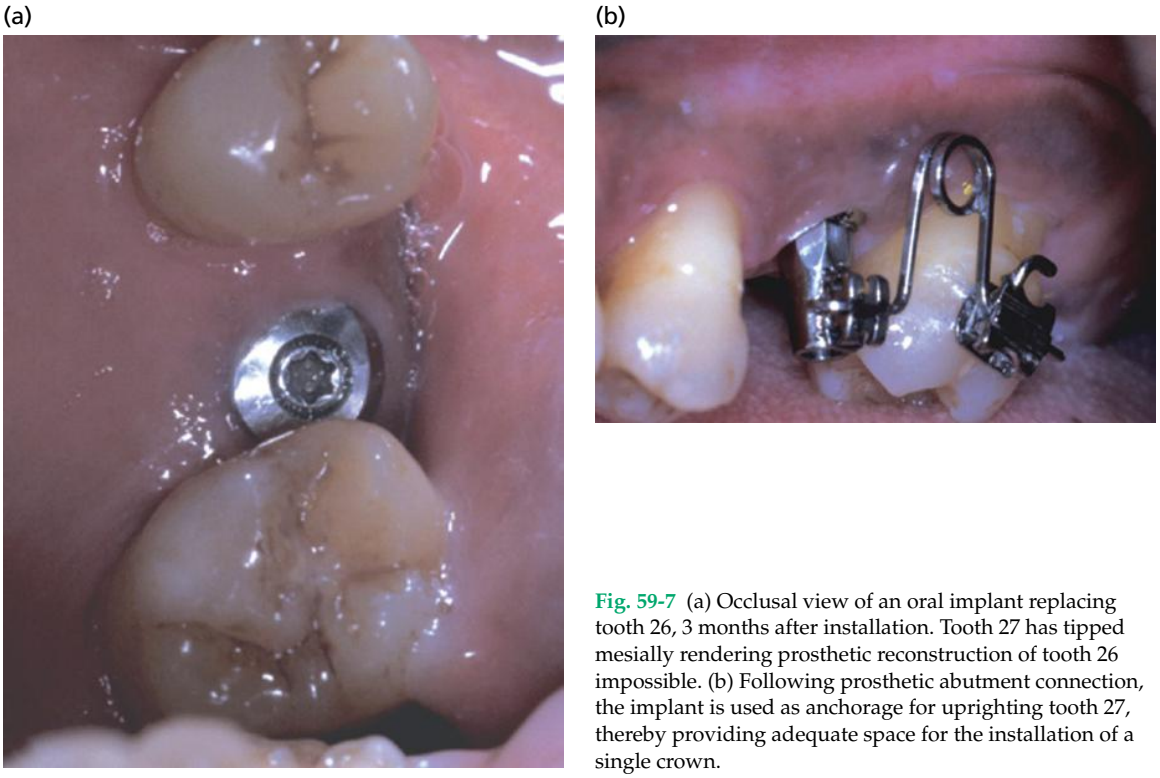


Fig. 59-7 (a) Occlusal view of an oral implant replacing tooth 26, 3 months after installation. Tooth 27 has tipped mesially rendering prosthetic reconstruction of tooth 26 impossible. (b) Following prosthetic abutment connection, the implant is used as anchorage for uprighting tooth 27, thereby providing adequate space for the installation of a single crown.

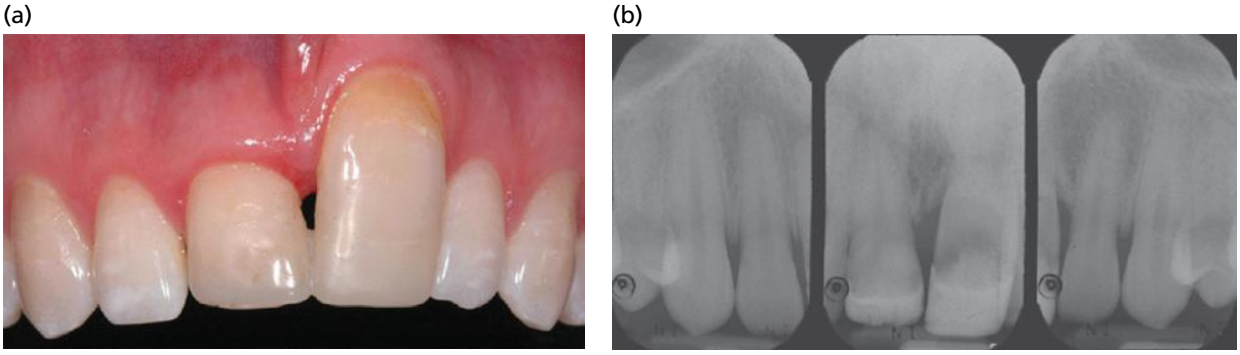


Fig.59-8 (a) Ankylosed tooth 21 after trauma and on-going composite adaptation throughout several years. Tooth 21 has not followed the changes associated with alveolar process growth. (b) Radiographic documentation 6 years following trauma of tooth 21, showing the development of the alveolar process with concomitant ankylosis of tooth 21.

studies (Ödman *et al.* 1991; Thilander *et al.* 1992; Sennerby *et al*. 1993). Like ankylosed teeth (Fig. 59-8), oral implants do not follow the developmental changes of the alveolar processes encountered in combination with continuous eruption of adjacent teeth (Fig. 59-9).

Moreover, the osseointegrated implants cannot be displaced in all dimensions during growth of the jaws (Thilander *et al.* 1994; Iseri & Solow 1996) and, hence, can impair the development of the surrounding bony structures and of adjacent teeth, leading to an infraocclusion of the single-tooth implant in the subsequent formative years (Bernard *et al.* 2004). Implant therapy in young individuals with residual growth potential has been addressed in several studies and identified major impairment in esthetic outcomes, especially in anterior implant-borne restorations.

However, treatment options for gaps between front teeth after dental trauma or agenesis in growing patients, based on skeletal anchorage, may serve as a useful adjunct (Figs. 59-10, 59-11) (Göllner *et al.* 2009a) to conventional options, such as space maintainers, adhesive bridges (Marinello *et al.* 1988), autotransplantation of teeth (Paulsen & Andreasen 1998; Czochrowska *et al.* 2000) or orthodontic space closure (Czochrowska *et al.* 2003; Kugel *et al*. 2006). Fixation of dentures to palatal implants ensures stability even in the presence of mixed dentition and may be fitted to the vertical growth of the alveolar process at any time by grinding the plastic base.

To assess the remaining facial growth potential, hand–wrist radiographs have been proposed, but do not appear to be specific enough. The best method of evaluating the completion of facial growth is based

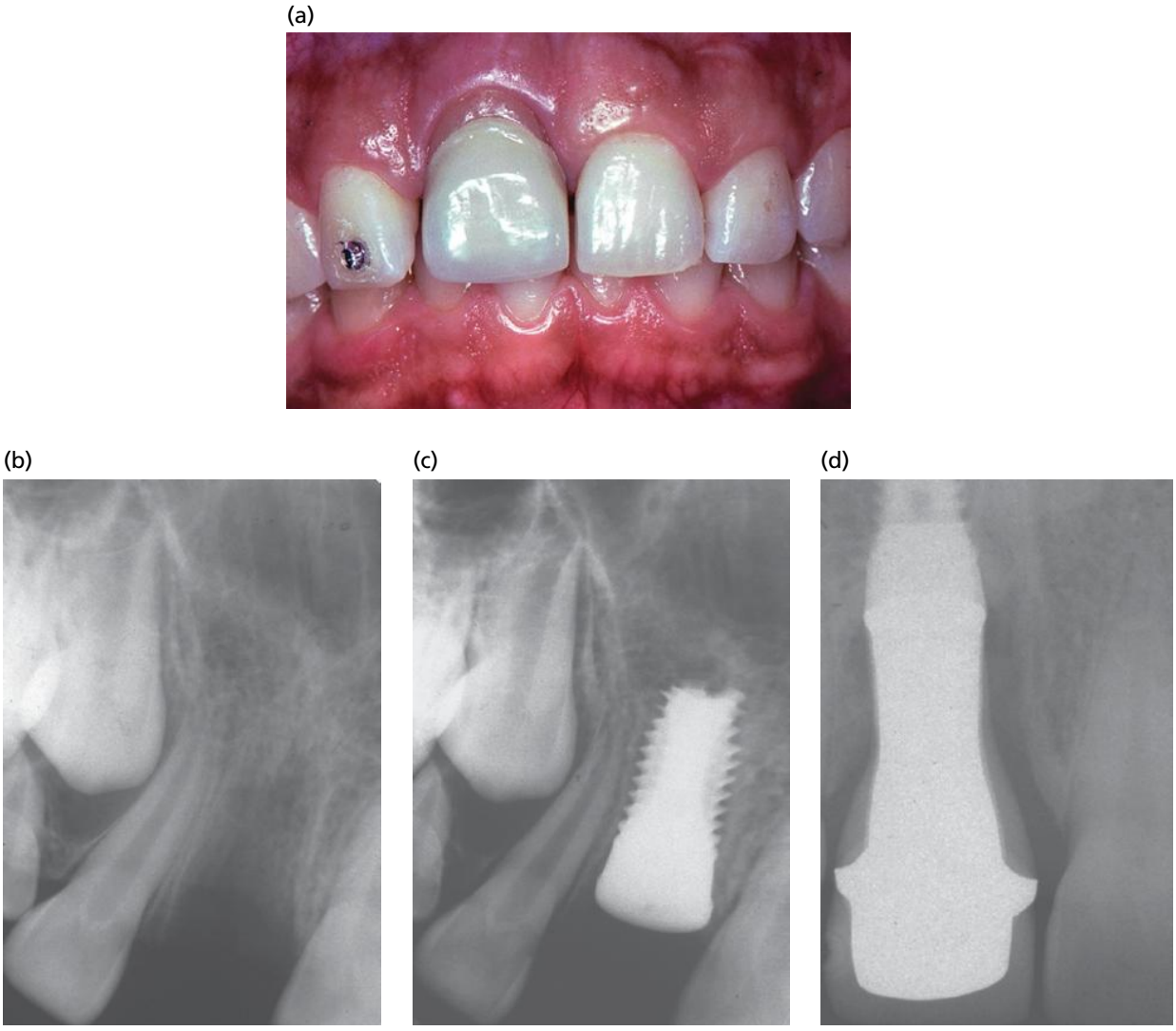


Fig.59-9 (a) Oral implant placed prematurely (at age 9 years) in a growing patient. The implant did not follow the growth development of the alveolar process, resulting in the need for multiple (3×) replacement of the prosthetic reconstruction until adolescence. Unsatisfactory esthetic outcomes persisted. Radiographic documentation: (b) following traumatic loss of tooth 11 at age 9 years; (c) implant placement in the growing maxilla; (d) oral implant 9 years after placement and third single tooth crown reconstruction. (Courtesy of G.E. Salvi, Berne.)

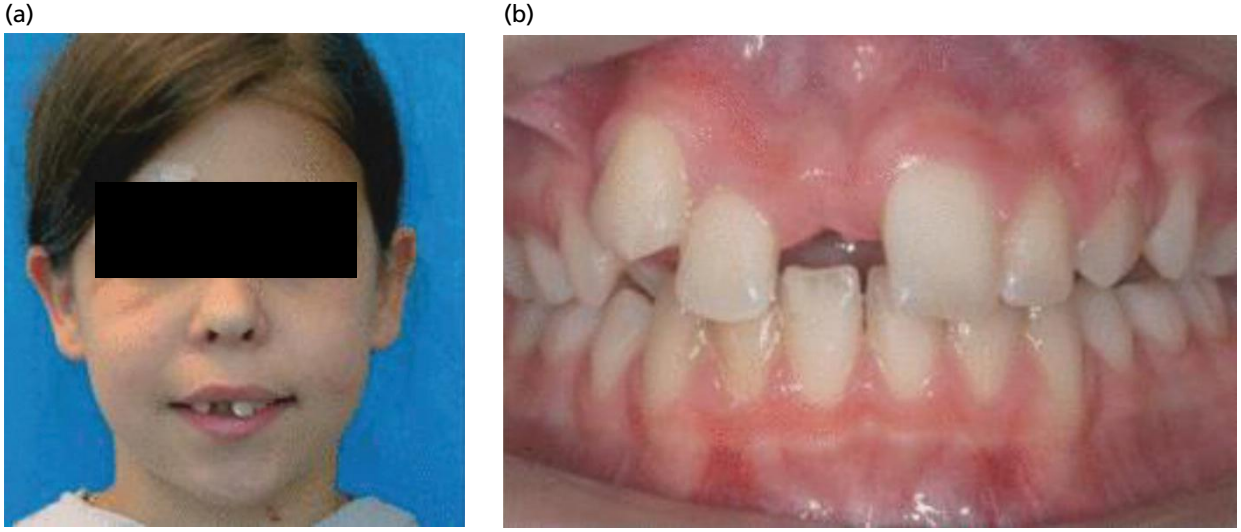


Fig. 59-10 (a) *En-face* photograph and (b) intraoral frontal view of the patient after the traumatic loss of tooth 11. (Source: Göllner *et al*. 2009a. Reproduced with permission from John Wiley & Sons.)

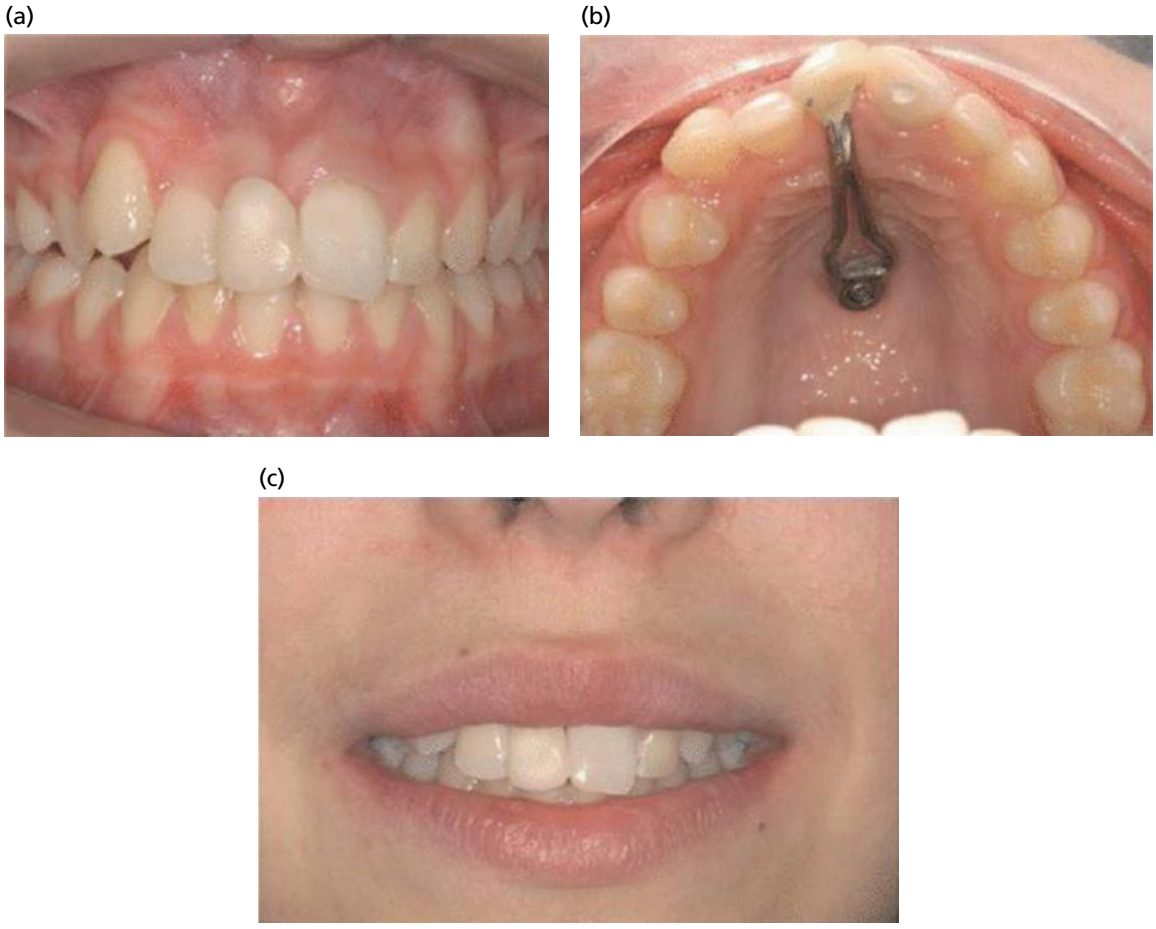


Fig. 59-11 Same patient as in Fig. 59-10. (a, b) intraoral and (c) extraoral photographs showing the new type of integrated temporary prosthetic substitution by means of a palatal implant. (Source: Göllner *et al*. 2009a. Reproduced with permission from John Wiley & Sons.)

on the superimposition of sequential cephalometric radiographs. It is, therefore, advisable to await the completion of adolescent growth in height. At that point, a cephalometric radiograph should be taken. Another radiograph should be taken at least 6 months to a year later. If, when these radiographs are superimposed, no change is seen in vertical facial height (nasion to menton), completion of facial growth may be assumed. The installation of an oral implant at that time may no longer be associated with significant eruption of adjacent teeth (Kokich 2004).

In most adult patients, however, completion of facial growth is assumed and yet, residual growth and aging changes affecting the alveolar process may be encountered. This was documented in a retrospective study (Bernard *et al*. 2004), supporting the assumption that mature adults also may exhibit major vertical steps in growth after anterior restorations were inserted on osseointegrated implants, due to continuing vertical eruption of the adjacent teeth.

Orthodontic implants as temporary anchorage devices

Fundamental differences with respect to implant dimensions, insertion sites, type of implant anchorage, and intended duration of implant use exist. The most important difference is whether or not a TAD is to be removed after completion of the intended orthodontic tooth movement (Daskalogiannakis 2000).

Implant designs and dimensions

As regular orthodontic patients do not display edentulous bony ridges for the insertion of an implant, implants for orthodontic anchorage must be placed in areas other than the usual topographic locations foreseen for the replacement of missing teeth. Besides the installation of orthodontic anchorage implants into the retromolar area of the mandible (Roberts *et al.* 1990; Higuchi & Slack 1991), the mid-sagittal palatal region (Triaca *et al.* 1992; Block & Hoffmann 1995; Wehrbein *et al*. 1996b) was also proposed.

The introduction of diameter-reduced TADs, such as mini-screws (<2 mm) of various lengths (Kanomi 1997; Costa *et al*. 1998) and titanium pins (Bousquet *et al*. 1996), as well as L-shaped miniplates with the long arm exposed to the oral cavity (Umemori *et al*. 1999) and zygomatic anchors (De Clerck *et al*. 2002) both fixed by bone screws, has offered new additional insertion sites: the interradicular septum (Bousquet *et al.* 1996; Kanomi 1997), the supra-apical and infra-zygomatical area (Kanomi 1997; Costa *et al*. 1998; Umemori *et al.* 1999;

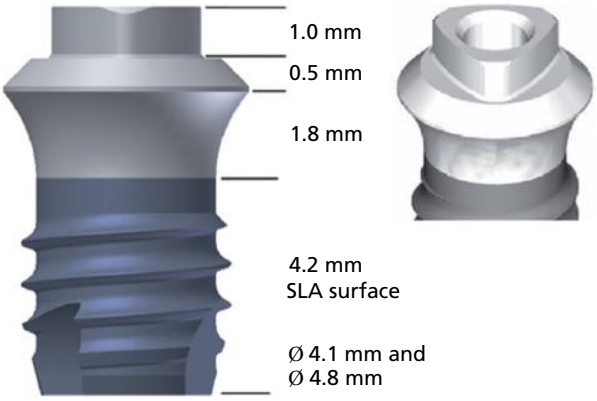


Fig. 59-12 Orthosystem® (Institut Straumann, Waldenburg, Switzerland) designed for orthodontic anchorage with an intraosseous SLA rough surface, a smooth transmucosal portion, and a trigonal orthodontic fixation base. (Courtesy of Institut Straumann AG.)

