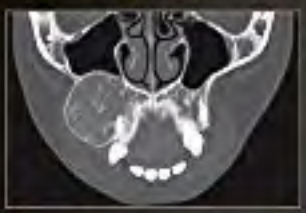
Oral and Maxillofacial PATHOLOGY

FOURTH EDITION



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Oral and Maxillofacial Pathology

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Fourth Edition

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This book is dedicated to three of our mentors:

Charles A. Waldron
William G. Shafer
Robert J. Gorlin

in appreciation for all that they taught us and in recognition of their contributions to the field of oral and maxillofacial pathology.

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Preface

About every seven years now, we receive a (dreaded?) phone call from our kindly editor suggesting that the time has arrived for us to write an updated edition of our textbook. This generally is followed by a lot of wailing and gnashing of teeth on the part of the authors—probably akin to the sound of children who have been asked to clean up their bedrooms. Just like children who may not see the necessity of changing their bed sheets, we often do not immediately appreciate the importance of revising our textbook. However, once the task is undertaken, the need becomes readily obvious.

It has become somewhat of a cliché to comment on how rapidly the world of dentistry and medicine is changing, but nothing could be closer to the truth. Admittedly, some areas seem to change very little (Fordyce granules will always be Fordyce granules). However, the expansion of our knowledge in many areas has been dramatic and, sometimes, even transformative (e.g., the relationship between high-risk strains of human papillomavirus and oropharyngeal carcinoma).

In addition to a complete update of information on previous topics, we also introduce a variety of new entities to this fourth edition, such as globodontia, lobodontia, localized juvenile spongiotic gingival hyperplasia, oral leishmaniasis, oral lesions associated with cosmetic fillers, IgG4-related disease, and mammary analogue secretory carcinoma of salivary gland origin. A total of 154 new images have been added, and we are greatly indebted to our many colleagues who have shared their excellent teaching photographs with us. We have attempted to be as thorough as possible in listing credit for these images. However, if someone's name has been inadvertently omitted, please accept our apologies.

A significant change in authorship has occurred in this fourth edition with the retirement of Dr. Jerry Bouquot, whose valuable efforts will be greatly missed. However, we are delighted and fortunate to add Dr. Angela Chi as full-fledged author/editor for this fourth edition, following up on the valuable contributions that she made to the third edition. Our great appreciation goes again to Dr. Edward Herschaft, who has updated his excellent chapter on Forensic Dentistry. We also thank Dr. Theresa Gonzales for her help with the revision of the chapter on Facial Pain and Neuromuscular Diseases. In addition, we must acknowledge the excellent guidance provided by the staff at Elsevier for their hard work and support in making this book a success. Special praise goes to Courtney Sprehe, Marquita Parker, and Kathy Falk for all of their efforts in the editorial process.

Finally, our greatest appreciation goes to our families, who again have provided us with their unconditional love and support during the long hours spent working on this latest edition. We never could have accomplished it without you.

Brad W. Neville
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1 Developmental Defects of the Oral and Maxillofacial Region

OROFACIAL CLEFTS

The formation of the face and oral cavity is complex in nature and involves the development of multiple tissue processes that must merge and fuse in a highly orchestrated fashion. Disturbances in the growth of these tissue processes or their fusion may result in the formation of **orofacial clefts.**

Development of the central face begins around the end of the fourth week of human development with the appearance of the nasal (olfactory) placodes on either side of the inferior aspect of the frontonasal process. Proliferation of ectomesenchyme on both sides of each placode results in the formation of the medial and lateral nasal processes. Between each pair of processes is a depression, or nasal pit, that represents the primitive nostril.

During the sixth and seventh weeks of development, the upper lip forms when the medial nasal processes merge with each other and with the maxillary processes of the first branchial arches. Thus the midportion of the upper lip is derived from the medial nasal processes, and the lateral portions are derived from the maxillary processes. The lateral nasal processes are not involved in the formation of the upper lip, but they give rise to the alae of the nose.

The **primary palate** also is formed by the merger of the medial nasal processes to form the intermaxillary segment. This segment gives rise to the premaxilla, a triangular-shaped piece of bone that will include the four incisor teeth. The **secondary palate,** which makes up 90% of the hard and soft palates, is formed from the maxillary processes of the first branchial arches.

During the sixth week, bilateral projections emerge from the medial aspects of the maxillary processes to form the palatal shelves. Initially, these shelves are oriented in a vertical position on each side of the developing tongue. As the mandible grows, the tongue drops down, allowing the palatal shelves to rotate to a horizontal position and grow toward one another. By the eighth week, sufficient growth has occurred to allow the anterior aspects of these shelves to begin fusion with one another. The palatal shelves also fuse with the primary palate and the nasal septum. The fusion of the palatal shelves begins in the anterior palate and progresses posteriorly; it is completed by the twelfth week.

Defective fusion of the medial nasal process with the maxillary process leads to **cleft lip (CL).** Likewise, failure of the palatal shelves to fuse results in **cleft palate (CP).** Frequently, CL and CP occur together. Approximately 45% of cases are CL + CP with 30% being CP only (CPO) and 25% being isolated CL. Both isolated CL and CL associated with CP are thought to be etiologically related conditions and can be considered as a group: CL, with or without CP (i.e., CL ± CP). Isolated CPO appears to represent a separate entity from CL ± CP.

The cause of CL ± CP and CPO is still being debated. First of all, distinguishing isolated clefts from cases associated with specific syndromes is important. Although many facial clefts are isolated anomalies, more than 400 developmental syndromes have been identified that may be associated with CL ± CP or CPO. Studies have suggested that up to 30% of patients with CL ± CP and 50% of those with CPO have associated anomalies. Some of these cases are single-gene syndromes that may follow autosomal dominant, autosomal recessive, or X-linked inheritance patterns. Other syndromes are the result of chromosome anomalies or are idiopathic.

The cause of nonsyndromic clefts does not follow any simple Mendelian pattern of inheritance but appears to be heterogeneous. Thus the propensity for cleft development may be related to a number of major genes, minor genes, and environmental factors that can combine to surpass a developmental threshold. Numerous candidate clefting genes and loci have been identified on different chromosome regions. Maternal alcohol consumption has been associated with an increased risk for both syndromic and nonsyndromic clefts. Maternal cigarette smoking at least doubles the frequency of cleft development compared with nonsmoking mothers. An increased frequency also has been related to anticonvulsant therapy, especially phenytoin, which causes a nearly tenfold greater risk of cleft formation. Although evidence has been mixed, a number of studies have suggested that folic acid supplementation may play a role in prevention of orofacial clefts.

CL ± CP and CPO represent the vast majority of orofacial clefts. However, other rare clefts also may occur.

The **lateral facial cleft** is caused by lack of fusion of the maxillary and mandibular processes and represents 0.3% of all facial clefts. This cleft may be unilateral or bilateral, extending from the commissure toward the ear, resulting in macrostomia. The lateral facial cleft may occur as an isolated defect, but more often it is associated with other disorders, such as the following:

- Mandibulofacial dysostosis (see page 41)
- Oculo-auriculo-vertebral spectrum (hemifacial microsomia)
- Nager acrofacial dysostosis
- Amniotic rupture sequence

The **oblique facial cleft** extends from the upper lip to the eye. It is nearly always associated with CP, and severe forms often are incompatible with life. The oblique facial cleft may involve the nostril, as in CL, or it may bypass the nose laterally as it extends to the eye. This cleft is rare, representing only 1 in 1300 facial clefts. Some of these clefts may represent failure of fusion of the lateral nasal process with the maxillary process; amniotic bands may cause others.

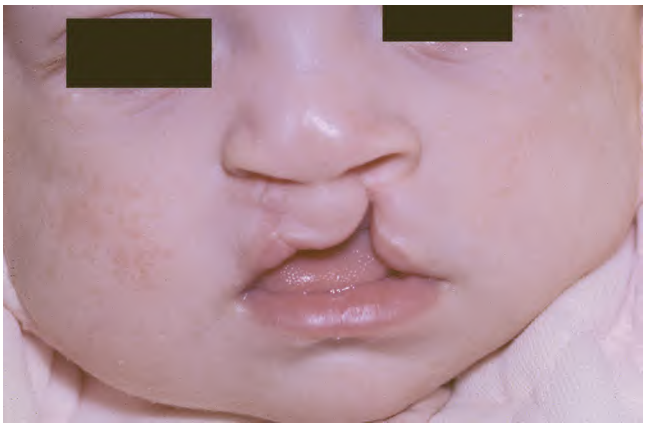
Median cleft of the upper lip is an extremely rare anomaly that results from failure of fusion of the medial nasal processes. It may be associated with a number of syndromes, including the oral-facial-digital syndromes and Ellis-van Creveld syndrome. Most apparent median clefts of the upper lip actually represent agenesis of the primary palate associated with holoprosencephaly.

Clinical and Radiographic Features

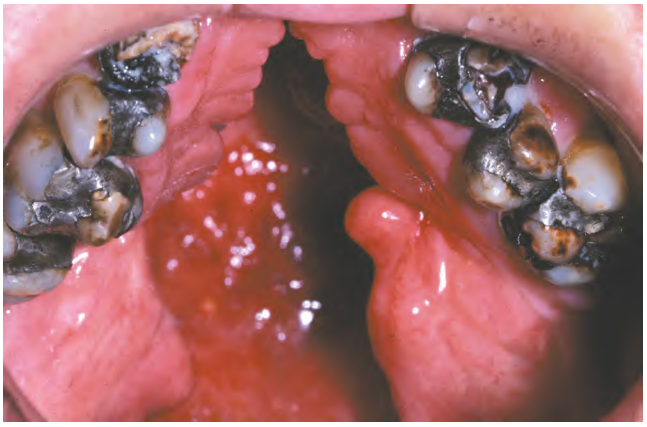
Clefting is one of the most common major congenital defects in humans. Considerable racial variation in prevalence is seen. In whites, CL ± CP occurs in 1 of every 700 to 1000 births. The frequency of CL ± CP in Asian populations is about 1.5 times higher than in whites. In contrast, the prevalence of CL ± CP in blacks is much lower, occurring in 0.4 of 1000 births. Native Americans appear to have the highest frequency, around 3.6 of 1000 births. CPO is less common than CL ± CP, with a frequency of 0.4 of 1000 births in whites and blacks.

CL ± CP is more common in males than in females. The more severe the defect, the greater the male predilection; the male-to-female ratio for isolated CL is 1.5 : 1; the ratio for CL + CP is 2 : 1. In contrast, CPO is more common in females. Likewise, the more severe the cleft, the greater the female predilection. Clefts of both the hard and soft palates are twice as common in females, but the ratio is nearly equal for clefts of the soft palate only.

Approximately 80% of cases of CL will be unilateral with 20% bilateral (Fig. 1-1). Approximately 70% of unilateral CLs occur on the left side. In addition, about 70% of unilateral CLs will be associated with CP, whereas the frequency of concomitant CP increases to 85% for patients with bilateral CL. A complete CL extends upward into the nostril, but an incomplete CL does not involve the nose. Complete clefts involving the alveolus usually occur between the lateral incisor and cuspid. It is not unusual for teeth, especially the lateral incisor, to be missing in the cleft area. Conversely, supernumerary teeth may be discovered. The bony defect can be observed on radiographs.



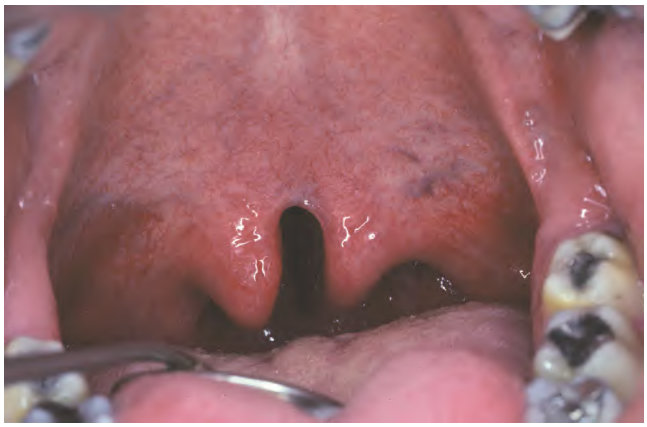
• **Fig. 1-1 Cleft Lip (CL).** Infant with bilateral cleft of the upper lip. (Courtesy of Dr. William Bruce.)



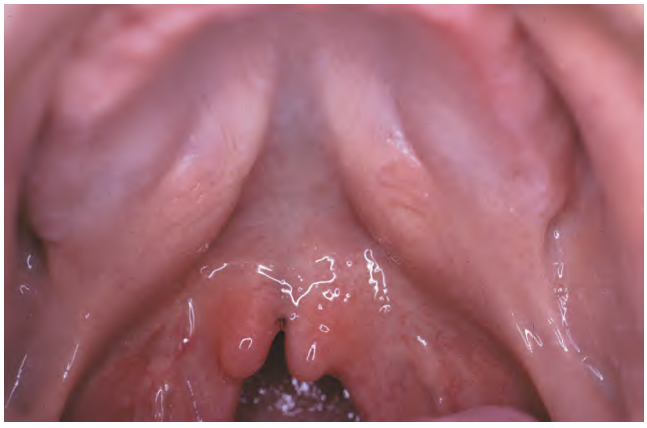
• **Fig. 1-2 Cleft Palate (CP).** Palatal defect resulting in communication with the nasal cavity.

A CP shows considerable range in severity (Fig. 1-2). The defect may involve the hard and soft palates or the soft palate alone. The minimal manifestation of CP is a **cleft** or **bifid uvula** (Fig. 1-3). The prevalence of cleft uvula is much higher than that of CP, with a frequency of 1 in every 80 white individuals. The frequency in Asian and Native American populations is as high as 1 in 10. Cleft uvula is less common in blacks, occurring in 1 out of every 250 persons.

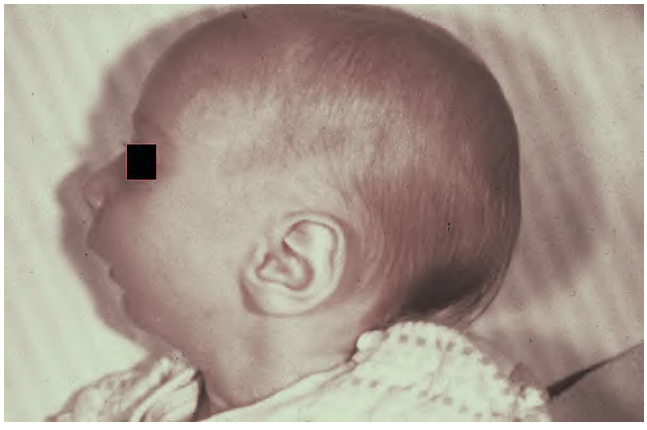
In some instances a **submucous palatal cleft** develops. The surface mucosa is intact, but a defect exists in the underlying musculature of the soft palate (Fig. 1-4). Frequently a notch in the bone is present along the posterior margin of the hard palate. This incomplete cleft occasionally appears as a bluish midline discoloration but is best identified by palpation with a blunt instrument. An associated cleft uvula also usually is seen.



• **Fig. 1-3 Bifid Uvula.**



• **Fig. 1-4 Submucous Palatal Cleft.** A cleft of the midline palatal bone exists, but the overlying mucosa is intact. A bifid uvula also is present.



• **Fig. 1-5 Pierre Robin Sequence.** Micrognathic mandible in an infant with cleft palate (CP). (Courtesy of Dr. Robert Gorlin.)

The **Pierre Robin sequence** (Pierre Robin anomalad) (Fig. 1-5) is a well-recognized presentation characterized by CP, mandibular micrognathia, and glossoptosis (airway obstruction caused by lower, posterior displacement of the tongue). The Pierre Robin sequence may occur as an isolated phenomenon, or it may be associated with a wide variety of syndromes or other anomalies. Stickler syndrome and velocardiofacial syndrome are the two most frequently associated genetic disorders. Researchers have theorized that constraint of mandibular growth *in utero* results in failure of the tongue to descend, thus preventing fusion of the palatal shelves. The retruded mandible results in the following:

- Posterior displacement of the tongue
- Lack of support of the tongue musculature
- Airway obstruction

Respiratory difficulty, especially when the child is in a supine position, usually is noted from birth and can cause asphyxiation. The palatal cleft often is U-shaped and wider than isolated CP.

The patient with a cleft is burdened with a variety of problems, some obvious and some less so. The most obvious problem is the clinical appearance, which may lead to psychosocial difficulties. Feeding and speech difficulties are inherent, especially with CP. Malocclusion is caused by collapse of the maxillary arch, possibly along with missing teeth, supernumerary teeth, or both.

Treatment and Prognosis

The management of the patient with an orofacial cleft is challenging. Ideally, treatment should involve a multidisciplinary approach, including (but not limited to) a pediatrician, oral and maxillofacial surgeon, otolaryngologist, plastic surgeon, pediatric dentist, orthodontist, prosthodontist, speech pathologist, and geneticist.

Surgical repair often involves multiple primary and secondary procedures throughout childhood. The specific types of surgical procedures and their timing will vary, depending on the severity of the defect and the philosophy of the treatment team. A detailed discussion of these procedures is beyond the scope of this text. However, primary lip closure usually is accomplished during the first few months of life, followed later by repair of the palate. Prosthetic and orthopedic appliances often are used to mold or expand the maxillary segments before closure of the palatal defect. Later in childhood, autogenous bone grafts can be placed in the area of the alveolar bone defect. Secondary soft tissue and orthognathic procedures may be used to improve function and cosmetic appearance. Distraction osteogenesis of the maxilla can prove useful in patients in whom palatal scarring limits the amount of advancement possible at the time of osteotomy.

Breathing difficulties in infants with Pierre Robin sequence are managed best with conservative measures, such as side and prone positioning. However, in children with significant airway obstruction, placement of a nasopharyngeal airway may be warranted. In more severe cases, mandibular distraction osteogenesis may be a preferable treatment alternative to tracheostomy.

Genetic counseling is important for the patient and family. In nonsyndromic cases of orofacial clefting, the risk for cleft development in a sibling or offspring of an affected

person is 3% to 5% if no other first-degree relatives also are affected. The risk increases to 10% to 20% if other first-degree relatives are affected. The risk may be even higher for those with clefts that are associated with syndromes, depending on the possible inheritance pattern.

◆ COMMISSURAL LIP PITS

Commissural lip pits are small mucosal invaginations that occur at the corners of the mouth on the vermilion border. Their location suggests that they may represent a failure of normal fusion of the embryonal maxillary and mandibular processes.

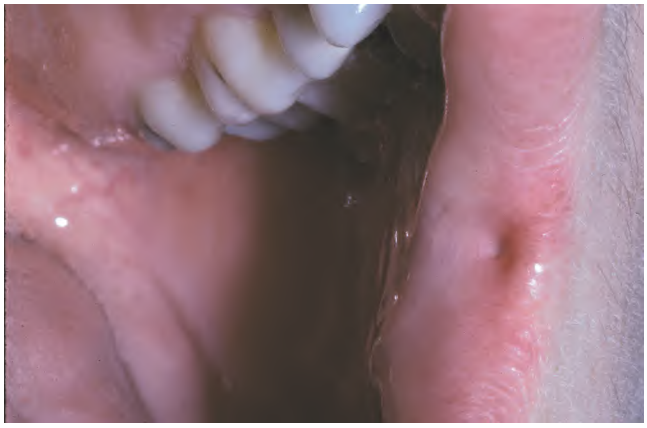
Commissural lip pits appear to be common in adults, where they have been reported in 12% to 20% of the population. Their prevalence in children is considerably lower, ranging from 0.2% to 0.7% of those examined.

Although commissural lip pits are generally considered to be congenital lesions, these figures suggest that these invaginations often develop later in life. Commissural pits are seen more often in males than in females. A family history suggestive of autosomal dominant transmission has been noted in some cases.

Clinical Features

Commissural lip pits usually are discovered on routine examination, and the patient often is unaware of their presence. These pits may be unilateral or bilateral. They manifest as blind fistulas that may extend to a depth of 1 to 4 mm (Fig. 1-6). In some cases, a small amount of fluid may be expressed when the pit is squeezed, presumably representing saliva from minor salivary glands that drain into the depth of the invagination.

Unlike **paramedian lip pits** (described in the following section), commissural lip pits are not associated with facial or palatal clefts. However, there does appear to be a significantly higher prevalence of preauricular pits (aural sinuses) in these patients.



• **Fig. 1-6 Commissural Lip Pit.** Depression at the labial commissure.

Histopathologic Features

Although biopsy rarely is performed for patients with commissural lip pits, microscopic examination reveals a narrow invagination lined by stratified squamous epithelium. Ducts from minor salivary glands may drain into this invagination.

Treatment and Prognosis

Because commissural lip pits are virtually always asymptomatic and innocuous, no treatment is usually necessary. In extremely rare instances, salivary secretions may be excessive or secondary infection may occur, necessitating surgical excision of the pit.

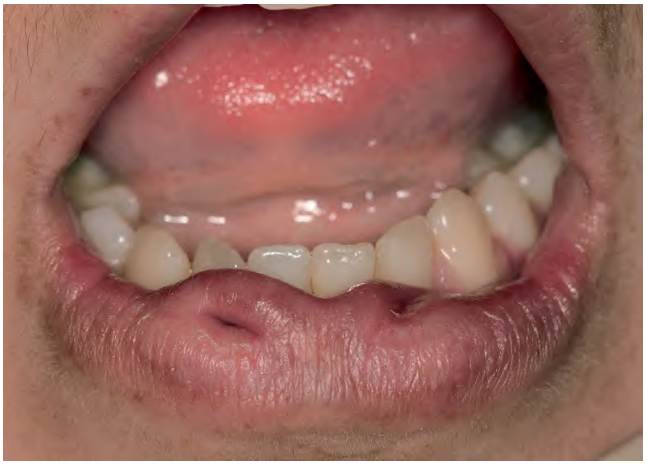
◆ PARAMEDIAN LIP PITS (CONGENITAL FISTULAS OF THE LOWER LIP; CONGENITAL LIP PITS)

Paramedian lip pits are rare congenital invaginations of the lower lip. They are believed to arise from persistent lateral sulci on the embryonic mandibular arch. These sulci normally disappear by 6 weeks of embryonic age.

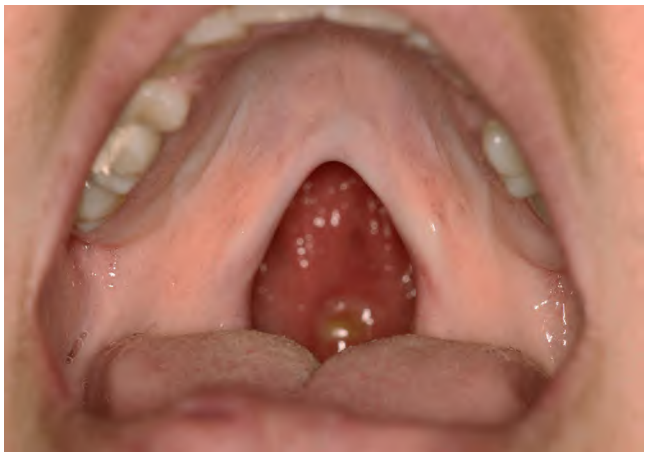
Clinical Features

Paramedian lip pits typically appear as bilateral and symmetric fistulas on either side of the midline of the vermilion of the lower lip (Fig. 1-7). Their appearance can range from subtle depressions to prominent humps. These blind sinuses can extend down to a depth of 1.5 cm and may express salivary secretions. Occasionally, only a single pit is present that may be centrally located or lateral to the midline.

The greatest significance of paramedian lip pits is that they usually are inherited as an autosomal dominant trait in combination with cleft lip (CL) and/or cleft palate (CP)



• **Fig. 1-7 Paramedian Lip Pits.** Bilateral pits on the lower lip in a patient with van der Woude syndrome. (Courtesy of Dr. Nadarajah Vigneswaran.)



• **Fig. 1-8 Van der Woude Syndrome.** Same patient as depicted in Figure 1-7 with a cleft of the soft palate. (Courtesy of Dr. Nadarajah Vigneswaran.)

(van der Woude syndrome) (Fig. 1-8). Van der Woude syndrome is the most common form of syndromic clefting and accounts for 2% of all cases of CL and CP. Associated hypodontia also may be observed. Genetic studies have shown that this condition is caused by mutations in the gene that encodes interferon regulatory factor 6 (IRF6), which has been mapped to chromosome locus 1q32-q41. Some people who carry the trait may not demonstrate clefts or may have a submucous CP; however, they may pass the full syndrome to their offspring.

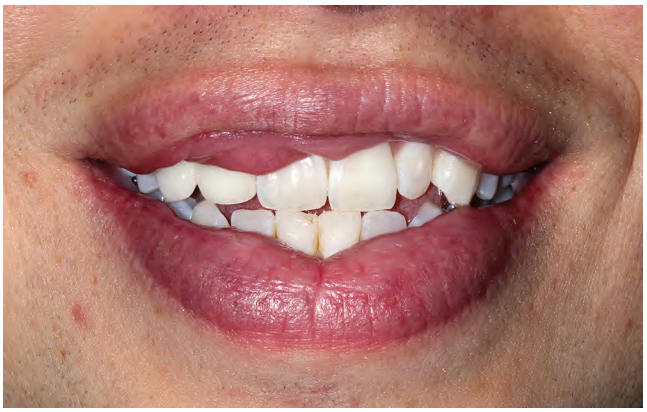
Paramedian lip pits also may be a feature of the **popliteal pterygium syndrome** and **Kabuki syndrome.** Popliteal webbing **(pterygia),** CL and/or CP, genital abnormalities, and congenital bands connecting the upper and lower jaws **(syngnathia)** characterize popliteal pterygium syndrome, which is closely related to van der Woude syndrome. Kabuki syndrome received its name because affected patients exhibit eversion of the lower lateral eyelids, which is reminiscent of the makeup used by actors in Kabuki, the traditional form of Japanese theater. Other common findings include intellectual disability, large ears, CL and/or CP, hypodontia, joint laxity, and various skeletal abnormalities.

Histopathologic Features

Microscopic examination of a paramedian lip pit shows a tract that is lined by stratified squamous epithelium. Minor salivary glands may communicate with the sinus. A chronic inflammatory cell infiltrate often is noted in the surrounding connective tissue.

Treatment and Prognosis

If necessary, the labial pits may be excised for cosmetic reasons. The most significant problems are related to associated congenital anomalies, such as CL and/or CP, and the potential for transmission of the trait to subsequent generations.



• **Fig. 1-9 Double Lip.** When the patient smiles, a redundant fold of tissue partially covers the right anterior maxillary teeth. (Courtesy of Dr. Logan Barnes.)

◆ DOUBLE LIP

Double lip is a rare oral anomaly characterized by a redundant fold of tissue on the mucosal side of the lip. Most often it is congenital in nature, but it may be acquired later in life. Congenital cases are believed to arise during the second to third month of gestation as a result of the persistence of the sulcus between the pars glabrosa and pars villosa of the lip. Acquired double lip may be a component of **Ascher syndrome,** or it may result from trauma or oral habits, such as sucking on the lip.

Clinical Features

In a patient with double lip, the upper lip is affected much more often than the lower lip; occasionally, both lips are involved. With the lips at rest, the condition is usually unnoticeable, but when the patient smiles or when the lips are tensed, the excess fold of tissue is visible (Fig. 1-9).

Ascher syndrome is characterized by a triad of features:

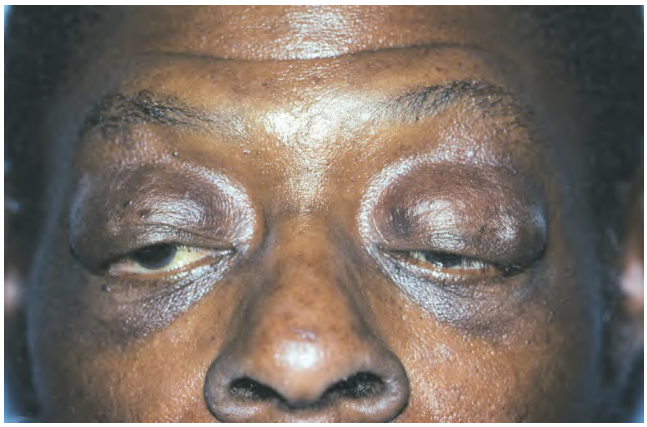
- Double lip
- Blepharochalasis
- Nontoxic thyroid enlargement

In a person with blepharochalasis, recurring edema of the upper eyelid leads to sagging of the lid at the outer canthus of the eye (Fig. 1-10). This drooping may be severe enough to interfere with vision. Both the double lip and blepharochalasis usually occur abruptly and simultaneously, but in some cases they develop more gradually.

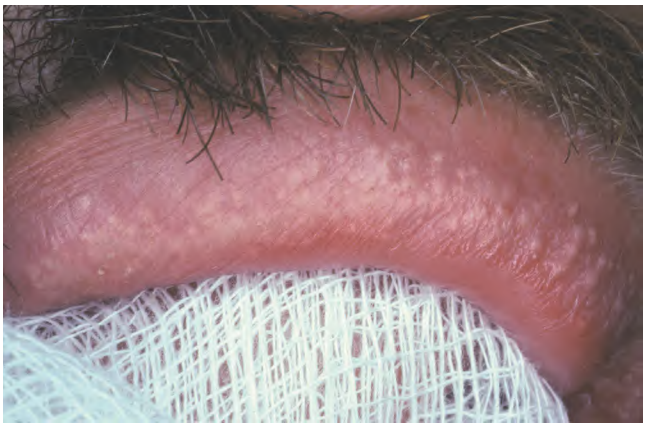
The nontoxic thyroid enlargement occurs in as many as 50% of patients with Ascher syndrome and may be mild in degree. The cause of Ascher syndrome is not certain; autosomal dominant inheritance has been suggested in some cases.

Histopathologic Features

On microscopic examination, double lip shows essentially normal structures. Often there is an abundance of minor



• **Fig. 1-10 Ascher Syndrome.** Edema of the upper eyelids (blepharochalasis).



• **Fig. 1-11 Fordyce Granules.** Yellow papules on the vermilion of the upper lip.

salivary glands. The blepharochalasis of Ascher syndrome usually shows hyperplasia of the lacrimal glands or prolapse of orbital fat.

Treatment and Prognosis

In mild cases of double lip, no treatment may be required. In more severe cases, simple surgical excision of the excess tissue can be performed for aesthetic purposes.

◆ FORDYCE GRANULES

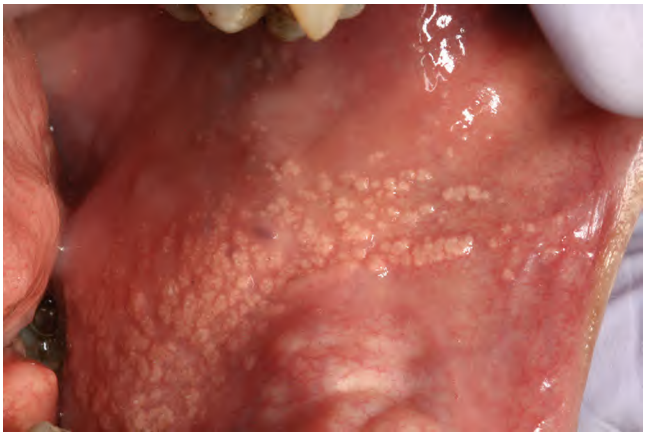
Fordyce granules are sebaceous glands that occur on the oral mucosa. Similar lesions also have been reported on the genital mucosa. Because sebaceous glands typically are considered to be dermal adnexal structures, those found in the oral cavity often have been considered to be "ectopic." However, because Fordyce granules have been reported in more than 80% of the population, their presence must be considered a normal anatomic variation.

Clinical Features

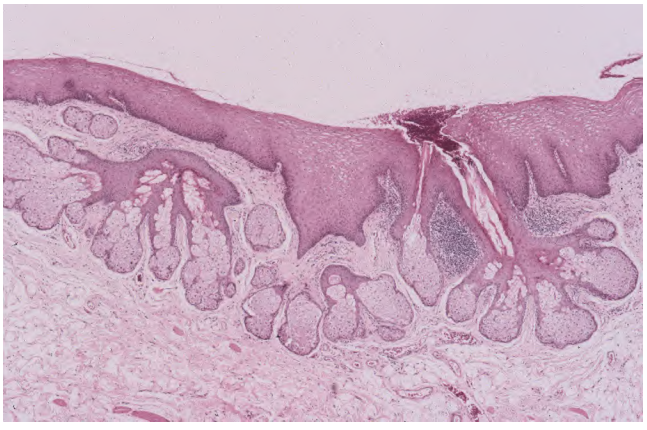
Fordyce granules appear as multiple yellow or yellow-white papules that are most common on the buccal mucosa and the lateral portion of the vermilion of the upper lip (Figs. 1-11 and 1-12). Occasionally, these glands also may appear in the retromolar area and anterior tonsillar pillar. They are more common in adults than in children, probably as a result of hormonal factors; puberty appears to stimulate their development. The lesions are typically asymptomatic, although patients may be able to feel a slight roughness to the mucosa. Considerable clinical variation may exist; some patients may have only a few lesions, whereas others may have literally hundreds of these "granules."

Histopathologic Features

Except for the absence of associated hair follicles, Fordyce granules closely resemble normal sebaceous glands found in the skin. Acinar lobules can be seen immediately beneath the epithelial surface, often communicating with the surface through a central duct (Fig. 1-13). The sebaceous cells in these lobules are polygonal in shape, containing centrally located nuclei and abundant foamy cytoplasm.



• **Fig. 1-12 Fordyce Granules.** Lesions on the buccal mucosa.



• **Fig. 1-13 Fordyce Granules.** Multiple sebaceous glands below the surface epithelium.

Treatment and Prognosis

Because Fordyce granules represent a normal anatomic variation and are asymptomatic, no treatment is indicated. Usually, the clinical appearance is characteristic and biopsy is not necessary for diagnosis.

On occasion, Fordyce granules may become hyperplastic or may form keratin-filled pseudocysts. Tumors arising from these glands are exceedingly rare.

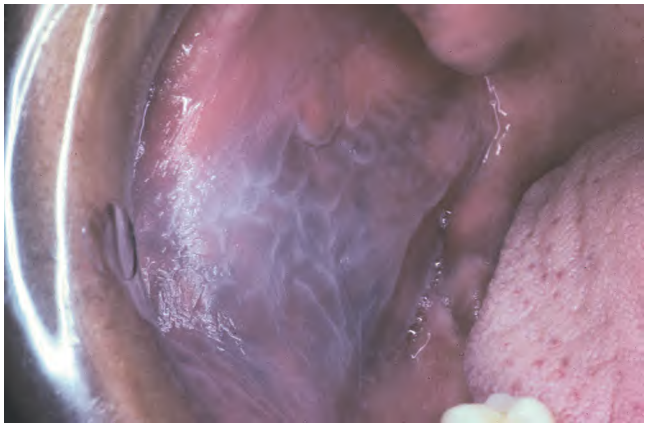
◆ LEUKOEDEMA

Leukoedema is a common oral mucosal condition of unknown cause. It occurs more commonly in blacks than in whites, supporting the likelihood of an ethnic predisposition to its development. Leukoedema has been reported in 70% to 90% of black adults and in 50% of black children. The prevalence in whites is considerably less, although published reports have ranged from less than 10% to more than 90%. This variation may reflect differing population groups, examination conditions, and stringency of criteria used to make the diagnosis. At any rate, leukoedema shows a much milder presentation in whites and often is hardly noticeable. The difference in racial predilection may be explained by the presence of background mucosal pigmentation in blacks that makes the edematous changes more noticeable.

Because leukoedema is so common, it can reasonably be argued that it represents a *variation of normal* rather than a disease. The finding of similar edematous mucosa in the vagina and larynx further supports this argument. Although leukoedema appears to be developmental in nature, some studies have indicated that it is more common and more severe in smokers and becomes less pronounced with cessation of smoking.

Clinical Features

Leukoedema is characterized by a diffuse, gray-white, milky, opalescent appearance of the mucosa (Fig. 1-14). The surface frequently appears folded, resulting in wrinkles or whitish streaks. The lesions do not rub off. Leukoedema typically occurs bilaterally on the buccal mucosa and may extend forward onto the labial mucosa. On rare occasions, it also can involve the floor of the mouth and palatopharyngeal tissues. Leukoedema can be easily diagnosed clinically because the white appearance greatly diminishes or disappears when the cheek is everted and stretched (Fig. 1-15).



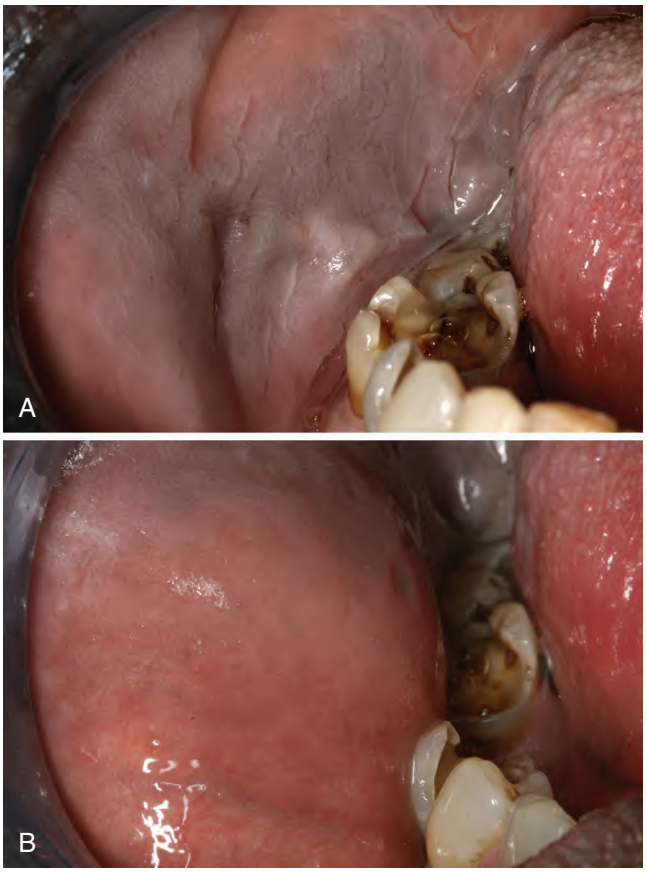
• **Fig. 1-14 Leukoedema.** White, wrinkled appearance of the buccal mucosa.

Histopathologic Features

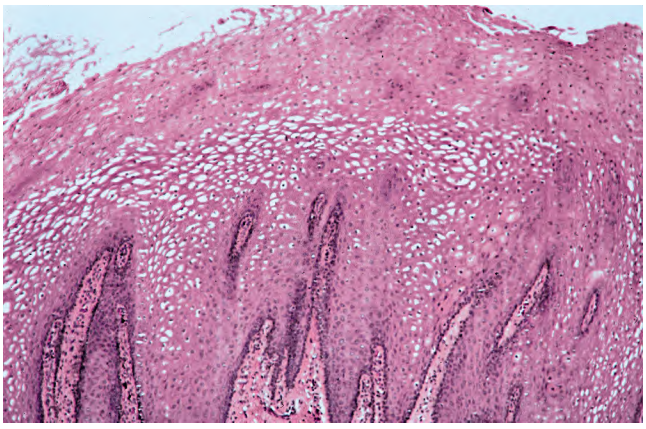
Biopsy specimens of leukoedema demonstrate an increase in thickness of the epithelium with striking intracellular edema of the spinous layer (Fig. 1-16). These vacuolated cells appear large and have pyknotic nuclei. The epithelial surface is frequently parakeratinized, and the rete ridges are broad and elongated.

Treatment and Prognosis

Leukoedema is a benign condition, and no treatment is required. The characteristic milky-white, opalescent lesions of the buccal mucosa that disappear when stretched help distinguish it from other common white lesions, such as leukoplakia, candidiasis, and lichen planus. The affected mucosa always should be stretched during clinical



• **Fig. 1-15 Leukoedema. A,** Diffuse white appearance of the buccal mucosa. **B,** Whiteness disappears when the cheek is stretched.



• **Fig. 1-16 Leukoedema.** Parakeratosis and intracellular edema of the spinous layer.

examination to rule out any underlying lesions that may be hidden by the edematous change.

◆ MICROGLOSSIA (HYPOGLOSSIA)

Clinical Features

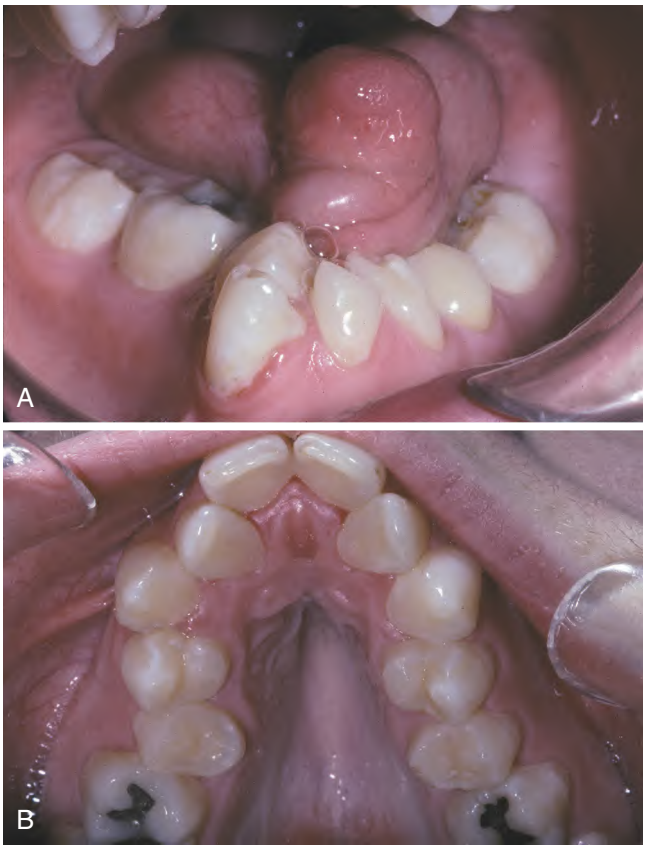
Microglossia is an uncommon developmental condition of unknown cause that is characterized by an abnormally small tongue. In rare instances, virtually the entire tongue may be missing **(aglossia).** Isolated microglossia is known to occur, and mild degrees of microglossia may be difficult to detect and may go unnoticed. However, most reported cases have been associated with one of a group of overlapping conditions known as **oromandibular-limb hypogenesis syndromes.** These syndromes feature associated limb anomalies, such as **hypodactylia** (i.e., absence of digits) and **hypomelia** (i.e., hypoplasia of part or all of a limb). Other patients have had coexisting anomalies, such as cleft palate, intraoral bands, and *situs inversus*. Microglossia frequently is associated with hypoplasia of the mandible, and the lower incisors may be missing (Fig. 1-17).

Treatment and Prognosis

Treatment of the patient with microglossia depends on the nature and severity of the condition. Surgery and orthodontics may improve oral function. Surprisingly, speech development often is quite good but depends on tongue size.

◆ MACROGLOSSIA

Macroglossia is an uncommon condition characterized by enlargement of the tongue. The enlargement may be caused by a wide variety of conditions, including congenital malformations and acquired diseases. The most frequent causes are vascular malformations and muscular hypertrophy. Box 1-1 lists the most common and important causes of macroglossia. Many of these diseases are discussed in greater detail in subsequent chapters of this book.



• **Fig. 1-17 Microglossia. A,** Abnormally small tongue associated with constricted mandibular arch. **B,** Same patient with associated constriction of the maxillary arch.

• BOX 1-1 Causes of Macroglossia

Congenital and Hereditary

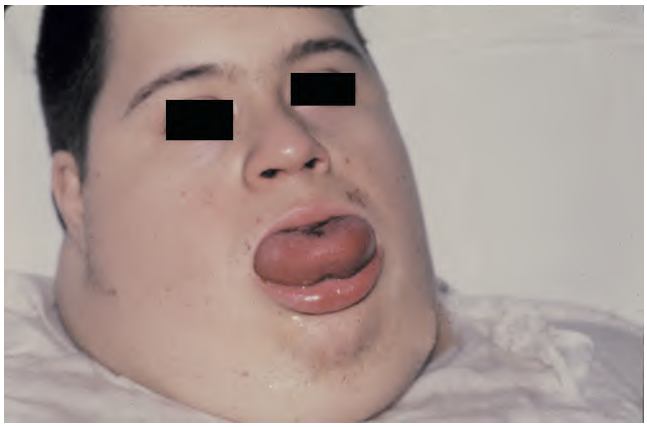
- Vascular malformations
- Lymphangioma
- Hemangioma
- Hemihyperplasia
- Cretinism
- Beckwith-Wiedemann syndrome
- Down syndrome
- Duchenne muscular dystrophy
- Mucopolysaccharidoses
- Neurofibromatosis type I
- Multiple endocrine neoplasia, type 2B

Acquired

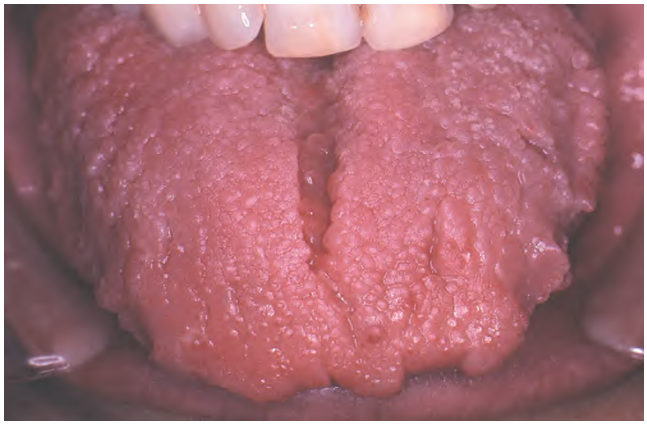
- Edentulous patients
- Amyloidosis
- Myxedema
- Acromegaly
- Angioedema
- Myasthenia gravis
- Amyotrophic lateral sclerosis
- Carcinoma and other tumors

Clinical Features

Macroglossia most commonly occurs in children and can range from mild to severe (Fig. 1-18). In infants,



• **Fig. 1-18 Macroglossia.** Large tongue in a patient with Down syndrome. (Courtesy of Dr. Sanford Fenton.)



• **Fig. 1-19 Macroglossia.** The tongue enlargement has resulted in a crenated border that corresponds to the embrasures between the teeth.

macroglossia may be manifested first by noisy breathing, drooling, and difficulty in eating. The tongue enlargement may result in a lisping speech. The pressure of the tongue against the mandible and teeth can produce a crenated lateral border to the tongue (Fig. 1-19), open bite, and mandibular prognathism. If the tongue constantly protrudes from the mouth, it may ulcerate and become secondarily infected or may even undergo necrosis. Severe macroglossia can produce airway obstruction.

Macroglossia is a characteristic feature of **Beckwith-Wiedemann syndrome,** a rare hereditary condition that includes many other possible defects, such as the following:

- Omphalocele (i.e., protrusion of part of the intestine through a defect in the abdominal wall at the umbilicus)
- Visceromegaly
- Gigantism
- Neonatal hypoglycemia

Individuals with Beckwith-Wiedemann syndrome have an increased risk for several childhood visceral tumors, including Wilms tumor, adrenal carcinoma, hepatoblastoma, rhabdomyosarcoma, and neuroblastoma. Facial features may include nevus flammeus of the forehead and eyelids, linear indentations of the earlobes, and maxillary hypoplasia (resulting in relative mandibular prognathism). Most examples of Beckwith-Wiedemann syndrome are sporadic, but 10% to 15% of cases show autosomal dominant inheritance with preferential maternal transmission. The genetic basis is complex, involving a variety of alterations within two domains of imprinted growth-regulatory genes on chromosome 11p15.

In patients with **hypothyroidism** (see page 777), Beckwith-Wiedemann syndrome, or neuromuscular disorders, the tongue usually shows a diffuse, smooth, generalized enlargement. In those with other forms of macroglossia, the tongue usually has a multinodular appearance. Examples of this nodular type include **amyloidosis** (see page 766) and neoplastic conditions, such as **neurofibromatosis** (see page 495) and **multiple endocrine neoplasia, type 2B** (see page 497).

In patients with **lymphangiomas** (see page 510), the tongue surface is characteristically pebbly and exhibits multiple vesicle-like blebs that represent superficial dilated lymphatic channels. The enlarged tongue in those with **Down syndrome** typically demonstrates a papillary, fissured surface.

In patients with **hemifacial hyperplasia** (see page 35), the enlargement will be unilateral. Some patients with neurofibromatosis also can have unilateral lingual enlargement.

In edentulous patients, the tongue often appears elevated and tends to spread out laterally because of loss of the surrounding teeth; as a result, wearing a denture may become difficult.

Histopathologic Features

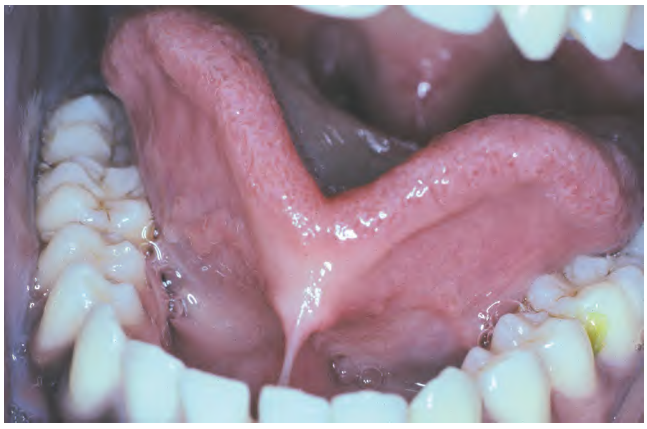
The microscopic appearance of macroglossia depends on the specific cause. In some cases, such as the tongue enlargement seen with Down syndrome or in edentulous patients, no histologic abnormality can be detected. When macroglossia is due to tumor, a neoplastic proliferation of a particular tissue can be found (e.g., lymphatic vessels, blood vessels, neural tissue). Muscular enlargement occurs in those with hemihyperplasia and Beckwith-Wiedemann syndrome. In neuromuscular disorders, such as myasthenia gravis or amyotrophic lateral sclerosis, tongue enlargement may result from muscular atrophy with prominent fatty replacement. In the patient with amyloidosis, an abnormal protein material is deposited in the tongue.

Treatment and Prognosis

The treatment and prognosis of macroglossia depend on the cause and severity of the condition. In mild cases, surgical treatment may not be necessary, although speech therapy may be helpful if speech is affected. In symptomatic patients, reduction glossectomy may be needed.

◆ ANKYLOGLOSSIA (TONGUE-TIE)

Ankyloglossia is a developmental anomaly of the tongue characterized by a short, thick lingual frenum resulting in



• **Fig. 1-20 Ankyloglossia.** Abnormal attachment of the lingual frenum, limiting tongue mobility.

limitation of tongue movement. It has been reported to occur in 1.7% to 10.7% of neonates, being more common in boys than in girls. In adults, mild forms are not unusual, but severe ankyloglossia is a relatively uncommon condition that has been estimated to occur in about two to three of every 10,000 people. Most examples of ankyloglossia appear to be sporadic, although evidence suggests that there could be a genetic influence in some cases.

Clinical Features

Ankyloglossia can range in severity from mild cases with little clinical significance to rare examples of complete ankyloglossia in which the tongue is actually fused to the floor of the mouth (Fig. 1-20). Sometimes the frenum extends forward and attaches to the tip of the tongue, and slight clefting of the tip may be seen.

Some investigators have speculated that ankyloglossia may lead to the development of an anterior open bite because the inability to raise the tongue to the roof of the mouth prevents development of the normal adult swallowing pattern. However, others have questioned this theory. It also is possible that a high mucogingival attachment of the lingual frenum may contribute to gingival recession, although a clear relationship has not been established.

It has been suggested that tongue-tie may result in speech defects. Usually, however, the shortened frenum results in only minor difficulties because most people can compensate for the limitation in tongue movement. Yet there are rare examples of patients who have experienced an immediate noticeable improvement in speech after surgical correction of ankyloglossia. With the increase in popularity of breast-feeding over the past several decades, clinicians have related tongue-tie with feeding problems, such as nipple pain or difficulty in the baby attaching to the breast.

Treatment and Prognosis

Because most cases of ankyloglossia result in few or no clinical problems, treatment is often unnecessary. For infants with specific breast-feeding problems, a frenotomy ("clipping" or simple release of the frenulum) can be performed, which has been shown to improve nipple-pain and breast-feeding scores. In children or adults with associated functional or periodontal difficulties, a frenuloplasty (release with plastic repair) may allow greater freedom of tongue movement. In young children, it often is recommended that surgery be postponed until age 4 or 5. Because the tongue is always short at birth, assessing the degree of tongue limitation caused by ankyloglossia is difficult in the infant's early life. As the infant grows, the tongue becomes longer and thinner at the tip, often decreasing the severity of the tongue-tie. The condition probably is self-correcting in many cases because it is less common in adults.

◆ LINGUAL THYROID

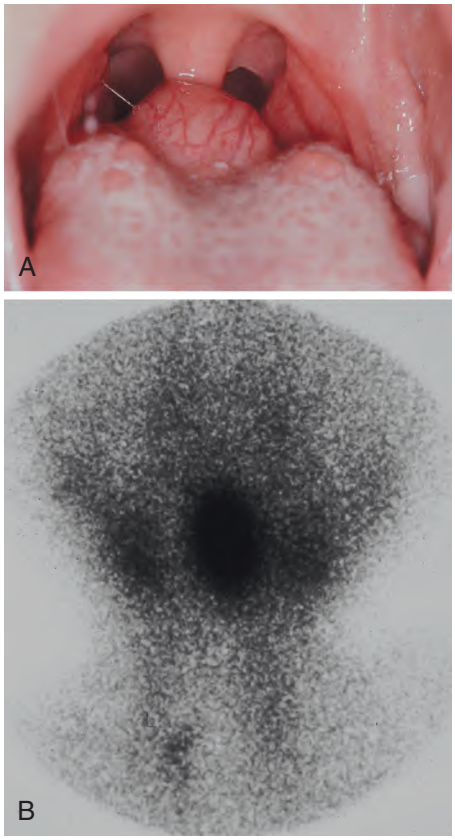
During the third to fourth week of fetal life, the thyroid gland begins as an epithelial proliferation in the floor of the pharyngeal gut. By the seventh embryonic week, this thyroid bud normally descends into the neck to its final resting position anterior to the trachea and larynx. The site where this descending bud invaginates later becomes the foramen cecum, located at the junction of the anterior two-thirds and posterior third of the tongue in the midline. If the primitive gland does not descend normally, ectopic thyroid tissue may be found between the foramen cecum and the epiglottis. Of all ectopic thyroids, 90% are found in this region.

Clinical Features

Based on autopsy studies, small asymptomatic remnants of thyroid tissue can be discovered on the posterior dorsal tongue in about 10% of both men and women. However, clinically evident or symptomatic **lingual thyroids** are much less common and are four to seven times more frequent in females, presumably because of hormonal influences. Symptoms most often develop during puberty, adolescence, pregnancy, or menopause. In 70% of cases, this ectopic gland is the patient's only thyroid tissue.

Lingual thyroids may range from small, asymptomatic, nodular lesions to large masses that can block the airway (Fig. 1-21). The most common clinical symptoms are dysphagia, dysphonia, and dyspnea. The mass often is vascular, but the physical appearance is variable, and there are no reliable features to distinguish it from other masses that might develop in this area. Hypothyroidism has been reported in up to 33% of patients. Many authors say that lingual thyroid enlargement is a secondary phenomenon, compensating for thyroid hypofunction. Interestingly, as many as 75% of patients with infantile hypothyroidism have some ectopic thyroid tissue.

Diagnosis is best established by thyroid scan using iodine isotopes or technetium-99m (^{99m}Tc). Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography can be helpful in delineating the size and extent



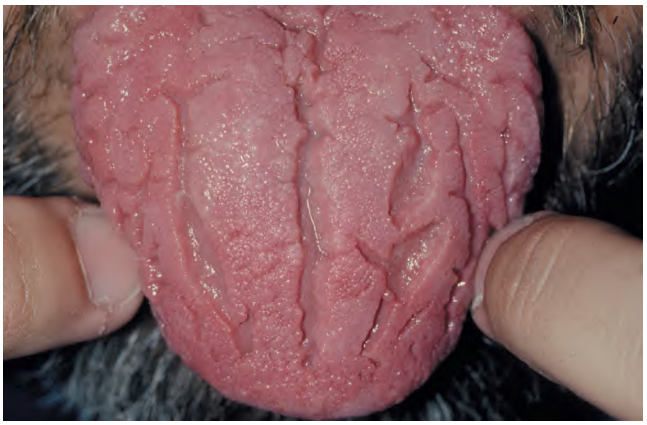
• **Fig. 1-21 Lingual Thyroid. A,** Nodular mass of the posterior dorsal midline of the tongue in a 4-year-old girl. **B,** Thyroid scan of the same patient. The scan shows localization (central dark zone) of iodine isotope in the tongue mass and minimal uptake in the neck.

of the lesion. Biopsy is often avoided because of the risk of hemorrhage and because the mass may represent the patient's only functioning thyroid tissue. In some cases, incisional biopsy may be needed to confirm the diagnosis or to rule out malignant changes.

Treatment and Prognosis

No treatment except periodic follow-up is required for patients with asymptomatic lingual thyroids. In symptomatic patients, suppressive therapy with supplemental thyroid hormone often can reduce the size of the lesion. Some authors advise that this treatment also should be tried in asymptomatic patients to prevent possible subsequent enlargement. If hormone therapy does not eliminate symptoms, surgical removal or ablation with radioactive iodine-131 can be performed. If the mass is excised, autotransplantation to another body site can be attempted to maintain functional thyroid tissue and to prevent hypothyroidism.

Rare examples of carcinomas arising in lingual thyroids have been reported; malignancy develops in about 1% of identified cases. Although lingual thyroids are decidedly more common in females, this predilection for females is less pronounced for lingual thyroid carcinomas. Because a disproportionate number of these malignancies have been documented in males, some authors have advocated prophylactic excision of lingual thyroids in men older than 30 years of age.



• **Fig. 1-22 Fissured Tongue.** Extensive fissuring involving the entire dorsal tongue surface. (Courtesy of Chris Neville.)

◆ FISSURED TONGUE (SCROTAL TONGUE)

Fissured tongue is a relatively common condition that is characterized by the presence of numerous grooves, or fissures, on the dorsal tongue surface. The cause is uncertain, but heredity appears to play a significant role. Evidence indicates that the condition may be either a polygenic trait or an autosomal dominant trait with incomplete penetrance. Aging or local environmental factors also may contribute to its development.

Clinical Features

Patients with fissured tongue exhibit multiple grooves, or furrows, on the surface of the tongue, ranging from 2 to 6 mm in depth (Fig. 1-22). Considerable variation can be seen. In the most severe cases, numerous fissures cover the entire dorsal surface and divide the tongue papillae into multiple separate "islands." Some patients have fissures that are located mostly on the dorsolateral areas of the tongue. Other patients exhibit a large central fissure with smaller fissures branching outward at right angles. The condition usually is asymptomatic, although some patients may complain of mild burning or soreness.

Most studies have shown that the prevalence of fissured tongue ranges from 2% to 5% of the overall population. The condition may be seen in children or adults, but the prevalence and severity appear to increase with age, with some studies noting the presence of fissured tongue in as many as 30% of older adults. In some investigations, a male predilection has been noted.

A strong association has been found between fissured tongue and **geographic tongue** (see page 726) with many patients having both conditions. A hereditary basis also has been suggested for geographic tongue, and the same gene

or genes may possibly be linked to both conditions. In fact, it even has been suggested that geographic tongue may *cause* fissured tongue. Fissured tongue also may be a component of **Melkersson-Rosenthal syndrome** (see page 313).

Histopathologic Features

Microscopic examination of fissured tongue reveals hyperplasia of the rete ridges and loss of the keratin "hairs" on the surface of the filiform papillae. The papillae vary in size and often are separated by deep grooves. Polymorphonuclear leukocytes can be seen migrating into the epithelium, often forming microabscesses in the upper epithelial layers. A mixed inflammatory cell infiltrate is present in the lamina propria.

Treatment and Prognosis

Fissured tongue is a benign condition, and no specific treatment is indicated. The patient should be encouraged to brush the tongue, because food or debris entrapped in the grooves may act as a source of irritation.

◆ HAIRY TONGUE (BLACK HAIRY TONGUE; COATED TONGUE)

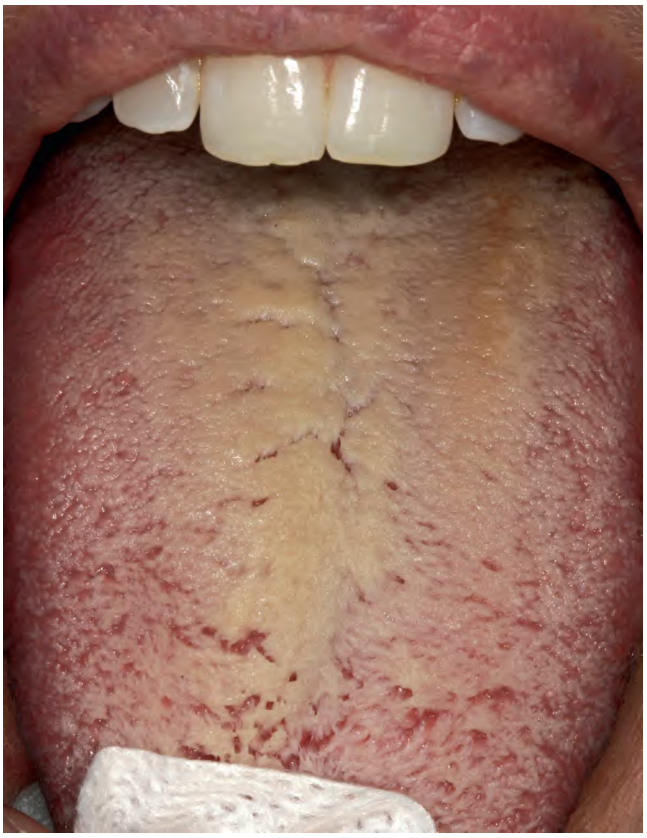
Hairy tongue is characterized by marked accumulation of keratin on the filiform papillae of the dorsal tongue, resulting in a hairlike appearance. The condition apparently represents an increase in keratin production or a decrease in normal keratin desquamation. Hairy tongue is found in about 0.5% of adults. Although the cause is uncertain, many affected people are heavy smokers. Other possible associated factors include general debilitation, poor oral hygiene, drugs that induce xerostomia, and a history of radiation therapy to the head and neck.

Clinical Features

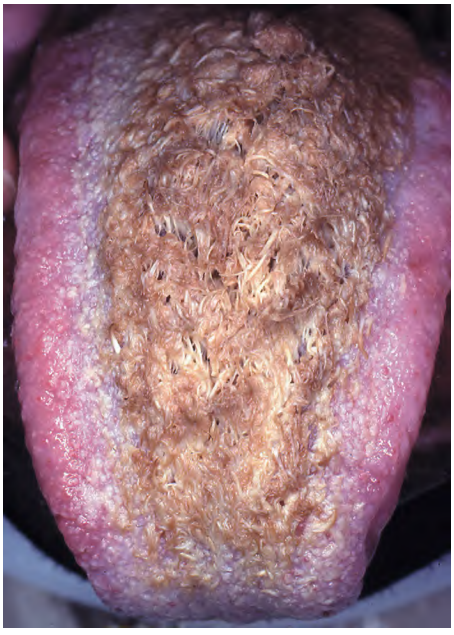
Hairy tongue most commonly affects the midline just anterior to the circumvallate papillae, sparing the lateral and anterior borders (Fig. 1-23). The elongated papillae are usually brown, yellow, or black as a result of growth of pigment-producing bacteria or staining from tobacco and food. Sometimes most of the dorsal tongue may be involved, resulting in a thick, matted appearance (Fig. 1-24). Multiple individual elongated filiform papillae may be elevated by using gauze or a dental instrument. The condition is typically asymptomatic, although occasionally patients complain of a gagging sensation or a bad taste in the mouth. Because the diagnosis usually can be made from the clinical appearance, biopsy is unnecessary in most instances.

In some individuals, numerous bacteria and desquamated epithelial cells accumulate on the dorsal tongue surface, but without the hairlike filiform projections (Fig. 1-25). Such cases, which often are designated as a **coated tongue,** also may be a source of oral malodor. Coated tongue often is misdiagnosed as candidiasis and treated unnecessarily with antifungal medications.

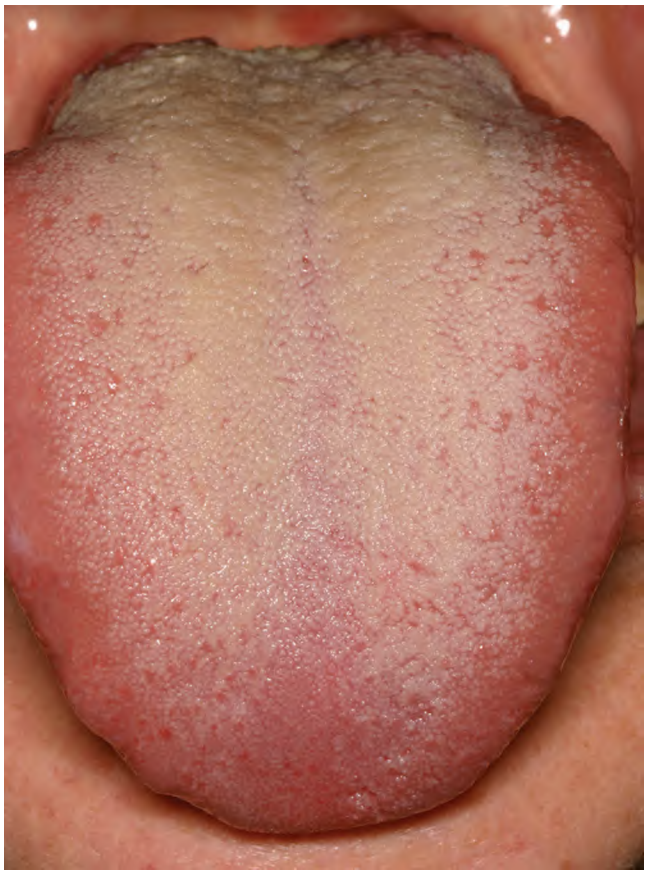
Transitory black staining of the dorsal tongue without elongation of the filiform papillae sometimes can occur in



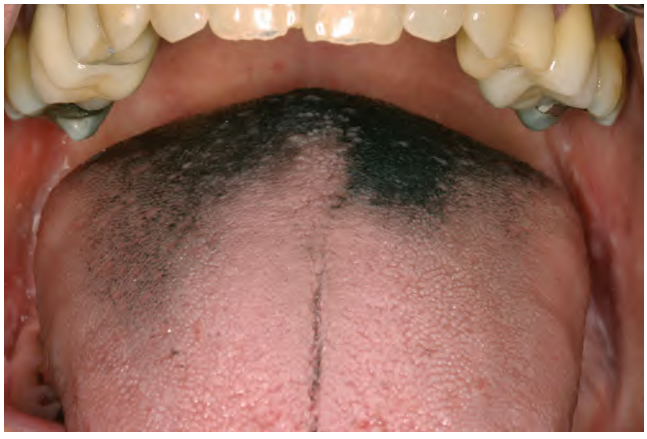
• **Fig. 1-23 Hairy Tongue.** Elongated, yellowish white filiform papillae on the dorsal surface of the tongue.



• **Fig. 1-24 Hairy Tongue.** Marked elongation and brown staining of the filiform papillae, resulting in a hairlike appearance.

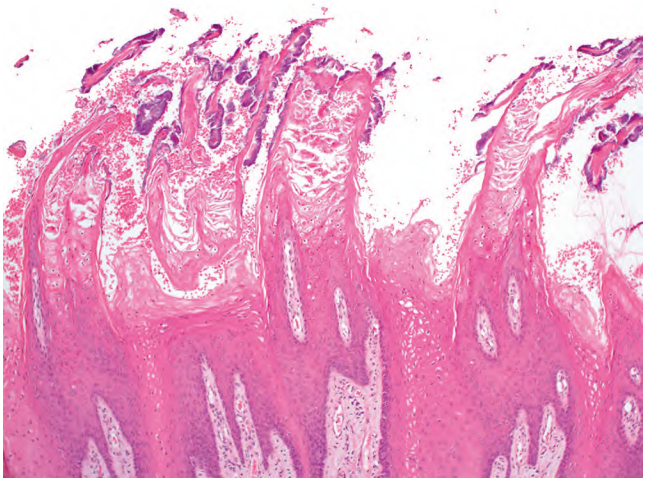


• **Fig. 1-25 Coated Tongue.** The dorsal tongue appears white and mildly thickened from the accumulation of keratin and bacteria on the surface.



• **Fig. 1-26 Bismuth Staining.** Transitory staining of the posterior dorsal tongue after using bismuth subsalicylate for an upset stomach.

patients who use bismuth subsalicylate to control upset stomach. The bismuth in such preparations can react with trace amounts of sulfur in the saliva to form bismuth sulfide, which accumulates on the tongue surface (Fig. 1-26). However, this discoloration rapidly resolves after discontinuation of the medication.



• **Fig. 1-27 Hairy Tongue.** Elongation and marked hyperkeratosis of the filiform papillae with bacterial accumulation on the surface.

Histopathologic Features

On histopathologic examination, hairy tongue is characterized by marked elongation and hyperparakeratosis of the filiform papillae (Fig. 1-27). Usually, numerous bacteria can be seen growing on the epithelial surface.

Treatment and Prognosis

Hairy or coated tongue is a benign condition with no serious sequelae. The major concern is often the aesthetic appearance of the tongue along with possible associated bad breath. Any predisposing factors, such as tobacco, should be eliminated, and excellent oral hygiene should be encouraged. Periodic scraping or brushing with a toothbrush or tongue scraper can promote desquamation of the hyperkeratotic papillae and surface debris. Keratolytic agents, such as podophyllin, also have been tried with success, but for safety reasons their use probably should not be encouraged.

Because of the similarity in names, care should be taken to avoid confusing hairy tongue with **hairy leukoplakia** (see page 242), which typically occurs on the lateral border of the tongue. Hairy leukoplakia is caused by the Epstein-Barr virus and usually is associated with human immunodeficiency virus (HIV) infection or other immunosuppressive conditions.

◆ VARICOSITIES (VARICES)

Varicosities, or **varices,** are abnormally dilated and tortuous veins. Age appears to be an important etiologic factor because varices are rare in children but common in older adults. This suggests that their development may be an age-related degeneration, in which a loss of connective tissue tone supporting the vessels occurs. One study found that people with varicose veins of the legs are more likely to have varicosities of the tongue. Although some studies have reported no connection between oral varices and

cardiopulmonary diseases, one recent investigation did show a significantly increased prevalence of sublingual varices in patients with a history of smoking or cardiovascular disease.

Clinical Features

The most common type of oral varicosity is the **sublingual varix,** which occurs in two-thirds of people older than 60 years of age. Sublingual varicosities classically present as multiple blue-purple, elevated or papular blebs on the ventral and lateral border of the tongue (Fig. 1-28). The lesions usually are asymptomatic, except in rare instances when secondary thrombosis occurs.

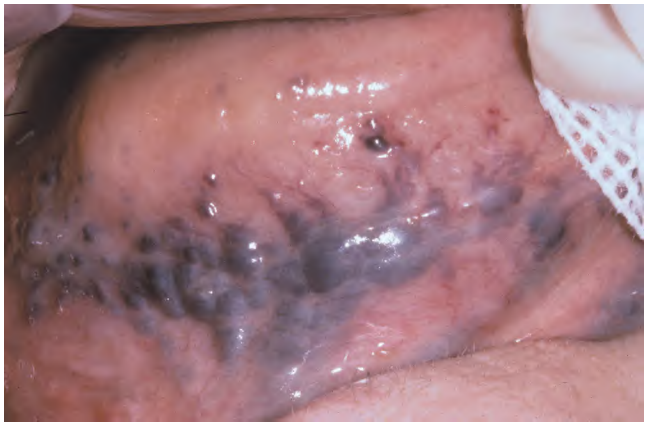
Less frequently, solitary varices occur in other areas of the mouth, especially the lips and buccal mucosa. These isolated varicosities often are first noticed after they have become thrombosed (Fig. 1-29). Clinically, a thrombosed varix presents as a firm, nontender, blue-purple nodule that may feel like a BB beneath the mucosal surface.

Histopathologic Features

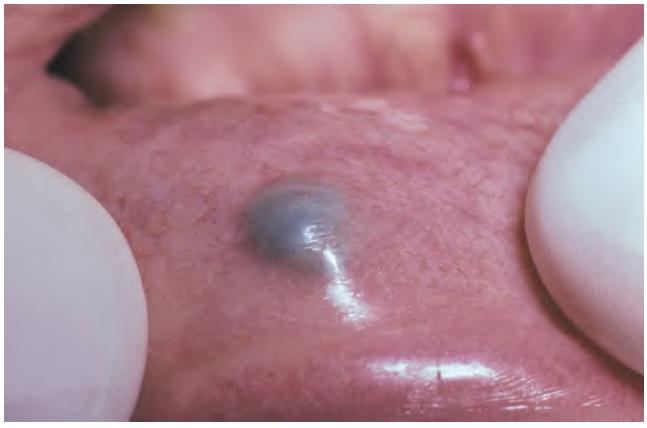
Microscopic examination of a varix reveals a dilated vein, the wall of which shows little smooth muscle and poorly developed elastic tissue. If secondary thrombosis has occurred, then the lumen may contain concentrically layered zones of platelets and erythrocytes (lines of Zahn). The clot can undergo organization via granulation tissue with subsequent recanalization. Older thrombi may exhibit dystrophic calcification, resulting in formation of a **phlebolith** (*phlebo* = vein; *lith* = stone).

Treatment and Prognosis

Sublingual varicosities typically are asymptomatic, and no treatment is indicated. Solitary varicosities of the lips and buccal mucosa may need to be surgically removed to confirm the diagnosis or for aesthetic purposes.



• **Fig. 1-28 Varicosities.** Multiple purple dilated veins on the ventral and lateral surface of the tongue.



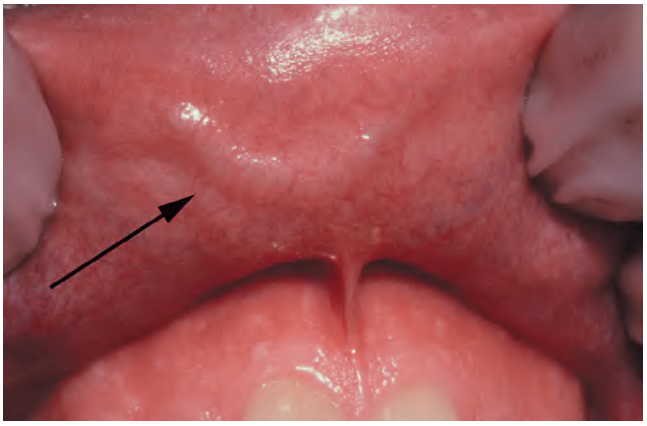
• **Fig. 1-29 Varicosity.** Firm, thrombosed varix on the lower lip.