De Clerck *et al.* 2002), and the mandibular symphysis (Costa *et al.* 1998).

Length-reduced orthodontic anchorage devices such as titanium flat screws (Triaca *et al.* 1992), resorbable orthodontic implant anchors (Glatzmaier *et al.* 1995), T-shaped orthodontic implants (Wehrbein *et al.* 1996a) (Orthosystem®; Institut Straumann, Waldenburg, Switzerland), and the Graz implant-supported pendulum (Byloff *et al.* 2000) were subsequently introduced.

Another device, the Onplant® (Block & Hofmann 1995), placed subperiostally, is a smooth titanium disk with a hydroxyapatite-coated surface that is supposed to connect to the bone. Owing to the submerged installation, the monitoring of the healing process of the Onplant® may be troublesome, and its osseointegration may be questionable (Celenza & Hochman 2000). In a systematic review on the survival and failure rates of orthodontic TAD, the Onplant® showed the highest failure rate of 17.2% (95% CI 5.9–35.8%) and it may therefore be regarded as obsolete (Schätzle *et al.* 2009b).

The most widely used orthodontic anchorage system is the Orthosytem® (Institut Straumann). This titanium implant has three distinct features (Fig. 59-12): a self-tapping endosseous body, 4.2 mm long and either 4.1 mm or 4.8 mm in diameter, designed to be inserted into bone; a smooth neck portion (4.8 mm in diameter and 1.8 mm in length) serving as the transmucosal part; and a trigonal head for orthodontic appliance fixation.

Insertion sites for palatal implants

The incomplete closure of the median palatal suture during childhood and early adolescence might be a limiting factor for the installation of orthodontic implants in the mid-sagittal region for fully grown juveniles and adults. When analyzing the palatal suture status on occlusal films of young adults, a radiologically invisible mid-palatal suture is not a histologic equivalent of a fused or closed suture, respectively. Rather, it corresponds histologically to a relatively large area of interdigitation, an oblique running suture course in relation to the X-ray path or bone structures projecting above the suture course (Wehrbein & Yildizhan 2001). Therefore, the paramedian regions of the hard palate (Bernhart *et al.* 2000, 2001) may represent a feasible alternative implant site. With respect to anatomic limitations, sites chosen for palatal orthodontic anchorage device insertion should be carefully evaluated to avoid perforation of the inferior nasal turbinate (Wehrbein *et al.* 1996b). Pre-implantation examinations of the anterior palate have shown that the vertical bone volume decreases from the anterior to the posterior region.

The presence of the palatal suture and the limited bone thickness of the hard palate available may be causes of concern for the achievement of stability of palatal implants. However, a histologic evaluation of palatal anatomic sites for implant insertion showed that in most cases, a good primary stability of TADs might be achieved in the mid-palatal and paramedian areas of the anterior palate, as the bone conditions are favorable and available bone quantity is high (Wehrbein 2008). From this point of view, the mid-palatal bone area is a favorable region for short TAD placement, as most frequently relatively compact bone is present in this area. Thereby, from a morphologic standpoint, a good primary stability should be achieved and the success rate as well as the bone-to-implant contact should be high in the palatal bone. However, a small percentage of cases (9%) remains in whom critical bone conditions for implant placement may be present (loose spongious bone) (Wehrbein 2008).

Nevertheless, it may be useful to perform imaging diagnosis before palatal implant insertion. Dental computed tomography (CT) and/or lateral cephalograms have been recommended for evaluating the vertical bone volume of the hard palate presurgically. Dental CT of the alveolar process is well established for the evaluation of the alveolar bone volume before implant placement (Lindh *et al.* 1995). It may also be used to assess the vertical bone volume of the hard palate and is currently the most accurate method for this.

A number of authors recommend the routine application of these procedures for preoperative diagnosis and planning of skeletal TADs, especially for palatal implants (Bernhart *et al.* 2000; Bantleon *et al.* 2002; Gahleitner *et al.* 2004; Kang *et al.* 2007; King *et al.* 2007; Wexler *et al.* 2007). However, this recommendation is largely based on theoretical considerations of potential complications, such as perforation of the nasal floor or damage to the incisory nerve (Jung *et al.* 2011b).

The greatest mean thickness of the vertical bone volume was identified on low-dose dental CT to be about 6–9 mm posterior to the incisal foramen in the mid-sagittal plane (Bernhart *et al.* 2000). Avoiding the

mid-palatal suture, the area suitable for implant placement is, therefore, located 6–9 mm posterior to the incisal foramen and 3–6 mm lateral to the mid-sagittal plane. If the necessary bone volume for an orthodontic implant installation is defined as 4 mm or more, 95% of the patients investigated in the study by Bernhart *et al.* (2000) had adequate vertical bone volume for accommodating palatal implants with a length of 4 mm, and this agreed with other clinical reports (Schiel *et al.* 1996). Insisting on obtaining precise information for the intended implant sites before placing palatal implants using lateral cephalograms rather than CT examination was proposed (Wehrbein *et al.* 1999a). Since the former are used for orthodontic diagnosis and treatment planning, this would spare patients from additional radiation exposure. Furthermore, superimposition of structures in CT scans renders this methodology complicated, imprecise, and hazardous for the presurgical assessment of bone volumes for orthodontic anchorage implants.

On wire-marked skulls, the highest bony demarcation of the palatal complex seen radiographically largely coincided with the nasal floor, rather than with the mid-sagittal nasal septum, which offers additional vertical bone height (Wehrbein *et al.* 1999a). Hence, it was suggested that the vertical bone heights in the anterior and middle thirds of the hard palate were at least 2 mm greater than identified on lateral cephalograms. A safety level of at least 2 mm is, therefore, recommended when planning treatment on the basis of lateral cephalograms (Wehrbein *et al.* 1999a). The vertical dimension on lateral cephalometry reflects the minimum quantity of bone, which is usually seen in the parasagittal plane, and not the maximum quantity of vertical bone in the median plane. Therefore, preoperative CT or cone-beam computed tomography (CBCT) is only indicated when lateral cephalometry reveals a marginal quantity of bone (Jung *et al.* 2011b, 2012b).

It must be realized that even though some implants may project beyond the nasal floor in lateral cephalograms, they may represent false-positive results rather than actual penetrations into the nasal cavity (Crismani *et al.* 2005c). If the palatal complex is perforated, intraoperative probing with a periodontal probe or a sinus probe must be performed for verification.

In addition to the palatal bony morphology, the anteroposterior location and inclination of the implant when placed mid-sagitally must also take into account both the pretreatment and planned final position of the maxillary central incisor (Figs. 59-13, 59-14).

A distinction has to be made between the vertical bone volume in the mid-sagittal and the paramedian regions as the indication for implant treatment in the mid-sagittal plane should be limited to adults and fully grown juveniles due to possible developmental disturbances of the palatal suture (Glatzmaier *et al.* 1995; Wehrbein *et al.* 1996).

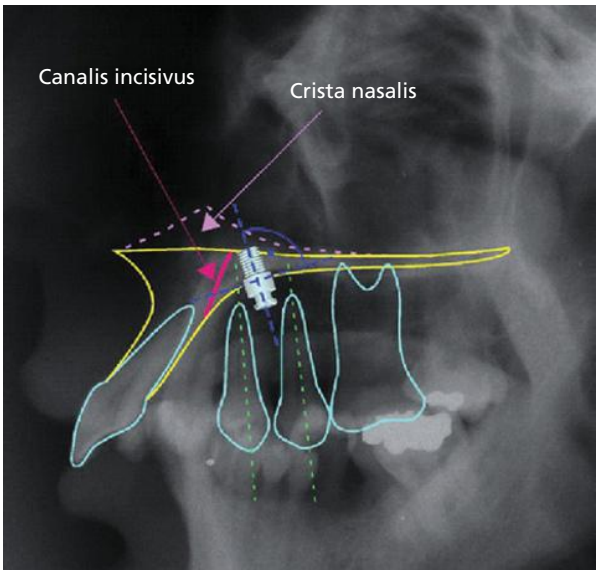


Fig. 59-13 Most palatal implants are installed satisfactorily when the location of entry into the cortical bone is at the anteroposterior level of the maxillary first and second premolars, perpendicular to the palatal surface (Source: Männchen & Schätzle 2008. Reproduced with permission from John Wiley & Sons.)

Palatal implants and their possible effects in growing patients

During growth, maxillary expansion in the transverse direction is the result of two processes: appositional remodeling of the alveolar process and growth of the palatal suture (Björk & Skieller 1974). While the remodeling process leads to the expansion of the dental arches, the growth in the median suture leads to the expansion of the palate and this is the most important factor in the development of the maxillary width. An average growth in maxillary width of 3 mm between the ages 10 and 18 years was demonstrated (Björk & Skieller 1977). Since the median or paramedian anterior palate may be chosen as the insertion site for palatal implants, the question arises whether or not the implantation of an orthodontic anchorage device may affect normal transversal palatal growth. Palatal implants affected normal transverse growth in an animal study (Asscherickx *et al.* 2005). It could be shown that implant placement resulted in less transversal sutural growth.

Deficient transverse maxillary width may also cause maxillary arch length discrepancies, as demonstrated for canine impaction (McConnell *et al.* 1996). Therefore, all interventions that might cause a restriction in normal transverse maxillary growth should be avoided. Because it has been shown that the insertion of implants in the median palatal suture in adolescent Beagle dogs could cause restriction in normal transverse development of the palate (McConnell *et al.* 1996), orthodontic palatal implants are better installed in paramedian areas in growing individuals. Moreover, studies have suggested that the installation of orthodontic implants in the mid-palatal suture of growing patients is contraindicated because of the

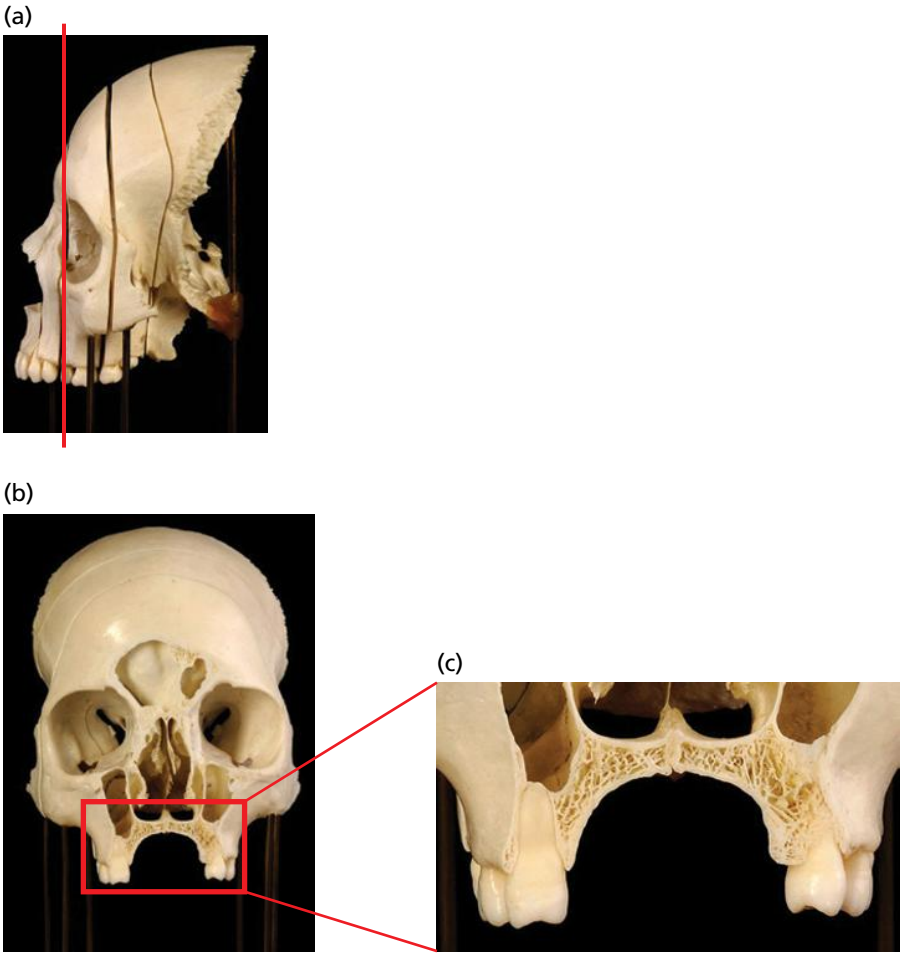
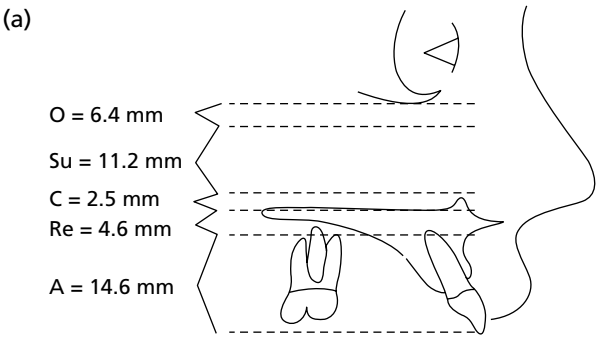


Fig. 59-14 (a–c) Macerated skull illustrating the location of the palatal implant insertion site at the anteroposterior level of the maxillary first and second premolars.

questionable quality of bone to provide adequate primary stability (Bernhart *et al.* 2001; Lioubavina-Hack *et al.* 2006). However, this could not be confirmed in a human histologic study (Wehrbein 2008). The paramedian region of the anterior palate, in contrast, is largely stable from a growth point of view (Thilander 1995).

The most important vertical growth changes are the result of the displacement of the maxillary complex and surface remodeling processes. The sutural lowering of the maxillary complex as well as the apposition at the orbital floor and at the infrazygomatic crest will not be affected by implant installation in the palate. The resorptive lowering of the nasal floor, however, and the increase of the maxillary alveolar bone height might be influenced. The mean degree of growth from the age of 4 years to adulthood has been identified (Björk & Skieller 1977). The nasal floor appears to drift 4.6 mm caudally, and the height of the maxillary alveolar bone appears to increase by 14.6 mm. Assuming that about one-third of these growth changes take place between the age of 12 years and adulthood implies a residual vertical growth of about 1.5 mm in the palate and of about 5 mm in the maxillary alveolar bone height (Fig. 59-15).



(b) Vertical growth 4 years – adult

O	Apposition, floor of orbit
Su	Sutural lowering of maxilla
C	Apposition at the infrazygomatic crest
Re	Amount of resorptive lowering of the nasal floor
A	Apposition, increasing height of the alveolar process

Fig. 59-15 Vertical growth-related changes encountered from age 4 years to adulthood. (Source: Björk & Skieller 1977. Reproduced with permission from Maney Publishing.)

Osseointegrated implants are in direct contact with bone, do not possess a periodontal ligament, and, hence, behave like anklyosed teeth. Therefore, an osseointegrated palatal implant will remain 1.5 mm behind its surrounding bone, whereas an implant placed in the alveolar bone will produce an infra-occlusion of 5 mm during the same period. Consequently, palatal implants directly or indirectly attached to teeth lead to an infra-eruption of a single tooth, several teeth or the whole upper dentition. By influencing the maxillary vertical growth dimension, the horizontal displacement of the mandible will also be affected and will, therefore, have a closing effect on the mandibular plane angle (anterior mandible rotation). It must be considered, however, that palatal implants as TAD usually remain *in situ* for 1–2 years. Thus, potential vertical and transversal growth impairments are likely to be limited to values of <1 mm.

Clinical procedures and loading time schedule for palatal implant installation

Patient stress during implantation and/or explantation and subsequent wound healing may be minimized by applying a minimally traumatic surgical

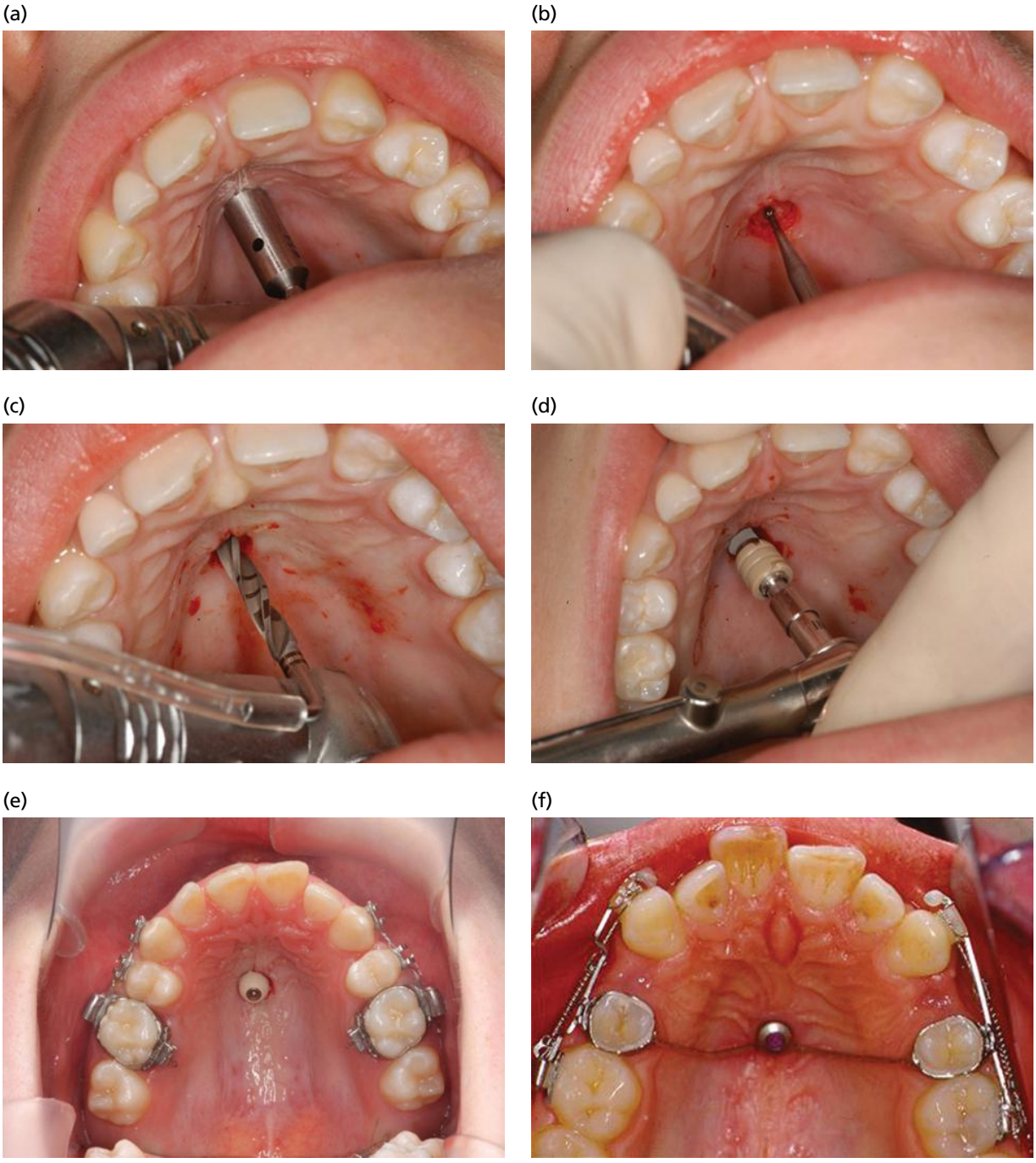


Fig. 59-16 Clinical procedures to install a palatal Orthosystem® (Institut Straumann, Waldenburg, Switzerland). (a) Perforation of the palatal mucosa using a system-compatible punch or trephine. (b) Marking the center of the intended implant site with a round bur. (c) Preparation of the implant bed at the location determined presurgically and perpendicular to the bone surface. (d) Tightening of the orthodontic implant using a ratchet. (e) Covering the device with a healing cap. (f) Affixation of the transpalatal arch for indirect loading (Source: Wehrbein *et al*. 1998) and (*Continued*)

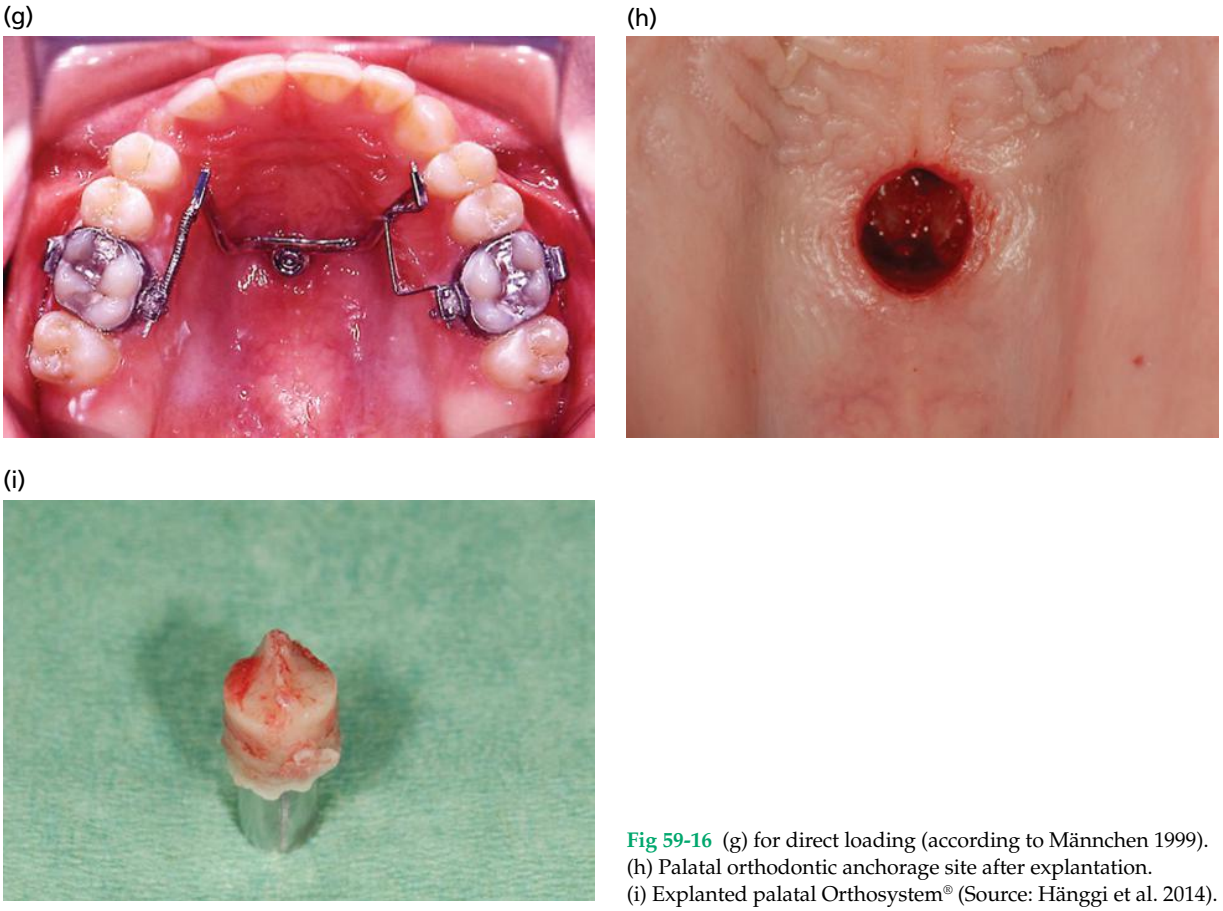


Fig 59-16 (g) for direct loading (according to Männchen 1999). (h) Palatal orthodontic anchorage site after explantation. (i) Explanted palatal Orthosystem® (Source: Hänggi et al. 2014).

technique. Under palatal local anesthesia, the palatal mucosa is perforated to the cortical bone using a mucosal punch or a system-compatible trephine during explantation, and removed with an elevator or a curette (Fig. 59-16a). After smoothing the exposed bone surface to prevent the profile drill from slipping, the center of the implant site is marked with a round bur (Fig. 59-16b). The implant bed is then prepared to the required depth using a series of pilot and twist drills (Fig. 59-16c). The drilling axis perpendicular to the bone surface is defined based on the presurgical cephalometric analysis. While preparing the insertion site, intermediate drilling and cooling of the drilling channel continuously with precooled physiologic saline or Ringer's solution should be performed. The implant is then hand-installed as far as possible, and a ratchet is used to tighten the implant to its final position (Fig. 59-16d). In a randomized clinical study of the pain intensity and discomfort in 120 patients following palatal implant placement and premolar extraction, it was shown that pain intensity after surgical installation of an Orthosystem® implant was significantly less than after installation of an Onplant® or premolar extraction (Feldmann *et al.* 2007). The implant is covered with the healing cap to prevent the inner screw well of the implant from clogging up and from being covered by hyperplastic mucosal tissue (Fig. 59-16e). After insertion, the palatal Orthosystem® implant is allowed to heal *in situ* for 12 weeks during which time it should not be loaded.

In some cases, there may be a premature loss of the implant prior to orthodontic load. This loss may be caused by the lack of adequate primary stability. Such insufficient primary stability causes an inappropriate healing and the possible premature loss of the implant (Friberg *et al.* 1991; Lioubavina-Hack *et al.* 2006). Therefore, it is generally recommended to use the 4.1-mm diameter palatal Orthosystem® implant. The 4.8-mm diameter device should only be used if the prerequisite of primary stability cannot be achieved with the smaller (regular 4.1 mm)-diameter implant.

Following the placement of an endosseous implant, primary mechanical stability is gradually replaced by biologic bonding. The transition from primary mechanical stability, provided by the implant design, to biologic stability provided by the osseointegration process occurs during the first month of wound healing (Berglundh *et al.* 2003; Schätzle *et al.* 2009a). In an experimental human study on the transition from primary to secondary stability by means of resonance frequency analysis, it could be shown that this transition from bone resorption to apposition corresponding to an increasing stability was evident 35 days (5 weeks) after implant installation and it took almost 84 days (12 weeks) to reach the initially measured values of the implant stability quotient (Crismani *et al.* 2006; Schätzle *et al.* 2009a). During this critical time, the orthodontic implant should not be used as anchorage.

The installation of implants as absolute anchorage devices facilitates and accelerates orthodontic

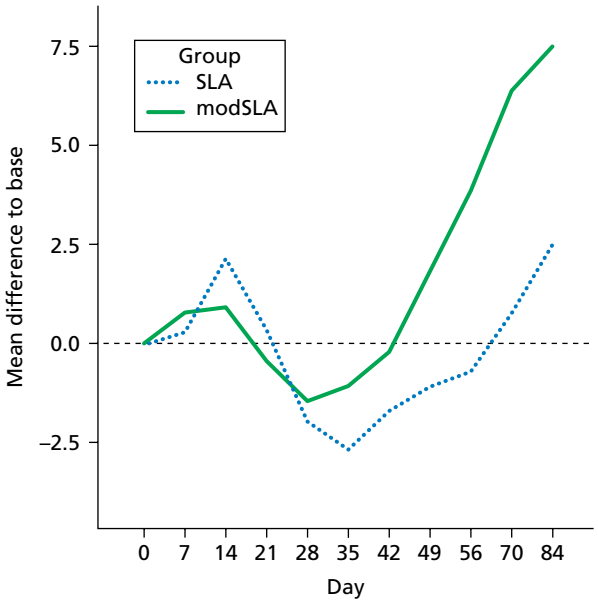


Fig. 59-17 Mean implant stability quotient (ISQ) changes in SLA and modSLA palatal implants from the baseline. (modSLA, modified sandblasted/acid-etched.) (Source: Schätzle *et al.* 2009a. Reproduced with permission from John Wiley & Sons.)

therapy (Trisi & Rebaudi 2002), even though there is still an inactive waiting time of at least 3 months after insertion (12 week healing time) (Wehrbein *et al.* 1996a, 1998; Keles *et al.* 2003; Crismani *et al.* 2005a, b). Especially in adult patients, there is a growing need to reduce this inactive waiting time and to reduce the risk for implant failure during early loading. There are several studies that have reported a successful outcome of early/immediate-loaded conventional dental implants placed in the edentulous ridge (Calandriello *et al.* 2003; Rocci *et al.* 2003; Bischof *et al.* 2004; Gallucci *et al.* 2004; Glauser *et al.* 2004; Jaffin *et al.* 2004). However, there are only two studies evaluating early loaded palatal orthodontic implants in humans by means of resonance frequency analysis (RFA). A retrospective clinical study of immediate versus conventional loading of palatal implants in humans reported a higher failure rate and a lower bone-to-implant contact rate for immediate indirect loading of palatal implants (Göllner *et al.* 2009b). On this basis, the possibility of loading palatal orthodontic implants earlier than recommended in the aforementioned literature was suggested with caution (Crismani *et al.* 2006; Schätzle *et al.* 2009a) (Fig. 59-17). A prospective multicenter study presented encouraging results: immediate indirect loading of palatal implants yielded success rates equivalent to those for conventional loading to 4 N after 6 months (Jung *et al.* 20011c). In a bicenter study, however, the vast majority of the implant failures occurred in the first and the second month post insertion (Jung *et al.* 2012a).

There is still a lack of histologic documentation about adequate healing periods before loading orthodontic implants in the palatal region. Further studies are needed to document the sequential histologic changes in the transition from primary stability to the process of osseointegration, and to define possible shorter appropriate healing periods.

After the recommended inactive healing period, an impression is taken for the construction of the transpalatal arch (TPA) connection (Fig. 59-16f, g). After integration of the TPA, the implant-related orthodontic treatment is begun. Depending on the treatment goal, schedule, and TPA design, different palatal arches may be necessary during the course of treatment in the same patient.

Direct or indirect orthodontic implant anchorage

Reliable three-dimensional attachment of orthodontic wires to the orthodontic implant is of crucial importance. There are two principles in using implants for orthodontic anchorage:

- Orthodontic forces are applied at anchorage teeth that are not to be moved and are to be kept in position through a rigid connection (e.g. TPA, lingual arch) with the implant (*indirect anchorage*) (Wehrbein *et al.* 1996). The element connected directly to teeth may limit the tooth movements and require adaptation or refabrication of the TPA by a dental technician (Fig. 59-16f).
- If force systems act directly between the teeth to be moved and the implant (*direct anchorage*), then the TPA may be adapted more easily by adjusting the active sectional wires (Männchen 1999). It must be considered, however, that the implant should be placed paramedian on the same side in order to keep the torque moments as low as possible, should a direct unilateral sagittal force is applied to the implant (Fig.59-16 g).

The three-dimensional attachment of the orthodontic wire to the implant may be guaranteed by using a clamping cap, a welding or soldering cap, or a post cap with a pre-lased wire.

Besides offering reliable fixation to the implant abutment, the connecting element must be sufficiently rigid to prevent deflection. A mean loss of anchorage of approximately 1 mm from retracting or torqueing of incisors to the buccal segment has been reported (Wehrbein *et al.* 1999). This was probably due to deformation of the TPA and/or a slight rotational play of the supraconstruction. Although this anchorage loss might be clinically irrelevant, the preactivation of the connecting element in the opposite direction may help to avoid this side effect.

It is clear that implant-supported teeth receive continuous loading stimulation. Unfavorable jiggling forces on anchor teeth, as found in compliance-dependent anchorage aids, might be reduced or

avoided. This may play a more decisive role in cases with reduced periodontal anchorage.

Stability and success rates

Despite the small dimensions, orthodontic implant anchoring devices must maintain positional stability under orthodontic loading in order to serve as absolute anchorage. As connective tissue encapsulation would initiate implant dislocation, osseointegration is a prerequisite. Histologic examination of explanted human orthodontic implant bone specimens inserted palatally revealed that osseointegration is maintained during long-term orthodontic loading under clinical conditions (see Figs. 59-2, 59-3). The percentage of implant-to-bone contact in patients varied between 34% and 93%, with an average of 75% (Wehrbein *et al.* 1998; Jung *et al.* 2011a), which is obviously an adequate anchorage to withstand orthodontic loading.

There are only two retrospective cohort studies reporting the success rate of 70 (Männchen & Schätzle 2008) and 239 (Jung *et al.* 2012a) palatal Orthosystem® implants. Of these, approximately 5% did not successfully osseointegrate and were lost during the healing phase, which might be attributed to either parafunctional activity of the tongue or artificial direct trauma due to a toothbrush (Asscherickx *et al.* 2010). The surgeon's experience also markedly influenced the success of palatal implants (Arcuri *et al.* 2007; Sandler *et al.* 2008; Jung et al. 2012a).

Due to the fact that only a very small percentage of loaded palatal implants were lost under orthodontic loading – 1.5% (Männchen & Schätzle) and 0.8% (Jung *et al.* 2012a) – no factors related to the design of the device, the concept of anchorage, loading forces or the direction of loading could be identified. In other words, palatal implants are largely robust against the variability in the type of appliance, the type of anchorage, and the dimension of loading forces or directions. This also holds true for demographic parameters as no association of implant survival with age or gender could be found (Jung *et al.* 2012a). The success rates for palatal implants after orthodontic loading are comparable to those reported for conventional oral implants (Berglundh *et al.* 2002; Pjetursson *et al.* 2007). On the basis of a systematic review, it was concluded that for the maxillary arch, palatal implants are a clearly superior treatment option compared with all other skeletal anchorage devices. Palatal implants offer safe and effective anchorage possibilities with a high survival rate (>90%) and few side effects or problems during treatment (Schätzle *et al.* 2009b).

Implant removal

No reports exist on "sleeping orthodontic palatal implants". As a consequence, they have to be removed after completion of the orthodontic

Fig. 59-18 Traditional removal set of a standard trephine of 5.5 mm in diameter and a mounted implant cylinder for guidance. (Source: Hänggi *et al.* 2014.)

Fig. 59-19 Customized implant key with an almost triangular-shaped internal notch (left) that precisely grasps the implant head as it is tightened with an occlusal screw (right). (Source: Hänggi *et al.* 2014.)

treatment. By means of a system-compatible trephine, the peri-implant bone is separated from the device. Then, the implant may be explanted together with the surrounding bone by slow rotations with an extraction forceps (Fig. 59-18). The implant is then retrieved (see Fig. 59-16 h, i). Full recovery at the original anchorage site may be observed 3–4 weeks after implant removal.

As a variation, the implant–bone contact may be broken by turning a customized implant key counterclockwise with an almost triangular-shaped internal notch securely grasping the implant head as it is tightened with an occlusal screw (Fig. 59-19) using the ratchet used for seating the implant. The explanted palatal implant may have no bone appending to it,

except in its apical antirotational grooves (Fig. 59-20) (Hänggi *et al*. 2014). Palatal implant removal without a drilling trephine might be beneficial. Furthermore, by reducing the amount of bone retrieved on implant removal, the range of surgical complications and adverse patient reactions might be reduced. Clinical studies, however, are necessary to document the superiority of this new non-invasive palatal implant removal procedure compared to removal with a trephine (Hänggi *et al*. 2014).

Fig. 59-20 Explanted palatal implant with no bone appending to it, except in its apical antirotational grooves. (Source: Hänggi *et al*. 2014.)

In a retrospective study (Fäh & Schätzle 2014), a wide spectrum of surgical complications and adverse patient reactions after palatal implant installation and removal was found. In all but one implantation, these were of a transitional nature and of minor severity. Prolonged hypoesthesia of the anterior palate occurred in one patient after implantation. Nasal floor perforation seems to be rather crucial during explantation and may need to be closed surgically to prevent a persistent oronasal fistula. Although the risk of permanent sensory impairment of the anterior palatal region or damage to the nerve–vessel thread is small, the patient must be well informed of this risk.

Advantages and disadvantages

Even though the orthodontic treatment may be completed faster and with more predictability with implants, patients have to undergo two minor surgical procedures. Additionally, an inactive waiting time after implant installation is still required. The extra cost for placing a palatal orthodontic implant must be balanced against other treatment options. Besides consideration of cooperation and esthetic aspects, the costs of orthognathic surgery and/or prosthetic reconstruction may be avoided or reduced by installation of an implant for orthodontic anchorage. In cases in which the palatal implant is directly loaded, bonding of the whole jaw or the entire dentition may not be necessary (Fig. 59-21). The main risks encountered with the use of orthodontic implant anchorage are the development of peri-implant infection, oroantral connection and/or implant loss prior to completion of orthodontic treatment.

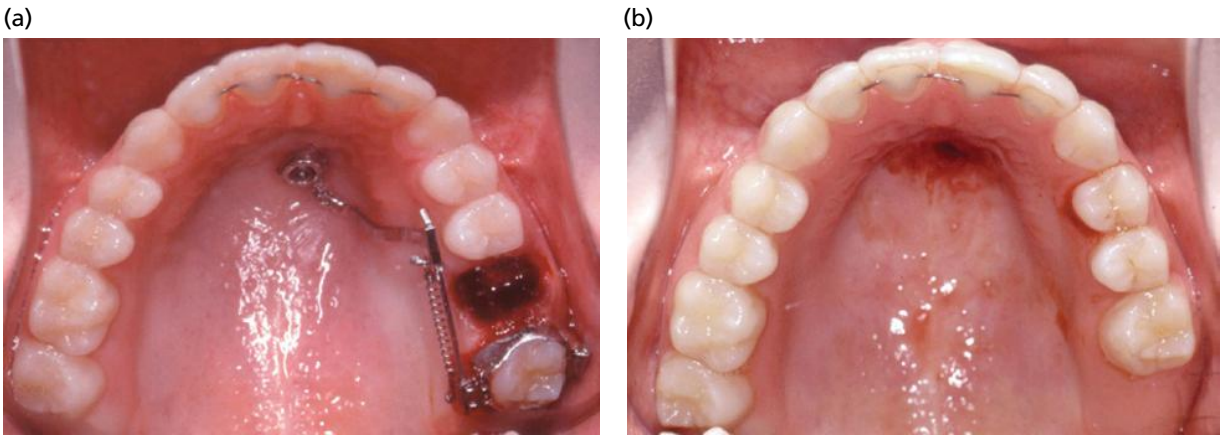


Fig. 59-21 Absolute anchorage by means of a palatal orthodontic implant avoiding the need for bonding the entire maxillary dentition with fixed orthodontic appliances. (a) After the extraction of tooth 26, protraction of tooth 27 was initiated by direct implant loading. (b) At implant and orthodontic appliance removal, the gap between teeth 25 and 27 has been completely closed, thereby avoiding the placement of a fixed partial denture. (Courtesy of R. Männchen, Winterthur.)