◆ CALIBER-PERSISTENT ARTERY

A **caliber-persistent artery** is a common vascular anomaly in which a main arterial branch extends up into the superficial submucosal tissues without a reduction in its diameter. Similar to oral varices, caliber-persistent arteries are seen more frequently in older adults. This suggests that their development may be an age-related degenerative phenomenon in which there is a loss of tone in the surrounding supporting connective tissue.

Clinical Features

The caliber-persistent artery occurs almost exclusively on the lip mucosa. Either lip may be affected, and some patients have bilateral lesions or lesions on both lips. The average patient age is 58 years, and the gender ratio is nearly equal. The lesion presents as a linear, arcuate, or papular elevation that ranges from pale to normal to bluish in color (Fig. 1-30). Stretching the lip usually causes the artery to become inconspicuous. The unique feature is pulsation—not only vertically but also in a lateral direction. However, usually it is not possible to feel a pulse in a caliber-persistent artery with gloved fingers.



• **Fig. 1-30 Caliber-Persistent Artery.** Linear, arcuate lesion on the upper labial mucosa *(arrow).* (Courtesy of Dr. John Lovas.)

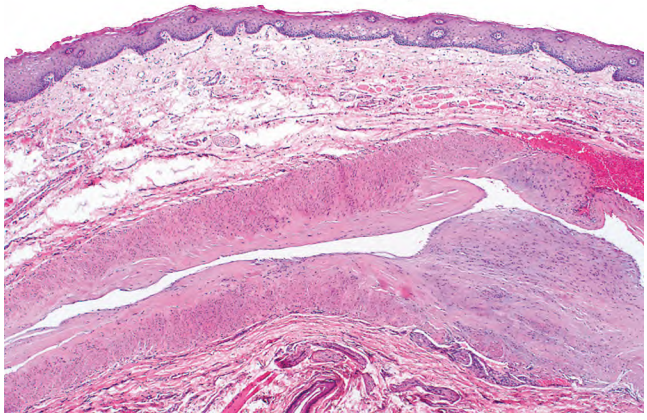
The lesion is usually asymptomatic, being discovered as an incidental finding during an oral examination; rarely a patient may notice a pulsatile lip nodule. A few cases have been associated with ulceration of the overlying mucosa. In addition, a couple of examples have been found adjacent to labial squamous cell carcinomas, although this is probably coincidental.

Histopathologic Features

Microscopic examination shows a thick-walled artery situated close to the mucosal surface (Fig. 1-31).

Treatment and Prognosis

If the true nature of the caliber-persistent artery can be recognized clinically, no treatment is necessary. Oftentimes a biopsy is performed when the lesion is mistaken for a mucocele or another vascular lesion, such as a varix or hemangioma. Brisk bleeding typically is encountered if the lesion is removed.



• **Fig. 1-31 Caliber-Persistent Artery.** Thick-walled artery located just beneath the mucosal surface.

◆ LATERAL SOFT PALATE FISTULAS

Lateral soft palate fistulas are rare anomalies of uncertain pathogenesis. Many cases appear to be congenital, possibly related to a defect in the development of the second pharyngeal pouch. Some fistulas may be the result of infection or surgery of the tonsillar region.

Clinical Features

Lateral soft palate fistulas usually are bilateral, but they may occur only on one side. They are more common on the anterior tonsillar pillar (Fig. 1-32), but they also may involve the posterior pillar. The perforations typically are asymptomatic, ranging from a few millimeters to more than 1 cm. A few cases have been associated with other anomalies, such as absence or hypoplasia of the palatine tonsils, hearing loss, and preauricular fistulas.

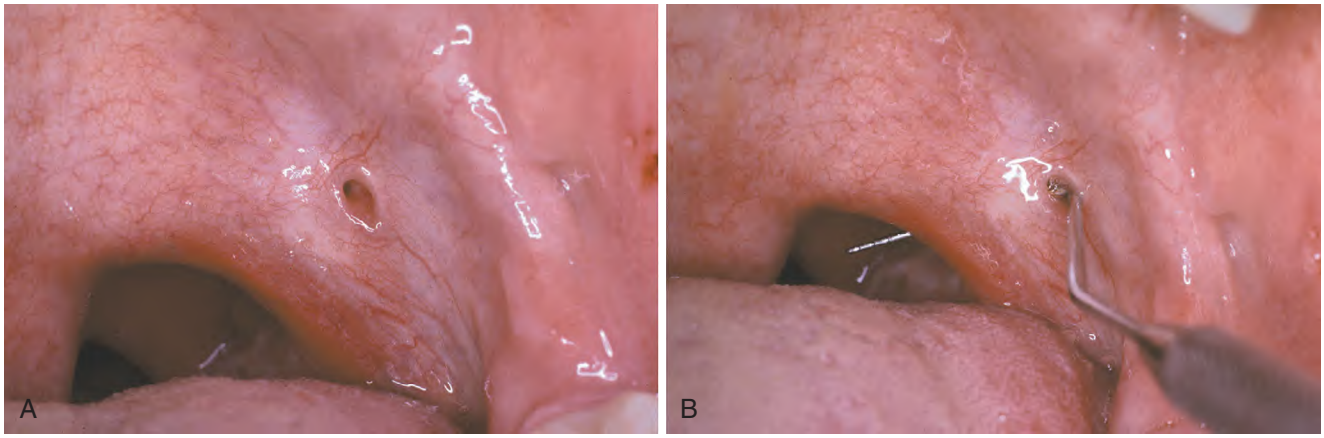
Treatment and Prognosis

The lesions are innocuous, and no treatment is necessary.

◆ CORONOID HYPERPLASIA

Hyperplasia of the coronoid process of the mandible is a rare developmental anomaly that may result in limitation of mandibular movement. The cause of **coronoid hyperplasia** is unknown, but the condition is three to five times more common in males than in females. Because most cases have been seen in pubertal males, an endocrine influence has been suggested. Heredity also may play a role, because cases have been noted in siblings.

Coronoid hyperplasia may be unilateral or bilateral, although bilateral cases are over four times more common than unilateral examples. Unilateral enlargement of the coronoid process also can result from a true tumor, such as an osteoma or osteochondroma, and such cases should be distinguished from pure coronoid hyperplasia. However,



• **Fig. 1-32 Lateral Palatal Fistula. A,** Asymptomatic "hole" in the anterior tonsillar pillar. **B,** Periodontal probe has been used to demonstrate the communication of the lesion with the tonsillar fossa.

some cases reported as tumors of the coronoid process actually may have been hyperplastic processes rather than true neoplasms.

Clinical and Radiographic Features

In a person with unilateral coronoid hyperplasia, the enlarged coronoid process impinges on the posterior surface of the zygoma, restricting mandibular opening. In addition, the mandible may deviate toward the affected side. Usually, there is no pain or associated abnormality in occlusion. Radiographs may reveal an irregular, nodular growth of the tip of the coronoid process.

In bilateral coronoid hyperplasia, the limitation of mandibular opening may progressively worsen over several years during childhood, reaching maximum severity during the late teens. The radiographic appearance is characterized by regular elongation of both processes. Because the coronoid process often is superimposed on the zygoma on conventional radiographs, CT scans often demonstrate the hyperplasia more effectively.

Treatment and Prognosis

Treatment of coronoid hyperplasia consists of surgical removal of the elongated coronoid process or processes to allow freedom of mandibular motion. Coronoidectomy or coronoidotomy usually is accomplished via an intraoral approach. Although initial improvement in oral opening can be effected, the long-term results in some patients can be disappointing because of surgically induced fibrosis and the tendency for coronoid regrowth. Postoperative physiotherapy is important for reestablishing normal function.

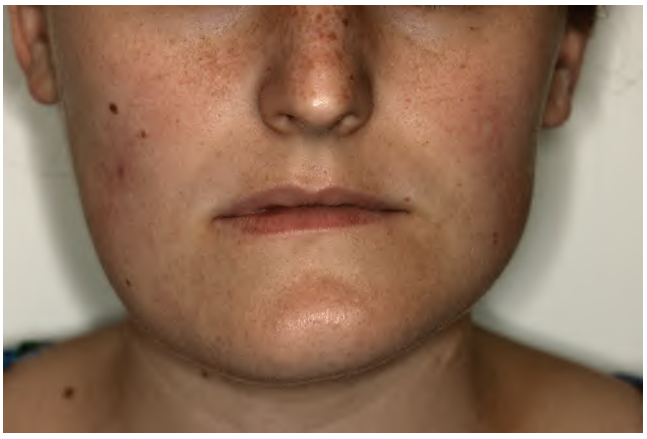
◆ CONDYLAR HYPERPLASIA

Condylar hyperplasia is an uncommon malformation of the mandible created by excessive growth of one of the condyles. The cause of this hyperplasia is unknown, but local circulatory problems, endocrine disturbances, and trauma have been suggested as possible etiologic factors.

Condylar hyperplasia can be difficult to distinguish from **hemifacial hyperplasia** (see page 35); however, in the latter condition the associated soft tissues and teeth also may be enlarged.

Clinical and Radiographic Features

Condylar hyperplasia may manifest itself in a variety of ways, including facial asymmetry, prognathism, crossbite, and open bite (Fig. 1-33). Sometimes compensatory maxillary growth and tilting of the occlusal plane occurs. The condition most commonly is discovered in adolescents and young adults. Several studies have shown a significant female predilection, with an overall female-to-male ratio of approximately 3 : 1.



• **Fig. 1-33 Condylar Hyperplasia.** Enlargement of the patient's right condyle has resulted in facial asymmetry.

The radiographic features are quite variable. Some patients have an enlargement of the condylar head, and others show elongation of the condylar neck (Fig. 1-34). Many cases also demonstrate hyperplasia of the entire ramus, suggesting that the condition sometimes affects more than just the condyle. Single-photon emission computed tomography (SPECT) and scintigraphy using ^{99m}Tc-methylenediphosphonate (MDP) have been advocated as useful methods for assessing the degree of bone activity in condylar hyperplasia.

Histopathologic Features

During active growth, proliferation of the condylar cartilage is noted. Once condylar growth has ceased, the condyle has a normal histologic appearance.

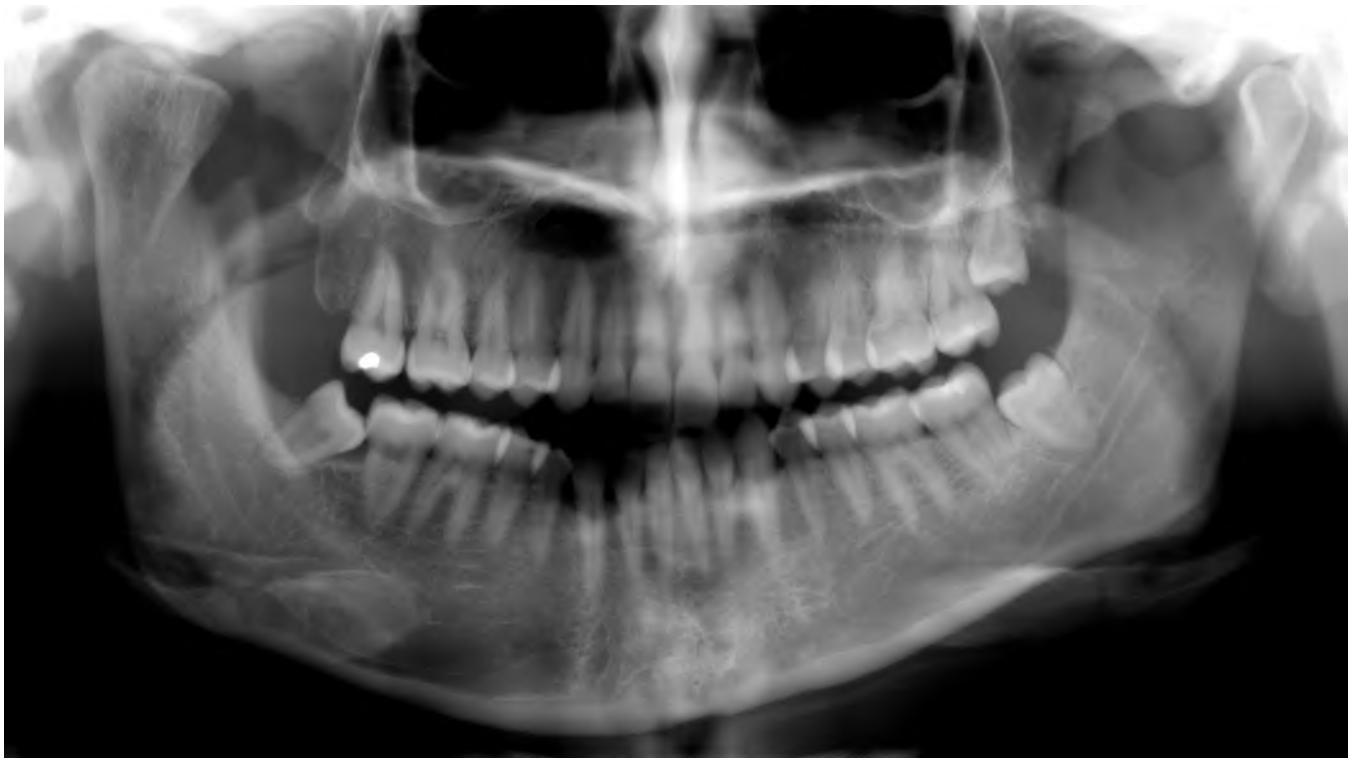
Treatment and Prognosis

Condylar hyperplasia is a self-limiting condition, and treatment is determined by the degree of functional difficulty and aesthetic change. Some patients can be treated with unilateral condylectomy, whereas others require unilateral or bilateral mandibular osteotomies. In patients with compensatory maxillary growth, a maxillary osteotomy also may be needed. Concomitant orthodontic therapy frequently is necessary.

◆ CONDYLAR HYPOPLASIA

Condylar hypoplasia, or underdevelopment of the mandibular condyle, can be either congenital or acquired. **Congenital condylar hypoplasia** often is associated with head and neck syndromes, including **mandibulofacial dysostosis** (see page 41), **oculoauriculovertebral syndrome (Goldenhar syndrome),** and **hemifacial microsomia.** In the most severe cases, complete agenesis of the condyle or ramus **(condylar aplasia)** is seen.

Acquired condylar hypoplasia results from disturbances of the growth center of the developing condyle. The



• **Fig. 1-34 Condylar Hyperplasia.** Panoramic radiograph of patient seen in Fig. 1-33, which shows prominent enlargement of the right mandibular condyle.

most frequent cause is trauma to the condylar region during infancy or childhood. Other causes include infections, radiation therapy, and rheumatoid or degenerative arthritis.

Clinical and Radiographic Features

Condylar hypoplasia can be unilateral or bilateral, producing a small mandible with a Class II malocclusion. Unilateral hypoplasia results in distortion and depression of the face on the affected side. The mandibular midline shifts to the involved side when the mouth is opened, accentuating the deformity. Ankylosis of the temporomandibular joint (TMJ) can develop in cases caused by trauma.

The deformity is observed easily on panoramic films and can range in severity. In severe cases the condyle or ramus may be totally absent. Milder types demonstrate a short condylar process, shallow sigmoid notch, and poorly formed condylar head. A prominent antegonial notch may be present. CT scans may be helpful in evaluating the condyles.

Treatment and Prognosis

Treatment of the patient with condylar hypoplasia depends on the cause and severity of the defect, but surgery often is required. If the condyle is missing, then a costochondral rib graft can be placed to help establish an active growth center. In addition, osteotomies sometimes provide a cosmetically acceptable result. In certain instances, distraction osteogenesis can be used to stimulate new bone formation.

BIFID CONDYLE

A **bifid condyle** is a rare developmental anomaly characterized by a double-headed mandibular condyle. Most bifid condyles have a medial and lateral head divided by an anteroposterior groove. Some condyles may be divided into an anterior and posterior head.

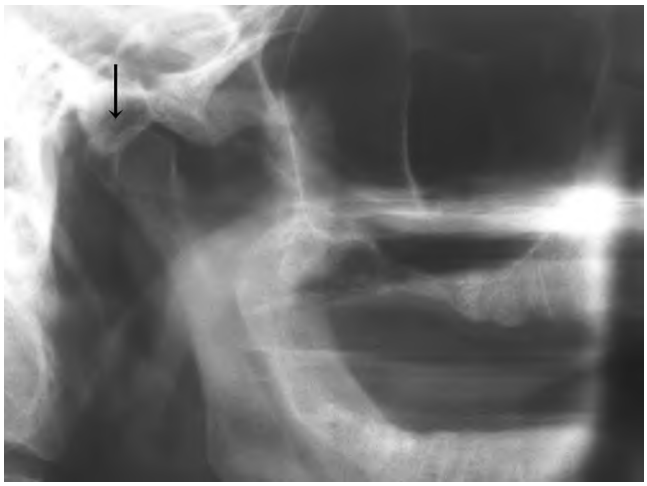
The cause of bifid condyle is uncertain. Anteroposterior bifid condyles may be of traumatic origin, such as a childhood fracture. Mediolaterally divided condyles may result from trauma, abnormal muscle attachment, teratogenic agents, or persistence of a fibrous septum within the condylar cartilage.

Clinical and Radiographic Features

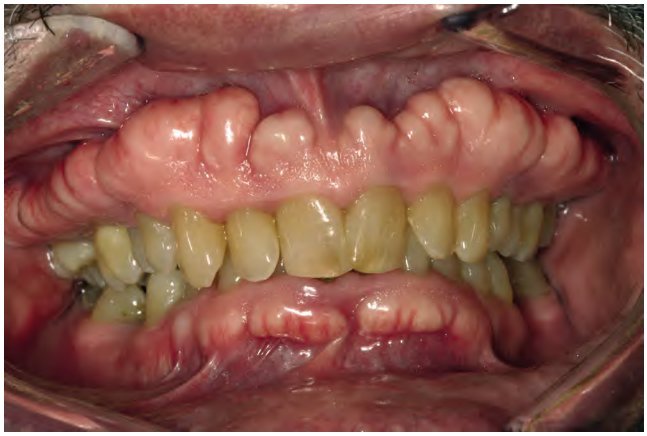
A bifid condyle usually is unilateral, but occasionally both sides may be affected. The malformation is often asymptomatic and may be discovered on routine radiographs, although some patients may have a "pop" or "click" of the TMJ when opening their mouths. Panoramic radiographs and CT scans demonstrate a bilobed appearance of the condylar head (Fig. 1-35). Extremely rare examples of trifid and tetrafid condyles also have been reported.

Treatment and Prognosis

Because a bifid condyle is usually asymptomatic, no treatment is necessary in most instances. If the patient has joint



• **Fig. 1-35 Bifid Condyle.** Radiograph of the mandibular condyle showing a double head *(arrow).*



• **Fig. 1-36 Exostoses.** Multiple buccal exostoses of the maxillary and mandibular alveolar ridges.

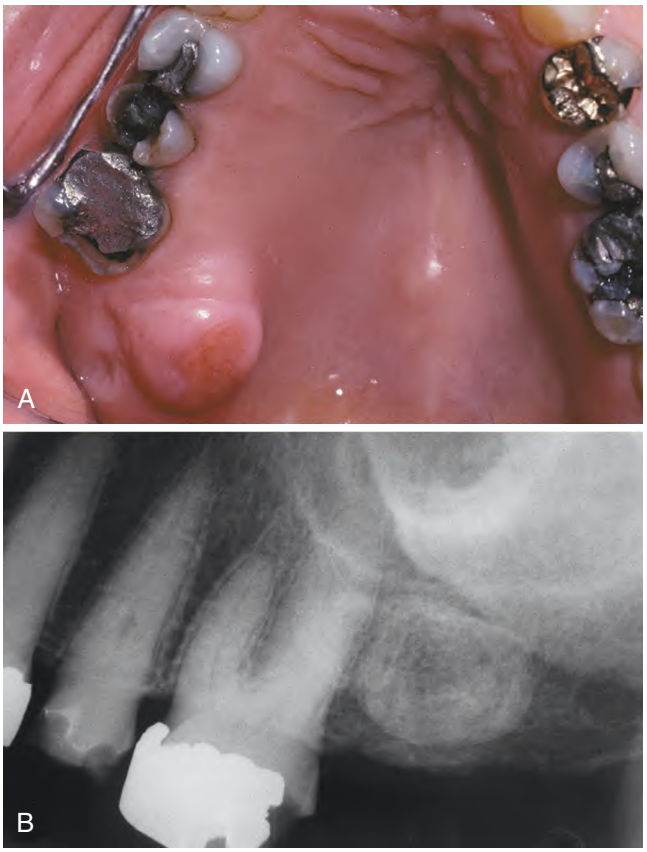
complaints, the appropriate temporomandibular therapy may be required.

◆ EXOSTOSES

Exostoses are localized bony protuberances that arise from the cortical plate. These benign growths frequently affect the jaws and may be related to stresses placed on the bone from the function of teeth. The best-known oral exostoses, the **torus palatinus** and the **torus mandibularis,** are described later in this chapter. Other types of exostoses also may affect the jaws and are considered here.

Clinical and Radiographic Features

Exostoses are discovered most often in adults. **Buccal exostoses** occur as a bilateral row of bony hard nodules along the facial aspect of the maxillary and/or mandibular alveolar ridge (Fig. 1-36). They usually are asymptomatic, unless the thin overlying mucosa becomes ulcerated from trauma. One



• **Fig. 1-37 Exostosis. A,** Secondarily ulcerated palatal exostosis. **B,** Radiograph shows an ovoid radiopacity distal to the molar.

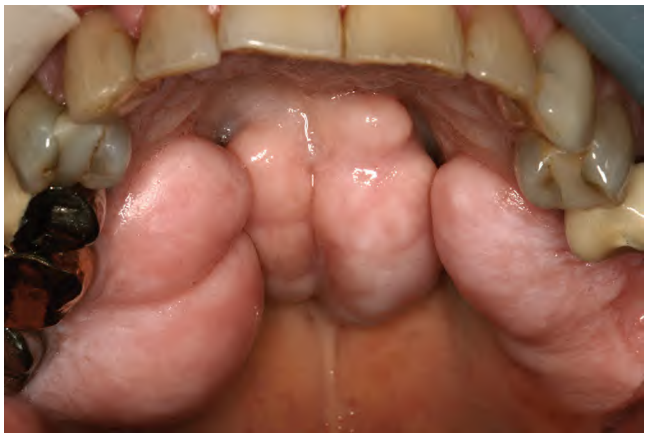
study reported that buccal exostoses were found in nearly 1 of every 1000 adults (0.09%); however, a more recent survey found a much higher prevalence of nearly 19%. This variation may be due to the different populations being studied or to the clinical criteria used to make the diagnosis.

Palatal exostoses (palatal tubercles) are similar bony protuberances that develop from the lingual aspect of the maxillary tuberosities. These lesions usually are bilateral but may affect only one side (Fig. 1-37). They are more common in males and have been reported in 8% to 69% of various populations. Many patients with buccal or palatal exostoses also will have palatal or mandibular tori (Fig. 1-38).

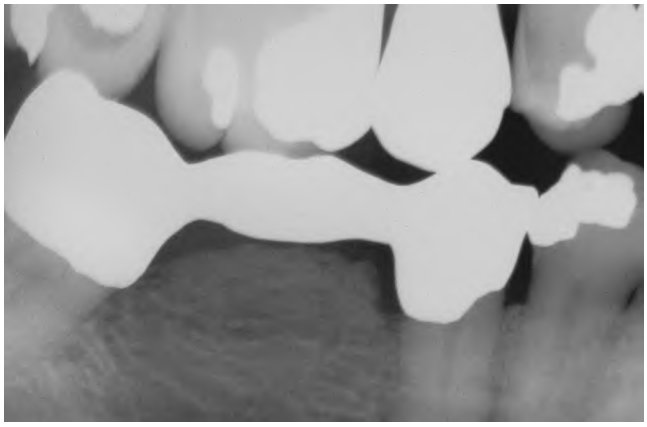
Less commonly, **solitary exostoses** may occur, possibly in response to local irritation. Such lesions may develop from the alveolar bone beneath free gingival grafts and skin grafts. Presumably placement of the graft acts as a stimulant to the periosteum to form new bone.

Another uncommon, interesting variant is the **reactive subpontine exostosis (subpontic osseous proliferation, subpontic osseous hyperplasia),** which may develop from the alveolar crestal bone beneath the pontic of a posterior bridge (Fig. 1-39).

If enough excess bone is present, exostoses may exhibit a relative radiopacity on dental radiographs (see Fig. 1-37, *B*). In rare instances an exostosis may become so large that distinguishing it from a tumor, such as an osteoma, is difficult (see page 605).



• **Fig. 1-38 Palatal Exostoses and Torus Palatinus.** Massive bilateral palatal exostoses in a patient with a large palatal torus.



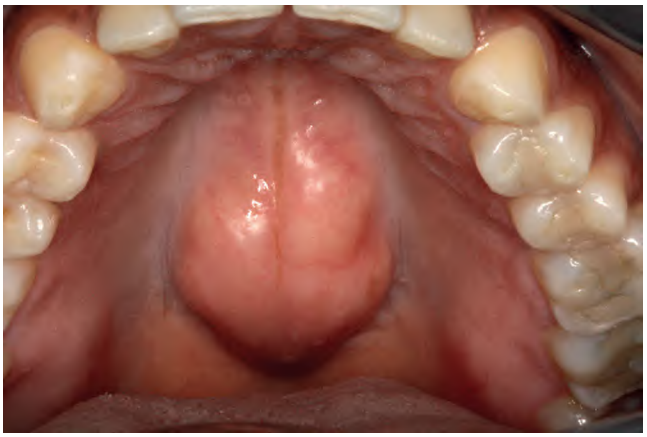
• **Fig. 1-39 Reactive Subpontine Exostosis.** Nodular growth of bone beneath the pontic of a posterior mandibular bridge.

Histopathologic Features

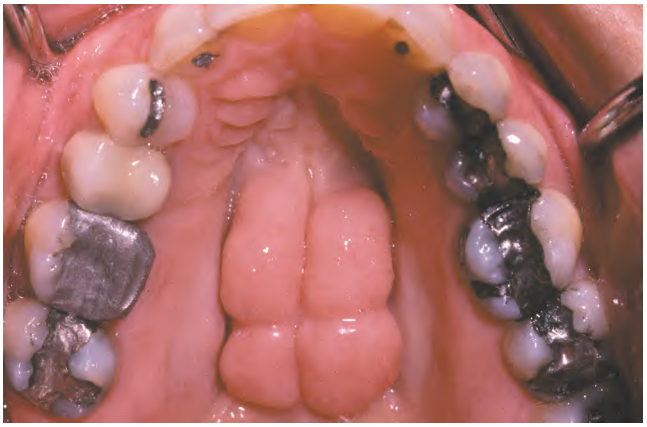
Microscopic examination reveals a mass of dense, lamellar, cortical bone with a small amount of fibrofatty marrow. In some cases an inner zone of trabecular bone also is present.

Treatment and Prognosis

Most exostoses are distinctive enough clinically to make biopsy unnecessary. If the diagnosis is uncertain, biopsy should be performed to rule out other bony pathosis. Sometimes the exostosis must be removed if it repeatedly has been exposed to trauma or has become ulcerated and painful. In addition, surgical removal may be required to accommodate a dental prosthesis or to allow for proper flap adaptation during periodontal surgery. Reactive subpontine exostoses may need to be removed if they interfere with oral hygiene or are associated with adjacent periodontal disease. Exostoses that develop secondary to adjacent tooth function may recur after removal if the teeth creating the stresses remain in place.



• **Fig. 1-40 Torus Palatinus.** Midline bony nodule of the palatal vault.



• **Fig. 1-41 Torus Palatinus.** Large, lobulated palatal mass.

TORUS PALATINUS

The **torus palatinus** is a common exostosis that occurs in the midline of the vault of the hard palate. The pathogenesis of these tori has long been debated with arguments centering on genetic versus environmental factors, such as masticatory stress. Some authorities have suggested that the torus palatinus is inherited as an autosomal dominant trait. However, others believe that the development of this lesion is multifactorial, including both genetic and environmental influences. In this model, patients are affected by a variety of hereditary and local environmental factors. If enough of these factors are present, then a "threshold" is surpassed and the trait (torus palatinus) is expressed.

Clinical and Radiographic Features

The torus palatinus presents as a bony hard mass that arises along the midline suture of the hard palate (Figs. 1-40 and 1-41). Tori sometimes are classified according to their morphologic appearance:

- The **flat torus** has a broad base and a slightly convex, smooth surface. It extends symmetrically onto both sides of the midline raphe.

- The **spindle torus** has a midline ridge along the palatal raphe. A median groove is sometimes present.
- The **nodular torus** arises as multiple protuberances, each with an individual base. These protuberances may coalesce, forming grooves between them.
- The **lobular torus** is also a multilobulated mass, but it rises from a single base. Lobular tori can be either sessile or pedunculated.

Most palatal tori are small, measuring less than 2 cm in diameter; however, they can slowly increase in size throughout life—sometimes to the extent that they fill the entire palatal vault. Most tori cause no symptoms, but in some cases the thin overlying mucosa may become ulcerated secondary to trauma.

The torus palatinus usually does not appear on routine dental radiographs. Rarely, it may be seen as a radiopacity on periapical films if the film is placed behind the torus when the radiograph is taken.

The prevalence of palatal tori has varied widely in a number of population studies, ranging from 9% to 60%. Some of this variation may be due to the criteria used to make the diagnosis and also may be based on whether the study was conducted on live patients or skulls. There appear to be significant racial differences, however, with a higher prevalence in Asian and Inuit populations. In the United States, most studies have shown a prevalence of 20% to 35%, although these figures likely include a significant number of relatively small lesions. Almost all studies from around the world have shown a pronounced female-to-male ratio of 2 : 1. The prevalence peaks during early adult life, tapering off in later years. This finding supports the theory that tori are dynamic lesions that are related, in part, to environmental factors; in later life, some may undergo resorption remodeling in response to decreased functional stresses.

Histopathologic Features

Microscopic examination of the torus shows a mass of dense, lamellar, cortical bone. An inner zone of trabecular bone sometimes is seen.

Treatment and Prognosis

Most palatal tori can be diagnosed clinically based on their characteristic appearance; therefore biopsy rarely is necessary. In edentulous patients, the torus may need to be removed surgically to accommodate a denture base. Surgical removal also may be indicated for palatal tori that repeatedly become ulcerated or that interfere with oral function. It also should be noted that palatal tori are prone to medication-related osteonecrosis (see page 271).

TORUS MANDIBULARIS

The **torus mandibularis** is a common exostosis that develops along the lingual aspect of the mandible. As with torus palatinus, the cause of mandibular tori probably is multifactorial, including both genetic and environmental influences.

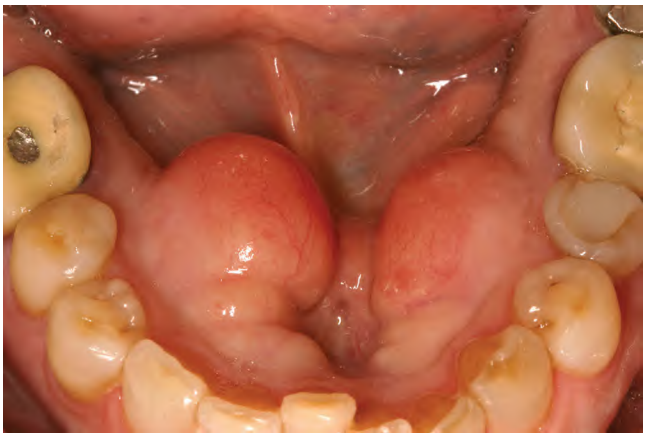


Fig. 1-42 Torus Mandibularis. Bilateral lobulated bony protuberances of the mandibular lingual alveolar ridge.

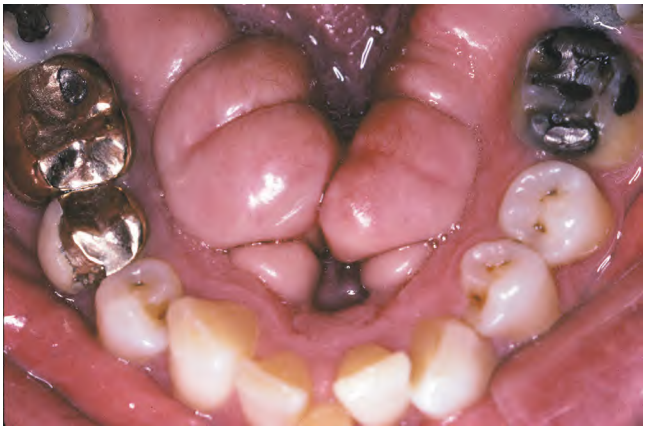
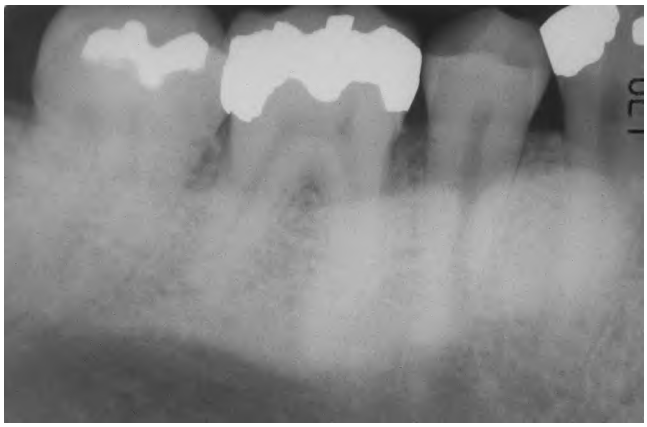


Fig. 1-43 Torus Mandibularis. Massive "kissing" tori meet in the midline.

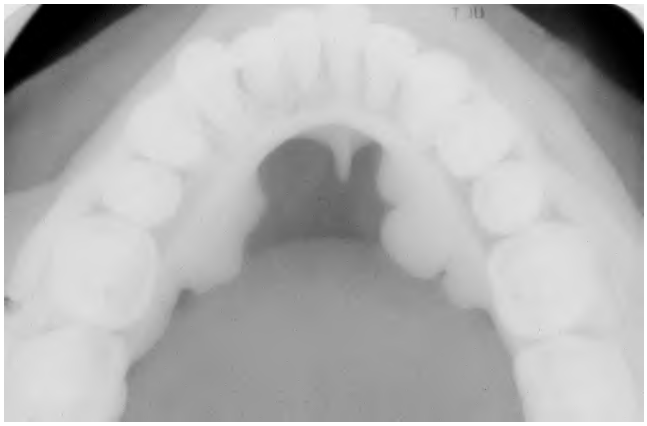
Clinical and Radiographic Features

The mandibular torus presents as a bony protuberance along the lingual aspect of the mandible above the mylohyoid line in the region of the premolars (Fig. 1-42). Bilateral involvement occurs in more than 90% of cases. Most mandibular tori occur as single nodules, although multiple lobules paralleling the teeth are not unusual. Patients often are unaware of their presence unless the overlying mucosa becomes ulcerated secondary to trauma. In rare instances, bilateral tori may become so large that they almost meet in the midline (Fig. 1-43). A large mandibular torus may appear on periapical radiographs as a radiopacity superimposed on the roots of the teeth (Fig. 1-44), especially on anterior films. Mandibular tori are easily visualized on occlusal radiographs (Fig. 1-45).

Most studies indicate that the torus mandibularis is not as common as the torus palatinus; the prevalence ranges from 5% to 40%. Like the torus palatinus, the mandibular torus appears to be more common in Asians and the Inuit. The prevalence in the United States ranges from 7% to 10%



• **Fig. 1-44 Torus Mandibularis.** Torus is causing a radiopacity that is superimposed over the roots of the mandibular teeth.



• **Fig. 1-45 Torus Mandibularis.** Occlusal radiograph showing bilateral mandibular tori.

with little difference between blacks and whites. A slight male predilection has been noted.

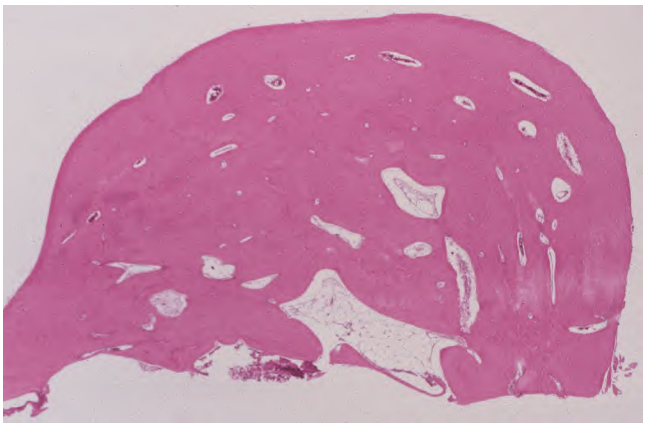
The prevalence of mandibular torus peaks in early adult life, tapering slightly in later years. In addition, the prevalence has been correlated with both bruxism and the number of teeth remaining present. These findings support the theory that the torus mandibularis is multifactorial in development and responds to functional stresses.

Histopathologic Features

The histopathologic appearance of the torus mandibularis is similar to that of other exostoses, consisting primarily of a nodular mass of dense, cortical lamellar bone (Fig. 1-46). An inner zone of trabecular bone with associated fatty marrow sometimes is visible.

Treatment and Prognosis

Most mandibular tori are easily diagnosed clinically, and no treatment is necessary. However, surgical removal may be required to accommodate a lower full or partial denture. Occasionally, tori may recur if teeth are still present in the area.



• **Fig. 1-46 Torus Mandibularis.** Nodular mass of dense, cortical bone. Some fatty marrow is visible at the base of the specimen.

◆ EAGLE SYNDROME (STYLOHYOID SYNDROME; CAROTID ARTERY SYNDROME; STYLALGIA)

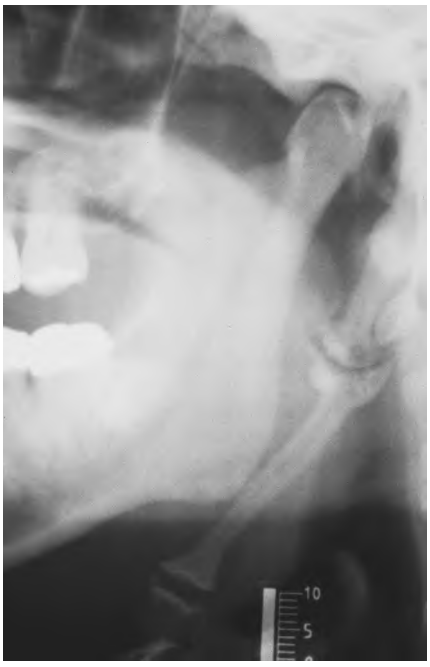
The styloid process is a slender bony projection that originates from the inferior aspect of the temporal bone, anterior and medial to the stylomastoid foramen. It is connected to the lesser cornu of the hyoid bone by the stylohyoid ligament. The external and internal carotid arteries lie on either side. Elongation of the styloid process or mineralization of the stylohyoid ligament complex is not unusual, having been reported in 18% to 84% of the population with an increasing incidence with advancing age. Such mineralization is usually bilateral, but it may affect only one side. Most cases are asymptomatic; however, a small number of such patients experience symptoms of **Eagle syndrome,** caused by impingement or compression of adjacent nerves or blood vessels.

Clinical and Radiographic Features

Eagle syndrome most commonly affects adults, occurring more often in women than men. The patient experiences vague facial pain, especially while swallowing, turning the head, or opening the mouth. Other symptoms may include dysphagia, dysphonia, otalgia, headache, dizziness, syncope, and transient ischemic attacks.

Elongation of the styloid process or mineralization of the stylohyoid ligament complex can be seen on panoramic or lateral-jaw radiographs (Fig. 1-47). The mineralized stylohyoid complex may be palpated in the tonsillar fossa area, and pain often is elicited.

Classic Eagle syndrome occurs after a tonsillectomy. Development of scar tissue in the area of a mineralized stylohyoid complex then results in cervicopharyngeal pain in the region of cranial nerves V, VII, IX, and X, especially during swallowing. Some authors reserve the term *Eagle syndrome* only for those cases in which the ossification of the stylohyoid chain occurs as a result of the tonsillectomy or other neck trauma.



• **Fig. 1-47 Eagle Syndrome.** Mineralization of the stylohyoid ligament is visible posterior to the mandibular ramus.

A second form of this condition unrelated to tonsillectomy is sometimes known as **carotid artery syndrome** or **stylohyoid syndrome.** The elongated, mineralized complex is thought to impinge on the internal or external carotid arteries and associated sympathetic nerve fibers. The patient may complain of pain in the neck when turning the head, and this pain may radiate to other sites in the head or neck.

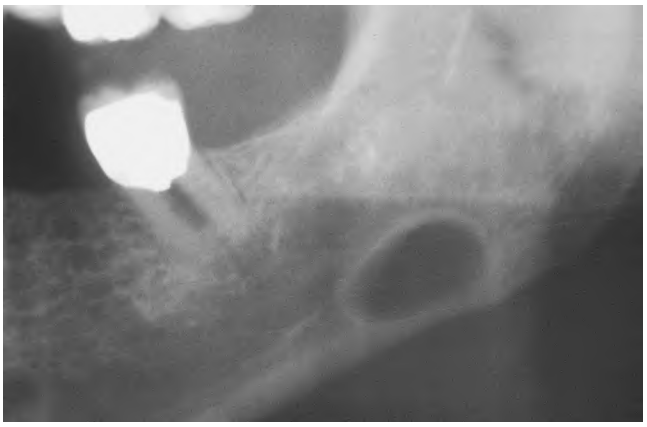
Traumatic Eagle syndrome also has been reported, in which symptoms develop after fracture of a mineralized stylohyoid ligament.

Treatment and Prognosis

Treatment of Eagle syndrome depends on the severity of the symptoms. For mild cases, no treatment may be necessary (except reassurance of the patient). Local injection of corticosteroids sometimes provides relief. In more severe cases, partial surgical excision of the elongated styloid process or mineralized stylohyoid ligament is required. Usually, this is accomplished via an intraoral approach, although an extraoral approach also can be used. The prognosis is good.

◆ STAFNE DEFECT (STAFNE BONE CYST; LINGUAL MANDIBULAR SALIVARY GLAND DEPRESSION; LATENT BONE CYST; STATIC BONE CYST; STATIC BONE DEFECT; LINGUAL CORTICAL MANDIBULAR DEFECT)

In 1942, Stafne described a series of asymptomatic radiolucent lesions located near the angle of the mandible.



• **Fig. 1-48 Stafne Defect.** Radiolucency of the posterior mandible below the mandibular canal.

Subsequent reports of similar lesions have shown that this condition represents a focal concavity of the cortical bone on the lingual surface of the mandible. In most cases, biopsy has revealed histologically normal salivary gland tissue, suggesting that these lesions represent developmental defects containing a portion of the submandibular gland. However, a few of these defects have been reported to be devoid of contents or to contain muscle, fibrous connective tissue, blood vessels, fat, or lymphoid tissue.

Similar lingual cortical defects also have been noted more anteriorly in the mandible, in the area of the incisor, canine, or premolar teeth. These rare defects have been related to the sublingual gland or to aberrant salivary gland tissue. In addition, one report has implicated the parotid gland as the cause of an apparent cortical defect in the upper mandibular ramus. Therefore, all of the major salivary glands appear to be capable of causing such cortical concavities.

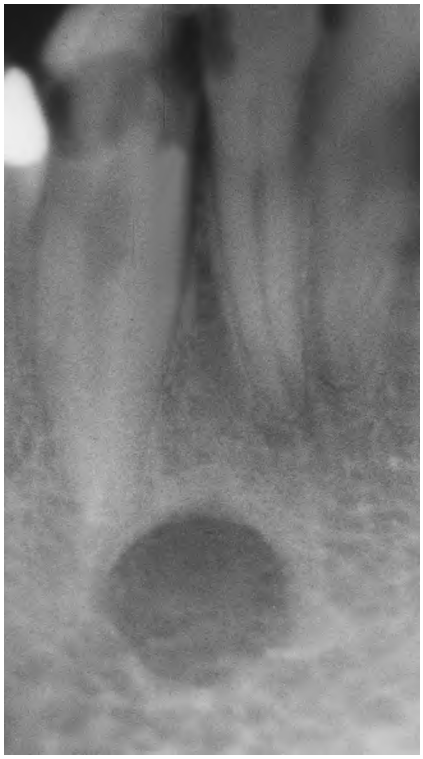
In rare examples, the radiolucent defect has been reported to be totally surrounded by intact bone. Such cases might be explained by entrapment of embryonic salivary gland tissue within the jawbone.

Clinical and Radiographic Features

The classic **Stafne defect** presents as an asymptomatic radiolucency below the mandibular canal in the posterior mandible, between the molar teeth and the angle of the mandible (Fig. 1-48). The lesion is typically well circumscribed and has a sclerotic border. Sometimes the defect may interrupt the continuity of the inferior border of the mandible, with a palpable notch observed clinically in this area. Most Stafne defects are unilateral, although bilateral cases may be seen. Anterior lingual salivary defects associated with the sublingual gland present as well-defined radiolucencies that may appear superimposed over the apices of the anterior teeth (Fig. 1-49).

Posterior Stafne defects are not rare, having been reported in 0.08% to 0.48% of panoramic radiographs. A striking male predilection is observed, with 80% to 90% of all cases seen in men.

Although the defect is believed to be developmental in nature, it does not appear to be present from birth. Most cases have been reported in middle-aged and older adults, with children rarely affected; this implies that the lesion usually "develops" at a later age. Stafne defects typically remain stable in size; hence the name **static bone cyst.** In a few cases, however, the lesion has increased in size over time (Fig. 1-50). This also indicates that these lesions are not congenital.



• **Fig. 1-49 Stafne Defect.** Anterior radiolucent lesion of the body of the mandible associated with the sublingual gland.

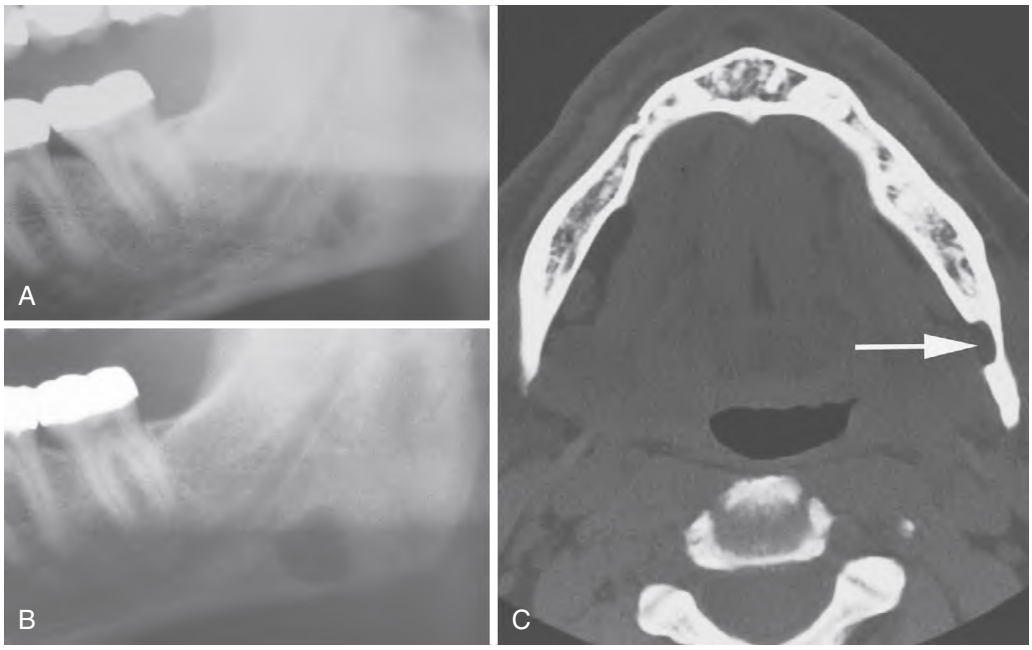
The diagnosis usually can be made on a clinical basis by the typical radiographic location and lack of symptoms. If the clinical diagnosis is in doubt, then it can be confirmed by conventional CT scans, cone beam CT, MRI, or sialography. CT scans and MRIs show a well-defined concavity on the lingual surface of the mandible. Sialograms may be able to demonstrate the presence of salivary gland tissue in the area of the defect.

Histopathologic Features

Because of the typical radiographic appearance, biopsy usually is not necessary to establish the diagnosis of Stafne defects of the posterior mandible. If biopsy is performed, normal submandibular gland tissue usually is seen. However, some defects are devoid of tissue or contain muscle, blood vessels, fat, connective tissue, or lymphoid tissue. In cases reported to be devoid of contents, it is possible that the gland was simply displaced at the time of biopsy.

Treatment and Prognosis

No treatment is necessary for patients with Stafne defects, and the prognosis is excellent. If the diagnosis is in question on plain films, appropriate CT imaging studies can confirm the presence of a well-defined, cupped-out lingual cortical defect, allowing a presumptive diagnosis to be made on a radiographic basis. Because anterior lingual salivary defects



• **Fig. 1-50 Stafne Defect. A,** Ill-defined radiolucency near the angle of the mandible. **B,** Appearance of the same defect several years later showing enlargement of the lesion. **C,** Computed tomography (CT) image of the same lesion showing a left lingual cortical defect *(arrow)*. (Courtesy of Dr. Carroll Gallagher.)

are more difficult to recognize, the diagnosis often is not suspected, and biopsy may be done to rule out other pathologic lesions.

DEVELOPMENTAL CYSTS

By definition, a **cyst** is a pathologic cavity (often fluid-filled) that is lined by epithelium. A number of different developmental cysts of the head and neck have been described. Some of these have been considered historically as "fissural" cysts because they were thought to arise from epithelium entrapped along embryonal lines of fusion. However, the concept of a fissural origin for many of these cysts has been questioned in more recent years. In many instances the exact pathogenesis of these lesions is still uncertain. Regardless of their origin, once cysts develop in the oral and maxillofacial region, they tend to slowly increase in size, possibly in response to a slightly elevated hydrostatic luminal pressure.

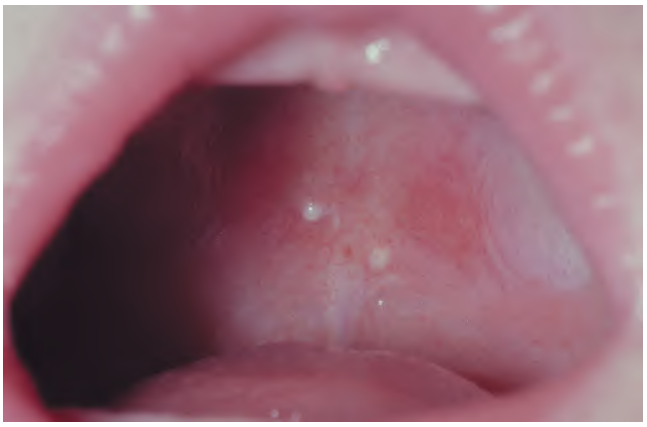
◆ PALATAL CYSTS OF THE NEWBORN (EPSTEIN'S PEARLS; BOHN'S NODULES)

Small developmental cysts are a common finding on the palate of newborn infants. Researchers have theorized that these "inclusion" cysts may arise in one of two ways. First, as the palatal shelves meet and fuse in the midline during embryonic life to form the secondary palate, small islands of epithelium may become entrapped below the surface along the median palatal raphe and form cysts. Second, these cysts may arise from epithelial remnants derived from the development of the minor salivary glands of the palate.

As originally described, **Epstein's pearls** occur along the median palatal raphe and presumably arise from epithelium entrapped along the line of fusion. **Bohn's nodules** are scattered over the hard palate, often near the soft palate junction and are believed to be derived from the minor salivary glands. However, these two terms have been used almost interchangeably in the literature and also have often been used to describe gingival cysts of the newborn (see page 644), similar-appearing lesions of dental lamina origin. Therefore, the term **palatal cysts of the newborn** may be preferable to help distinguish them from gingival cysts of the newborn. In addition, because these cysts are most common near the midline at the junction of the hard and soft palates, it is usually difficult to ascertain clinically whether they are arising from epithelium entrapped by fusion of the palate or from the developing minor salivary glands.

Clinical Features

Palatal cysts of the newborn are quite common and have been reported in as many as 55% to 85% of neonates. The cysts are small, 1- to 3-mm, white or yellow-white papules that appear most often along the midline near the junction of the hard and soft palates (Fig. 1-51). Occasionally, they may occur in a more anterior location along the raphe or on the posterior palate lateral to the midline. Frequently a cluster of two to six cysts is observed, although the lesions also can occur singly.



• **Fig. 1-51 Epstein's Pearls.** Small keratin-filled cysts at the junction of the hard and soft palates. (Courtesy of Tristan Neville.)

Histopathologic Features

Microscopic examination reveals keratin-filled cysts that are lined by stratified squamous epithelium. Sometimes these cysts demonstrate a communication with the mucosal surface.

Treatment and Prognosis

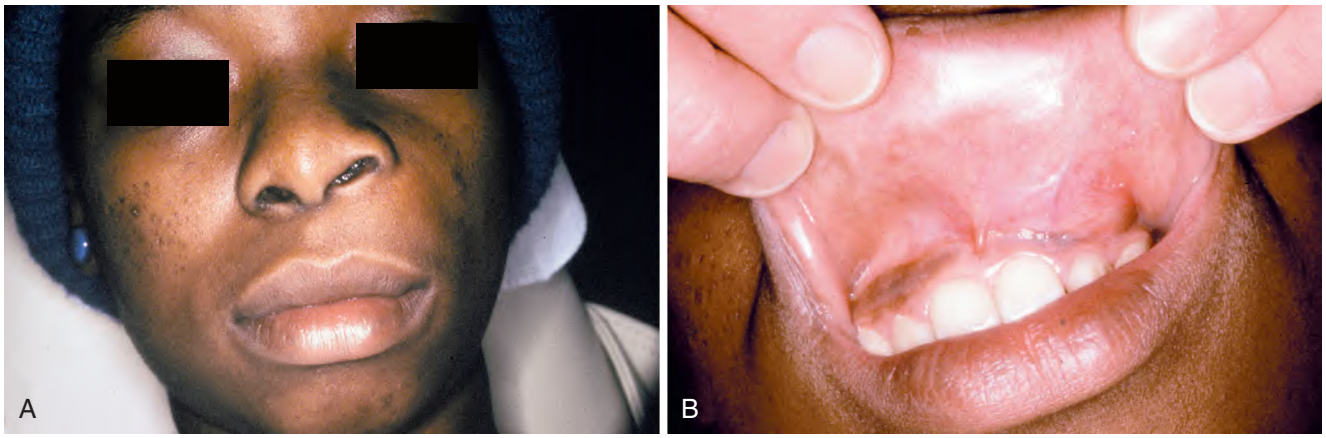
Palatal cysts of the newborn are innocuous lesions, and no treatment is required. They are self-healing and rarely observable several weeks after birth. Presumably the epithelium degenerates, or the cysts rupture onto the mucosal surface and eliminate their keratin contents.

◆ NASOLABIAL CYST (NASOALVEOLAR CYST; KLESTADT CYST)

The **nasolabial cyst** is a rare developmental cyst that occurs in the upper lip lateral to the midline. The pathogenesis is uncertain, although there are two major theories. One theory considers the nasolabial cyst to be a "fissural" cyst arising from epithelial remnants entrapped along the line of fusion of the maxillary, medial nasal, and lateral nasal processes. A second theory suggests that these cysts develop from misplaced epithelium of the nasolacrimal duct because of their similar location and histologic appearance.

Clinical and Radiographic Features

The nasolabial cyst usually appears as a swelling of the upper lip lateral to the midline, resulting in elevation of the ala of



• **Fig. 1-52 Nasolabial Cyst. A,** Enlargement of the left upper lip with elevation of the ala of the nose. **B,** Intraoral swelling fills the maxillary labial fold. (Courtesy of Dr. Jim Weir.)

the nose. The enlargement often elevates the mucosa of the nasal vestibule and obliterates the maxillary mucolabial fold (Fig. 1-52). On occasion, this expansion may result in nasal obstruction or may interfere with the wearing of a denture. Pain is uncommon unless the lesion is secondarily infected. The cyst may rupture spontaneously and may drain into the oral cavity or nose.

Nasolabial cysts are most commonly seen in adults, with peak prevalence in the fourth and fifth decades of life. A significant predilection exists for women, with a female-to-male ratio of 3 : 1. Approximately 10% of the reported cases have been bilateral.

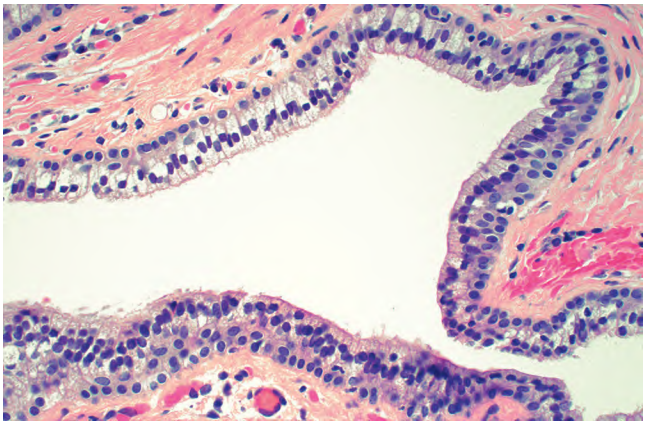
Because the nasolabial cyst arises in soft tissues, in most cases no radiographic changes are seen. Occasionally, pressure resorption of the underlying bone may occur.

Histopathologic Features

The nasolabial cyst is characteristically lined by pseudostratified columnar epithelium, often demonstrating goblet cells and cilia (Fig. 1-53). Areas of cuboidal epithelium and squamous metaplasia are not unusual. Apocrine changes also have been reported. The cyst wall is composed of fibrous connective tissue with adjacent skeletal muscle. Inflammation may be seen if the lesion is secondarily infected.

Treatment and Prognosis

Complete surgical excision of the cyst via an intraoral approach has been the traditional treatment of choice. Because the lesion is often close to the floor of the nose, it is sometimes necessary to sacrifice a portion of the nasal mucosa to ensure total removal. However, an alternative transnasal approach has been developed that allows endoscopic marsupialization of the lesion, converting the cyst into an air-containing sinus with its opening on the nasal floor. Recurrence is rare.



• **Fig. 1-53 Nasolabial Cyst.** Pseudostratified columnar epithelial lining.

◆ "GLOBULOMAXILLARY CYST"

As originally described, the "**globulomaxillary cyst**" was purported to be a fissural cyst that arose from epithelium entrapped during fusion of the globular portion of the medial nasal process with the maxillary process. This concept has been questioned, however, because the globular portion of the medial nasal process is primarily united with the maxillary process and a fusion does not occur. Therefore, epithelial entrapment should not occur during embryologic development of this area.

Virtually all cysts in the globulomaxillary region (between the lateral incisor and canine teeth) can be explained on an odontogenic basis. Many are lined by inflamed stratified squamous epithelium and are consistent with **periapical cysts** (see page 119). Some exhibit specific histopathologic features of an **odontogenic keratocyst** (see page 636) or developmental **lateral periodontal cyst** (see page 645). On rare occasions, cysts in the globulomaxillary area may be lined by pseudostratified, ciliated, columnar epithelium. Such cases may lend credence to the fissural theory of

origin. However, this epithelium may be explained by the close proximity of the sinus lining. In addition, respiratory epithelium also has been reported in periapical cysts, dentigerous cysts, and glandular odontogenic cysts found in other locations.

Because a fissural cyst in this region probably does not exist, the term *globulomaxillary cyst* should no longer be used. When a radiolucency between the maxillary lateral incisor and canine is encountered, the clinician should first consider an odontogenic origin for the lesion.

◆ NASOPALATINE DUCT CYST (INCISIVE CANAL CYST)

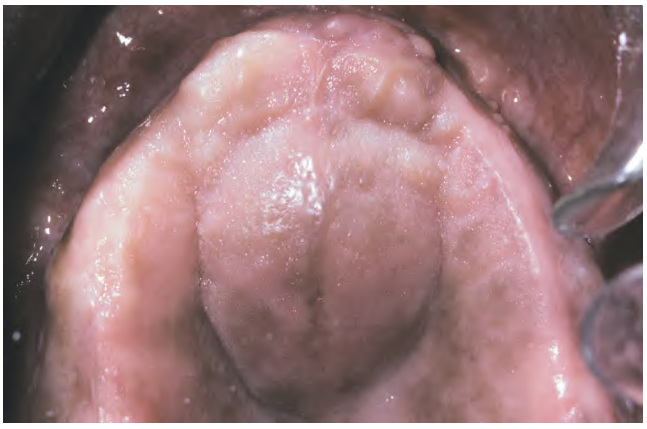
The **nasopalatine duct cyst** is the most common nonodontogenic cyst of the oral cavity, occurring in about 1% of the population. The cyst is believed to arise from remnants of the **nasopalatine duct,** an embryologic structure connecting the oral and nasal cavities in the area of the incisive canal.

In the 7-week-old fetus, the developing palate consists of the **primary palate,** which is formed by the fusion of the medial nasal processes. Behind the primary palate, downgrowth of the nasal septum produces two communications between the oral and nasal cavities, the primitive nasal choanae. Formation of the **secondary palate** begins around the eighth intrauterine week, with downward growth of the medial parts of the maxillary processes (palatine processes) to a location on either side of the tongue.

As the mandible develops and the tongue drops down, these palatine processes grow horizontally, fusing with the nasal septum in the midline and with the primary palate along their anterior aspect. Two passageways persist in the midline between the primary and secondary palates (the **incisive canals**). Also formed by this fusion and found within the incisive canals are epithelial structures—the **nasopalatine ducts.** These ducts normally degenerate in humans but may leave epithelial remnants behind in the incisive canals.

The incisive canals begin on the floor of the nasal cavity on either side of the nasal septum, coursing downward and forward to exit the palatal bone via a common foramen in the area of the incisive papilla. In addition to the nasopalatine ducts, these canals contain the nasopalatine nerve plus anastomosing branches of the descending palatine and sphenopalatine arteries. Occasionally, two smaller foramina carrying the nasopalatine nerves—the **canals of Scarpa**—are found within the incisive foramen.

In some mammals the nasopalatine ducts remain patent and provide communication between the oral and nasal cavities. On rare occasions, patent or partially patent nasopalatine ducts may be encountered in humans. In mammals the nasopalatine ducts may communicate with the vomernasal **organ of Jacobson,** acting as an accessory olfactory organ. However, in humans, Jacobson's organ usually recedes in uterine life to become a vestigial structure.



• **Fig. 1-54 Nasopalatine Duct Cyst.** Fluctuant swelling of the anterior hard palate.

Researchers have suggested that the nasopalatine duct cyst may arise from the epithelium of Jacobson's organ, but this appears highly unlikely. Trauma or infection of the duct and mucous retention of adjacent minor salivary glands also have been mentioned as possible etiologic factors, but the role of each has been questioned. Although the pathogenesis of this lesion is still uncertain, the lesion most likely represents a spontaneous cystic degeneration of remnants of the nasopalatine duct.

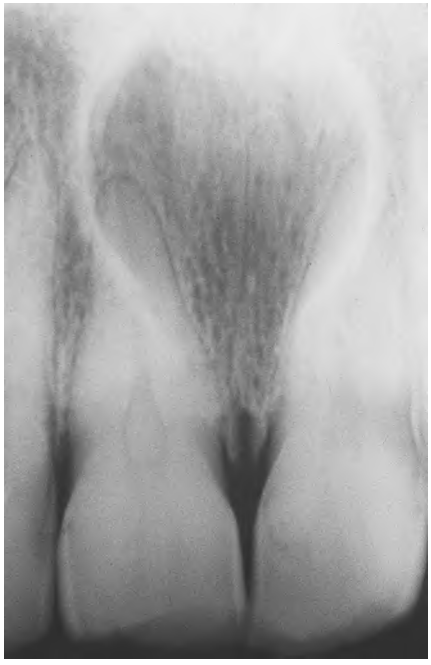
Clinical and Radiographic Features

The nasopalatine duct cyst may develop at almost any age but is most common in the fourth to sixth decades of life. In spite of its being a "developmental" cyst, the nasopalatine duct cyst is rarely seen during the first decade. Most studies have shown a male predilection.

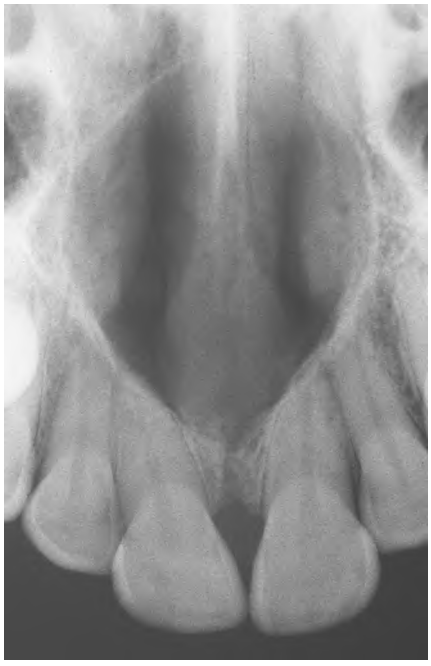
The most common presenting symptoms include swelling of the anterior palate, drainage, and pain (Fig. 1-54). Patients sometimes relate a long history of these symptoms, probably because of their intermittent nature. However, many lesions are asymptomatic and are discovered on routine radiographs. Rarely a large cyst may produce a "through-and-through" fluctuant expansion involving the anterior palate and labial alveolar mucosa.

Radiographs usually demonstrate a well-circumscribed radiolucency in or near the midline of the anterior maxilla, between and apical to the central incisor teeth (Figs. 1-55 and 1-56). Root resorption rarely is noted. The lesion most often is round or oval with a sclerotic border. Some cysts may have an inverted pear shape, presumably because of resistance of adjacent tooth roots. Other examples may show a classic heart shape as a result of superimposition of the nasal spine or because they are notched by the nasal septum.

The radiographic diameter of nasopalatine duct cysts can range from small lesions, less than 6 mm, to destructive lesions as large as 6 cm. However, most cysts are in the range of 1.0 to 2.5 cm, with an average diameter of 1.5 to 1.7 cm.



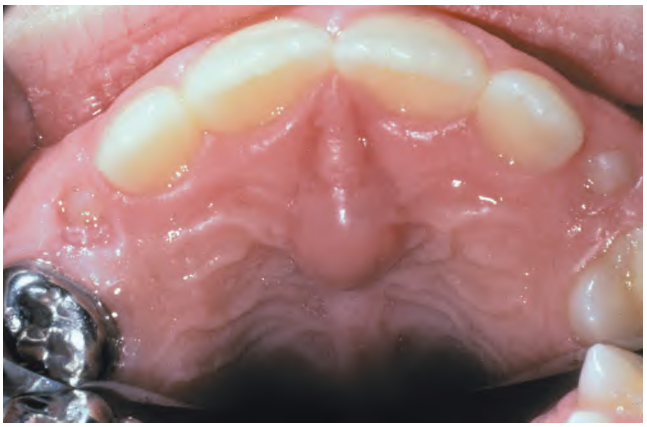
• **Fig. 1-55 Nasopalatine Duct Cyst.** Well-circumscribed radiolucency between and apical to the roots of the maxillary central incisors.



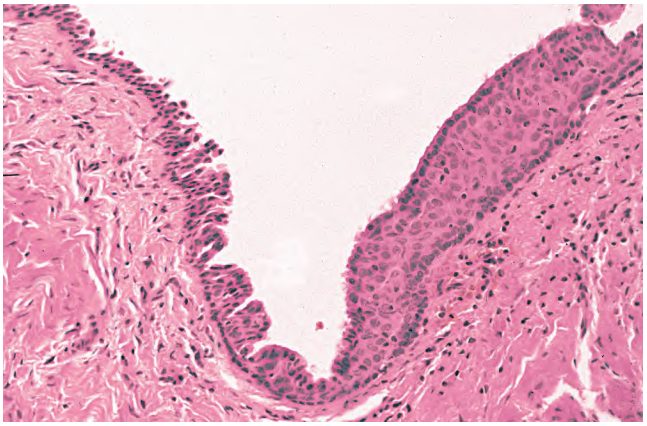
• **Fig. 1-56 Nasopalatine Duct Cyst.** Large destructive cyst of the palate.

It may be difficult to distinguish a small nasopalatine duct cyst from a large incisive foramen. It is generally accepted that a diameter of 6 mm is the upper limit of normal size for the incisive foramen. Therefore, a radiolucency that is 6 mm or smaller in this area usually is considered a normal foramen unless other clinical signs or symptoms are present.

In rare instances, a nasopalatine duct cyst may develop in the soft tissues of the incisive papilla area without any bony involvement. Such lesions often are called **cysts of the incisive papilla.** These cysts frequently demonstrate bluish discoloration as a result of the fluid contents in the cyst lumen (Fig. 1-57).



• **Fig. 1-57 Cyst of the Incisive Papilla.** Swelling of the incisive papilla.



• **Fig. 1-58 Nasopalatine Duct Cyst.** Cystic lining showing transition from pseudostratified columnar to stratified squamous epithelium.

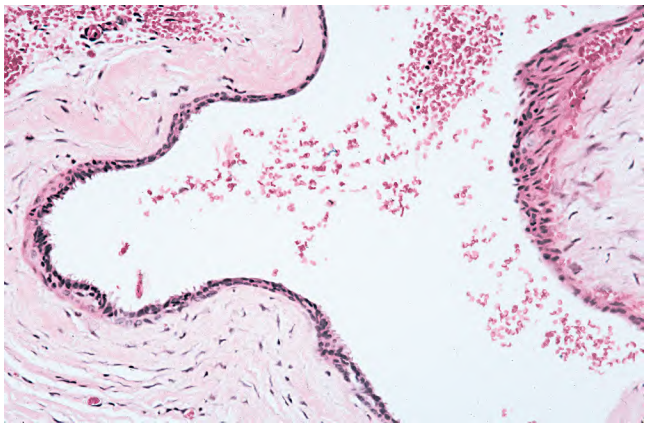
Histopathologic Features

The epithelial lining of nasopalatine duct cysts is highly variable (Figs. 1-58 and 1-59). It may be composed of the following:

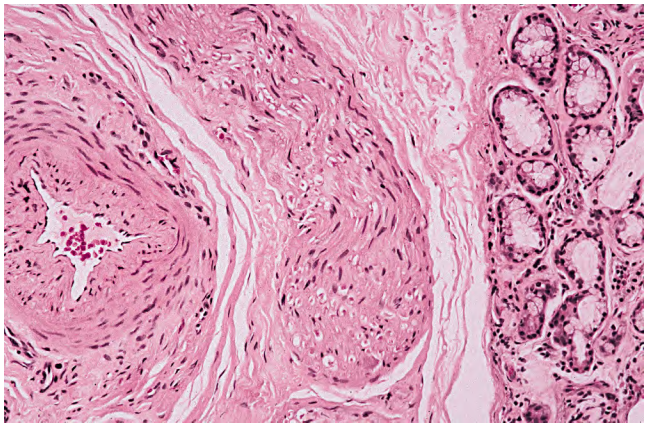
- Stratified squamous epithelium
- Pseudostratified columnar epithelium
- Simple columnar epithelium
- Simple cuboidal epithelium

Frequently, more than one epithelial type is found in the same cyst. Stratified squamous epithelium is most common, present in at least three fourths of all cysts. Pseudostratified columnar epithelium has been reported in from one-third to three-fourths of all cases. Simple cuboidal or columnar epithelium is discovered less frequently.

Cilia and goblet cells may be found in association with columnar linings. The type of epithelium may be related to the vertical position of the cyst within the incisive canal.



• **Fig. 1-59 Nasopalatine Duct Cyst.** Flattened cuboidal epithelial lining.



• **Fig. 1-60 Nasopalatine Duct Cyst.** Cyst wall showing blood vessels, nerve bundles, and minor salivary glands.

Cysts developing within the superior aspect of the canal near the nasal cavity are more likely to demonstrate respiratory epithelium; those in an inferior position near the oral cavity are more likely to exhibit squamous epithelium.

The contents of the cyst wall can be a helpful diagnostic aid. Because the nasopalatine duct cyst arises within the incisive canal, moderate-sized nerves and small muscular arteries and veins usually are found in the wall of the cyst (Fig. 1-60). Small mucous glands have been reported in as many as one-third of cases. Occasionally, the clinician may see small islands of hyaline cartilage. Frequently, an inflammatory response is noted in the cyst wall and may range from mild to heavy. This inflammation usually is chronic in nature and is composed of lymphocytes, plasma cells, and histiocytes. Associated acute inflammatory cells (neutrophils) sometimes may be seen.

Treatment and Prognosis

Nasopalatine duct cysts are treated by surgical enucleation. Biopsy is recommended because the lesion is not diagnostic radiographically; other benign and malignant lesions have been known to mimic the nasopalatine duct cyst. The lesion is best approached with a palatal flap that is reflected after an incision is made along the lingual gingival margin of the anterior maxillary teeth. Recurrence is rare. Malignant transformation has been reported in a couple of cases, but this is an extremely rare complication.

◆ MEDIAN PALATAL (PALATINE) CYST

The median palatal cyst is a rare fissural cyst that theoretically develops from epithelium entrapped along the embryonic line of fusion of the lateral palatal shelves of the maxilla. This cyst may be difficult to distinguish from a nasopalatine duct cyst. In fact, most "median palatal cysts" may represent posteriorly positioned nasopalatine duct cysts. Because the nasopalatine ducts course posteriorly and superiorly as they extend from the incisive canal to the nasal cavity, a nasopalatine duct cyst that arises from posterior remnants of this duct near the nasal cavity might be mistaken for a median palatal cyst. On the other hand, if a true median palatal cyst were to develop toward the anterior portion of the hard palate, then it could easily be mistaken for a nasopalatine duct cyst.

Clinical and Radiographic Features

The median palatal cyst presents as a firm or fluctuant swelling of the midline of the hard palate posterior to the palatine papilla (Fig. 1-61). The lesion appears most frequently in young adults. Often it is asymptomatic, but some patients complain of pain or expansion. The average size of this cyst is 2 × 2 cm, but sometimes it can become quite large. Occlusal radiographs demonstrate a well-circumscribed radiolucency in the midline of the hard palate (Fig. 1-62). Occasional reported cases have been associated with divergence of the central incisors, although it may be difficult to rule out a nasopalatine duct cyst in these instances.

To differentiate the median palatal cyst from other cystic lesions of the maxilla, Gingell and associates suggested the following diagnostic criteria:

- Grossly appears symmetrical along the midline of the hard palate
- Located posterior to the palatine papilla
- Appears ovoid or circular radiographically
- Not intimately associated with a nonvital tooth
- Does not communicate with the incisive canal
- Shows no microscopic evidence of large neurovascular bundles, hyaline cartilage, or minor salivary glands in the cyst wall

It must be stressed that a true median palatal cyst should exhibit clinical enlargement of the palate. A midline radiolucency without clinical evidence of expansion is probably a nasopalatine duct cyst.