Conclusion

Osseointegrated implants provide absolute orthodontic anchorage under low-to-moderate orthodontic loading and, hence, are considered to be superior to any orthodontic tooth-borne anchorage device (Schätzle *et al*. 2009b). Indications for orthodontic implant anchorage include: inadequate periodontal anchorage, non-compliant patients for extra- and/or intra-oral anchorage aids, prevention of potential side effects of conventional anchorage devices, esthetic aspects or avoidance of orthognathic surgery after growth completion. Moreover, prosthetic reconstruction may be avoided. The simplicity of their use, minimal stress during surgical implant installation (Feldmann *et al*. 2007) and removal (Fäh & Schätzle 2014), as well as the reliable success rates are prerequisites for the high acceptance of this treatment by orthodontic patients. It must be kept in mind, however, that treatment objectives may be achieved with several treatment plans. Proper orthodontic anchorage should be chosen according to the preceding diagnosis and to fit the appropriate treatment plan.

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Part 18: Supportive Care

Chapter 60

Supportive Periodontal Therapy

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Clinical trials on the long-term effects of the treatment of periodontitis have clearly demonstrated that post-therapeutic professional maintenance care is an integral part of this treatment. This also constitutes the only means of assuring the maintenance of long-term beneficial therapeutic effects. Re-infection could be prevented or kept to a minimum in most patients, mainly through rigid surveillance involving visits to professionals at regular intervals. However, the maintenance systems presented in the various studies do not give a clear concept with general validity for the frequency of maintenance visits to professionals and the mode of maintenance therapy. In some patients there may be a danger that re-infection and recurrent disease are neglected, while in others there may be a tendency to over treat.

Objective criteria for assessing the patient's individual risk for recurrent disease have been the focus of attention in recent years. However, this evaluation still has to be based on a probability estimate derived from the assessment of the patient, tooth or tooth-site risk.

The purpose of this chapter is to discuss the basics of continuous patient monitoring following active periodontal therapy in order to prevent re-infection and progression of periodontal disease following therapy. The mode and extent of interceptive therapeutic measures needed to achieve this goal will also be evaluated.

Definition

Periodontal treatment includes:

1. Systemic evaluation of the patient's health
2. Cause-related therapeutic phase with, in some cases
3. Corrective phase involving periodontal surgical procedures
4. Maintenance phase.

The 3rd World Workshop of the American Academy of Periodontology (1989) renamed this treatment phase "supportive periodontal therapy" (SPT). This term expresses the essential need for therapeutic measures to support the patient's own efforts to control periodontal infections and to avoid re-infection. Regular visits to the therapist should serve as a positive

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feedback mechanism between the patient and the therapist with the purpose of ensuring that patients can maintain their dentitions in a healthy status for the longest possible time. An integral part of SPT is the continuous diagnostic monitoring of the patient in order to intercept with adequate therapy and to optimize the therapeutic interventions tailored to the patient's needs.

Basic paradigms for the prevention of periodontal disease

Periodontal maintenance care, or SPT, follows the paradigms of the etiology and pathogenesis of periodontal disease and must consider the fact that these diseases represent opportunistic infections.

Almost 50 years ago, a cause–effect relationship between the accumulation of bacterial plaque on teeth and the development of gingivitis was proven (Löe *et al*. 1965). This relationship was also documented by the restoration of gingival health following plaque removal. Ten years later, this relationship was further characterized when loss of connective tissue attachment and resorption of alveolar bone with plaque accumulation and the development of periodontal disease was shown in laboratory animals (Lindhe *et al*. 1975). Since some of these animals did not develop periodontal disease despite a persistent plaque accumulation for 48 months, it must be considered that the composition of the microbiota or the host's defense mechanisms or susceptibility to disease may vary from individual to individual. Nevertheless, in the study mentioned, the initiation of periodontal disease was always preceded by obvious signs of gingivitis. Hence, it seems reasonable to predict that the elimination of gingival inflammation and the maintenance of healthy gingival tissues will prevent both the initiation and the recurrence of periodontal disease. In fact, as early as 1746, Fauchard stated that "little or no care as to the cleaning of teeth is ordinarily the cause of all diseases that destroy them".

From the clinical point of view, the above-mentioned results must be translated into the necessity for proper and regular personal plaque elimination, at least in patients treated for or susceptible to periodontal disease. This simple principle may be difficult to implement in all patients; however, interceptive professional supportive therapy at regular intervals may, to a certain extent, compensate for the lack of personal compliance with regard to oral hygiene standards.

These aspects have been imitated in a Beagle dog model with naturally occurring periodontal disease (Morrison *et al*. 1979). Two groups of animals were used. The test group was subjected to initial scaling and root planing and, subsequently, plaque was eliminated by daily toothbrushing and biweekly polishing with rubber cups for a period of 3 years. In the control group, no initial scaling and no oral hygiene practices were performed during the same period of time. Every 6 months, however, the teeth in two diagonally opposed jaw quadrants in both test and control animals were scaled and root planed. The results showed that the reduction of probing pocket depth (PPD) and the gain of probing attachment obtained after the initial scaling and root planing in the test animals, were maintained throughout the entire course of the study irrespective of whether or not repeated scaling and root planing had been performed. The control animals, on the other hand, continued to show increasing PPD and loss of attachment in all quadrants irrespective of whether or not repeated scaling and root planing had been performed. However, in the jaw quadrants where the teeth were repeatedly instrumented every 6 months, the progression of periodontal destruction was significantly less pronounced (Fig. 60-1). These results indicate that professional supportive therapy, performed at regular intervals, may, to a certain extent, compensate for a "suboptimal" personal oral hygiene standard. In this respect, it has been demonstrated that following root instrumentation, the subgingival microbiota is significantly altered in quantity and quality (Listgarten *et al*. 1978), and that the re-establishment of a disease-associated, subgingival microbiota may take several months (Listgarten *et al*. 1978; Slots *et al*. 1979; Mousquès *et al*. 1980; Caton *et al*. 1982; Magnusson *et al*. 1984).

In a number of longitudinal clinical studies on the outcome of periodontal therapy, the crucial role of SPT in maintaining successful results has been documented (Ramfjord *et al*. 1968; Lindhe & Nyman 1975; Ramfjord *et al*. 1975; Rosling *et al*. 1976; Nyman *et al*. 1977; Knowles *et al*. 1979, 1980; Badersten *et al*. 1981, Hill *et al*. 1981; Lindhe *et al*. 1982a, b; Pihlström *et al*. 1983; Westfelt *et al*. 1983a; Lindhe & Nyman 1984; Westfelt *et al*. 1985; Isidor & Karring 1986; Badersten *et al*. 1987; Kaldahl *et al*. 1988). In all these studies, PPD and clinical attachment level were maintained as a result of a well-organized professional maintenance care program (recall intervals varying between 3 and 6 months), irrespective of the initial treatment modality performed.

In one of the studies (Nyman *et al*. 1977), an alarming result was that patients treated for advanced periodontal disease involving surgical techniques, but not enrolled in a supervised maintenance care program, exhibited recurrent periodontitis, including loss of attachment, at a rate three to five times higher than documented for natural progression of periodontal disease in population groups with high disease susceptibility (Löe *et al*. 1978, 1986). Within this area, the effect of negligence in providing adequate supportive maintenance care following periodontal treatment was studied over a 6-year period by Axelsson and Lindhe (1981a). Following presurgical root instrumentation and instruction in oral hygiene practices, all study patients were subjected to modified Widman flap procedures. During a 2-month healing period, professional tooth cleaning was performed

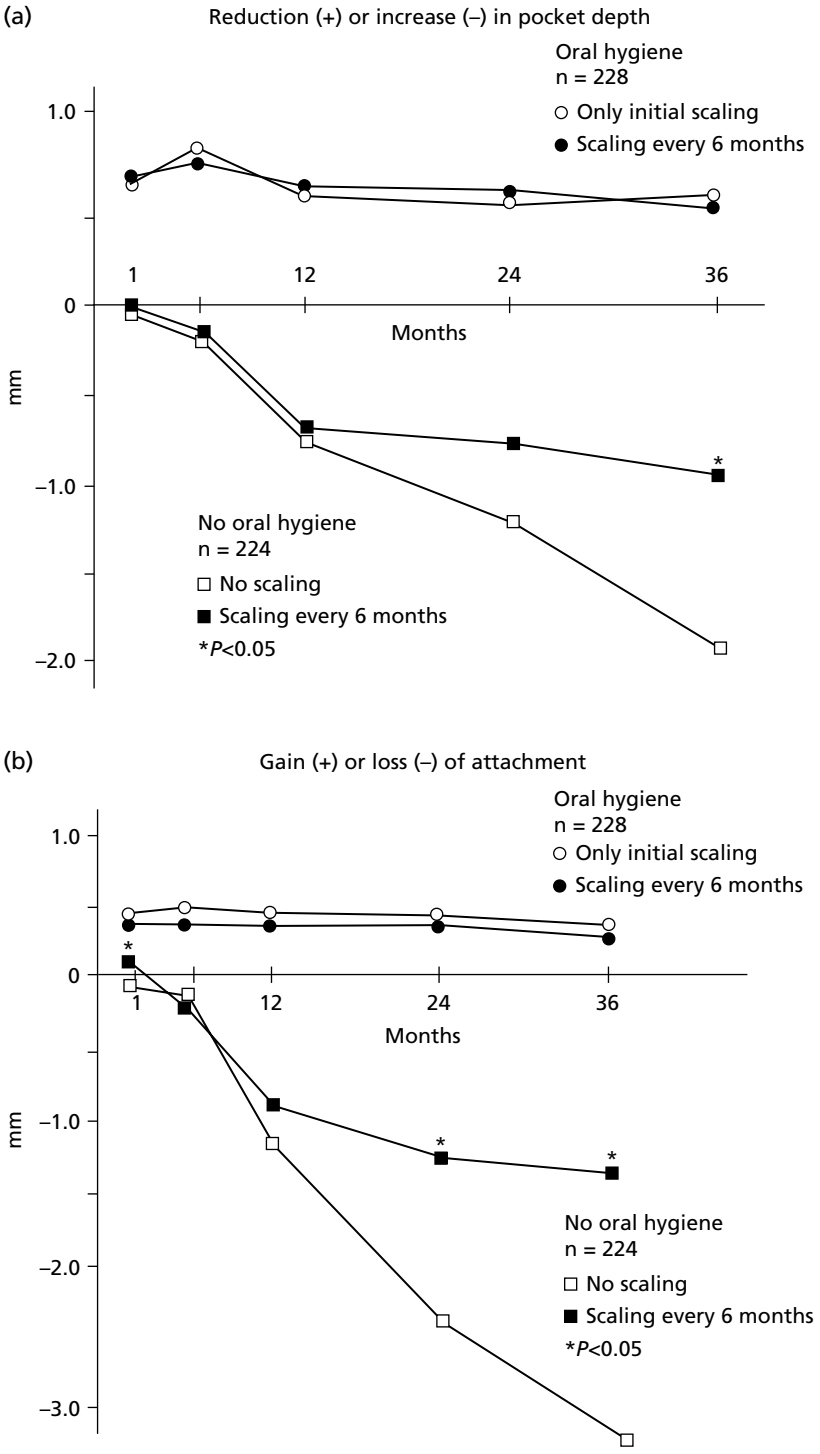

Fig. 60-1 (a) Mean probing depth reduction (+) or increase in probing depth (–) in millimeters with or without repeated scaling and root planing in experimental (oral hygiene) and control (no oral hygiene) animals relative to baseline means. (b) Mean gain (+) or loss (–) of probing attachment with or without repeated scaling and root planing in experimental (oral hygiene) and control (no oral hygiene) animals relative to baseline means. (Data from Morrison *et al*. 1979.)

every 2 weeks. Following this time period, baseline clinical data were obtained and one in every three patients was dismissed from the clinic, while the other two were enrolled in a professionally conducted maintenance program with a recall once every 3 months. These patients maintained excellent oral hygiene and consequently yielded a very low frequency of bleeding sites. In addition, PPD and probing attachment levels were maintained unchanged over the 6-year period. In contrast, the non-recalled patients demonstrated obvious signs of recurrent periodontitis at the 3-year and 6-year re-examinations. Further evidence for the likelihood of recurrent disease in patients not subjected to professional maintenance care was presented by Kerr (1981). Five years after successful treatment, 45% of the patients presented with periodontal conditions similar to their status before treatment. Supportive therapy had only been provided at intervals varying between 9 and 18 months.

Even though the number of well-controlled longitudinal clinical trials is rather limited for patients who, in addition to periodontal treatment, have undergone extensive reconstructive therapy, it should be realized that the concept of professional maintenance care has unrestricted validity. In a longitudinal study of

combined periodontal and prosthetic treatment of patients with advanced periodontal disease, periodontal health could be maintained over a study period of 5–8 years with regular recall appointments scheduled every 3–6 months (Nyman & Lindhe 1979). Similar results have been presented by Valderhaug and Birkeland (1976) and by Valderhaug (1980) for periods of up to 15 years. Another study of 36 patients who received extensive poly-unit cantilevered bridgework following periodontal therapy, confirmed the maintenance of periodontal health over 5–12 years (Laurell *et al*. 1991). More recent studies on the long-term maintenance of periodontal patients who, following successful treatment of chronic periodontitis, were reconstructed with extensive fixed reconstructions, revealed that regularly performed SPT resulted in periodontal stability. Only 1.3% (Hämmerle *et al*. 2000) and 2.0% (Moser *et al*. 2002) of the abutments showed some minor attachment loss during these long periods of observation (10 and 11 years, respectively). In contrast, a report of insurance cases who were not regularly maintained by SPT yielded a recurrence rate for periodontitis of almost 10% after an observation of 6.5 years (Randow *et al*. 1986).

Summary: The etiology of gingivitis and periodontitis is fairly well understood. However, the causative factors, that is the microbial challenge which induces and maintains the inflammatory response, may not be completely eliminated from the dentogingival environment for any length of time. This requires the professional removal of all microbial deposits in the supragingival and subgingival areas at regular intervals, since recolonization will occur following the debridement procedures, leading to a re-infection of the ecologic niche and, hence, further progression of the disease process. Numerous well-controlled clinical trials, however, have documented that such a development can be prevented over very long periods of time only by regular interference with the subgingival environment aimed at removal of the subgingival bacteria.

Patients at risk for periodontitis without supportive periodontal therapy

The effect of omission of SPT in patients with periodontitis may best be studied either in untreated populations or patient groups with poor compliance.

One of the few studies documenting untreated periodontitis-susceptible patients reported on the continuous loss of periodontal attachment as well as teeth in Sri Lankan tea plantation workers receiving no dental therapy (Löe *et al*. 1986). In this – for the Western world – rather unique model situation, an average loss of 0.3 mm per tooth surface and per year was encountered. Also, the laborers lost between 0.1 and 0.3 teeth per year as a result of periodontitis. In another untreated group in the US, 0.61 teeth were lost per year during an observation period of 4 years (Becker *et al*. 1979). This is in dramatic contrast to reports on tooth loss in well-maintained patients treated for periodontitis (e.g. Hirschfeld & Wasserman 1978; McFall 1982; Becker *et al*. 1984; Wilson *et al*. 1987). Such patients were either completely stable and lost no teeth during maintenance periods ranging up to 22 years, or lost only very little periodontal attachment and only 0.03 teeth (Hirschfeld & Wasserman 1978) or 0.06 teeth (Wilson *et al*. 1987).

Non-complying, but periodontitis-susceptible, patients receiving no SPT following periodontal surgical interventions continued to lose periodontal attachment at a rate of approximately 1 mm per year regardless of the type of surgery chosen (Nyman *et al*. 1977). This is almost three times greater than would be expected as a result of the "natural" course of periodontal disease progression (Löe *et al*. 1978, 1986).

In a British study of a private practice situation (Kerr 1981) where the patients were referred back to the general dentist after periodontal therapy, 45% of the patients showed complete re-infection after 5 years.

Similar results have been described for private practice patients who decided not to participate in an organized maintenance care program following active periodontal therapy (Becker *et al*. 1984). Subsequent examinations revealed clear signs of recurrent periodontal disease, including increased PPD and involvement of furcations of multirooted teeth concomitant with tooth loss. Also, loss of alveolar bone observed on radiographs and tooth loss have been reported for a group of patients in whom post-therapeutic supportive maintenance care was provided less frequently than once every 12 months (De Vore *et al*. 1986).

From all these studies, it is evident that periodontal treatment is ineffective in maintaining periodontal health if supportive maintenance care is neglected, denied or omitted.

The most impressive documentation of the lack of SPT in disease-susceptible individuals is probably that from a clinical trial in which one-third of the patients had been sent back to the referring general practitioner for maintenance, while two-thirds of the patients received SPT in a well-organized maintenance system (Axelsson & Lindhe 1981a). The 77 patients were examined before treatment, 2 months after the last surgical procedure, and 3 and 6 years later. The 52 patients on the carefully designed SPT system visited the program every 2 months for the first 2 years and every 3 months for the remaining 4 years of the observation period. The results obtained from the second examination (2 months after the last surgery) showed that the effect of the initial treatment was good in both groups. Subsequently, the recall patients were able to maintain proper oral hygiene and unaltered attachment levels. In the non-recall group, plaque scores increased markedly from the baseline values, as did the number of inflamed gingival units (Fig. 60-2a). Concomitantly, there were obvious signs of recurrent periodontitis. The mean

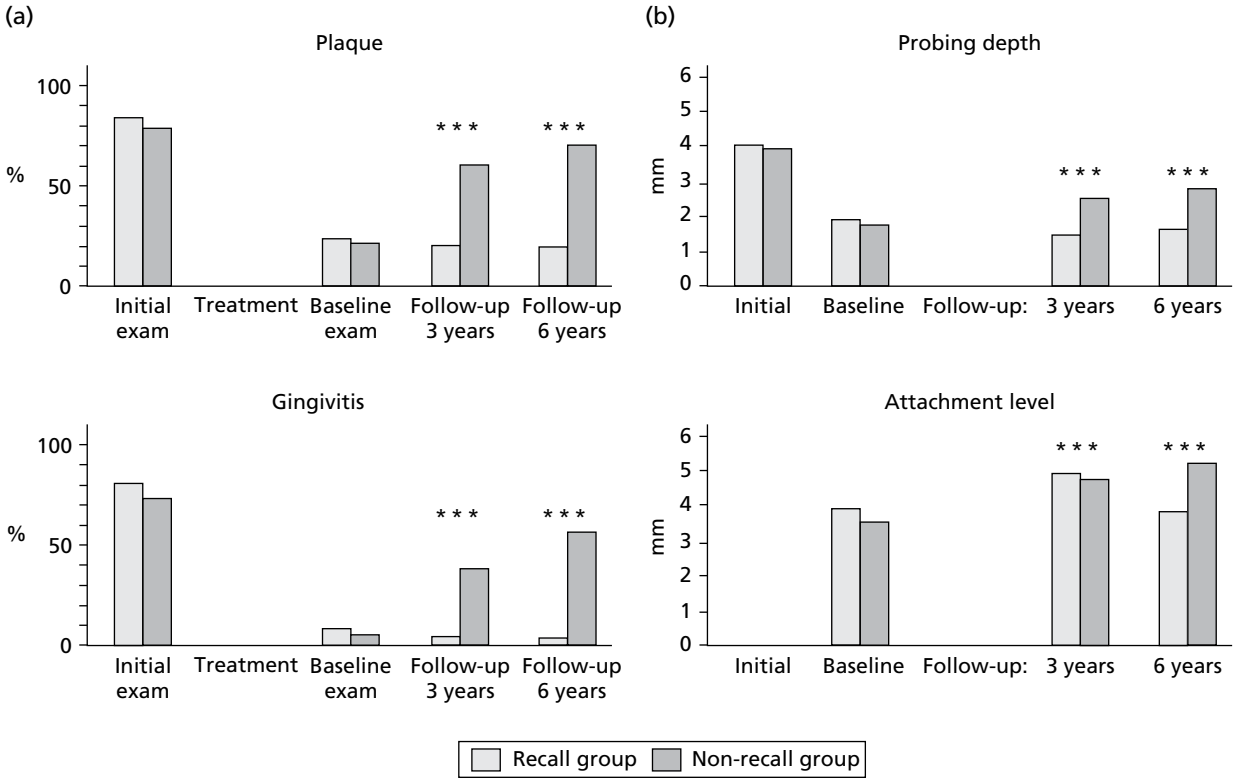

Fig. 60-2 Histograms showing (a) average percentages of tooth surfaces harboring visible plaque (above) and inflamed gingival units (bleeding on probing) (below), and (b) average probing depth (above) and probing attachment levels (below), at initial, baseline, and follow-up examinations. (Data from Axelsson & Lindhe 1981b.)

Table 60-1 Percentage of sites showing various changes in probing attachment level between baseline examination, 2 months after completion of active periodontal therapy, and at follow-up examination 6 years later.

Change in attachment level	Percentage of surfaces showing change	
	Recall	Non-recall
Attachment level improved	17	1
No change	72	10
Attachment level worse by:		
≥1 mm	10	34
2–5 mm	1	55

Adapted from Axelsson & Lindhe (1981b), with permission from John Wiley & Sons.

values for pocket depth and attachment levels at the 3-year and 6-year examinations were higher than at baseline (Fig. 60-2b). In the recall group, approximately 99% of the tooth surfaces showed either improvement, no change or <1 mm loss of attachment, compared to 45% in the non-recall group (Table 60-1). In the latter patients, 55% of the sites showed a further loss of attachment of 2–5 mm at the 6-year examination, and 20% of the pockets were 4 mm deep or more (Tables 60-1, 60-2).

Summary: Patients susceptible to periodontal disease are at high risk for re-infection and progression of periodontal lesions without meticulously organized and performed SPT. Since all patients who are treated for periodontal diseases belong to this risk category by virtue of their past history, an adequate maintenance care program is of utmost importance for a beneficial long-term treatment outcome. SPT has to be aimed at the regular removal of the subgingival microbiota and must be supplemented by the patient's efforts for optimal supragingival plaque control.

Supportive periodontal therapy for patients with gingivitis

Several studies, predominantly in children, have documented that periodic professional prophylactic visits in conjunction with reinforcement of personal oral hygiene are effective in controlling gingivitis (Badersten *et al*. 1975; Poulsen *et al*. 1976; Axelsson & Lindhe 1981a, b; Bellini *et al*. 1981). This, however, does not imply that maintenance visits in childhood preclude the development of more severe disease later in life. It is obvious, therefore, that SPT must be a lifelong commitment of both the patient and the profession.

Adults whose effective oral hygiene was combined with periodic professional prophylaxis were clearly healthier periodontally than patients who did not participate in such programs (Lövdal *et al*. 1961; Suomi *et al*. 1971). One particular study of historical significance was performed on 1428 adults from an industrial company in Oslo, Norway (Lövdal *et al*. 1961). Over a 5-year observation period, the subjects were recalled two to four times per year for

Table 60-2 Percentage of various probing depths in recall and non-recall patients at the initial examination, 2 months after active periodontal treatment, and at 3- and 6-year follow-up visits.

Examinations	Percentage of pockets of various depths					
	≤3 mm		4–6 mm		≥7 mm	
	Recall	Non-recall	Recall	Non-recall	Recall	Non-recall
Initial	35	50	58	38	8	12
Baseline	99	99	1	1	0	0
3 years	99	91	1	9	0	0
6 years	99	80	1	19	0	1

Adapted from Axelsson & Lindhe (1981b), with permission from John Wiley & Sons.

instruction in oral hygiene and supragingival and subgingival scaling. Gingival conditions improved by approximately 60% and tooth loss was reduced by about 50% of what would be expected without these efforts.

In another study (Suomi *et al*. 1971), loss of periodontal tissue support in young individuals with gingivitis or only loss of small amounts of attachment was followed over 3 years. An experimental group receiving scaling and instruction in oral hygiene every 3 months yielded significantly less plaque and gingival inflammation than the control group in which no special efforts had been made. The mean loss of probing attachment was only 0.08 mm per surface in the experimental as opposed to 0.3 mm in the control group.

When adult patients with gingivitis were treated with scaling and root planing, but did not improve their oral hygiene procedures, the gingival condition did not improve compared with individuals receiving prophylaxis at 6-month intervals (Listgarten & Schifter 1982).

Summary: The available information indicates that the prevention of gingival inflammation and early loss of attachment in patients with gingivitis depends primarily on the level of personal plaque control, but also on further measures to reduce the accumulation of supragingival and subgingival plaque.

Supportive periodontal therapy for patients with periodontitis

As mentioned previously, a series of longitudinal studies on periodontal therapeutic modalities have been performed, first at the University of Michigan, USA, later at the University of Gothenburg, Sweden, and also at the Universities of Minnesota, Nebraska, and Loma Linda, USA. These studies always enrolled patients into a well-organized maintenance care system with recall visits at regular intervals (generally 3–4 months). Although the patients performed plaque control with various degrees of efficacy, the SPT resulted in excellent maintenance of postoperative attachment levels in most patients (Knowles 1973; Ramfjord *et al*. 1982).

On average, excellent treatment results with maintained reduced PPD and maintained gains of probing attachment were documented for most of the patients in the longitudinal studies irrespective of the treatment modality chosen (Ramfjord *et al*. 1975; Lindhe & Nyman 1975; Rosling *et al*. 1976; Nyman *et al*. 1977; Knowles *et al*. 1979, 1980; Badersten *et al*. 1981; Hill *et al*. 1981; Hill *et al*. 1981; Lindhe *et al*. 1982a; Pihlström *et al*. 1983; Westfelt *et al*. 1983a, b, 1985; Isidor & Karring 1986; Badersten *et al*. 1987).

In a study on 75 patients with extremely advanced periodontitis, who had been successfully treated for the disease with cause-related therapy and modified Widman flap procedures (Lindhe & Nyman 1984), recurrent infection occurred in only very few sites during a 14-year period of effective SPT. However, it has to be realized that recurrent periodontitis was noted at completely unpredictable time intervals, but was concentrated in about 25% of the patient population (15 of 61). This suggests that, in a periodontitis-susceptible risk population, the majority of patients can be "cured" provided an optimally organized SPT is performed, while a relatively small proportion of patients (20–25%) will suffer from occasional episodes of recurrent periodontal re-infection. It is obviously a challenge for the therapist to identify such patients with very high disease susceptibility and to monitor the dentitions for recurrent periodontitis on a long-term basis.

In contrast to the study by Lindhe and Nyman (1984), which exclusively involved patients with advanced periodontitis, another study on 52 patients with generalized mild-to-moderate adult periodontitis addressed the efficacy of SPT 8 years following completion of cause-related periodontal therapy (Brägger *et al*. 1992). Full-mouth intraoral radiographs were used to assess changes in the radiographic alveolar bone height as a percentage of the total tooth length. As a result of cause-related therapy, a gain in probing attachment was followed by a loss of 0.5–0.8 mm over the following 8 years. The radiographic loss of alveolar bone height in the same time period was <2% and thus clinically insignificant. In this patient group initially presenting with mild-to-moderate periodontitis, the frequency of SPT rendered per year did not affect the rate of progression of periodontal disease. However, patients seeking SPT less frequently than once per year over 8 years lost further periodontal attachment during the period of

observation. From these studies it is evident that patients who have had periodontitis need some kind of SPT. Obviously, the frequency of SPT visits has to be adapted to the risk of susceptibility for the disease. Patients with advanced periodontitis may need SPT at a regular and rather short time interval (3–4 months), while for mild-to-moderate forms of periodontitis, one annual visit may be enough to prevent further loss of attachment.

More recently, the effect of a 30-year plaque-control–based maintenance program in a private dental office on tooth mortality, caries, and periodontal disease progression was presented (Axelsson *et al*. 2004). This prospective controlled cohort study initially included 375 test and 180 control patients who received traditional maintenance care (by the referring dentist once or twice a year). After 6 years, the control group was discontinued. The test group was subjected to prophylactic visits every second month for the first 2 years and every 3–12 months (according to their individual needs) over 3–30 years. The prophylactic visits to the dental hygienist included plaque disclosure and professional mechanical tooth cleaning, including the use of a fluoride-containing dentifrice. During the 30 years of maintenance, very few teeth were lost (0.4–1.8), and rare teeth loss was predominately the result of root fractures. Over the 30 years of maintenance, 1.2–2.1 new carious lesions (>80% secondary caries) were found. During this period, only 2–4% of all sites exhibited periodontal attachment loss of ≥2 mm. This unique study clearly demonstrated that SPT based on plaque control tailored to the individual needs of the patient will result in very low tooth mortality, minimal recurrent caries, and almost complete periodontal stability.

Summary: SPT is an absolute prerequisite to guarantee beneficial treatment outcomes with maintained levels of clinical attachment over long periods of time. For the majority of patients, the maintenance of treatment results has been documented for up to 14 years, and in a private practice situation even up to 30 years, but it has to be realized that a small proportion of patients will experience recurrent infections with progression of periodontal lesions in a few sites in a completely unpredictable mode. The continuous risk assessment at subject, tooth, and tooth-site levels, therefore, represents a challenge for the SPT concept.

Continuous multilevel risk assessment

As opposed to an initial periodontal diagnosis which considers the sequelae of the disease process, in other words documents the net loss of periodontal attachment, the concomitant formation of periodontal pockets, and the existence of inflammation, clinical diagnosis during SPT has to be based on the variations of the health status following successful active periodontal treatment. This, in turn, means that a new baseline has to be established once the treatment goals of active periodontal therapy (i.e. phases 1–3) are reached and periodontal health is restored (Claffey 1991). This baseline includes the level of clinical attachment achieved while the inflammatory parameters are supposed to be under control. Under optimal circumstances, supportive periodontal care would maintain the clinical attachment levels obtained after active therapy for many years. However, if re-infection occurs, the loss of clinical attachment will progress. The relevant question is, therefore, which clinical parameters serve as early indicators for a new onset or recurrence of the periodontal disease process, that is re-infection and progression of periodontal breakdown of a previously treated periodontal site? It is also very important to achieve consistency in the definition of a "progressive" case in order to be able to interpret the results of clinical studies evaluating risk factors/indicators for the disease progression. Such a definition was proposed during the 5th European Workshop in Periodontology (Tonetti & Claffey 2005): presence of two or more teeth with longitudinal loss of proximal attachment of ≥3 mm. Where serial proximal attachment level measurements are not available, longitudinal radiographic bone loss of ≥2 mm at two or more teeth may be used as a substitute.

From a clinical point of view, the stability of periodontal conditions reflects a dynamic equilibrium between bacterial aggression and effective host response. As such, this homeostasis is prone to sudden changes whenever one of the two factors prevails. Hence, it is evident that the diagnostic process must be based on continuous monitoring of the multilevel risk profile. The intervals between diagnostic assessments must also be chosen based on the overall risk profile and the expected benefit. To schedule patients for SPT on the basis of an individual risk evaluation for recurrence of disease has been demonstrated to be cost-effective (Axelsson & Lindhe 1981a, b; Axelsson *et al*. 1991).

By virtue of their previous disease predisposition, patients under a periodontal maintenance program represent a population with a moderate-to-high risk for recurrent periodontal infection. As opposed to the general population without such a history, periodontal patients need to participate in a well-organized recall system which should provide both continuous risk assessment and adequate supportive care. Without this, the patients are likely to experience progressive loss of periodontal attachment (Axelsson & Lindhe 1981a; Kerr 1981; Becker *et al*. 1984; Cortellini *et al*. 1994, 1996). On the other hand, it is important to determine the level of risk for progression in each individual patient in order to be able to determine the frequency and extent of professional support necessary to maintain the attachment levels obtained following active therapy. The determination of such risk level would thus prevent undertreatment and also excessive overtreatment during SPT (Brägger *et al*. 1992).

Subject periodontal risk assessment

The patient's risk for recurrence of periodontitis may be evaluated on the basis of a number of clinical conditions whereby no single parameter displays a paramount role. The entire spectrum of risk factors and risk indicators should be evaluated simultaneously. For this purpose, a functional diagram has been constructed (Fig. 60-3) (Lang & Tonetti 2003) including the following aspects:

- Percentage of bleeding on probing (BoP)
- Prevalence of residual pockets >4 mm
- Loss of teeth from a total of 28 teeth
- Loss of periodontal support in relation to the patient's age
- Systemic and genetic conditions
- Environmental factors such as cigarette smoking.

Each parameter has its own scale for minor, moderate, and high-risk profiles. A comprehensive evaluation of these factors after active periodontal therapy will provide an individualized total risk profile and determine the frequency and complexity of SPT visits. Modifications may be made to the functional diagram if additional factors become important in the future. The validity of the periodontal risk assessment (PRA) in identifying various patient-based risk levels for disease progression following active periodontal treatment has been tested in several cohort studies around the world (Lang *et al.* 2015).

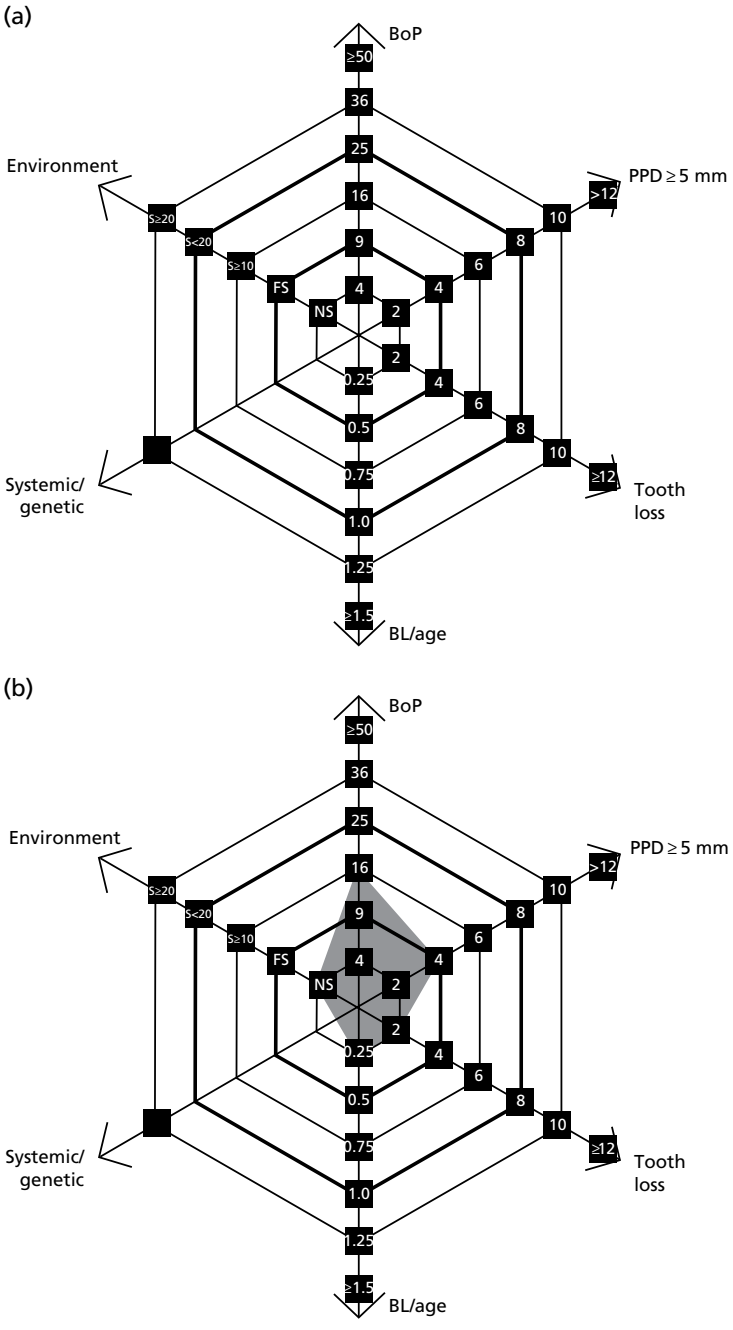

Fig. 60-3 (a) Functional diagram to evaluate the patient's risk for recurrence of periodontitis. Each vector represents one risk factor or indicator with an area of relatively low risk, an area of moderate risk, and an area of high risk for disease progression. All factors have to be evaluated together and hence the area of relatively low risk is found within the center circle of the polygon, while the area of high risk is found outside the periphery of the second polygon in bold. Between the two rings in bold, there is the area of moderate risk. (b) Functional diagram of a low-risk maintenance patient. Bleeding on probing (BoP) is 15%, four residual pockets of ≥5 mm are diagnosed, two teeth have been lost, the bone factor in relation to the patient's age is 0.25, no systemic factor is known, and the patient is a non-smoker.

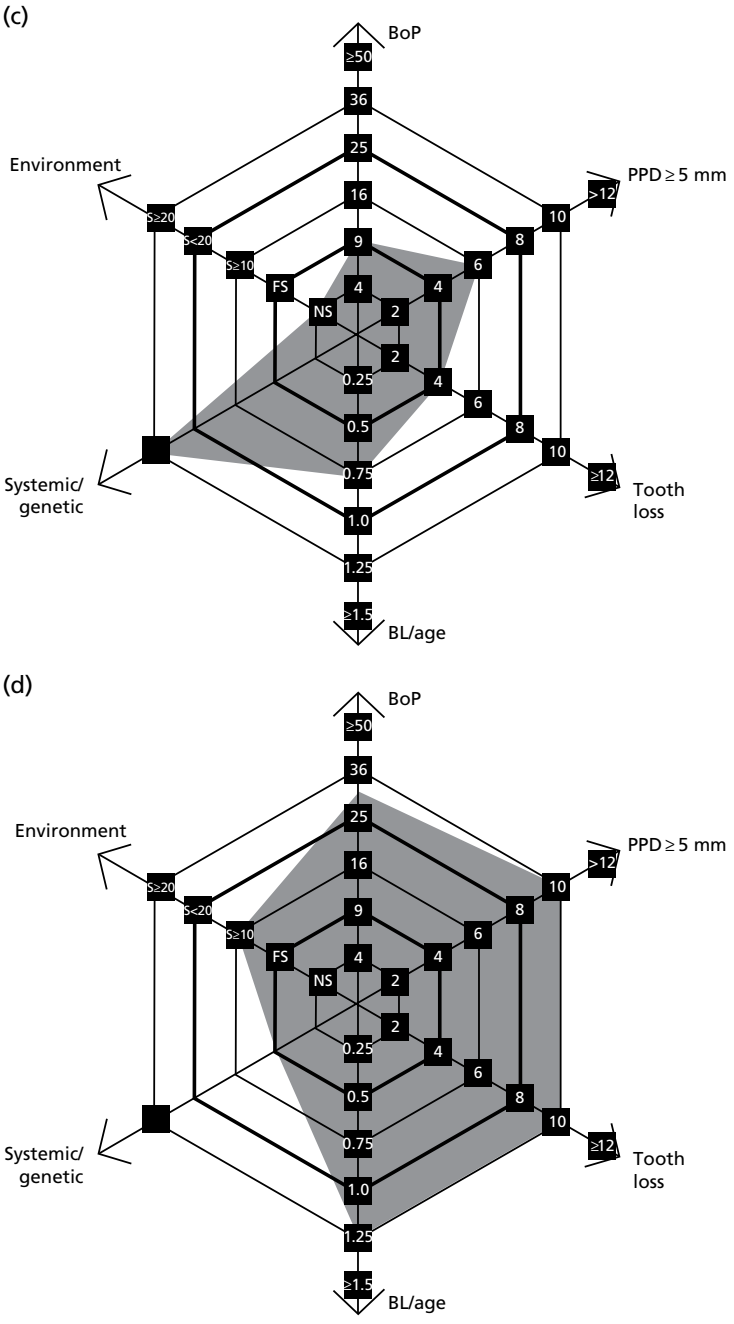

Fig. 60-3 (*continued*). (c) Functional diagram of a medium-risk maintenance patient. BoP is 9%, six residual pockets of ≥5 mm are diagnosed, four teeth have been lost, the bone factor in relation to the patient's age is 0.75, the patient has type I diabetes, but is a non-smoker. (d) Functional diagram of a high-risk maintenance patient. BoP is 32%, ten residual pockets of ≥5 mm are diagnosed, ten teeth have been lost, the bone factor in relation to the patient's age is 1.25, no systemic factors are known, and the patient is an occasional smoker. (BL, bone loss; PPD, probing pocket depth.)