Histopathologic Features

Microscopic examination shows a cyst that usually is lined by stratified squamous epithelium. Areas of ciliated

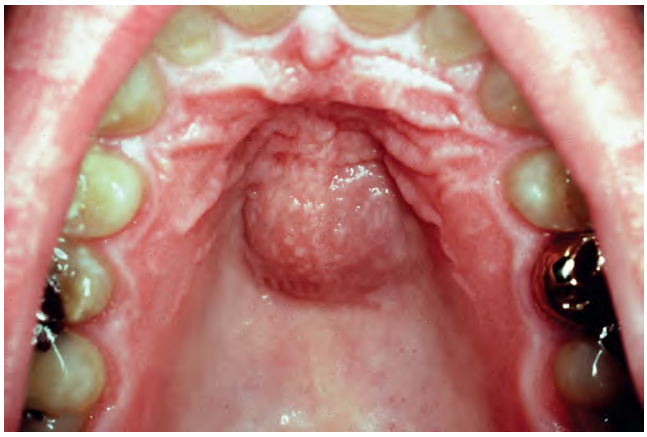


Fig. 1-61 Median Palatal Cyst. Compressible mass in the midline of the hard palate posterior to the incisive papilla. (Courtesy of Dr. Craig Fowler.)

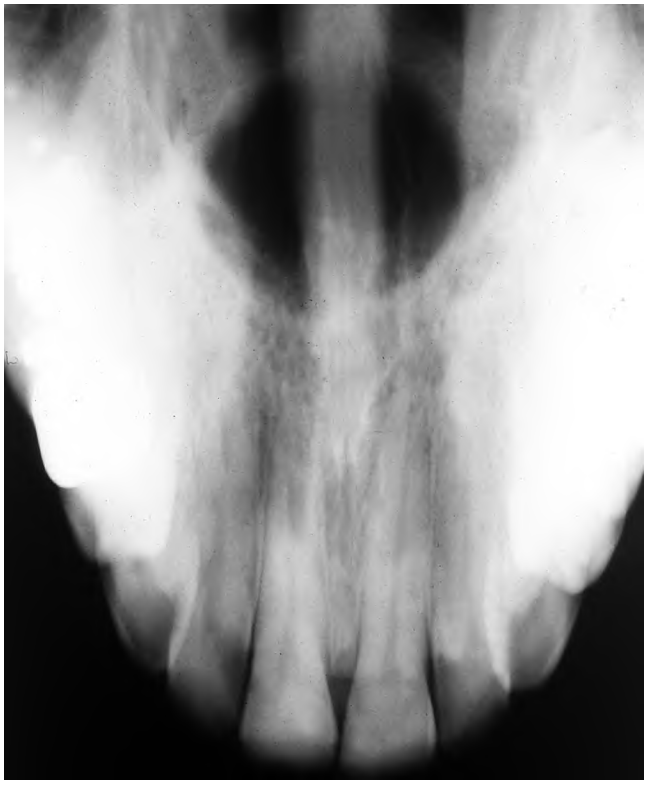


Fig. 1-62 Median Palatal Cyst. Occlusal radiograph of same patient depicted in Figure 1-61. A well-circumscribed midline radiolucent defect can be seen, which is separate from the incisive canal. (Courtesy of Dr. Craig Fowler.)

pseudostratified columnar epithelium have been reported in some cases. Chronic inflammation may be present in the cyst wall.

Treatment and Prognosis

The median palatal cyst is treated by surgical removal. Recurrence should not be expected.

"MEDIAN MANDIBULAR CYST"

The **"median mandibular cyst"** is a controversial lesion of questionable existence. Theoretically, it represents a fissural cyst in the anterior midline of the mandible that develops from epithelium entrapped during fusion of the halves of the mandible during embryonic life. However, the mandible actually develops as a single bilobed proliferation of mesenchyme with a central isthmus in the midline. As the mandible grows, this isthmus is eliminated. Therefore, because no fusion of epithelium-lined processes occurs, entrapment of epithelium should not be possible.

Because respiratory prosoplasia is not uncommon in odontogenic cysts, it appears likely that most (if not all) of these midline cysts are of odontogenic origin. Many purported cases would be classified today as examples of the *glandular odontogenic cyst* (see page 649), which has a propensity for occurrence in the midline mandibular region. Others could be classified as *periapical cysts, odontogenic keratocysts,* or *lateral periodontal cysts.* Because a fissural cyst in this region probably does not exist, the term *median mandibular cyst* should no longer be used.

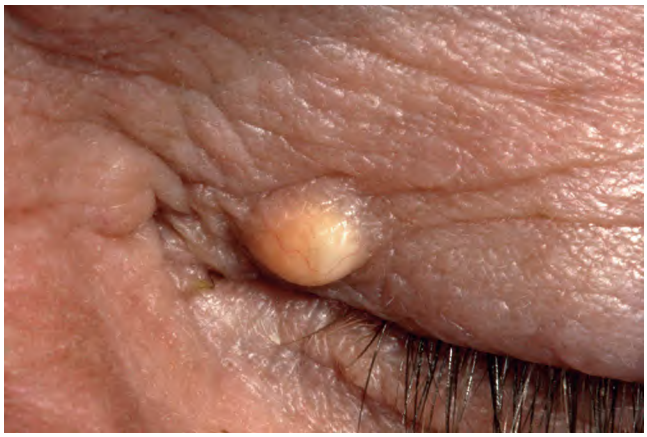
FOLLICULAR CYSTS OF THE SKIN

Follicular cysts of the skin are common keratin-filled lesions that arise from one or more portions of the hair follicle. The most common type, which is derived from the follicular infundibulum, is known as an **epidermoid** or **infundibular cyst.** These cysts often arise after localized inflammation of the hair follicle and probably represent a nonneoplastic proliferation of the infundibular epithelium resulting from the healing process. The term **sebaceous cyst** sometimes is used mistakenly as a synonym for both the epidermoid cyst and another cyst of the scalp known as a **pilar, trichilemmal,** or **isthmus-catagen cyst.** However, because both the epidermoid cyst and pilar cyst are derived from the hair follicle rather than the sebaceous gland, the term *sebaceous cyst* should be avoided.

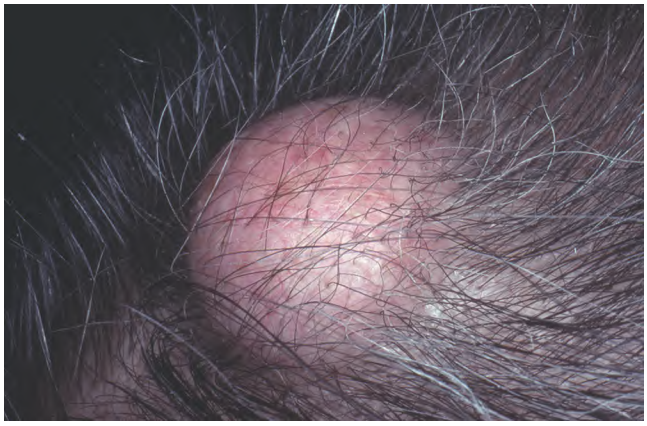
Keratin-filled cysts of the skin may occasionally arise after traumatic implantation of epithelium, although such lesions may be difficult to distinguish from an infundibular cyst. Rarely, such **epidermal inclusion (implantation) cysts** also can develop in the mouth. These small inclusion cysts should be distinguished from oral epidermoid cysts that occur in the midline floor of mouth region and represent the minimal manifestation of the teratoma-dermoid cyst-epidermoid cyst spectrum (see page 31).

Clinical Features

Epidermoid (infundibular) cysts account for approximately 80% of follicular cysts of the skin and are most common in the acne-prone areas of the head, neck, and back. They are unusual before puberty unless they are associated with **Gardner syndrome** (see page 606). Young adults are more likely to have cysts on the face, whereas older adults are



• **Fig. 1-63 Epidermoid Cyst.** Yellow nodule at the medial aspect of the eyelid.



• **Fig. 1-64 Pilar Cyst.** Nodular mass on the scalp.

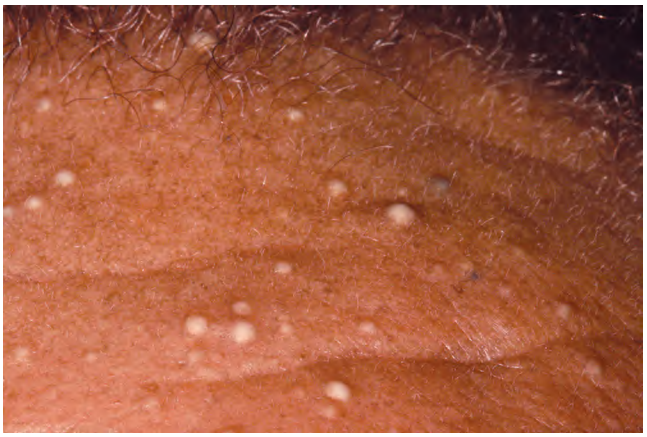
more likely to have cysts on the back. Males are affected more frequently than females.

Epidermoid cysts present as nodular, fluctuant subcutaneous lesions that may or may not be associated with inflammation (Fig. 1-63). If a noninflamed lesion presents in an area of thin skin, such as the earlobe, then it may be white or yellow.

Pilar (trichilemmal) cysts comprise approximately 10% to 15% of skin cysts, occurring most frequently on the scalp (Fig. 1-64). They are twice as common in women as in men. The lesion is usually movable and shells out easily. **Milia** (singular: **milium**) are tiny keratin-filled cysts that resemble miniature epidermoid cysts (Fig. 1-65). A variety of such lesions have been described, including primary congenital milia, genodermatosis-associated milia, and milia that develop secondary to bullous disorders, trauma, or certain medications. Primary milia are thought to arise from the sebaceous collar of vellus hairs, whereas secondary milia may develop from eccrine ducts, hair follicles, or the overlying epidermis.

Histopathologic Features

Microscopic examination of an epidermoid cyst reveals a cavity that is lined by stratified squamous epithelium resembling epidermis (Fig. 1-66). A well-developed granular cell layer is seen, and the lumen is filled with degenerating orthokeratin. Not infrequently, the epithelial lining will be disrupted. When this occurs, a prominent granulomatous inflammatory reaction, including multinucleated giant cells, can be present in the cyst wall because the exposed keratin is recognized as a foreign material.



• **Fig. 1-65 Milia.** Multiple tiny keratin-filled cysts on the forehead.

The pilar cyst also is lined by stratified squamous epithelium, although a granular cell layer usually is absent or greatly diminished (Fig. 1-67). The keratinocytes remain large in the upper epithelial layers with an abrupt transition to dense, compact keratin that fills the cyst lumen.

Treatment and Prognosis

Epidermoid and pilar cysts usually are treated by conservative surgical excision, and recurrence is uncommon. Malignant transformation has been reported but is exceedingly rare.

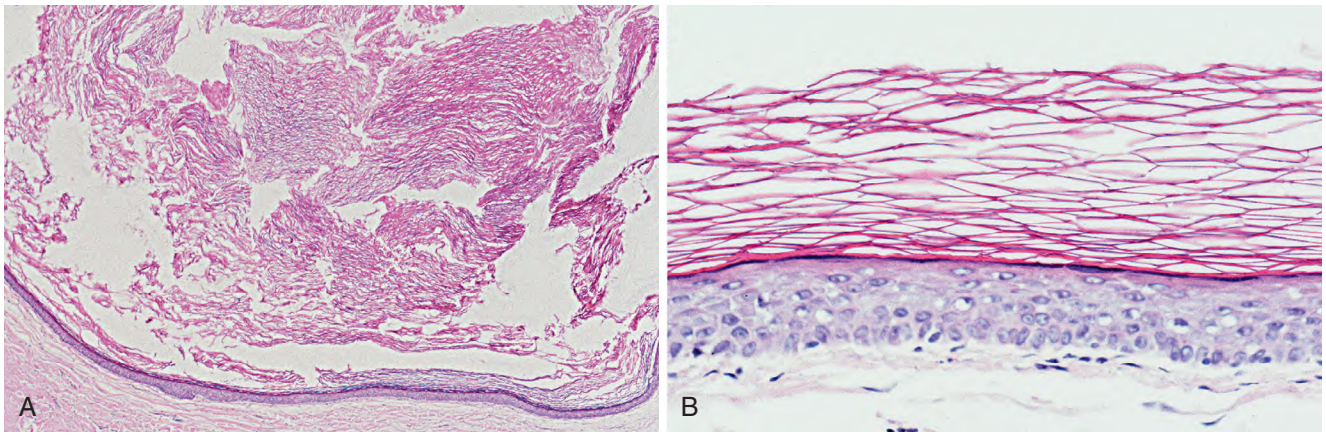
An individual milium can be removed by evacuation, in which the lesion is nicked by a scalpel blade, followed by application of pressure with a comedone extractor or curette. Multiple milia can be managed via electrocautery or application of topical retinoids.

◆ DERMOID CYST (DYSONTOGENIC CYST)

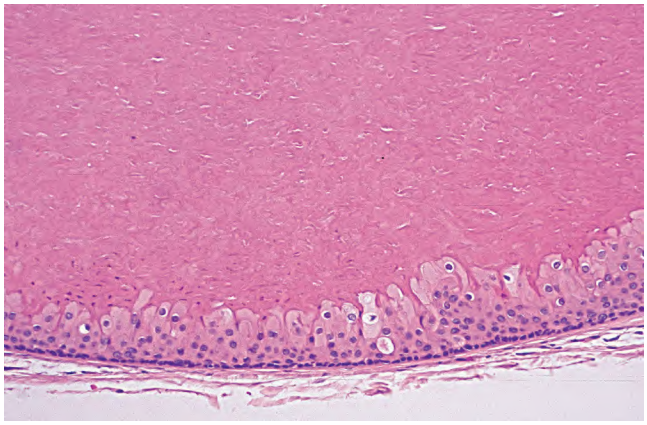
The **dermoid cyst** is an uncommon developmental cystic malformation. The cyst is lined by epidermis-like epithelium and contains dermal adnexal structures in the cyst wall. It is generally classified as a benign cystic form of **teratoma.**

By definition, a teratoma is a developmental tumor composed of tissue from more than one germ layer and sometimes all three: 1) ectoderm, 2) mesoderm, and 3) endoderm. Such tumors are believed to arise from germ cells or entrapped totipotent blastomeres, which can produce derivatives of all three germ layers.

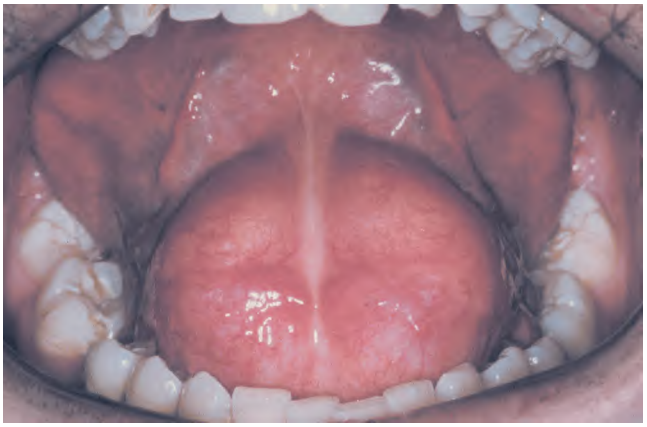
Teratomatous malformations have a spectrum of complexity. In their most complex form, these lesions produce multiple types of tissue that are arranged in a disorganized



• **Fig. 1-66 Epidermoid Cyst. A,** Low-power view showing a keratin-filled cystic cavity. **B,** High-power view showing stratified squamous epithelial lining with orthokeratin production.



• **Fig. 1-67 Pilar Cyst.** Medium-power view showing an abrupt transition between the stratified squamous epithelial lining and compact keratin without the presence of a transitional granular cell layer.



• **Fig. 1-68 Dermoid Cyst.** Fluctuant midline swelling in the floor of the mouth. (From Budnick SD: *Handbook of pediatric oral pathology,* Chicago, 1981, Year Book Medical.)

fashion. These "complex" teratomas are most common in the ovaries or testes and can be benign or malignant. Occasionally, ovarian teratomas (or "dermoids") produce well-formed teeth, or even partially complete jaws. Complex teratomas of the oral cavity are rare and usually are congenital in nature. When they occur, they usually extend through a cleft palate from the pituitary area via Rathke's pouch. Cervical teratomas also have been reported.

The term **teratoid cyst** has been used to describe a cystic form of teratoma that contains a variety of germ layer derivatives:

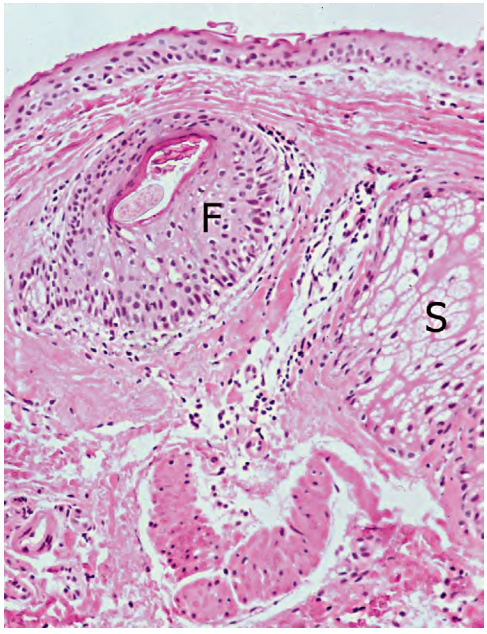
1. Skin appendages, including hair follicles, sebaceous glands, and sweat glands
2. Connective tissue elements, such as muscle, blood vessels, and bone
3. Endodermal structures, such as gastrointestinal lining

Rarely, oral cysts may be lined entirely by gastrointestinal epithelium. These **heterotopic oral gastrointestinal cysts (enterocystomas, enteric duplication cysts)** usually are considered to be choristomas, or histologically normal tissue found in an abnormal location. However, these lesions probably can be included under the broad umbrella of teratomatous lesions, especially because they occasionally are found in combination with dermoid cysts.

Dermoid cysts are simpler in structure than complex teratomas or teratoid cysts. Although they do not contain tissue from all three germ layers, they probably represent a *forme fruste* of a teratoma. Similar cysts of the oral cavity can be seen that are lined by epidermis-like epithelium, but they contain no dermal appendages in the cyst wall. These lesions have been called **epidermoid cysts** and represent the simplest expression of the teratoma spectrum. These intraoral epidermoid cysts should not be confused with the more common **epidermoid cyst of the skin** (see page 29), a non-teratomatous lesion that arises from the hair follicle. Because the teratoid cyst/dermoid cyst/epidermoid cyst spectrum represents defective embryologic development, these cysts sometimes are known collectively as **dysontogenic cysts**.

Clinical and Radiographic Features

Dermoid cysts most commonly occur in the midline of the floor of the mouth (Fig. 1-68), although occasionally they are displaced laterally or develop in other locations. If the



• **Fig. 1-69 Dermoid Cyst.** Squamous epithelial lining *(top),* with hair follicle *(F),* sebaceous glands *(S)* in the cyst wall.

cyst develops above the geniohyoid muscle, then a sublingual swelling may displace the tongue toward the roof of the mouth and create difficulty in eating, speaking, or even breathing. Cysts that occur below the geniohyoid muscle often produce a submental swelling, with a "double-chin" appearance.

Oral dermoid cysts can vary in size from a few millimeters to 12 cm in diameter. They are most common in children and young adults; 15% of reported cases have been congenital. The lesion is usually slow growing and painless, presenting as a doughy or rubbery mass that frequently retains pitting after application of pressure. Secondary infection can occur, and the lesion may drain intraorally or onto the skin. MRIs, CT scans, or contrast medium radiographs may be helpful in delineating the extent of the lesion.

Histopathologic Features

Dermoid cysts are lined by orthokeratinized stratified squamous epithelium with a prominent granular cell layer. Abundant keratin often is found within the cyst lumen. On rare occasions, areas of respiratory epithelium can be seen. The cyst wall is composed of fibrous connective tissue that contains one or more skin appendages, such as sebaceous glands, hair follicles, or sweat glands (Fig. 1-69).

Treatment and Prognosis

Dermoid cysts are treated by surgical removal. Those located above the geniohyoid muscle can be removed by an intraoral incision, and those below the geniohyoid muscle may require an extraoral approach. Recurrence is uncommon. Malignant transformation into squamous cell carcinoma has been reported only rarely.

◆ THYROGLOSSAL DUCT CYST (THYROGLOSSAL TRACT CYST)

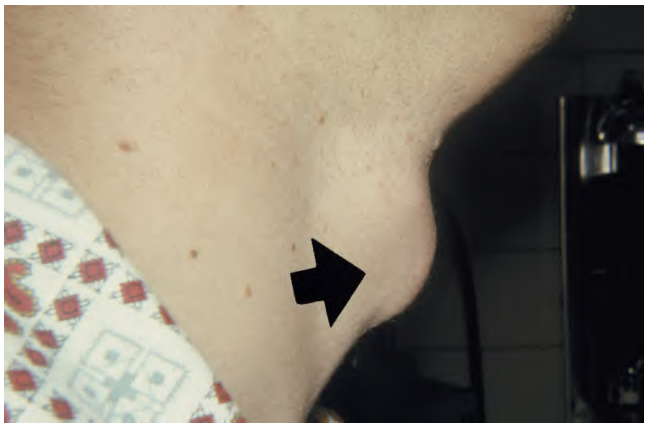
The thyroid gland begins its development during the third to fourth week of embryonic life as a proliferation of endodermal cells from the ventral floor of the pharynx, between the tuberculum impar and copula of the developing tongue—a point that later becomes the foramen cecum. This thyroid anlage descends into the neck as a bilobed diverticulum anterior to the developing hyoid bone and reaches its definitive level below the thyroid cartilage by the seventh embryonic week. Along this path of descent, an epithelial tract or duct is formed, maintaining an attachment to the base of the tongue. This thyroglossal duct becomes intimately associated with the developing hyoid bone. As the hyoid matures and rotates to its adult position, the thyroglossal duct passes in front and beneath the hyoid, looping upward and behind it before curving downward again into the lower neck. The caudal segment of this duct often persists, forming the pyramidal lobe of the thyroid gland.

The thyroglossal duct epithelium normally undergoes atrophy and is obliterated, although autopsy studies have shown that as many as 7% of the population will have *thyroglossal tract remnants.* These epithelial remnants usually are asymptomatic, although some can give rise to cysts along this tract known as **thyroglossal duct cysts.** The impetus for cystic degeneration is uncertain. Inflammation is the most frequently suggested stimulus, especially from adjacent lymphoid tissue that may react to draining infections of the head and neck. Retention of secretions within the duct is another possible factor. In addition, there are several reports of familial occurrence of such cysts.

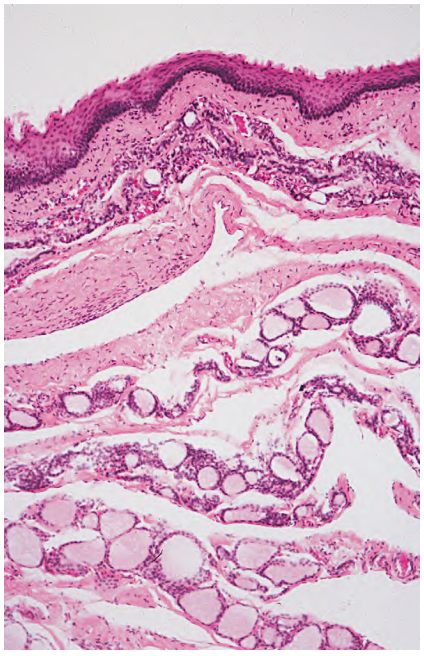
Clinical Features

Thyroglossal duct cysts classically develop in the midline and may occur anywhere from the foramen cecum area of the tongue to the suprasternal notch. In 60% to 80% of cases, the cyst develops adjacent to the hyoid bone. Suprahyoid cysts may be submental in location. Cysts that develop in the area of the thyroid cartilage often are deflected lateral to the midline because of the sharp anterior margin of the thyroid cartilage. Intralingual cysts are rare.

Thyroglossal duct cysts may develop at any age, but they are most commonly diagnosed in the first two decades of life; about 50% of cases occur before the age of 20. There is no sex predilection. The cyst usually presents as a painless, fluctuant, movable swelling unless it is complicated by secondary infection (Fig. 1-70). Lesions that develop at the base of the tongue may cause laryngeal obstruction. Most thyroglossal duct cysts are smaller than 3 cm in diameter, but occasional cysts may reach 10 cm in size. If the cyst



• **Fig. 1-70 Thyroglossal Duct Cyst.** Swelling *(arrow)* of the anterior midline of the neck. (Courtesy of Dr. Philip Sprinkle.)



• **Fig. 1-71 Thyroglossal Duct Cyst.** Cyst *(top)* lined by stratified squamous epithelium. Thyroid follicles can be seen in the cyst wall *(bottom)*.

maintains an attachment to the hyoid bone or tongue, it will move vertically during swallowing or protrusion of the tongue. Sinus tracts to the skin or mucosa develop in as many as one-third of cases, usually from rupture of an infected cyst or as a sequela of surgery.

Histopathologic Features

Thyroglossal duct cysts usually are lined by columnar or stratified squamous epithelium, although occasionally, cuboidal or even small intestine epithelium may be documented (Fig. 1-71). Sometimes a mixture of epithelial types is present, or an intact epithelial lining cannot be found due to secondary inflammation. Thyroid tissue may occur in the cyst wall, but this is not a constant finding.

Treatment and Prognosis

Thyroglossal duct cysts are best treated by a Sistrunk procedure. In this operation the cyst is removed in addition to the midline segment of the hyoid bone and a generous portion of muscular tissue along the entire thyroglossal tract. The recurrence rate associated with this procedure is less than 10%. A much higher recurrence rate can be expected with less aggressive surgery.

Carcinoma arising in a thyroglossal duct cyst is a rare complication that occurs in approximately 1% to 2% of cases. Most of these have been papillary thyroid adenocarcinomas. Fortunately, metastases from thyroglossal carcinoma are rare, and the prognosis for people with these tumors is good.

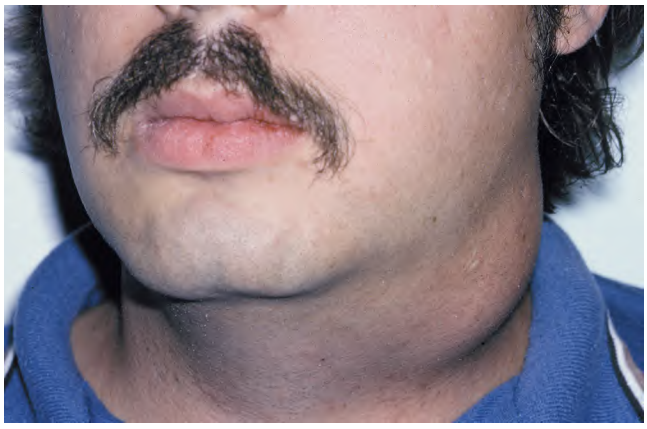
◆ BRANCHIAL CLEFT CYST (CERVICAL LYMPHOEPITHELIAL CYST)

The **branchial cleft cyst** is a developmental cyst that is derived from remnants of the branchial arches. During the fourth week of gestation, the head and neck region of the embryo develops paired branchial arches, which are covered by ectoderm on the external surface and endoderm on the internal surface. The outer arch surfaces are separated by clefts and the inner surfaces are divided by pouches. In fish and amphibians, the branchial arches are destined to become the gill apparatus; in humans, the clefts and pouches gradually are eliminated during embryonic life by ingrowth of mesenchyme. However, incomplete obliteration of these pharyngeal clefts and pouches may give rise to branchial cleft anomalies, such as cysts, fistulae, or sinus tracts. About 95% of these anomalies are believed to arise from the second branchial arch, with the remaining 5% originating from the first, third, and fourth branchial arches.

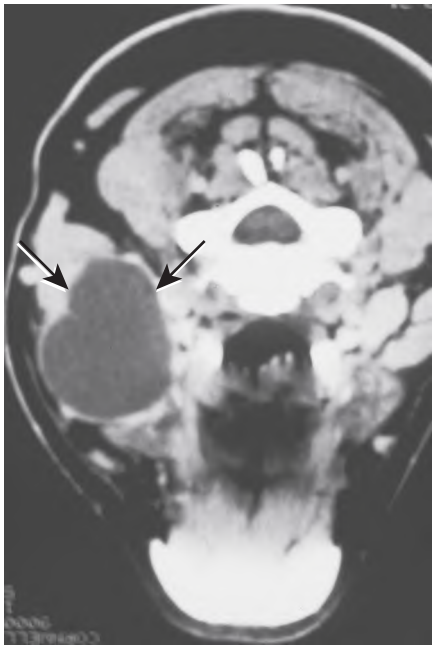
Clinical Features

Branchial cleft cysts from the second arch occur in the upper lateral neck anterior or deep to the sternocleidomastoid muscle (Figs. 1-72 and 1-73). They most frequently develop in children and young adults between the ages of 10 and 40. Clinically, the cyst appears as a soft, fluctuant mass that can range from 1 to 10 cm in diameter. Associated tenderness or pain sometimes may occur with secondary infection. Occasionally, the lesion becomes evident after an upper respiratory tract infection or trauma. Some branchial cleft anomalies appear as sinuses or fistulae that may produce a mucoid discharge onto the skin. In rare instances, bilateral cysts may develop.

Anomalies from the first branchial arch comprise approximately 1% of branchial cleft malformations and usually are found in close proximity to the parotid gland. Third-cleft and fourth-cleft anomalies are rare and may develop in the lower neck or mediastinum.



• **Fig. 1-72 Branchial Cleft Cyst.** Fluctuant swelling of the lateral neck.



• **Fig. 1-73 Branchial Cleft Cyst.** Imaging study of the same cyst depicted in Figure 1-72, showing a well-circumscribed lesion of the lateral neck *(arrows)*.

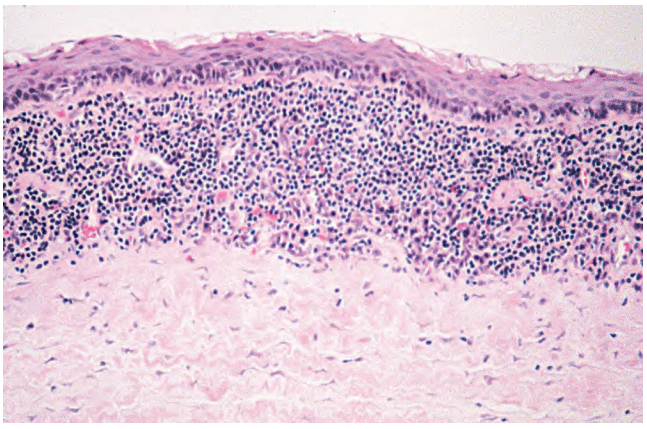
Histopathologic Features

More than 90% of branchial cleft cysts are lined by stratified squamous epithelium that may or may not be keratinized (Fig. 1-74), although some cysts will exhibit respiratory epithelium. Those anomalies that present as sinus tracts or fistulae also will often have respiratory epithelium. The wall of the cyst typically contains lymphoid tissue, often demonstrating germinal center formation. However, occasional cysts have been reported without lymphoid tissue.

Treatment and Prognosis

The branchial cleft cyst is treated by surgical removal. The lesion almost never recurs.

Rare examples of malignant transformation in these cysts have been reported. Although such an occurrence is theoretically possible, most suspected cases actually represent



• **Fig. 1-74 Branchial Cleft Cyst.** Medium-power view showing a cyst lined by stratified squamous epithelium. Note the lymphoid tissue in the cyst wall.

cystic metastases from previously undetected carcinomas of the head and neck region, especially human papillomavirus (HPV)-related tumors from the base of tongue, lingual tonsil, or palatine tonsil. When evaluating patients with cystic neck masses, fine-needle aspiration biopsy can be helpful to rule out the possibility of malignancy before surgery.

◆ ORAL LYMPHOEPITHELIAL CYST

The **oral lymphoepithelial cyst** is an uncommon lesion of the mouth that develops within oral lymphoid tissue. It is microscopically similar to the branchial cleft cyst (cervical lymphoepithelial cyst) but much smaller in size.

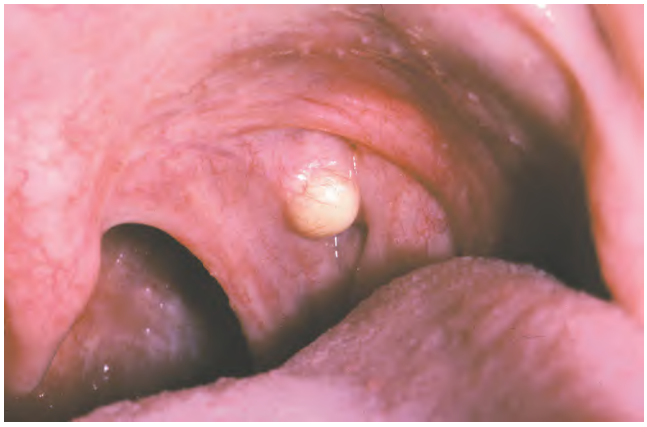
Lymphoid tissue is normally found in the oral cavity and pharynx, principally consisting of **Waldeyer ring,** which includes the palatine tonsils, lingual tonsils, and pharyngeal adenoids. In addition, accessory oral tonsils or lymphoid aggregates may occur in the floor of the mouth, ventral surface of the tongue, and soft palate.

Oral lymphoid tissue has a close relationship with the overlying mucosal epithelium. This epithelium demonstrates invaginations into the tonsillar tissue, resulting in blind pouches or tonsillar crypts that may fill up with keratin debris. The tonsillar crypt may become obstructed or pinched off from the surface, producing a keratin-filled cyst within the lymphoid tissue just below the mucosal surface. It also is possible that oral lymphoepithelial cysts may develop from salivary or surface mucosal epithelium that becomes enclaved in lymphoid tissue during embryogenesis. It even has been suggested that these cysts may arise from the excretory ducts of the sublingual gland or minor salivary glands, and that the associated lymphoid tissue represents a secondary immune response.

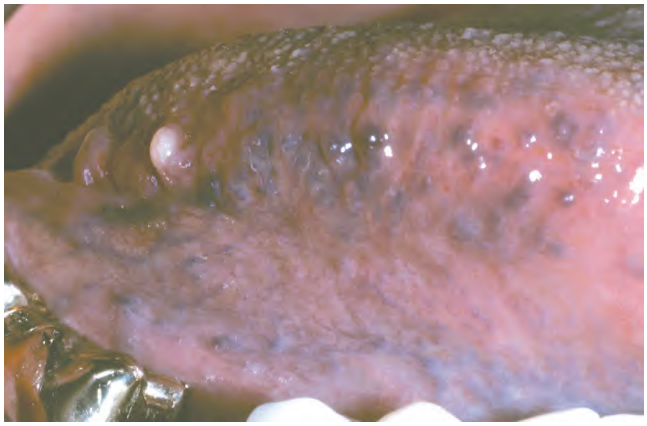
Clinical Features

The oral lymphoepithelial cyst presents as a small submucosal mass that is usually less than 1 cm in diameter; rarely will the lesion be greater than 1.5 cm (Figs. 1-75 and 1-76).

The cyst may feel firm or soft to palpation, and the overlying mucosa is smooth and nonulcerated. The lesion is typically white or yellow and often contains creamy or cheesy keratinous material in the lumen. The cyst is usually asymptomatic, although occasionally, patients may complain of swelling or drainage. Pain is rare but may occur secondary to trauma.



• **Fig. 1-75 Oral Lymphoepithelial Cyst.** Small yellow-white nodule of the tonsillar fossa.



• **Fig. 1-76 Oral Lymphoepithelial Cyst.** Small white papule of the posterior lateral border of the tongue.

Oral lymphoepithelial cysts may develop in people of almost any age, but they are most common in young adults. The most frequently reported locations are the floor of the mouth, ventral tongue, posterior lateral border of the tongue, palatine tonsil, and soft palate. All of these locations represent sites of normal or accessory oral lymphoid tissue.

Histopathologic Features

Microscopic examination of the oral lymphoepithelial cyst demonstrates a cystic cavity that is lined by stratified squamous epithelium without rete ridges (Fig. 1-77). This epithelium is typically parakeratinized with desquamated epithelial cells seen filling the cyst lumen. In rare instances the epithelial lining also may contain mucous cells. Occasional cysts may communicate with the overlying mucosal surface.

The most striking feature is the presence of lymphoid tissue in the cyst wall. In most instances, this lymphoid tissue encircles the cyst, but sometimes it involves only a portion of the cyst wall. Germinal centers are usually, but not always, present.

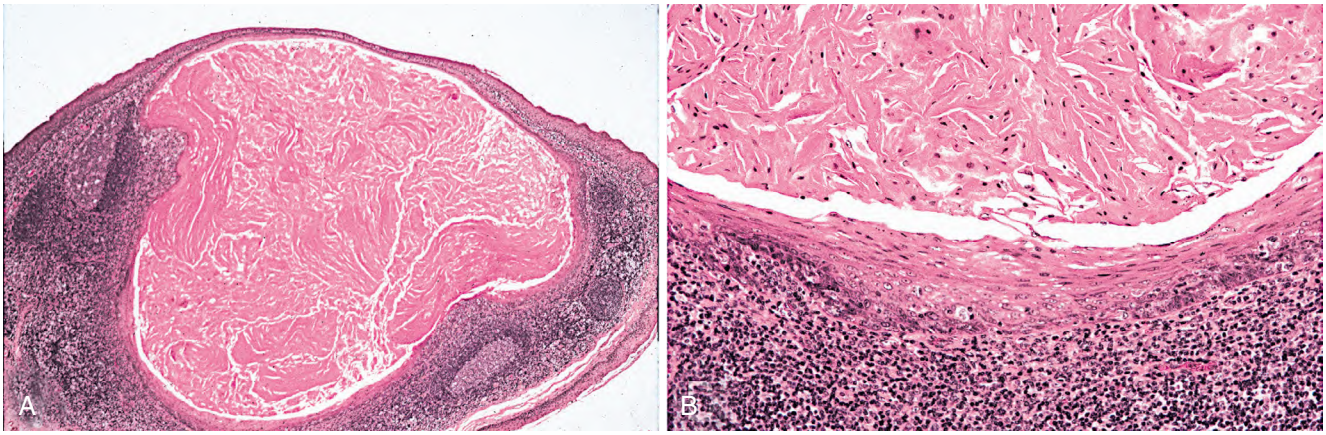
Treatment and Prognosis

The oral lymphoepithelial cyst usually is treated with surgical excision and should not recur. Because the lesion is typically asymptomatic and innocuous, biopsy may not always be necessary if the lesion is distinctive enough to make the diagnosis on a clinical basis.

OTHER RARE DEVELOPMENTAL ANOMALIES

◆ HEMIHYPERPLASIA (HEMIHYPERTROPHY)

Hemihyperplasia is a rare developmental anomaly characterized by asymmetric overgrowth of one or more body



• **Fig. 1-77 Oral Lymphoepithelial Cyst. A,** Low-power view showing a keratin-filled cyst below the mucosal surface. Lymphoid tissue is present in the cyst wall. **B,** High-power view showing lymphoid tissue adjacent to the cystic lining.

parts. Although the condition sometimes is known as **hemihypertrophy,** it actually represents a hyperplasia of the tissues rather than a hypertrophy. Hemihyperplasia can be an isolated finding, but it also may be associated with a variety of malformation syndromes (Box 1-2).

Almost all cases of isolated hemihyperplasia are sporadic. A number of possible etiologic factors have been suggested, but the cause remains obscure. Various theories include vascular or lymphatic abnormalities, central nervous system disturbances, endocrine dysfunctions, and aberrant twinning mechanisms. Occasionally, chromosomal anomalies have been documented.

• BOX 1-2 Malformation Syndromes Associated with Hemihyperplasia

- Beckwith-Wiedemann syndrome
- Neurofibromatosis
- Klippel-Trénaunay-Weber syndrome
- Proteus syndrome
- McCune-Albright syndrome
- Epidermal nevus syndrome
- Triploid/diploid mixoploidy
- Langer-Giedion syndrome
- Multiple exostoses syndrome
- Maffucci syndrome
- Ollier syndrome
- Segmental odontomaxillary dysplasia

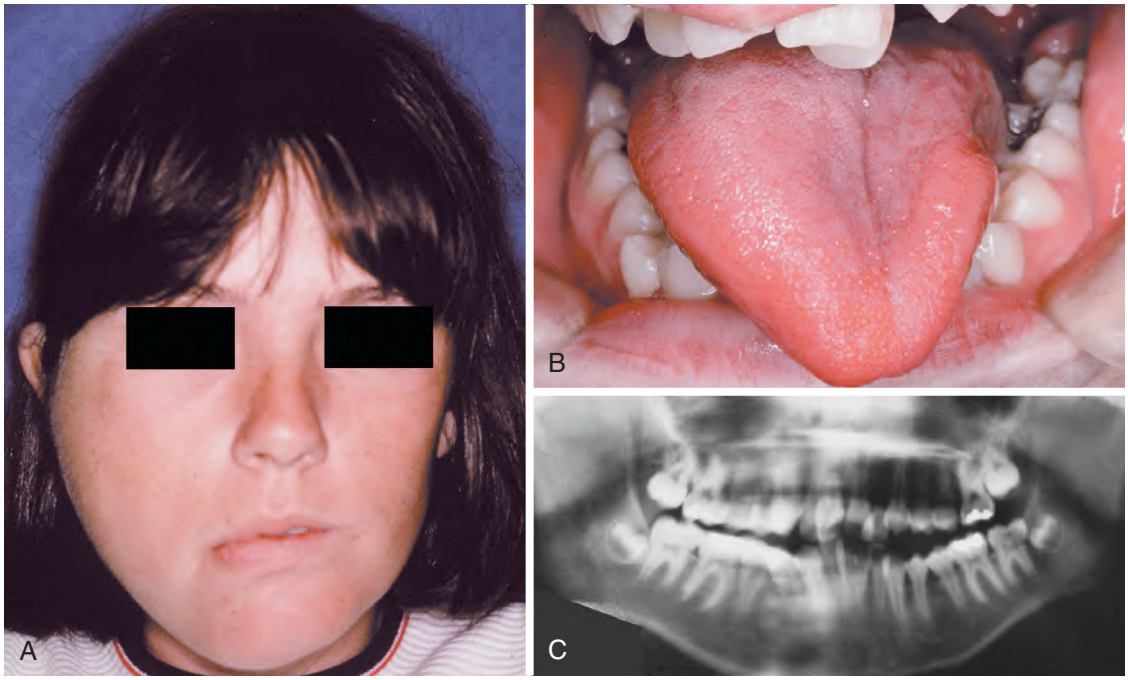
Clinical and Radiographic Features

In a person with hemihyperplasia, one entire side of the body **(complex hemihyperplasia)** may be affected or the enlargement may be limited to a single limb **(simple hemihyperplasia).** If the enlargement is confined to one side of the face, the term **hemifacial hyperplasia** may apply. The condition occasionally can be crossed, involving different areas on both sides of the body. Hemihyperplasia shows a nearly 2:1 female-to-male predilection, and it occurs more often on the right side of the body.

Asymmetry often is noted at birth, although in some cases the condition may not become evident until later in childhood (Fig. 1-78). The enlargement becomes more accentuated with age, especially at puberty. This disproportionate growth continues until the patient's overall growth ceases, resulting in permanent asymmetry.

The changes may involve all the tissues on the affected side, including the underlying bone. Often the skin is thickened and may demonstrate increased pigmentation, hypertrichosis, telangiectasias, or nevus flammeus (see page 508). About 20% of those affected are intellectually disabled. One of the most significant features is an increased prevalence of abdominal tumors, especially Wilms tumor, adrenal cortical carcinoma, and hepatoblastoma. These tumors have been reported in 5.9% of patients with isolated hemihyperplasia, and they do not necessarily occur on the same side as the somatic enlargement.

Unilateral **macroglossia,** featuring prominent tongue papillae, is common. Enlargement of other oral soft tissues



• Fig. 1-78 Hemihyperplasia. A, Enlargement of the right side of the face. **B,** Same patient with associated enlargement of the right half of the tongue. **C,** Panoramic radiograph of the same patient showing enlargement of the mandible and teeth on the right side. (Courtesy of Dr. George Blozis.)

and bone can occur. The mandibular canal may be increased in size on radiographs. The crowns of the teeth on the affected side, especially the permanent cuspids, premolars, and first molars, can be larger. Premature development of these teeth, along with precocious eruption, may be obvious. The roots also may be larger, but some reports have described root resorption. Malocclusion with open bite is not unusual.

Histopathologic Features

Microscopic examination shows an increase in thickness of the epithelium with hyperplasia of the underlying connective tissues.

Treatment and Prognosis

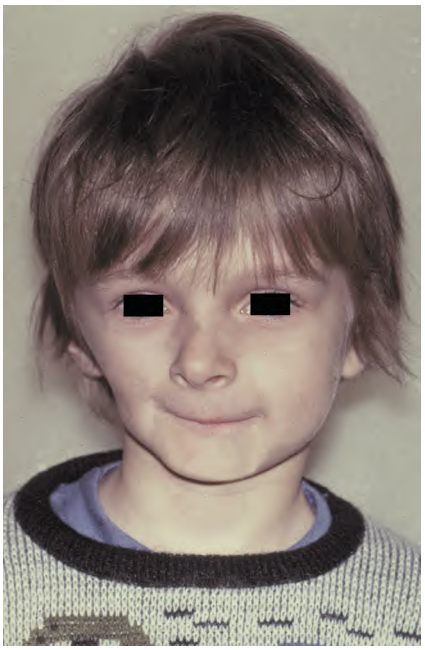
A complete workup should be undertaken to rule out other possible causes of unilateral growth, such as Beckwith-Wiedemann syndrome, Proteus syndrome, and neurofibromatosis type I (see page 495), which can exhibit hemihyperplasia. During childhood, periodic ultrasound examination should be performed to rule out development of abdominal tumors. After the patient's growth has ceased, cosmetic surgery can be performed, including soft tissue debulking, face lifts, and orthognathic surgery. Orthodontic therapy also frequently is needed.

◆ PROGRESSIVE HEMIFACIAL ATROPHY (PROGRESSIVE FACIAL HEMIATROPHY; ROMBERG SYNDROME; PARRY-ROMBERG SYNDROME)

Progressive hemifacial atrophy is an uncommon and poorly understood degenerative condition characterized by atrophic changes affecting one side of the face. The cause of these changes remains obscure. Speculation has considered trophic malfunction of the cervical sympathetic nervous system. A history of trauma has been documented in some cases, and other reports have considered *Borrelia spp.* infection (Lyme disease) in the cause. Usually, the condition is sporadic, but a few familial cases have been reported, suggesting a possible hereditary influence. Progressive hemifacial atrophy exhibits many features similar to a localized form of **scleroderma** (see page 744), indicating a close relationship between these two disorders.

Clinical and Radiographic Features

The onset of the syndrome is usually during the first two decades of life. The condition begins as atrophy of the skin and subcutaneous structures in a localized area of the face (Fig. 1-79). This atrophy progresses at a variable rate and affects the dermatome of one or more branches of the trigeminal nerve. Hypoplasia of the underlying bone also may occur. Osseous hypoplasia is more common when the condition begins during the first decade. Occasionally, bilateral facial atrophy may occur, or the condition may affect one side of the entire body. Females are affected more often than males.



• **Fig. 1-79 Progressive Hemifacial Atrophy.** Young girl with right-sided facial atrophy.

The overlying skin often exhibits dark pigmentation. Some patients have a sharp line of demarcation, resembling a large linear scar, between normal and abnormal skin near the midline of the forehead, known as *linear scleroderma "en coup de sabre"* (i.e., "strike of the sword"). Ocular involvement is common, and the most frequent manifestation is enophthalmos because of loss of periorbital fat. Local alopecia may occur. Occasionally, trigeminal neuralgia, facial paresthesia, migraine, or epilepsy may develop. MRI studies may reveal a variety of central nervous system abnormalities.

The mouth and nose are deviated toward the affected side. Atrophy of the upper lip may expose the maxillary teeth. Unilateral atrophy of the tongue also can occur. Unilateral posterior open bite often develops as a result of mandibular hypoplasia and delayed eruption of the teeth. The teeth on the affected side may exhibit deficient root development or root resorption.

Histopathologic Features

Microscopic examination of the affected skin reveals atrophy of the epidermis and a variable perivascular infiltrate of lymphocytes and monocytes. In cases showing clinical features of linear scleroderma, dermal fibrosis can be seen. Degenerative changes in the vascular endothelium can be identified with electron microscopy.

Treatment and Prognosis

The atrophy typically progresses slowly for 2 to 20 years and then becomes stable. Plastic surgery may be tried to correct

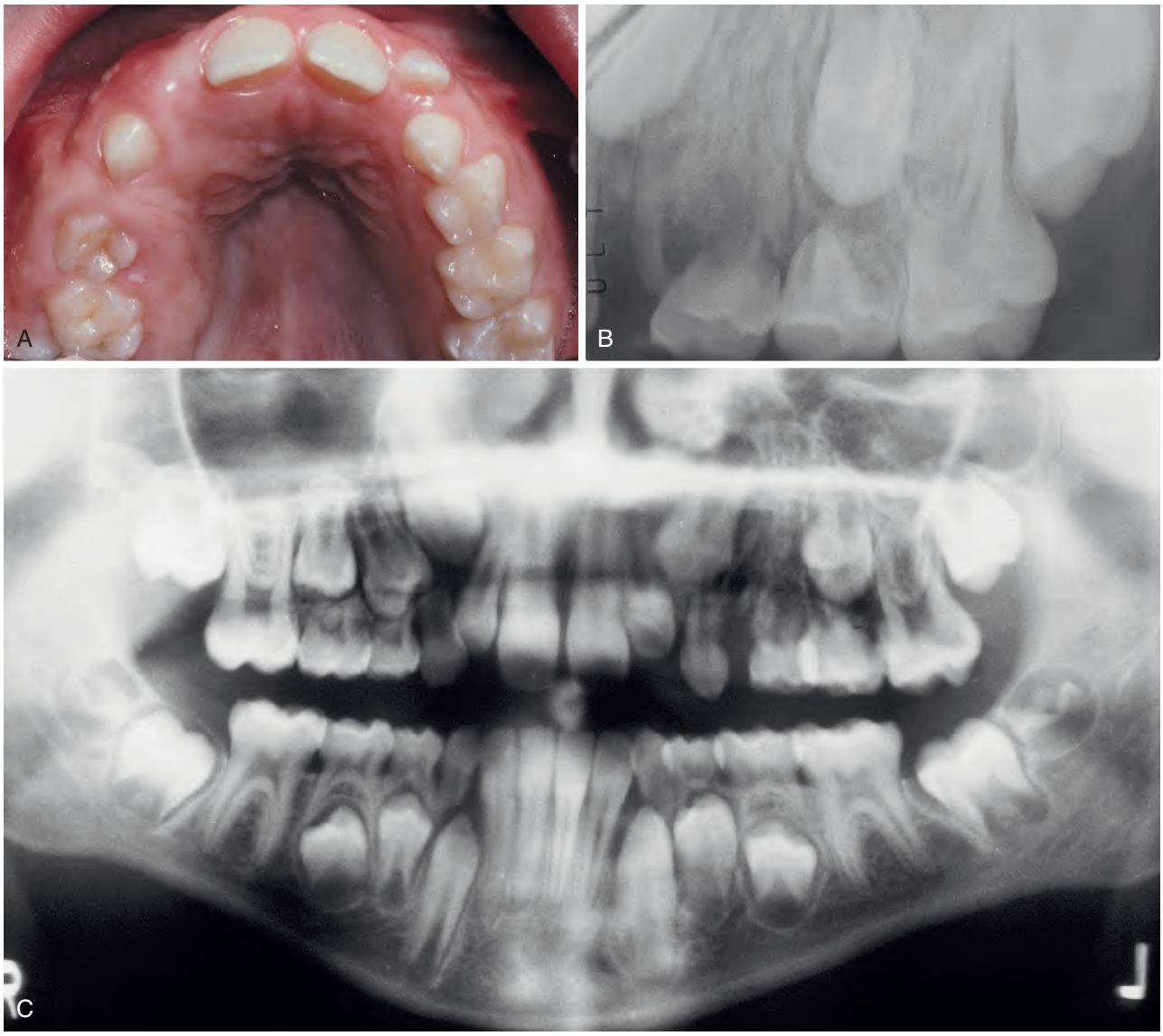
the cosmetic deformity, and orthodontic therapy may be helpful to treat any associated malocclusion.

◆ SEGMENTAL ODONTOMAXILLARY DYSPLASIA (HEMIMAXILLOFACIAL DYSPLASIA)

Segmental odontomaxillary dysplasia is a recently recognized developmental disorder that affects the jaw and (sometimes) the overlying facial tissues. The cause is unknown. Clinically, it is frequently mistaken for craniofacial fibrous dysplasia or hemifacial hyperplasia, but it represents a distinct and separate entity.

Clinical and Radiographic Features

Segmental odontomaxillary dysplasia usually is discovered during childhood and is characterized by painless, unilateral enlargement of the maxillary bone, along with fibrous hyperplasia of the overlying gingival soft tissues (Fig. 1-80). Mild facial asymmetry may be evident, often described as prominence of the upper lip. One or both developing maxillary premolars frequently are missing, and the primary teeth in the affected area may be hypoplastic or show enamel defects. Radiographic examination reveals thickened trabeculae that often are vertically oriented, which results in a relatively radiopaque, granular appearance. The maxillary sinus may be smaller on the affected side. Several cases have



• **Fig. 1-80 Segmental Odontomaxillary Dysplasia. A,** Unilateral enlargement of the maxilla and overlying gingival soft tissues. **B,** Periapical radiograph showing coarse trabecular pattern with absence of the first premolar. **C,** Panoramic radiograph showing irregular bone pattern of the left maxilla expanding into the maxillary sinus.

been associated with hypertrichosis or rough erythema of the overlying facial skin. One patient was described with a **Becker nevus** (hypertrichosis and hyperpigmentation) of the ipsilateral face and neck.

Histopathologic Features

The gingival soft tissues may show nonspecific fibrosis. The affected maxillary bone consists of irregular trabeculae with a woven appearance. This bone shows numerous resting and reversal lines, but it lacks significant osteoblastic and osteoclastic activity. Deciduous teeth in the involved area may exhibit irregular dentinal tubules, a focally deficient odontoblastic layer, and external resorption.

Treatment and Prognosis

Once diagnosed, segmental odontomaxillary dysplasia remains relatively stable and may not require surgical intervention. Although the lesion can show gradual enlargement, the increase in size is proportional to the overall growth of the patient. When necessary, surgical recontouring can be performed for cosmetic purposes, to improve access for oral hygiene, or to facilitate tooth eruption. Successful placement of dental implants has been reported.

◆ CROUZON SYNDROME (CRANIOFACIAL DYSOSTOSIS)

Crouzon syndrome is one of a rare group of syndromes characterized by craniosynostosis, or premature closing of the cranial sutures. It is believed to be caused by one of a variety of mutations of the fibroblast growth factor receptor 2 *(FGFR2)* gene on chromosome 10q26. The condition occurs in about 1 of every 65,000 births and is inherited as an autosomal dominant trait. A significant number of cases, however, represent new mutations, often apparently related to increased paternal age.

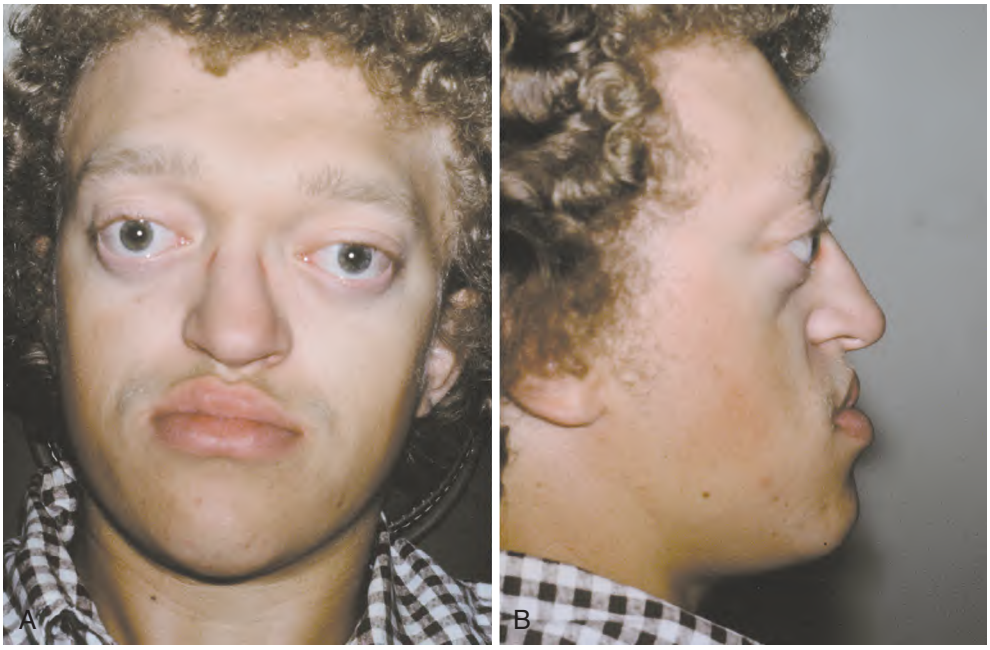
Clinical and Radiographic Features

Crouzon syndrome exhibits a wide variability in expression. The premature sutural closing leads to cranial malformations, such as **brachycephaly** (short head), **scaphocephaly** (boat-shaped head), or **trigonocephaly** (triangle-shaped head). The most severely affected patients can demonstrate a "cloverleaf" skull (*kleeblattschädel* deformity). The orbits are shallow, resulting in characteristic ocular proptosis (Fig. 1-81). Visual impairment or total blindness and a hearing deficit may occur. Some patients report headaches, attributable to increased intracranial pressure. Marked mental deficiency is rarely seen. Skull radiographs typically show increased digital markings (i.e., "beaten-metal" pattern).

The maxilla is underdeveloped, resulting in midface hypoplasia. Often the maxillary teeth are crowded, and occlusal disharmony usually occurs. Some patients will exhibit one or more congenitally missing teeth. Cleft lip and cleft palate are rare, but lateral palatal swellings may produce a midline maxillary pseudocleft.

Treatment and Prognosis

The clinical defects of Crouzon syndrome can be treated surgically, but multiple procedures may be necessary. Early craniectomy often is needed to alleviate the raised



• **Fig. 1-81 Crouzon Syndrome.** Ocular proptosis and midface hypoplasia. (Courtesy of Dr. Robert Gorlin.)

intracranial pressure. Fronto-orbital advancement can be performed to correct the ocular defects, with midfacial advancement used to correct the maxillary hypoplasia.

◆ APERT SYNDROME (ACROCEPHALOSYNDACTYLY)

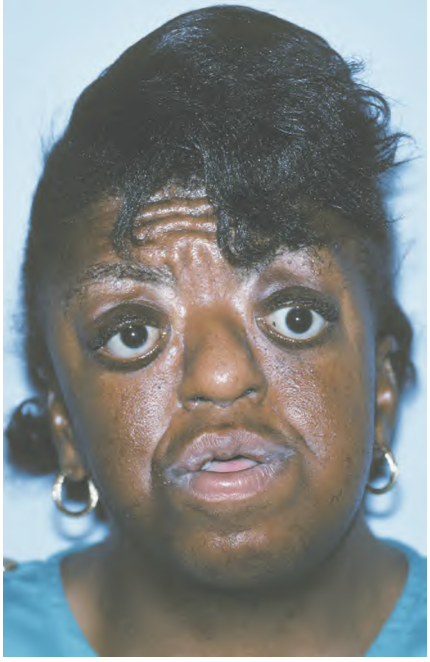
Like Crouzon syndrome, **Apert syndrome** is a rare condition that is characterized by craniosynostosis. It occurs in about 1 of every 65,000 births and usually is caused by one of two point mutations in the *FGFR2* gene, which is located on chromosome 10q26. Although it is inherited as an autosomal dominant trait, most cases represent sporadic new mutations, which are thought to be exclusively of paternal origin and often associated with increased paternal age.

Clinical and Radiographic Features

Craniosynostosis typically produces **acrobrachycephaly** (tower skull); severe cases may demonstrate the *kleeblattschädel* deformity (cloverleaf skull). The occiput is flattened, and a tall appearance to the forehead is noted. Ocular proptosis is a characteristic finding, along with hypertelorism and downward-slanting lateral palpebral fissures (Fig. 1-82). Visual loss can result from the following:

- Chronic exposure of the unprotected eyes
- Increased intracranial pressure
- Compression of the optic nerves

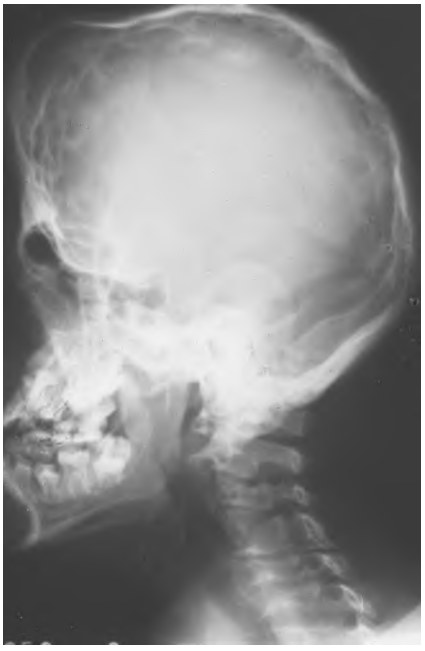
Skull films may demonstrate digital impressions similar to those of Crouzon syndrome (Fig. 1-83).



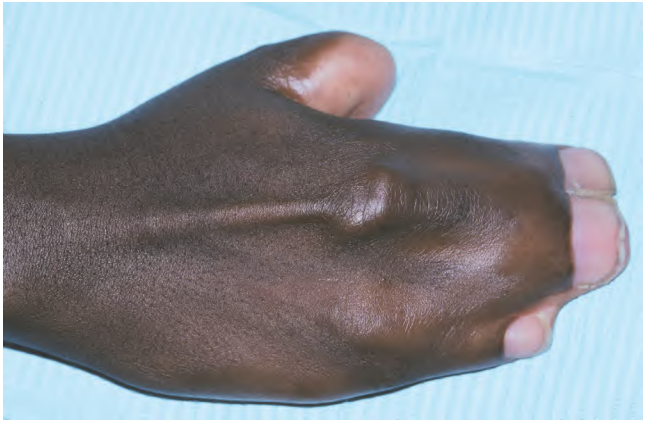
• **Fig. 1-82 Apert Syndrome.** Midface hypoplasia and ocular proptosis.

The middle third of the face is significantly retruded and hypoplastic, resulting in a relative mandibular prognathism. The reduced size of the nasopharynx and narrowing of the posterior choanae can lead to respiratory distress in the young child. To compensate for this, most infants become mouth breathers, contributing to an "open-mouth" appearance. Sleep apnea may develop. Middle-ear infections are common, as is conductive hearing loss.

Characteristic limb defects help distinguish Apert syndrome from other craniosynostosis syndromes. Syndactyly of the second, third, and fourth digits of the hands and feet always is observed (Fig. 1-84). Associated synonychia also may occur. The first and fifth digits may be separate or joined to the middle digits. Synostosis of adjacent phalanges may be observed on radiographs. The average height of affected patients is below that of the general population.



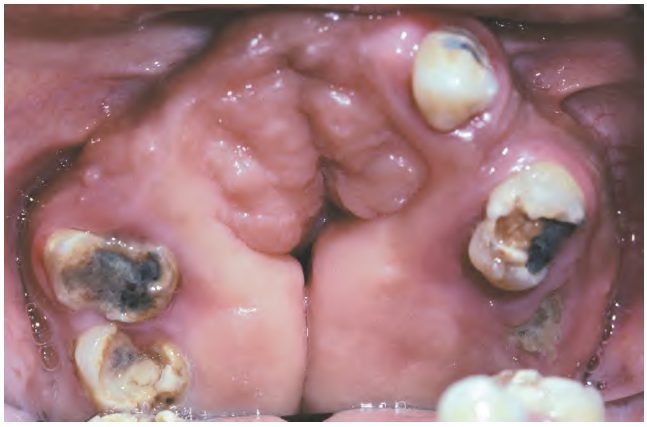
• **Fig. 1-83 Apert Syndrome.** Radiograph showing "tower skull," midface hypoplasia, and digital markings. Similar digital impressions are apparent in people with Crouzon syndrome. (Courtesy of Dr. Robert Gorlin.)



• **Fig. 1-84 Apert Syndrome.** Syndactyly of the hand.

Intellectual disability is reported in a large proportion of patients with Apert syndrome. An unusual acnelike eruption develops in most of the patients and involves the forearms.

Specific oral manifestations include a trapezoid-shaped appearance to the lips when they are relaxed, resulting from the midface hypoplasia and mouth breathing. Approximately 30% of patients exhibit either a cleft of the soft palate or a bifid uvula. The maxillary hypoplasia leads to a V-shaped arch and crowding of the teeth. Class III malocclusion typically occurs and may be associated with anterior open bite plus anterior and posterior crossbite. Swellings are observed along the lateral hard palate from the accumulation of glycosaminoglycans, especially hyaluronic acid (Fig. 1-85). These swellings often enlarge with age to produce a pseudocleft of the hard palate. Gingival thickening may be associated with delayed eruption of the teeth. One recent study showed that 35% of patients with Apert syndrome were missing one or two permanent teeth, especially maxillary lateral incisors or mandibular second premolars.



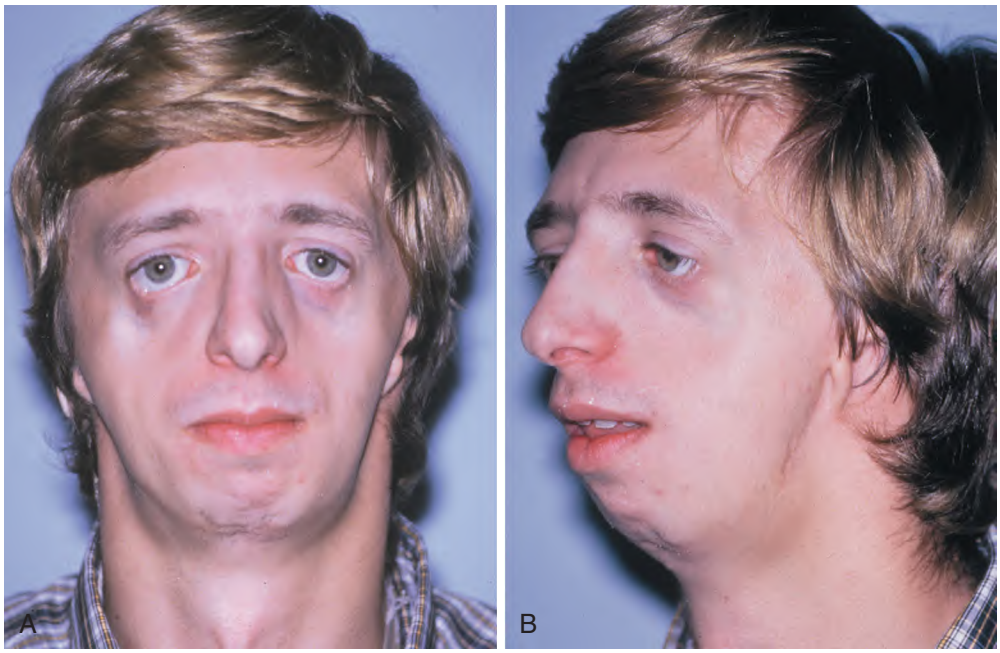
• **Fig. 1-85 Apert Syndrome.** Abnormal shape of the maxilla, with swellings of the posterior lateral hard palate, resulting in pseudocleft formation.

Treatment and Prognosis

The cosmetic and functional defects of Apert syndrome can be treated by an interdisciplinary approach using multiple surgical procedures. Although this condition historically has been associated with intellectual disability, early surgical intervention to allow for brain growth may contribute to greater intellectual and social development. Craniectomy often is performed during the first year of life to treat the craniosynostosis. Frontofacial advancement and midface advancement can be done later to correct the proptosis and midface hypoplasia. Coordinated orthodontic therapy often is necessary to bring unerupted teeth into place and to improve occlusion. Surgery also can be used to separate the fused fingers.

◆ MANDIBULOFACIAL DYSOSTOSIS (TREACHER COLLINS SYNDROME; FRANCESCHETTI-ZWAHLEN-KLEIN SYNDROME)

Mandibulofacial dysostosis is a rare syndrome that is characterized primarily by defects of structures derived from the first and second branchial arches. It is inherited as an autosomal dominant trait and occurs with a frequency of 1 in 50,000 live births. The condition has variable expressivity, and the severity of the clinical features often tends to be greater in subsequent generations of the same family.



• **Fig. 1-86 Mandibulofacial Dysostosis.** Patient exhibits a hypoplastic mandible, downward-slanting palpebral fissures, and ear deformities. (Courtesy of Dr. Tom Brock.)

Approximately 60% of cases represent new mutations, and these often are associated with increased paternal age. The gene for mandibulofacial dysostosis (treacle or *TCOF1*) has been mapped to chromosome 5q32-q33.1.

Clinical and Radiographic Features

Individuals with mandibulofacial dysostosis exhibit a characteristic facies (Fig. 1-86), although the features occasionally can be so mild that they are easily overlooked. The zygomas are hypoplastic, resulting in a narrow face with depressed cheeks and downward-slanting palpebral fissures. In 75% of patients, a **coloboma,** or notch, occurs on the outer portion of the lower eyelid. Approximately half of the patients have no eyelashes medial to the coloboma. Often the sideburns show a tongue-shaped extension toward the cheek.

The ears may demonstrate a number of anomalies. The pinnae frequently are deformed or misplaced, and extra ear tags may be seen. Ossicle defects or absence of the external auditory canal often result in conductive hearing loss.

The mandible is underdeveloped, resulting in a markedly retruded chin. Radiographs often demonstrate hypoplasia of the condylar and coronoid processes with prominent antegonial notching. The mouth is downturned, and about 15% of patients have lateral facial clefting (see page 2) that produces macrostomia. Cleft palate is seen in about one-third of cases. The parotid glands may be hypoplastic or may be totally absent (see page 42).

A number of infants may experience respiratory and feeding difficulties because of hypoplasia of the nasopharynx, oropharynx, and hypopharynx. Choanal atresia may be present, and the larynx and trachea are often narrow. Combined with the mandibular hypoplasia and resultant improper tongue position, these defects can lead to the infant's death from respiratory complications.

Treatment and Prognosis

Patients with mild forms of mandibulofacial dysostosis may not require treatment. In more severe cases the clinical appearance can be improved with cosmetic surgery. Because of the extent of facial reconstruction required, multiple surgical procedures usually are necessary. Individual operations may be needed for the eyes, zygomas, jaws, ears, and nose. Combined orthodontic therapy is needed along with the orthognathic surgery.

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2 Abnormalities of Teeth

ENVIRONMENTAL ALTERATIONS OF TEETH

The abnormalities of the teeth can be divided into those that are influenced by environmental forces and those that are idiopathic and appear hereditary in nature. Later parts of this chapter delineate the idiopathic and hereditary alterations of teeth. Box 2-1 lists the major categories of tooth alteration that can be affected by environmental influences. In many cases the cause and effect are obvious; in others the primary nature of the problem is less distinct.

◆ ENVIRONMENTAL EFFECTS ON TOOTH STRUCTURE DEVELOPMENT

The ameloblasts in the developing tooth germ are extremely sensitive to external stimuli, and many factors can result in abnormalities in the enamel (Box 2-2). When multiple factors are active simultaneously, the severity of the enamel defects is worse. The primary hereditary abnormalities of the enamel that are unrelated to other disorders are termed **amelogenesis imperfecta** (see page 92).

Dental enamel is unique in that remodeling does not occur after initial formation. Therefore, abnormalities in enamel formation are etched permanently on the tooth surface. The enamel develops in three major stages: 1) **matrix formation,** 2) **mineralization,** and 3) **maturation.** During matrix formation, the enamel proteins are laid down. In the next phase, minerals are deposited and the majority of the original proteins are removed. During the final maturation period, the enamel undergoes final mineralization and the remnants of the original proteins are removed. In the early stage of mineralization, the enamel is dull, white, and relatively soft. During the late stage of maturation, the final hard translucent enamel replaces this diffuse opaque enamel.

The timing of the ameloblastic damage has a great effect on the location and appearance of the defect in the enamel. The cause of the damage does not appear to be of major importance, because many different local and systemic stimuli can result in defects that have similar clinical appearances. The final enamel represents a record of all significant insults received during tooth development. Deciduous enamel contains a neonatal ring, and the rate of enamel apposition is estimated to be 0.023 mm/day. Using this knowledge, the clinician can accurately estimate the timing of an insult to the deciduous teeth to within 1 week. In the permanent dentition, the position of the enamel defects provides a rough estimate of the time of damage; however, available data on the chronology of tooth development are derived from a relatively small sample size, and the ranges of normal values are wide. In addition, gender and racial variations are not established thoroughly.

Clinical and Radiographic Features

Almost all visible environmental enamel defects can be classified into one of three patterns:

1. Hypoplasia
2. Diffuse opacities
3. Demarcated opacities

Subtle enamel defects can be masked by saliva, plaque, or poor illumination. When attempting to detect areas of altered enamel, the dentition should be cleaned thoroughly; then it should be dried with gauze. Dental operatory lights are an ideal light source (direct sunlight should be avoided). Plaque-disclosing solution can be used to highlight small defects. The altered enamel may be localized or present on numerous teeth, and all or part of the surfaces of each affected tooth may be involved. **Enamel hypoplasia** is a quantitative defect and occurs in the form of pits, grooves, or larger areas of missing enamel. **Enamel** opacities are a qualitative defect that may be diffuse or demarcated and appear as variations in the translucency of the enamel. The affected enamel is of normal thickness. When diffuse, the affected teeth demonstrate an increased white opacity with no clear boundary with the adjacent normal enamel. **Demarcated opacities** of enamel show areas of decreased translucence, increased opacity, and a sharp boundary with the adjacent enamel. The opacity may be white, cream, yellow, or brown. Yellow or brown opacities typically are more porous than white opacities and are more strongly associated with posteruptive loss of enamel.