Compliance with recall system

Several investigations have indicated that only a minority of periodontal patients comply with the prescribed supportive periodontal care (Wilson *et al*. 1984; Mendoza *et al*. 1991; Checchi *et al*. 1994; Demetriou *et al*. 1995). Since it has been clearly established that treated periodontal patients who comply with regular periodontal maintenance appointments have a better prognosis than patients who do not comply (Axelsson & Lindhe 1981a; Becker *et al*. 1984; Cortellini *et al*. 1994, 1996), non-compliant or poorly compliant patients should be considered at higher risk for periodontal disease progression. A report that investigated the personality differences of patients participating in a regular recall program following periodontal therapy as compared to patients who did not, revealed that the latter patients had higher incidences of stressful life events and less stable personal relationships (Becker *et al*. 1988).

Oral hygiene

Since bacterial plaque is by far the most important etiologic agent for the occurrence of periodontal diseases (for review see Kornman & Löe 1993), it is evident that the full-mouth assessment of the bacterial load must have a pivotal role in the determination of the risk for disease recurrence. It has to be realized, however, that regular interference with the microbial ecosystem during periodontal maintenance will eventually obscure such obvious associations. In patients treated with various surgical and non-surgical modalities, it has been clearly established that

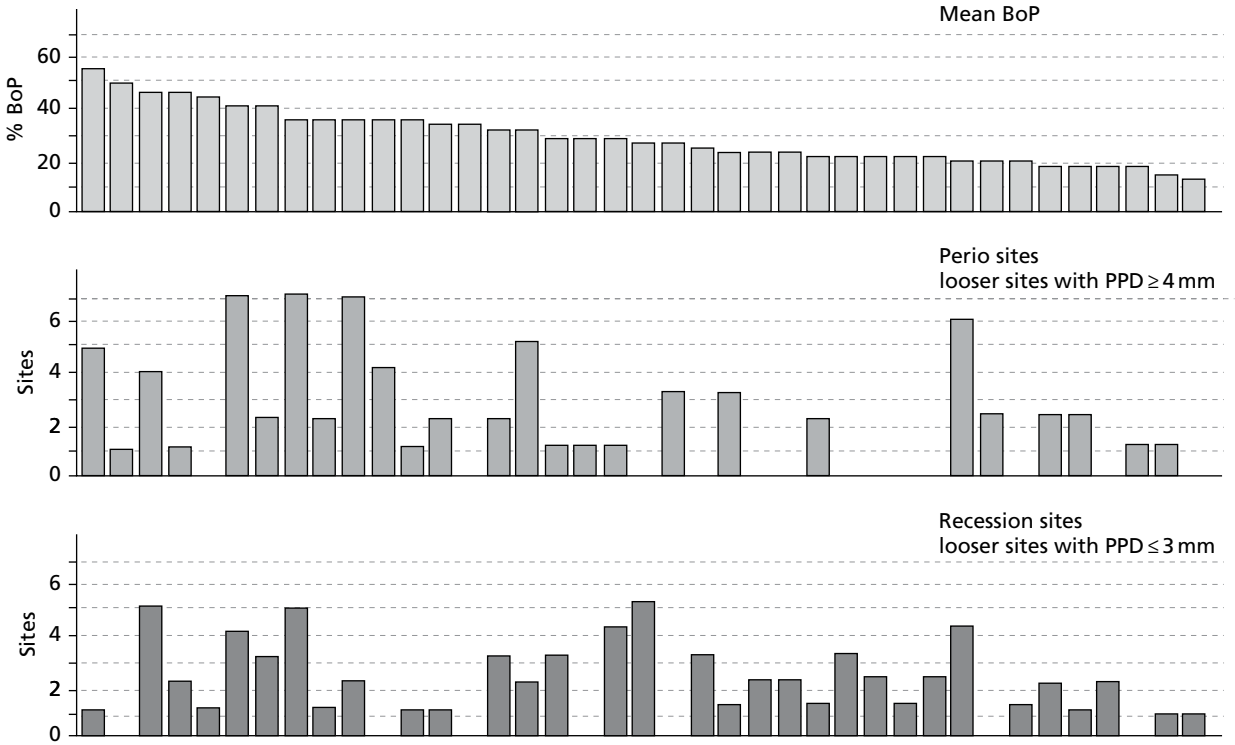

Fig. 60-4 Distribution of "looser" sites [probing pocket depth (PPD) of ≥4 mm) due to periodontal disease progression with or without concomitant recession, dependent on the mean bleeding on probing (BoP) percentage during an observation period of 4 years. Patients are sorted by decreasing mean BoP percentages. Patients with <20% BOP have a significantly lower risk for disease recurrence. (Data from Joss *et al*. 1994.)

plaque-infected dentitions will yield recurrence of periodontal disease in multiple locations, while dentitions under plaque control and regular supportive care maintain periodontal stability for many years (Rosling *et al*. 1976; Axelsson & Lindhe 1981a, b). Studies have thus far not identified a level of plaque infection compatible with maintenance of periodontal health. However, in a clinical set-up, a plaque control record of 20–40% might be tolerated by most patients. It is important to realize that the full-mouth plaque score has to be related to the host response of the patient, in other words compared to inflammatory parameters.

Percentage of sites with bleeding on probing

Bleeding on gentle probing represents an objective inflammatory parameter which has been incorporated into index systems for the evaluation of periodontal conditions (Löe & Silness 1963; Mühlemann & Son 1971) and is also used as a parameter on its own. In a patient's risk assessment for recurrence of periodontitis, BoP reflects, at least in part, the patient's compliance and standards of oral hygiene performance. No acceptable level of prevalence of BoP in the dentition above which there is a higher risk for disease recurrence has been established. However, a BoP prevalence of 25% was the cut-off point between patients with maintained periodontal stability for 4 years and patients with recurrent disease in the same timeframe in a prospective study in a private practice (Joss *et al*. 1994) (Fig. 60-4). Further evidence of BoP percentages between 20% and 30% determining a higher risk for disease progression originates from studies by Claffey *et al*. (1990) and Badersten *et al*. (1990).

In assessing the patient's risk for disease progression, BoP percentages reflect a summary of the patient's ability to perform proper plaque control, his/her host response to the bacterial challenge, and his/her compliance. The percentage of BoP, therefore, is used as the first risk factor in the functional diagram of risk assessment (see Fig. 60-3). The scale runs in a quadratic mode with 4, 9, 16, 25, 36, and >49% being the divisions on the vector.

Individuals with low mean BoP percentages (<10% of the surfaces) may be regarded as patients with a low risk for recurrent disease (Lang *et al*. 1990), while patients with mean BoP percentages of >25% should be considered to be at high risk for re-infection.

Prevalence of residual pockets of >4 mm

The enumeration of the residual pockets with a PPD of >4 mm represents, to a certain extent, the degree of success of the periodontal treatment rendered. Although this depth *per se* does not make much sense when considered as a sole parameter, the evaluation in conjunction with other parameters, such as BoP and/or suppuration, will reflect existing ecologic niches from and in which re-infection might occur. It is, therefore, conceivable that periodontal stability in a dentition is reflected by a minimal number of

residual pockets. At a site level, the presence of deep residual pockets after initial periodontal therapy and deepening of pockets during supportive periodontal care has been associated with high risk for disease progression (Badersten *et al*. 1990; Claffey *et al*. 1990). At the patient level, however, this evidence is scarce. In one study of 16 patients suffering from advanced periodontitis (Claffey & Egelberg 1995), the presence of high proportions of residual PPD of ≥6 mm after initial periodontal therapy indicated patient susceptibility for further attachment loss over a 42-month period. In a recent retrospective study of mean duration of 11.3 years, SPT was provided for 172 patients treated for periodontitis (Matuliene *et al*. 2008). Analysis of the data at the patient level demonstrated that, besides heavy smoking (≥20 cigarettes/day), SPT duration exceeding 10 years, initial diagnosis of advanced periodontitis (Tonetti and Claffey 2005), and the presence of at least one site with PPD of ≥6 mm or nine or more sites with PPD of ≥5 mm contribute significantly to the risk of periodontitis progression (Matuliene *et al*. 2008).

On the other hand, it has to be realized that an increased number of residual pockets does not necessarily imply an increased risk for re-infection or disease progression, since a number of longitudinal studies have established that, depending on the individual supportive therapy provided, even deeper pockets may be stable without further disease progression for years (e.g. Knowles *et al*. 1979; Lindhe & Nyman 1984).

Nevertheless, in assessing the patient's risk for disease progression, the number of residual pockets with a PPD of ≥5 mm is assessed as the second risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 60-3). The scale runs in a linear mode with 2, 4, 6, 8, 10, and ≥12% being the divisions on the vector. Individuals with up to four residual pockets may be regarded as at a relatively low risk, while patients with more than eight residual pockets may be regarded as at high risk for recurrent disease.

Loss of teeth from a total of 28 teeth

Although the reason for tooth loss may not be known, the number of remaining teeth in a dentition reflects the functionality of the dentition. Mandibular stability and individual optimal function may be assured even with a shortened dental arch of premolar to premolar occlusion, that is 20 teeth. The shortened dental arch does not seem to predispose the individual to mandibular dysfunction (Witter *et al*. 1990, 1994). However, if more than eight teeth from a total of 28 teeth are lost, oral function is usually impaired (Käyser 1981, 1994, 1996). Since tooth loss also represents a true end-point outcome variable reflecting the patient's history of oral diseases and trauma, it is logical to incorporate this risk indicator as the third parameter in the functional diagram of risk assessment (see Fig. 60-3). The number of teeth lost from the dentition without the third molars (28 teeth) is counted, irrespective of their replacement. The scale runs also in a linear mode with 2, 4, 6, 8, 10, and ≥12% being the divisions on the vector.

Individuals with up to four teeth lost may be regarded as patients at low risk, while patients with more than eight teeth lost may be considered as being at high risk.

Loss of periodontal support in relation to the patient's age

The extent and prevalence of periodontal attachment loss (i.e. previous disease experience and susceptibility), as evaluated by the height of the alveolar bone on radiographs, may represent the most obvious indicator of subject risk when related to the patient's age. In light of the present understanding of periodontal disease progression, and the evidence that both onset and rate of progression of periodontitis might vary among individuals and over different timeframes (van der Velden 1991), it has to be realized that previous attachment loss in relation to the patient's age does not rule out the possibility of rapidly progressing lesions. Therefore, the actual risk for further disease progression in a given individual may occasionally be underestimated. Hopefully, the rate of progression of disease has been positively affected by the treatment rendered and, hence, previous attachment loss in relation to the patient's age may be a more accurate indicator during SPT than before active periodontal treatment. Given the hypothesis that a dentition may be functional for the most likely life expectancy of the subject in the presence of a reduced height of periodontal support (i.e. 25–50% of the root length), the risk assessment in treated periodontal patients may represent a reliable prognostic indicator for the stability of the overall treatment goal of keeping a functional dentition for a lifetime (Papapanou *et al*. 1988).

The estimation of the loss of alveolar bone is performed in the posterior region on either periapical radiographs, in which the worst site affected is estimated gross as a percentage of the root length, or on bitewing radiographs in which the worst site affected is estimated in millimeters. One millimeter equates to 10% bone loss. The percentage is then divided by the patient's age. This results in a factor. As an example, a 40-year-old patient with 20% bone loss (BL) at the worst posterior site affected would be scored BL/Age = 0.5. Another 40-year-old patient with 50% BL at the worst posterior site scores BL/Age = 1.25.

In assessing the patient's risk for disease progression, the extent of alveolar bone loss in relation to his/her age is estimated as the fourth risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 60-3). The scale runs in increments of 0.25 of the factor BL/Age, with 0.5 being the division between low and moderate risk, and 1.0

being the division between moderate and high risk for disease progression. This, in turn, means that a patient who has lost a higher percentage of posterior alveolar bone than expected for his/her own age is at high risk regarding this vector in a multifactorial assessment of risk.

Systemic conditions

The most substantiated evidence for modification of disease susceptibility and/or progression of periodontal disease arises from studies on type I and type II (insulin-dependent and non–insulin-dependent) diabetes mellitus populations (Gusberti *et al*. 1983; Emrich *et al*. 1991; Genco & Löe 1993).

It has to be realized that the impact of diabetes on periodontal diseases has been documented in patients with untreated periodontal disease, while, as of today, no clear evidence is available for treated patients. It is reasonable, however, to assume that the influence of systemic conditions may also affect recurrence of disease.

In recent years, genetic markers have become available to determine various genotypes of patients regarding their susceptibility for periodontal diseases. Research on the interleukin-1 (IL-1) polymorphisms has indicated that *IL-1* genotype-positive patients show more advanced periodontitis lesions than *IL-1* genotype-negative patients of the same age group (Kornman *et al*. 1997). Also, there is a trend to higher tooth loss in the *IL-1* genotype-positive subjects (McGuire & Nunn 1999). In a retrospective analysis of over 300 well-maintained periodontal patients, the *IL-1* genotype-positive patients showed significantly higher BoP percentages, and a higher proportion of these patients yielded higher BoP percentages during a 1-year recall period than the *IL-1* genotype-negative control patients (Lang *et al*. 2000). Also, the latter group had twice as many patients with improved BoP percentages during the same maintenance period, indicating that *IL-1* genotype-positive subjects do indeed represent a group of hyperreactive subjects even if they are regularly maintained by effective SPT (Lang *et al*. 2000). In a prospective study over 5 years on Australian white and blue collar workers at a university campus, the *IL-1* genotype-positive group aged above 50 years showed significantly deeper PPD than their *IL-1* genotype-negative counterparts, especially when they were non-smokers.

In assessing the patient's risk for disease progression, systemic factors are only considered, if known, as the fifth risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 60-3). In this case, the area of high risk is marked for this vector. If not known or absent, systemic factors are not taken into account in the overall evaluation of risk.

Research on the association and/or modifying influence on susceptibility and progression of periodontitis of physical or psychological stress is sparse (Cohen-Cole *et al*. 1981; Green *et al*. 1986; Freeman & Goss 1993). The hormonal changes associated with this condition, however, are well documented (Selye 1950).

Cigarette smoking

Consumption of tobacco, predominantly in the form of smoking or chewing, affects the susceptibility and the treatment outcome of patients with adult periodontitis. Classical explanations for these observations have included the association between smoking habits and poor oral hygiene, as well as lack of awareness of general health issues (Pindborg 1949; Rivera-Hidalgo 1986). More recent evidence, however, has established that smoking *per se* represents not only a risk marker, but probably also a true risk factor for periodontitis (Ismail *et al*. 1983; Bergström 1989; Bergström *et al*. 1991; Haber *et al*. 1993). In a young population (19–30 years of age), 51–56% of periodontitis was associated with cigarette smoking (Haber *et al*. 1993). The association of smoking and periodontitis has been shown to be dose-dependent (Haber *et al*. 1993). It has also been shown that smoking affects the treatment outcome after scaling and root planing (Preber & Bergström 1985), modified Widman flap surgery (Preber & Bergström 1990), and regenerative periodontal therapy (Tonetti *et al*. 1995). Furthermore, a high proportion of so-called refractory patients has been identified as smokers (Bergström & Blomlöf 1992). The impact of cigarette smoking on the long-term effects of periodontal therapy in a population undergoing supportive periodontal care has been reported. Smokers displayed less favorable healing responses both at re-evaluation and during a 6-year period of supportive periodontal care (Baumert-Ah *et al*. 1994). This was confirmed in another study in which higher percentages of heavy smokers experienced more multiple (≥9) residual pockets (≥5 mm) than non-smokers both after active periodontal therapy (31.2% versus 7.3%, respectively) and after 11 years of SPT (52.4% versus 14.8%, respectively) (Matuliene *et al*. 2008). In this study, heavy smoking was found to be a significant risk factor for periodontitis progression. Moreover, smoking was the main statistically significant risk factor for the recurrence of periodontitis after 10.5 years of SPT in the 84 patients with aggressive periodontitis. More than half of the current smokers in this study showed a recurrence of disease at re-examination and had a ten-fold increased risk for a relapse compared with non-smokers (Bäumer *et al*. 2011). In a systematic review of 13 observational studies of long-term periodontal maintenance, smoking was found to be associated with tooth loss, which could be interpreted as the end-point event of periodontitis progression (Chambrone *et al*. 2010).

In conclusion, today there is enough evidence relating cigarette smoking to impaired outcomes

during supportive periodontal care. Therefore, it seems reasonable to include heavy smokers (>20 cigarettes/day) in a higher risk group during maintenance.

In assessing the patient's risk for disease progression, environmental factors such as smoking must be considered as the sixth risk factor for recurrent disease in the functional diagram of risk assessment (see Fig. 60-3). While non-smokers (NS) and former smokers (FS) (>5 years since cessation) have a relatively low risk for recurrence of periodontitis, heavy smokers (HS), as defined by smoking more than one pack per day, are definitely at high risk. Occasional (OS; <10 cigarettes/day) and moderate smokers (MS; 11–19 cigarettes/day) may be considered at moderate risk for disease progression.

Calculating the patient's individual periodontal risk assessment

Based on the six parameters specified above, a multifunctional diagram is constructed for the PRA. In this diagram, the vectors have been constructed on the basis of the scientific evidence available. It is obvious that ongoing validation may result in slight modifications.

- *Low periodontal risk (PR) patient*: all parameters within the low-risk categories or at the most one parameter in the moderate-risk category (Fig. 60-3b)
- *Moderate PR patient*: at least two parameters in the moderate category, but at most only one parameter in the high-risk category (Fig. 60-3c)
- *High PR patient*: at least two parameters in the high-risk category (Fig. 60-3d).

The application of the multifunctional diagram for the subject-based PRA was validated in several studies. A 4-year prospective cohort study (Persson *et al*. 2003) yielded complete periodontal stability after individually tailored recall intervals for all patients with a negative *IL-1* gene polymorphism. For the *IL-1* genotype-positive patients, however, the PRA resulted only in periodontal stability for 90% of the patients. On the other hand, two recently published studies of 100 and 160 patients evaluating the results of SPT of mean duration of >10 years demonstrated that patients with a high-risk profile after active periodontal therapy were more prone to recurrence of periodontitis (Matuliene *et al.* 2010) and to tooth loss (Eickholz *et al*. 2008; Matuliene *et al*. 2010) than the patients with a moderate- or a low-risk profile.

Summary: The subject risk assessment may estimate the risk for susceptibility to progression of periodontal disease. It consists of an assessment of the level of infection (full-mouth BoP), the prevalence of residual periodontal pockets, tooth loss, an estimation of the loss of periodontal support in relation to the patient's age, an evaluation of the systemic conditions of the patient, and finally, an evaluation of environmental and behavioral factors such as smoking and stress. All these factors should be contemplated and evaluated together. A functional diagram (see Fig. 60-3) may help the clinician in determining the risk for disease progression at the subject level. This may be useful in customizing the frequency and content of SPT visits.