The crowns of the deciduous dentition begin to develop at approximately the fourteenth week of gestation and continue until the child is 12 months of age. Development of the crowns of the permanent dentition occurs from approximately 6 months to 15 years of age. The site of coronal

• BOX 2-1 Environmental Alterations of Teeth

- Developmental tooth defects
- Postdevelopmental structure loss
- Discolorations of teeth
- Localized disturbances in eruption

• BOX 2-2 Factors Associated with Enamel Defects

Systemic

- Birth-related trauma: Breech presentations, hypoxia, multiple births, premature birth, prolonged labor
- Chemicals: Amoxicillin, antineoplastic chemotherapy, cigarette smoke, fluoride, lead, tetracycline, thalidomide, vitamin D
- Chromosomal abnormalities: Trisomy 21
- Infections: Chicken pox, cytomegalovirus (CMV), gastrointestinal infections, measles, pneumonia, otitis media, respiratory infections, rubella, syphilis, tetanus, urinary tract infections
- Inherited diseases: Amelo-cerebro-hypohidrotic syndrome, amelo-onycho-hypohidrotic syndrome, epidermolysis bullosa, galactosemia, mucopolysaccharidosis IV, Nance-Horan syndrome, oculo-dento-osseous dysplasia, phenylketonuria, pseudohypoparathyroidism, tricho-dento-osseous syndrome, tuberous sclerosis, vitamin D–dependent rickets
- Malnutrition: Generalized malnutrition, vitamin-D deficiency, vitamin-A deficiency
- Medical conditions: Asthma, cardiac disease, celiac disease, gastrointestinal malabsorption, gastrointestinal lymphangiectasia, hepatobiliary disease, hyperbilirubinemia, hypocalcemia, hypothyroidism, hypoparathyroidism, maternal diabetes, renal disease, toxemia of pregnancy
- Neurologic disorders: Cerebral palsy, intellectual disability, sensorineural hearing defects

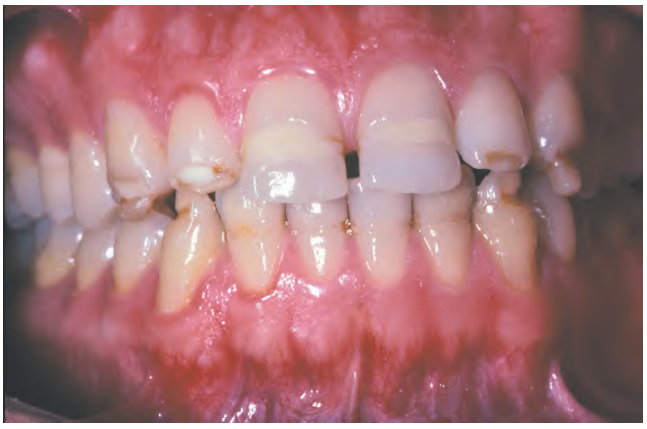
Local

- Local acute mechanical trauma: Falls, gunshots, neonatal mechanical ventilation, ritual mutilation, surgery, vehicular accidents
- Electrical burn
- Irradiation
- Local infection: Acute neonatal maxillitis, periapical inflammatory disease

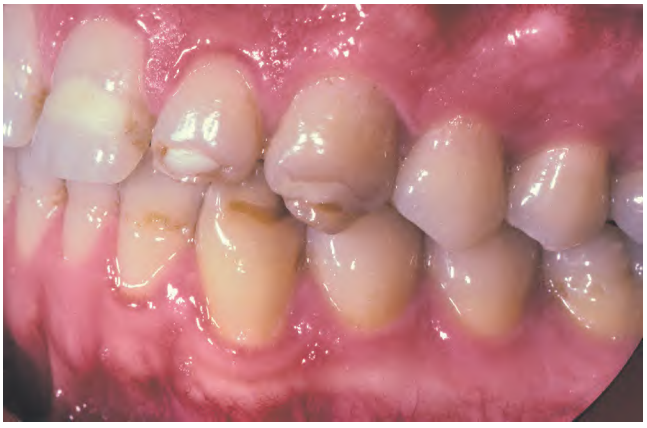
damage correlates with the area of ameloblastic activity at the time of the injury; the affected enamel is restricted to the areas in which secretory activity or active maturation of the enamel matrix was occurring.

Environmental enamel abnormalities are extremely common. In a review of more than 1500 children from 12 to 15 years of age in an industrialized nation, the prevalence of enamel defects in the permanent dentition was 68.4%. Within this group, 67.2% demonstrated opacities, 14.6% revealed hypoplasia, and both patterns were seen in 13.4% of the children. The average number of affected teeth per individual was 3.6, with greater than 10% of the children having 10 or more teeth involved.

A common pattern is seen as a result of systemic influences, such as exanthematous fevers, that occur during the first 2 years of life. Horizontal rows of pits or diminished enamel are present on the anterior teeth and first molars (Figs. 2-1 and 2-2). The enamel loss is bilaterally symmetric, and the location of the defects correlates well with the developmental stage of the affected teeth. A similar pattern of enamel defects can be seen in the cuspids, bicuspids, and second molars when the inciting event occurs around the age of 4 to 5 years (Fig. 2-3).



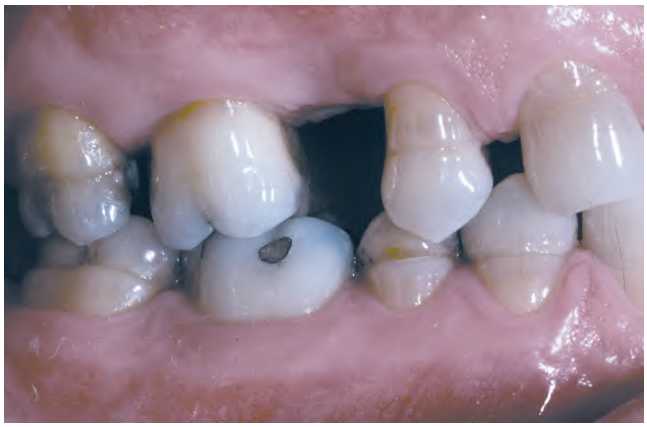
• Fig. 2-1 Environmental Enamel Hypoplasia. Bilaterally symmetrical pattern of horizontal enamel hypoplasia of the anterior dentition. Maxillary central incisors have been restored previously. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)



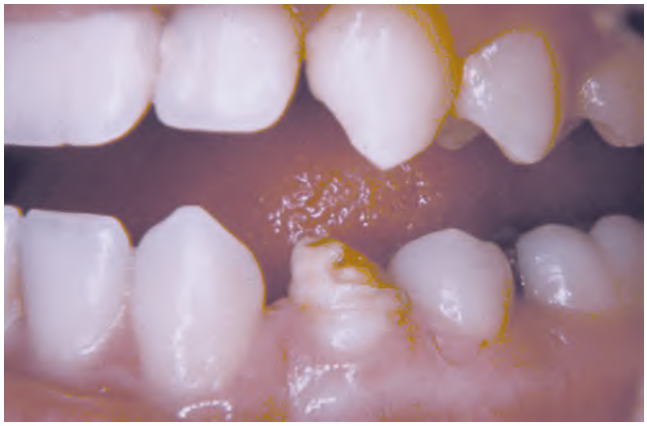
• Fig. 2-2 Environmental Enamel Hypoplasia. Same patient as depicted in Fig. 2-1. Note the lack of enamel damage on bicuspids. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)

Turner Hypoplasia

Another frequent pattern of enamel defects seen in permanent teeth is caused by periapical inflammatory disease of the overlying deciduous tooth. The altered tooth is called a **Turner tooth** (after the clinician whose publications allowed this problem to be widely recognized). The appearance of the affected area varies according to the timing and severity of the insult. The enamel defects vary from focal areas of white, yellow, or brown discoloration to extensive hypoplasia, which can involve the entire crown. The process is noted



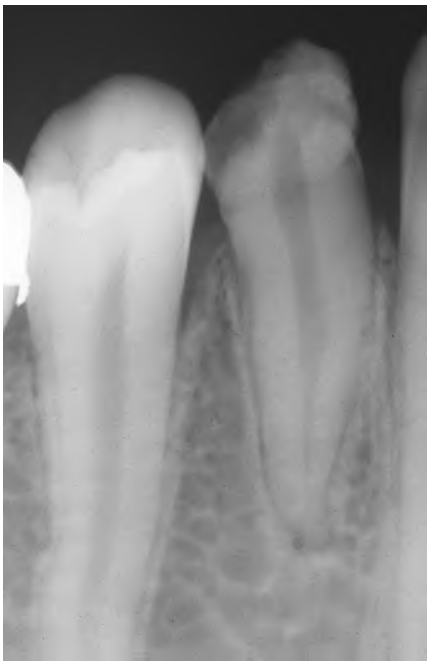
• **Fig. 2-3 Environmental Enamel Hypoplasia.** Horizontal enamel hypoplasia of the bicuspids and second molars. Note sparing of the first molars. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)



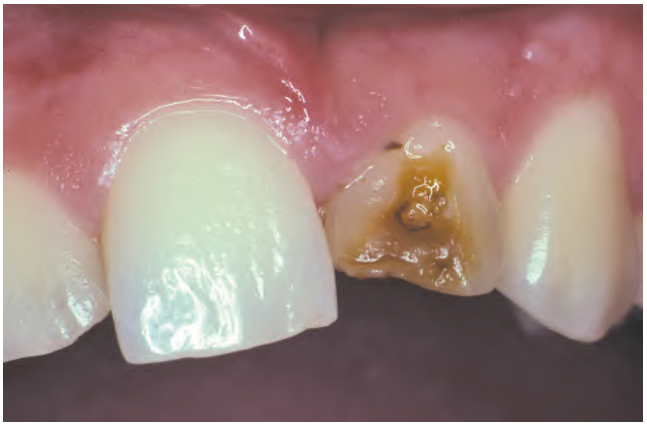
• **Fig. 2-4 Turner Hypoplasia.** Extensive enamel hypoplasia of mandibular first bicuspid secondary to previous inflammatory process associated with overlying first deciduous molar. (From Halstead CL, Blozis GG, Drinnan AJ, et al: *Physical evaluation of the dental patient,* St Louis, 1982, Mosby.)

most frequently in the permanent bicuspids because of their relationship to the overlying deciduous molars (Figs. 2-4 and 2-5). Anterior teeth are involved less frequently because crown formation is usually complete before the development of any apical inflammatory disease in the relatively caries-resistant anterior deciduous dentition. Factors that determine the degree of damage to the permanent tooth by the overlying infection include the stage of tooth development, length of time the infection remains untreated, the virulence of the infective organisms, and the host resistance to the infection.

In addition to classic Turner teeth, an increased prevalence of demarcated opacities has been reported in the permanent successors of carious primary teeth. In one report, if the primary tooth developed caries, the successor was twice as likely to demonstrate a circumscribed enamel defect. In addition, if the primary tooth was extracted for any reason other than trauma, then the prevalence of a demarcated enamel defect increased fivefold.



• **Fig. 2-5 Turner Hypoplasia.** Radiograph of the same tooth depicted in Fig. 2-4. Note the lack of significant enamel and irregularity of the dentin surface. (From Halstead CL, Blozis GG, Drinnan AJ, et al: *Physical evaluation of the dental patient,* St Louis, 1982, Mosby.)



• **Fig. 2-6 Turner Hypoplasia.** Extensive coronal hypoplasia of permanent maxillary left central incisor secondary to previous trauma to deciduous central incisor.

Traumatic injury to deciduous teeth also can cause significant alterations of the underlying dentition and the formation of Turner teeth. This is not a rare occurrence; up to 45% of all children sustain injuries to their primary teeth. In a prospective study of 114 children with 255 traumatized primary teeth, 23% of the corresponding permanent teeth demonstrated developmental disturbances. The maxillary central incisors are affected in the majority of the cases; the maxillary lateral incisors are altered less frequently (Fig. 2-6). In several large reviews, the prevalence of involvement of the posterior teeth or mandibular incisors was less than 10% of all cases.

The frequency of traumatic damage of the anterior maxillary dentition is not surprising, considering the common

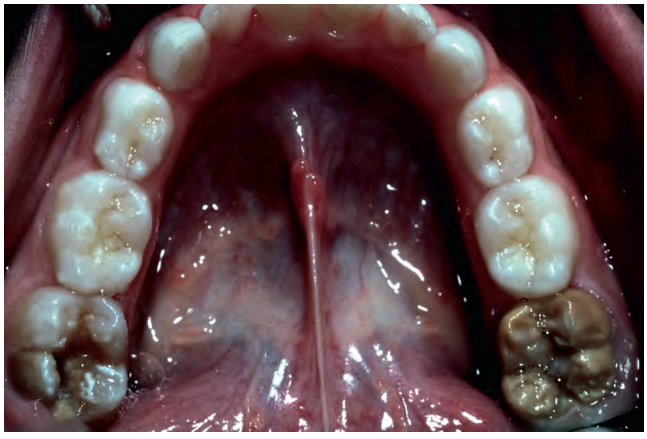
occurrence of trauma to the deciduous dentition of the prominent anterior maxilla and the close anatomic relationship between the developing tooth bud and the apices of the overlying primary incisors. As would be expected, the clinical appearance of the alteration varies according to the timing and severity of the damage.

Because of the position of the primary apices relative to the tooth bud, the facial surface of the maxillary incisors is the location most frequently affected. Typically, the affected area appears as a zone of white or yellowish-brown discoloration with or without an area of horizontal enamel hypoplasia. The trauma also can cause displacement of the already formed hard-tooth substance in relation to the soft tissue of the remaining developing tooth. This results in a bend of the tooth known as **dilaceration** and can affect either the crown or the root of a tooth (see page 89). Severe trauma early in the development of the tooth can result in such disorganization of the bud that the resultant product may resemble a complex odontoma (see page 674). Similar levels of damage late in the formative process can lead to partial or total arrest in root formation.

Molar-Incisor Hypomineralization

In the 1970s, studies from Scandinavia described a pattern of hypomineralization that predominantly affected the permanent first molars, and eventually this was designated as **molar-incisor hypomineralization (MIH)** in 2001. The process is defined as a hypomineralization of one to four permanent first molars, although the incisors also are affected frequently. Since this original description, prevalence studies have identified MIH not only in Europe but also in New Zealand, Australia, Brazil, Libya, Kenya, and Hong Kong. The reported prevalence varies widely from a low of 2.4% in Germany to a high of 40.2% in Brazil. Similar prevalence studies from North America are lacking.

Patients affected with MIH have enamel defects of one or more first permanent molars. The altered enamel may be white, yellow, or brown, with a sharp demarcation between the defective and surrounding normal enamel (Fig. 2-7).



• **Fig. 2-7 Molar-Incisor Hypomineralization (MIH).** First permanent mandibular molars demonstrating brown hypomaturation with areas of coronal breakdown.

Yellow or brown opacities appear to be more porous and often are associated with posteruptive enamel loss. With loss of enamel, the teeth become more sensitive leading to avoidance of proper oral hygiene with rapid caries development. During attempts at dental therapy, these teeth often are highly sensitive and very difficult to anesthetize. There appears to be spectrum of the disease in which only the molars may be affected or the incisors also may be involved. The extent of incisor involvement appears to correlate with the number of affected molars. Affected incisors demonstrate only white opacities that primarily create aesthetic problems.

The etiology of MIH remains unclear. It may be multifactorial, and suggested influences include the nutritional status, birth and neonatal factors, previous childhood illnesses, high fever, antibiotics such as tetracycline or amoxicillin, environmental toxins, long duration of breast feeding (thought to transmit pollutants such as dioxin), and fluoride.

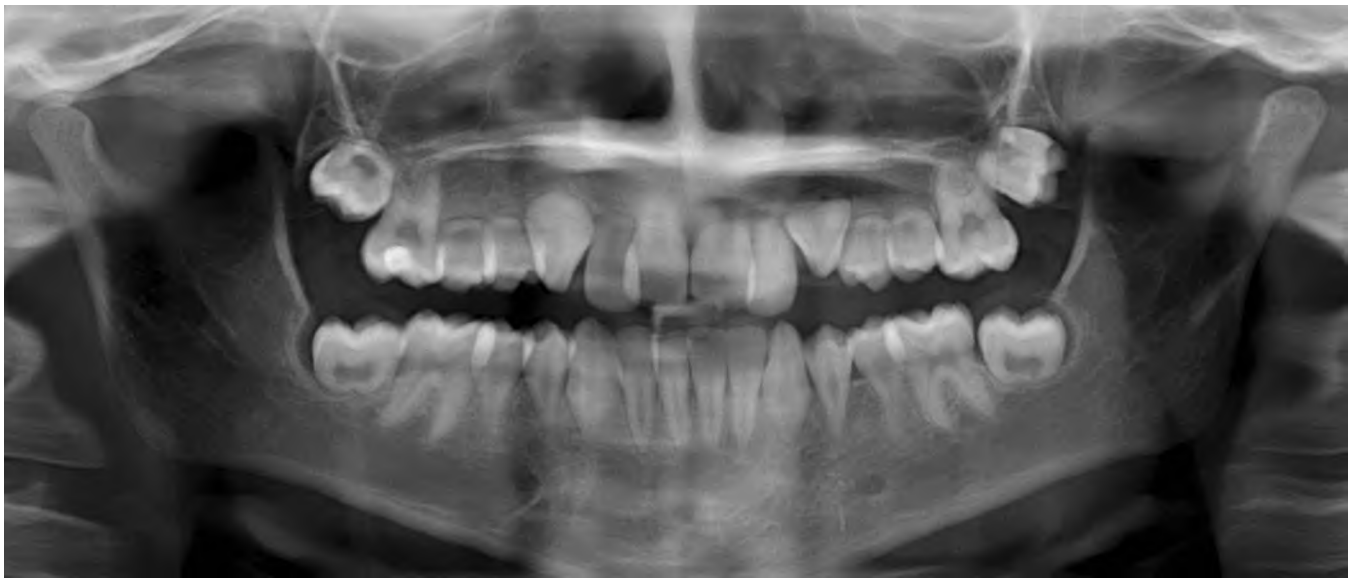
Hypoplasia Caused by Antineoplastic Therapy

As modern medicine increases the prevalence of successful therapy against childhood cancer, it has become evident that a number of developmental alterations arise secondary to use of therapeutic radiation or chemotherapy. As would be expected, developing teeth are affected most severely, with these therapies producing clinically obvious alterations most commonly in patients younger than 12 years and most extensively in those younger than 5 years. The degree and severity of the developmental alterations are related to the patient's age at treatment, the form of therapy, and the dose and field of radiation, if used.

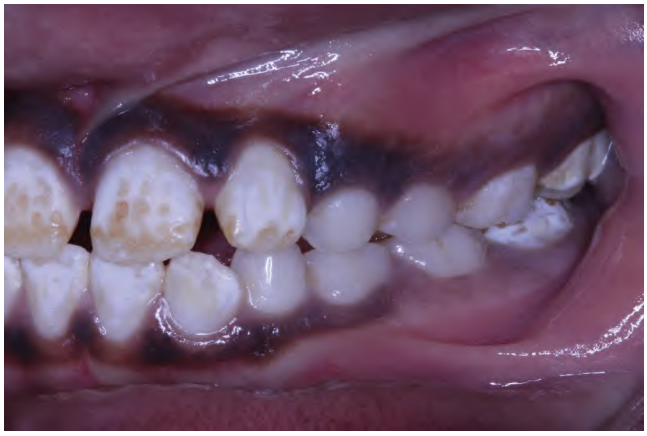
Although both chemotherapeutic agents and radiation therapy can be responsible for developmental abnormalities, the most severe alterations are associated with radiation. Doses as low as 0.72 Gy are associated with mild developmental defects in both enamel and dentin. As the dose escalates, so does the effect on the developing dentition and jaws. Frequently noted alterations include hypodontia, microdontia, radicular hypoplasia, and enamel hypoplasia (Fig. 2-8). In addition, mandibular hypoplasia and a reduction of the vertical development of the lower third of the face are not rare. The mandibular hypoplasia may be the direct effect of the radiation, reduced alveolar bone growth secondary to impaired root development, or (possibly) growth failure related to altered pituitary function caused by cranial radiation. Chemotherapy alone results in much less dramatic alterations but can produce an increased number of enamel hypoplasias and discolorations, slightly smaller tooth size, and occasional radicular hypoplasia that is less severe than that secondary to radiation.

Dental Fluorosis

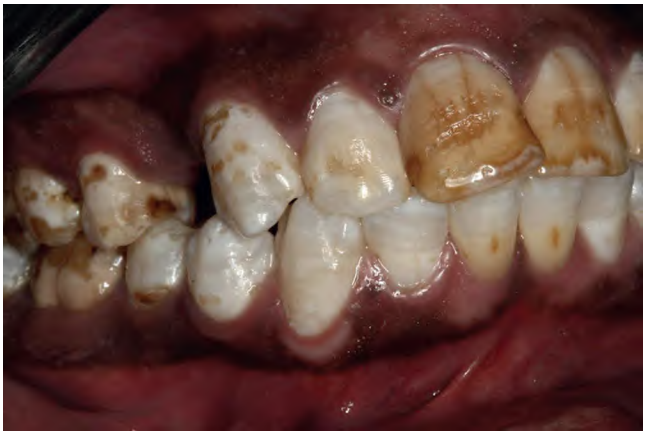
The ingestion of excess amounts of fluoride also can result in significant enamel defects known as **dental fluorosis.** Fluoride appears to create enamel defects through retention of the amelogenin proteins in the enamel structure. This



• **Fig. 2-8 Hypoplasia Caused by Antineoplastic Therapy.** Multiple teeth demonstrating radicular hypoplasia secondary to radiation and chemotherapy for cancer. (Courtesy of Dr. Bret Johnson.)



• **Fig. 2-9 Dental Fluorosis.** Dentition exhibiting lusterless, white, and opaque enamel with areas of chipping. Notice that the deciduous teeth are spared.



• **Fig. 2-10 Dental Fluorosis.** Diffuse white opaque alteration of the dentition with areas of brown enamel mottling. Patient spent his childhood in Kenya.

leads to the formation of hypomineralized enamel that alters light reflection and creates the appearance of white, chalky areas. Most of the problems associated with dental fluorosis are aesthetic, particularly when the anterior teeth are affected.

The severity of dental fluorosis is dose dependent, with greater ingestion of fluoride during critical periods of tooth development causing more severe fluorosis. Interestingly, individuals who consume similar levels of fluoride may demonstrate varying degrees of dental fluorosis, suggesting a genetic influence. The affected teeth are caries resistant, and the altered tooth structure appears as areas of lusterless white opaque enamel that may have zones of yellow to dark-brown discoloration (Figs. 2-9 and 2-10). In the past, areas of moderate-to-severe enamel fluorosis were termed **mottled enamel.** True enamel hypoplasia is uncommon but can occur as deep, irregular, and brownish pits. Because other factors can result in a similar pattern of enamel damage, a definitive diagnosis requires that the defects be present in a bilaterally symmetric distribution, plus evidence of prior excessive fluoride intake or elevated levels of fluoride in the enamel or other tissues should be found.

Initially, fluoride's ability to reduce caries was thought to be secondary to its incorporation into developing enamel, resulting in a stronger and more acid-resistant fluorapatite crystal. Most investigators now agree that the posteruptive effects of fluoride are predominant and control caries by altering the demineralization and remineralization process that occurs at the tooth/bacterial biofilm interface. Nevertheless, fluoridated water remains an important topical source of application. Even though fluoride is present in numerous dental products, foods, and beverages, studies have shown that cessation of water fluoridation has been associated with an approximately 18% increase in dental caries. Consumption of optimally fluoridated water has been associated with a low frequency of altered enamel,

which usually is mild in degree. However, an increased prevalence of dental fluorosis has been noted in recent years. The US Centers for Disease Control and Prevention reported that from 1986 to 1987, 22.6% of adolescents demonstrated some degree of fluorosis, whereas a similar group from 1999 to 2004 revealed a prevalence of 40.7%. Water fluoridation typically aims for a concentration between 0.7 to 1.2 ppm. In warm climates, the recommended concentration is 0.7 ppm due to higher consumption of water, whereas regions with more temperate climates use a concentration of 1 ppm. In 2011, the US Department of Health and Human Services recommended a nationwide standardized level of 0.7 ppm of fluoride.

The crowns of the maxillary central incisors are the most cosmetically important and demonstrate completion of their development by age 3. Therefore, close monitoring of all sources of fluoride intake during the first 3 years of life is recommended strongly. A significant reduction in dental fluorosis can be seen if brushing with fluoride toothpaste does not start until after 12 months of age. In addition, reconstitution of infant formula with fluoridated water should be avoided. Because of the dissemination of fluoride through the food supply, the need for supplements in non-fluoridated areas is declining. Fluoride supplements are recommended only in non-fluoridated areas for children who are at high risk for rampant caries.

Syphilitic Hypoplasia

Congenital syphilis (see page 172) results in a pattern of enamel hypoplasia that is well known but currently so rare that lengthy discussion is not warranted. Anterior teeth altered by syphilis are termed **Hutchinson incisors** and exhibit crowns that are shaped like straight-edge screwdrivers, with the greatest circumference present in the middle one-third of the crown and a constricted incisal edge. The middle portion of the incisal edge often demonstrates a central hypoplastic notch. Altered posterior teeth are termed **mulberry molars** and demonstrate constricted occlusal tables with a disorganized surface anatomy that resembles the bumpy surface of a mulberry.

Treatment and Prognosis

Most defects in the enamel are cosmetic rather than functional dental problems. Those affected by dental fluorosis often benefit from surface microabrasion, which produces a dramatic and permanent improvement in the surface brown or yellow discoloration. Improvement in the white surface markings usually requires further restorative dentistry. Other types of environmental enamel hypoplasia have been associated with an increased prevalence of caries, with one study reporting more than twice the level in patients with such enamel defects. The decreased caries resistance is thought to be secondary to focal loss of enamel or because of imperfect enamel. The areas most frequently associated with an increased prevalence of caries demonstrate full-thickness enamel defects. Aesthetically or functionally defective teeth can be restored through a variety of cosmetically pleasing techniques, such as the following:

- Acid-etched composite resin restorations
- Labial veneers
- Full crowns

◆ POSTDEVELOPMENTAL LOSS OF TOOTH STRUCTURE

Tooth structure can be lost after its formation by a variety of influences beyond the obvious cases related to caries or traumatic fractures. Destruction can begin on the enamel surface of the crown through abrasion, attrition, erosion, or abfraction. In addition, loss of tooth structure can begin on the dentin or cemental surfaces of the teeth by external or internal resorption.

TOOTH WEAR

Tooth wear, also termed *tooth surface loss,* is a normal physiologic process that occurs with aging but must be considered pathologic when the degree of destruction creates functional, aesthetic, or dental sensitivity problems. Although the four causes of tooth wear (i.e., **attrition, abrasion, erosion,** and **abfraction**), often are discussed as independent pathoses, most of these types of tooth loss are the result of a combination of influences. Many cases of attrition are accelerated by the presence of abrasive materials in the mouth. Erosion or abrasion often further damages areas of dentin exposed by attrition or abfraction. Areas softened by erosion are more susceptible to attrition, abrasion, and abfraction. The clinician should appreciate that acquired environmental loss of tooth structure often is multifactorial.

Most researchers agree that the reported prevalence of tooth wear is increasing. This is explained partly by a greater awareness among clinicians and by the adult population retaining more natural teeth as they age. In addition, younger individuals appear to exhibit an increased tooth surface loss that many believe may be caused by a more acidic diet (e.g., acidic soft drinks, diet foods, and fresh fruits). This belief is supported by the knowledge that consumption of acidic soft drinks in the United States has increased 300% over the past 20 years.

Attrition is the loss of tooth structure caused by tooth-to-tooth contact during occlusion and mastication. The term comes from the Latin verb *attritum,* which refers to the action of rubbing against another surface. Some degree of attrition is physiologic, and the process becomes more noticeable with age. When the amount of tooth loss is extensive and begins to affect aesthetic appearance and function, the process must be considered pathologic.

The following factors can accelerate tooth destruction:

- Poor-quality or absent enamel (e.g., fluorosis, environmental or hereditary enamel hypoplasia, or dentinogenesis imperfecta)

- Premature contacts (edge-to-edge occlusion)
- Intraoral abrasives, erosion, and grinding habits

Abrasion is the pathologic wearing away of tooth structure or restoration secondary to the mechanical action of an external agent. The term arises from the Latin verb *abrasum,* which literally means *to scrape off* and implies wear or partial removal through a mechanical process. The most common cause of abrasion is toothbrushing that combines abrasive toothpaste with heavy pressure and a horizontal brushing stroke. Other items frequently associated with dental abrasion include pencils, toothpicks, pipe stems, and bobby pins. Chewing tobacco, cracking nuts and seeds, biting fingernails or thread, and using dental floss inappropriately also can cause clinically significant abrasion. When tooth wear is accelerated by chewing an abrasive substance between opposing teeth, the process has been termed **demastication** and exhibits features of both attrition and abrasion.

Erosion is the loss of tooth structure caused by a nonbacterial chemical process. The term is derived from the Latin verb *erosum,* which literally means *to corrode* and implies gradual destruction of a surface by a chemical or electrolytic process. Some investigators have suggested that the term *dental corrosion* would be a more appropriate designation for this process, but both terms are acceptable, with little need for a disruption in the long-held nomenclature of tooth wear. Typically, the exposure to an acid is to blame, but chelating agents are occasionally the primary cause. Although saliva aids remineralization and contains bicarbonate with a significant buffering ability, the bicarbonate level of saliva is directly correlated to salivary flow, with the buffering capability reduced in situations with low flow rates. Causes for salivary gland hypofunction include salivary gland aplasia, dehydration, therapeutic radiation, medications, and systemic conditions such as Sjögren syndrome, bulimia nervosa, and diabetes. The acidic source often is foods or drinks, but other causes include some medications (e.g., chewable vitamin C and aspirin tablets), swimming pools with poorly monitored pH, chronic involuntary regurgitation (e.g., hiatal hernia, esophagitis, chronic alcoholism, and pregnancy), voluntary regurgitation (e.g., psychologic problems, bulimia, and occupations that require low body weight), and industrial environmental exposure. Erosion from dental exposure to gastric secretions is termed **perimolysis.** Because saliva has the ability to remineralize tooth surfaces exposed to acid, it appears that areas of erosive damage must have some abrasive component that removes the softened enamel before remineralization.

Agreement on the prevalence of dental erosion does not exist. Some investigators believe erosion rarely is responsible solely for loss of tooth structure. Others support the idea that there is an epidemic of erosion associated with increased numbers of young women with eating disorders, teenage males who ingest large quantities of sports drinks and soft drinks, middle-aged males with gastroesophageal reflux, and elderly individuals with age- and medication-related xerostomia.

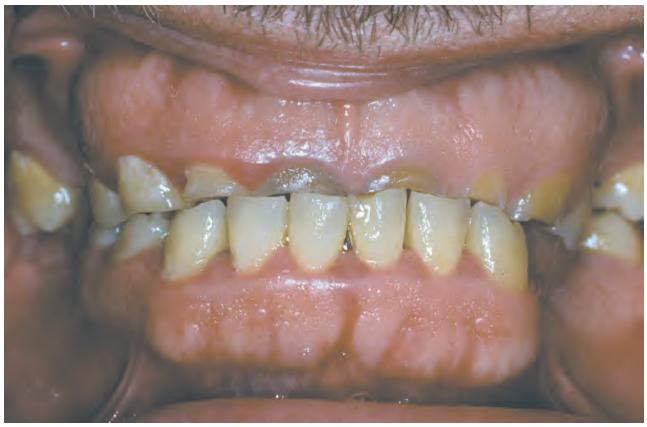
Abfraction refers to the loss of tooth structure from occlusal stresses that create repeated tooth flexure with failure of enamel and dentin at a location away from the point of loading. The term is derived from the Latin words *ab* and *fractio,* which respectively translate into *away* and *breaking.* Dentin is able to withstand greater tensile stress than enamel. When occlusal forces are applied eccentrically to a tooth, the tensile stress is concentrated at the cervical fulcrum, leading to flexure that may produce disruption in the chemical bonds of the enamel crystals in the cervical areas. Once damaged, the cracked enamel can be lost or more easily removed by erosion or abrasion.

Like erosion, agreement on the prevalence of abfraction does not exist. Some propose that abfraction causes most cervical tooth loss; others believe that little evidence exists to indicate that this sequence of events actually occurs in the mouth. Some investigators have suggested that the engineering models used to justify abfraction have not taken into consideration the cushioning provided by the surrounding bone and periodontium, which may dissipate occlusal forces acting on a tooth. The pattern of cervical tooth loss tends to occur at sites with diminished serous salivary flow and could be explained by the initial loss of salivary protection rather than excess occlusal forces. Involvement by abfraction of the facial cervical areas of the anterior maxillary dentition is very puzzling, because the flexure during function would occur on the palatal surface of the tooth, not the facial surface. During function, investigators have found little evidence that strains in lingual enamel and dentin are any different from those that occur in facial sites; however, areas of focal cervical tooth loss occur almost exclusively on the facial surfaces. Others contend that the bone on the facial surface of the alveolar ridge is thinner and more flexible allowing lingual to facial forces to dissipate tensile loads on the lingual surfaces. Review of skulls from ancient Australian aborigines has revealed advanced tooth wear both occlusally and interproximally; and despite evidence of heavy occlusal forces that one would expect to be associated with abfraction, no lesions were found. Finally, studies of patients demonstrating high levels of bruxism failed to demonstrate an association between heavy occlusal loads and cervical tooth wear. Due to the uncertain causes for this pattern of enamel loss, investigators have warned against destructive, irreversible treatment such as extensive occlusal adjustments.

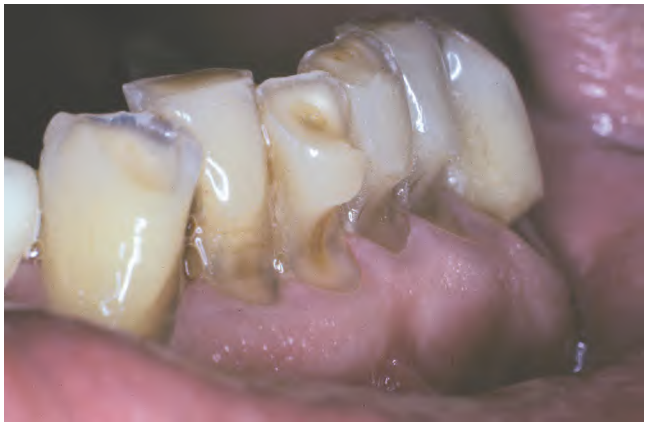
Clinical Features

Attrition

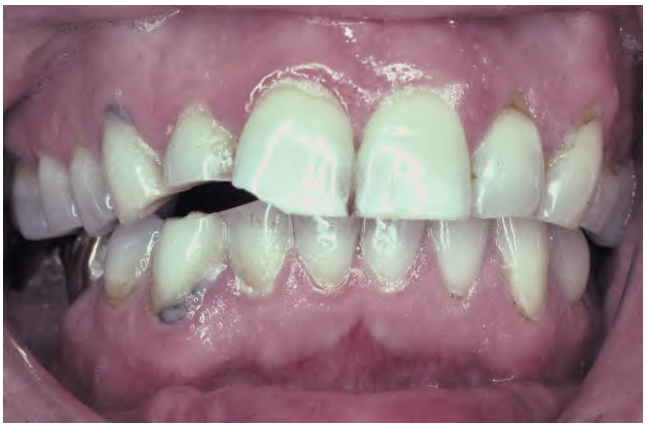
Attrition can occur in both the deciduous and the permanent dentitions. As would be expected, the surfaces predominantly affected are those that contact the opposing dentition. Most frequently, the incisal and occlusal surfaces are involved, in addition to the lingual of the anterior maxillary teeth and the labial of the anterior mandibular teeth. Large, flat, smooth, and shiny wear facets are found in a relationship that corresponds to the pattern of occlusion. The interproximal contact points also are affected from the



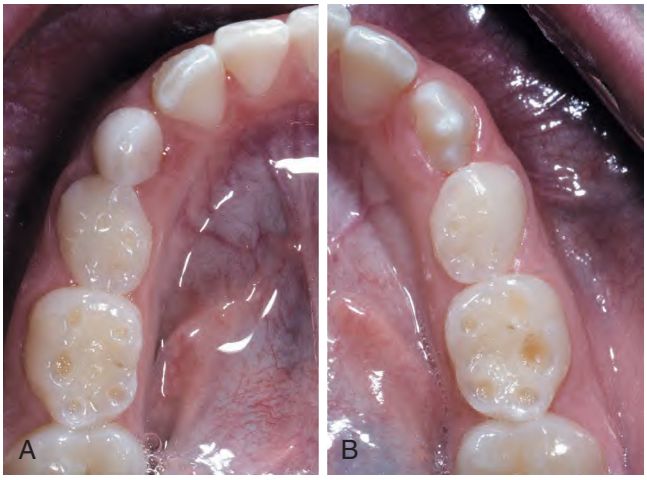
• **Fig. 2-11 Attrition.** Extensive loss of coronal tooth height without pulp exposure in patient with anterior edge-to-edge occlusion.



• **Fig. 2-12 Abrasion.** Horizontal cervical notches on the anterior mandibular dentition. Note visible pulp canals that have been filled with tertiary dentin.



• **Fig. 2-13 Abrasion.** Notching of the anterior dentition on the right side caused by long-term use of tobacco pipe.



• **Fig. 2-14 Erosion.** Multiple cupped-out depressions corresponding to the cusp tips.

vertical movement of the teeth during function. Over time, this interproximal loss can result in a shortening of the arch length. Pulp exposure and dentin sensitivity are rare because of the slow loss of tooth structure and the apposition of reparative secondary dentin within the pulp chamber (Fig. 2-11).

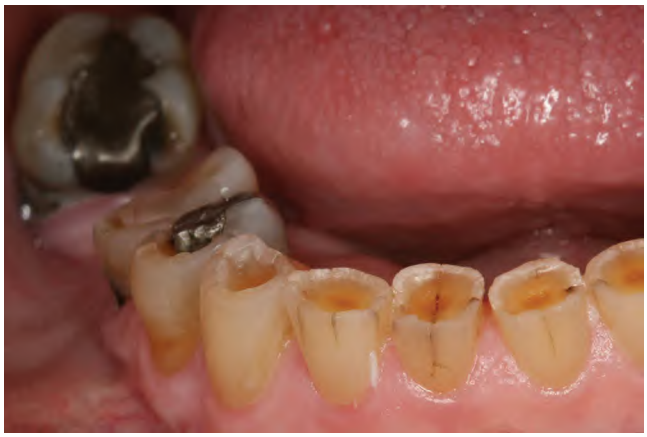
Abrasion

Abrasion has a variety of patterns, depending on the cause. Toothbrush abrasion typically appears as horizontal cervical notches on the buccal surface of exposed radicular cementum and dentin (Fig. 2-12). The defects usually have sharply defined margins and a hard, smooth surface. If acid also is present, then the lesions are more rounded and shallower. The degree of loss is greatest on prominent teeth (i.e., cuspids, bicuspids, and teeth adjacent to edentulous areas) and occasionally is more advanced on the side of the arch opposite the dominant hand. Thread biting or the use of pipes or bobby pins usually produces rounded or V-shaped notches in the incisal edges of anterior teeth (Fig. 2-13). The inappropriate use of dental floss or toothpicks results in the loss of interproximal radicular cementum and dentin.

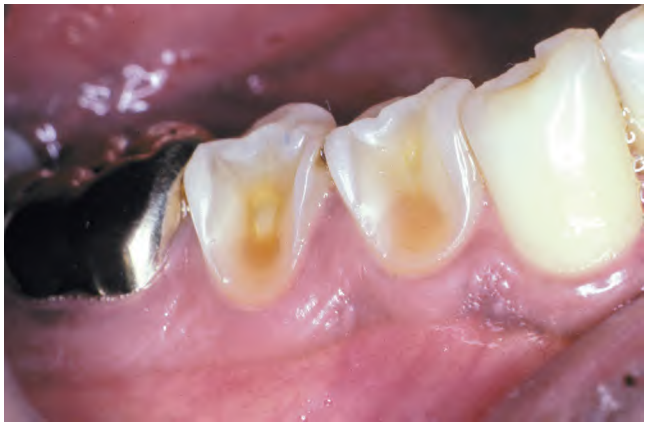
Erosion

In patients with **erosion,** the tooth loss does not correlate with functional wear patterns or with those typically associated with known abrasives. The predominant sites of tooth loss appear to correlate closely with those areas not protected by the serous secretions of the parotid and submandibular glands. The facial and palatal surfaces of the maxillary anterior teeth and the facial and occlusal surfaces of the mandibular posterior teeth are affected most frequently. Involvement of the lingual surfaces of the entire mandibular dentition is uncommon, possibly because of the protective buffering capacity of the submandibular serous saliva.

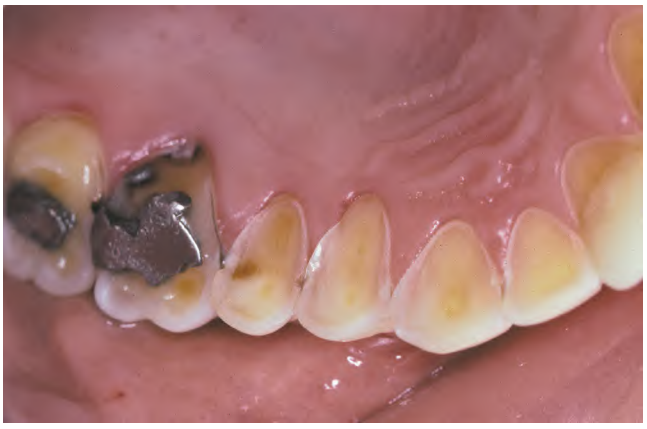
The classic pattern of dental erosion is the cupped lesion in which a central depression of dentin is surrounded by elevated enamel. Cupped areas are seen on the occlusal cusp tips, incisal edges, and marginal ridges (Fig. 2-14). In contrast to abrasion, erosion commonly affects the facial surfaces of the maxillary anteriors and appears as shallow spoon-shaped depressions in the cervical portion of the crown. The posterior teeth frequently exhibit extensive loss of the occlusal surface, and the edges of metallic restorations subsequently may be above the level of the tooth structure



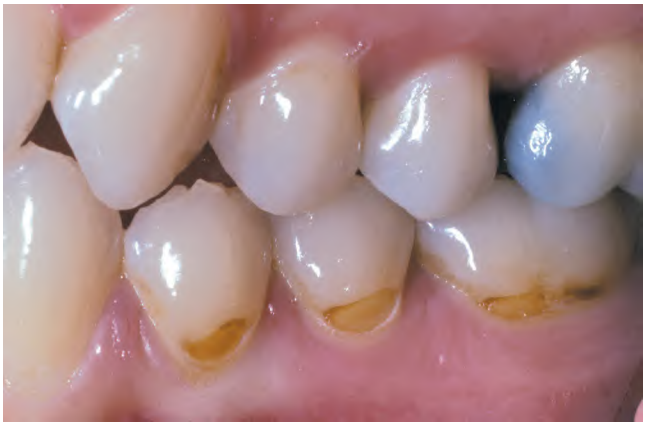
• **Fig. 2-15 Erosion.** Multiple mandibular anterior teeth exhibiting depressions of dentin surrounded by elevated rims of enamel. Note the amalgam in the first bicuspid that is raised above the surface of the surrounding depressed dentin.



• **Fig. 2-16 Erosion.** Extensive loss of enamel and dentin on the buccal surface of the maxillary bicuspids. The patient had sucked chronically on tamarinds (an acidic fruit).



• **Fig. 2-17 Erosion.** Palatal surfaces of the maxillary dentition in which the exposed dentin exhibits a concave surface and a peripheral white line of enamel. The patient had bulimia.



• **Fig. 2-18 Abfraction.** Deep and narrow enamel cervical defects on the facial surface of the mandibular dentition. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)

(Fig. 2-15). After a portion of the cuspal enamel has been lost, the dentin is destroyed more rapidly than the remaining enamel, often resulting in a concave depression of the dentin surrounded by an elevated rim of enamel (see Fig. 2-15). The more rapid dissolution of the dentin can lead to undermined enamel that often is lost easily by chipping. Occasionally, entire buccal cusps are lost and replaced by ski slope–like depressions that extend from the lingual cusp to the buccal cementoenamel junction (Fig. 2-16). When palatal surfaces are affected, the exposed dentin has a concave surface and shows a peripheral white line of enamel (Fig. 2-17). Active erosion typically reveals a clean, unstained surface, whereas inactive sites become stained and discolored.

Erosion limited to the facial surfaces of the maxillary anterior dentition often is associated with dietary sources of acid. When the tooth loss is confined to the incisal portions of the anterior dentition of both arches, an external environmental source is suggested. When erosion is located on the palatal surfaces of the maxillary anterior teeth and the occlusal surfaces of the posterior teeth of both dentitions, regurgitation of gastric secretions is a probable cause. The location of the tooth structure loss may suggest the cause of the damage but is not completely reliable.

Abfraction

Abfraction appears as wedge-shaped defects limited to the cervical area of the teeth and may closely resemble cervical abrasion or erosion. Clues to the diagnosis include defects that are deep, narrow, and V-shaped (which do not allow the toothbrush to contact the base of the defect) and often affect a single tooth with adjacent unaffected teeth (Fig. 2-18). In addition, occasional lesions are subgingival, a site typically protected from abrasion and erosion. The lesions predominantly affect the facial surfaces of the bicuspids and molars.

In all forms of tooth wear, the process typically proceeds at a slow rate that allows deposition of tertiary dentin and prevents pulp exposure, even when extensive loss of tooth structure is present (see Fig. 2-12). In some cases, especially in the deciduous dentition, the tooth loss can proceed at a

more accelerated rate, which results in a near or frank exposure of the pulp.

Treatment and Prognosis

Normal levels of attrition require no therapy, with intervention reserved for those cases that create a pathologic degree of tooth loss. Early diagnosis and intervention may assist in preserving the permanent dentition. Before any definitive action, the clinician must remember that tooth wear almost invariably has a multifactorial cause. Failure to recognize the interrelationships of these pathoses can lead to inappropriate therapy and failure of any attempted repair. Intervention should emphasize detailed diagnosis, preventive measures, and long-term monitoring. Immediate therapy should be directed toward resolution of tooth sensitivity and pain, but identifying the causes of tooth structure loss and protecting the remaining dentition also are important goals.

In patients affected by dental erosion, preventive interventions should attempt not only to reduce acid exposure but also to improve the oral cavity's ability to resist the effects of acid. Upon exposure to an acid, the saliva has the ability to achieve remineralization with time, but teeth are vulnerable to abrasion before completion of this action. Although some investigators have recommended a minimum 1-hour interval between acid exposure and toothbrushing in an attempt to minimize abrasion of the weakened enamel, other studies have shown that a 6-hour remineralization time is necessary to completely reharden enamel softened by acid exposure. Patients with erosion should limit toothbrushing to once a day in the morning because of the increased vulnerability of acid-etched enamel to abrasion and attrition. Low-abrasive toothpaste and professional guidance to prevent inappropriate, overzealous, or too frequent toothbrushing may assist in reducing associated abrasion. Consumption of buffering substances such as milk, cheese, and sugar-free antacids also is thought to be beneficial. Rinsing the mouth with water after acid exposure and proper hydration have been suggested to reduce the severity of demineralization and maintain sufficient salivary flow with appropriate buffering capability. A suspected common cause of tooth loss is decreased salivary flow secondary to dehydration, often associated with strenuous work or athletic activities and possibly complicated by use of acidic soft drinks or sports beverages in the place of water. Chewing xylitol gum has been suggested as a method for decreasing dental erosion by increasing salivary flow after acid exposure, but others have demonstrated that enamel softened by acid can be damaged by the adjacent soft tissues during the movements of chewing in this time of vulnerability. Patients should be informed of the potential for loss of tooth structure associated with the overuse of acidic foods and drinks (e.g., wine, carbonated beverages, foods pickled in acetic acid, and citrate-containing fruits, fruit juices, and candies), chronic regurgitation, and improper oral hygiene techniques. Mouth guards and occlusal adjustment can be used to slow nocturnal attrition and to protect the teeth from frequent exposure to acid from regurgitation or industrial sources. Dental sensitivity can be reduced through the use of varnishes, mouthwashes, or toothpastes containing strontium chloride, stannous fluoride, or monofluorophosphate. If initially unsuccessful, these agents can be combined with iontophoresis.

Active restorative therapy is premature in the presence of ongoing tooth wear and should be postponed until the patient expresses strong aesthetic concerns, exhibits dental sensitivity that is nonresponsive to conservative interventions, or demonstrates progressive and uncontrollable wear. Once indicated, the minimum treatment necessary to solve the problem should be implemented. In lesions thought to represent abfraction, glass ionomer materials are recommended because of their greater resilience that allows the material to flex with the tooth. In areas of abrasion, a material with optimum resistance to the abrasive process should be chosen. Replacement of lost posterior teeth and avoidance of edge-to-edge occlusion limit the effects of attrition. Lost tooth structure can be restored with composite resins, veneers, onlays, or full crowns. Restorative procedures that do not involve significant removal of remaining tooth structure are preferable in patients demonstrating extensive tooth wear.

INTERNAL AND EXTERNAL RESORPTION

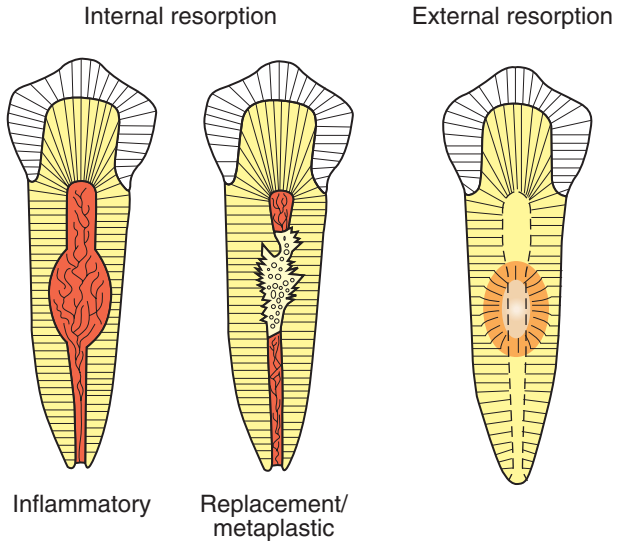
In addition to loss of tooth structure that begins on the exposed coronal surfaces, destruction of teeth also can occur through resorption, which is accomplished by cells located in the dental pulp (i.e., **internal resorption**) or in the periodontal ligament (PDL) (i.e., **external resorption**). Internal resorption is a relatively rare occurrence, and most cases develop after injury to pulpal tissues, such as physical trauma or caries-related pulpitis. The resorption can continue as long as vital pulp tissue remains and may result in communication of the pulp with the PDL.

By contrast, external resorption is extremely common; with close examination, all patients are most likely to have root resorption on one or more teeth. In one radiographic review of 13,263 teeth, all patients showed evidence of root resorption, and 86.4% of the examined teeth demonstrated external resorption, with an average of 16 affected teeth per patient. Most areas of resorption are mild and of no clinical significance, but 10% of patients exhibit unusual amounts of external resorption.

The potential for resorption is inherent within the periodontal tissue of each patient, and this individual susceptibility to resorption is the most important factor in the degree of resorption that will occur after a stimulus. The factors reported to increase the severity of external resorption are delineated in Box 2-3. Many cases have been termed *idiopathic* because no factor could be found to explain the accelerated resorption. Although local factors may exert a strong influence, many researchers believe genetic predisposition plays a strong role. One investigation demonstrated a 5.6-fold increase in root resorption during orthodontics in patients demonstrating homozygosity for the interleukin-1

• BOX 2-3 Factors Associated with External Resorption

- Cysts
- Dental trauma
- Excessive mechanical forces (e.g., orthodontic therapy)
- Excessive occlusal forces
- Grafting of alveolar clefts
- Hormonal imbalances
- Hyperparathyroidism
- Intracoronal bleaching of pulpless teeth
- Local involvement by herpes zoster
- Paget disease of bone
- Periodontal treatment
- Periradicular inflammation
- Pressure from impacted teeth
- Reimplantation of teeth
- Tumors



• Fig. 2-19 Tooth Resorption. Illustration contrasting the common patterns of internal and external tooth resorption. Internal resorption will result in a radiolucent enlargement of the pulp chamber or canal. In external resorption, the radiolucency is superimposed on the pulp canal, which should not be enlarged.

beta (IL-1B) allele. In addition, examples of families with generalized idiopathic root resorption and monozygotic twins presenting with identical patterns of root resorption have been reported. Genetics appears to be a modifying factor that can increase the severity of external resorption when triggered by a secondary influence. When pretreatment radiographs of a given patient exhibit a degree of resorption beyond that which is normally seen, the clinician should realize the potential risks involved in initiating procedures (e.g., orthodontics) that are known to be associated with an increased risk of external resorption.

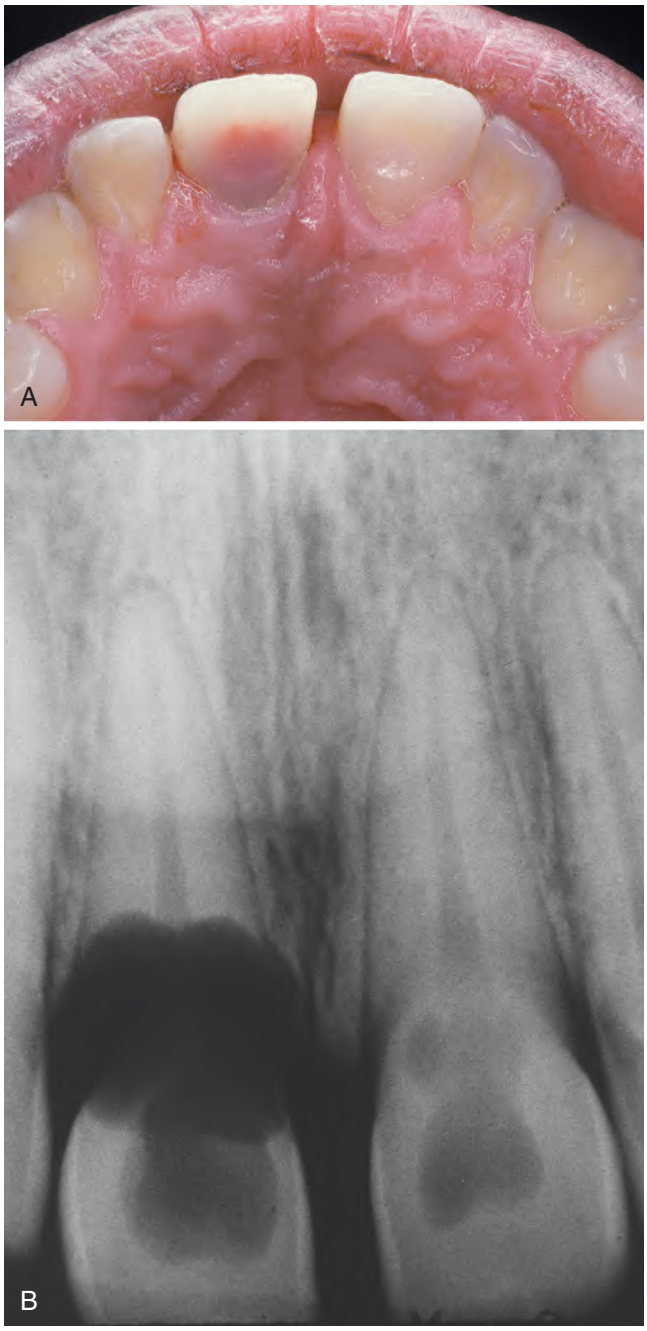
Clinical and Radiographic Features

Resorption of dentin or cementum can occur at any site that contacts vital soft tissue. Internal resorption usually is asymptomatic and discovered through routine radiographs. Pain may be reported if the process is associated with significant pulpal inflammation. Two main patterns are seen: 1) **inflammatory resorption** and 2) **replacement** or **metaplastic resorption** (Fig. 2-19). In inflammatory resorption, the resorbed dentin is replaced by inflamed granulation tissue. Although this pattern may involve any portion of the canal, the cervical zone is affected most frequently (and the pulpal inflammation is usually caused by bacterial invasion). The resorption continues as long as vital pulp remains; typically, the coronal pulp is necrotic with the apical portion remaining vital. The results of pulp testing are variable. In this pattern, the area of destruction usually appears as a uniform, well-circumscribed symmetric radiolucent enlargement of the pulp chamber or canal. When it affects the coronal pulp, the crown can display a pink discoloration **(pink tooth of Mummery)** as the vascular resorptive process approaches the surface (Fig. 2-20). When it occurs in the root, the original outline of the canal is lost and a balloonlike radiographic dilation of the canal is seen (Fig. 2-21). If the process continues, the destruction eventually can perforate the lateral root surface, which may be difficult to distinguish from external root resorption. Internal resorption secondary to infectious pulpitis may cease upon necrosis of the responsible cells within the pulp. Although many cases are progressive, some cases are self-limiting and usually arise in traumatized teeth or those that have recently undergone orthodontic or periodontal therapy.

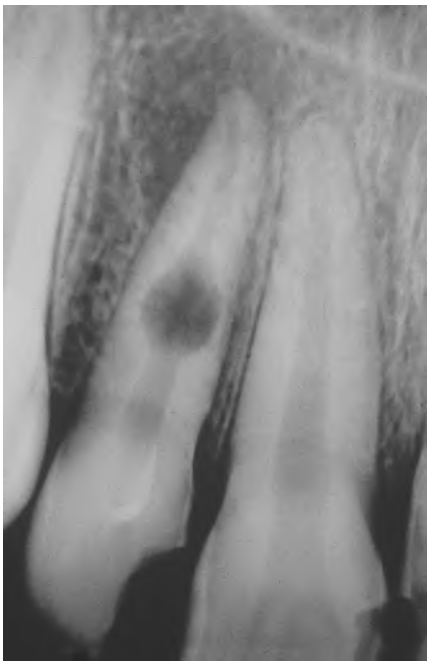
The remaining pattern of internal resorption is termed *replacement* or *metaplastic resorption.* In this form, portions of the pulpal dentinal walls are resorbed and replaced with bone or cementum-like bone (see Fig. 2-19). Radiographically, replacement resorption appears as an enlargement of the canal, which is filled with a material that is less radiodense than the surrounding dentin. Because a central zone of the pulp is replaced with bone, the radiographic appearance often demonstrates partial obliteration of the canal. The outline of destruction is less defined than that seen in inflammatory resorption.

By contrast, external resorption typically appears as a "moth-eaten" loss of tooth structure in which the radiolucency is less well defined and demonstrates variations in density (Figs. 2-22 to 2-25). If the lesion overlies the pulp canal, then close examination demonstrates the retention of the unaltered canal through the area of the defect. Most cases involve the apical or midportions of the root. External resorption can create significant defects in the crowns of teeth before eruption (see Fig. 2-24). This pattern frequently is misdiagnosed as preeruptive caries and is thought by some investigators to be caused by defects in the enamel epithelium that allow connective tissue to come into direct contact with the enamel.

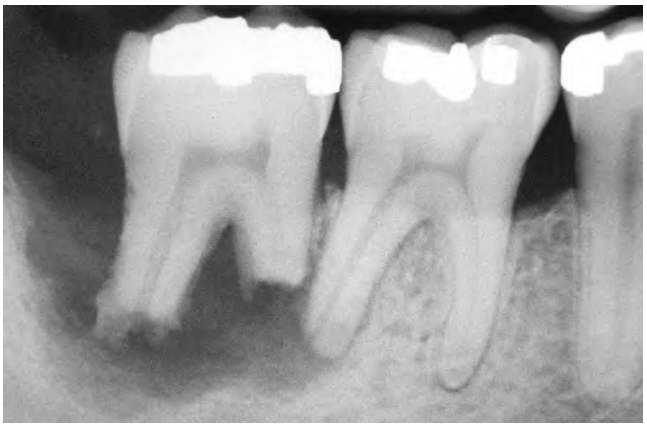
In reimplanted avulsed teeth, extensive external resorption of the root is extremely common without rapid and appropriate intervention (see Fig. 2-23). If the tooth remains outside of the socket without being placed in a proper storage medium, then the PDL cells undergo necrosis.



• **Fig. 2-20 Internal Resorption (Pink Tooth of Mummery). A,** Pink discoloration of the maxillary central incisor. **B,** Radiograph of same patient showing extensive resorption of both maxillary central incisors.



• **Fig. 2-21 Internal Resorption.** Balloonlike enlargement of the root canal.

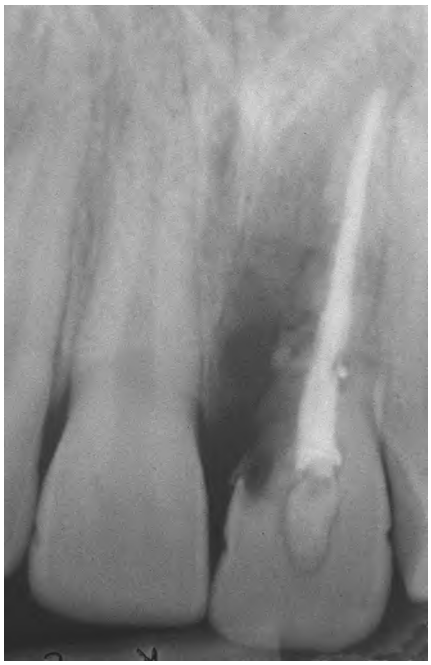


• **Fig. 2-22 External Resorption.** Extensive irregular destruction of both roots of the mandibular second molar associated with chronic periodontitis. (Courtesy of Dr. Tommy Shimer.)

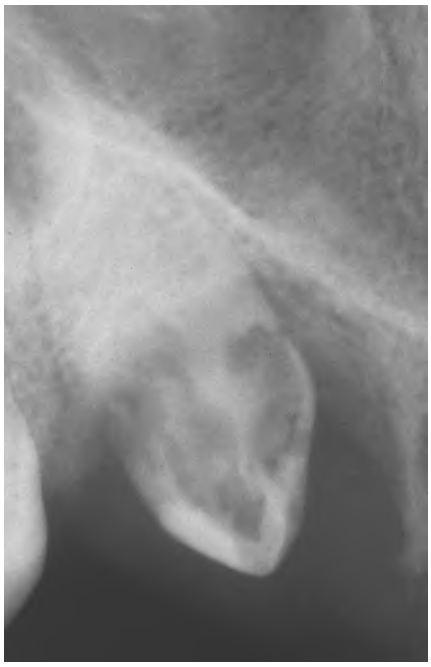
Without vital PDL cells, the surrounding bone views the tooth as a foreign object and initiates resorption and replacement by bone.

External resorption occurring during orthodontics appears to be influenced most strongly by the patient's individual susceptibility. However, heavy forces have been shown to induce a greater degree of resorption, and compressive forces appear more strongly related than tensile forces. The single most important local factor is the distance a tooth is moved during therapy. The maxillary anterior teeth typically are the most severely affected, particularly in patients who have been treated with premolar extractions. Movement of teeth with an abnormal root shape (such as, dilaceration) also has been associated with an increased severity of external resorption. In patients who have demonstrated significant resorption during therapy, a 2 to 3 month treatment pause has been shown to reduce the final amount of treatment-associated external resorption.

Occasionally, external resorption may begin in the cervical area and extend from a small opening to involve a large area of the dentin between the cementum and the pulp. The resorption can extend apically into the pulp or coronally under the enamel and simulate the pink tooth seen in internal resorption. The cervical pattern of external resorption often is rapid and has been termed **invasive cervical resorption.** In some instances, several teeth may be involved, and an underlying cause for the accelerated destruction may not be obvious **(multiple idiopathic root resorption)**

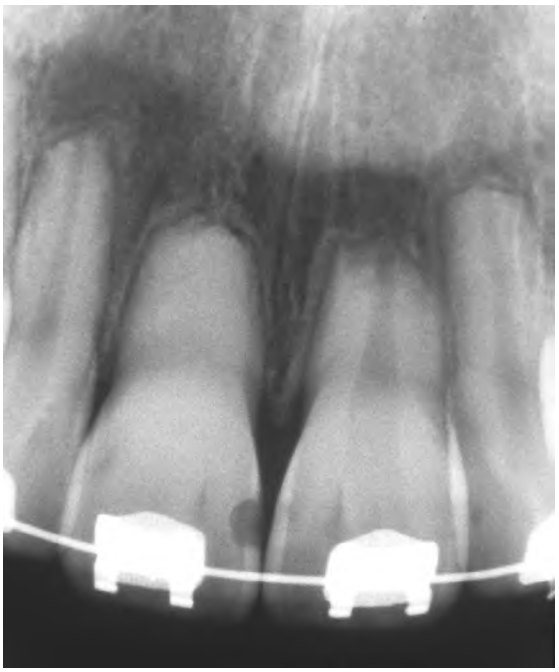


• **Fig. 2-23 External Resorption.** "Moth-eaten" radiolucent alteration of the maxillary left central incisor. The tooth had been reimplanted after traumatic avulsion. (Courtesy of Dr. Harry Meyers.)

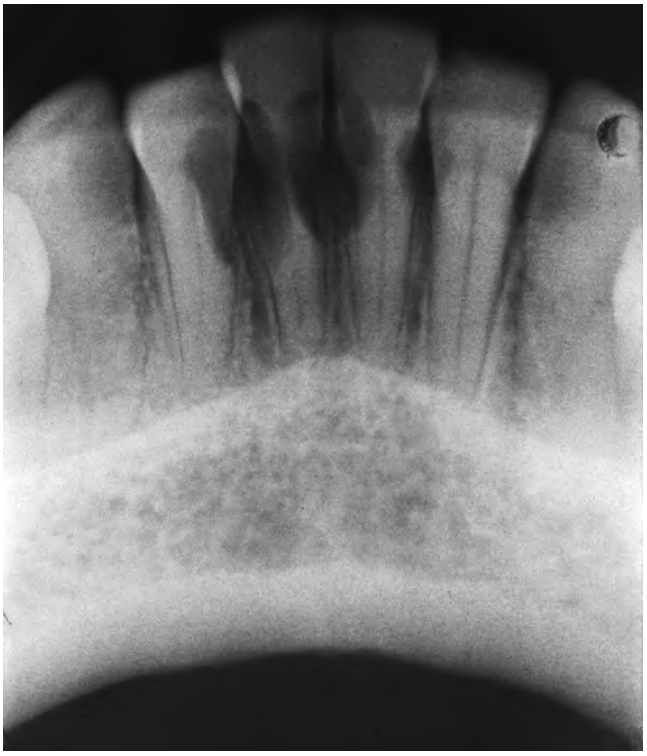


• **Fig. 2-24 External Resorption.** Extensive external resorption of the crown of the impacted right maxillary cuspid. Histopathologic examination revealed resorption without bacterial contamination or caries.

(Fig. 2-26). The exact cause of this pattern of resorption has been elusive, and it may result from a variety of inflammatory, traumatic, or bacterial stimuli affecting the clastic cells within the PDL. The process has been noted after orthodontic therapy, orthognathic surgery, other dentoalveolar surgery, root scaling or planing, internal bleaching of endodontically treated teeth, local trauma, bruxism, and tooth fracture. Other investigators believe this pattern of



• **Fig. 2-25 External Resorption.** Diffuse external resorption of radicular dentin of maxillary dentition. This process arose after initiation of orthodontics.



• **Fig. 2-26 Multiple Idiopathic Root Resorption.** Extensive invasive cervical resorption of several anterior mandibular teeth. (Courtesy of Dr. Keith Lemmerman.)

resorption can be triggered by periodontal pathogens and have seen good response to local mechanical débridement combined with systemic antibiotics.

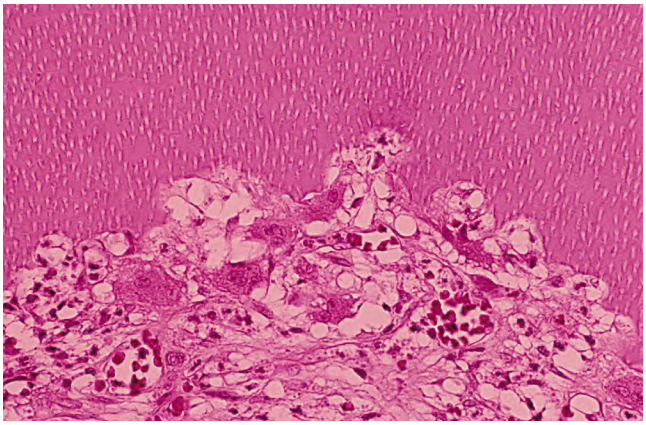
In addition to invasive cervical resorption, generalized and progressive external resorption also can affect the apical portion of the roots. Although this pattern can occur

secondary to an endocrine disturbance or one of a small number of systemic conditions, many of these cases are idiopathic and difficult to arrest. On occasion, the idiopathic apical resorption demonstrates a bilaterally symmetrical pattern that suggests the possibility of occlusal interferences triggering resorption in a genetically predisposed patient (Fig. 2-27).

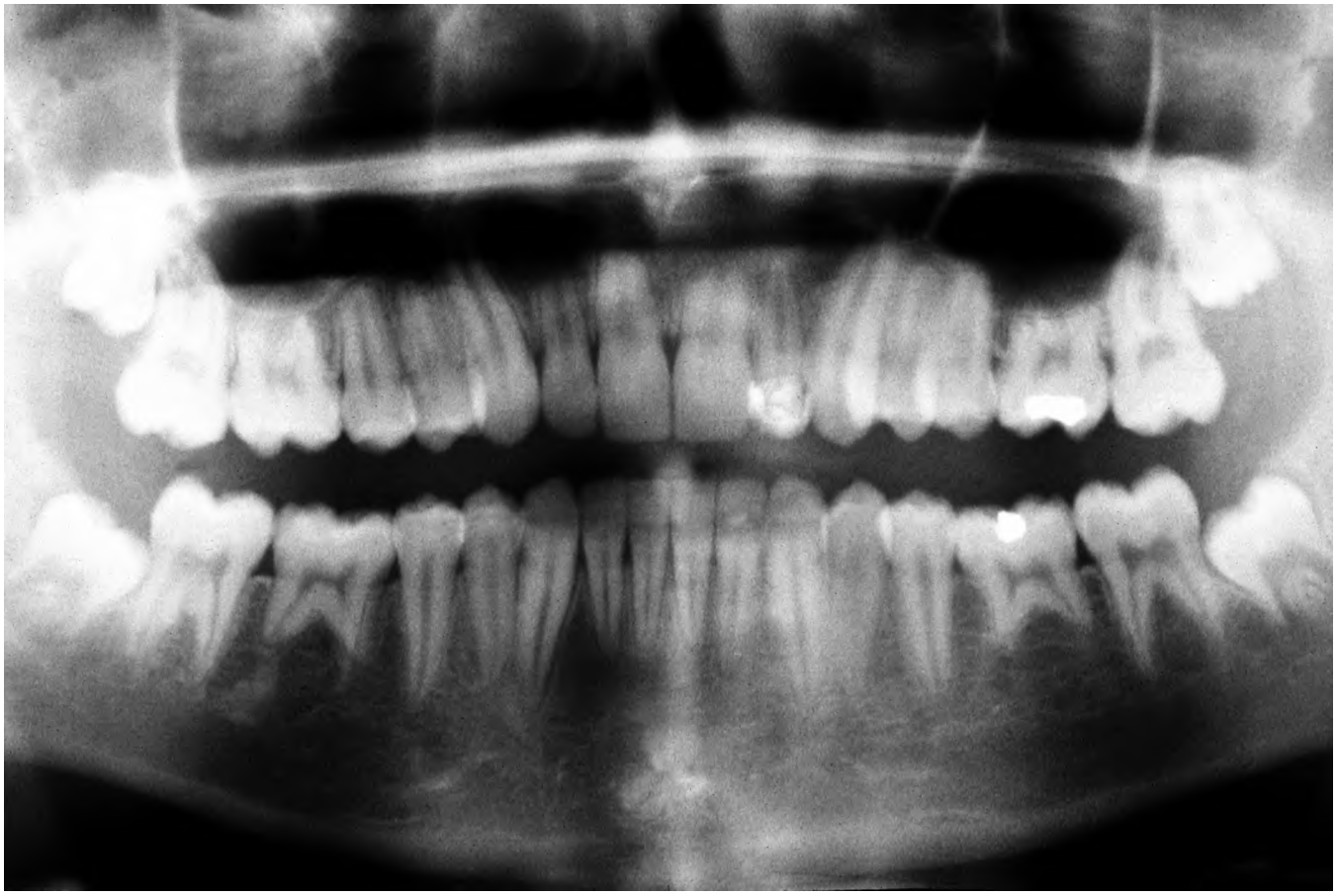
If difficulty arises in distinguishing external from internal resorption, then the mesial-buccal-distal rule can be used through two radiographic exposures: one perpendicular and one mesial (objects closer to the source of radiation shift distally). With this technique, the sites of external resorption appear to shift away from the pulp canal when the radiographs are compared. In addition, the radiographs can reveal which side of the root is affected in cases of external resorption. Although these plain film techniques remain valid, the diagnostic accuracy of cone beam computed tomography (CT) has been shown to be superior and should be considered if standard views provide insufficient information.

Histopathologic Features

In patients with internal inflammatory resorption, the pulp tissue in the area of destruction is vascular and exhibits increased cellularity and collagenization. Immediately adjacent to the dentinal wall are numerous multinucleated dentinoclasts, which are histologically and functionally identical to osteoclasts (Fig. 2-28). An inflammatory infiltrate characterized by lymphocytes, histiocytes, and polymorphonuclear leukocytes is not uncommon. In replacement resorption, the normal pulp tissue is replaced by woven bone that fuses with the adjacent dentin. External



• **Fig. 2-28 Internal Resorption.** Resorption of the inner dentinal wall of the pulp. Note cellular and vascular fibrous connective tissue, which exhibits an adjacent inflammatory infiltrate and numerous dentinoclasts within resorptive lacunae.



• **Fig. 2-27 Idiopathic External Resorption.** First molars in all four quadrants demonstrate extensive radicular external resorption.

resorption is similar in appearance, with numerous multinucleated dentinoclasts located in the areas of structure loss. Areas of resorption often are repaired through deposition of osteodentin. In large defects, external inflammatory resorption results in deposition of inflamed granulation tissue, and areas of replacement with woven bone may also be seen. Extensive bony replacement in areas of external resorption can lead to ankylosis.

Treatment and Prognosis

The treatment of internal and external resorption centers on the removal of all soft tissue from the sites of dental destruction. Internal resorption can be stopped consistently if endodontic therapy successfully removes all vital pulp tissue before the process perforates into the PDL. Once perforation occurs, therapy becomes more difficult and the prognosis is poor. In such cases, initial placement of calcium hydroxide paste occasionally may result in remineralization of the site of perforation and stop the resorptive process. If remineralization of cervical sites of perforation is not successful, then surgical exposure and restoration of the defect may halt the process. Extraction often is necessary for radicular perforations that do not respond to therapy.

The first step in treating external resorption is the identification and elimination of any accelerating factor. Apically located sites cannot be approached without significant damage created by attempts at access. Those cases located in the cervical areas can be treated by surgical exposure, removal of all soft tissue from the defects, and restoration of the lost structure of the tooth. Because the cells responsible for the resorption are located within the PDL, endodontic therapy is not effective in stopping the process. In one report of generalized cervical resorption, therapy directed against local periodontal pathogens (débridement combined with systemic metronidazole and amoxicillin) stopped the resorption and was associated with an increased density of the adjacent crestal bone. In patients with idiopathic root resorption, evaluation and elimination of obvious occlusal interferences appear appropriate.

For avulsed teeth, the best way to prevent resorption is to maintain PDL vitality by immediate reimplantation or short-term use of a physiologic storage solution. Teeth reimplanted with an open apex should be monitored monthly; for teeth with a closed apex, endodontic therapy is necessary. Avulsed teeth with an open apex and nonvital PDL cells should not be implanted.

◆ ENVIRONMENTAL DISCOLORATION OF TEETH

The color of normal teeth varies and depends on the shade, translucency, and thickness of the enamel. In primary teeth, the normal color is bluish white, whereas permanent teeth tend to be grayish white or yellowish white. With aging, the enamel thins and the dentin thickens, leading to teeth that are more yellow or grayish yellow. Abnormal colorations may be **extrinsic** or **intrinsic.** Extrinsic stains occur from surface accumulation of an exogenous pigment and typically can be removed with a surface treatment, whereas intrinsic discolorations arise from an endogenous material that is incorporated into the enamel or dentin and cannot be removed by prophylaxis with toothpaste or pumice. Box 2-4 lists the most frequently documented causes of tooth discolorations.