Tooth risk assessment

Tooth position within the dental arch

Early clinical surveys have associated the prevalence and severity of periodontal diseases with malocclusion and irregularities of tooth position (Ditto & Hall 1954; Bilimoria 1963). However, many subsequent studies using clinical evaluation methods could not confirm these conclusions (Beagrie & James 1962; Geiger 1962; Gould & Picton 1966). Although a relationship between crowding and increased plaque retention and gingival inflammation has been established (Ingervall *et al*. 1977; Buckley 1980; Griffith & Addy 1981; Hörup *et al*. 1987), no significant correlation between anterior overjet and overbite (Geiger *et al*. 1973), crowding and spacing (Geiger *et al*. 1974) or axial inclinations and tooth drifts (Geiger & Wasserman 1980) and periodontal destruction, that is attachment loss subsequent to gingival inflammation, could be established. It is evident from the literature mentioned that crowding of teeth might eventually affect the amount of plaque mass formed in dentitions with irregular oral hygiene practices, thus contributing to the development of chronic gingivitis. However, as of today, it remains to be demonstrated whether tooth malposition within the dental arch leads to an increased risk for periodontal attachment loss.

Furcation involvement

Multirooted teeth with periodontal lesions extending into the furcation area have been the subject of intensive therapeutic studies for many years (Kalkwarf & Reinhardt 1988). Retrospective analyses of large patient populations in the private periodontal practices of periodontal specialists (Hirschfeld & Wasserman 1978; McFall 1982) have clearly established that multirooted teeth appear to be at high risk for loss during the maintenance phase. The most impressive long-term documentation maintained 600 patients for an average duration of 22 years, and 10% of these patients were even maintained for >30 years (Hirschfeld & Wasserman 1978). While 83% of the patients could be considered "well maintained" and had lost only 0–3 teeth during the observation period, a patient group of 4% (25) was identified with an extreme risk for disease progression and had lost between 10 and 23 teeth during a regularly scheduled maintenance program. Irrespective of whether the patient group was of low, moderate, or high risk for

disease progression during maintenance, the majority of the teeth lost were furcation-involved molars (Hirschfeld & Wasserman 1978). Similar results were obtained in a study of 100 treated periodontal patients maintained for 15 years or longer (McFall 1982).

Prospective studies on periodontal therapy in multirooted teeth have also revealed significant differences between non-molar sites and molar flat surfaces on the one hand, and molar furcation sites on the other, when looking at treatment outcomes evaluated as BoP frequency, PPD reductions, and levels of attachment (Nordland *et al*. 1987). Again, teeth with furcation involvement and an original PPD of >6 mm had reduced treatment outcomes.

The assumption that the prognosis for single-rooted teeth and non–furcation-involved multirooted teeth is better than that for furcation-involved multirooted teeth was also confirmed by Ramfjord *et al*. (1987) in a prospective study over 5 years. It has to be realized, however, that these results are not intended to imply that furcation-involved teeth should be extracted, since all the prospective studies have documented a rather good overall prognosis for such teeth if regular supportive care is provided by a well-organized maintenance program.

Iatrogenic factors

Overhanging restorations and ill-fitting crown margins certainly represent areas for plaque retention, and there is an abundance of association studies documenting increased prevalence of periodontal lesions in the presence of iatrogenic factors (for review see Leon 1977). Depending on the supragingival or subgingival location of such factors, their influence on the risk for disease progression has to be considered. It has been established that slightly subgingivally located overhanging restorations will, indeed, change the ecologic niche, providing more favorable conditions for the establishment of a Gram-negative anaerobic microbiota (Lang *et al*. 1983). There is no doubt that shifts in the subgingival microflora towards a more periodontopathic microbiota, if unaffected by treatment, represent an increased risk for periodontal breakdown.

Residual periodontal support

Although many clinicians believe that teeth with reduced periodontal support are unable to function alone and should be extracted or splinted, there is clear evidence from longitudinal studies that teeth with severely reduced, but healthy, periodontal support can function either individually or as abutments for many years without any further loss of attachment (Nyman & Lindhe 1979; Nyman & Ericsson 1982; Brägger *et al*. 1990). Hence, teeth that have been successfully periodontally treated can be maintained over decades and function as abutments in fixed bridgework or as individual chewing units irrespective of the amount of residual periodontal support, provided that physiologic masticatory forces do not subject such teeth to a progressive trauma which may lead to spontaneous extraction. Obviously, by virtue of the already reduced support, should disease progression occur in severely compromised teeth, they may exfoliate spontaneously.

Mobility

In light of the discussion on abutment teeth with severely reduced but healthy periodontal support, tooth mobility may be an indicator for progressive traumatic lesions, provided that the mobility is increasing continuously (Nyman & Lang 1994). When assessing tooth mobility, it has to be realized that two factors may contribute to hypermobility: (1) a widening of the periodontal ligament as a result of unidirectional or multidirectional forces to the crown, high and frequent enough to induce resorption of the alveolar bone walls; and (2) the height of the periodontal supporting tissues. If this is reduced due to prior periodontal disease, but the width of the periodontal ligament is unchanged, the amplitude of root mobility within the remaining periodontium is the same as in a tooth with normal height, but the leverage on the tooth following application of forces to the crown is changed. Therefore, it has to be realized that all teeth that have lost periodontal support have increased tooth mobility as defined by crown displacement upon application of a given force. Nevertheless, this hypermobility should be regarded as physiologic (Nyman & Lindhe 1976).

Since tooth mobility is probably more frequently affected by reduced periodontal height rather than unidirectional or multidirectional application of forces on the tooth, its significance in the evaluation of periodontal conditions has to be questioned. Several studies have indicated that tooth mobility varies greatly before, during, and after periodontal therapy (Persson 1980, 1981a, b). From these studies it can be concluded that periodontally involved teeth show a decrease in mobility following non-surgical and/or surgical periodontal procedures. However, following surgical procedures, tooth mobility may temporarily increase during the healing phase and may resume decreased values later on. Provisional splinting as an adjunct to non-surgical or surgical therapy does not seem to affect the final tooth mobility.

Summary: The tooth risk assessment encompasses an estimation of the residual periodontal support, an evaluation of tooth positioning, furcation involvements, presence of iatrogenic factors, and a determination of tooth mobility to evaluate functional stability. A risk assessment at tooth level may be useful in evaluating the prognosis and function of an individual tooth and may indicate the need for specific therapeutic measures during SPT visits.

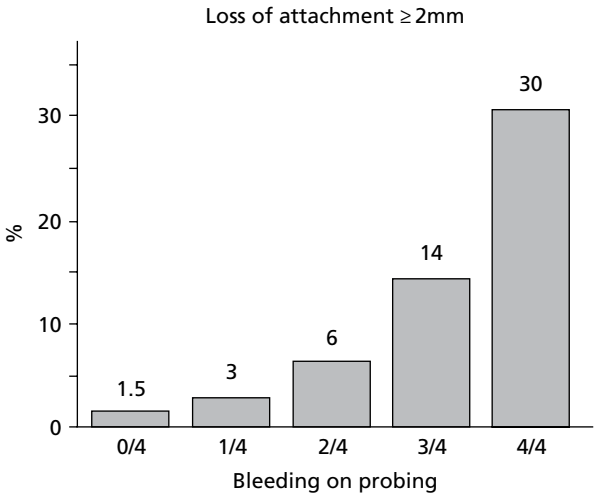

Fig. 60-5 Positive predictive values for loss of probing attachment of ≥2 mm in 2 years in sites which bled on probing 0, 1, 2, 3 or 4 times at four SPT visits in a total of 48 patients following active periodontal therapy. (Data from Lang *et al*. 1986.)

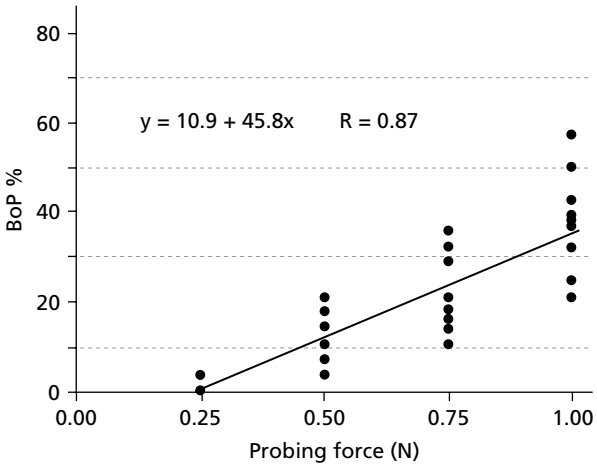

Fig. 60-6 Regression analysis between mean bleeding on probing (BoP) percentage and probing forces applied in young dental hygiene students with a healthy gingiva and normal anatomy. A very high correlation coefficient (R = 0.87) and an almost linear correlation between probing force and BoP percentage was found. (Data from Lang *et al*. 1991.)

Site risk assessment

Bleeding on probing

Absence of BoP is a reliable parameter to indicate periodontal stability if the test procedure for assessing BoP has been standardized (Lang *et al*. 1990). Presence of bleeding upon standardized probing will indicate the presence of gingival inflammation. Whether or not repeated BoP over time will predict the progression of a lesion is, however, questionable (Lang *et al*. 1986, 1990; Vanooteghem *et al*. 1987). Nevertheless, a 30% probability for attachment loss occurring in the future may be predicted for sites repeatedly positive for BoP (Fig. 60-5) (Badersten *et al*. 1985; Lang *et al*. 1986; Vanooteghem *et al*. 1987; Badersten *et al*. 1990; Claffey *et al*. 1990; Vanooteghem *et al*. 1990).

Obviously, BoP is rather sensitive to the different forces applied to the tissues. An almost linear relationship (R = 0.87) existed between the probing force applied and the percentage of bleeding sites in a study of healthy young adults (Fig. 60-6) (Lang *et al*. 1991). If the probing force exceeded 0.25 N (25 g), the tissues were traumatized and bleeding was provoked as a result of trauma, rather than as a result of tissue alterations due to inflammation. To assess the "true" percentage of bleeding sites due to inflammation, a probing force of 0.25 N or less should be applied, which clinically means a light probing force. This has also been confirmed for patients who have experienced loss of attachment, in other words with successfully treated advanced periodontitis (Fig. 60-7) (Karayiannis *et al*. 1991; Lang *et al*. 1991).

Since absence of BoP at 0.25 N indicated periodontal stability with a negative predictive value of 98–99% (Lang *et al*. 1990), this clinical parameter is the most reliable for monitoring patients over time in daily practice. Non-bleeding sites may be considered periodontally stable. On the other hand, bleeding

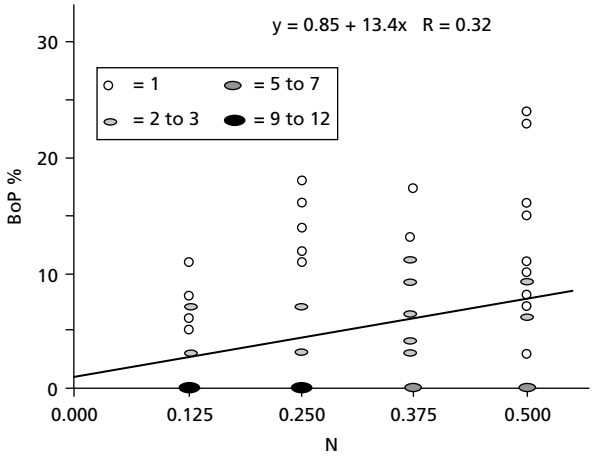

Fig. 60-7 Regression analysis between mean bleeding on probing (BoP) percentage and probing forces applied in subjects with successfully treated periodontitis: a reduced, but healthy, periodontium. (Data from Karayiannis *et al*. 1991.)

sites seem to have an increased risk for progression of periodontitis, especially when the same site bleeds at repeated evaluations over time (Lang *et al*. 1986; Claffey *et al*. 1990).

It is, therefore, advisable to register the sites with BoP in a dichotomous way using a constant force of 0.25 N. This allows the calculation of the mean BoP for the patient, and also yields the topographic location of the bleeding site. Repeated scores during maintenance will reveal the surfaces at higher risk for loss of attachment.

Probing depth and loss of attachment

Clinical probing is the most commonly used parameter both to document loss of attachment and to establish a diagnosis of periodontitis. There are, however, some sources of error inherent in this method which contribute to the variability in the

measurements. Among these are (1) the dimension of the periodontal probe; (2) the placement of the probe and obtaining a reference point; (3) the crudeness of the measurement scale; (4) the probing force; and (5) the gingival tissue conditions.

In spite of the recognized method errors inherent in clinical probing, this diagnostic procedure has not only been the most commonly used but is also the most reliable parameter for the evaluation of the periodontal tissues. It has to be realized that increased PPD and loss of probing attachment are parameters which reflect the history of periodontitis rather than its current state of activity. In order to obtain a more realistic assessment of the disease progression or, more commonly, the healing following therapy, multiple evaluations should be performed. Obviously, the first evaluation prior to therapy will yield results confounded by greater measurement error than evaluations following therapy. The reference point (cementoenamel junction) may be obstructed by calculus or by dental restorations, and the condition of the gingival tissues may allow an easy penetration of the periodontal probe into the tissues, even though the probe position and force applied are standardized. These biologic variables (tissue conditions and calculus) may be minimized following initial periodontal therapy, and hence, repeated periodontal evaluations using probing will improve the metric assessment. The first periodontal evaluation after healing following initial periodontal therapy should, therefore, be taken as the baseline for long-term clinical monitoring (Claffey 1994).

Suppuration

In a proportion of periodontal lesions, pus will develop and may drain through the orifice of a pocket. This criterion of suppuration may be recognized while clinically probing the lesion, or preferably, by using a ball burnisher (Singh *et al*. 1977). Several longitudinal studies on the results of periodontal therapy have evaluated clinical parameters, including suppuration, for the prediction of future loss of attachment (Badersten *et al*. 1985, 1990; Claffey *et al*. 1990). In all these studies, the presence of suppuration increased the positive predictive value for disease progression in combination with other clinical parameters, such as BoP and increased probing depth. Hence, following therapy, a suppurating lesion may provide evidence that the periodontitis site is undergoing a period of exacerbation (Kaldahl *et al*. 1990).

Summary: The tooth site risk assessment includes the registration of BoP, probing depth, loss of attachment, and suppuration. A risk assessment at the site level may be useful in evaluating periodontal disease activity and determining periodontal stability or ongoing inflammation. The site risk assessment is essential for the identification of the sites to be instrumented during SPT.

Radiographic evaluation of periodontal disease progression

As a consequence of the clinical risk assessments, the decision may be made to gather radiographic information on the periodontal conditions as well (Hirschmann *et al*. 1994). The task may be related to a generalized pattern of disease progression or a localized monitoring. Not only periodontal aspects, but also a comprehensive approach, should influence the choice of the radiographic technique (Rohlin & Akerblom 1992). Periodic radiographic surveys that are not based on clinical signs and symptoms should not be scheduled simply to confirm health.

Radiographic perception of periodontal changes is characterized by a high specificity, but a low sensitivity, with underestimation of the severity of a periodontal defect (Hämmerle *et al*. 1990; Åkesson *et al*. 1992). The undetectability of minute changes at the alveolar crest is related to overprojections and variations in projection geometry when taking repeated radiographs (Lang & Hill 1977; Goodson *et al*. 1984; Jenkins *et al*. 1992). This may result in mimicked variations in the alveolar bone height, obscured furcation status, etc. In addition, film processing variations may result in unreliable assessments of alveolar bone density changes (Rams *et al*. 1994).

The standard procedure for periodontal evaluations is based on a film-holder system with alignment for a long-cone paralleling technique (Rushton & Horner 1994). The addition of simple pins to the film-holder to provide a repositioning reference impressively reduced the methodologic error (Carpio *et al*. 1994).

In general, standards in oral radiology related to choice of a technique, quality of film processing, and diagnosis need to be improved (Brägger 1996).

Clinical implementation

The *three levels* of risk assessment presented represent a logical sequence for the clinical evaluation prior to rendering treatment during maintenance. The information gathered from a stepwise evaluation should not impinge on, but should rather improve, the efficacy of secondary prophylactic periodontal care and treatment. A logical sequence of checks and examinations may be easily obtained in a short period of time and at no extra cost in terms of laboratory tests. The information obtained from clinical monitoring and multilevel risk assessment facilitates an immediate appreciation of the periodontal health status of an individual and his/her possible risk for further infection and/or disease progression.

Most longitudinal studies published to date have been based on single-level, that is site or tooth, risk assessment, rather than accounting for the most evident factor in risk assessment: the patient. Ample evidence indicates that a minority of patients will continue to present problems and hence, the appropriate maintenance program for them will differ

completely from that visualized in the majority of the patients. Even in those studies where this fact has been explicitly addressed (Hirschfeld & Wasserman 1978), the factors determining whether a patient belongs to a well-maintained group or to a group with continuous loss of periodontal attachment have not been identified.

Summary: It is suggested that patients are evaluated at the *three different levels* mentioned. At the patient level, loss of support in relation to patient age, full-mouth plaque and/or BoP scores, and prevalence of residual pockets are evaluated, together with the presence of systemic conditions or environmental factors, such as smoking, which can influence the prognosis. The clinical utility of this first level of risk assessment influences primarily the determination of the recall frequency and time requirements of maintenance. It should also provide a perspective for the evaluation of the risk assessment conducted at the tooth and tooth-site levels.

At the tooth and tooth-site levels, residual periodontal support, inflammatory parameters and their persistence, presence of difficult to access ecologic niches, such as furcations, and presence of iatrogenic factors have to be put into perspective with the patient's overall risk profile (Fig. 60-8). The clinical utility of tooth and tooth-site risk assessment relates to the rational allocation of the recall time available for therapeutic intervention to the sites with higher risk, and possibly to the selection of different forms of therapeutic intervention.

Objectives for supportive periodontal therapy

The objective of maintenance care must be the continued preservation of gingival and periodontal health, obtained as a result of the active periodontal treatment. Irrespective of whether or not additional treatment such as prosthetic reconstructions or placement of implants has been rendered, the regular and adequate removal of supragingival plaque by the patient is, therefore, a prerequisite for a good long-term prognosis. In order to achieve these goals, regular clinical re-evaluations with appropriate interceptive treatment, continued psychological support and encouragement of the patient, and a lifelong commitment by the therapists are required.