• BOX 2-4 Tooth Discolorations

Extrinsic

- Bacterial stains
- Iron
- Tobacco
- Foods and beverages
- Gingival hemorrhage
- Restorative materials
- Medications

Intrinsic

- Amelogenesis imperfect (AI)
- Dentinogenesis imperfecta (DGI)
- Dental fluorosis
- Erythropoietic porphyria
- Hyperbilirubinemia
- Ochronosis
- Trauma
- Localized red blood cell breakdown
- Medications

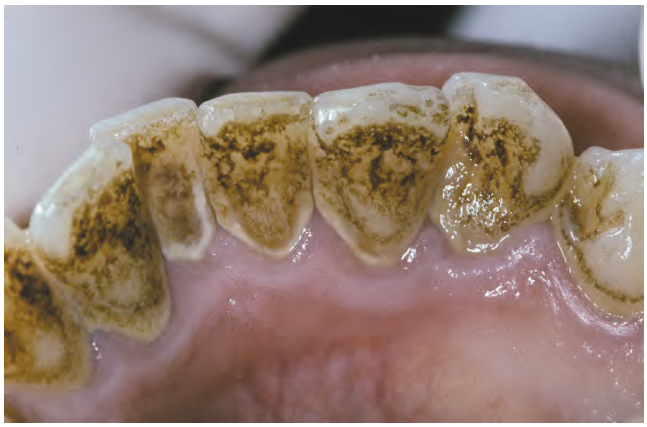
Dental fluorosis is discussed in the section on environmental effects on the structural development of the teeth (see page 52). The alterations associated with **amelogenesis imperfecta** (see page 92) and **dentinogenesis imperfecta (DGI)** (see page 98) are presented later in this chapter in the text devoted to primary developmental alterations of the teeth.

Clinical Features

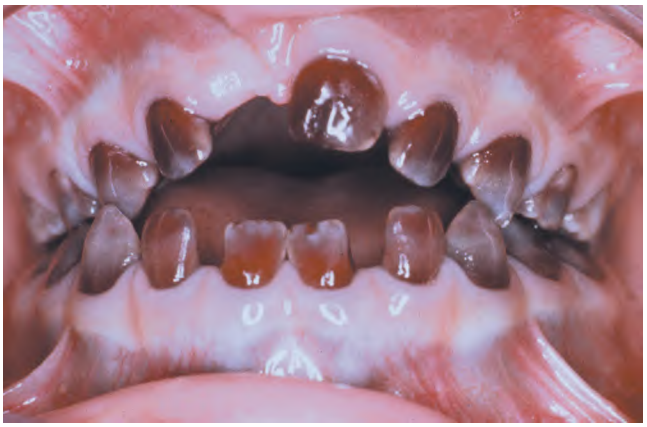
Extrinsic Stains

Bacterial stains are a common cause of surface staining of exposed enamel, dentin, and cementum. Chromogenic bacteria can produce colorations that vary from green or black-brown to orange. The discoloration occurs most frequently in children and usually is seen initially on the labial surface of the maxillary anterior teeth in the gingival one-third. In contrast to most plaque-related discolorations, the black-brown stains most likely are not primarily of bacterial origin but are secondary to the formation of ferric sulfide from an interaction between bacterial hydrogen sulfide and iron in the saliva or gingival crevicular fluid.

Extensive use of **tobacco** products, **tea,** or **coffee** often results in significant brown discoloration of the surface enamel (Fig. 2-29). The tar within the tobacco dissolves in the saliva and easily penetrates the pits and fissures of the enamel. Smokers (of tobacco or marijuana) most frequently exhibit involvement of the lingual surface of the mandibular



• **Fig. 2-29 Tobacco Discoloration.** Extrinsic brown stains of the enamel on the lingual surfaces of the anterior mandibular dentition secondary to long-term tobacco abuse.



• **Fig. 2-30 Erythropoietic Porphyria–related Discoloration.** Red-brown discoloration of the maxillary dentition.

incisors; users of smokeless tobacco often demonstrate involvement of the enamel in the area of tobacco placement. Stains from beverages also often involve the lingual surface of the anterior teeth, but the stains are usually more widespread and less intense. In addition, foods that contain abundant chlorophyll can produce a green discoloration of the enamel surface.

The green discoloration associated with chromogenic bacteria or the frequent consumption of chlorophyll-containing foods can resemble the pattern of green staining seen secondary to **gingival hemorrhage.** As would be expected, this pattern of discoloration occurs most frequently in patients with poor oral hygiene and erythematous, hemorrhagic, and enlarged gingiva. The color results from the breakdown of hemoglobin into green biliverdin.

A large number of **medications** may result in surface staining of the teeth. In the past, use of products containing high amounts of iron or iodine was associated with significant black pigmentation of the teeth. Exposure to sulfides, silver nitrate, or manganese can cause stains that vary from gray to yellow to brown to black. Copper, nickel, or ciprofloxacin may produce a green stain; cadmium, essential oils, doxycycline, linezolid, glibenclamide, and amoxicillin-clavulanic acid may be associated with a yellow to brown discoloration.

More recently, the most frequently reported culprits include **stannous fluoride** and **chlorhexidine.** Fluoride staining may be associated with the use of 8% stannous fluoride and is thought to be secondary to the combination of the stannous (tin) ion with bacterial sulfides. This black stain occurs predominantly in people with poor oral hygiene in areas of a tooth previously affected by early carious involvement. The labial surfaces of anterior teeth and the occlusal surfaces of posterior teeth are the most frequently affected. Chlorhexidine is associated with a yellow-brown stain that predominantly involves the interproximal surfaces near the gingival margins. The degree of staining varies with the concentration of the medication and the patient's susceptibility. Although an increased frequency has been associated with the use of tannin-containing beverages, such as tea and wine, effective brushing and flossing or frequent gum chewing can minimize staining. Chlorhexidine is not alone in its association with tooth staining; many oral antiseptics, such as Listerine and sanguinarine, also may produce similar changes.

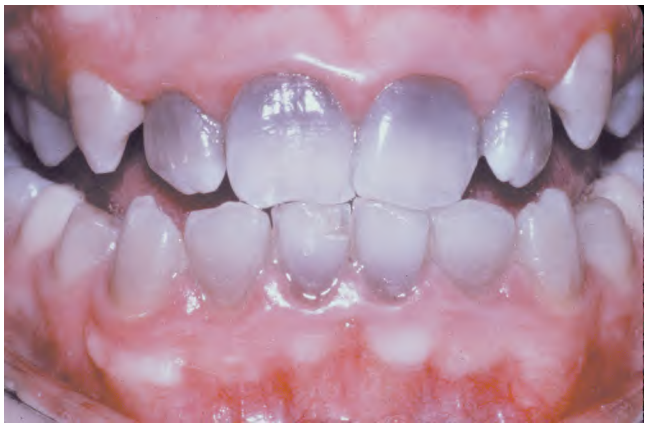
Intrinsic Stains

Congenital erythropoietic porphyria (Günther disease) is an autosomal recessive disorder of porphyrin metabolism that results in the increased synthesis and excretion of porphyrins and their related precursors. Significant diffuse discoloration of the dentition is noted as a result of the deposition of porphyrin in the teeth (Fig. 2-30). Affected teeth demonstrate a marked red-brown coloration that exhibits a red fluorescence when exposed to a Wood's ultraviolet (UV) light. The deciduous teeth demonstrate a more intense coloration because porphyrin is present in the enamel and the dentin; in the permanent teeth, only the dentin is affected. Excess porphyrins also are present in the urine, which may reveal a similar fluorescence when exposed to a Wood's light.

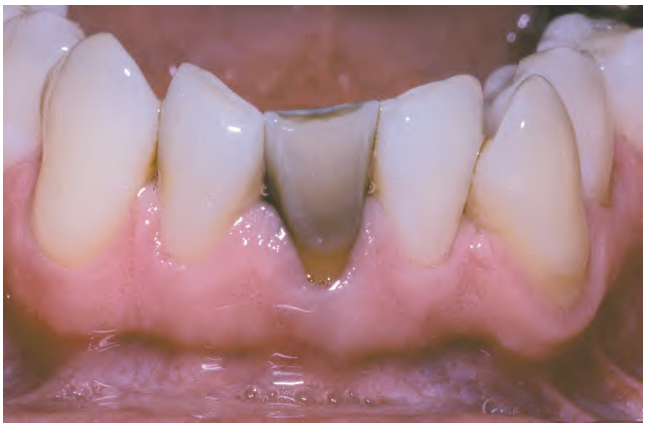
Another autosomal recessive metabolic disorder, **alkaptonuria,** is associated with a blue-black discoloration termed *ochronosis* that occurs in connective tissue, tendons, and cartilage. On rare occasions, a blue discoloration of the dentition may be seen in patients who also are affected with Parkinson disease.

Bilirubin is a breakdown product of red blood cells, and excess levels can be released into the blood in a number of conditions. The increased amount of bilirubin can accumulate in the interstitial fluid, mucosa, serosa, and skin, resulting in a yellow-green discoloration known as **jaundice** (see page 765). During periods of **hyperbilirubinemia,** developing teeth also may accumulate the pigment and become stained intrinsically. In most cases the deciduous teeth are affected as a result of hyperbilirubinemia during the neonatal period. The two most common causes are **erythroblastosis fetalis** and **biliary atresia.** Other diseases that less frequently display intrinsic staining of this type include the following:

- Premature birth
- ABO incompatibility



• **Fig. 2-31 Hyperbilirubinemia-Related Discoloration.** Diffuse grayish-blue discoloration of the dentition. Cervical portions are stained most intensely. (Courtesy of Dr. John Giunta.)



• **Fig. 2-32 Amalgam Discoloration.** Green-gray discoloration of mandibular central incisor, which had endodontic access preparation restored with amalgam.

- Neonatal respiratory distress
- Significant internal hemorrhage
- Congenital hypothyroidism
- Biliary hypoplasia
- Metabolic diseases (tyrosinemia, α1-antitrypsin deficiency)
- Neonatal hepatitis

The extent of the dental changes correlates with the period of hyperbilirubinemia, and most patients exhibit involvement limited to the primary dentition. Occasionally, the cusps of the permanent first molars may be affected. In addition to enamel hypoplasia, the affected teeth frequently demonstrate a green discoloration **(chlorodontia).** The color is the result of the deposition of biliverdin (the breakdown product of bilirubin that causes jaundice) and may vary from yellow to deep shades of green (Fig. 2-31). The color of tooth structure formed after the resolution of the hyperbilirubinemia appears normal. The teeth often demonstrate a sharp dividing line, separating green portions (formed during hyperbilirubinemia) from normal-colored portions (formed after normal levels of bilirubin were restored).

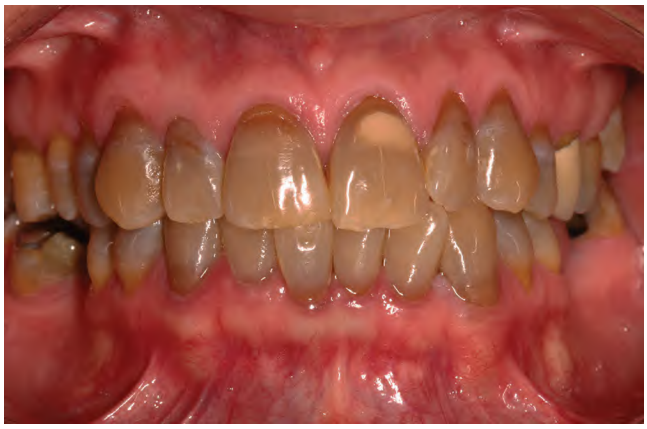
Coronal discoloration is a frequent finding after **trauma,** especially in the deciduous dentition. Posttraumatic injuries may create pink, yellow, or dark-gray discoloration. Temporary pink discoloration that arises 1 to 3 weeks after trauma may represent localized vascular damage and often returns to normal in 1 to 3 weeks. In these instances, periapical radiographs are warranted to rule out internal resorption that may produce a similar clinical presentation. A yellow discoloration is indicative of pulpal obliteration, termed **calcific metamorphosis,** and is discussed more fully in Chapter 3 (see page 114). Occasionally, during a postmortem examination, a pink discoloration of teeth is found. The crowns and necks of the teeth are affected most frequently, and the process is thought to arise from hemoglobin breakdown within the necrotic pulp tissue in patients in whom blood has accumulated in the head.

A similar pink or red discoloration of the maxillary incisors has been reported in living patients with **lepromatous leprosy** (see page 179). Although controversial, some investigators believe these teeth are involved selectively because of the decreased temperature preferred by the causative organism. This process is thought to be secondary to infection-related necrosis and the rupture of numerous small blood vessels within the pulp, with a secondary release of hemoglobin into the adjacent dentinal tubules.

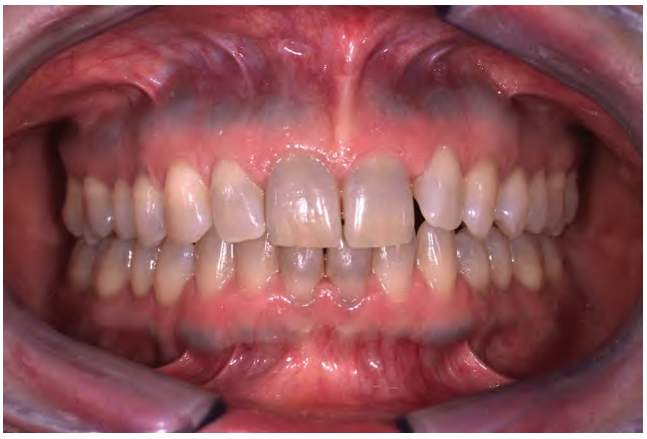
Dental **restorative materials,** especially amalgam, can result in black-gray discolorations of teeth. This most frequently arises in younger patients who presumably have more open dentinal tubules. Large Class II proximal restorations of posterior teeth can produce discoloration of the overlying facial surface. In addition, deep lingual metallic restorations on anterior incisors can significantly stain underlying dentin and produce visible grayish discoloration on the labial surface. To help reduce the possibility of discoloration, the clinician should not restore endodontically treated anterior teeth with amalgam (Fig. 2-32).

Several different **medications** can become incorporated into the developing tooth and result in clinically evident discoloration. The severity of the alterations is dependent on the time of administration, the dose, and the duration of the drug's use. The most infamous is **tetracycline,** with the affected teeth varying from bright yellow to dark brown and, in UV light, showing a bright yellow fluorescence (Fig. 2-33). After chronic exposure to ambient light, the fluorescent yellow discoloration fades over months to years into a nonfluorescent brown discoloration. Often the facial surfaces of the anterior teeth will darken while the posterior dentition and lingual surfaces remain a fluorescent yellow. The drug and its homologues can cross the placental barrier; therefore, administration should, if possible, be avoided during pregnancy and in children up to 8 years of age. All homologues of tetracycline are associated with discoloration and include chlortetracycline (gray-brown discoloration) and demethylchlortetracycline and oxytetracycline (yellow).

One semisynthetic derivative of tetracycline, **minocycline hydrochloride,** has been shown to produce significant discoloration of the dentition and also may affect teeth that are fully developed. Minocycline is a widely used



• **Fig. 2-33 Tetracycline-Related Discoloration.** Diffuse brownish discoloration of the permanent dentition.



• **Fig. 2-34 Minocycline-Related Discoloration.** Dentition demonstrating grayish discoloration predominantly noted on the incisal half of the teeth. Note the horizontal bands of bluish alteration of the maxillary and mandibular alveolar ridges. (Courtesy of Dr. Roger Miller.)

medication for the treatment of acne and also is occasionally prescribed to treat rheumatoid arthritis. Its prevalence of use is increasing (and, presumably, so will the number of patients affected with discolored teeth and bone).

Although the mechanism is unknown, minocycline appears to bind preferentially to certain types of collagenous tissues (e.g., dental pulp, dentin, bone, and dermis). Once in these tissues, oxidation occurs and may produce the distinctive discoloration. Some investigators believe supplementation with ascorbic acid (an antioxidant) can block formation of the discoloration. No matter the cause, once the pulp tissues are stained, the coloration can be seen through the overlying translucent dentin and enamel. The staining is not universal; only 3% to 6% of long-term users become affected. In those affected, the period of time before discoloration becomes evident can range from just 1 month to several years.

In susceptible individuals, minocycline creates discoloration in the skin, oral mucosa (see page 290), nails, sclera, conjunctiva, thyroid, bone, and teeth. Coloration of the bone occasionally results in a distinctive blue-gray appearance of the palate, mandibular tori, or anterior alveolar mucosa, which represents the black bone showing through the thin, translucent oral mucosa (Fig. 2-34). Several patterns of staining are noted in the dentition. Fully erupted teeth typically reveal a blue-gray discoloration of the incisal three-fourths, with the middle one-third being maximally involved (see Fig. 2-34). The exposed roots of erupted teeth demonstrate a dark-green discoloration, although the roots of developing teeth are stained dark black.

Another antibiotic, ciprofloxacin, is given intravenously to infants for *Klebsiella spp.* infections. Although less notable than tetracycline, this medication also has been associated with intrinsic tooth staining—usually a greenish discoloration.

Treatment and Prognosis

Careful polishing with fine pumice can remove most extrinsic stains on the teeth; typically, normal prophylaxis paste is insufficient. Stubborn stains often are resolved by mixing 3% hydrogen peroxide with the pumice or by using bicarbonate spray solutions. The use of jet prophylactic devices with a mild abrasive is the most effective. Recurrence of the stains is not uncommon unless the cause is reduced or eliminated. Improving the level of oral hygiene often minimizes the chance of recurrence.

Intrinsic discoloration is much more difficult to resolve because of the frequent extensive involvement of the dentin. Suggested aesthetic remedies include external bleaching of vital teeth, internal bleaching of nonvital teeth, bonded restorations, composite buildups, laminate veneer crowns, and full crowns. The treatment must be individualized to fulfill the unique needs of each patient and his or her specific pattern of discoloration.

◆ LOCALIZED DISTURBANCES IN ERUPTION

DELAYED ERUPTION

Eruption is the movement of a tooth from its position of development within the bone to its functional location in the mouth. After the tooth is in full occlusion, slight eruption continues in order to compensate for normal attrition and continued vertical growth of the face. Although delayed eruption is not a rare problem, few well-written reviews have been published on the subject.

Emergence is the moment of eruption when the first part of the cusp or crown is visible through the gingiva. This process normally occurs when the dental root is approximately two-thirds its final length. Emergence occurs over a broad chronologic age range and differs according to a number of influences, such as racial and gender variations. Eruption is considered delayed if emergence has not occurred within 12 months of the normal range or by the time 75% root formation is complete. Box 2-5 lists local conditions reported in the literature that can be associated

with delayed eruption; Box 2-6 highlights systemic disorders associated with delayed eruption.

Clinical and Radiographic Features

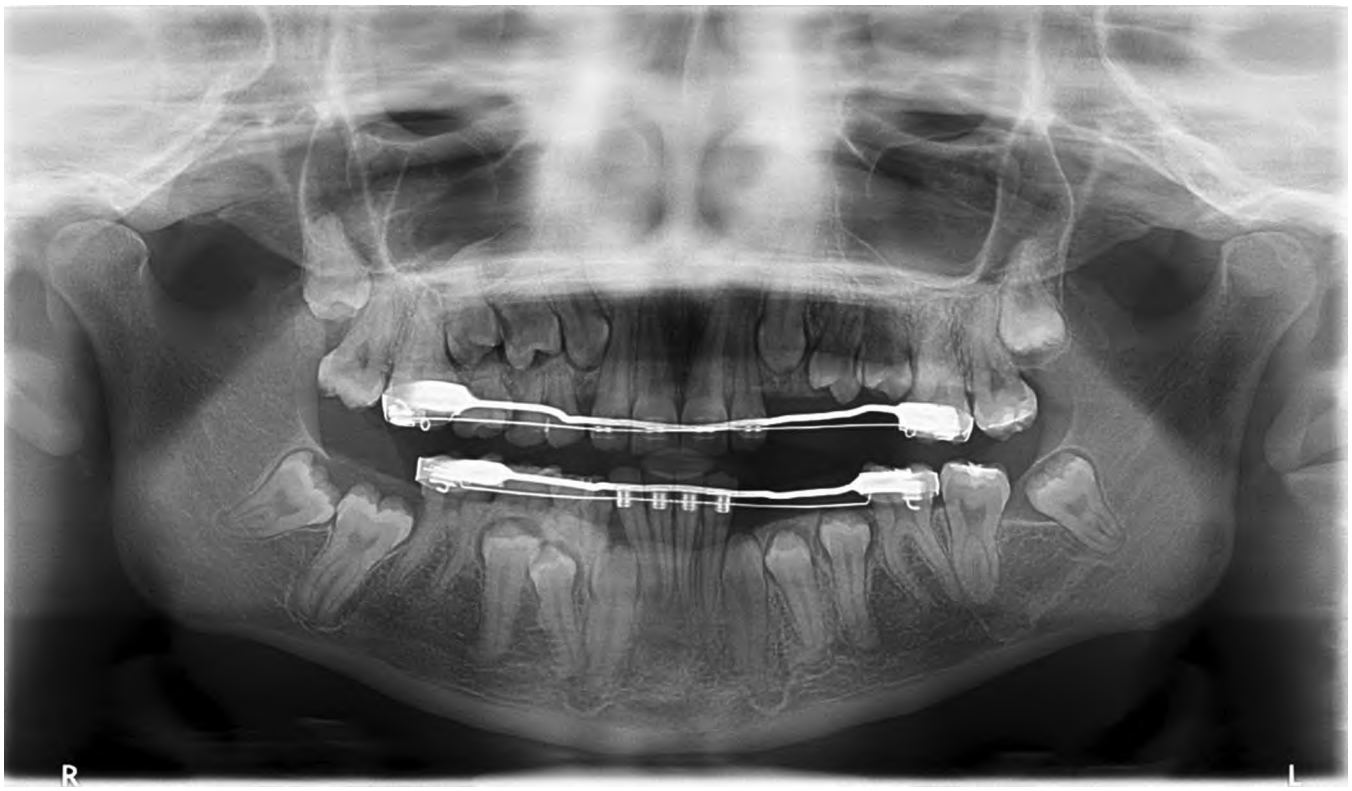
The failure of eruption may be localized or diffuse. In many localized examples, the cause is readily apparent upon radiographic examination when objects are discovered in the path of eruption. In other cases, the cause is not obvious and may be discovered after surgical exploration (such as a small intramural odontogenic hamartoma within the follicular sac). Diffuse delayed eruption often is more problematic and frequently is associated with a systemic disorder (Fig. 2-35). An excellent example is presented during the discussion of hypothyroidism in Chapter 17 (see page 777).

• BOX 2-5 Local Conditions Associated with Delayed Eruption

- Ankylosis of deciduous tooth
- Arch-length deficiency
- Ectopic eruption
- Enamel pearls
- Failure of resorption of deciduous tooth
- Gingival fibromatosis or hyperplasia
- Impaction of deciduous tooth
- Injury or infection of deciduous tooth
- Mucosal barriers, such as scar tissue
- Oral clefts
- Premature loss of deciduous tooth
- Radiation damage
- Regional odontodysplasia
- Segmental odontomaxillary dysplasia
- Supernumerary teeth
- Tumors, odontogenic and nonodontogenic

• BOX 2-6 Systemic Conditions Associated with Delayed Eruption

- Anemia
- Celiac disease
- Cerebral palsy
- Chemotherapy
- Dysosteosclerosis
- Drugs, such as phenytoin
- Endocrine disorders (e.g., hypothyroidism, hypopituitarism, hypoparathyroidism, pseudohypoparathyroidism)
- Genetic disorders
- Heavy metal intoxication
- Human immunodeficiency virus (HIV) infection
- Hypobaria
- Ichthyosis
- Inadequate nutrition
- Low birth weight
- Renal failure
- Tobacco smoke
- Vitamin D–resistant rickets



• **Fig. 2-35 Delayed Eruption.** Adult patient presenting with multiple unerupted permanent teeth without obvious causation. (Courtesy of Dr. Mark Lingen.)

Treatment and Prognosis

For localized delayed emergence, removal of any pathosis in the path of eruption may be sufficient to allow eruption to occur. If eruption does not proceed, surgical exposure accompanied by orthodontic traction has been shown to be successful. When the delayed eruption is generalized, the patient should be evaluated for systemic diseases known to be associated with the process. Successful resolution of the underlying disorder often is followed by completion of eruption.

IMPACTION

Teeth that cease to erupt before emergence are **impacted.** Some authors subdivide these non-erupted teeth into those that are obstructed by a physical barrier (impacted) and those that appear to exhibit a lack of eruptive force (embedded). In many cases a tooth may appear to be embedded; however, on removal a previously undetected overlying odontogenic hamartoma or neoplasm is discovered. Therefore, it appears appropriate to classify all these teeth as impacted.

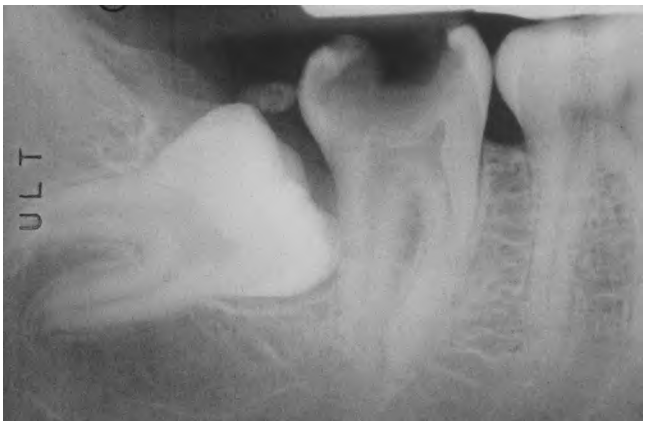
Clinical and Radiographic Features

Impaction of deciduous teeth is extremely rare; when seen, it most commonly involves second molars. Analysis of cases suggests that ankylosis plays a major role in the pathogenesis. In the permanent dentition, the most frequently impacted teeth are the mandibular third molar, followed by maxillary third molars and maxillary cuspids. In decreasing order of frequency, impaction also may occur with mandibular premolars, mandibular canines, maxillary premolars, maxillary central incisors, maxillary lateral incisors, and mandibular second molars. First molars and maxillary second molars are rarely affected.

Lack of eruption most frequently is caused by crowding and insufficient maxillofacial development. Procedures that create more space, such as removal of bicuspids for orthodontic purposes, are associated with a decreased prevalence of third molar impaction. Impacted teeth are frequently diverted or angulated and eventually lose their potential to erupt (on completion of root development). Other factors known to be associated with impaction include the following:

- Overlying cysts or tumors
- Trauma
- Reconstructive surgery
- Thickened overlying bone or soft tissue
- A host of systemic disorders, diseases, and syndromes

Impacted teeth may be partially erupted or completely encased within the bone (i.e., full bony impaction). In addition, the impaction may be classified according to the angulation of the tooth in relationship to the remaining dentition: mesioangular, distoangular, vertical, horizontal, or inverted. On occasion, a small spicule of nonvital bone may be seen radiographically or clinically overlying the crown of partially erupted permanent posterior tooth (Fig. 2-36). The process is termed an **eruption sequestrum** and occurs when the osseous fragment becomes separated from the contiguous bone during eruption of the associated tooth. On occasion, mild sensitivity is noted in the area, especially during eating.



• **Fig. 2-36 Eruption Sequestrum.** A radiopaque fragment of sequestrating bone can be seen overlying an impacted third molar.

Treatment and Prognosis

The choices of treatment for impacted teeth include the following:

- Long-term observation
- Orthodontically assisted eruption
- Transplantation
- Surgical removal

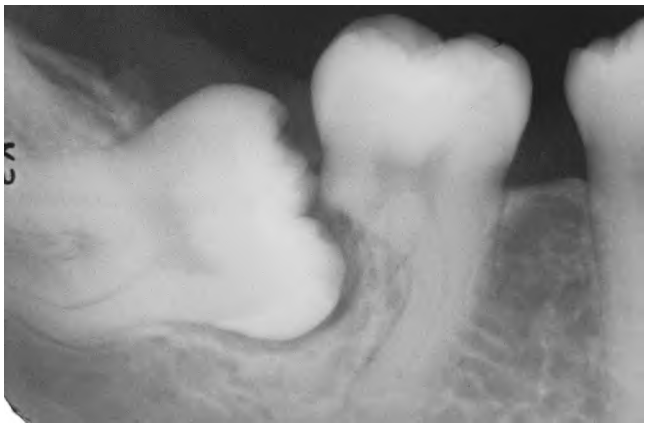
The presence of infection, nonrestorable carious lesions, cysts, tumors, or destruction of adjacent tooth and bone mandates extraction. Surgical removal of impacted teeth is the procedure performed most frequently by oral and maxillofacial surgeons. The choice of therapy in asymptomatic cases is an area of hot debate, and no immediate resolution is obvious. The risks associated with nonintervention include the following:

- Crowding of dentition
- Resorption, caries, and worsening of the periodontal status of adjacent teeth (Fig. 2-37)
- Development of pathologic conditions, such as infections, cysts, and tumors

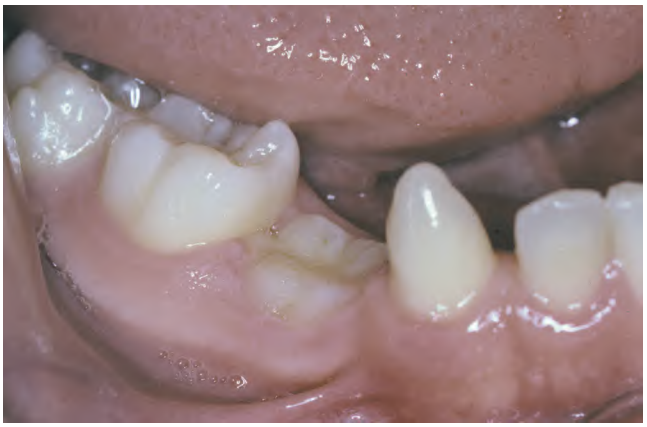
The risks of intervention include the following:

- Transient or permanent sensory loss
- Alveolitis
- Trismus
- Infection
- Fracture
- Temporomandibular joint (TMJ) injury
- Periodontal injury
- Injury to adjacent teeth

Dental referral patterns provide a variety of perspectives of different dental practitioners. Many specialists (e.g., oral



• **Fig. 2-37 Impaction-Related Tooth Resorption.** Mesioangular impaction of the right mandibular third molar associated with significant resorption of the distal root of the second molar. (Courtesy of Dr. Richard Brock.)



• **Fig. 2-38 Ankylosis.** Deciduous molar well below the occlusal plane of the adjacent teeth.

and maxillofacial surgeons, oral and maxillofacial pathologists) see a large percentage of significant pathologic conditions associated with impacted teeth compared with the experience of other clinicians. Although pathology rarely is associated with impacted teeth in children and young adults, numerous reports have documented an increased prevalence of problems in the later decades; therefore, any meaningful prospective studies must be lifelong rather than confined to just a few years. One review of 2646 pericoronal lesions submitted to an active oral pathology service revealed that 32.9% of cases had pathologically significant lesions, with strong relationship between increasing age and the prevalence of pericoronal pathosis. In this 6-year review were six primary squamous cell carcinomas arising from dentigerous cysts in addition to numerous odontogenic keratocysts and odontogenic tumors. Because of the frequent occurrence of significant pericoronal pathology, specialists often recommend extraction over close observation of impacted teeth.

The eruption sequestrum requires no therapy and usually undergoes spontaneous resorption or exfoliation.

ANKYLOSIS

Eruption continues after the emergence of the teeth to compensate for masticatory wear and the growth of the jaws. The cessation of eruption after emergence is termed **ankylosis** and occurs from an anatomic fusion of tooth cementum or dentin with the alveolar bone. Although the areas of union may be too subtle to be detected clinically and radiographically, histopathologic examination demonstrates fusion between the affected tooth and the adjacent bone in almost all cases. Other terms for this process within the literature include **infraocclusion, secondary retention, submergence, reimpaction,** and **reinclusion.** *Secondary retention* is an acceptable term but may be confused with *retained primary teeth,* which maintain their emergence. *Submergence, reimpaction,* and *reinclusion* connote an active depression, and this is not the case.

The pathogenesis of ankylosis is unknown and may be secondary to one of many factors. Disturbances from changes in local metabolism, trauma, injury, chemical or thermal irritation, local failure of bone growth, and abnormal pressure from the tongue have been suggested. The periodontal ligament (PDL) might act as a barrier that prevents osteoblasts from applying bone directly onto cementum. Ankylosis could arise from a variety of factors that result in a deficiency of this natural barrier. Such loss could arise from trauma or a genetically decreased PDL gap. Other theories point to a disturbance between normal root resorption and hard tissue repair. Several investigators believe genetic predisposition has a significant influence and point to monozygotic twins who demonstrate strikingly similar patterns of ankylosis to support this hypothesis.

Clinical and Radiographic Features

Ankylosis may occur at any age; however, clinically the condition is most obvious if the fusion develops during the first two decades of life. Most patients reported in the literature with obvious alterations in occlusion are between the ages of 7 and 18 years, with a peak prevalence occurring in 8- to 9-year-old children. The reported prevalence of clinically detectable ankylosis in children varies from 1.3% to 8.9% and has been reported to be as high as 44% in siblings of those affected.

Although any tooth may be affected, the most commonly involved teeth in order of frequency are the mandibular primary first molar, the mandibular primary second molar, the maxillary primary first molar, and the maxillary primary second molar. Ankylosis of permanent teeth is uncommon. In the deciduous dentition, mandibular teeth are affected ten times as often as the maxillary dentition. The occlusal plane of the involved tooth is below that of the adjacent dentition (infraocclusion) in a patient with a history of previous full occlusion (Fig. 2-38). A sharp, solid sound may be noted on percussion of the involved tooth but can be detected only when more than 20% of the root is fused to the bone. Radiographically, absence of the PDL

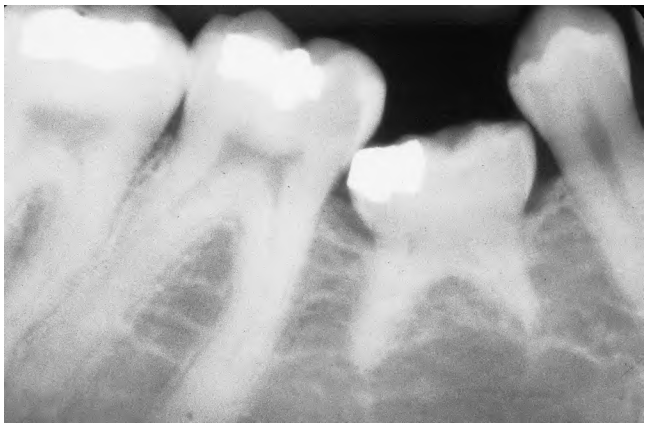


Fig. 2-39 Ankylosis. Radiograph of an ankylosed deciduous molar. Note the lack of periodontal ligament (PDL) space.

space may be noted; however, the area of fusion is often in the bifurcation and interradicular root surface, making radiographic detection most difficult (Fig. 2-39).

Ankylosed teeth that are allowed to remain in position can lead to a number of dental problems. The adjacent teeth often incline toward the affected tooth, frequently with the development of subsequent occlusal and periodontal problems. In addition, the opposing teeth often exhibit overeruption. Occasionally, the ankylosed tooth leads to a localized deficiency of the alveolar ridge or impaction of the underlying permanent tooth. An increased frequency of lateral open bite and crossbite is seen.

Treatment and Prognosis

Because they are fused to the adjacent bone, ankylosed teeth fail to respond to normal orthodontic forces, with attempts to move the ankylosed tooth occasionally resulting in intrusion of the anchor teeth. Recommended therapy for ankylosis of primary molars is variable and often is determined by the severity and timing of the process. When an underlying permanent successor is present, extraction of the ankylosed primary molar should not be performed until it becomes obvious that exfoliation is not proceeding normally or adverse occlusal changes are developing. After extraction of an ankylosed molar, the permanent tooth will erupt spontaneously in the majority of cases. In permanent teeth or primary teeth without underlying successors, prosthetic buildup can be placed to augment the occlusal height. Severe cases in primary teeth are treated best with extraction and space maintenance. Luxation of affected permanent teeth may be attempted with extraction forceps in an effort to break the ankylosis. It is hoped that the subsequent inflammatory reaction results in the formation of a new fibrous ligament in the area of previous fusion. In these cases, reevaluation in 6 months is mandatory. Finally, several reports have documented successful repositioning of an ankylosed permanent tooth with a combination of orthodontics, segmental osteotomy, and distraction osteogenesis.

BOX 2-7 Developmental Alterations of Teeth

Number
- Hypodontia
- Hyperdontia

Size
- Microdontia
- Macrodontia

Shape
- Gemination
- Fusion
- Concrescence
- Accessory cusps
- Dens invaginatus
- Ectopic enamel
- Taurodontism
- Hypercementosis
- Accessory roots
- Dilaceration

Structure
- Amelogenesis imperfecta (AI)
- Dentinogenesis imperfecta (DGI)
- Dentin dysplasia type I (DD-I)
- Dentin dysplasia type II (DD-II)
- Regional odontodysplasia

DEVELOPMENTAL ALTERATIONS OF TEETH

Numerous developmental alterations of teeth can occur. Box 2-7 delineates the major reported alterations, and the following text pertains to these entities. These alterations may be primary or arise secondary to environmental influences (e.g., concrescence, hypercementosis, and dilaceration). For the sake of convenience, both the primary and the environmental forms will be discussed together.

DEVELOPMENTAL ALTERATIONS IN THE NUMBER OF TEETH

Variations in the number of teeth that develop are common. Several terms are useful in the discussion of the numeric variations of teeth. **Anodontia** refers to a total lack of tooth development. **Hypodontia** denotes the lack of development of one or more teeth; **oligodontia** (a subdivision of hypodontia) indicates the lack of development of six or more teeth excluding third molars. **Hyperdontia** is the development of an increased number of teeth, and the additional teeth are termed **supernumerary.** Terms such as *partial anodontia* are oxymorons and should be avoided. In addition, these terms pertain to teeth that failed to develop and should not be applied to teeth that developed but are impacted or have been removed.

• BOX 2-8 Syndromes Associated with Hypodontia

- Ankyloglossia superior
- Böök
- Cockayne
- Coffin-Lowry
- Cranio-oculo-dental
- Crouzon
- Down
- Ectodermal dysplasia
- Ectodermal dysplasia, cleft lip (CL), cleft palate (CP)
- Ehlers-Danlos
- Ellis-van Creveld
- Focal dermal hypoplasia
- Freire-Maia
- Frontometaphyseal dysplasia
- Goldenhar
- Gorlin
- Gorlin-Chaudhry-Moss
- Hallermann-Streiff
- Hanhart
- Hurler
- Hypoglossia-hypodactylia
- Incontinentia pigmenti
- Johanson-Blizzard
- Lacrimo-auriculo-dento-digital (LADD)
- Lipoid proteinosis
- Marshall-White
- Melanoleukoderma
- Monilethrix-anodontia
- Oral-facial-digital type I
- Otodental dysplasia
- Palmoplantar keratosis, hypotrichosis, cysts of eyelid
- Progeria
- Rieger
- Robinson
- Rothmund-Thomson
- Sturge-Weber
- Tooth-and-nail
- Turner
- Wilkie

• BOX 2-9 Syndromes Associated with Hyperdontia

- Apert
- Cleidocranial dysplasia
- Craniometaphyseal dysplasia
- Crouzon
- Curtius
- Down
- Ehlers-Danlos
- Ellis-van Creveld
- Fabry-Anderson
- Fucosidosis
- Gardner
- Hallermann-Streiff
- Incontinentia pigmenti
- Klippel-Trénaunay-Weber
- Laband
- Leopard
- Nance-Horan
- Oral-facial-digital types I and III
- Sturge-Weber
- Tricho-rhino-phalangeal

Genetic control appears to exert a strong influence on the development of teeth. Hypodontia and hyperdontia have been noted in patients with a variety of syndromes (Boxes 2-8 and 2-9). In all of these syndromes, an increased prevalence of hypodontia or hyperdontia exists, but the strength of the association varies. Furthermore, the actual genetic contribution to the increased or decreased number of teeth may be unclear in some of these conditions. In addition to these syndromes, an increased prevalence of hypodontia is noted in patients with nonsyndromic cleft lip (CL) or cleft palate (CP).

Genetic influences still may affect nonsyndromic numeric alterations of teeth, because more than 200 genes are known to play a role in odontogenesis. Because of the complexity of the system, variations in tooth number arise in a wide variety of patterns. A large percentage of primary hypodontia cases appear to be inherited in an autosomal dominant fashion, with incomplete penetrance and variable expressivity, whereas a minority of examples presents an autosomal recessive or sex-linked pattern. The environment is not without its influence, with occasional examples suggesting multifactorial inheritance. Several investigators have reported variable expression of hypodontia in monozygotic twins (confirmed by DNA fingerprinting). This discordance confirms the occasional multifactorial nature of the process. Overall, hypodontia most likely represents a variety of disorders caused by variable genetic and epigenetic factors.

Research has identified a gene mutation in only a small percentage of nonsyndromic hypodontia cases. Although this list will continue to lengthen over time, the most frequently implicated genes include the *PAX9* gene, the *MSX1* gene, and the *AXIN2* gene. Other mutations mentioned less frequently include the He-Zhao deficiency and the *EDA*, *WNT10A*, and the *LTBP3* genes. Although variable expressivity is common, most of these examples represent oligodontia and exhibit numerous missing teeth. Interestingly, the affected gene tends to correlate to the pattern of missing teeth. It must be stressed that these genes are involved in only a very small number of affected patients with hypodontia, and the genetic basis for the vast majority of hypodontia cases remains elusive.

Less information is available on the genetics of hyperdontia; however, like hypodontia, almost every possible pattern of inheritance has been suggested. In all likelihood, many cases are multifactorial and arise from a combination of genetics and environmental influences. In spite of this, studies on certain kindreds have suggested an autosomal dominant pattern of inheritance with incomplete penetrance, autosomal recessive inheritance with lesser penetrance in females, and X-linked inheritance.

Some investigators have implied that hypodontia is a normal variant, suggesting that humans are in an

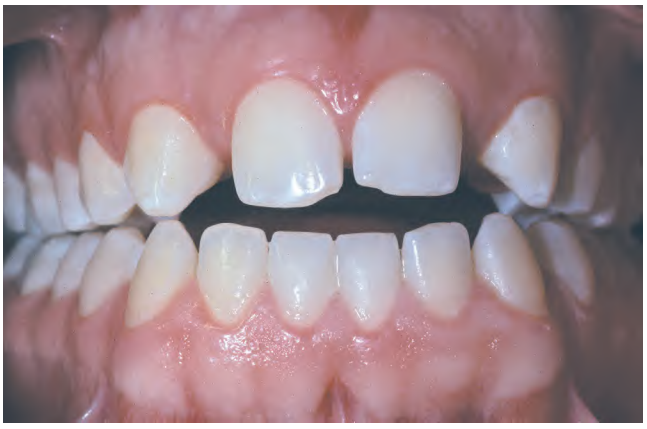
intermediate stage of dentitional evolution. A proposed future dentition would contain one incisor, one canine, one premolar, and two molars per quadrant. Conversely, others have suggested that hyperdontia represents atavism—the reappearance of an ancestral condition. The latter hypothesis is difficult to accept because some patients have had as many as four premolars in one quadrant, a situation that has never been reported in other mammals. The most widely accepted theory is that hyperdontia is the result of a localized and independent hyperactivity of dental lamina.

In contrast, hypodontia correlates with the absence of appropriate dental lamina. As discussed, the loss of the developing tooth buds in most instances appears to be genetically controlled. In spite of this, the environment most likely influences the final result or, in some cases, may be responsible completely for the lack of tooth formation. The dental lamina is extremely sensitive to external stimuli, and damage before tooth formation can result in hypodontia. Trauma, infection, radiation, chemotherapeutic medications, endocrine disturbances, and severe intrauterine disturbances have been associated with missing teeth.

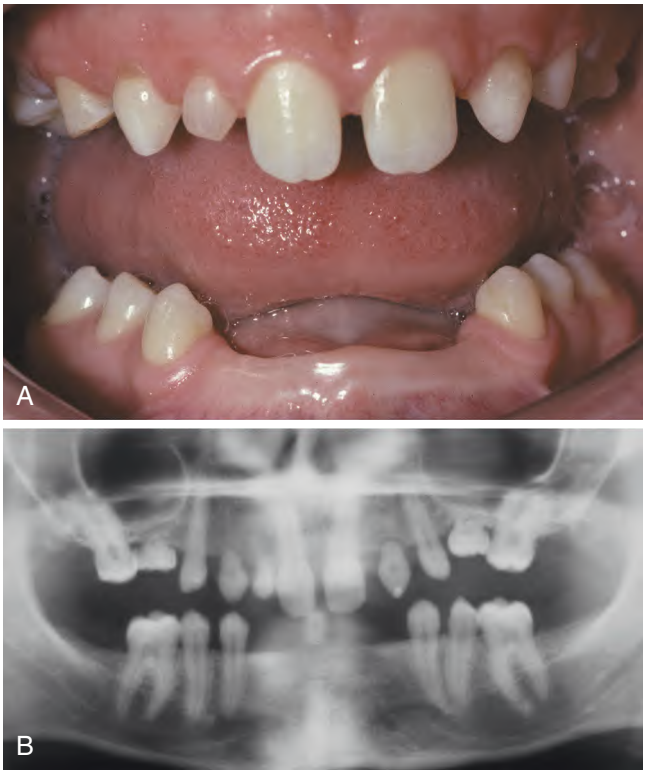
Clinical Features

Hypodontia

Failure of teeth to form is one of the most common dental developmental abnormalities, with a reported prevalence of 3% to 10% in permanent teeth when absence of third molars is excluded. The prevalence increases to 20% if third molars are considered. A female predominance of approximately 1.5 : 1 is reported. Anodontia is rare, and most cases occur in the presence of hereditary hypohidrotic ectodermal dysplasia (see page 690). Indeed, when the number of missing teeth is high or involves the most stable teeth (i.e., maxillary central incisors or first molars), the patient should be evaluated for ectodermal dysplasia. **Hypodontia** is uncommon in the deciduous dentition with a prevalence of less than 1%. Absence of a deciduous tooth is associated strongly with an increased prevalence of a missing successor. Missing teeth in the permanent dentition are not rare, with third molars being the most commonly affected. After the molars, the second premolars and lateral incisors are absent most frequently (Fig. 2-40). The teeth least likely to be missing are the maxillary central incisors and mandibular first molars and canines. In Caucasians with missing teeth, approximately 80% demonstrate loss of only one or two teeth. Ethnic differences have been documented, with Japanese and Chinese populations more frequently having absent mandibular central incisors when compared to Caucasians. In contrast, when compared to Caucasians, American blacks demonstrate a significantly decreased prevalence of hypodontia and a reduced average number of missing teeth per individual. In the deciduous dentition, 90% of missing teeth involve the maxillary lateral incisors and mandibular incisors. Hypodontia is associated positively with microdontia (see page 76), reduced alveolar development, increased freeway space, anterior malocclusion, and retained primary teeth (Fig. 2-41).



• **Fig. 2-40 Hypodontia.** Developmentally missing maxillary lateral incisors. Radiographs revealed no underlying teeth, and there was no history of trauma or extraction.



• **Fig. 2-41 Hypodontia. A,** Multiple developmentally missing permanent teeth and several retained deciduous teeth in a female adult. **B,** The panoramic radiograph shows no unerupted teeth in either jaw.

Mutation of the *PAX9* gene creates an autosomal dominant pattern of oligodontia that can involve various teeth but most commonly affects most of the permanent molars. In severe cases, loss of the primary molars, second premolars, and permanent mandibular central incisors also may be seen. Mutation of the *MSX1* gene also is inherited as an autosomal dominant trait. Those affected with this mutation tend to demonstrate loss of the distal tooth of each type, with more severely affected individuals also revealing anterior progression of the agenesis. In these patients, the most commonly missing teeth are the second premolars and third molars. In more severe cases, often the maxillary first

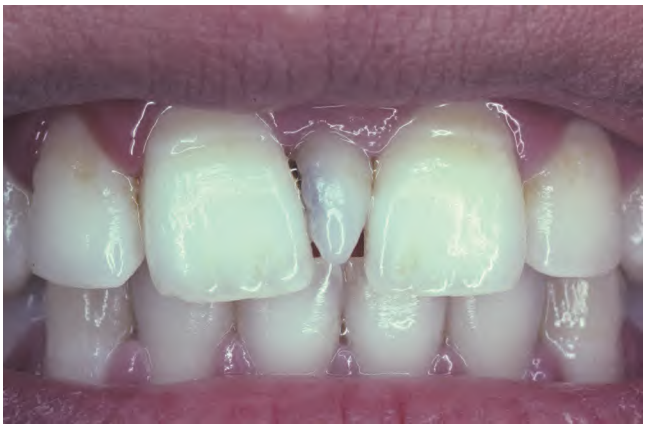
premolars and maxillary lateral incisors also are missing. With the *MSX1* mutation, the degree of oligodontia is severe with an average of approximately 12 missing teeth per patient. The He-Zhao deficiency arose in a large kindred from northwest China, whereas the *LTBP3* gene was discovered in a Pakistani. Both of these genes are associated with a highly variable pattern of missing teeth. The *EDA* gene is associated with a nonsyndromic X-linked pattern of hypodontia, which primarily affects the maxillary and mandibular central incisors, lateral incisors, cuspids, and premolars. Hypodontia associated with nonsyndromic mutation of the *WNT10A* gene appears limited to maxillary and mandibular lateral incisors and second premolars.

For dentists and their patients, the most critical discovery related to hypodontia revolves around the mutation of the *AXIN2* gene. This pattern of oligodontia is inherited as an autosomal dominant disorder, with the most commonly missing teeth being the permanent second and third molars, second premolars, lower incisors, and maxillary lateral incisors. The maxillary central incisors always are present and usually accompanied by the canines, first premolars, and first molars. However, the number and type of missing teeth are highly variable, a typical finding of inheritable oligodontia. Although the missing teeth can produce a significant oral problem, the presence of the *AXIN2* mutation in these kindreds also has been associated with development of adenomatous polyps of the colon and colorectal carcinoma. This suggests that patients with similar examples of oligodontia should be questioned closely for a family history of colon cancer, with further medical evaluation recommended for those possibly at risk.

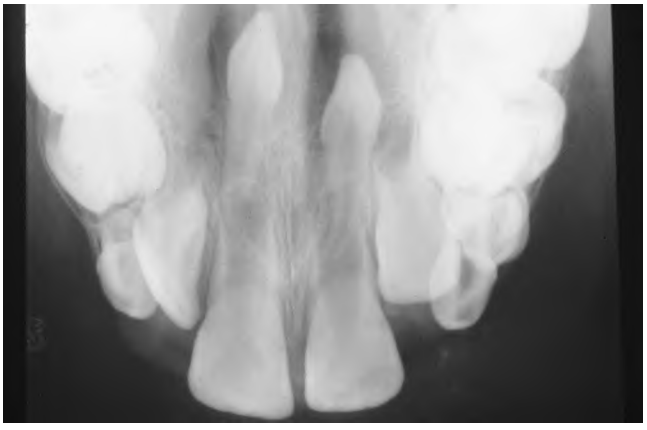
Even in kindreds with an obviously inherited pattern of hypodontia or oligodontia, it must be stressed that, in the majority of the cases, the genes are yet to be discovered.

Hyperdontia

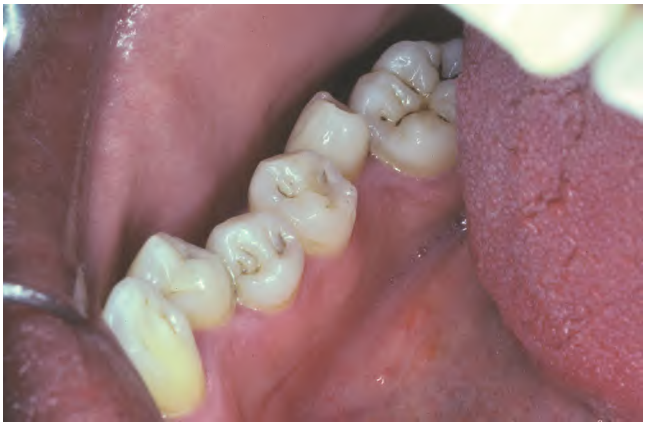
The prevalence of supernumerary permanent teeth in whites is between 0.1% and 3.8%, with a slightly higher rate seen in Asian populations. Although limited data is available, the prevalence in American blacks appears significantly higher with reports documenting an increased frequency up to nine times that seen in whites. The frequency in the deciduous dentition is much lower and varies from 0.3% to 0.8%. Approximately 76% to 86% of cases represent single-tooth **hyperdontia,** with two supernumerary teeth noted in 12% to 23%, and three or more extra teeth noted in less than 1% of cases. Single-tooth hyperdontia occurs more frequently in the permanent dentition, and approximately 95% present in the maxilla, with a strong predilection for the anterior region. However, these widely-accepted data appear to be associated with a strong racial bias. Limited prevalence studies in American blacks reveal that fourth molars are the most common extra teeth, with a comparatively low frequency of supernumerary incisors. When all prevalence studies are combined, the most common site is the maxillary incisor region, followed by maxillary fourth molars and mandibular fourth molars, premolars, canines, and lateral incisors (Fig. 2-42). Supernumerary mandibular incisors are very rare. Although supernumerary teeth may be bilateral, most occur unilaterally (Fig. 2-43). In contrast to single-tooth hyperdontia, nonsyndromic multiple supernumerary teeth occur most frequently in the mandible. These multiple supernumerary teeth occur most often in the premolar region, followed by the molar and anterior regions, respectively (Fig. 2-44).



• **Fig. 2-42 Hyperdontia (Mesiodens).** Erupted supernumerary, rudimentary tooth of the anterior maxilla.



• **Fig. 2-43 Hyperdontia (Mesiodens).** Bilateral inverted supernumerary teeth of the anterior maxilla.



• **Fig. 2-44 Hyperdontia.** Right mandibular dentition exhibiting four erupted bicuspids.

Although most supernumerary teeth occur in the jaws, examples have been reported in the gingiva, maxillary tuberosity, soft palate, maxillary sinus, sphenomaxillary fissure, nasal cavity, and between the orbit and the brain. The eruption of accessory teeth is variable and dependent on the degree of space available; 75% of supernumerary teeth in the anterior maxilla fail to erupt. Unlike hypodontia, hyperdontia is positively correlated with macrodontia (see page 76) and exhibits a 2 : 1 male predominance. Although examples may be identified in older adults, most supernumerary teeth develop during the first two decades of life.

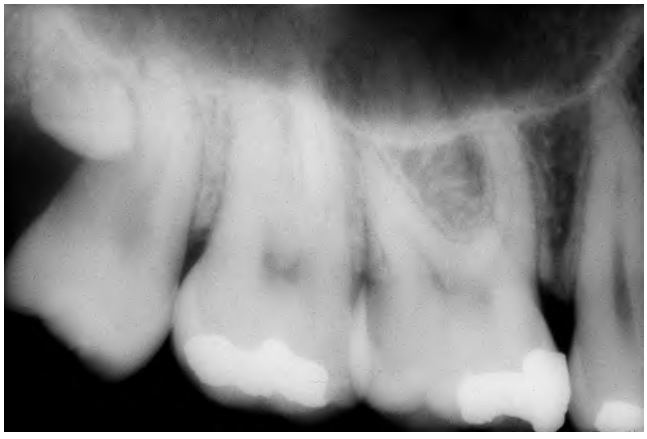
Several terms have been used to describe supernumerary teeth, depending on their location. A supernumerary tooth in the maxillary anterior incisor region is termed a **mesiodens** (see Fig. 2-42); an accessory fourth molar is often called a **distomolar** or **distodens** (Fig. 2-45). A posterior supernumerary tooth situated lingually or buccally to a molar tooth is termed a **paramolar** (Fig. 2-46).

Supernumerary teeth are divided into **supplemental** (normal size and shape) or **rudimentary** (abnormal shape and smaller size) types. Rudimentary supernumerary teeth are classified further into **conical** (small, peg-shaped), **tuberculate** (barrel-shaped anterior with more than one cusp), and **molariform** (small premolar-like or molar-like). Although odontomas are considered hamartomas and could be placed within this classification, these lesions traditionally are included in the list of odontogenic neoplasms and are discussed in Chapter 15 (page 674). The conical mesiodens represents one of the more common supernumerary teeth and can erupt spontaneously, whereas tuberculate examples are less frequent and rarely erupt.

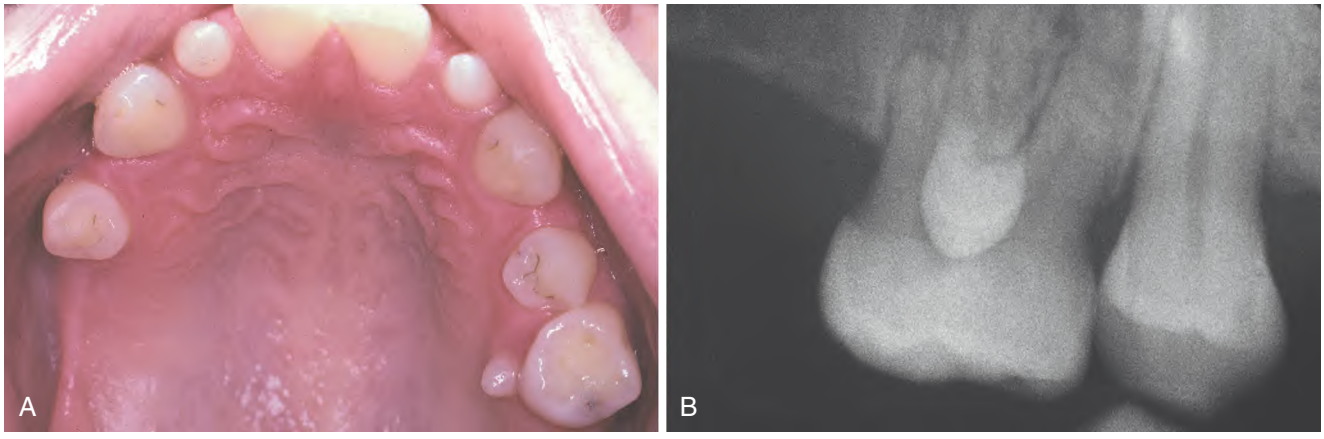
On rare occasions, an affected patient can present with both hypodontia and hyperdontia, which has been termed **hypohyperdontia.** The process most commonly involves missing mandibular incisors followed by second premolars; in contrast, supernumerary teeth are seen most frequently in the anterior maxilla followed by supplemental canines or maxillary premolars.

Occasionally, normal teeth may erupt into an inappropriate position (e.g., a canine present between two premolars). This pattern of abnormal eruption is called **dental transposition.** Such misplaced teeth have been confused with supernumerary teeth; but in reality, patients exhibiting dental transposition have been reported to exhibit an increased prevalence of hypodontia, not hyperdontia. The teeth involved most frequently in transposition are the maxillary canines and first premolars (Fig. 2-47). Crowding or malocclusion of these normal teeth may dictate reshaping, orthodontics, or extraction.

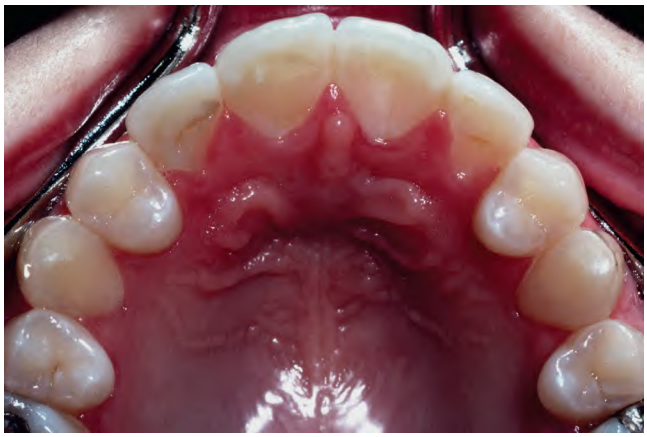
Accessory teeth may be present at or shortly after birth. Historically, teeth present in newborns have been called **natal teeth;** those arising within the first 30 days of life are designated **neonatal teeth.** This is an artificial distinction, and it appears appropriate to call all of these teeth *natal teeth* (Fig. 2-48). Although some authors have suggested that these teeth may represent predeciduous supernumerary teeth, most are prematurely erupted deciduous teeth (not supernumerary teeth). Approximately 85% of natal teeth are mandibular incisors, 11% are maxillary incisors, and 4% are posterior teeth.



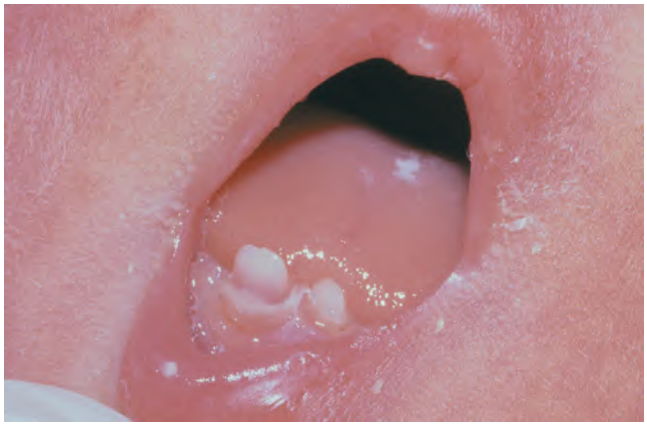
• **Fig. 2-45 Hyperdontia (Distodens).** Supernumerary maxillary fourth molar.



• **Fig. 2-46 Paramolar. A,** Rudimentary tooth situated palatal to a maxillary molar in a patient who also exhibits hypodontia. **B,** Radiograph of the same patient showing a fully formed tooth overlying the crown of the adjacent molar.



• **Fig. 2-47 Dental Transposition.** Maxillary dentition exhibiting cuspids and first bicuspids in inappropriate positions bilaterally. (Courtesy of Dr. Wendy Humphrey.)



• **Fig. 2-48 Natal Teeth.** Mandibular central incisors that were erupted at birth.

Treatment and Prognosis

Sequelae associated with hypodontia include abnormal spacing of teeth, delayed tooth formation, delayed deciduous tooth exfoliation, late permanent tooth eruption, and altered dimension of the associated gnathic regions. The management of the patient with hypodontia depends on the severity of the case. No treatment may be required for a single missing tooth; prosthetic replacement often is needed when multiple teeth are absent. Therapeutic options include removable partial dentures, traditional fixed prosthodontics, resin-bonded bridges, or osseointegrated implants with associated prosthetic crowns. Use of fixed prosthodontics typically is not recommended for children because of the risk of pulp exposure during abutment preparation and because further growth can lead to infraocclusion and ankylosis of teeth held together by the prosthesis. Likewise, because implants act more like ankylosed teeth than erupting teeth, their use is not recommended before completion of skeletal growth except for patients with anodontia. For these reasons, a removable appliance or resin-bonded bridge often is appropriate in children and young adults while waiting for full dental and skeletal maturation.

In some cases of hypodontia, orthodontic therapy may improve the restorative treatment or even negate its need in selected patients. Patients with oligodontia exhibit an increased prevalence of orthodontics-associated external root resorption. This may be due to the altered root anatomy or to the extensive tooth movement that is required in some patients. Follow-up radiographs are recommended after 6 to 9 months of therapy to evaluate the root morphology for evidence of excessive resorption.

The presence of supernumerary teeth should be suspected if a significant delay is observed in the eruption of a localized portion of the dentition. Because of the decreased clarity in the anterior portion of a panoramic radiograph, this image should be combined with occlusal and periapical radiographs to fully visualize the area. Supernumerary teeth may develop long after eruption of the permanent dentition. Several publications have documented supernumerary bicuspids arising up to 11 years after completion of normal teeth development. In patients previously diagnosed with supernumerary teeth, or in those genetically predisposed, long-term monitoring for additional tooth development is warranted.

Early diagnosis and treatment often are crucial in minimizing the aesthetic and functional problems of the adjacent teeth. Because only 7% to 20% of supernumerary teeth exist without clinical complications, the standard of care is removal of the accessory tooth during the time of the early mixed dentition. Complications created by anterior supernumerary teeth tend to be more significant than those associated with extra teeth in the posterior regions. Reports have documented spontaneous eruption of the adjacent dentition in 75% of the cases if the supernumerary tooth is removed early. After removal of the supernumerary tooth, full eruption typically occurs within 18 months to 3 years. Impacted permanent teeth having closed apices or those associated with a tuberculate mesiodens may show a reduced tendency for spontaneous eruption. Permanent teeth that fail to erupt are treated best by surgical exposure with orthodontic eruption. Removal of unerupted deciduous teeth is not recommended, because most will erupt spontaneously.

A consequence of late therapy may include the delayed eruption, resorption of the adjacent teeth, displacement of the teeth with associated crowding, dilaceration, malocclusion, diastema formation, or eruption into the nasal cavity. Supernumerary teeth also predispose the area to subacute pericoronitis, gingivitis, periodontitis, abscess formation, and the development of any one of a large number of odontogenic cysts and tumors. In selected cases, clinical judgment may not dictate surgical removal, or patient resistance to therapy may be present. In these instances, regular monitoring is appropriate.

A study attempting to determine the optimum time for removal of mesiodentes in a pediatric population suggested that removal after age 10 was associated with a higher prevalence of developmental defects of the adjacent permanent teeth such as dilaceration and root resorption. Although a cautious surgical approach is necessary to avoid damage to the adjacent developing incisor, removal of mesiodentes

prior to 6 to 7 years of age appears advantageous in decreasing local developmental complications.

Natal teeth must be approached individually with sound clinical judgment guiding appropriate therapy. Radiographs may be difficult to obtain but could be helpful in distinguishing premature eruption of a deciduous tooth from a supernumerary tooth. As stated, the erupted teeth in most cases represent the deciduous dentition, and removal should not be performed hastily. If the teeth are mobile and at risk for aspiration, removal is indicated. The surgical procedure must ensure complete removal of the associated dental papillae and epithelial root sheath to prevent formation of residual root fragments. If mobility is not a problem and the teeth are stable, then they should be retained. Traumatic ulcerations of the adjacent soft tissue **(Riga-Fede disease)** (see page 260) may occur during breast feeding but often can be resolved with appropriate measures.

◆ DEVELOPMENTAL ALTERATIONS IN THE SIZE OF TEETH

Tooth size is variable among different races and between the sexes. The presence of unusually small teeth is termed **microdontia;** the presence of teeth larger than average is termed **macrodontia.** Although heredity is the major factor, both genetic and environmental influences affect the size of developing teeth. The deciduous dentition appears to be affected more by maternal intrauterine influences; the permanent teeth seem to be more affected by environment.

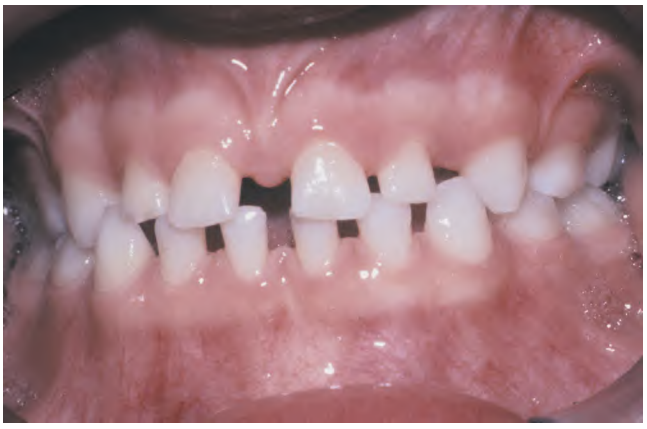
Clinical Features

Although the size of teeth is variable, the two sides of the jaws are usually symmetrical. Despite this, when significant size variation is present, the entire dentition rarely is affected. Typically, only a few teeth are altered significantly in size. Differences in tooth sizes cannot be considered in isolation. Microdontia is associated strongly with hypodontia (see page 72); macrodontia often is seen in association with hyperdontia (see page 73). Females demonstrate a higher frequency of microdontia and hypodontia; males have a greater prevalence of macrodontia and hyperdontia.

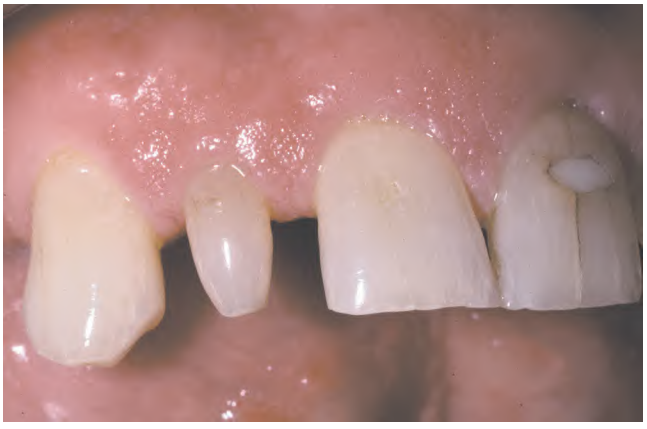
Microdontia

The term **microdontia** should be applied only when the teeth are physically smaller than usual. Normal-sized teeth may appear small when widely spaced within jaws that are larger than normal. This appearance has been historically termed **relative microdontia,** but it represents **macrognathia** (not microdontia). Diffuse true microdontia is uncommon but may occur as an isolated finding in Down syndrome, in pituitary dwarfism, and in association with a small number of rare hereditary disorders that exhibit multiple abnormalities of the dentition (Fig. 2-49).

Isolated microdontia within an otherwise normal dentition is not uncommon. The maxillary lateral incisor is affected most frequently and typically appears as a peg-shaped crown overlying a root that often is of normal length (Fig. 2-50). The mesiodistal diameter is reduced, and the proximal surfaces converge toward the incisal edge. The reported prevalence varies from 0.8% to 8.4% of the population, and the alteration appears to be autosomal dominant with incomplete penetrance. In addition, isolated microdontia often affects third molars. Interestingly, the maxillary lateral incisors and the third molars are among the most frequent teeth to be congenitally missing. When a peg-shaped tooth is present, the remaining permanent teeth often exhibit a slightly smaller mesiodistal size.



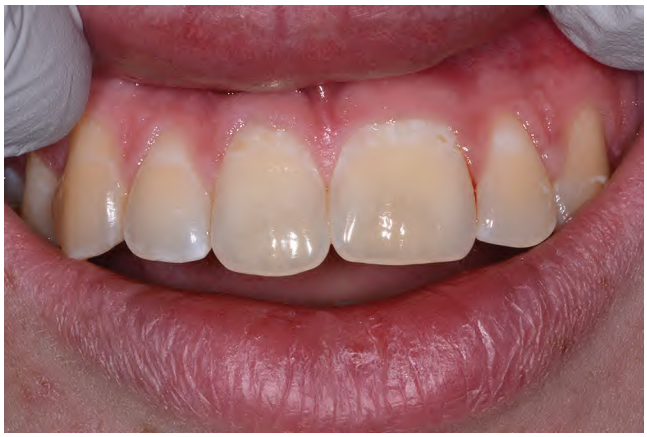
• **Fig. 2-49 Diffuse Microdontia.** Dentition in which the teeth are smaller than normal and widely spaced within the arch.



• **Fig. 2-50 Isolated Microdontia (Peg Lateral).** Small, cone-shaped right maxillary lateral incisor.

Macrodontia

Analogous to microdontia, the term **macrodontia (megalodontia, megadontia)** should be applied only when teeth are physically larger than usual and should not include normal-sized teeth crowded within a small jaw (previously termed **relative macrodontia**). In addition, the term *macrodontia* should not be used to describe teeth that have been altered by fusion or gemination. Diffuse involvement is rare, and typically only a few teeth are abnormally large. Diffuse macrodontia has been noted in association with pituitary gigantism (see page 775), otodental syndrome, XYY males,



• **Fig. 2-51 Macrodontia.** The patient's left maxillary central incisor is abnormally large. (Courtesy of Dr. Peter Fam.)

and pineal hyperplasia with hyperinsulinism. Macrodontia with unilateral premature eruption is not rare in hemifacial hyperplasia (see page 35). Authors have postulated that the unilateral bone growth resulting from this condition may also affect developing teeth on the altered side. Isolated macrodontia is reported to occur most frequently in incisors or canines but also has been seen in second premolars and third molars (Fig. 2-51). In such situations, the alteration often occurs bilaterally.

Treatment and Prognosis

Treatment of the dentition is not necessary unless desired for aesthetic considerations. Maxillary peg laterals often are restored to full size by porcelain crowns.

◆ DEVELOPMENTAL ALTERATIONS IN THE SHAPE OF TEETH

GEMINATION, FUSION, AND CONCRESCENCE

Double teeth (connate teeth, conjoined teeth) are two separate teeth exhibiting union by dentin and (perhaps) their pulps. The union may be the result of fusion of two adjacent tooth buds or the partial splitting of one into two. The development of isolated large or joined (i.e., double) teeth is not rare, but the literature is confusing when the appropriate terminology is presented. Historically, *gemination* was defined as an attempt of a single tooth bud to divide, with the resultant formation of a tooth with a bifid crown and, usually, a common root and root canal. Conversely, *fusion* was considered the union of two normally separated tooth buds with the resultant formation of a joined tooth with confluence of dentin. Finally, *concrescence* was the union of two teeth by cementum without confluence of the dentin.

Many investigators have found these definitions confusing and open to debate. A double tooth found in the place of a maxillary permanent central incisor is a good example of the controversy. If the joined tooth is counted as one and the tooth number is correct, then the anomaly could result from the division of a single tooth bud or the fusion of the permanent tooth bud with the bud of an adjacent mesiodens. Some have suggested that the terms *gemination, fusion,* and *concrescence* should be discontinued, and all of these anomalies should be termed *twinning*. This also is confusing because other investigators use *twinning* to refer to the development of two separate teeth that arose from the complete separation of one tooth bud (this also is arguable).

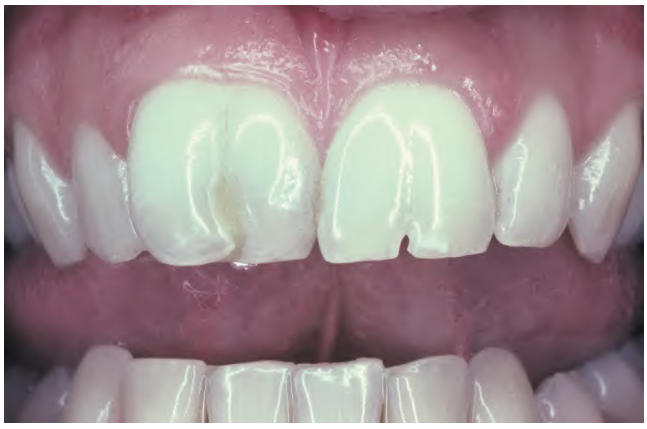
Because of this confusion in terminology, the use of the term *twinning* cannot be recommended. Extra teeth are termed **supernumerary,** and another name is not necessary. Even though the exact pathogenesis may be questionable in some cases (whether caused by fusion of adjacent buds or partial split of one bud), the terms *gemination, fusion,* and *concrescence* serve a useful purpose because they are the most descriptive of the clinical presentation. **Gemination** is defined as a single enlarged tooth or joined (i.e., double) tooth in which the tooth count is normal when the anomalous tooth is counted as one. **Fusion** is defined as a single enlarged tooth or joined (i.e., double) tooth in which the tooth count reveals a missing tooth when the anomalous tooth is counted as one. **Concrescence** is union of two adjacent teeth by cementum alone, without confluence of the underlying dentin. Unlike fusion and gemination, concrescence may be developmental or postinflammatory. When two teeth develop in close proximity, developmental union by cementum is possible. In addition, areas of inflammatory damage to the roots of teeth are repaired by cementum once the inciting process resolves. Concrescence of adjacent teeth may arise in initially separated teeth in which cementum deposition extends between two closely approximated roots in a previous area of damage.

Clinical Features

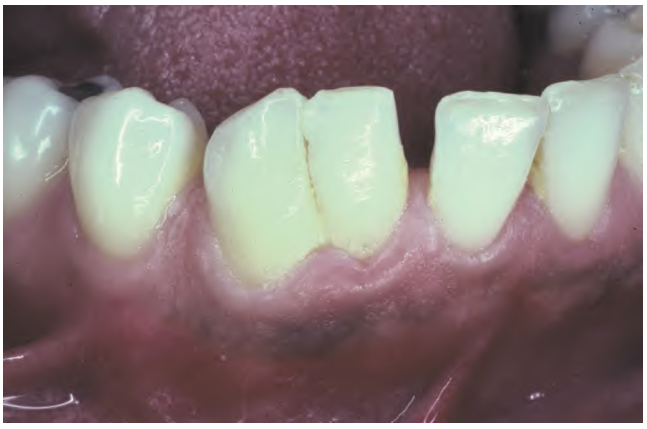
Gemination and Fusion

Double teeth **(gemination** and **fusion)** occur in both the primary and the permanent dentitions, with a higher frequency in the anterior and maxillary regions (Figs. 2-52 to 2-56). In the permanent dentition, the prevalence of double teeth in whites is approximately 0.3% to 0.5%, whereas the frequency in deciduous teeth is greater, with a reported prevalence from 0.5% to 2.5%. Asian populations tend to demonstrate a higher occurrence that exceeds 5% in some studies. In both dentitions, incisors and canines are the most commonly affected teeth. Involvement of posterior primary teeth, premolars, and permanent molars also can occur. Gemination is more common in the maxilla, whereas fusion tends to occur more frequently in the mandible. Bilateral cases are uncommon (Fig. 2-57).

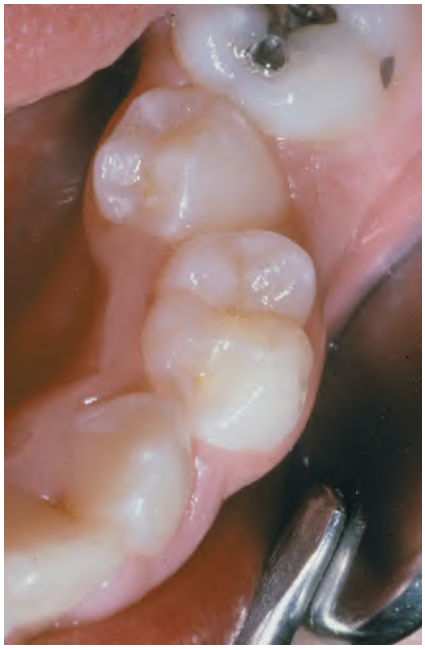
Gemination and fusion appear similar and may be differentiated by assessing the number of teeth in the dentition. Some authors have suggested that gemination demonstrates a single root canal. Separate canals are present in fusion, but this does not hold true in all cases (Fig. 2-58). A variety of appearances are noted with both fusion and gemination. The processes may result in an otherwise anatomically correct tooth that is greatly enlarged. A bifid



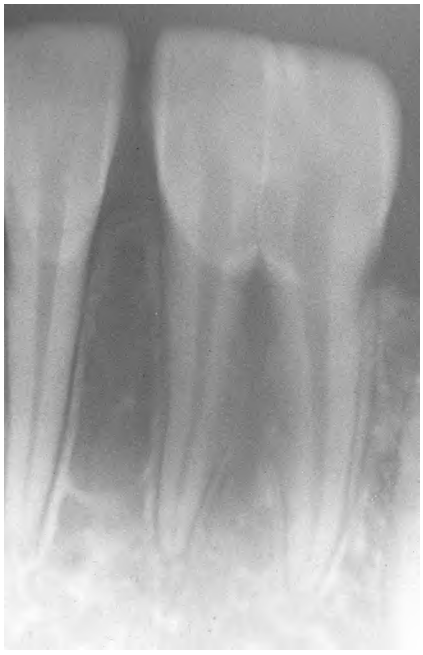
• **Fig. 2-52 Bilateral Gemination.** Two double teeth. The tooth count was normal when each anomalous tooth was counted as one.



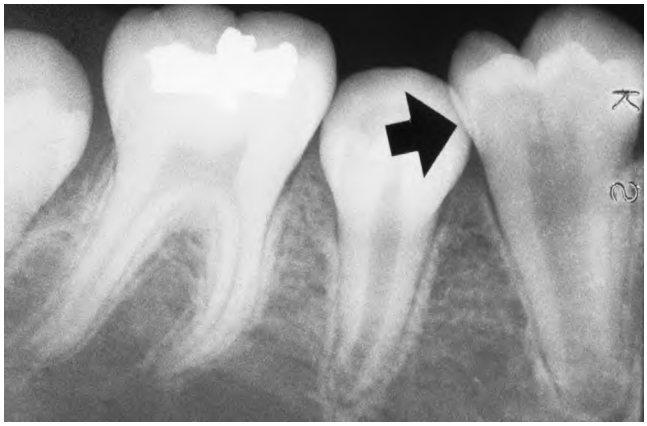
• **Fig. 2-55 Fusion.** Double tooth in the place of the mandibular right lateral incisor and cuspid.



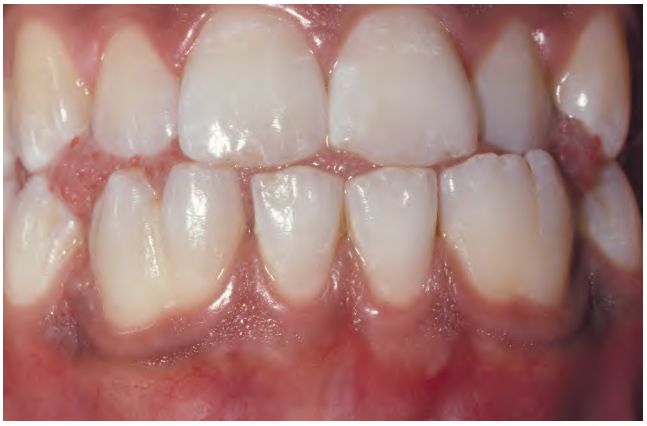
• **Fig. 2-53 Gemination.** Mandibular bicuspid exhibiting bifid crown.



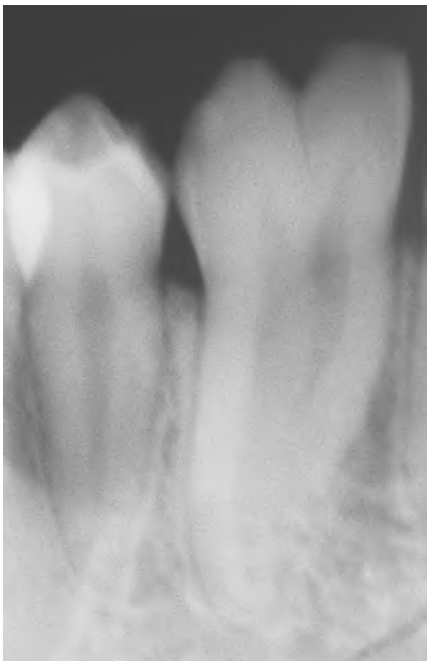
• **Fig. 2-56 Fusion.** Radiographic view of double tooth in the place of the mandibular central and lateral incisors. Note separate root canals.



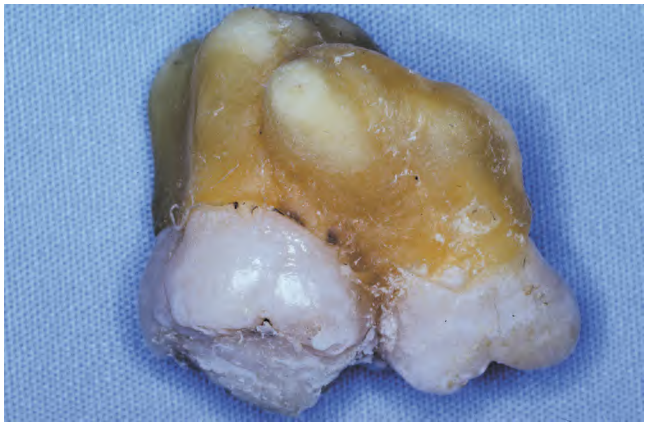
• **Fig. 2-54 Gemination.** Same patient as depicted in Fig. 2-53. Note the bifid crown and shared root canal.



• **Fig. 2-57 Fusion.** Bilateral double teeth in the place of the mandibular lateral incisors and cuspids.



• **Fig. 2-58 Fusion.** Radiograph of the same patient depicted in Fig. 2-57. Note the bifid crown overlying the single root canal; the contralateral radiograph revealed a similar pattern.

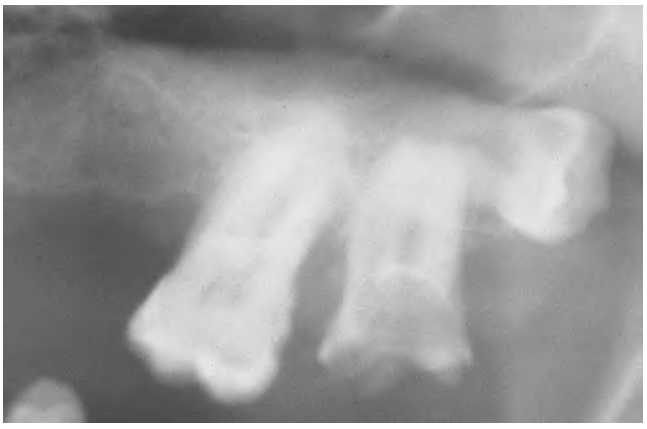


• **Fig. 2-59 Concrescence.** Union by cementum of adjacent maxillary molars.

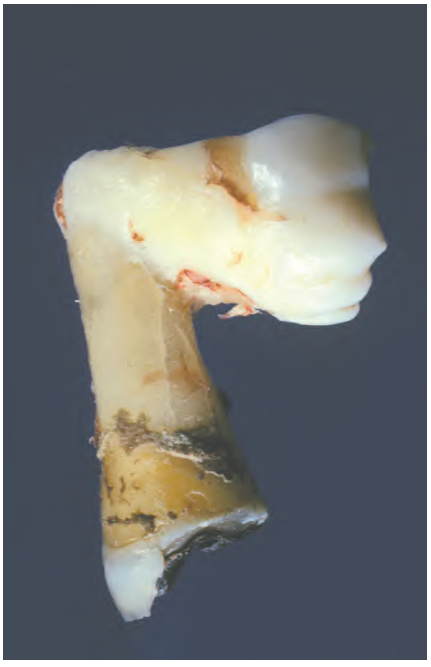
crown may be seen overlying two completely separated roots, or the joined crowns may blend into one enlarged root with a single canal.

Concrescence

Concrescence is two fully formed teeth, joined along the root surfaces by cementum. The process is noted more frequently in the posterior and maxillary regions. The developmental pattern often involves a second molar tooth in which its roots closely approximate the adjacent impacted third molar (Fig. 2-59). The postinflammatory pattern frequently involves carious molars in which the apices overlie the roots of horizontally or distally angulated third molars. This latter pattern most frequently arises in a carious tooth that exhibits large coronal tooth loss. The resultant large pulpal exposure often permits pulpal drainage, leading to a



• **Fig. 2-60 Concrescence.** Union by cementum of maxillary second and third molars. Note the large carious defect of the second molar.



• **Fig. 2-61 Concrescence.** Gross photograph of the same teeth depicted in Fig. 2-60. Histopathologic examination revealed that union occurred in the area of cemental repair previously damaged by a periapical inflammatory lesion.

resolution of a portion of the intrabony pathosis. Cemental repair then occurs (Figs. 2-60 and 2-61).

Treatment and Prognosis

The presence of double teeth (i.e., gemination or fusion) in the deciduous dentition can result in crowding, abnormal spacing, and delayed or ectopic eruption of the underlying permanent teeth. When detected, the progression of eruption of the permanent teeth should be monitored closely by careful clinical and radiographic observation. When appropriate, extraction may be necessary to prevent an abnormality in eruption. Occasionally, fusion in the primary dentition is associated with absence of the underlying permanent successor.

Several approaches are available for the treatment of joined teeth in the permanent dentition, and the treatment of choice is determined by the patient's particular needs. In gemination, if the double teeth have separate pulps, hemisection may be successful without root canal therapy. The separation may be done intraorally or require extraction with extraoral sectioning if the union extends close to the apex. If extraction is necessary, immediate (within 5 minutes) replantation of the desirable half may result in preservation of vitality and long-term survival of the tooth. In double teeth that share a common pulp, endodontic therapy is necessary if sectioning is considered. Selected shaping with or without placement of full crowns has been used in many cases. Other patients exhibit pulpal or coronal anatomic features that are resistant to reshaping and require surgical removal with prosthetic replacement. Double teeth often will demonstrate a pronounced labial or lingual groove that may be prone to develop caries. In such cases, placement of a fissure sealant or composite restoration is appropriate if the tooth is to be retained.

Patients with concrescence often require no therapy unless the union interferes with eruption; then surgical removal may be warranted. Postinflammatory concrescence must be kept in mind whenever extraction is planned for nonvital teeth with apices that overlie the roots of an adjacent tooth. Significant extraction difficulties can be experienced on attempted removal of a tooth that is unexpectedly joined to its neighbor. Surgical separation often is required to complete the procedure without loss of a significant portion of the surrounding bone.

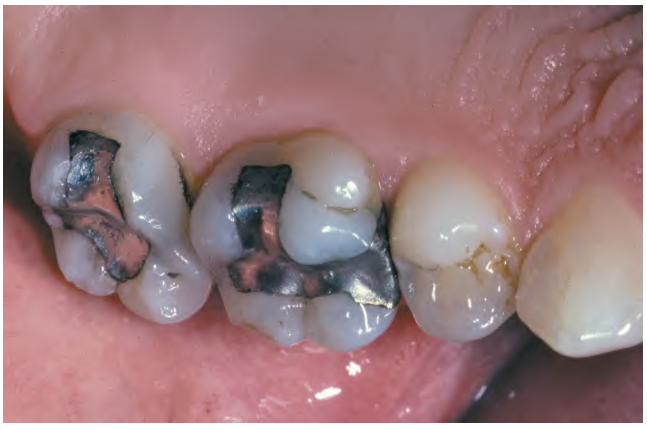
ACCESSORY CUSPS

The cuspal morphology of teeth exhibits minor variations among different populations; of these, three distinctive patterns deserve further discussion: 1) **cusp of Carabelli,** 2) **talon cusp,** and 3) **dens evaginatus.** When an accessory cusp is present, the other permanent teeth often exhibit a slightly increased tooth size.

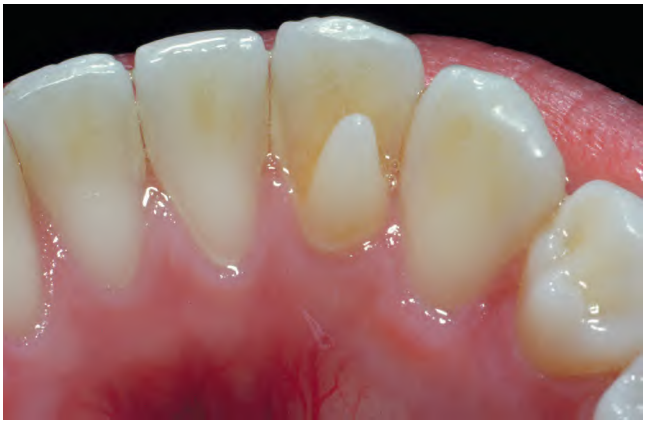
Clinical and Radiographic Features

Cusp of Carabelli

The **cusp of Carabelli** is an accessory cusp located on the palatal surface of the mesiolingual cusp of a maxillary molar (Fig. 2-62). The cusp may be seen in the permanent or deciduous dentitions and varies from a definite cusp to a small indented pit or fissure. When present, the cusp is most pronounced on the first molar and is increasingly less obvious on the second and third molars. When a cusp of Carabelli is present, the remaining permanent teeth often are larger than normal mesiodistally, but a similar association in deciduous tooth size is typically not noted. A significant variation exists among different populations, with the prevalence reported to be as high as 90% in whites and rare in Asians. An analogous accessory cusp is seen occasionally on the mesiobuccal cusp of a mandibular permanent or deciduous molar and is termed a *protostylid.*



• **Fig. 2-62 Cusp of Carabelli.** Accessory cusp on the mesiolingual surface of the maxillary first molar.

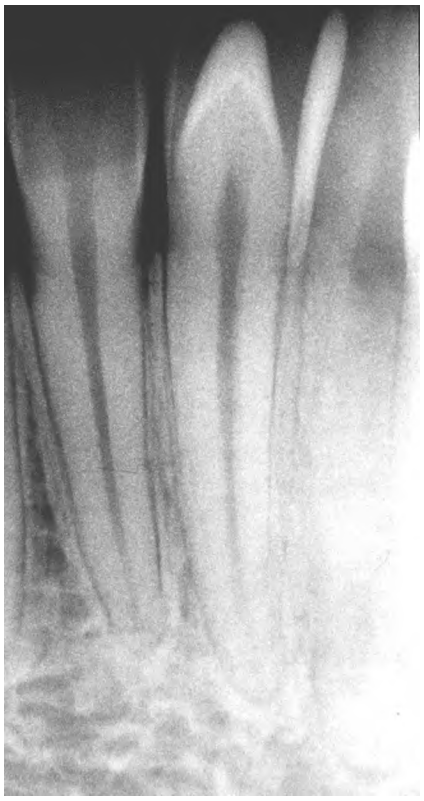


• **Fig. 2-63 Talon Cusp.** Accessory cusp present on the lingual surface of a mandibular lateral incisor.

Talon Cusp

A **talon cusp** is a well-delineated additional cusp that is located on the surface of an anterior tooth and extends at least half the distance from the cementoenamel junction to the incisal edge. A talon cusp is thought to represent the end of a continuum that extends from a normal cingulum, to an enlarged cingulum, to a small accessory cusp, and, finally, to a full-formed talon cusp. Investigators have muddied the literature associated with this spectrum by categorizing all enlarged cingula as talon cusps and developing a classification system for the degree of enlargement. These classification systems make prevalence data difficult to evaluate and should be discouraged.

Three-fourths of all reported talon cusps are located in the permanent dentition. The cusps predominantly occur on permanent maxillary lateral (55%) or central (33%) incisors but have been seen less frequently on mandibular incisors (6%) and maxillary canines (4%) (Fig. 2-63). Their occurrence in the deciduous dentition is very rare, with the vast majority noted on maxillary central incisors. In almost all cases, the accessory cusp projects from the lingual surface of the affected tooth and forms a three-pronged pattern that resembles an eagle's talon. On rare occasions, the cusp may



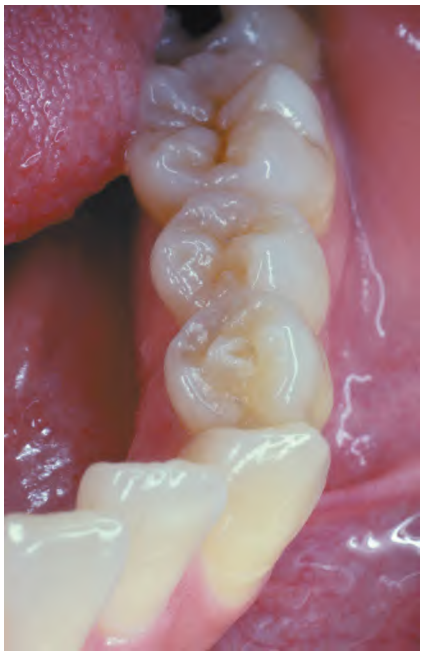
• **Fig. 2-64 Talon Cusp.** Radiograph of same patient shown in Fig. 2-63. Note the enamel and dentin layers within the accessory cusp.

project from the facial surface or from both surfaces of a single tooth. A deep developmental groove may be present where the cusp fuses with the underlying surface of the affected tooth. Most, but not all, talon cusps contain a pulpal extension. Radiographically, the cusp is seen overlying the central portion of the crown and includes enamel and dentin (Fig. 2-64). Only a few cases demonstrate visible pulpal extensions on dental radiographs.

Talon cusps appear to occur more frequently in Asians, Native Americans, the Inuit, and those of Arab descent. Both sexes may be affected, and the occurrence may be unilateral or bilateral. In isolated cases, genetic influences appear to have an effect, because identical talon cusps occasionally have been documented in twins. Talon cusps also have been seen in patients with Rubinstein-Taybi syndrome, Mohr syndrome, Ellis-van Creveld syndrome, incontinentia pigmenti achromians, Berardinelli-Seip syndrome, and Sturge-Weber angiomatosis. Although the strength of association between the presence of talon cusps and these syndromes generally is not clear, Rubinstein-Taybi syndrome is strongly correlated as demonstrated by a study of 45 affected patients in which 92% demonstrated talon cusps.

Dens Evaginatus

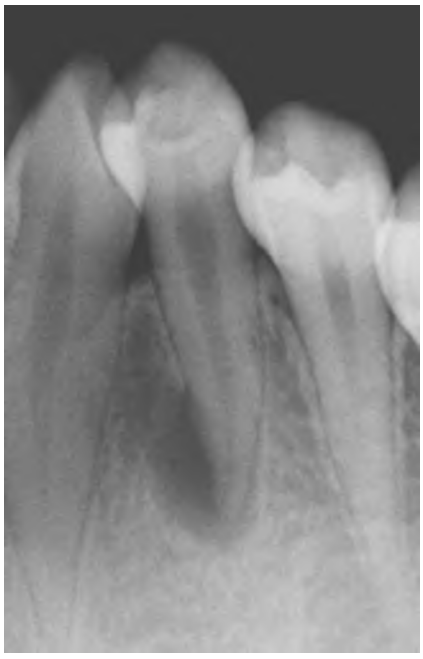
Dens evaginatus (central tubercle, tuberculated cusp, accessory tubercle, occlusal pearl, evaginated odontome, Leong premolar, tuberculated premolar) is a cusplike elevation of enamel located in the central groove or lingual ridge



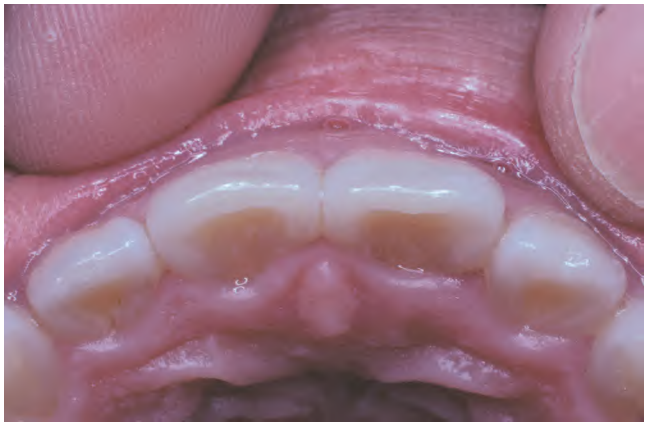
• **Fig. 2-65 Dens Evaginatus.** Cusplike elevation located in the central groove of mandibular first bicuspid.

of the buccal cusp of premolar or molar teeth (Fig. 2-65). Although this pattern of accessory cusps has been reported on molars, dens evaginatus typically occurs on premolar teeth, is usually bilateral, and demonstrates a marked mandibular predominance. Deciduous molars are affected infrequently. The accessory cusp normally consists of enamel and dentin, with pulp present in about half of the cases. Although the prevalence is variable, most reviews suggest a frequency between 1% and 4%. The anomaly is encountered most frequently in Asians, the Inuit, and Native Americans but is rare in whites. Researchers expect an increased prevalence of this anomaly in the United States secondary to immigration by Asians and by Hispanics of mestizo heritage (i.e., those of mixed European and Native American ancestry). Radiographically, the occlusal surface exhibits a tuberculated appearance, and often a pulpal extension is seen in the cusp (Fig. 2-66). The accessory cusp frequently creates occlusal interferences that are associated with significant clinical problems. In one large study, more than 80% of the tubercles were worn or fractured, with pulpal pathosis noted in more than 25% of patients. Pulpal necrosis is common and may occur through a direct exposure or invasion of patent, immature dentinal tubules. In addition to abnormal wear and pulpal pathosis, the accessory cusp also may result in dilaceration, displacement, tilting, or rotation of the tooth.

Frequently, dens evaginatus is seen in association with another variation of coronal anatomy, **shovel-shaped incisors.** This alteration also occurs predominantly in Asians, with a prevalence of approximately 15% in whites but close to 100% in Native Americans and the Inuit. Affected incisors demonstrate prominent lateral margins, creating a hollowed lingual surface that resembles the scoop of a shovel



• **Fig. 2-66 Dens Evaginatus.** Radiograph of teeth depicted in Fig. 2-65. Note the tuberculated occlusal anatomy. Attrition on the accessory cusp led to pulpal necrosis and periapical inflammatory disease.



• **Fig. 2-67 Shovel-Shaped Incisors.** Chinese patient exhibiting maxillary incisors with prominent lateral margins, which create a hollowed lingual surface.

(Fig. 2-67). Typically, the thickened marginal ridges converge at the cingulum; not uncommonly, a deep pit, fissure, or dens invaginatus is found at this junction. Maxillary lateral and central incisors most frequently are affected, with mandibular incisors and canines less commonly reported.

Treatment and Prognosis

Patients with cusps of Carabelli require no therapy unless a deep groove is present between the accessory cusp and the surface of the mesiolingual cusp of the molar. These deep grooves should be sealed to prevent carious involvement.

Patients with talon cusps on mandibular teeth often require no therapy; talon cusps on maxillary teeth frequently interfere with occlusion and should be removed. Other complications include compromised aesthetics, displacement of teeth, caries, periodontal problems, and irritation of the adjacent soft tissue (e.g., tongue or labial mucosa). Because many of these cusps contain pulp, rapid removal often results in pulpal exposure. Removal without the loss of vitality may be accomplished through periodic grinding of the cusp, with time allowed for tertiary dentin deposition and pulpal recession. At the end of each grinding session, the exposed dentin should be coated with a desensitizing agent such as fluoride varnish, which also may speed the rate of pulpal recession. Even with slow reduction and no direct pulp exposure, loss of vitality is possible when large numbers of immature dentin tubules are exposed. After successful removal of the cusp, the exposed dentin can be covered with calcium hydroxide, the peripheral enamel etched, and a composite resin placed.

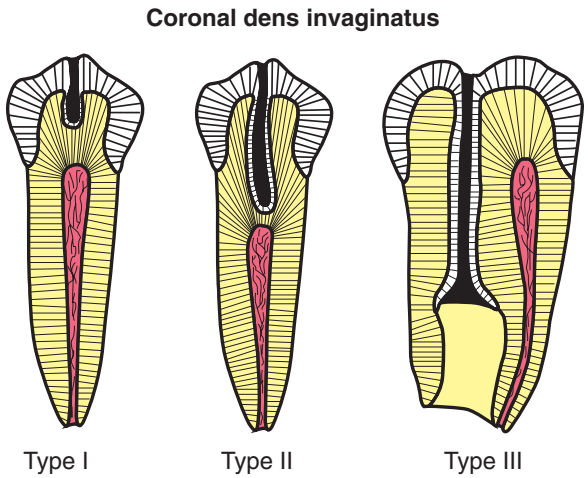
On eruption, the affected tooth should be inspected for the presence of a deep fissure at the junction between the talon cusp and the surface of the tooth. If a fissure is present, it should be restored to avoid early carious extension into the nearby dental pulp. Reports also have documented the continuation of this fissure down the surface of the root, with subsequent development of lateral radicular inflammatory lesions secondary to the access provided to oral flora by the deep groove. In these latter cases, further surgery is required to expose the groove for appropriate cleansing.

Dens evaginatus typically results in occlusal problems and often leads to pulpal death. In affected teeth, removal of the cusp often is indicated, but attempts to maintain vitality have met with only partial success. Slow, periodic grinding of the cusp exposes immature patent dentinal tubules and may lead to irreversible pulpitis without direct exposure. To reduce the chance of pulpal pathosis, elimination of opposing occlusal interferences combined with removal of minimal dentin and treatment of the area with stannous fluoride has been recommended. More rapid cuspal removal with indirect or direct pulp capping also has proven beneficial in some patients. Other investigators support removal of occlusal interferences, protection of the cusp from fracture by the placement of surrounding resin reinforcement, and delaying cuspal removal until evidence of significant dentinal maturation, pulpal recession, and apical root closure are present.

Shovel-shaped incisors should be inspected for surface defects at the point where the marginal ridges converge. Any deep fissures or invaginations should be restored shortly after eruption to prevent carious exposure of the adjacent pulp.

DENS INVAGINATUS (DENS IN DENTE)

Dens invaginatus is a deep surface invagination of the crown or root that is lined by enamel. Oehlers described this condition thoroughly in three classic articles published from 1957 to 1958. Two forms, coronal and radicular, are recognized.



• **Fig. 2-68 Dens Invaginatus.** Illustration depicting the three types of coronal dens invaginatus.

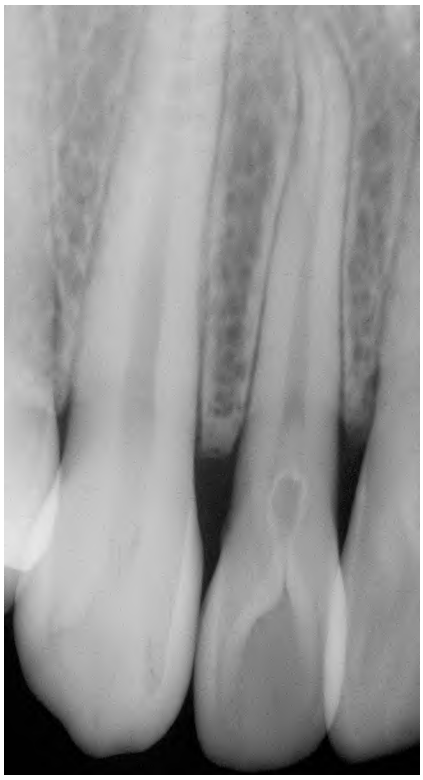
Clinical and Radiographic Features

By a great margin, **coronal dens invaginatus** is seen more frequently; the reported prevalence varies from 0.04% to 10% of all patients. In order of decreasing frequency, the teeth affected most often include the permanent lateral incisors, central incisors, premolars, canines, and molars. Involvement of deciduous teeth has been reported but is uncommon. A strong maxillary predominance is seen.

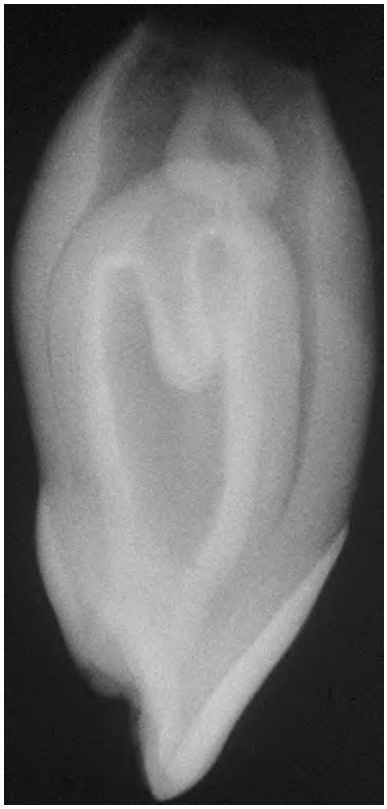
The depth of the invagination varies from a slight enlargement of the cingulum pit to a deep infolding that extends to the apex. As would be expected, before eruption, the lumen of the invagination is filled with soft tissue similar to the dental follicle (i.e., reduced enamel epithelium with a fibrous connective tissue wall). On eruption, this soft tissue loses its vascular supply and becomes necrotic.

Historically, coronal dens invaginatus has been classified into three major types (Fig. 2-68). Type I exhibits an invagination that is confined to the crown. The invagination in type II extends below the cementoenamel junction and ends in a blind sac (Figs. 2-69 and 2-70). Large invaginations may become dilated and contain dystrophic enamel in the base of the dilatation (Fig. 2-71). In some cases, the enamel lining of the invagination is incomplete, and channels communicate between the invagination and the pulp. These connections can result in pulpal necrosis long before the apex has closed. Type III extends through the root and perforates in the apical or lateral radicular area without any immediate communication with the pulp. In this latter type, the enamel that lines the invagination is often replaced by cementum close to the radicular perforation. This perforation provides direct communication from the oral cavity to the intraosseous periradicular tissues and often produces inflammatory lesions in the presence of a vital pulp (Figs. 2-72 and 2-73). Type I is by far the most common pattern (79%) followed by type II (15%) and type III (5%).

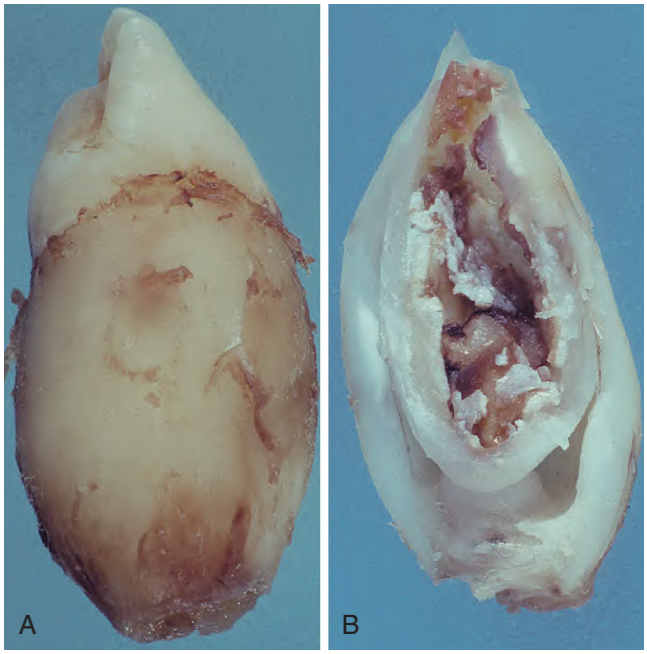
Occasionally, the invagination may be rather large and resemble a tooth within a tooth; hence the term **dens in dente.** In other cases the invagination may be dilated and



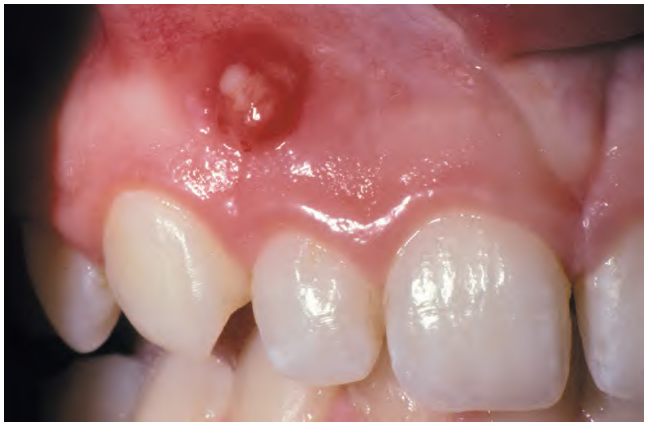
• **Fig. 2-69 Coronal Dens Invaginatus Type II.** Maxillary lateral incisor exhibiting invagination of the surface enamel that extends below the cementoenamel junction.



• **Fig. 2-70 Coronal Dens Invaginatus Type II.** Bulbous maxillary cuspid exhibiting a dilated invagination lined by enamel.



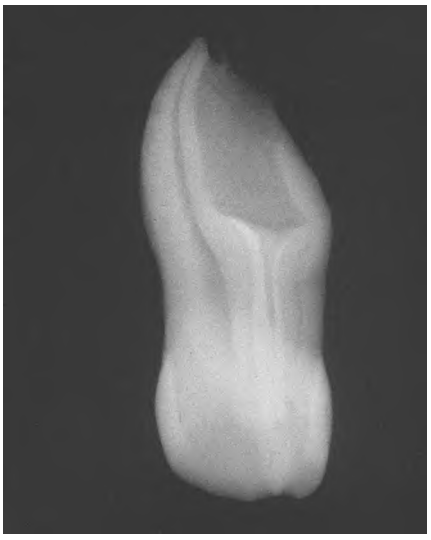
• **Fig. 2-71 Coronal Dens Invaginatus Type II.** Gross photograph of a sectioned tooth. Note the dilated invagination with apical accumulation of dystrophic enamel.



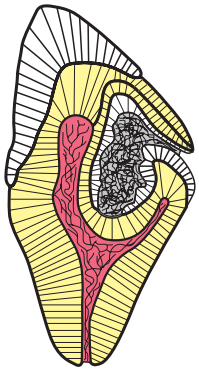
• **Fig. 2-72 Coronal Dens Invaginatus Type III.** Parulis overlying vital maxillary cuspid and lateral incisor. The cuspid contained a dens invaginatus that perforated the mesial surface of its root.

disturb the formation of the tooth, resulting in anomalous tooth development termed **dilated odontome.** Involvement may be singular, multiple, or bilateral.

Radicular dens invaginatus is rare and thought to arise secondary to a proliferation of Hertwig root sheath, with the formation of a strip of enamel that extends along the surface of the root. This pattern of enamel deposition is similar to that frequently seen in association with radicular **enamel pearls** (see Ectopic Enamel). Rather than protrude from the surface (as seen in an enamel pearl), the altered enamel forms a surface invagination into the dental papilla (Fig. 2-74). Cementum-lined invaginations of the root have been reported, but these represent a simple variation of root morphology and should not be included under the term *radicular dens invaginatus.*



• **Fig. 2-73 Coronal Dens Invaginatus Type III.** Maxillary cuspid exhibiting an enamel invagination that parallels the pulp canal and perforates the lateral root surface. (Courtesy of Dr. Brian Blocher.)



• **Fig. 2-74 Radicular Dens Invaginatus.** Illustration depicting the radicular form of dens invaginatus.

Radiographically, the affected tooth demonstrates an enlargement of the root. Close examination often reveals a dilated invagination lined by enamel, with the opening of the invagination situated along the lateral aspect of the root.

Treatment and Prognosis

In small type I invaginations, the opening of the invagination should be restored after eruption in an attempt to prevent carious involvement and subsequent pulpal inflammation. If the invagination is not detected quickly, then pulpal necrosis frequently results. With larger invaginations, the contents of the lumen and any carious dentin must be removed; then a calcium hydroxide base may be placed to help treat any possible microcommunications with the adjacent pulp. In cases with obvious pulpal communication or signs of pulpal pathosis, both the invagination and the adjacent pulp canal require endodontic therapy. In teeth with open apices, apexification with calcium hydroxide or mineral trioxide aggregate often is successful, followed by final obturation.

Type III invaginations associated with periradicular inflammatory lesions require endodontic-like therapy of the perforating invagination. Once again, before final obturation with gutta-percha, temporary placement of calcium hydroxide helps to build dentinal bridges and maintain vitality of the adjacent pulp. If vitality is lost, endodontic therapy of the parallel root canal also becomes necessary. Some cases do not respond to conservative endodontic therapy and require periapical surgery and retrofill. Large and extremely dilated invaginations often have abnormal crowns and need to be extracted.

If the invagination does not significantly disrupt the morphologic appearance of the tooth, then complications of radicular dens invaginatus are rare unless the radicular opening is exposed to the oral cavity. After exposure occurs, carious involvement often leads to pulpal necrosis. Openings close to the anatomic neck of the tooth should be exposed and restored to minimize damage to the tooth and surrounding structures.

ECTOPIC ENAMEL

Ectopic enamel refers to the presence of enamel in unusual locations, mainly the tooth root. The most widely known are **enamel pearls.** These are hemispheric structures that may consist entirely of enamel or contain underlying dentin and pulp tissue. Most enamel pearls project from the surface of the root and are thought to arise from a localized bulging of the odontoblastic layer. This bulge may provide prolonged contact between Hertwig root sheath and the developing dentin, triggering induction of enamel formation. Similar internal projections of enamel into the underlying dentin rarely have been reported in the crowns of teeth.

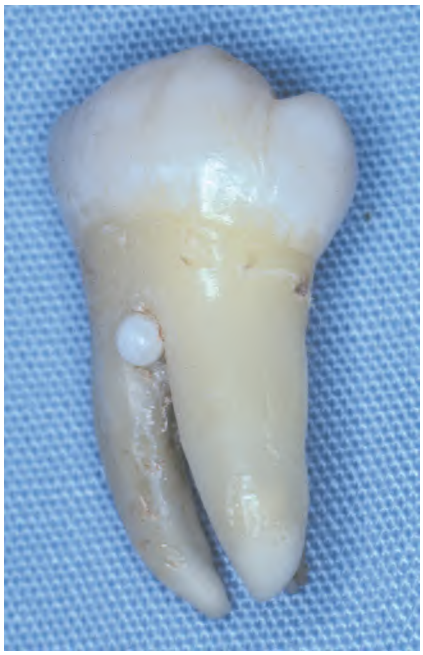
In addition to enamel pearls, **cervical enamel extensions** also occur along the surface of dental roots. These extensions represent a dipping of the enamel from the cementoenamel junction toward the bifurcation of molar teeth. This pattern of ectopic enamel forms a triangular extension of the coronal enamel that develops on the buccal surface of molar teeth directly overlying the bifurcation. The base of the triangle is continuous with the inferior portion of the coronal enamel; the leading point of the triangle extends directly toward the bifurcation of the tooth. These areas of ectopic enamel have been called *cervical enamel projections,* but this terminology is confusing because no significant exophytic projections are seen.

Clinical and Radiographic Features

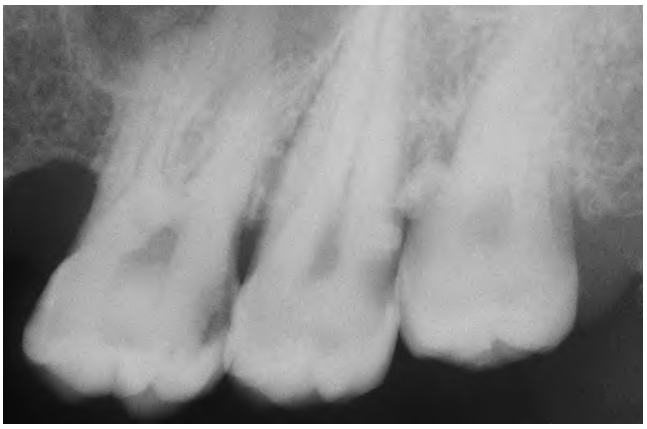
Enamel Pearls

Enamel pearls usually develop on the roots of the maxillary permanent molars followed in prevalence by the mandibular permanent molars. Premolars and incisors rarely are affected. Involvement of deciduous molars has been reported. The prevalence of enamel pearls varies (1.1% to 9.7% of all patients) according to the population studied and is highest in Asians. In most cases, one pearl is found, but as many as four pearls have been documented on a single tooth. The majority occur on the roots at the furcation area or near the cementoenamel junction (Fig. 2-75). Radiographically, pearls appear as well-defined, radiopaque nodules along the root's surface (Fig. 2-76) and can be discerned easily during volumetric CT. Mature internal enamel pearls appear as well-defined circular areas of radiodensity, extending from the dentinoenamel junction (DEJ) into the underlying coronal dentin.

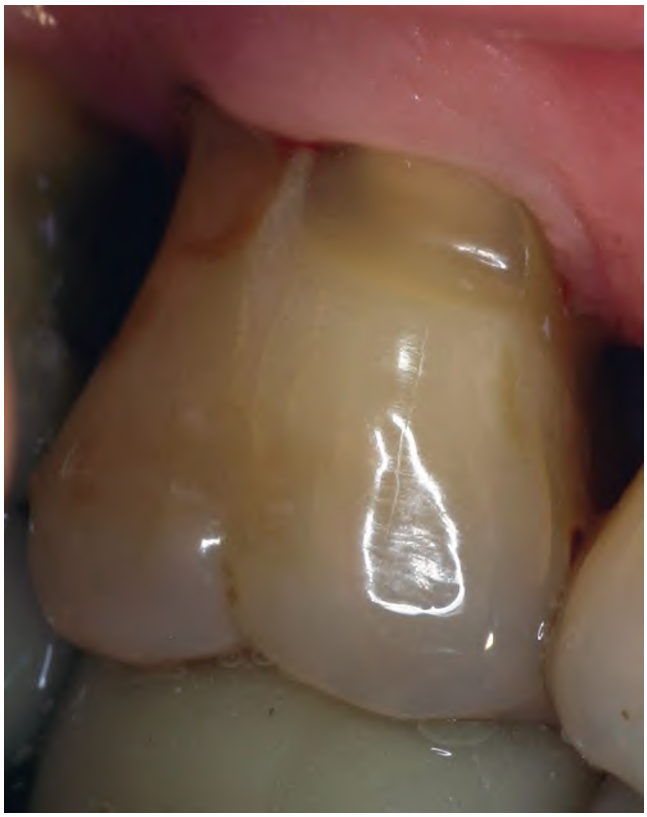
The enamel surface of pearls precludes normal periodontal attachment with connective tissue, and a hemidesmosomal junction probably exists. This junction is less resistant to breakdown; once separation occurs, rapid loss of attachment is likely. In addition, the exophytic nature of the pearl is conducive to plaque retention and inadequate cleansing.



• **Fig. 2-75 Enamel Pearl.** Mass of ectopic enamel located in the furcation area of a molar tooth. (Courtesy of Dr. Joseph Beard.)



• **Fig. 2-76 Enamel Pearl.** Radiopaque nodule on the mesial surface of the root of the maxillary third molar. Another less distinct enamel pearl is present on the distal root of the second molar.

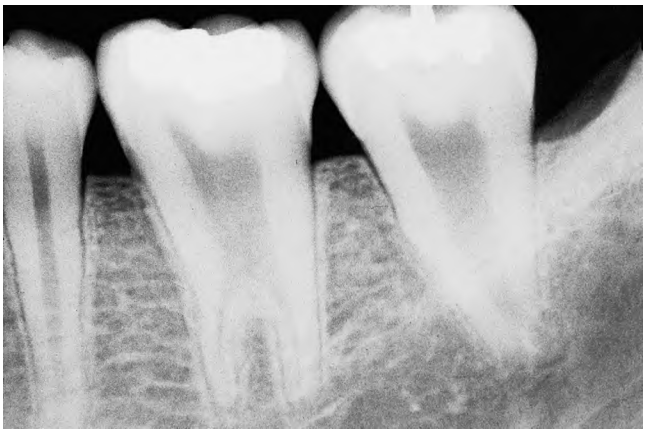


• **Fig. 2-77 Cervical Enamel Extension.** Flat V-shaped extension of enamel into the bifurcation of a maxillary molar. (Courtesy of Dr. Keith Lemmerman.)

Cervical Enamel Extensions

As mentioned previously, **cervical enamel extensions** are located on the buccal surface of the root overlying the bifurcation (Fig. 2-77). Mandibular molars are affected slightly more frequently than maxillary molars. In reviews of extracted teeth in the lower 48 United States, the prevalence is surprisingly high, with approximately 20% of molars being affected. Similar studies demonstrate an even greater prevalence in other locations, such as Japan, China, and Alaska, with cervical enamel extensions discovered in 50% to 78% of extracted molars. Cervical enamel extensions may occur on any molar, but they are seen less frequently on third molars. Because connective tissue cannot attach to enamel, these extensions have been correlated positively with localized loss of periodontal attachment with furcation involvement. On review of a large number of dentitions with periodontal furcation involvement, a significantly higher frequency of cervical enamel extensions was found compared with dentitions without furcation involvement. In addition, the greater the degree of cervical extension, the higher the frequency of furcation involvement.

In addition to periodontal furcation involvement, cervical enamel extensions (in some cases) have been associated with the development of inflammatory cysts that are histopathologically identical to inflammatory periapical cysts. The cysts develop along the buccal surface over the bifurcation and most appropriately are called **buccal bifurcation cysts** (see page 650). The association between cervical enamel extensions and this unique inflammatory cyst is controversial.



• **Fig. 2-78 Taurodontism.** Mandibular molar teeth exhibiting increased pulpal apico-occlusal height with apically positioned pulpal floor and bifurcation. (Courtesy of Dr. Michael Kahn.)

Treatment and Prognosis

When enamel pearls are detected radiographically, most are incidental findings that require no therapy. In spite of this, the area should be viewed as a weak point of periodontal attachment. Meticulous oral hygiene should be maintained in an effort to prevent localized loss of periodontal support and exposure of the enamel mass. If an enamel pearl becomes exposed and removal is contemplated, then the clinician must remember that lesion occasionally contains vital pulp tissue.

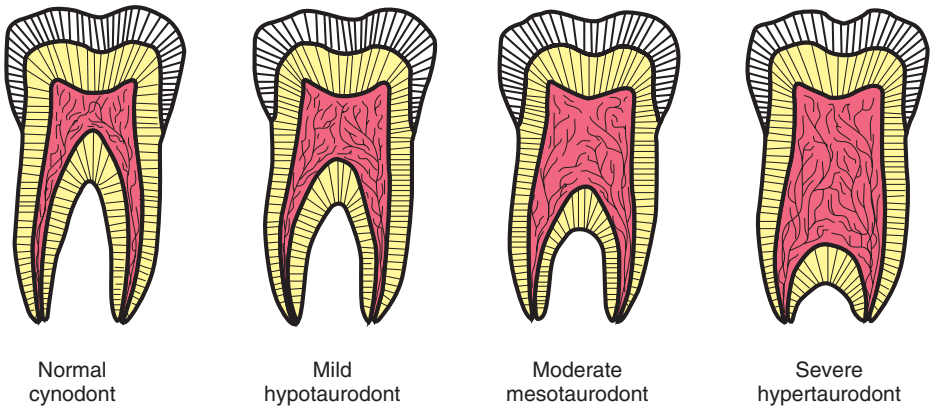
For teeth with cervical enamel extensions and associated periodontal furcation involvement, therapy is directed at achieving a more durable attachment and providing access to the area for appropriate cleaning. Reports have suggested that flattening or removing the enamel in combination with an excisional new attachment procedure and furcation plasty may accomplish this.

TAURODONTISM

Taurodontism is an enlargement of the body and pulp chamber of a multirooted tooth, with apical displacement of the pulpal floor and bifurcation of the roots. This pattern of molar formation has been found in ancient Neanderthals, and the overall shape of the taurodont resembles that of the molar teeth of cud-chewing animals (*tauro* = bull; *dont* = tooth).

Clinical and Radiographic Features

Affected teeth tend to be rectangular and exhibit pulp chambers with a dramatically increased apico-occlusal height and a bifurcation close to the apex (Fig. 2-78). The



• **Fig. 2-79 Taurodontism.** Illustration exhibiting the classification of taurodontism according to the degree of apical displacement of the pulpal floor.

diagnosis usually is made subjectively from the radiographic appearance. The degree of taurodontism has been classified into *mild* **(hypotaurodontism),** *moderate* **(mesotaurodontism),** and *severe* **(hypertaurodontism),** according to the degree of apical displacement of the pulpal floor (Fig. 2-79). Witkop and colleagues and Shifman and Chanannel presented useful biometric criteria for the determination of taurodontism. These reports contain information that is useful in epidemiologic studies of the process.

Some investigators include examples of taurodontism in premolar teeth; others argue that taurodontism is not shown by premolars. This argument is academic because the presence of taurodontism in premolars cannot be documented *in situ.* Investigations of taurodontism in premolar teeth require the examination of extracted teeth, because the necessary radiographs depict the tooth in a mesiodistal orientation.

Taurodontism may be unilateral or bilateral and affects permanent teeth more frequently than deciduous teeth. There is no sex predilection. The reported prevalence is highly variable (0.5% to 46%) and most likely is related to different diagnostic criteria and racial variations. In the United States most reports indicate a prevalence of 2.5% to 3.2% of the population. Some investigators believe the alteration is more of a variation of normal rather than a definitive pathologic anomaly. The process often demonstrates a field effect with the involvement of all molars. When this occurs, the first molar is usually affected least with increasing severity noted in the second and third molars, respectively.

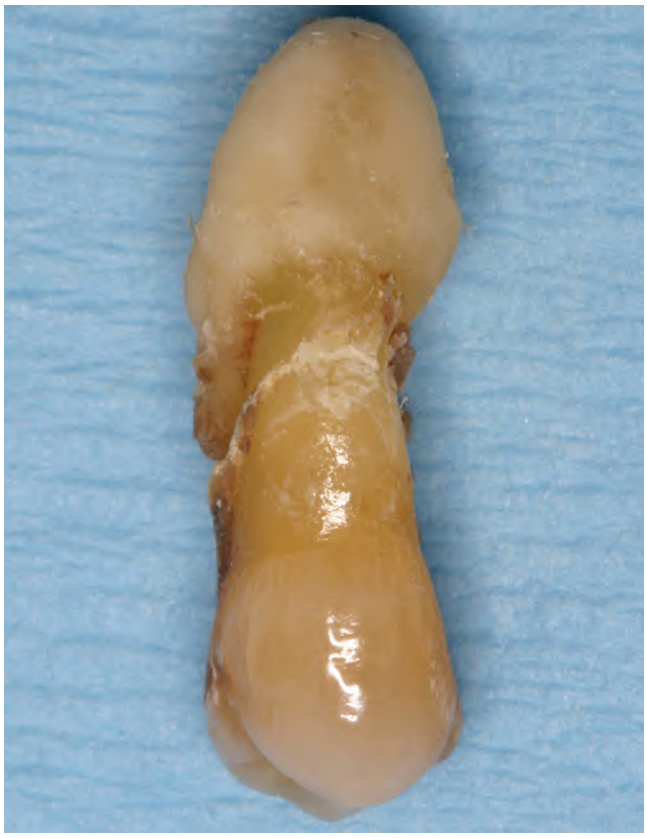
Taurodontism may occur as an isolated trait or as a component of various syndromes (Box 2-10). An increased frequency of taurodontism has been reported in patients with hypodontia, cleft lip, and cleft palate. Investigations have shown that taurodontism may develop in the presence of any one of a large number of different genetic alterations. These findings suggest that chromosomal abnormalities may disrupt the development of the tooth's form and that taurodontism is not the result of a specific genetic abnormality.

• BOX 2-10 Syndromes Associated with Taurodontism

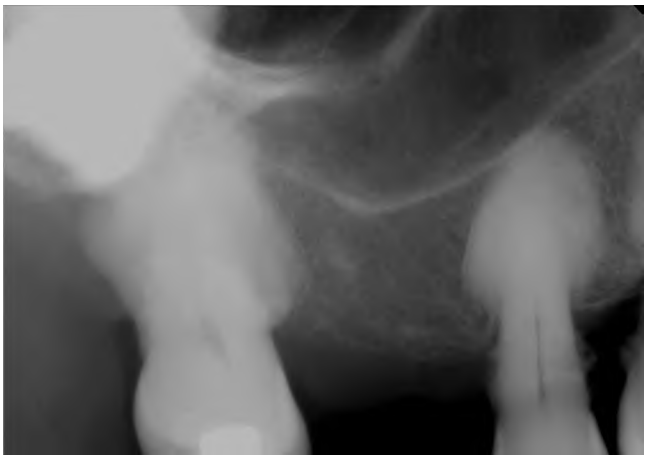
- Amelogenesis imperfecta, hypoplastic type IE
- Amelogenesis imperfecta-taurodontism type IV
- Cranioectodermal dysplasia
- Down
- Ectodermal dysplasia
- Ellis-van Creveld
- Hyperphosphatasia-oligophrenia-taurodontism
- Hypophosphatasia
- Klinefelter
- Lowe
- Microcephalic dwarfism-taurodontism
- Microdontia-taurodontia-dens invaginatus
- Oculo-dento-digital dysplasia
- Oral-facial-digital type II
- Rapp-Hodgkin
- Scanty hair-oligodontia-taurodontia
- Sex chromosomal aberrations (e.g., XXX, XYY)
- Tricho-dento-osseous types I, II, and III
- Tricho-onycho-dental
- Wolf-Hirschhorn

Treatment and Prognosis

Patients with taurodontism require no specific therapy. Coronal extension of the pulp is not seen; therefore, the process does not interfere with routine restorative procedures. Some investigators have suggested the taurodontic shape may exhibit decreased stability and strength as an abutment tooth in prosthetic procedures due to decreased root surface area, but this hypothesis has not been verified. If endodontic therapy is required, then the shape of the pulp chamber frequently increases the difficulty of locating, instrumenting, and obturating the pulp canals. In addition, the presence of supernumerary roots and canals mandates careful exploration of all orifices and chamber grooves, with magnification being highly beneficial. One bit of good news is that patients have to demonstrate significant periodontal destruction before bifurcation involvement occurs.



• **Fig. 2-80 Hypercementosis.** Gross photograph of a maxillary bicuspid that exhibits thickening and blunting of the apical portion of the root. (Courtesy of Dr. David Hicklin.)



• **Fig. 2-81 Hypercementosis.** Periapical radiograph of the tooth depicted in Fig. 2-80. Note the radiopaque enlargement of the apical portion of the tooth. (Courtesy of Dr. David Hicklin.)

HYPERCEMENTOSIS

Hypercementosis (cemental hyperplasia) is a nonneoplastic deposition of excessive cementum that is continuous with the normal radicular cementum.

Clinical and Radiographic Features

Radiographically, affected teeth demonstrate a thickening or blunting of the root, but the exact amount of increased cementum often is difficult to ascertain because cementum and dentin demonstrate similar radiodensities (Figs. 2-80 and 2-81). The enlarged root is surrounded by the radiolucent PDL space and the adjacent intact lamina dura. On occasion, the enlargement may be significant enough to suggest the possibility of a cementoblastoma (see page 610). However, the cementoblastoma usually can be distinguished on the basis of associated pain, cortical expansion, and continued enlargement.

Hypercementosis may be isolated, involve multiple teeth, or appear as a generalized process. In a study of more than 22,000 affected teeth, the mandibular molars were affected most frequently, followed by the mandibular and maxillary second premolars and mandibular first premolars. In this study, a 2.5:1 mandibular predominance was noted.

Hypercementosis occurs predominantly in adulthood, and the frequency increases with age, which is most likely secondary to cumulative exposure to causative influences. Its occurrence has been reported in younger patients, and many of these cases demonstrate a familial clustering, suggesting hereditary influence.

Box 2-11 lists several local and systemic factors that have been associated with an increased frequency of the cemental deposition. All of the listed systemic factors exhibit a weak association with hypercementosis except for **Paget disease of bone** (see page 582). Numerous authors have reported significant hypercementosis in patients with Paget disease, and this disorder should be considered whenever generalized hypercementosis is discovered in a patient of the appropriate age. In spite of the association with a number of disorders, most localized cases of hypercementosis are not related to any systemic disturbance.

• BOX 2-11 Factors Associated with Hypercementosis

Local Factors

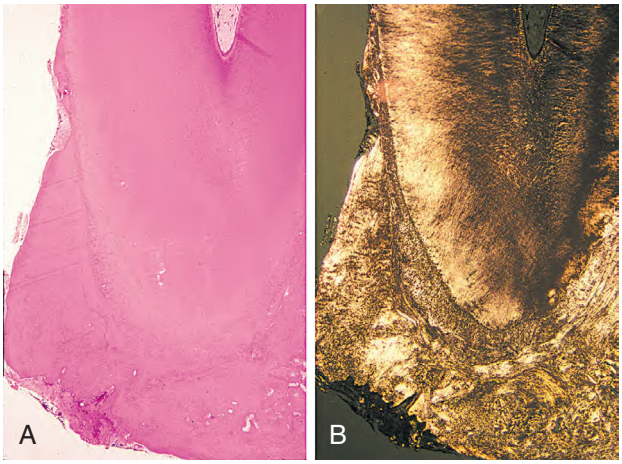
- Abnormal occlusal trauma
- Adjacent inflammation (e.g., pulpal, periapical, periodontal)
- Unopposed teeth (e.g., impacted, embedded, without antagonist)
- Repair of vital root fracture

Systemic Factors

- Acromegaly and pituitary gigantism
- Arthritis
- Calcinosis
- Paget disease of bone
- Rheumatic fever
- Thyroid goiter
- Gardner syndrome
- Vitamin A deficiency (possibly)

Histopathologic Features

The periphery of the root exhibits deposition of an excessive amount of cementum over the original layer of primary



• **Fig. 2-82 Hypercementosis. A,** Dental root exhibiting excessive deposition of cellular and acellular cementum. The dividing line between dentin and cementum is indistinct. **B,** Polarized light demonstrating the sharp dividing line between the tubular dentin and osteocementum.

cementum. The excessive cementum may be hypocellular or exhibit areas of cellular cementum that resemble bone (osteocementum). Often the material is arranged in concentric layers and may be applied over the entire root or be limited to the apical portion. On routine light microscopy, distinguishing between dentin and cementum often is difficult, but viewing the section with polarized light helps to discriminate between the two different layers (Fig. 2-82).

Treatment and Prognosis

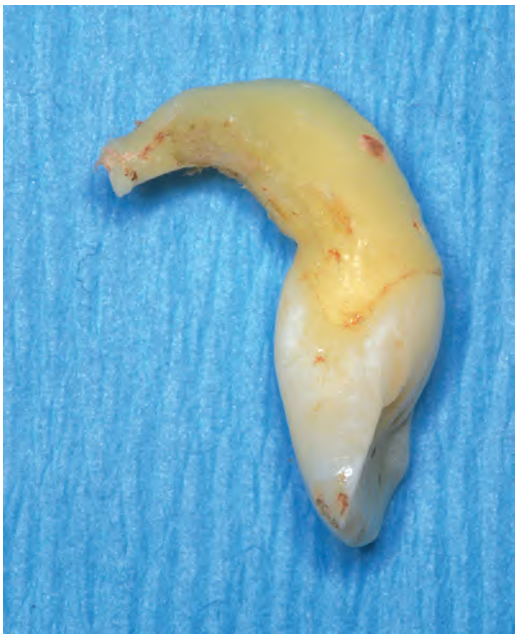
Patients with hypercementosis require no treatment. Because of a thickened root, occasional problems have been reported during the extraction of an affected tooth. Sectioning of the tooth may be necessary in certain cases to aid in removal.

DILACERATION

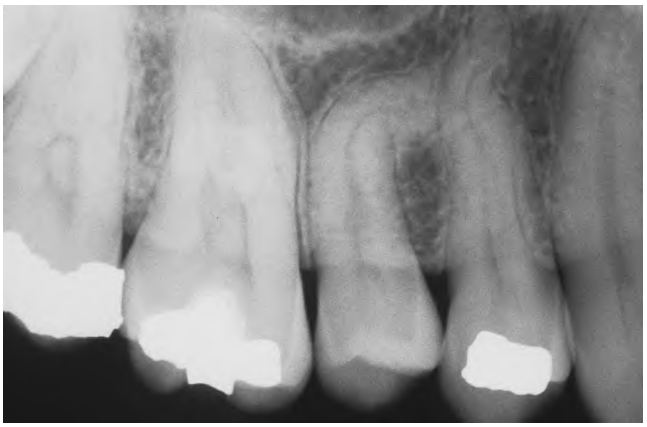
Dilaceration is an abnormal angulation or bend in the root or, less frequently, the crown of a tooth (Figs. 2-83 and 2-84). Although most examples are idiopathic, a number of teeth with dilaceration appear to arise after an injury that displaces the calcified portion of the tooth germ, and the remainder of the tooth is formed at an abnormal angle. The damage frequently follows avulsion or intrusion of the overlying primary predecessor, an event that usually occurs before 4 years of age. Injury-related dilaceration more frequently affects the anterior dentition and often creates both a functional and a cosmetic dental problem. Less frequently the bend develops secondary to the presence of an adjacent anatomic structure, cyst, tumor, or odontogenic hamartoma (e.g., odontoma, supernumerary tooth) (Fig. 2-85).

Clinical and Radiographic Features

In one review of 1166 randomly selected patients, 176 dilacerated teeth were identified. Of these teeth, the most

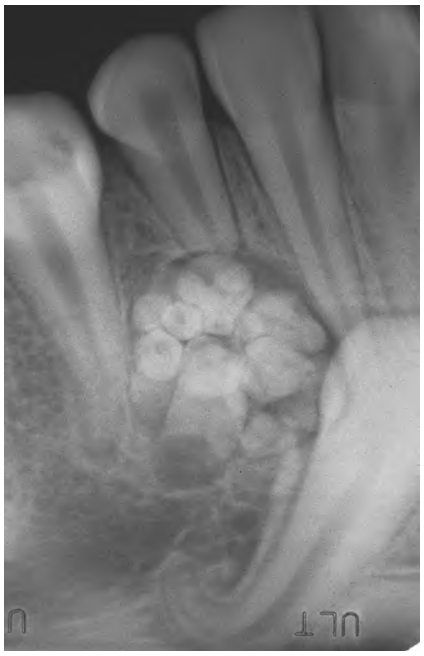


• **Fig. 2-83 Dilaceration.** Sharp curvature of the root of a maxillary central incisor.



• **Fig. 2-84 Dilaceration.** Maxillary second bicuspid exhibiting mesial inclination of the root. The patient reported no history of injury to this area. (Courtesy of Dr. Lawrence Bean.)

commonly affected were the mandibular third molars, followed by the maxillary second premolars and mandibular second molars. The maxillary and mandibular incisors were the least frequently affected, representing approximately 1% of the series. This contrasts with other authors who have reported a high frequency of dilaceration involving anterior teeth. In reality, the molars most likely demonstrate the highest prevalence of dilaceration but are not highlighted because of a lack of associated clinical problems in most instances. Occasionally, involvement of the deciduous teeth is reported, and some have been associated with prior trauma secondary to neonatal laryngoscopy and endotracheal intubation. Several publications have mentioned an increased prevalence associated with several syndromes, including Smith-Magenis syndrome, variants of



• **Fig. 2-85 Dilaceration.** Root angulation of a mandibular cuspid. Development has been altered by the presence of an adjacent compound odontoma. (Courtesy of Dr. Brent Bernard.)

Ehlers-Danlos syndrome, Axenfeld-Rieger syndrome, and congenital ichthyosis.

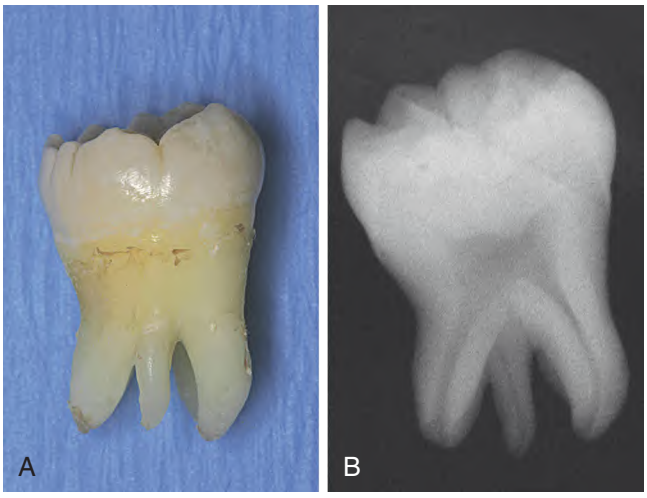
The bend may occur anywhere along the length of the crown or root. One review stated that dilaceration occurs most frequently in the apical third of anterior or premolar teeth, whereas the middle third is most common in molars, and the cervical third is involved most frequently in third molars. The maxillary central incisors are the most common teeth to demonstrate crown dilacerations, followed by the mandibular incisors. Impaction of the affected tooth occurs in approximately 50% of these cases.

Dilaceration usually is radiographically obvious if the bend occurs in a mesial or distal direction. Roots that bend facially or lingually may be more difficult to detect. Often, the apical portion of these teeth will demonstrate a round increased radiodensity with a central radiolucent dark spot that correlates to the root canal of the bent tooth. The dilacerated portion of the root often may demonstrate a radiolucent halo that represents the associated periodontal ligament.

Treatment and Prognosis

The treatment and prognosis vary according to the severity of the deformity. Altered deciduous teeth often demonstrate inappropriate resorption and result in delayed eruption of the permanent teeth. Extraction is indicated when necessary for the normal eruption of the succedaneous teeth. Patients with minor dilaceration of permanent teeth frequently require no therapy. Those teeth that exhibit delayed or abnormal eruption may be exposed and orthodontically moved into position. The possibility that orthodontic movement of severely dilacerated teeth may result in severe external root resorption must be considered during treatment planning. In some cases with extensive deformation of the affected tooth, perforation of the buccal alveolar ridge by the malpositioned root may occur on repositioning. In such cases, amputation of the root apex with subsequent endodontic therapy may be necessary. Grossly deformed teeth require surgical removal. The extraction of affected teeth may be difficult and result in root fracture on removal. When attempting to perform endodontic procedures, the clinician must use great care to avoid root perforation of teeth with significant dilaceration.

Root dilaceration concentrates stress if the affected tooth is used as an abutment for a dental prosthetic appliance. This increased stress may affect the stability and longevity of the abutment tooth. Splinting of the dilacerated tooth to an adjacent tooth results in a multirooted abutment and overcomes the stress-related problems.



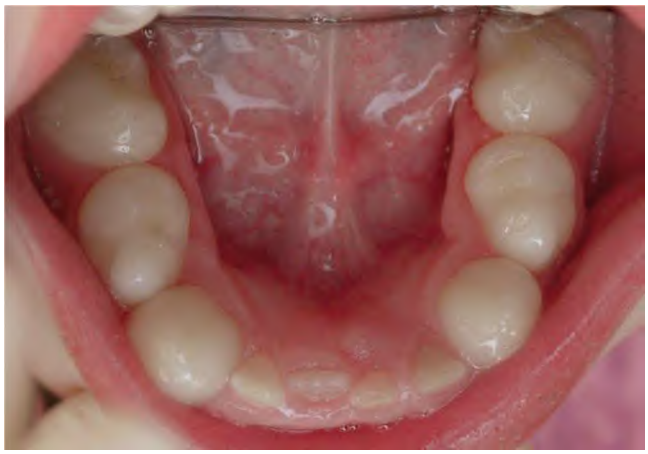
• **Fig. 2-86 Supernumerary Root. A,** Gross photograph showing a mandibular molar with a supernumerary root. **B,** Periapical radiograph of the extracted tooth.

SUPERNUMERARY ROOTS

The term **supernumerary roots** refers to the development of an increased number of roots on a tooth compared with that classically described in dental anatomy.

Clinical and Radiographic Features

Any tooth may develop accessory roots, and involvement has been reported in both the deciduous and the permanent dentitions. Data on the frequency of supernumerary roots are sparse, but the prevalence appears to vary significantly among different races. The most frequently affected teeth are the permanent molars (especially third molars) from either arch and mandibular cuspids and premolars (Fig. 2-86). In some instances the supernumerary root is divergent and seen easily on radiographs; in other cases the additional root is small, superimposed over other roots, and difficult to ascertain.



• **Fig. 2-87 Globodontia.** Dentition demonstrating clinically normal anterior teeth and posterior teeth with enlarged bulbous crowns. Patient had undiagnosed hearing loss that was discovered following identification of otodental syndrome by dentist. (Courtesy of Dr. John Eric Yezerski.)

Treatment and Prognosis

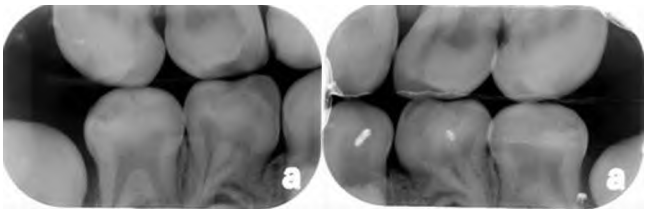
No treatment is required for supernumerary roots, but the detection of the accessory root is of critical importance when endodontic therapy or exodontia is undertaken. Extracted teeth always should be examined closely to ensure that all roots have been removed successfully, because accessory roots may not be obvious on the presurgical radiographs. Just as important is the search for accessory canals during endodontic access procedures, because failure to discover these additional openings often results in a lack of resolution of the associated inflammatory process.

GLOBODONTIA

The gigantic globe-shaped teeth of **globodontia** and high-frequency sensorineural hearing loss are the primary diagnostic features of **otodental syndrome.** This autosomal dominant disorder has been localized to chromosome 11q13, and the clinical findings are thought to be due to haploinsufficiency of the FGF3 gene.

Clinical and Radiographic Features

Both the deciduous and permanent dentitions are affected with the cuspids and molars demonstrating dramatically enlarged and bulbous crowns (Figs. 2-87 and 2-88). The normal cusp and groove anatomy of the molars is replaced by numerous developmental grooves that radiate from a central depression onto the facial, lingual, and proximal surfaces, resulting in an occlusal surface that has been described as resembling the *tied end of a sausage.* The canines are distorted similarly, often with three large bulbous projections separated by shallow grooves. The premolars often are missing or reduced in size; when present, they may demonstrate normal anatomy or appear conical. The incisors are unaffected. The globodont roots are short, and the



• **Fig. 2-88 Globodontia.** Bite-wing radiographs demonstrating posterior teeth with bulbous crowns and complex pulpal anatomy. (Courtesy of Dr. John Eric Yezerski.)

pulp chambers often appear bisected with vertical septa and occasional pulp stones. Focal areas of yellow coronal hypomaturation may occur, especially on the facial surfaces of the canines.

The onset of the hearing loss varies from early childhood to middle age, but it often begins in infancy and progresses to a plateau in the fourth decade. A loss of approximately 65db is noted at all frequencies but is more pronounced at about 1000 Hz. Other less consistent findings include ocular colobomas, odontomas, and numerous microdontic teeth.

Treatment and Prognosis

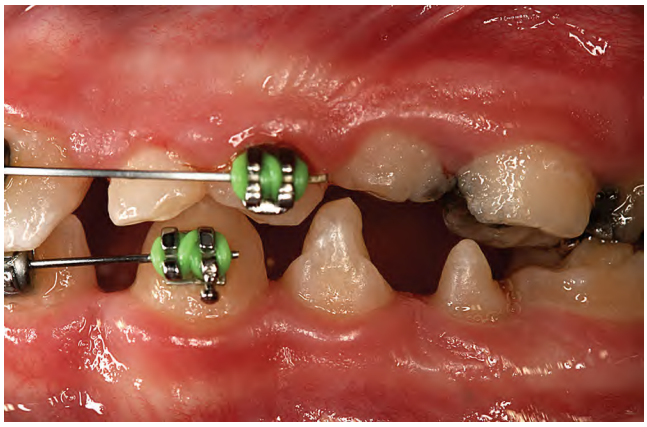
Due to the grossly distorted anatomy, misalignment of the teeth and malocclusion are frequent problems. If an affected tooth develops dental caries, routine dental restorative treatment can be provided. Endodontic therapy can be very challenging in the molar teeth due to the complexity of the pulpal anatomy. Patients also have a propensity to develop endodontic-periodontic lesions, possibly due to the abnormal coronal and pulpal configuration. An excellent program of oral hygiene with regular professional care should be encouraged.