General rules regarding frequency of maintenance care visits are difficult to define. However, there are a few aspects to consider in this respect: the patient's individual oral hygiene standard, the prevalence of sites exhibiting BoP, and the pretherapeutic attachment level and alveolar bone height. This in turn means that patients with suboptimal plaque control and/or concomitant high prevalence of bleeding sites should be recalled more frequently than patients exhibiting excellent plaque control and healthy gingival tissues. Nevertheless, patients with healthy gingival conditions, but with a severely reduced height of periodontal support, should also be recalled at short time intervals (not exceeding 3–4 months) in order to exclude or at least reduce the risk of additional tooth

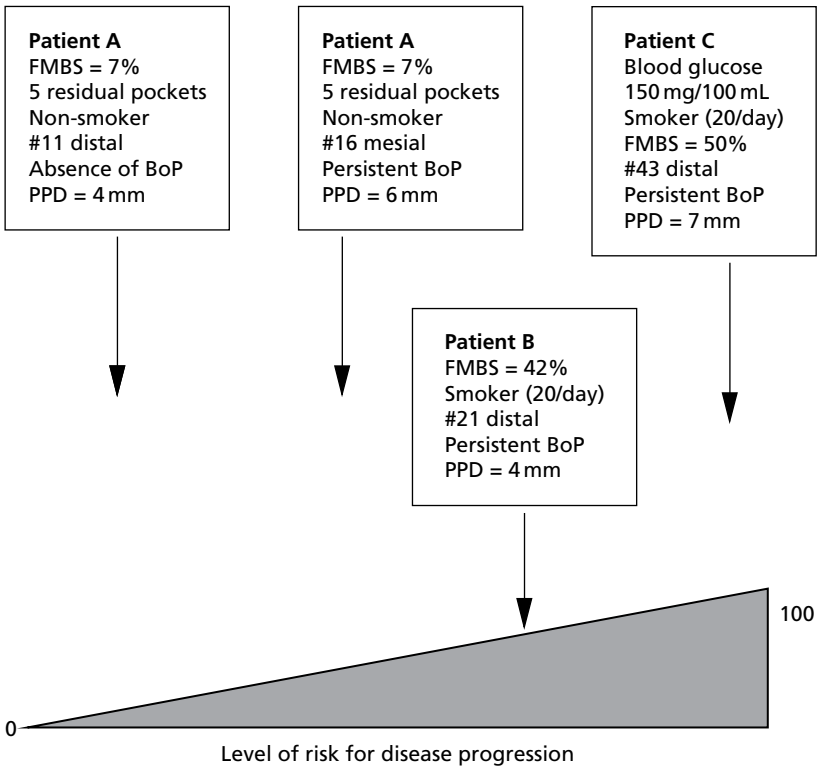

Fig. 60-8 Continuous multiple level risk assessment. Subject, tooth, and site parameters are combined to establish the clinical risk for disease progression. Note that different sites in the same patient may have a different level of risk. Subject-based risk factors are used to put the tooth and/or site risk assessment in perspective. (FMBS, full-mouth bleeding score; PPD, probing pocket depth.)

loss. In most of the longitudinal studies referred to above, positive treatment results were maintained with regular maintenance care provided at 3–6-month intervals. It seems reasonable to commence post-therapeutic maintenance with recall visits once every 3–4 months and then shorten or prolong these intervals in accordance with the aspects discussed above.

Since clinical attachment levels are usually stable 6 months following active periodontal therapy, it has been suggested that the first 6 months after completion of therapy be considered a healing phase (Westfelt *et al*. 1983b) during which frequent professional tooth cleaning has been recommended. Following this healing phase, it is generally agreed to recall patients treated for periodontal disease at intervals of 3–4 months in a well-organized system of SPT. It has to be realized that tissue contours may be subjected to remodeling processes despite stable clinical attachment levels and, hence, morphologic changes may still improve the accessibility of all tooth surfaces to oral hygiene practices for months and even years. Proper oral hygiene practices appear to be the most important patient factor that can guarantee long-term stability of treatment results (Knowles *et al*. 1979; Ramfjord *et al*. 1982; Lindhe & Nyman 1984; Ramfjord *et al*. 1987). This, in turn, necessitates optimization of the patient's skills and continuous motivation and reinforcement to perform adequate mechanical oral hygiene practices, although chemical agents, such as the potent antiseptic chlorhexidine, may substitute and later complement the patient's efforts during the healing phase, when mechanical practices are difficult (Westfelt *et al*. 1983a). It is obvious that regular recall visits for SPT should be scheduled soon after completion of cause-related therapy, even if periodontal surgical procedures are still to be performed following a careful re-evaluation of the tissue response. To postpone the organization of a maintenance care program until corrective procedures such as surgery, endodontic, implant, operative or reconstructive therapy have been performed may reinforce a possible misconception by the patient that the professional visits to a therapist or hygienist guarantee positive treatment outcomes and optimal long-term prognosis rather than the patient's own regular performance of individually optimal and adequate oral hygiene practices.

Supportive periodontal therapy in daily practice

The recall hour should be planned to meet the patient's individual needs. It basically consists of four different sections which may require various amounts of time during a regularly scheduled visit:

1. Examination, re-evaluation, and diagnosis (ERD)
2. Motivation, re-instruction, and instrumentation (MRI)
3. Treatment of re-infected sites (TRS)
4. Polishing of the entire dentition, application of fluorides, and determination of future SPT (PFD).

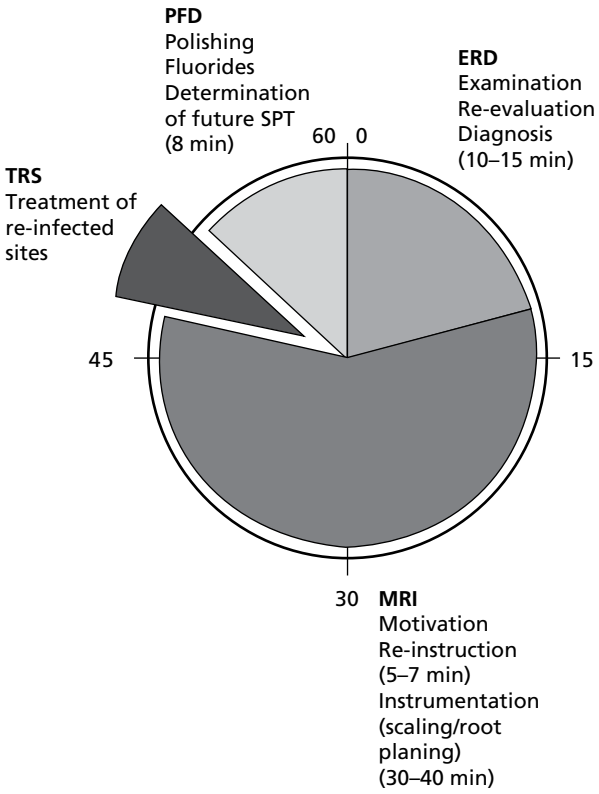

Fig. 60-9 SPT recall hour is divided into four sections. (1) Examination, re-evaluation, and diagnosis (ERD) providing information on stable and inflamed sites. This segment uses 10–15 minutes. (2) Motivation, re-instruction of oral hygiene where indicated, and instrumentation (MRI) use the bulk of the recall hour (30–40 minutes). Sites diagnosed as not stable are instrumented. (3) Treatment of re-infected sites (TRS) may require a second appointment. (4) Polishing all tooth surfaces, application of fluorides, and determination of the future recall interval (PFD) conclude the recall hour (5–10 minutes).

The SPT recall hour (Fig. 60-9) generally consists of 10–15 minutes of diagnostic procedures (ERD) followed by 30–40 minutes of motivation, re-instruction, and instrumentation (MRI), with the instrumentation concentrated on the sites diagnosed with persistent inflammation. Treatment of re-infected sites (TRS) may include small surgical corrections, applications of local drug delivery devices or just intensive instrumentation under local anesthesia. Such procedures, if judged necessary, may require an additional appointment. The recall hour is normally concluded with polishing of the entire dentition, application of fluorides, and another assessment of the situation, including the determination of future SPT visits (PFD). Approximately 5–10 minutes have to be reserved for this section.

Examination, re-evaluation, and diagnosis

Since patients on SPT may experience significant changes in their health status and the use of

medications, an update of the information on general health issues is appropriate. Changes in health status and medications should be noted. In middle-aged to elderly patients especially, these aspects might influence the future management of the patient. An extraoral and intraoral soft tissue examination should be performed at any SPT visit to detect any abnormalities and to act as a screening for oral cancer. The lateral borders of the tongue and the floor of the mouth should be inspected in particular. An evaluation of the patient's risk factors will also influence the choice of future SPT and the determination of the recall interval at the end of the maintenance visit. Following the assessment of the subject's risk factors, the tooth site-related risk factors are evaluated. As indicated above, the diagnostic procedure usually includes an assessment of the following:

- Oral hygiene and plaque situation
- Determination of sites with BoP, indicating persistent inflammation
- Scoring of clinical probing depths and clinical attachment levels. The latter is quite time-consuming and requires the assessment of the location of the cementoenamel junction as a reference mark on all (six) sites of each root. Therefore, an SPT evaluation usually only includes scoring of clinical probing depths
- Inspection of re-infected sites with pus formation
- Evaluation of existing reconstructions, including vitality checks for abutment teeth
- Exploration for carious lesions.

All these evaluations are performed for both teeth and oral implants. Occasionally, conventional dental radiographs should be obtained at SPT visits. Especially for devitalized teeth, abutment teeth and oral implants, single periapical films exposed with a parallel and preferably standardized technique are of great value. Bitewing radiographs are of special interest for caries diagnostic purposes. They also reveal plaque-retentive areas such as overhanging fillings and ill-fitting crown margins. Since only approximately 10–15 minutes are available for this section, these assessments have to be performed in a well-organized fashion. It is preferable to have a dental assistant available to note all the results of the diagnostic tests unless a voice-activated computer-assisted recording system is used.

Motivation, re-instruction, and instrumentation

This aspect uses most of the available time of the SPT visit. When informed about the results of the diagnostic procedures, for example the total percentage BoP score or the number of pockets exceeding 4 mm, the patient may be motivated either in a confirmatory way in the case of low scores or in a challenging fashion in the case of high scores. Since encouragement usually has a greater impact on future positive developments than negative criticism, every effort should be made to acknowledge the patient's performance.

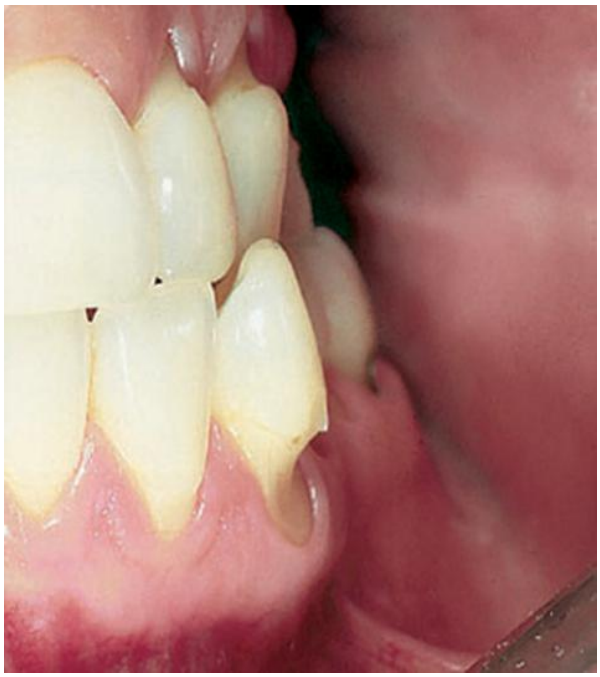

Fig. 60-10 Wedge-shaped defects apical to the cementoenamel junction following recession of the gingival tissues resulting from overzealous or faulty toothbrushing.

Patients who have experienced a relapse in their adequate oral hygiene practices need to be further motivated. Positive encouragement is especially appropriate if a patient's personal life situation has influenced his/her performance. Standard "lecturing" should be replaced by an individual approach.

Occasionally, patients present with hard tissue lesions (wedge-shaped dental defects) which suggest overzealous and/or faulty mechanical tooth cleaning (Fig. 60-10). Such habits should be broken and the patient re-instructed in toothbrushing techniques which emphasize vibratory rather than scrubbing movements.

Since it appears impossible to instrument 168 tooth sites in a complete dentition in the time allocated, only those sites which exhibit signs of inflammation and/or active disease progression will be re-instrumented during SPT visits. Trauma from repeated instrumentation of healthy sites will inevitably result in continued loss of attachment (Lindhe *et al*. 1982a). In contrast, residual pockets of ≥6 mm may lead to periodontitis progression and tooth loss (Badersten *et al*. 1990; Claffey *et al*. 1990, Matuliene *et al*. 2008). Interestingly, the association of the residual PPD with tooth loss over a mean of 11.3 years of maintenance was calculated at the site and at the tooth level (Table 60-3). Starting from a residual PPD of 4 mm, the increase of the PPD by 1 mm was highly statistically significantly associated with tooth loss

Table 60-3 Results from multilevel logistic regression models for the association of site probing pocket depth (PPD) and deepest PPD of a tooth at the end of therapy with tooth loss during supportive periodontal therapy of mean duration of 11.3 years (not accounting for bleeding on probing).

PPD (mm)	Site level			Tooth level		
	OR	95% CI	*P* value	OR	95% CI	*P* value
≤3	1.0					
4	2.6	2.2–3.1	<0.0001	2.5	1.8–3.6	<0.0001
5	5.8	4.3–7.9	<0.0001	7.7	4.8–12.3	<0.0001
6	9.3	6.2–13.9	<0.0001	11.0	6.1–20.1	<0.0001
≥7	37.9	17.9–80.2	<0.0001	64.2	24.9–165.1	<0.0001

Adapted from Matuliene *et al*. (2008), with permission from John Wiley & Sons.
OR, odds ratio; CI, confidence interval.

(Matuliene *et al*. 2008). Hence, all the BoP-positive sites and all pockets with a PPD exceeding 4 mm are carefully rescaled and root planed as instrumenting healthy sites repeatedly will inevitably result in mechanically-induced loss of attachment (Lindhe *et al*. 1982a).

Similar observations were made in clinical studies by Claffey *et al*. (1988): loss of clinical attachment levels immediately following instrumentation was observed in 24% of the sites. It is also known from regression analyses of several longitudinal studies (e.g. Lindhe *et al*. 1982b) that probing attachment may be lost following instrumentation of pockets below a "critical probing depth" of approximately 2.9 mm. Instrumentation of shallow sulci is, therefore, not recommended. As it has been shown in several studies that sites that do not bleed on probing represent stable sites (Lang *et al*. 1986, 1990; Joss *et al*. 1994), it appears reasonable to leave non-bleeding sites for polishing only and to concentrate on periodontal sites with a positive BoP test or PPD of >5 mm. To protect the hard tissues, root planing should be performed with great caution. The deliberate removal of "contaminated" cementum during SPT is no longer justified (Nyman *et al*. 1986, 1988; Mombelli *et al*. 1995). During SPT visits, root surface instrumentation should be aimed especially at the removal of subgingival plaque rather than "diseased" cementum. This may require a more differentiated approach than hitherto recommended. In this respect, the use of ultrasonics may have to be re-evaluated.

Treatment of re-infected sites

Single sites, especially furcation sites or sites that are difficult to access, may occasionally be re-infected and demonstrate suppuration. Such sites require a thorough instrumentation under anesthesia, the local application of antibiotics in controlled-release devices or even open debridement with surgical access. It is evident that such therapeutic procedures may be too time-consuming to be performed during the routine recall hour, and hence, it may be necessary to reschedule the patient for another appointment. Omission of thorough retreatment of such sites or only performing incomplete root instrumentation during SPT may result in continued loss of probing attachment (Kaldahl *et al*. 1988; Kalkwarf *et al*. 1989).

Treatment choices for re-infected sites should be based on an analysis of the most likely causes for the re-infection. Generalized re-infections are usually the result of inadequate SPT. Although not all sites positive for BoP may further progress and lose attachment, high BoP percentages call for more intensive care and more frequent SPT visits. Sometimes, a second visit 2–3 weeks after the recall may be indicated to check the patient's performance in oral home care. It is particularly important to supervise patients closely for advanced periodontitis if they have a high subject risk assessment (Westfelt *et al*. 1983b; Ramfjord 1987). Local re-infections may either be the result of inadequate plaque control in a local area or the formation of ecologic niches conducive to periodontal pathogens. The risk assessment at the tooth level may identify such niches which are inaccessible for regular oral hygiene practices. Furcation involvements often represent special periodontal risk factors which may require additional therapy to be performed following diagnosis in the regular SPT visit.

Polishing, fluorides, and determination of recall interval

The recall hour is concluded with polishing the entire dentition to remove all remaining soft deposits and stains. This may give the patient a feeling of freshness and facilitates the diagnosis of early carious lesions. Following polishing, fluorides should be applied in high concentration in order to replace the fluorides which may have been removed by instrumentation from the superficial layers of the teeth. Fluoride or chlorhexidine varnishes may also be applied to prevent root surface caries, especially in areas with gingival recession. The determination of future SPT visits must be based on the patient's risk assessment.

Summary: Figure 60-11 provides a flowchart for SPT. The SPT recall hour is divided into four sections. While the first 10–15 minutes are reserved for examination, re-evaluation, and diagnosis, the second and most time-consuming section of 30–40 minutes is devoted to re-instruction and instrumentation of sites identified to be at risk in the diagnostic process. Some re-infected sites may require further treatment, and hence, the patient may have to be rescheduled for an additional appointment. The recall hour is concluded by polishing the dentition, applying fluorides, and determining the frequency of future SPT visits.

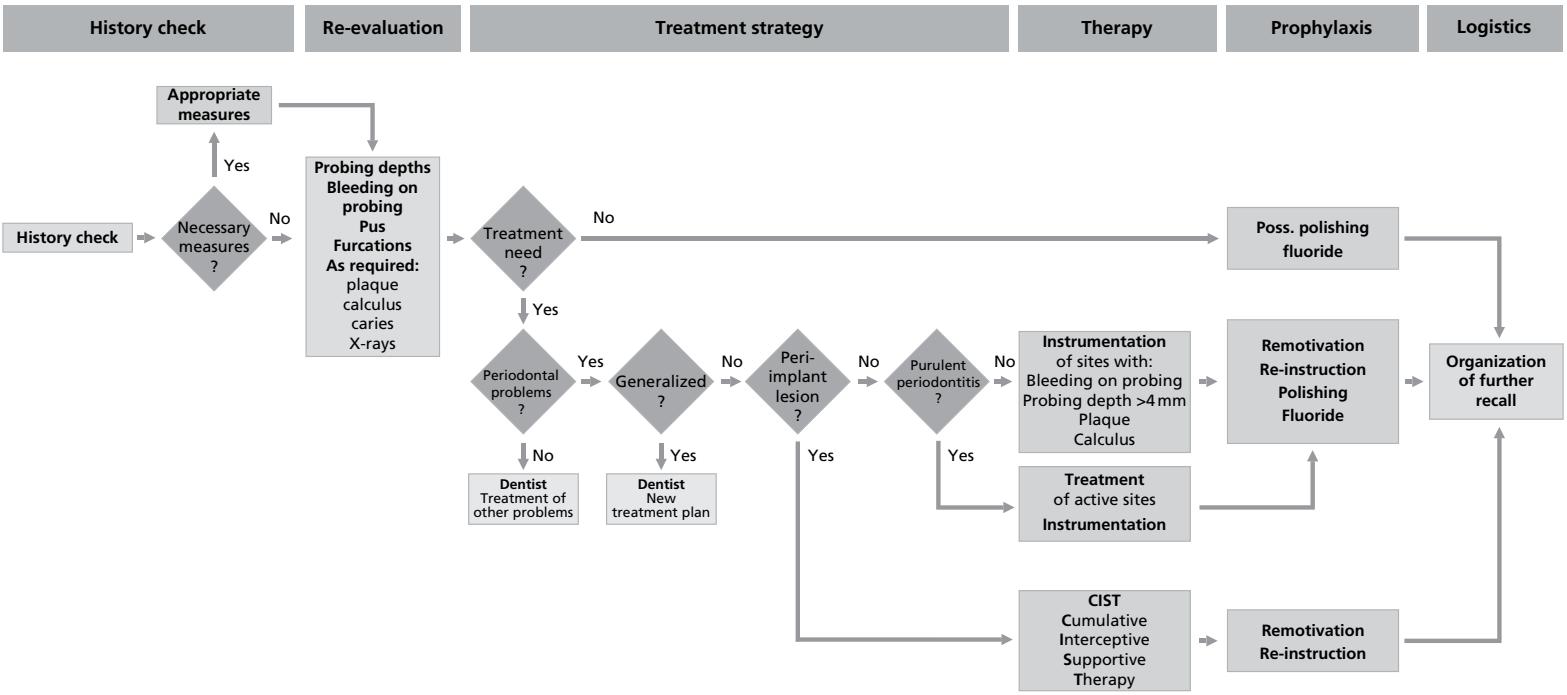

Fig. 60-11 Flow sheet of supportive periodontal therapy (SPT) with strategic decision tree for the recall visit.

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