LOBODONTIA

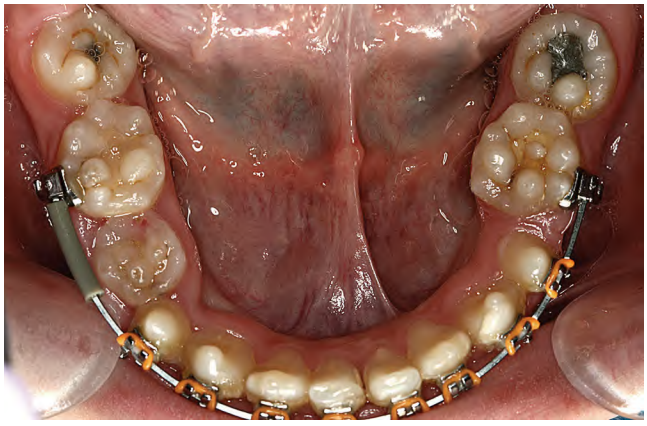
Lobodontia refers to a rare hereditary dental anomaly in which numerous teeth resemble those noted in carnivores. The term is derived from *lobo,* the Spanish word for wolf that arose from the Latin word *lupus.* The abnormality is extremely rare and is inherited as an autosomal dominant trait.

Clinical and Radiographic Features

The most distinctive features are the cuspids and premolars, which demonstrate pointed fang-like cusps (Fig. 2-89). The middle lobes of the cuspid crowns are conical with the lateral lobes being dramatically reduced. The premolars demonstrate prominent cone-shaped buccal cusps, often with diminutive lingual cusps. The occlusal anatomy of the molars also is altered significantly and demonstrates a multitubercular appearance (Fig. 2-90). Additionally, a generalized reduction in tooth size is common. Other less consistent findings include shovel-shaped incisors with prominent



• **Fig. 2-89 Lobodontia.** Premolar demonstrating pointed fang-like cusps.



• **Fig. 2-90 Lobodontia.** Mandibular molars demonstrating a multitubercular appearance.

cingulum pits, hypodontia, dens invaginatus of premolars or incisors, and single conical roots of the molar teeth.

Treatment and Prognosis

Thorough radiographic examination is prudent to discover and restore teeth with dens invaginatus prior to devitalization. The occlusal cusps of the multitubercular molars are similar to dens evaginatus with traumatic occlusion, attrition, or fracture predisposing to loss of pulp vitality. Although appropriate therapy has not been described, composite reinforcement of the prominent cusps may reduce cuspal damage and allow time for pulpal recession from the coronal protuberances.

◆ DEVELOPMENTAL ALTERATIONS IN THE STRUCTURE OF TEETH

AMELOGENESIS IMPERFECTA

Amelogenesis imperfecta encompasses a complicated group of conditions that demonstrate developmental alterations in the structure of the enamel in the absence of a systemic disorder or syndrome. Box 2-2 (see page 50) lists several systemic diseases associated with enamel disorders that are not considered isolated amelogenesis imperfecta. Although the definition of amelogenesis imperfecta excludes any association with a syndrome, a number of other dental anomalies are accepted within the spectrum of the disease: pulpal calcification, taurodontism, delayed eruption, gingival overgrowth, open-bite malocclusion, and rarely prognathism.

The formation of enamel is a multistep process, and problems may arise in any one of the steps. In general, the development of enamel can be divided into three major stages:

1. Elaboration of the organic matrix
2. Mineralization of the matrix
3. Maturation of the enamel

Historically, the hereditary defects of the formation of enamel are divided along these lines: hypoplastic, hypocalcified, and hypomaturation. Numerous hereditary subtypes of amelogenesis imperfecta exist, with a wide variety of clinical manifestations and patterns of inheritance. An ideal classification system for amelogenesis imperfecta has not been established yet. Witkop's classification (Table 2-1) relies on the phenotype and pedigree (i.e., clinical appearance and apparent pattern of inheritance). Classification by clinical appearance is problematic, because different phenotypes have been noted within a single affected family. In addition, similar phenotypes may be seen in individuals with very different molecular patterns of disease. One example of the potential confusion occurs in kindreds affected with certain variants of autosomal dominant amelogenesis imperfecta in which homozygotes exhibit generalized thin hypoplasia, whereas heterozygotes exhibit localized enamel pitting. Using Witkop's system, different individuals within this kindred would be placed into multiple categories (e.g., types IB, ID, IF).

Although the molecular basis underlying many patterns of amelogenesis imperfecta remains poorly defined, the genetics associated with several variations of amelogenesis imperfecta has been clarified. This has led investigators to suggest a future classification system based primarily on the mode of inheritance with secondary discriminators that include the phenotype, molecular basis (site and type of chromosomal mutation, when known), and the biochemical result (protein affected, when known). Although much remains to be discovered, the information necessary for this new classification system is accumulating rapidly, with movement to this new pattern of classification being inevitable. A discussion of the mutation type, mutation result, and protein affected is beyond the scope of this text, and interested parties are referred to the references associated with this section.

Investigations into the genetics are ongoing and producing results that are not only interesting but also directly applicable to patient care. To date, mutations in seven genes have been associated with amelogenesis imperfecta. Each gene can be mutated in a variety of ways, often creating diverse and distinct phenotypic patterns.

The ***AMELX* gene** is associated with the enamel protein **amelogenin,** which constitutes up to 90% of enamel

TABLE 2-1 Classification of Amelogenesis Imperfecta

Type	Pattern	Specific Features	Inheritance
IA	Hypoplastic	Generalized pitted	Autosomal dominant
IB	Hypoplastic	Localized pitted	Autosomal dominant
IC	Hypoplastic	Localized pitted	Autosomal recessive
ID	Hypoplastic	Diffuse smooth	Autosomal dominant
IE	Hypoplastic	Diffuse smooth	X-linked dominant
IF	Hypoplastic	Diffuse rough	Autosomal dominant
IG	Hypoplastic	Enamel agenesis	Autosomal recessive
IIA	Hypomaturation	Diffuse pigmented	Autosomal recessive
IIB	Hypomaturation	Diffuse	X-linked recessive
IIC	Hypomaturation	Snow-capped	X-linked
IID	Hypomaturation	Snow-capped	Autosomal dominant?
IIIA	Hypocalcified	Diffuse	Autosomal dominant
IIIB	Hypocalcified	Diffuse	Autosomal recessive
IVA	Hypomaturation-hypoplastic	Taurodontism present	Autosomal dominant
IVB	Hypoplastic-hypomaturation	Taurodontism present	Autosomal dominant

Modified from Witkop CJ Jr: Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification, *J Oral Pathol* 17:547-553, 1988.

matrix. *AMELX*-associated variants of amelogenesis imperfecta are X-linked with 14 different mutations currently known. Because of the effect of lyonization, the male and female phenotypes are variable but often associated with the genotype. The male phenotypes include both the diffuse smooth hypoplastic and the hypomaturation variants.

The ***ENAM* gene** is associated with another enamel protein, **enamelin,** which represents approximately 1% to 5% of enamel matrix. Mutations of the *ENAM* gene have been correlated with some autosomal dominant and recessive patterns of hypoplastic amelogenesis imperfecta, ranging from minor pitting to diffuse generalized thin enamel.

The ***MMP-20* gene** codes for a proteinase named **enamelysin;** mutation of this gene has been associated with the autosomal recessive, pigmented hypomaturation variant of amelogenesis imperfecta.

The protease, **kallikrein-4,** is associated with the ***KLK4* gene,** the mutation of which has been shown to be involved with some forms of hypomaturation amelogenesis imperfecta. Both enamelysin and kallikrein-4 are thought necessary for the removal of enamel matrix proteins during the maturation stage of enamel development.

Mutations in the ***FAM83H* gene** have been associated with autosomal dominant hypocalcified amelogenesis imperfecta. Of the currently discovered genes, *FAM83H* is associated with the highest prevalence of disease and the most severe enamel alterations. The majority of these mutations result in involvement over the entire crown, whereas some examples create areas of hypocalcification that localize in the cervical half of the crown.

The function of the ***WDR72* gene** is unknown, but it is thought to be a scaffold for protein-protein interactions. Mutations in this gene have been associated with autosomal recessive patterns of hypomaturation amelogenesis imperfecta.

The ***C4orf26* gene** encodes an extracellular matrix protein in the enamel organ and has been associated with an autosomal recessive pattern of hypomineralized amelogenesis imperfecta. The mutation was discovered initially in an Omani family and led investigators to sequence another 57 apparently unrelated individuals presenting with recessive patterns of amelogenesis imperfecta from across the world. This research confirmed the mutation in an additional eight families with previously undefined mutations.

The ***DLX3* gene** belongs to a group of genes that code for a number of proteins that are critical for craniofacial, tooth, hair, brain, and neural development; mutation of this gene has been associated with the hypoplastic-hypomaturation variants of amelogenesis imperfecta with taurodontism. Some investigators have removed the gene from the list of those associated with amelogenesis imperfecta due to the belief this pattern is a variant of the tricho-dento-osseous syndrome. Others have documented an identical pattern of abnormal enamel in patients with the

DLX3 mutation, but with no other features of tricho-dento-osseous syndrome (see page 97).

Although no one has compiled a complete list of amelogenesis imperfecta types using the proposed new classification, Table 2-2 provides a rough idea of how this might be organized. Despite these exciting molecular genetic discoveries, it must be stressed how much remains to be investigated.

Clinical and Radiographic Features

Amelogenesis imperfecta may be inherited as an autosomal dominant, autosomal recessive, or X-linked disorder, with both the deciduous and the permanent dentitions diffusely involved in the vast majority. Due to differing gene pools, the rate of occurrence varies geographically with a prevalence of 1:700 in Sweden and a frequency in the United States of 1:14,000.

Hypoplastic Amelogenesis Imperfecta

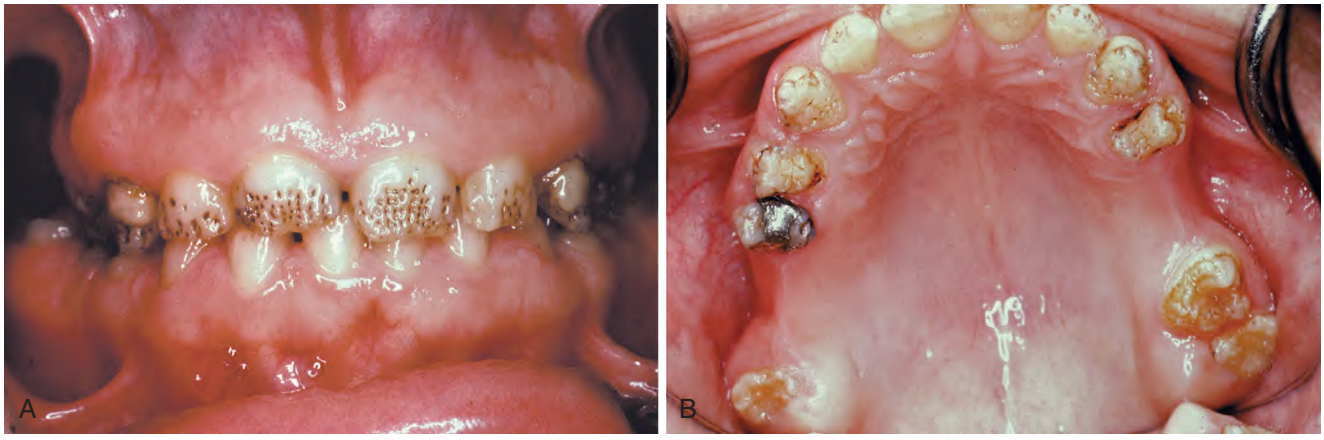
In patients with hypoplastic amelogenesis imperfecta, the basic alteration centers on inadequate deposition of enamel matrix. Any matrix present is mineralized appropriately and radiographically contrasts well with the underlying dentin. In the **generalized pattern,** pinpoint-to-pinhead–sized pits are scattered across the surface of the teeth and do not correlate with a pattern of environmental damage (Fig. 2-91). The buccal surfaces of the teeth are affected more severely, and the pits may be arranged in rows or columns. Staining of the pits may occur. Variable expressivity is seen within groups of affected patients. The enamel between the pits is of normal thickness, hardness, and coloration.

In the **localized pattern,** the affected teeth demonstrate horizontal rows of pits, a linear depression, or one large area of hypoplastic enamel. Typically, the altered area is located in the middle third of the buccal surfaces of the teeth. The

TABLE 2-2 Modified Classification of Amelogenesis Imperfecta

Inheritance	Phenotype	Related Genes
Autosomal dominant	Generalized pitted	
Autosomal dominant	Localized hypoplastic	*ENAM*
Autosomal dominant	Generalized thin	*ENAM*
Autosomal dominant	Diffuse hypocalcification	*FAM83H*
Autosomal dominant	Localized hypocalcified	*FAM83H*
Autosomal dominant	With taurodontism	*DLX3**
Autosomal recessive	Localized hypoplastic	
Autosomal recessive	Generalized thin	*ENAM*
Autosomal recessive	Diffuse hypomaturation	*WDR72*
Autosomal recessive	Pigmented hypomaturation	*MMP20, KLK4, C4orf26*
X-linked	Generalized thin	*AMELX*
X-linked	Diffuse hypomaturation	*AMELX*
X-linked	Diffuse hypoplasia/ hypomaturation	*AMELX*
X-linked	Snow-capped hypomaturation	

*Please refer to discussion of *DLX3* gene in the text portion.



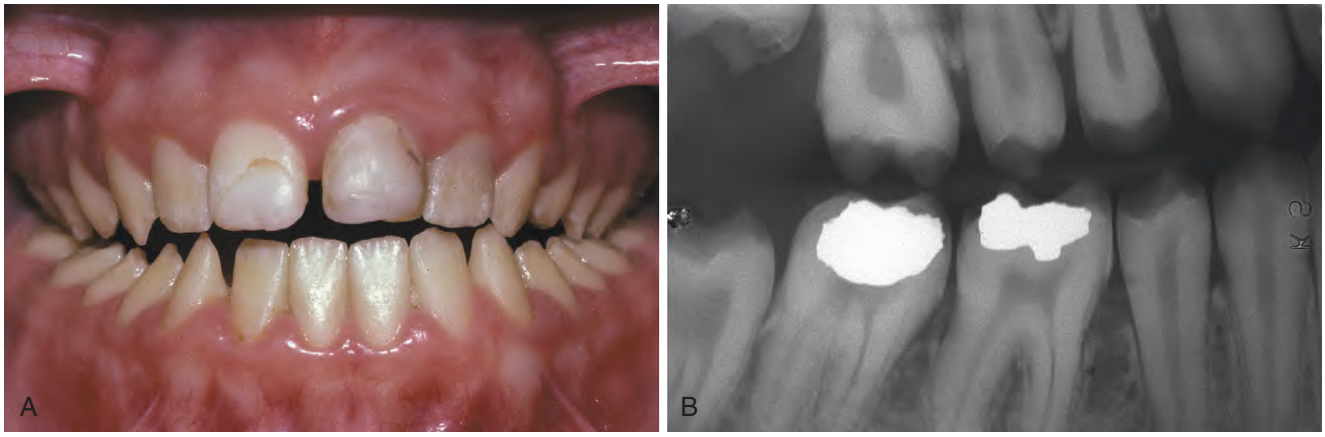
• **Fig. 2-91 Hypoplastic Amelogenesis Imperfecta, Generalized Pitted Pattern. A,** Note the numerous pinpoint pits scattered across the surface of the teeth. The enamel between the pits is of normal thickness, hardness, and coloration. **B,** Occlusal view of same patient showing diffuse involvement of all maxillary teeth, which would be inconsistent with environmental damage. (**A,** From Stewart RE, Prescott GH: *Oral facial genetics,* St Louis, 1976, Mosby. **B,** Courtesy of Dr. Joseph S. Giansanti.)

incisal edge or occlusal surface usually is not affected. Both dentitions, or only the primary teeth, may be affected. All of the teeth may be altered, or only scattered teeth may be affected. When the involvement is not diffuse, the pattern of affected teeth does not correlate with a specific time in development. The autosomal recessive type is more severe and typically demonstrates involvement of all teeth in both dentitions.

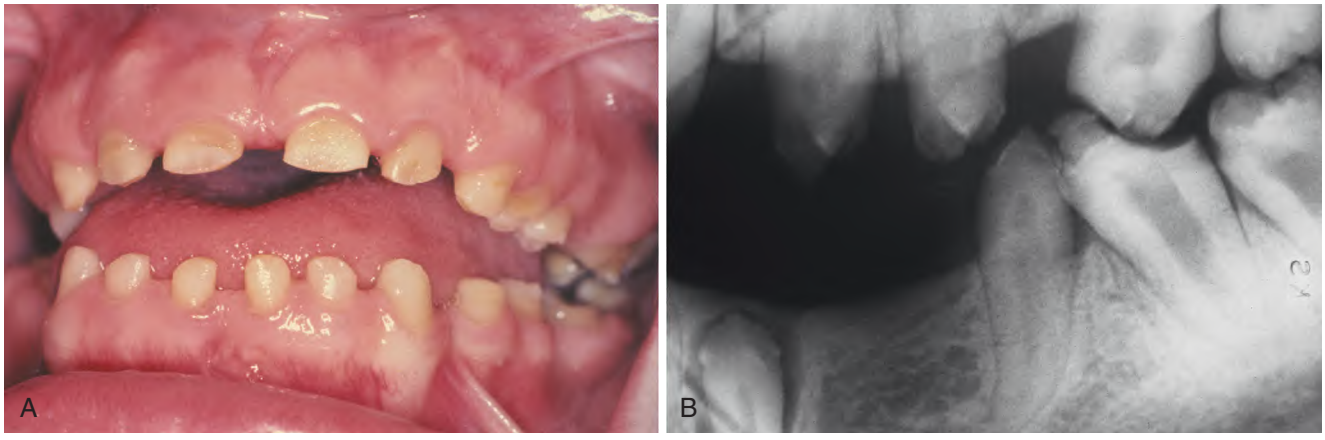
In Witkop's phenotypic classification, amelogenesis imperfecta with diffusely reduced enamel thickness was subclassified as *smooth*, *rough,* and *enamel agenesis.* This system has proved to be problematic due to significant intrafamily phenotypic variability and poor correlation between the phenotype and the molecular defect. As an example, certain mutations of autosomal dominant *ENAM* create thin hypoplastic enamel, with different patients demonstrating variations of surface texture ranging from smooth with and without shallow grooves to rough with numerous shallow pits. In addition, in patients diagnosed with enamel agenesis, the presence of a thin band of enamel has been confirmed in many affected individuals. As a result, these previously separated phenotypic patterns have been merged into one category, **generalized thin hypoplastic amelogenesis imperfecta.**

In the **generalized thin variants,** the enamel is extremely thin with teeth that are shaped like crown preparations and demonstrate open contact points. The surface texture varies from smooth with or without shallow grooves to rough with or without scattered pits (Figs. 2-92 and 2-93). The color of the teeth varies from opaque white to yellow to brown. Anterior open bite is not rare. Radiographically, a thin peripheral outline of radiopaque enamel will be noted on many teeth. Often, unerupted teeth exhibiting resorption are seen.

The X-linked patterns of generalized thin amelogenesis imperfecta are a lesson in the lyonization effect. On approximately the sixteenth day of embryonic life in all individuals with two X chromosomes, one member of the pair is inactivated in each cell. As a result of this event, females are mosaics, with a mixture of cells, some with active maternal



• **Fig. 2-92 Hypoplastic Amelogenesis Imperfecta, Autosomal Dominant Smooth Pattern (Generalized Thin Pattern). A,** Small, yellowish teeth exhibiting hard, glossy enamel with numerous open contact points and anterior open bite. **B,** Radiograph of the same patient demonstrating thin peripheral outline of radiopaque enamel. (**B,** Courtesy of Dr. John G. Stephenson.)



• **Fig. 2-93 Hypoplastic Amelogenesis Imperfecta, Rough Pattern (Generalized Thin Pattern). A,** Small, yellow teeth with rough enamel surface, open contact points, significant attrition, and anterior open bite. **B,** Radiograph of the same patient. Note the impacted tooth and the thin peripheral outline of radiodense enamel.

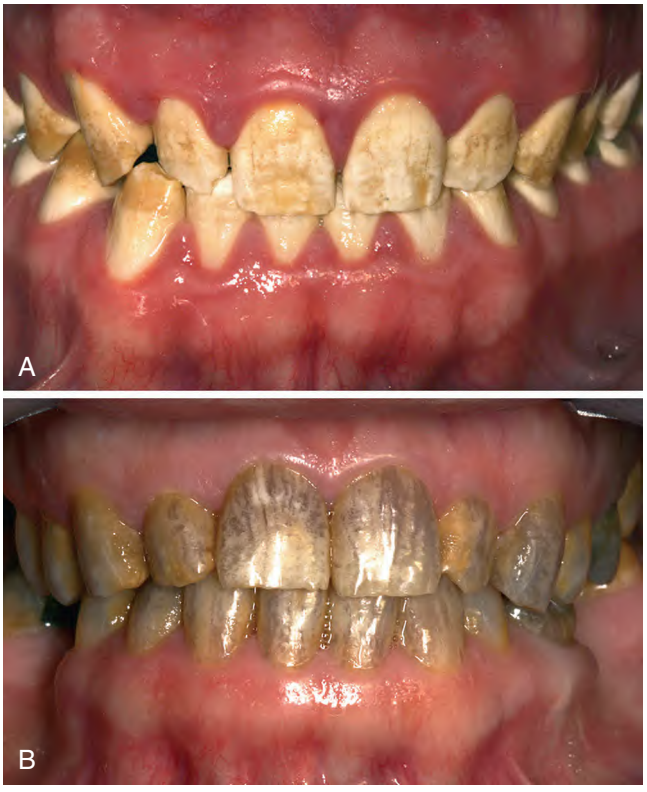
X chromosomes and others with active paternal X chromosomes. Usually the mix is of approximately equal proportions. If one X were to direct the formation of defective enamel and the other X were to form normal enamel, then the teeth would exhibit alternating zones of normal and abnormal enamel. Hemizygous males exhibit diffuse thin enamel in both dentitions. On the other hand, heterozygous females exhibit vertical furrows of thin hypoplastic enamel, alternating between bands of normal thickness. The banding often is detectable with dental radiographs.

Hypomaturation and Hypocalcification Variants of Amelogenesis Imperfecta (Hypomineralization Amelogenesis Imperfecta)

Both of these variants demonstrate defects in mineralization, with hypomature teeth containing residual enamel protein and hypocalcified teeth demonstrating lack of enamel protein with more severe enamel abnormalities. Classically, the hypomaturation pattern is associated with enamel that chips and fractures easily but does not demonstrate massive loss upon eruption. In contrast, the hypocalcification pattern has been associated with "cheesy" enamel that is lost rapidly and diffusely except for a residual band in the cervical portion of the teeth. In reality, the distinction is hazy with a spectrum of enamel quality encountered. At the ends of the spectrum, the separation between hypomaturation and hypocalcification can be made easily; however, the center of the spectrum contains numerous patterns that are difficult to classify on a phenotypic basis. For this reason, many investigators prefer the term **hypomineralization** for both variants. When struggling to choose between these two patterns, it should be remembered that most hypocalcified types are autosomal dominant, whereas the hypomaturation variants usually are autosomal recessive or X-linked.

Prior to eruption, both forms of hypomineralization radiographically demonstrate enamel of normal thickness with a radiodensity that is similar to dentin. In a person with **hypomaturation amelogenesis imperfecta,** the affected teeth are normal in shape but exhibit white opaque enamel that may reveal areas of mottling. Upon eruption, variable degrees of brown discoloration and enamel chipping are seen. The presentation may closely resemble dental fluorosis, making definitive diagnosis difficult in many patients. On occasion, fluorosis may demonstrate horizontal white banding that corresponds to periods of increased fluoride intake. If present, a chronological distribution also is helpful in interpreting the clinical appearance (such as sparing of the deciduous dentition or premolars and second molars [see Fig. 2-9, page 53]).

In the **pigmented hypomaturation pattern,** the surface enamel is mottled and agar-brown. The enamel often fractures from the underlying dentin and is soft enough to be punctured by a dental explorer. Anterior open bite and unerupted teeth exhibiting resorption are uncommon. Occasionally, the surface enamel may be affected severely and be similar in softness to that of hypocalcified patterns with rapid enamel loss upon eruption. These cases often demonstrate extensive calculus deposition. A combined hypomaturation and hypoplastic phenotype can be seen, but posteruption enamel loss can complicate classification.



• **Fig. 2-94 Hypomaturation Amelogenesis Imperfecta, X-Linked. A,** Male patient exhibiting diffuse yellow-white dentition. **B,** The patient's mother exhibits vertical bands of white, opaque enamel and translucent enamel. (Courtesy of Dr. Carlos Salinas.)

The **X-linked hypomaturation pattern** is another lesson in lyonization; however, the lyonization is not as obvious as that seen in the X-linked hypoplastic pattern. Affected males exhibit different patterns in the deciduous and permanent dentitions. The deciduous teeth are opaque white with a translucent mottling, whereas the permanent teeth are opaque yellow and may darken with age (Fig. 2-94, *A*). Heterozygous females exhibit a similar pattern in both dentitions. The teeth demonstrate vertical bands of white opaque enamel and translucent enamel; the bands are random and asymmetric (see Fig. 2-94, *B*). The banding can be seen under regular lighting but is more obvious with transillumination.

The **snow-capped hypomaturation patterns** exhibit a zone of white opaque enamel on the incisal or occlusal one-quarter to one-third of the crown (Fig. 2-95). The altered areas do not exhibit a distribution that would support an environmental origin, and the surface lacks the iridescent sheen seen with mild fluorosis. The affected teeth often demonstrate an anterior-to-posterior distribution and have been compared with a denture dipped in white paint (only affected anteriors, the anteriors back to the bicuspids, or the

anteriors back to the molars). Both the deciduous and the permanent dentitions are affected.

In **hypocalcified amelogenesis imperfecta,** the teeth are appropriately shaped on eruption, but the enamel is very soft and easily lost. On eruption, the enamel is yellow-brown or orange, but it often becomes stained brown to black and exhibits rapid calculus apposition (Fig. 2-96). With years of function much of the coronal enamel is removed, except for the cervical portion that is occasionally calcified better. Unerupted teeth and anterior open bite are not rare.

Amelogenesis Imperfecta with Taurodontism (Hypomaturation/Hypoplastic Amelogenesis Imperfecta)

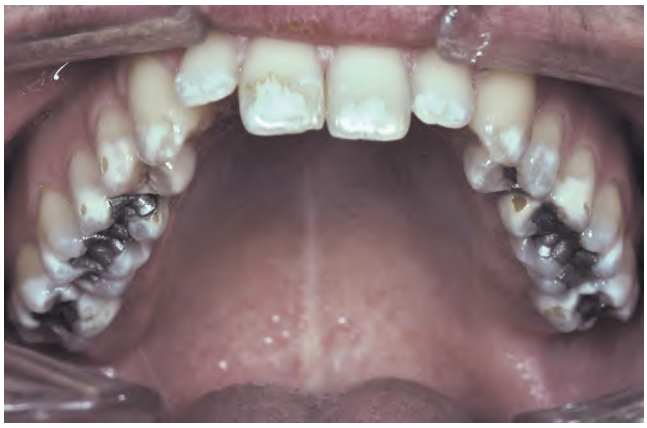
This type of amelogenesis imperfecta exhibits enamel hypoplasia in combination with hypomaturation. The deciduous and the permanent dentitions are diffusely involved. Historically, two patterns have been recognized that are similar but differentiated by the thickness of the enamel and the overall tooth size. When studying a single kindred, phenotypic variation is seen that would place members of the same family in both divisions; therefore, many believe these divisions should be joined into one phenotype termed merely **amelogenesis imperfecta with taurodontism.**

In the presentation known as the **hypomaturation-hypoplastic pattern,** the predominant defect is one of enamel hypomaturation in which the enamel appears as mottled yellow-white to yellow-brown. Pits are seen frequently on the buccal surfaces of the teeth. Radiographically, the enamel appears similar to dentin in density, and large pulp chambers may be seen in single-rooted teeth in addition to varying degrees of taurodontism.

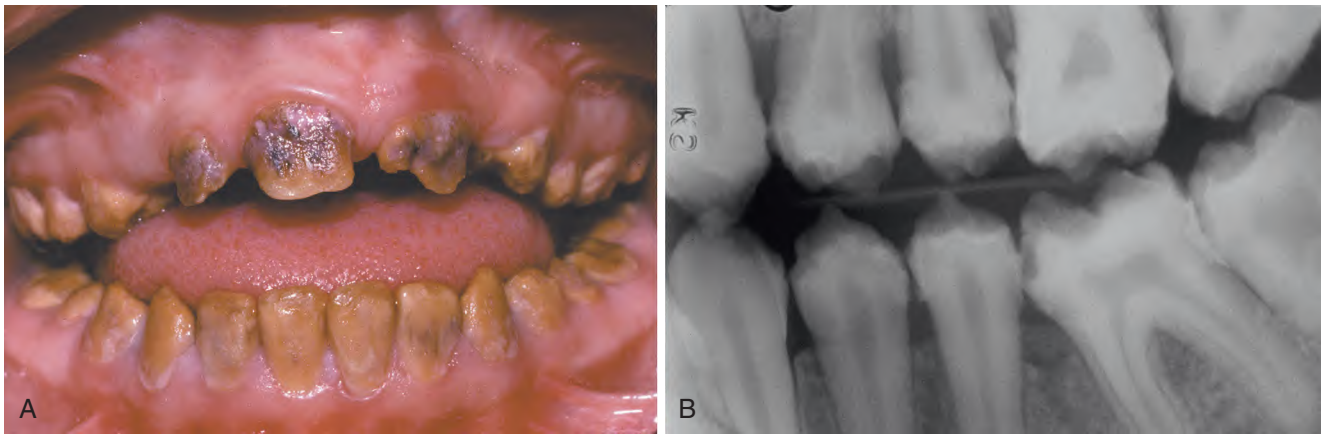
In the **hypoplastic-hypomaturation pattern,** the predominant defect is one of enamel hypoplasia in which the enamel is thin but also hypomature. Except for the decrease in the thickness of the enamel, this pattern is radiographically similar to the hypomaturation-hypoplastic variant.

A pattern of teeth alteration similar to amelogenesis imperfecta with taurodontism is seen in the systemic disorder, **tricho-dento-osseous syndrome.** This autosomal dominant disorder is mentioned here because the diagnosis may not be readily apparent without a high index of suspicion (Fig. 2-97). In addition to the dental findings, the predominant systemic changes are present variably and include kinky hair, osteosclerosis, and brittle nails. The kinky hair is present at birth but may straighten with age. The osteosclerosis primarily affects the base of the skull and the mastoid process. The mandible often exhibits a shortened ramus and an obtuse angle.

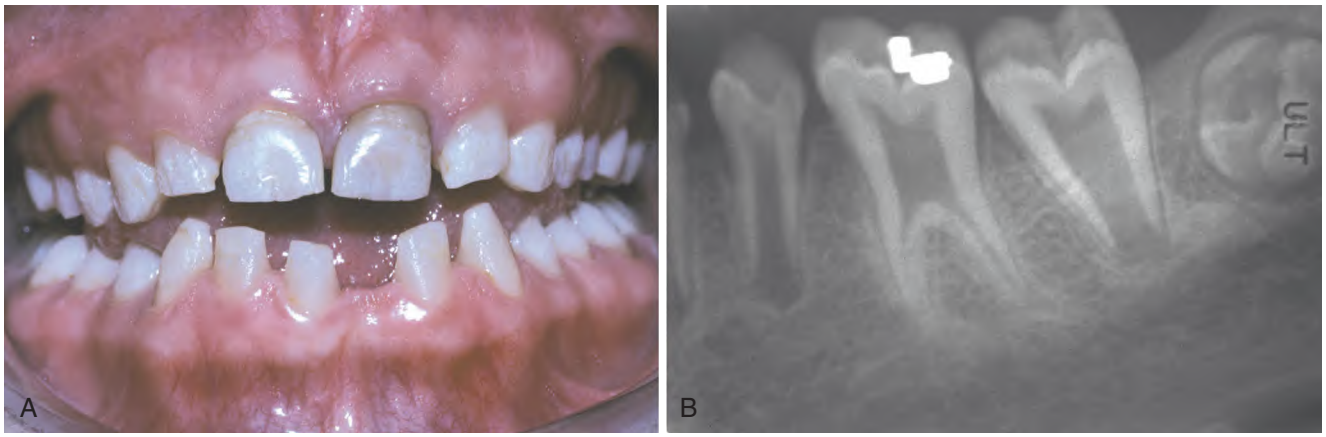
Some authors have suggested that amelogenesis imperfecta with taurodontism may represent partial expression of the tricho-dento-osseous syndrome. Studies have identified distinctly different gene mutations that are responsible for tricho-dento-osseous syndrome and amelogenesis imperfecta with taurodontism. However, other investigators dispute this fact, showing evidence that some examples of



• **Fig. 2-95 Hypomaturation Amelogenesis Imperfecta, Snow-Capped Pattern.** Dentition exhibiting zone of white opaque enamel in the incisal and occlusal one-fourth of the enamel surface. (Courtesy of Dr. Heddie O. Sedano.)



• **Fig. 2-96 Hypocalcified Amelogenesis Imperfecta. A,** Dentition exhibiting diffuse yellow-brown discoloration. Note numerous teeth with loss of coronal enamel except for the cervical portion. **B,** Radiograph of the same patient. Note the extensive loss of coronal enamel and the similar density of enamel and dentin.



• **Fig. 2-97 Tricho-Dento-Osseous Syndrome. A,** Dentition exhibiting diffuse enamel hypoplasia and hypomaturation. At birth, the patient exhibited a kinky "steel wool" texture to her hair; with time, the hair straightened. A high index of suspicion was required to arrive at the diagnosis. **B,** Radiograph of the same patient showing significant taurodontism of the first molar and thin enamel, which is similar in density to the dentin.

this pattern of amelogenesis imperfecta appear allelic (different mutation on the same gene) to the syndrome.

Histopathologic Features

The histopathologic alterations present in amelogenesis imperfecta are not evident in routine preparations. Because decalcification of the teeth is necessary before processing to allow sectioning of paraffin-embedded specimens, all of the enamel is lost. To examine the enamel structure of altered teeth, ground sections of nondecalcified specimens are prepared. The alterations discovered are highly diverse and vary with each clinical type of amelogenesis imperfecta. Detailed descriptions of such alterations were provided by Witkop and Sauk.

Treatment and Prognosis

The clinical implications of amelogenesis imperfecta vary according to the subtype and its severity, but the main problems are aesthetics, dental sensitivity, and loss of vertical dimension. In addition, in some types of amelogenesis imperfecta there is an increased prevalence of caries, anterior open bite, delayed eruption, tooth impaction, or associated gingival inflammation.

Patients with generalized thin enamel hypoplasia demonstrate minimal normal enamel associated with rapid attrition. These variants require full coverage as soon as is practical; if the treatment is delayed, a loss of usable crown length occurs. In those patients without sufficient crown lengths, full dentures (overdentures in some cases) often become the only satisfactory approach.

The other types of amelogenesis imperfecta demonstrate less rapid tooth loss, and the aesthetic appearance often is the prime consideration. Many less severe cases can be improved by the placement of full crowns or facial veneers on clinically objectionable teeth. In some cases, a lack of good enamel bonding of veneers occurs and does not result in a durable restoration. The use of glass ionomer cements with dentinal adhesives often overcomes this weakness.

Generalized delayed eruption and impaction of teeth affected by generalized thin hypoplastic amelogenesis imperfecta has been identified as a component of a very rare syndrome that includes nephrocalcinosis and sometimes renal failure. The renal changes often are not clinically overt, and mortality associated with renal failure has been reported in affected patients. Such patients should be referred for renal evaluation.

HEREDITARY DISORDERS OF DENTIN

Hereditary disorders of dentin can occur in association with a number of syndromes or arise as an isolated disorder of teeth with no systemic manifestations. Osteogenesis imperfecta is the syndrome most frequently associated with dental manifestations that mimic dentinogenesis imperfecta, but Ehlers-Danlos syndrome, Goldblatt syndrome, and Schimke immuno-osseous dysplasia also have been associated with similar dental changes. In addition, sporadic reports of patients with dentinogenesis imperfecta–like alterations as part of an obviously systemic, but as yet undefined, syndrome have been noted. In addition to a dentinogenesis imperfecta–like phenotype, a variety of other dentin abnormalities have been noted in vitamin-D resistant rickets, vitamin-D dependent rickets, tumoral calcinosis, and calcinosis universalis. The following section concentrates on the nonsyndromic disorders of dentin.

As mentioned previously, the classification of amelogenesis imperfecta is very complicated and is evolving as the genetic profile of the numerous phenotypic variations is being established. Although the variations in hereditary dentin disorders are much less complicated, the classification of these conditions currently is in disarray and needs clarification.

TABLE 2-3 Dentinogenesis Imperfecta, Classical Nomenclature

Shields	Clinical Presentation	Witkop
Dentinogenesis imperfecta I	Osteogenesis imperfecta with opalescent teeth	Dentinogenesis imperfecta
Dentinogenesis imperfecta II	Isolated opalescent teeth	Hereditary opalescent teeth
Dentinogenesis imperfecta III	Isolated opalescent teeth	Brandywine isolate

Data from Shields ED: A new classification of heritable human enamel defects and a discussion of dentin defects. In Jorgenson RJ, Paul NW: *Dentition: genetic effects (birth defects original article series),* vol 19, no 1, pp 107-127, New York, 1983, Alan R Liss; Witkop CJ Jr: Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification, *J Oral Pathol* 17:547-553, 1988.

Mature dentin is about 70% mineral, 20% organic matrix, and 10% water. About 85% to 90% of the organic matrix is type I collagen, with two genes intimately involved in its production: *COL1A1* and *COL1A2.* The most abundant non-collagenous proteins in dentin are derived from dentin sialophosphoprotein (DSPP) that is cleaved to form three important dentin proteins: dentin sialoprotein (DSP), dentin glycoprotein (DGP), and dentin phosphoprotein (DPP). The primary gene guiding the formation of these proteins is the *DSPP* gene.

Dentinogenesis imperfecta (DGI) is a hereditary developmental disturbance of the dentin in the absence of any systemic disorder and has been shown to be associated with any one of a number of mutations of the *DSPP* gene. In about half of affected patients, similar dental changes are seen in conjunction with the systemic hereditary disorder of bone, **osteogenesis imperfecta** (see page 572); but genetic studies have shown that the dental alterations are related to mutations in the *COL1A1* and *COL1A2* genes. Extensive pedigrees of individuals with DSPP-related dentinogenesis imperfecta have been studied, and none have exhibited other changes suggestive of osteogenesis imperfecta. This groundbreaking research has confirmed that osteogenesis imperfecta with opalescent teeth is clearly a separate disease from dentinogenesis imperfecta.

Two systems for classification of hereditary dentin disorders, one by Witkop and the other by Shields, historically were well accepted but not totally satisfactory (Table 2-3). The Shields system has been the most widely utilized, but the recent advances in genetics have made the nomenclature problematic. The Mendelian Inheritance of Man (MIM) database is the most current classification system for the molecular genetics of human pathoses. In the MIM system, dentinogenesis imperfecta type I as defined by the original Shield's classification (DGI-I) has been removed from the list of DGI and is classified appropriately as *osteogenesis imperfecta.* DGI-II has become DGI-I, whereas DGI-III and the dentin dysplasias (dentin dysplasia type I [DD-I] and dentin dysplasia type II [DD-II]) have retained their previous names. The Shields and MIM systems currently are contradictory, resulting in confusion with respect to the definition of dentinogenesis imperfecta type I.

Dentinogenesis imperfecta formerly was divided into DGI-II *(hereditary opalescent dentin)* and DGI-III *(Brandywine isolate).* The defining phenotypic feature of the Brandywine isolate was the presence of unusual pulpal enlargement known as *shell teeth* with multiple pulp exposures seen primarily in the deciduous teeth. Current evidence strongly suggests that DGI-III simply represents variable expression of dentinogenesis imperfecta. The original review of the isolate identified only 8% of the kindred with shell teeth. Investigators have documented enlarged pulps in affected individuals whose parents and children have classic dentinogenesis imperfecta. Identical patterns of expression also have been seen in other large kindreds with no connection to the Brandywine isolate. Finally, identical mutations of the *DSPP* gene have been shown to manifest as DGI-II and DGI-III in different families. It seems very clear that *dentinogenesis imperfecta type II* and *dentinogenesis imperfecta type III* represent a single disease with variable expressions.

The confusion does not end with DGI-II/III controversy. Dentin dysplasia type II (DD-II) also has been shown to arise from similar or even identical mutations of the *DSPP* gene. A number of authorities now believe that DD-II, DGI-II, and DGI-III represent a spectrum of the same disease, with DD-II being the mild end of the continuum and DGI-III representing the severe end. Any modern classification will remain problematic until DD-II is renamed and the genetics of DD-I become clarified. In spite of this, the classification system in Table 2-4 is an attempt to clarify the nomenclature based on the current phenotypic and genotypic findings.

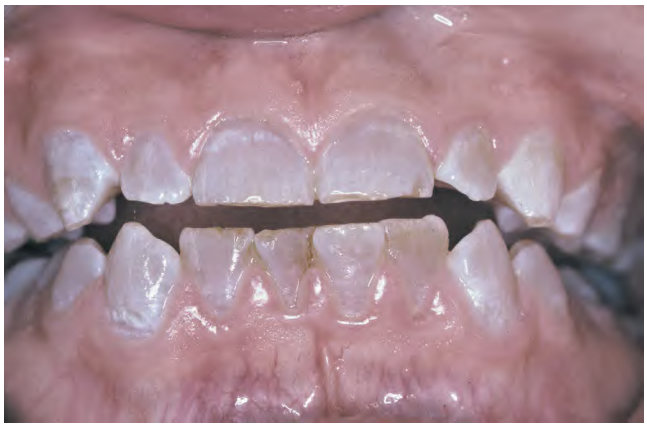
DENTIN SIALOPHOSPHOPROTEIN–ASSOCIATED DENTIN DEFECTS

Clinical and Radiographic Features

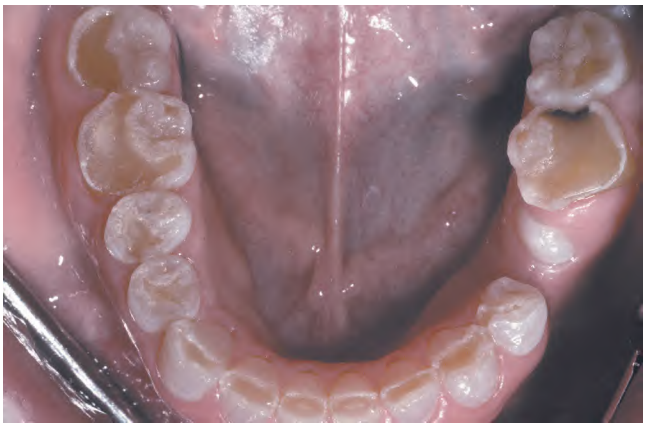
As the nomenclature of DSPP-associated dentin defects evolves, it is expected that the diseases will be listed in the order of phenotypic severity from the mildest to most severe (DD-II, DGI-II, and DGI-III). In spite of this, these disorders are described most efficiently when DGI-II is presented first.

TABLE 2-4 Modified Classification of Hereditary Disorders Affecting Dentin

Disorder	Inheritance	Involved Gene or Genes
Osteogenesis imperfecta with opalescent teeth	Autosomal dominant or recessive	*COL1A1, COL1A2*
DSPP-associated dentin disorders • Dentin dysplasia type II (DD-II) • Dentinogenesis imperfecta (includes old DGI-II and DGI-III)	Autosomal dominant	*DSPP*
Dentin dysplasia type I (DD-I)	Autosomal dominant	*??*



• **Fig. 2-98 Dentinogenesis Imperfecta (DGI).** Dentition exhibiting diffuse brownish discoloration and slight translucence.



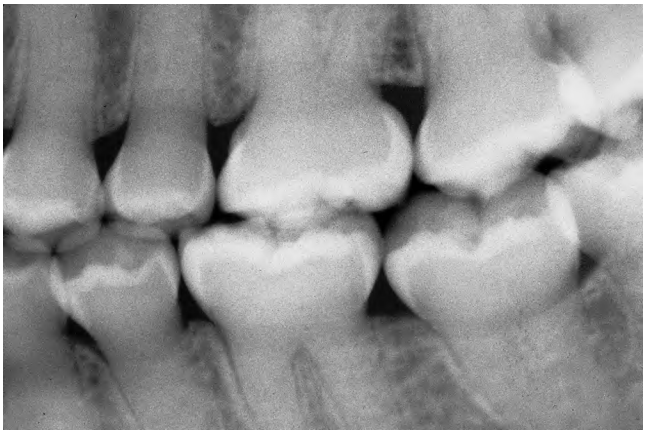
• **Fig. 2-99 Dentinogenesis Imperfecta (DGI).** Dentition exhibiting grayish discoloration with significant enamel loss and attrition.

The prevalence of **dentinogenesis imperfecta** (hereditary opalescent dentin, Capdepont's teeth) is not randomly distributed throughout the United States and Europe. Most cases can be traced to whites (people of English or French ancestry) from communities close to the English Channel. The disorder is autosomal dominant and occurs in about 1:8000 whites in the United States.

Dentinogenesis imperfecta affects teeth in both dentitions with the severity of the dental alterations varying with the age at which the tooth develops. Deciduous teeth are affected most severely, followed by the permanent incisors and first molars, with the second and third molars being least altered.

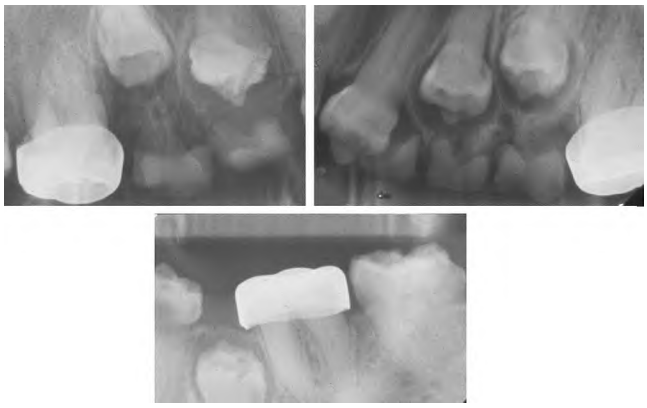
The dentitions have a blue-to-brown discoloration, often with a distinctive translucence (Fig. 2-98). The enamel frequently separates easily from the underlying defective dentin. Once exposed, the dentin often demonstrates significantly accelerated attrition (Fig. 2-99). Radiographically, the teeth have bulbous crowns, cervical constriction, thin roots, and early obliteration of the root canals and pulp chambers (Fig. 2-100).

The trait exhibits close to 100% penetrance but variable expressivity. Clinically obvious enamel hypoplasia is noted in some patients (Fig. 2-101). During the initial development of the dentinoenamel junction (DEJ), there is a temporary expression of enamel proteins by odontoblasts and a similar expression of dentin proteins by pre-ameloblasts. Some investigators have suggested that the enamel hypoplasia may be secondary to expression of mutant DSPP protein by pre-ameloblasts during the early formative stage of the DEJ.

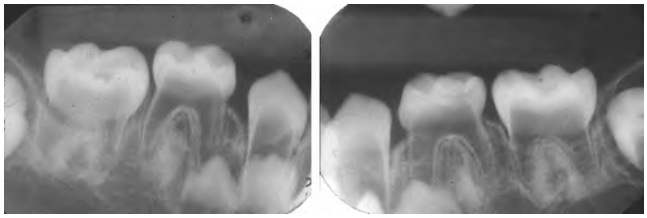


• **Fig. 2-100 Dentinogenesis Imperfecta (DGI).** Radiograph of dentition exhibiting bulbous crowns, cervical constriction, and obliterated pulp canals and chambers.

Although the pulps usually are obliterated by excess dentin production, some teeth may show normal-sized pulps or significant pulpal enlargement. Those with expanded pulps are termed **shell teeth** and demonstrate normal-thickness enamel in association with extremely thin dentin and dramatically enlarged pulps (Fig. 2-102). The



• **Fig. 2-101 Dentinogenesis Imperfecta (DGI).** Radiograph of dentition exhibiting bulbous crowns, early obliteration of the pulp, and enamel hypoplasia. (From Levin LS, Leaf SH, Jelmine RJ, et al: Dentinogenesis imperfecta in the Brandywine isolate (DI type III): clinical, radiologic, and scanning electron microscopic studies of the dentition, *Oral Surg Oral Med Oral Pathol* 56:267-274, 1983.)

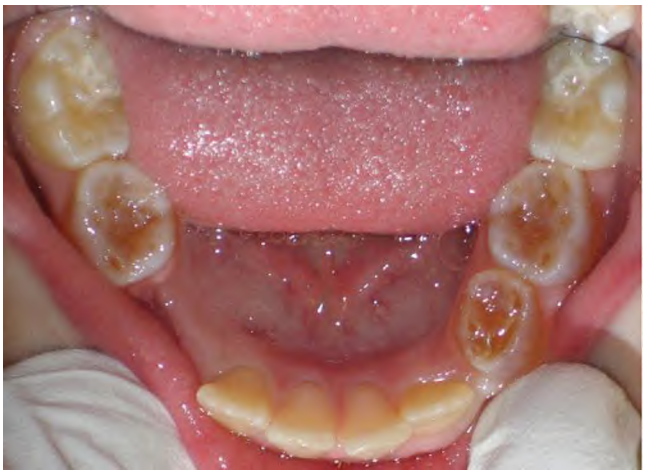


• **Fig. 2-102 Shell Teeth.** Dentition exhibiting normal thickness enamel, extremely thin dentin, and dramatically enlarged pulps.

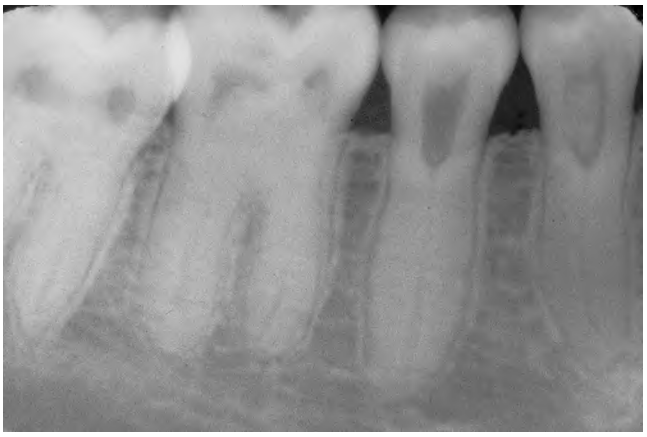
thin dentin may involve the entire tooth or be isolated to the root. This rare abnormality has been seen most frequently in deciduous teeth in the presence of dentinogenesis imperfecta and often is associated with pulp exposures. The alteration may be unassociated with dentinogenesis imperfecta as an isolated finding in both dentitions and demonstrate normal tooth shape and coloration, a negative family history, and diffuse involvement. In the isolated variant, slow but progressive root resorption occurs.

Several kindreds affected with dentinogenesis imperfecta also have been shown to demonstrate progressive, sensorineural, high-frequency hearing loss. Jaw position has been shown to affect the anatomy of the inner ear, and premature tooth loss has been associated with hearing deficits. At this time, it is unclear if the hearing loss is correlated with the *DSPP* mutation or an alteration secondary to the primary gnathic changes. Investigators wonder if dental restoration may prevent the hearing loss or if the *DSPP* gene may directly affect bone formation and the structure of the inner ear.

Dentin dysplasia type II (DD-II; coronal dentin dysplasia) has dramatically different appearances in the primary and succedaneous dentitions. The primary teeth have a blue-to-amber-to-brown translucence, similar to dentinogenesis imperfecta (Fig. 2-103). Radiographically, the dental changes include bulbous crowns, cervical constriction, thin roots, and early obliteration of the pulp. The permanent teeth have a normal color clinically; however, radiographically, the pulp



• **Fig. 2-103 Dentin Dysplasia Type II (DD-II).** Dentition demonstrating darkened and translucent deciduous molars in association with permanent incisors and first molars that appear clinically normal. (Courtesy of Dr. James Zettler.)



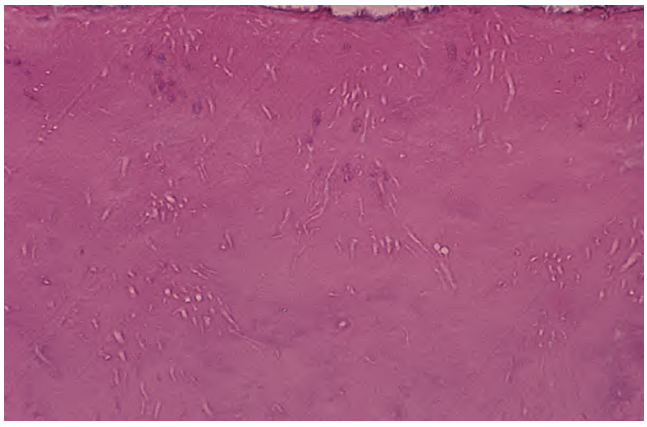
• **Fig. 2-104 Dentin Dysplasia Type II (DD-II).** Radiographic appearance of the permanent dentition exhibiting thistle tube–shaped enlargements of the pulp chambers and numerous pulp stones.

chambers exhibit significant enlargement and apical extension. These enlarged pulp chambers have been described as *thistle tube–shaped* or *flame-shaped* (Fig. 2-104). Pulp stones develop in the enlarged pulp chambers.

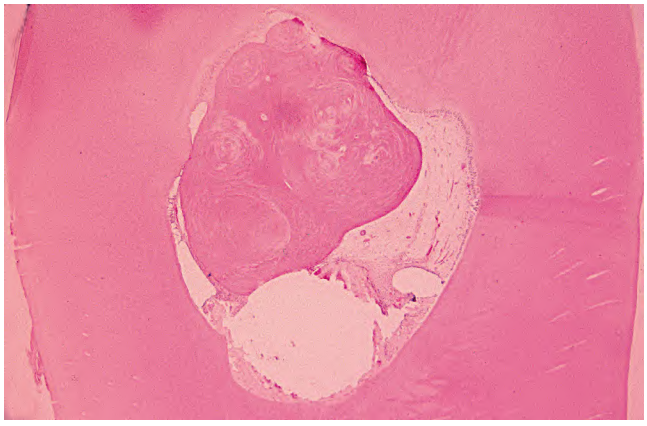
A similar but unrelated disorder is **pulpal dysplasia.** This process develops in teeth that are normal clinically. Radiographically, both dentitions exhibit thistle tube–shaped pulp chambers and multiple pulp stones.

Histopathologic Features

In dentinogenesis imperfecta, the dentin adjacent to the enamel junction appears similar to normal dentin, but the remainder is distinctly abnormal. Short misshapen tubules course through an atypical granular dentin matrix, which often demonstrates interglobular calcification (Fig. 2-105). Scanty atypical odontoblasts line the pulp surface, and cells can be seen entrapped within the defective dentin. In ground sections the enamel is normal in most patients;



• **Fig. 2-105 Dentinogenesis Imperfecta (DGI).** Coronal dentin exhibiting short misshapen tubules within atypical granular dentin matrix.



• **Fig. 2-106 Dentin Dysplasia Type II (DD-II).** Affected tooth exhibiting large pulp stone within the pulp chamber.

however, about one-third of the patients have hypoplastic or hypocalcified defects.

In patients with dentin dysplasia type II, the deciduous teeth demonstrate the pattern noted in dentinogenesis imperfecta. The permanent teeth exhibit normal enamel and coronal dentin. Adjacent to the pulp, numerous areas of interglobular dentin are seen. The radicular dentin is atubular, amorphous, and hypertrophic. Pulp stones develop in any portion of the chamber (Fig. 2-106).

Treatment and Prognosis

In dentinogenesis imperfecta, the entire dentition is at risk because of numerous problems. The root canals become threadlike and may develop microexposures, resulting in periapical inflammatory lesions. In spite of the risk of enamel loss and significant attrition, the teeth often are not good candidates for full crowns because of cervical fracture. The success of full coverage is best in teeth with crowns and roots that exhibit close to a normal shape and size. Overlay dentures placed on teeth that are covered with fluoride-releasing glass ionomer cement have been used with success in some cases.

• BOX 2-12 Systemic Diseases Correlated with Dentin Dysplasia-like Alterations

- Calcinosis universalis
- Rheumatoid arthritis and hypervitaminosis D
- Sclerotic bone and skeletal anomalies
- Tumoral calcinosis

The success of therapy varies with the severity of the dental changes in individual patients. In those with extensive attrition, the vertical dimension can be rebuilt by placing nonprecious metal castings with adhesive luting agents on teeth that have received no preparation and are not subject to significant occlusal stress. The newer composites combined with a dentin-bonding agent have been used in areas subject to occlusal wear. When large kindreds have been followed over a long term, many of those affected are candidates for full dentures or implants by 30 years of age in spite of the numerous interventions. Newer materials and techniques may alter this outlook.

The deciduous teeth in dentin dysplasia type II can be approached in a manner similar to that described for dentinogenesis imperfecta. Although not frequent, periapical inflammatory lesions have been seen in association with the permanent teeth of some affected patients. Because the pulp canals usually are not obliterated completely, endodontic therapy is accomplished more readily.

DENTIN DYSPLASIA TYPE I

Dentin dysplasia was initially categorized in 1939. Two major patterns have been described: type I and type II. However, type II currently is thought to be a variation of dentinogenesis imperfecta, and the discussion of this condition is included in that section (see page 101). By definition, dentin dysplasia should have no correlation with systemic disease. Systemic diseases reported to be associated with similar dentin changes are listed in Box 2-12.

Clinical and Radiographic Features

Dentin dysplasia type I (DD-I; radicular dentin dysplasia) has been referred to as **rootless teeth,** because the loss of organization of the root dentin often leads to a shortened root length. The process exhibits an autosomal dominant pattern of inheritance and is one of the rarest forms of human dentin disorders with an approximate prevalence of 1:100,000. The enamel and coronal dentin are normal clinically and well formed (Fig. 2-107), but the radicular dentin loses all organization and subsequently is shortened dramatically (Fig. 2-108). Wide variation in root formation is produced because dentinal disorganization may occur during different stages of tooth development. If the dentin organization is lost early in tooth development, markedly deficient roots are formed; later disorganization results in

minimal root malformation. The variability is most pronounced in permanent teeth and may vary not only from patient to patient but also from tooth to tooth in a single patient. Because of the shortened roots, the initial clinical signs are extreme tooth mobility and premature exfoliation, spontaneously or secondary to minor trauma. Less frequently, delayed eruption is the presenting symptom. The strength of the radicular dentin is reduced, with the teeth being predisposed to fracture during extractions.

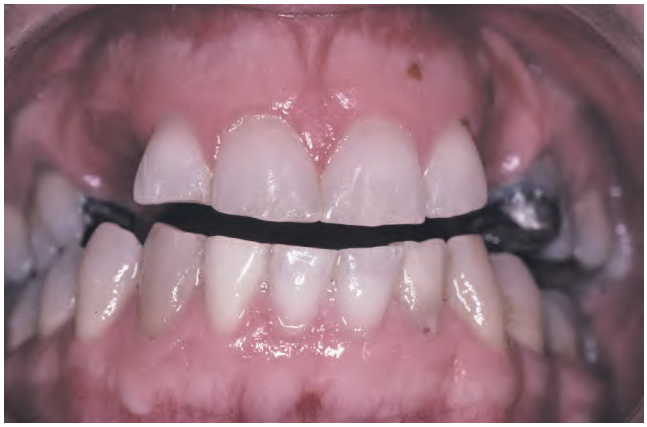
Radiographically, variations in radicular anatomy have been described, and a subclassification of dentin dysplasia type I has been proposed (Box 2-13; Fig. 2-109). The deciduous teeth often are affected severely, with little or no detectable pulp, and roots that are markedly short or absent (similar to type DDIa). In most patients, the permanent teeth demonstrate short roots with no canals and a small crescent-shaped pulpal remnant parallel of the cementoenamel junction (types DDIb and DDIc). Type DDId is most unusual and should warn the clinician to rule out systemic diseases, such as tumoral calcinosis, that can produce identical changes.

In general, the teeth without root canals are those that frequently develop periapical radiolucencies without obvious cause (see Fig. 2-108). The radiolucencies represent periapical inflammatory disease and appear secondary to caries or spontaneous coronal exposure of microscopic threads of pulpal remnants present within the defective dentin.

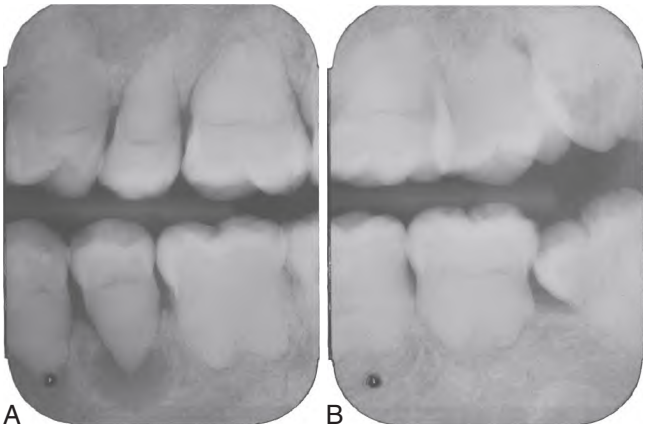
A similar but unrelated disorder is **fibrous dysplasia of dentin.** This autosomal dominant disorder exhibits teeth

• BOX 2-13 Subclassification of Dentin Dysplasia Type I

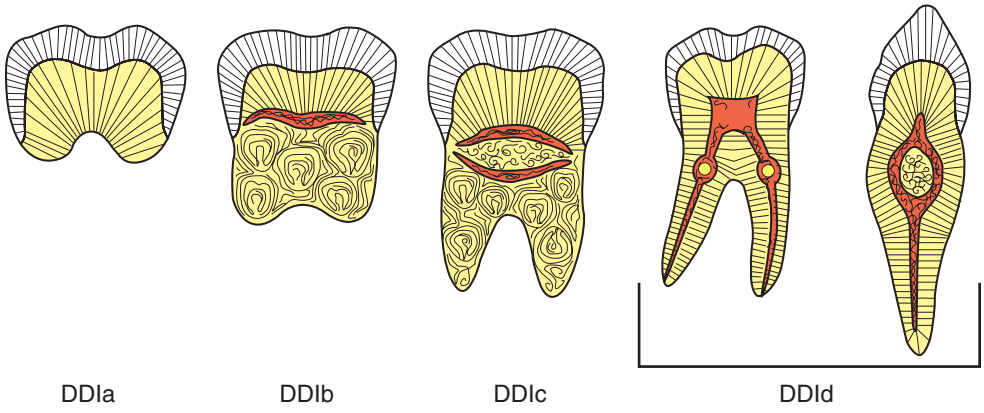
- DDIa: No pulp chambers, no root formation, and frequent periapical radiolucencies
- DDIb: A single small horizontally oriented and crescent-shaped pulp, roots only a few millimeters in length, and frequent periapical radiolucencies
- DDIc: Two horizontally oriented and crescent-shaped pulpal remnants surrounding a central island of dentin, significant but shortened root length, and variable periapical radiolucencies
- DDId: Visible pulp chambers and canals, near normal root length, enlarged pulp stones that are located in the coronal portion of the canal and create a localized bulging of the canal and root, constriction of the pulp canal apical to the stone, and few periapical radiolucencies



• Fig. 2-107 Dentin Dysplasia Type I (DD-I). Dentition exhibiting attrition but otherwise normal coronal coloration and morphology.



• Fig. 2-108 Dentin Dysplasia Type I (DD-I). Posterior dentition exhibiting dramatically shortened roots, absence of pulp canals, and small, crescent-shaped pulp chambers. Note radiolucency at apex of mandibular bicuspid. (Courtesy of Dr. Michael Quinn.)



• Fig. 2-109 Dentin Dysplasia Type I (DD-I). Illustration demonstrating the variability of the radiographic appearance according to the degree of dentin disorganization within the root.

• **Fig. 2-110 Dentin Dysplasia Type I (DD-I).** Polarized light view of affected tooth demonstrating a classic "stream flowing around boulders" appearance.

that are normal clinically. Radiographically the teeth are normal in shape but demonstrate a radiodense product filling the pulp chambers and canals. In contrast to dentinogenesis imperfecta, small foci of radiolucency can be seen in the pulp. Unlike dentin dysplasia type I, no crescent pulp chambers or decrease in root length is seen. The radiodense intrapulpal material consists of fibrotic dentin.

Histopathologic Features

In patients with dentin dysplasia type I, the coronal enamel and dentin are normal. Apical to the point of disorganization, the central portion of the root forms whorls of tubular dentin and atypical osteodentin. These whorls exhibit a peripheral layer of normal dentin, giving the root the appearance of a "stream flowing around boulders" (Fig. 2-110).

Treatment and Prognosis

In patients with dentin dysplasia type I, preventive care is of foremost importance. Perhaps as a result of shortened roots, early loss from periodontitis is frequent. In addition, pulp vascular channels extend close to the dentinoenamel junction; therefore, even shallow occlusal restorations can result in pulpal necrosis. Meticulous oral hygiene must be established and maintained.

If periapical inflammatory lesions develop, the root length guides the therapeutic choice. Conventional endodontic therapy requires mechanical creation of canal paths and has been successful in teeth without extremely short roots. Teeth with short roots demonstrate pulpal ramifications that eliminate conventional endodontic treatment as an appropriate therapeutic option. Periapical curettage and retrograde amalgam seals have demonstrated short-term success.

• BOX 2-14 Pathoses Noted in Association with Regional Odontodysplasia

- Ectodermal dysplasia
- Epidermal nevi
- Hydrocephalus
- Hypophosphatasia
- Ipsilateral facial hypoplasia
- Neurofibromatosis
- Orbital coloboma
- Rh factor incompatibility
- Vascular nevi

• BOX 2-15 Proposed Causations for Regional Odontodysplasia

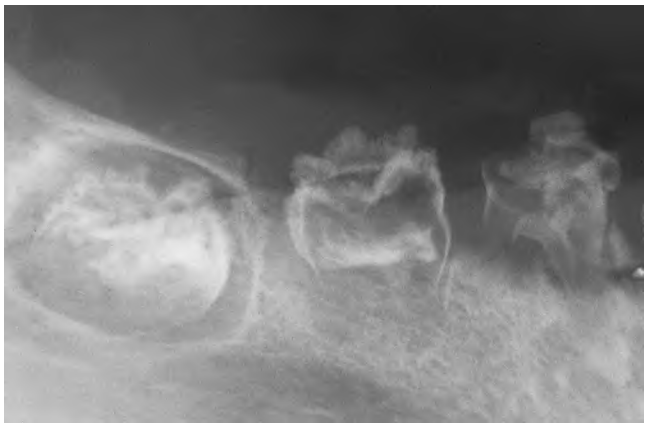
- Abnormal migration of neural crest cells
- Latent virus
- Local circulatory deficiency
- Local trauma or infection
- Hyperpyrexia
- Malnutrition
- Medication used during pregnancy
- Radiation therapy
- Somatic mutation

REGIONAL ODONTODYSPLASIA (GHOST TEETH)

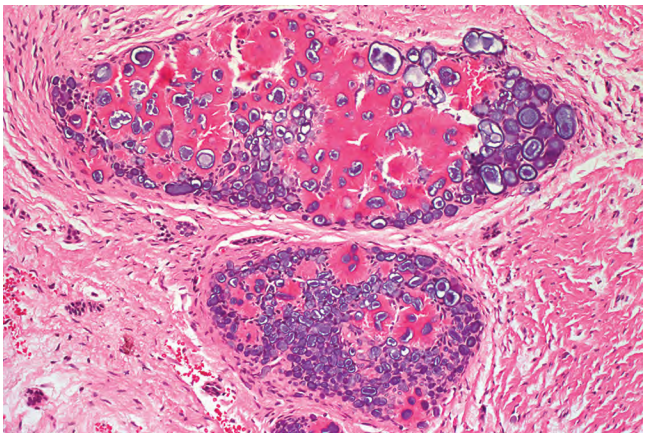
Regional odontodysplasia is a localized, nonhereditary developmental abnormality of teeth with extensive adverse effects on the formation of enamel, dentin, and pulp. Most cases are idiopathic, but a number have been related to various syndromes, growth abnormalities, neural disorders, and vascular malformations (Box 2-14). A number of causes have been proposed (Box 2-15), but the most popular theory revolves around an alteration in the vascular supply. Several cases have occurred in patients with vascular nevi of the head and neck; in addition, similar changes have been induced in animals by restricting the vascular flow to an area of the jaws.

Clinical and Radiographic Features

Regional odontodysplasia is an uncommon finding that occurs in both dentitions and exhibits no racial predilection and a slight female predominance. A review of the age at the time of diagnosis reveals a bimodal peak that correlates with the normal time of eruption of the deciduous (2 to 4 years) and permanent (7 to 11 years) dentitions. Typically, the process affects a focal area of the dentition, with involvement of several contiguous teeth. A maxillary predominance



• **Fig. 2-111 Regional Odontodysplasia (Ghost Teeth).** Posterior mandibular dentition exhibiting enlarged pulps and extremely thin enamel and dentin. (Courtesy of Dr. John B. Perry.)



• **Fig. 2-112 Regional Odontodysplasia.** Follicular tissue contains scattered collections of enameloid conglomerates and islands of odontogenic epithelium.

exists with a predilection for the anterior teeth. Occasionally, an unaffected tooth may be intermixed within a row of altered teeth. Ipsilateral involvement of both arches and bilateral changes in the same jaw have been reported. Although rare generalized involvement has been documented, the presence of regional odontodysplasia in more than two quadrants is rare. Involvement of the deciduous dentition typically is followed by similarly affected permanent teeth. In the area of altered teeth, the surrounding bone often exhibits a lower density; in addition, hyperplasia of the soft tissue may be noted overlying affected teeth that are impacted.

Many of the affected teeth fail to erupt. Erupted teeth demonstrate small irregular crowns that are yellow to brown, often with a very rough surface. Caries and associated periapical inflammatory lesions are fairly common. Because of dentinal clefts and very long pulp horns, pulpal necrosis is common (often in the absence of an obvious cause). Radiographically, the altered teeth demonstrate extremely thin enamel and dentin surrounding an enlarged radiolucent pulp, resulting in a pale wispy image of a tooth; hence the term **ghost teeth** (Fig. 2-111). A lack of contrast is seen between the dentin and the enamel, with an indistinct or "fuzzy" appearance of the coronal silhouette. Short roots and open apices may be seen. The enlarged pulps frequently demonstrate one or more prominent pulp stones. The most common presenting signs and symptoms include delayed or failure of eruption, early exfoliation, abscess formation, malformed teeth, and noninflammatory gingival enlargement.

Histopathologic Features

In ground sections the thickness of the enamel varies, resulting in an irregular surface. The prism structure of the enamel is irregular or lacking, with a laminated appearance. The dentin contains clefts scattered through a mixture of interglobular dentin and amorphous material. Globular areas of poorly organized tubular dentin and scattered cellular inclusions often are seen. The pulp tissue contains free or attached stones that may exhibit tubules or consist of laminated calcification. The follicular tissue surrounding the crown may be enlarged and typically exhibits focal collections of basophilic enamel-like calcifications called **enameloid conglomerates** (Fig. 2-112). This pattern of calcification is not specific for regional odontodysplasia and has been seen in other processes with disturbed enamel formation, such as amelogenesis imperfecta. Scattered islands of odontogenic epithelium and other patterns of intramural calcification also are seen.

Treatment and Prognosis

Currently no therapeutic consensus exists with respect to management of patients affected by regional odontodysplasia. Careful evaluation of each patient's individual findings is important in order to develop the most appropriate treatment plan. Unerupted teeth should remain untouched, restoring function with a removable partial prosthesis until the skeletal growth period has passed. Erupted teeth can be covered with etched-retained restorations or stainless steel crowns until final restorations can be placed after the completion of growth. Because of the fragile nature of the coronal hard tissue and the ease of pulp exposure, tooth preparation is contraindicated. Severely affected and infected teeth often are not salvageable and need to be removed.

Although vitality of the abnormal dentition often is difficult to maintain, such efforts may permit continued dentinal development of teeth affected by regional odontodysplasia. The resultant teeth tend to demonstrate hypoplastic crowns and short roots with more normal appearing canals and well-developed apices.

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3 Pulpal and Periapical Disease

PULPITIS

Like the brain, the dental pulp is encased in hard tissue that can alter the response to local insults. The surrounding dentin provides rigid mechanical support and protection from the bacteria-rich oral cavity. A focal breach in this barrier can adversely affect the health of the dental pulp. Inflammatory vascular changes increase the pulpal volume, but swelling is restricted due to the surrounding dentinal walls, often triggering pain. Normal pulpal stroma is a resilient gelatin-like material that attempts to localize the increased pressures to the site of damage.

If the inflammatory process is not contained, the dental pulp is uniquely hampered in its response because the only source of vascularity enters through the apical foramen without a collateral blood supply. Upon exposure, the contaminated pulp space acts as a conduit between the oral cavity and the usually sterile alveolar bone. Spread of pulpal infection into bone can lead to serious complications, such as cavernous sinus thrombosis (see page 127), Ludwig angina (see page 126), or systemic sepsis with life-threatening complications. Pulpitis-related pain is an important defense mechanism that can lead to therapeutic intervention prior to serious complications.

Four main types of noxious stimuli are common causes of pulpal inflammation **(pulpitis):**

1. *Mechanical damage:* Mechanical sources of injury include traumatic accidents, iatrogenic damage from dental procedures, attrition, abrasion, and barometric changes.
2. *Thermal injury:* Severe thermal stimuli can be transmitted through large uninsulated metallic restorations or may occur from such dental procedures as cavity preparation, polishing, and exothermic chemical reactions of dental materials.
3. *Chemical irritation:* Chemical-related damage can arise from erosion or from the inappropriate use of acidic dental materials.
4. *Bacterial effects:* Bacteria can damage the pulp through toxins or directly after extension from caries or transportation via the vasculature.

The best classification system for pulpitis is one that guides the appropriate treatment. *Reversible pulpitis* denotes a level of pulpal inflammation in which the tissue is capable of returning to a normal state of health if the noxious stimuli are removed. *Irreversible pulpitis* implies that a higher level of inflammation has developed in which the dental pulp has been damaged beyond the point of recovery. Often, frank invasion by bacteria is the crossover point from reversible to irreversible pulpitis.

Clinical Features

Evaluation of pulpal pain (pulpalgia) includes a combination of the clinical presentation and the response of the tooth to a variety of vitality testing procedures. The predictive value of these tests is sometimes less than optimal. When the procedures demonstrate that the pulp is disease free, the results are highly reliable. However, when a pulp appears to test positively for irreversible pulpitis, histopathologic examination may demonstrate no obvious evidence of pulpal disease. The practitioner should use all available tests, clinical information, and personal judgment in an attempt to arrive at an appropriate diagnosis.

Clinically Normal Pulp

Clinically, a normal pulp exhibits no signs or symptoms that suggest pulpitis. These teeth respond to cold with mild pain that resolves in 1 to 2 seconds, whereas heat is not associated with pulpal discomfort. Pain to percussion will not be evident, and the radiographic examination of the periradicular bone will be within normal limits.

Reversible Pulpitis

A tooth with **reversible pulpitis** is acutely painful when a stimulus (usually cold or sweet foods, but sometimes heat) is applied, but the discomfort resolves within a few seconds after elimination of the stimulus. Typically, the tooth responds to electric pulp testing at lower levels of current than an appropriate control tooth. Mobility and sensitivity to percussion are absent. A cracked tooth or defective restoration often is present if this pattern of pulpal pain is noted in association with discomfort upon biting. If the pulpitis is allowed to progress, then the duration of the pain on stimulation can become longer and the pulp may become affected irreversibly.

A similar pattern of pulpal pain can occur when exposed dentin receives a thermal, chemical, or physical stimulus.

Dentin sensitivity should be considered if exposed dentin is present and triggers for reversible pulpitis such as caries, tooth fractures, and defective or newly placed restorations are not present.

Irreversible Pulpitis

Patients with early **irreversible pulpitis** generally have sharp, severe pain on thermal stimulation, and the pain continues for a longer period of time after the stimulus is removed. Cold is especially uncomfortable, although heat or sweet and acidic foods also can elicit pain. In addition, the pain may be spontaneous or continuous and may be exacerbated when the patient lies down. The tooth responds to electric pulp testing at lower levels of current.

In the early stages of irreversible pulpitis, the pain often can be localized easily to the individual offending tooth; with increasing discomfort, however, the patient may be unable to identify the offending tooth within a quadrant. Although pulpal pain never crosses the midline, it can be referred from arch to arch, making pulp testing of both arches a necessity in difficult cases.

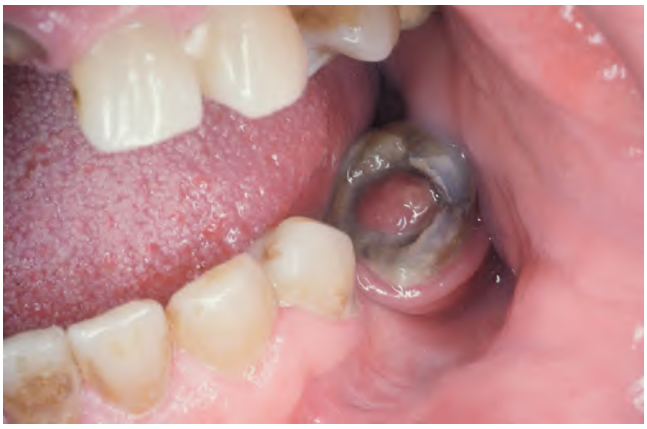
In the later stages of irreversible pulpitis, the pain increases in intensity and is experienced as a throbbing pressure that can keep patients awake at night. At this point, heat increases the pain; however, cold may produce relief. The tooth responds to electric pulp testing at higher levels of current or demonstrates no response. Mobility and sensitivity to percussion are usually absent because significant inflammation has not spread yet to the apical area. If pulpal drainage occurs (e.g., crown fracture, fistula formation), then the symptoms may resolve—only to return if the drainage ceases.

Pulpal Necrosis

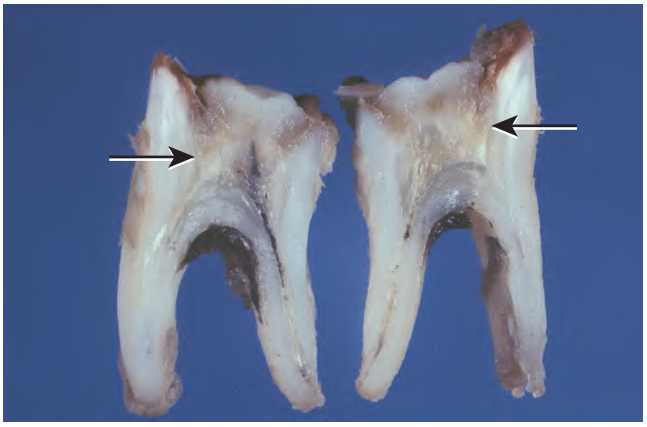
Pulpal necrosis should be suspected when the tooth fails to respond to electric or thermal sensitivity testing. Partial pulpal necrosis (pulpal necrobiosis) often occurs and may be isolated to the coronal portion or one canal of a multirooted tooth. Teeth with necrotic pulps present with symptoms that vary from none to acute pain with or without bite sensitivity and hyperocclusion.

Chronic Hyperplastic Pulpitis

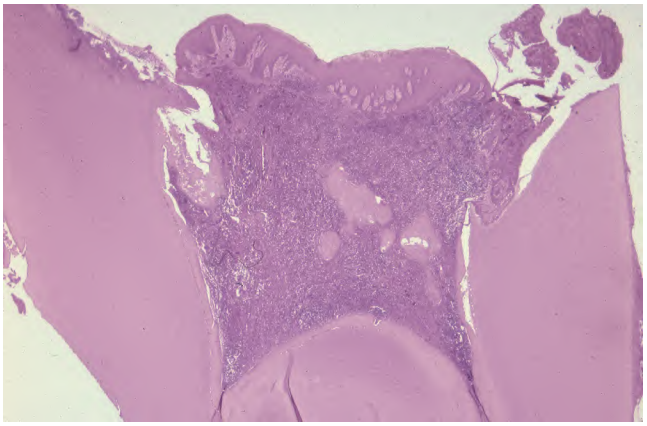
One unique pattern of pulpal inflammation is **chronic hyperplastic pulpitis (pulp polyp).** This condition occurs in children and young adults who have large exposures of the pulp in which the entire dentinal roof often is missing. The most frequently involved teeth are the deciduous or succedaneous molars, which have large pulp chambers in these age groups. Mechanical irritation and bacterial invasion result in a level of chronic inflammation that produces hyperplastic granulation tissue that extrudes from the chamber and often fills the associated dentinal defect (Figs. 3-1 to 3-3). The apex may be open and reduces the chance of pulpal necrosis secondary to venous compression. The tooth is asymptomatic except for a possible feeling of pressure when it is placed into masticatory function.



• **Fig. 3-1 Chronic Hyperplastic Pulpitis.** Erythematous granulation tissue extruding from the pulp chamber of the mandibular first molar.



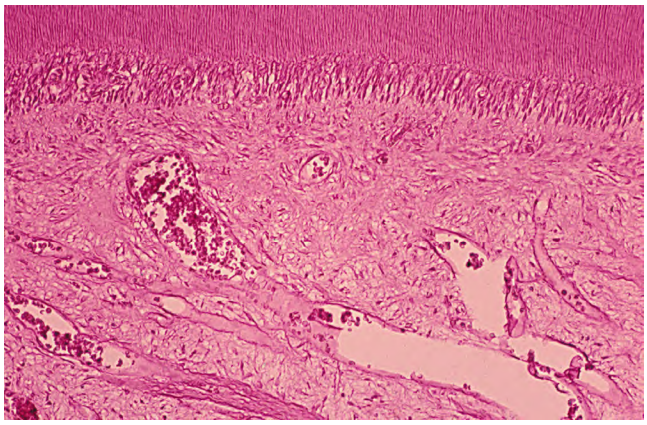
• **Fig. 3-2 Chronic Hyperplastic Pulpitis.** Gross photograph demonstrating hyperplastic pulp tissue filling a large coronal carious defect. *Arrows* delineate the previous roof of the pulp chamber.



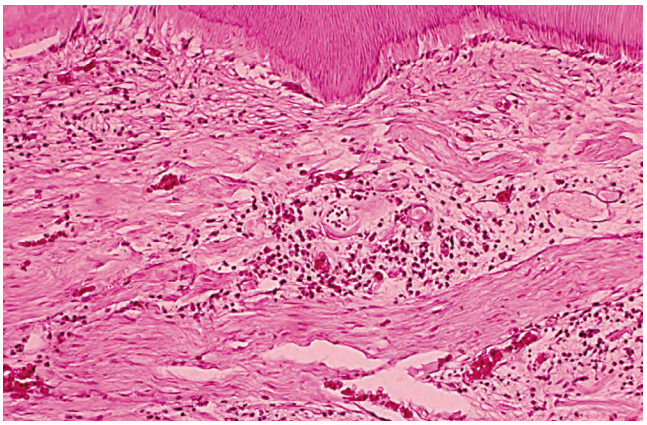
• **Fig. 3-3 Chronic Hyperplastic Pulpitis.** Same tooth as depicted in Fig. 3-2. Chronically inflamed granulation tissue fills the coronal defect. Note surface stratified squamous epithelium.

Histopathologic Features

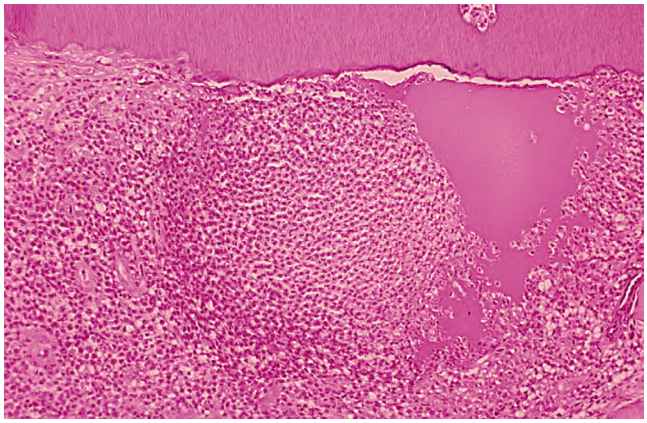
Basically, the histopathology is primarily of academic interest and usually does not affect treatment significantly. Numerous investigations have shown a surprising lack of correlation between histopathologic findings and the clinical symptoms in the majority of pulps examined.



• **Fig. 3-4 Reversible Pulpitis.** Dental pulp exhibiting hyperemia and edema. The adjacent dentin was cut recently during placement of a dental restoration.



• **Fig. 3-6 Irreversible Pulpitis.** Same tooth as depicted in Fig. 3-5. The dental pulp exhibits an area of fibrosis and chronic inflammation peripheral to the zone of abscess formation.



• **Fig. 3-5 Irreversible Pulpitis.** Dental pulp exhibiting acute inflammatory infiltrate consisting predominantly of polymorphonuclear leukocytes.

In patients with reversible pulpitis, the pulp usually shows hyperemia, edema, and a few inflammatory cells underlying the area of affected dentinal tubules (Fig. 3-4). Tertiary dentin may be noted in the adjacent dentinal wall, and scattered acute inflammatory cells are found occasionally.

Irreversible pulpitis often demonstrates congestion of the venules that results in focal necrosis. This necrotic zone contains polymorphonuclear leukocytes and histiocytes (Fig. 3-5). The surrounding pulp tissue usually exhibits fibrosis and a mixture of plasma cells, lymphocytes, and histiocytes (Fig. 3-6).

Chronic hyperplastic pulpitis demonstrates a cap of subacutely inflamed granulation tissue that fills the entire space of the original pulp chamber and histopathologically resembles a pyogenic granuloma (see page 483). The surface of the polyp may or may not be covered with stratified squamous epithelium, which migrates from the adjacent gingiva or arises from sloughed epithelium within the oral fluids (see Fig. 3-3). The deeper pulp tissue within the canals typically demonstrates fibrosis and a chronic inflammatory infiltrate. Pulpal calcifications are common in both the radicular and coronal portions. Often the apical portion of the pulp tissue is normal with minimal inflammation or fibrosis.

Treatment and Prognosis

Reversible pulpitis is treated by removal of the local irritant. On occasion, analgesic medications sometimes are desirable. The prognosis of reversible pulpitis is good if action is taken early enough. The pulp status should be evaluated periodically over the next 3 months to ensure that healing has occurred and the process has not progressed to irreversible pulpitis or necrosis.

Irreversible and chronic hyperplastic pulpitis are treated by extraction of the tooth or by root canal therapy.

◆ SECONDARY AND TERTIARY DENTIN

Formation of dentin proceeds throughout life. The dentin formed before completion of the crown is called **primary dentin.** This process is followed by the formation of **secondary dentin.** The same odontoblasts that formed the primary dentin remain functional and produce secondary dentin. With advancing age in functioning teeth, dentin is deposited diffusely along the inner walls and leads to smaller pulp chambers and canals. This type of dentin is termed **physiologic secondary dentin** and exhibits slow and gradual deposition that increases after the age of 35 to 40 years. A significantly decreased amount of secondary dentin has been described in impacted teeth, suggesting that functional forces of occlusion promote the deposition. Deposition within the pulp chamber often is not totally uniform. In posterior teeth, the greatest deposition is seen on the pulpal floor, to a lesser extent on the roof, and least on the sidewalls. Therefore, with age, pulp chambers decrease significantly in height but not extensively in width. Forensic scientists have suggested that the formation of this secondary dentin occurs so consistently that the width ratio of the dentin taken at three different root levels correlates very closely with age. Other investigators dispute this finding

and believe the process does not occur in a linear manner, making age estimation difficult, especially in young adults.

Physiologic secondary dentin is more advanced in males and has been associated positively with calcification-related diseases (e.g., arthritis, gout, kidney stones, gall stones, atherosclerosis, and hypertension). Early widespread formation of secondary dentin has been seen in association with **progeria,** a condition characterized by accelerated aging. On occasion, significant traumatic injury can lead to early obliteration of the pulp chamber and canal **(calcific metamorphosis)** in the affected tooth.

Localized new dentin also is laid down in areas of focal injury. This dentin is more haphazardly organized and is termed **tertiary (reactionary, reparative, irregular,** or **irritation) dentin.** This localized dentin formation may occur in response to the following:

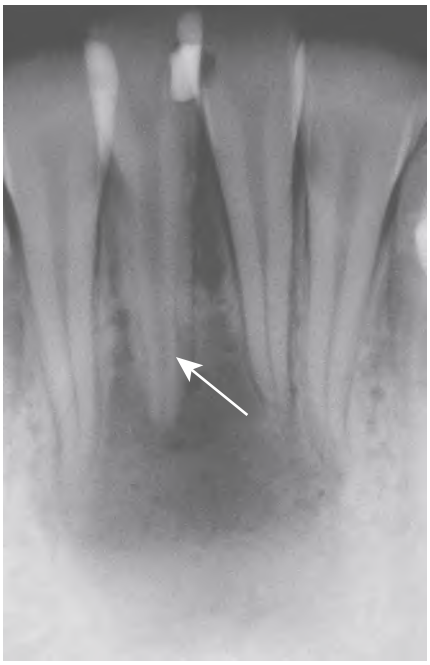
- Attrition
- Fracture
- Erosion
- Abrasion
- Caries
- Periodontal disease
- Mechanical injury from dental procedures
- Irritation from dental materials

Injury of the peripheral odontoblastic processes is all that is required to initiate tertiary dentin formation. If the stimulus is mild to moderate, then the tertiary dentin typically is produced by surviving odontoblasts and is termed *reactionary dentin.* This type of tertiary dentin is more regular in appearance and continuous with the tubules of the primary and secondary dentin. If the stimulus is more severe and leads to the death of the primary odontoblasts, then a new generation of odontoblasts may arise from undifferentiated cells within the pulp and continue to form tertiary dentin that is termed *reparative dentin.* Demineralization of dentin during caries also releases significant amounts of calcium and phosphates. These minerals often diffuse toward the pulp and assist in sclerosis of the tubules as calcium phosphate.

The initial layer of reparative dentin is atubular and known as *interface dentin (fibrodentin).* This thin band may be acellular or exhibit scattered nuclear inclusions. After deposition of the interface dentin, the remainder of the reparative dentin is tubular but not continuous with the primary, secondary, or reactionary dentin. This lack of communication further assists in protecting the pulp from the external stimulus. When the primary odontoblasts die, their dentinal tubules are filled with degenerated odontoblastic processes and are termed *dead tracts.* These tubules usually are sealed off from the pulp by the reparative dentin.

Clinical and Radiographic Features

As noted on periapical radiographs, the deposition of secondary dentin results in diminishing size of pulp chambers and canals. Secondary dentin appears to reduce sensitivity of the affected teeth, susceptibility to dentinal caries, and the trauma of dental procedures. Although production of secondary dentin makes pulp exposure during operative procedures less likely, it also increases the difficulty of locating the pulp chamber and canals during endodontic therapy. On occasion, large inflammatory lesions may involve more than one apex; the size of the canals can be used to help determine the original focus of infection because the canal may be larger in the tooth that became nonvital earlier (Fig. 3-7). Teeth affected by calcific metamorphosis often are discovered clinically by a yellow discoloration of the crown; radiographically, the affected teeth exhibit an accelerated closure of the pulp chamber and canal when compared with adjacent or contralateral teeth (Fig. 3-8). In such cases, the pulpal space may appear to be obliterated completely or reduced dramatically. This alteration usually follows trauma to the tooth and may be seen as early as 3 months after the traumatic episode; however, usually the condition is not detected for about 1 year.

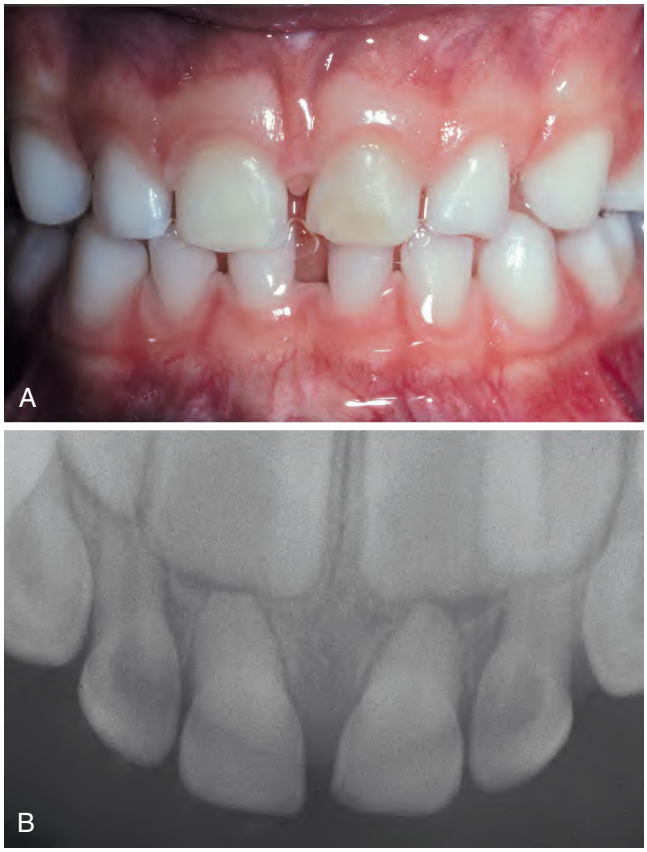


• **Fig. 3-7 Physiologic Secondary Dentin.** Periapical abscess with all four teeth nonresponsive to electric pulp testing. Decreased deposition of physiologic secondary dentin on the right central incisor *(arrow)* delineated the origin of the infection; endodontic treatment of this tooth resolved the lesion.

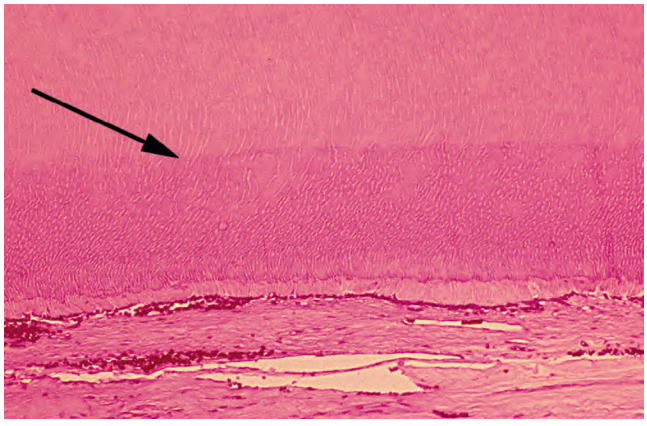
Histopathologic Features

Physiologic secondary dentin consists of regular tubular dentin that is applied onto the primary dentin. These two layers of dentin can be separated by a line of demarcation, often indicated by a bending of the tubules (Fig. 3-9). With advancing age, as the odontoblasts undergo degenerative changes, the physiologic secondary dentin becomes more irregular with fewer tubules.

The quality and appearance of tertiary dentin depend on the severity of the noxious stimulus that promoted its

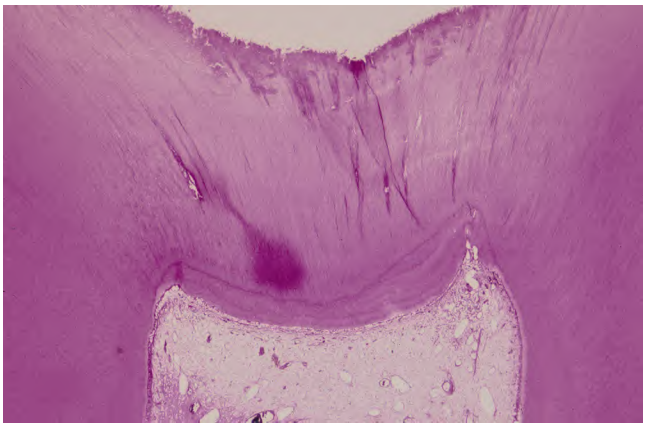


• **Fig. 3-8 Calcific Metamorphosis. A,** Left deciduous maxillary central incisor exhibiting yellow discoloration. **B,** Radiograph of the same patient showing total calcification of the pulp chambers and canals of the deciduous maxillary incisors. (Courtesy of Dr. Jackie L. Banahan.)



• **Fig. 3-9 Physiologic Secondary Dentin.** A distinct line of demarcation *(arrow)* separates the primary dentin and physiologic secondary dentin.

formation. Tertiary dentin is localized to the pulpal end of the odontoblastic processes that were affected (Fig. 3-10). With a mild stimulus, such as abrasion or attrition, reactionary dentin exhibits slow deposition characterized by tubules that are continuous with the secondary dentin and only slightly irregular. With more severe damage (e.g., a rapidly progressing carious lesion), reparative dentin is formed, a process that occurs more rapidly and consists of



• **Fig. 3-10 Reparative Secondary Dentin.** Localized deposition of secondary dentin *(bottom)* at the pulpal end of the dentinal tubules affected by the carious process.

a thin layer of interface dentin on which is deposited irregular dentin with widely scattered, disorganized tubules.

Treatment and Prognosis

In studies of teeth exhibiting calcific metamorphosis, the vast majority of affected teeth never develop clinical or radiographic features suggestive of periapical inflammatory disease; therefore, endodontic therapy should be performed only if periapical pathosis or negative vitality testing is present. Even if a canal space cannot be identified radiographically, conventional root canal therapy usually can locate and negotiate the pulp canal. Because of the dramatically reduced canal space, location of the pulp canal can be difficult, and care must be exercised during access preparation to prevent perforation. If endodontic therapy is unsuccessful, then periapical surgery can be performed in those cases with evidence of periapical inflammatory disease. If vitality testing is positive, then periodic reevaluation appears prudent. To improve dental aesthetics, full coverage is recommended for discolored anterior teeth with large restorations. Otherwise, bleaching often effectively resolves the discoloration.

◆ PULPAL CALCIFICATIONS

Calcifications within the dental pulp are not rare, but the frequency is difficult to determine. Reported rates vary from 8% to 90%, but several investigators have documented a prevalence of approximately 20% in individual teeth reviewed radiographically. Because radiographically detectable pulp stones typically exceed 200 µm in diameter, the prevalence in a histopathologic review would be expected to be much higher. An increased prevalence of pulp stones has been reported in association with a variety of chronic pulpal irritants, such as attrition, abrasion, erosion, caries, periodontitis, dental restorative procedures, orthodontic tooth movement, and tooth injury. Although many examples remain idiopathic, pulpal calcification also has been

associated with aging, fluoride supplementation, hypervitaminosis D, and a few genetic disorders, such as dentin dysplasia type II (see page 101).

The three types of pulpal calcifications are:

1. Denticles
2. Pulp stones
3. Diffuse linear calcifications

All pulpal calcifications start out as free bodies within the pulp tissue, but many may become attached or embedded in the dentinal walls of the pulp.

Denticles are believed to form as a result of an epitheliomesenchymal interaction within the developing pulp. Epithelial strands originating from the root sheath, or cervical extensions into the pulp chamber adjacent to furcations, induce odontoblastic differentiation of the surrounding mesenchyme of the dental papilla, forming the core of the denticle. Odontoblasts deposit tubular dentin as they move away from the central epithelium and produce thimble-shaped structures surrounding the epithelium.

Pulp stones are believed to develop around a central nidus of pulp tissue (e.g., collagen fibril, ground substance, necrotic cell remnants). Initial calcification begins around the central nidus and extends outward in a concentric or radial pattern of regular calcified material. Pulp stones are formed within the coronal portions of the pulp and may arise as a part of age-related or local pathologic changes.

Diffuse linear calcifications do not demonstrate the lamellar organization of pulp stones; they exhibit areas of fine, fibrillar, irregular calcification that often parallel the vasculature. These calcifications may be present in the pulp chamber or canals, and the frequency increases with age.

Clinical and Radiographic Features

Denticles and pulp stones can reach sufficient size to be detected on intraoral radiographs as radiopaque enlargements within the pulp chamber or canal (Fig. 3-11). Diffuse calcifications are not detectable radiographically.

Other than rare difficulties during endodontic procedures, pulpal calcifications are typically of little clinical significance. Some investigators associate the calcifications with dental neuralgias, but the high frequency of these lesions in the absence of clinical symptoms argues against this relationship. Others have suggested a relationship between pulpal calcification and carotid artery calcification, which potentially could be a marker for cardiovascular disease. In spite of this, studies of the association by multiple groups have not proven a strong correlation. Prominent pulpal calcifications have been noted in association with certain disease processes, such as the following:

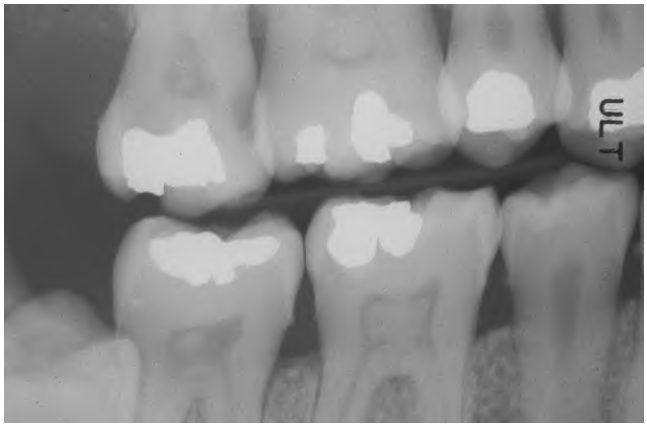
- Dentin dysplasia type Id (see page 102)
- Dentin dysplasia type II (see page 101)
- Pulpal dysplasia (see page 101)
- Tumoral calcinosis
- Calcinosis universalis
- Ehlers-Danlos syndrome (see page 703)
- End-stage renal disease

Histopathologic Features

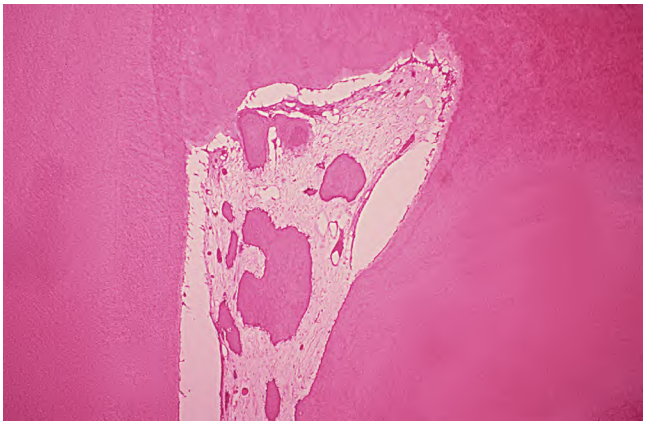
Denticles consist of tubular dentin surrounding a central nest of epithelium. With time, the central epithelium degenerates and the tubules undergo sclerosis, making their detection difficult. Most denticles are attached or embedded. Those that remain free in the pulp occasionally develop outer layers of irregular fibrillar calcification or lamellated layers of calcification similar to those seen in pulp stones.

Pulp stones demonstrate a central amorphous mass of irregular calcification surrounded by concentric lamellar rings of regular calcified material (Fig. 3-12). Occasionally, a peripheral layer of tubular dentin may be applied by odontoblasts, which arise from the surrounding pulp tissue in response to the presence of the pulp stone. In addition, fibrillar irregular calcified material also may be evident on the periphery of pulp stones.

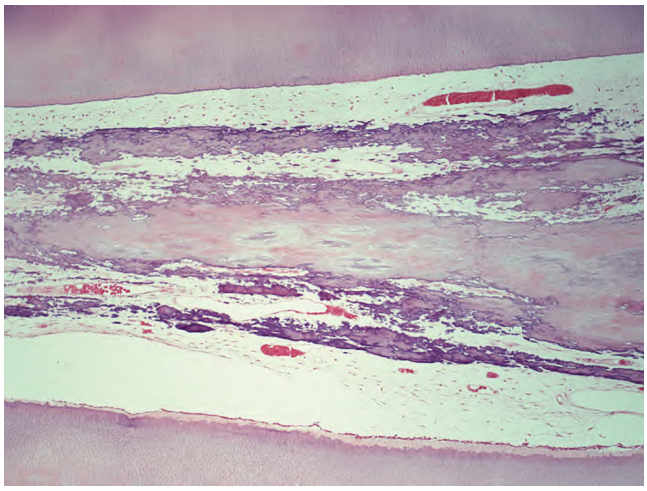
Diffuse linear calcifications consist entirely of fine, fibrillar, and irregular calcifications that develop in the pulp chambers and canals (Fig. 3-13). This material often is deposited in a linear fashion along the course of a blood vessel or nerve.



• **Fig. 3-11 Pulp Stones.** Multiple teeth demonstrating radiographically obvious calcifications within the pulp chambers.



• **Fig. 3-12 Pulp Stones.** Multiple stones within the pulp chamber.



• **Fig. 3-13 Diffuse Linear Pulpal Calcifications.** Fine, fibrillar calcifications parallel the course of the neurovascular channels within the pulp canal.

Treatment and Prognosis

No treatment is required. Most pulpal calcifications are not associated with any significant clinical alterations.

◆ PERIAPICAL GRANULOMA (CHRONIC APICAL PERIODONTITIS)

The term **periapical granuloma** refers to a mass of chronically or subacutely inflamed granulation tissue at the apex of a nonvital tooth. This commonly used name is not totally accurate because the lesion does not show true granulomatous inflammation microscopically. Although the term **apical periodontitis** may be more appropriate, it may prove confusing to the clinician. Formation of apical inflammatory lesions represents a defensive reaction secondary to the presence of microbial infection in the root canal with spread of related toxic products into the apical zone. Initially, the defense reaction eliminates noxious substances that exit the canals. With time, however, the host reaction becomes less effective with microbial invasion or spread of toxins into the apical area.

In the early stages of infection, neutrophils predominate and radiographic alterations are not present; this phase of periapical inflammatory disease is termed *acute apical periodontitis.* The involved inflammatory cells are primarily neutrophils and release prostaglandins, which activate osteoclasts to resorb the surrounding bone, leading to a detectable periapical radiolucency. With time, chronic inflammatory cells begin to dominate the host response. Chronic lesions often are asymptomatic and demonstrate little additional change radiographically.

Periapical granulomas may arise after quiescence of a **periapical abscess** or may develop as the initial periapical pathosis. These lesions are not necessarily static. In addition to possible **periapical cyst** formation, a worsening of the pulpal infection can lead to a reappearance of inflammation, redevelopment of symptoms, and possible enlargement of the associated radiolucency. Secondary acute inflammatory changes within a periapical granuloma have been termed a *phoenix abscess,* after the mythical bird that would die, only to arise again from its own ashes. In progressive periapical granulomas, the enlargement often is not continuous but occurs in spurts associated with periodic acute exacerbations.

Clinical and Radiographic Features

The initial phase of periapical inflammatory disease—acute periapical periodontitis—creates a constant dull, throbbing pain. The associated tooth responds negatively to vitality testing or reveals a delayed positive result. Typically, pain on biting or percussion is present, and no obvious radiographic alterations are noted. If the acute inflammatory process evolves into a chronic pattern, then the associated symptoms diminish. In many instances, chronic periapical inflammatory disease is detected without any previous recollection of a prior acute phase.

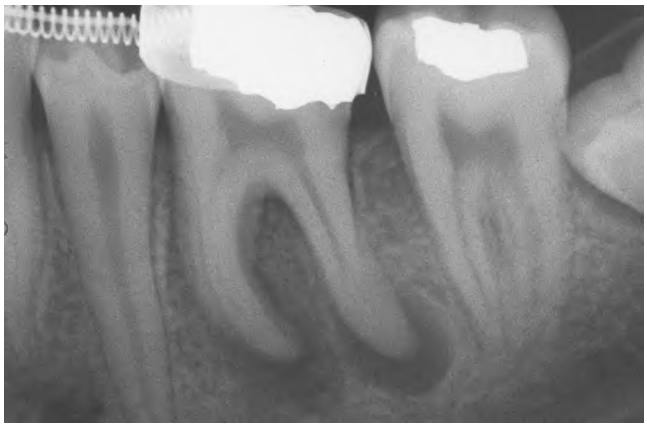
Most periapical granulomas are asymptomatic, but pain and sensitivity can develop if acute exacerbation occurs. Typically, the involved tooth does not demonstrate mobility or significant sensitivity to percussion. The soft tissue overlying the apex may or may not be tender. The tooth does not respond to thermal or electric pulp tests unless the pulpal necrosis is limited to a single canal in a multirooted tooth.

Most lesions are discovered on routine radiographic examination. The associated radiolucencies are variable, ranging from small, barely perceptible lesions to lucencies exceeding 2 cm in diameter (Figs. 3-14 to 3-16). Affected teeth typically reveal loss of the apical lamina dura. The lesion may be circumscribed or ill-defined and may or may not demonstrate a surrounding radiopaque rim. Root resorption is not uncommon (Fig. 3-17). Although lesions greater than 200 mm^2 often represent periapical cysts, numerous investigators have been unable to distinguish periapical granulomas from periapical cysts simply on the basis of size and radiographic appearance. Because periapical inflammatory disease is not static and granulomas can transform into cysts or abscesses (and vice versa) without significant radiographic change, it is not surprising that the radiographic features are not diagnostic.

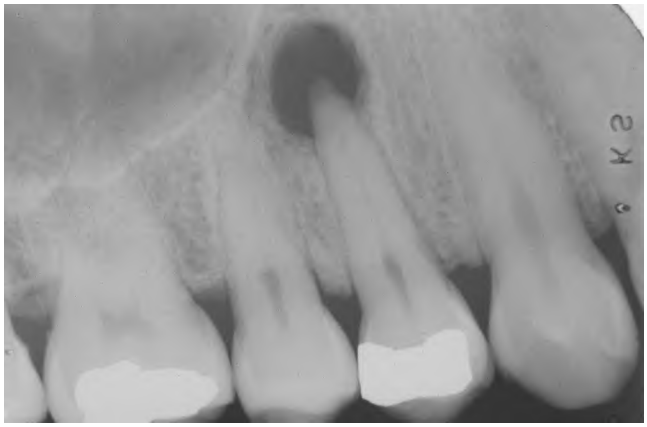
Cone-beam computed tomography (CT) has demonstrated a greater accuracy for detection of periapical inflammatory disease when compared to periapical or panoramic radiographs. This technique should be considered when clinical tests suggest periapical pathology but standard radiographs demonstrate no detectable lesions.

Histopathologic Features

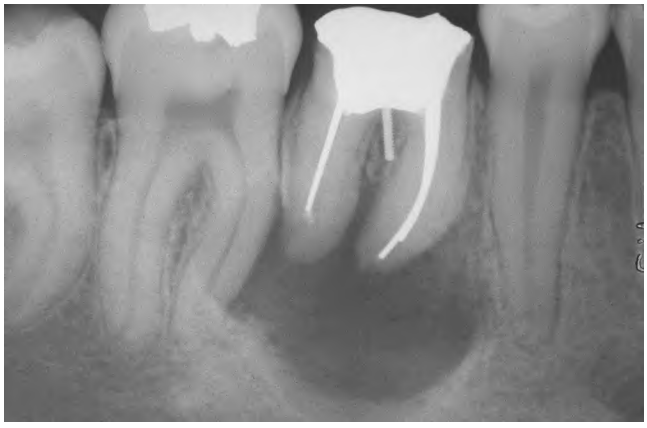
Periapical granulomas consist of inflamed granulation tissue surrounded by a fibrous connective tissue wall. The



• **Fig. 3-14 Periapical Granulomas.** Discrete periapical radiolucencies associated with the apices of the mandibular first molar. (Courtesy of Dr. Garth Bobrowski.)

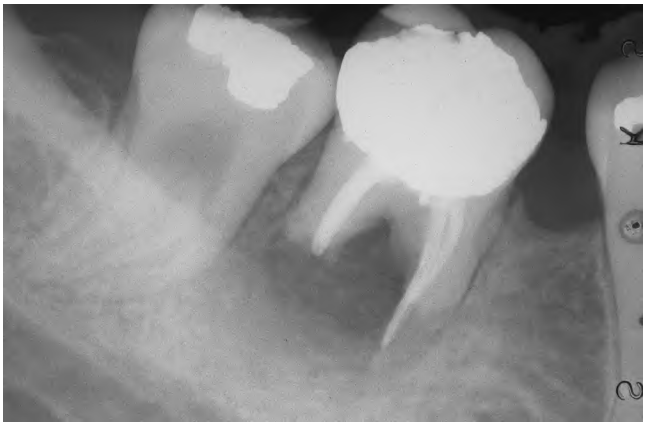


• **Fig. 3-15 Periapical Granuloma.** Well-defined radiolucency associated with the apex of the maxillary first bicuspid. (Courtesy of Dr. Frank Beylotte.)

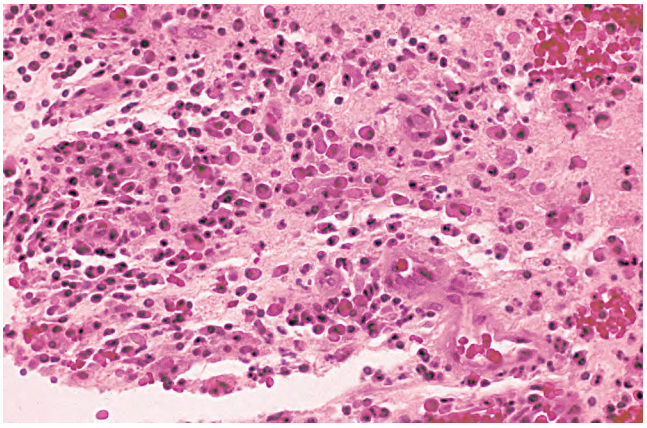


• **Fig. 3-16 Periapical Granuloma.** Large, well-defined radiolucency associated with the apices of the mandibular first molar. (Courtesy of Dr. Robert E. Loy.)

granulation tissue demonstrates a variably dense lymphocytic infiltrate that is intermixed frequently with neutrophils, plasma cells, histiocytes, and, less frequently, mast cells and eosinophils (Fig. 3-18). When numerous plasma cells are present, scattered eosinophilic globules of gamma



• **Fig. 3-17 Periapical Granuloma.** Ill-defined radiolucency associated with the mandibular first molar, which exhibits significant root resorption.



• **Fig. 3-18 Periapical Granuloma.** Granulation tissue exhibits mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and histiocytes.

globulin **(Russell bodies)** may be seen. In addition, clusters of lightly basophilic particles **(pyronine bodies)** also may be present in association with the plasmacytic infiltrate. Both of these plasma cell products are not specific for the periapical granuloma and may be found within any accumulation of plasma cells. Epithelial rests of Malassez may be identified within the granulation tissue. Collections of cholesterol clefts, with associated multinucleated giant cells and areas of red blood cell extravasation with hemosiderin pigmentation, may be present. Small foci of acute inflammation with focal abscess formation may be seen but do not warrant the diagnosis of periapical abscess.

Treatment and Prognosis

Apical inflammatory lesions result from the presence of microorganisms or their toxic products in the root canal, the apical tissues, or both. Successful treatment depends on the reduction and control of the offending organisms. Because of the anatomic complexity of the root canal systems, some investigators believe absolute eradication of

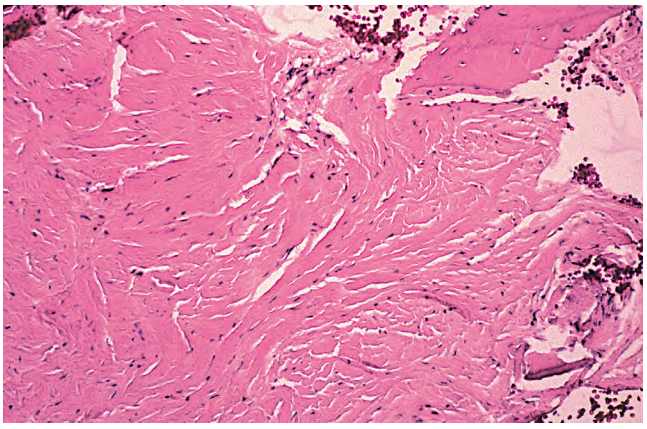
all microorganisms is unlikely; the goal of endodontics is to reduce the microbial load to a level that is insufficient to maintain periapical inflammation. If the tooth can be maintained, then root canal therapy can be performed. Nonrestorable teeth must be extracted, followed by curettage of all apical soft tissue. In symptomatic cases, nonsteroidal antiinflammatory drugs (NSAIDs) are beneficial; use of systemic antibiotic medications is not recommended unless associated swelling or systemic changes are present.

Teeth treated endodontically should be evaluated at 1- and 2-year intervals (at a minimum) to rule out possible lesional enlargement and to ensure appropriate healing. In addition, many clinicians believe that evaluations at 1, 3, and 6 months are appropriate. Strong emphasis should be placed on the importance of the recall appointments.

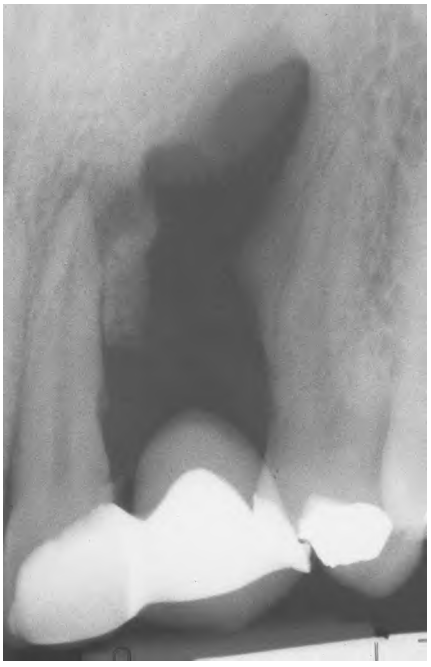
Research has shown the most important factor for the successful treatment of periapical inflammatory disease is the quality of the endodontic treatment. In addition, the coronal restoration is critical, and failure can occur in cases with excellent endodontic therapy but poor coronal restoration.

If initial conventional therapy is unsuccessful, endodontic retreatment represents the best approach for minimizing the bacterial contamination and should be considered before periapical surgery. Periapical surgery remains an important tool for resolution of periapical inflammatory disease, but often it is reserved for lesions larger than 2 cm or those associated with teeth that are not appropriate for conventional endodontic therapy. Periapical surgery should include thorough curettage of all periradicular soft tissue, amputation of the apical portion of the root, and sealing the foramen of the canal. All soft tissue removed during periapical surgical procedures should be submitted for histopathologic examination. These surgical sites represent areas that have failed to respond to appropriate therapy; as such, histopathologic examination and diagnostic confirmation are mandatory.

On occasion, the defect created by periapical inflammatory lesions may fill with dense collagenous tissue rather than normal bone (Fig. 3-19). These **fibrous (periapical) scars** occur most frequently when both the facial and lingual cortical plates have been lost (Fig. 3-20); however, they occasionally arise in areas with intact cortical plates. If during surgery both plates are discovered to be missing, then the patient should be informed of the possibility of scar formation. The development of a periapical scar is not an indication for future surgery.



• **Fig. 3-19 Periapical Fibrous Scar.** Dense, fibrous connective tissue with vital bone and no significant inflammatory infiltrate.



• **Fig. 3-20 Periapical Fibrous Scar.** Periapical radiolucency of maxilla at the previous site of extraction in which both cortical plates were lost. The site was filled with dense collagenous tissue. (Courtesy of Dr. James Tankersley.)

◆ PERIAPICAL CYST (RADICULAR CYST; APICAL PERIODONTAL CYST)

Epithelium at the apex of a nonvital tooth presumably can be stimulated by inflammation to form a true epithelium-lined cyst, or **periapical cyst.** The source of the epithelium is usually a rest of Malassez but also may be traced to crevicular epithelium, sinus lining, or epithelial lining of sinus tracts. Cyst development is common with a wide range of prevalence noted that most likely is related to the stringency of the diagnostic criteria used in a particular study.

When the cyst and root are removed totally, two variations of periapical cyst have been described. **Periapical pocket cysts** are characterized by an incomplete epithelial lining because of extension of the apical portion of the tooth into the cyst lumen. **Periapical true cysts** form a complete epithelium-lined baglike structure that is adjacent to, but separated from, the tooth apex. Studies have shown an inability to separate a "pocket" cyst from a "true" cyst unless the entire tooth and associated soft tissue are removed *in toto,* which makes the separation most impractical. Because distinguishing between an epithelialized periapical granuloma, a "pocket" cyst, or a "true" cyst has little

postsurgical implications, laborious histopathologic examination and subclassification are impractical.

Periapical cysts represent a fibrous connective tissue wall lined by epithelium with a lumen containing fluid and cellular debris. Theoretically, as the epithelium desquamates into the lumen, the protein content is increased. Fluid enters the lumen in an attempt to equalize the osmotic pressure, and slow enlargement occurs. Most periapical cysts grow slowly and do not attain a large size.

On occasion, a similar cyst, best termed a **lateral radicular cyst,** may appear along the lateral aspect of the root. Like the periapical cyst, this lesion also usually arises from rests of Malassez, and the source of inflammation may be periodontal disease or pulpal necrosis with spread through a lateral foramen. Radiographically, these cysts mimic developmental **lateral periodontal cysts** (see page 645). Histopathologically, however, they are consistent with cysts of inflammatory origin.

Periapical inflammatory tissue that is not curetted at the time of tooth removal may give rise to an inflammatory cyst called a **residual periapical cyst.** With time, many of these cysts exhibit an overall reduction in size, and spontaneous resolution can occur from a lack of continued inflammatory stimulus.

Clinical and Radiographic Features

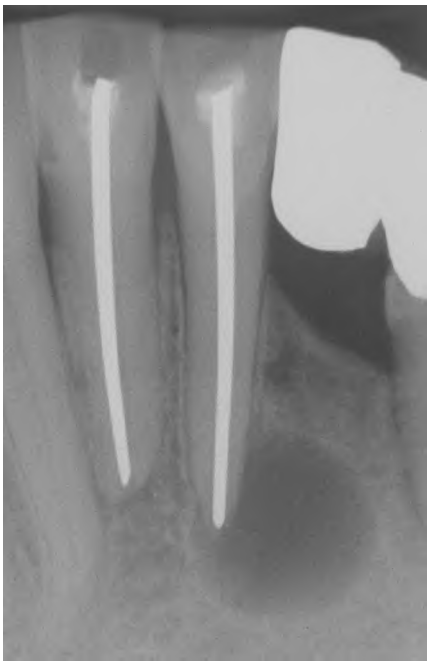
Periapical Cyst

Typically, patients with periapical cysts have no symptoms unless there is an acute inflammatory exacerbation. In addition, if the cyst reaches a large size, then swelling and mild sensitivity may be noted. Movement and mobility of adjacent teeth are possible as the cyst enlarges. The tooth from which the cyst originated does not respond to thermal and electric pulp testing.

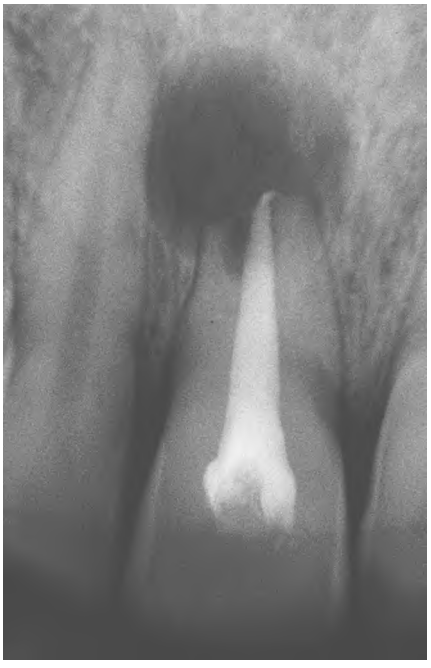
The radiographic pattern is identical to that of a periapical granuloma. Cysts may develop even in small periapical radiolucencies, and the radiographic size cannot be used for the definitive diagnosis. A loss of the lamina dura is seen along the adjacent root, and a rounded radiolucency encircles the affected tooth apex (Fig. 3-21). Root resorption is common (Fig. 3-22). With enlargement, the radiolucency often flattens out as it approaches adjacent teeth. Significant growth is possible, and lesions occupying an entire quadrant have been noted (Fig. 3-23). Although periapical cysts more frequently achieve greater size than periapical granulomas, neither the size nor the shape of the lesion can be considered a definitive diagnostic criterion. The inability to separate these pathoses on a consistent basis holds true even with newer radiographic techniques, such as cone-beam CT. Periapical cysts also are known to involve deciduous teeth. These are most frequently associated with molar teeth and appear as a radiolucent zone that surrounds the roots and fills the interradicular space at the bifurcation (Fig. 3-24).

Lateral Radicular Cyst

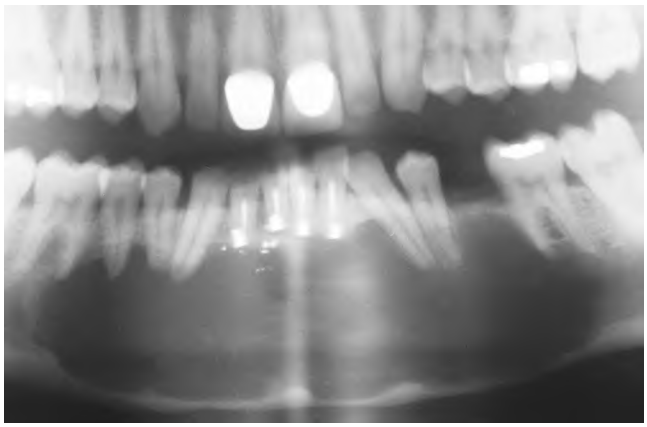
Lateral radicular cysts appear as discrete radiolucencies along the lateral aspect of the root (Fig. 3-25). Loss of lamina dura and an obvious source of inflammation may not be detected without a high index of suspicion. Before surgical exploration of laterally positioned radiolucencies, a thorough evaluation of the periodontal status and vitality of adjacent teeth should be performed. Many examples of the so-called globulomaxillary cyst (see page 25) prove to be of inflammatory origin and represent lateral radicular cysts (Fig. 3-26).



• **Fig. 3-21 Periapical Cyst.** Well-circumscribed radiolucency intimately associated with the apex of the mandibular central incisor. Note the loss of lamina dura in the area of the lesion.



• **Fig. 3-22 Periapical Cyst.** Radiolucency associated with the maxillary central incisor, which exhibits significant root resorption.



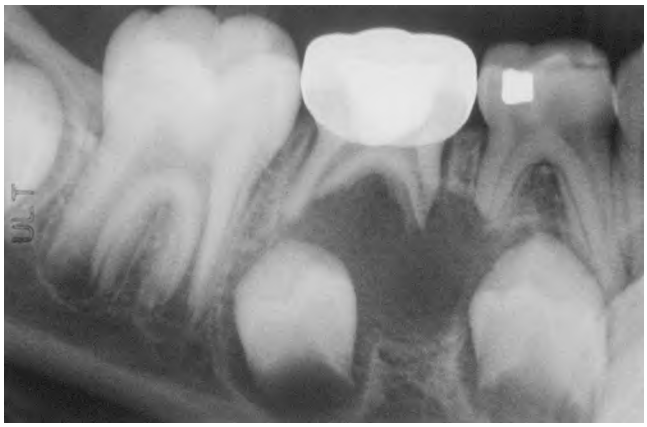
• **Fig. 3-23 Periapical Cyst.** Large unilocular radiolucency extending from the mandibular first molar to the contralateral first molar. (Courtesy of Dr. John R. Cramer.)

Residual Periapical Cyst

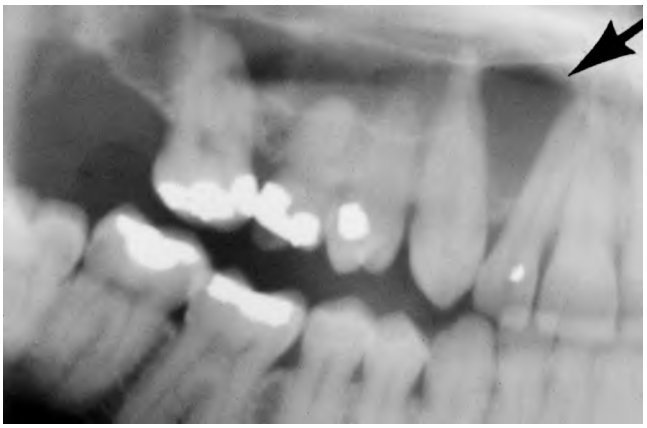
The residual periapical cyst appears as a round-to-oval radiolucency of variable size within the alveolar ridge at the site of a previous tooth extraction (Fig. 3-27). As the cyst ages, degeneration of the cellular contents within the lumen occasionally leads to dystrophic calcification and central luminal radiopacity.

Histopathologic Features

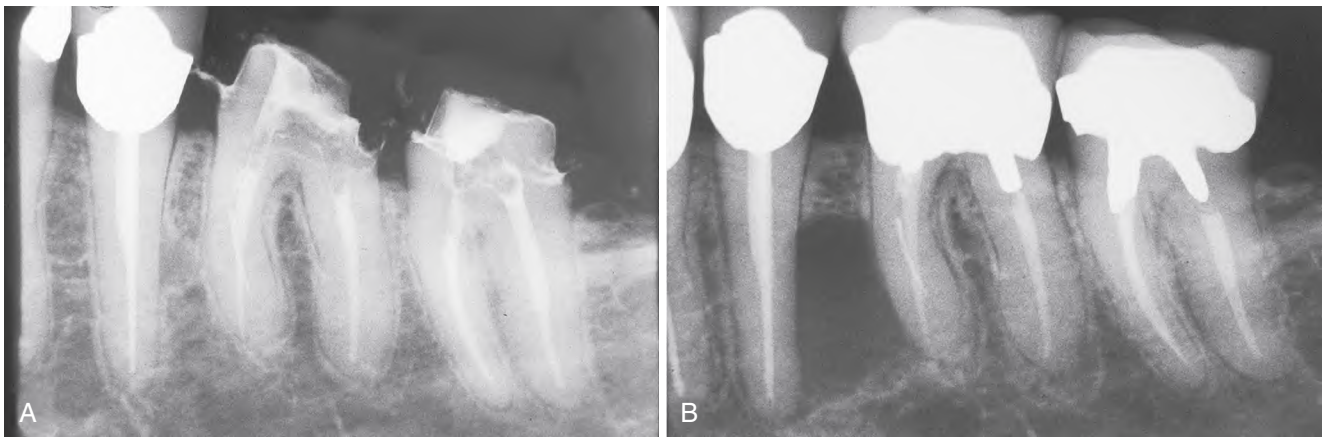
The histopathologic features of all three types of inflammatory cysts are similar. The cyst is lined by stratified squamous epithelium, which may demonstrate exocytosis, spongiosis, or hyperplasia (Fig. 3-28). As seen in dentigerous cysts, scattered mucous cells or areas of ciliated pseudostratified columnar epithelium may be noted in periapical cysts (Fig. 3-29). Although some maxillary periapical cysts lined by pseudostratified columnar epithelium



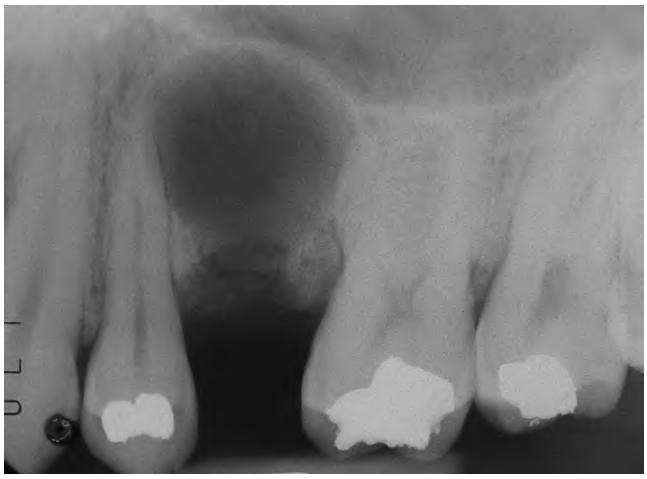
• **Fig. 3-24 Periapical Cyst.** Radiolucency involving the bifurcation and apices of the deciduous right mandibular second molar.



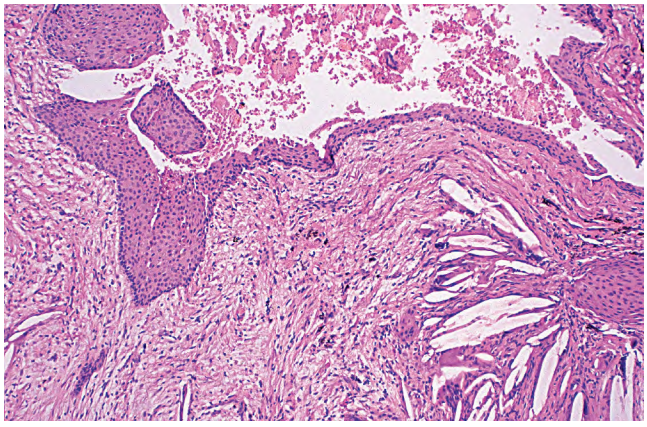
• **Fig. 3-26 Lateral Radicular Cyst.** Inverted pear-shaped radiolucency between the maxillary lateral incisor and cuspid *(arrow)*. The lateral incisor ultimately proved to be nonvital.



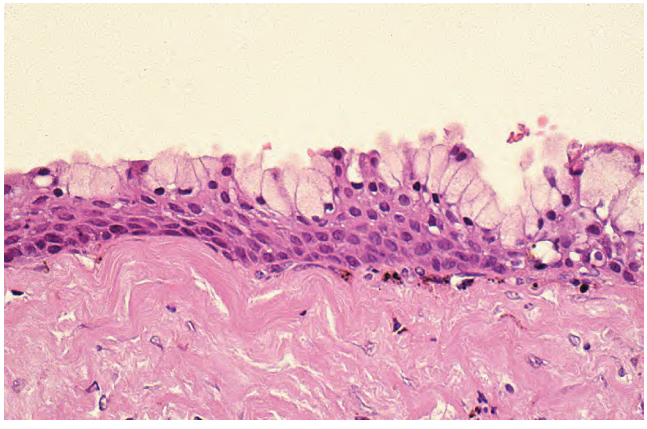
• **Fig. 3-25 Lateral Radicular Cyst. A,** Periapical radiograph of the left side of the posterior mandible taken at time of completion of endodontic therapy of the bicuspid and molars. **B,** Subsequent radiograph taken 27 months later. Note radiolucency between bicuspid and first molar extending laterally from the mesial root of the first molar. (Courtesy of Dr. Carroll Gallagher.)



• **Fig. 3-27 Residual Periapical Cyst.** Well-circumscribed radiolucency of the maxilla at the site of previous tooth extraction.

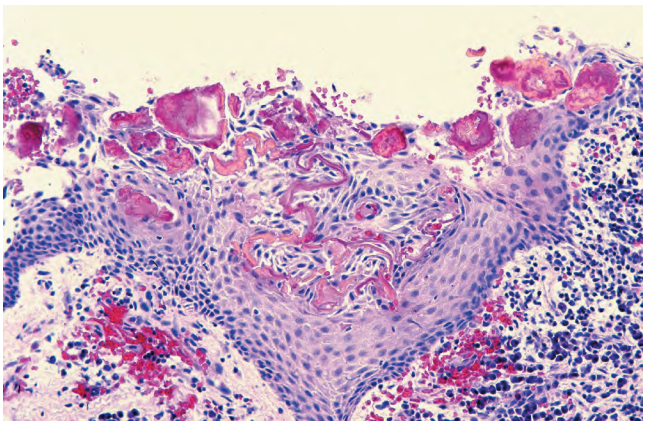


• **Fig. 3-28 Periapical Cyst.** Cyst lined by stratified squamous epithelium. Note connective tissue wall, which contains a chronic inflammatory infiltrate and numerous cholesterol clefts.



• **Fig. 3-29 Periapical Cyst.** Stratified squamous epithelial lining containing numerous mucous cells.

may have originated from the adjacent sinus lining, the presence of mucous cells or respiratory-like epithelium also can be observed in mandibular cysts. The ability of odontogenic epithelium to demonstrate such specialized differentiation represents an example of *prosoplasia* (forward

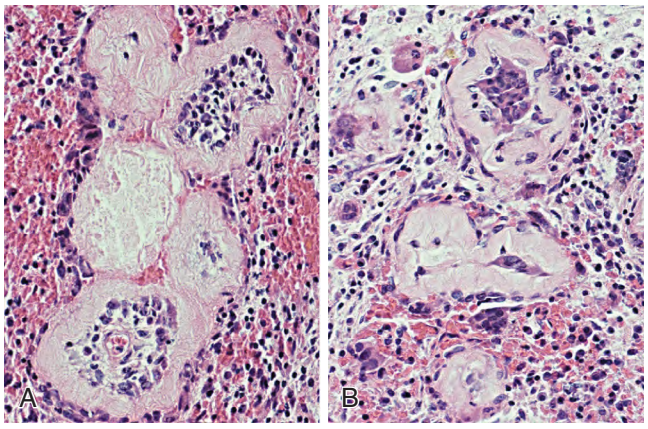


• **Fig. 3-30 Periapical Cyst.** Squamous epithelial cyst lining exhibiting numerous irregular and curvilinear Rushton bodies.

metaplasia) and highlights the diverse potential of odontogenic epithelium. The cyst lumen may be filled with fluid and cellular debris. On occasion, the lining epithelium may demonstrate linear or arch-shaped calcifications known as *Rushton bodies* (Fig. 3-30). The wall of the cyst consists of dense fibrous connective tissue—often with an inflammatory infiltrate containing lymphocytes variably intermixed with neutrophils, plasma cells, histiocytes, and (rarely) mast cells and eosinophils. Dystrophic calcification, cholesterol clefts with multinucleated giant cells, red blood cells, and areas of hemosiderin pigmentation may be present in the lumen, wall, or both. Due to the inability of macrophages and giant cells to remove cholesterol, its presence may be partially responsible for failure of healing of cysts in which the original focus of infection was treated appropriately.

Intramural islands of odontogenic epithelium that closely resemble squamous odontogenic tumor (see page 668) rarely have been noted, which could be misdiagnosed as a neoplastic process. Studies have shown these proliferations are not neoplastic and mandate no further treatment beyond the usual standard of care for periapical cysts.

Occasionally, the walls of inflammatory cysts will contain scattered **hyaline bodies (pulse granuloma, giant-cell hyaline angiopathy).** These bodies appear as small circumscribed pools of eosinophilic material that exhibits a corrugated periphery of condensed collagen often surrounded by lymphocytes and multinucleated giant cells (Fig. 3-31). Initially, these foci were thought to be a vascular degenerative process or a foreign body reaction to machinery oil or vegetable matter. Subsequently, these bodies have been shown to represent pools of inflammatory exudate (i.e., extravasated serum) that ultimately undergoes fibrosis and occasionally dystrophic calcification. The multinucleated giant cells are drawn to the site for removal of insoluble hemosiderin granules. Hyaline bodies may be found in any area of chronic intraosseous inflammation, especially periapical inflammatory disease.



• **Fig. 3-31 Hyaline Bodies. A,** Multiple hyaline bodies appearing as corrugated collagenous rings surrounding lymphocytes and plasma cells; note early hyaline body filled with serum. **B,** Multiple hyaline bodies with numerous multinucleated giant cells within and around the corrugated collagenous rings.

Treatment and Prognosis

A periapical cyst is treated in the same manner as a periapical granuloma. When clinical and radiographic features indicate a periapical inflammatory lesion, extraction or conservative nonsurgical endodontic therapy is performed. Although some authors believe that large cystic lesions cannot be resolved with conventional endodontics, experienced clinicians have successfully used nonsurgical root canal therapy for large areas of periapical inflammatory disease that approach 2 cm in diameter. Larger lesions associated with restorable teeth have been treated successfully with conservative endodontic therapy when combined with biopsy and marsupialization, decompression, or fenestration. As with any periapical inflammatory lesion, minimal follow-up at 1 and 2 years is advised strongly.

If the radiolucency fails to resolve, then the lesion often can be managed successfully by nonsurgical endodontic retreatment. As previously mentioned, periapical surgery typically is performed for lesions exceeding 2 cm and those associated with teeth that are not suitable for conventional endodontics. Biopsy is indicated to rule out other possible pathologic processes.

Because any number of odontogenic and nonodontogenic cysts and tumors can mimic the appearance of a residual periapical cyst, all of these cysts should be excised surgically. All inflammatory foci in the area of a lateral radicular cyst should be eliminated and the patient observed in a manner similar to that described for the periapical cyst. In some instances, lateral radicular cysts are removed before tooth vitality testing or periodontal evaluation for an adjacent focus of infection. If this diagnosis is made, then a thorough evaluation for an inflammatory source is mandatory.

◆ PERIAPICAL ABSCESS

The accumulation of acute inflammatory cells at the apex of a nonvital tooth is termed a **periapical abscess.** Acute inflammatory lesions with abscess formation may arise as the initial periapical pathosis or from an acute exacerbation of a chronic periapical inflammatory lesion (see discussion of *phoenix abscess,* page 117). Frequently, the source of the infection is obvious. On occasion, however, pulpal death may be trauma related, and the tooth may contain neither a cavity nor a restoration.

In the earliest stage of all forms of periapical inflammatory disease, the periapical periodontal ligament (PDL) fibers may exhibit acute inflammation but no frank abscess formation. This localized alteration, best termed **acute apical periodontitis,** may or may not proceed to abscess formation. Although this process often occurs in association with a nonvital tooth, acute apical periodontitis may be found in vital teeth secondary to trauma, high occlusal contacts, or wedging by a foreign object. The clinical presentation often closely resembles that of a periapical abscess and must be considered in the differential diagnosis.

Clinical and Radiographic Features

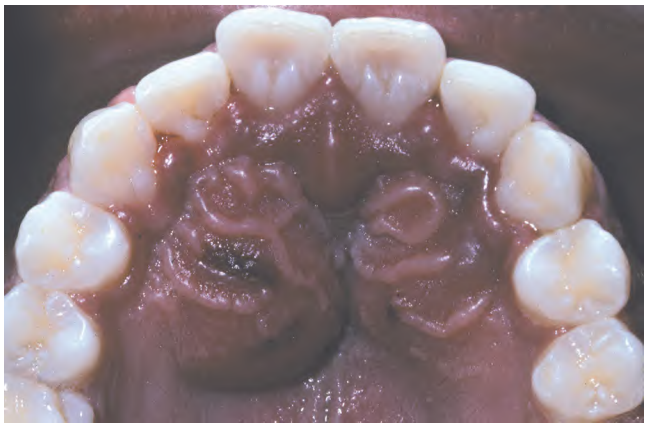
Many investigators subdivide periapical abscesses into **acute** and **chronic** types. However, these are misnomers because both types represent acute inflammatory reactions. Periapical abscesses should be designated as **symptomatic** or **asymptomatic** on the basis of their clinical presentations.

Periapical abscesses become symptomatic as the purulent material accumulates within the alveolus. The initial stages produce tenderness of the affected tooth that often is relieved by direct application of pressure. With progression, the pain becomes more intense, often with extreme sensitivity to percussion, extrusion of the tooth, and swelling of the tissues. The offending tooth does not respond to cold or electric pulp testing. Headache, malaise, fever, and chills may be present.

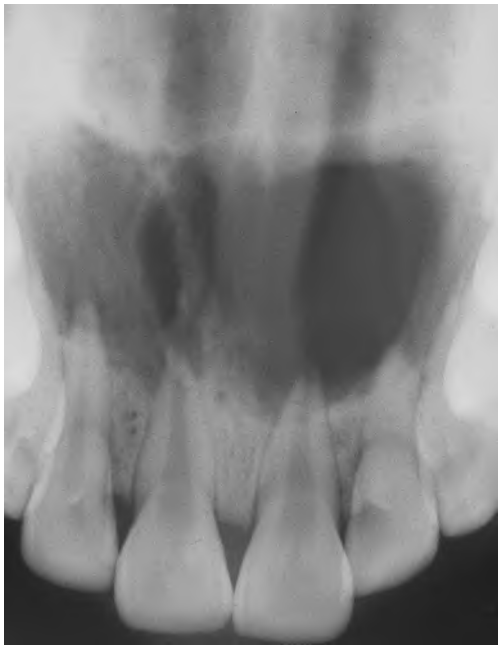
Radiographically, abscesses may demonstrate a thickening of the apical periodontal ligament, an ill-defined radiolucency, or both; however, often no appreciable alterations can be detected because insufficient time has occurred for significant bone destruction. Phoenix abscesses demonstrate the outline of the original chronic lesion, with or without an associated ill-defined bone loss.

With progression, the abscess spreads along the path of least resistance. The purulence may extend through the medullary spaces away from the apical area, resulting in **osteomyelitis,** or it may perforate the cortex and spread diffusely through the overlying soft tissue (as **cellulitis**). Each of these occurrences is described later in the chapter.

Once an abscess is in soft tissue, it can cause cellulitis or may channelize through the overlying soft tissue. The cortical plate may be perforated in a location that permits entrance into the oral cavity. The purulent material can accumulate in the connective tissue overlying the bone and can create a sessile swelling or perforate through the surface epithelium and drain through an intraoral sinus (Figs. 3-32 and 3-33). At the intraoral opening of a sinus tract, a mass of subacutely inflamed granulation tissue often is found,



• **Fig. 3-32 Periapical Abscess.** Bilateral soft tissue swelling of the anterior palate.

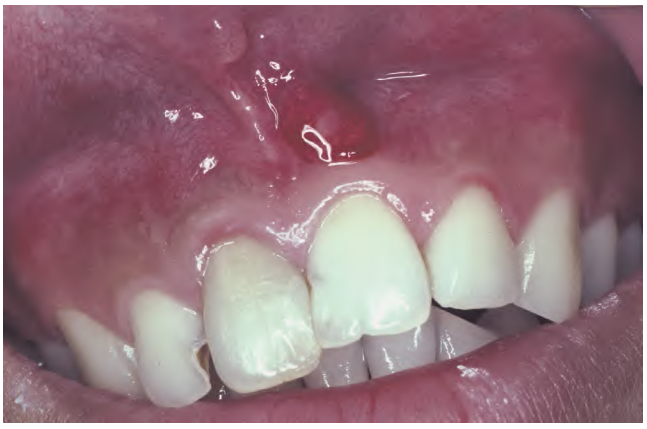


• **Fig. 3-33 Periapical Abscess.** Same patient as depicted in Fig. 3-32. Multiple, overlapping radiolucencies of the anterior maxilla are present. All four maxillary incisors exhibit pulpal necrosis.

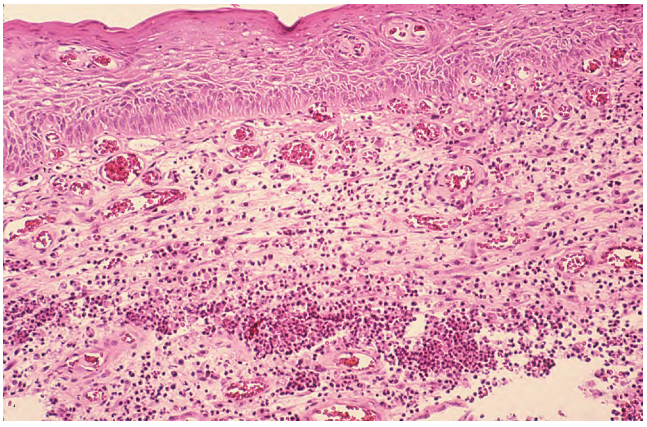
known as a **parulis (gum boil)** (Figs. 3-34 and 3-35). Occasionally, the nonvital tooth associated with the parulis may be difficult to determine, and insertion of a gutta-percha point into the tract can aid in detection of the offending tooth during radiographic examination (Fig. 3-36). Dental abscesses also may channelize through the overlying skin and drain via a **cutaneous sinus** (Fig. 3-37).

Most dental-related abscesses perforate buccally because the bone is thinner on the buccal surface. However, infections associated with maxillary lateral incisors, the palatal roots of maxillary molars, and mandibular second and third molars typically drain through the lingual cortical plate.

If a chronic path of drainage is achieved, a periapical abscess typically becomes asymptomatic because of a lack of accumulation of purulent material within the alveolus.



• **Fig. 3-34 Parulis.** Erythematous mass of granulation tissue overlying the left maxillary central incisor. Note discoloration of the maxillary right central incisor.

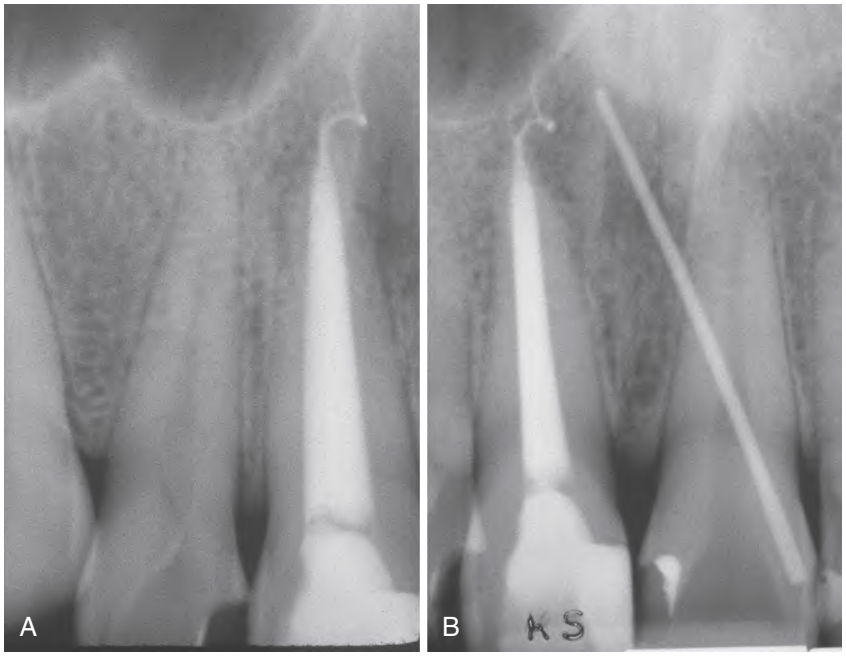


• **Fig. 3-35 Parulis.** Normal connective tissue has been replaced by acutely inflamed granulation tissue, which exhibits focal areas of neutrophilic abscess formation. Note the central sinus tract, which courses from the base of the specimen toward the surface epithelium.

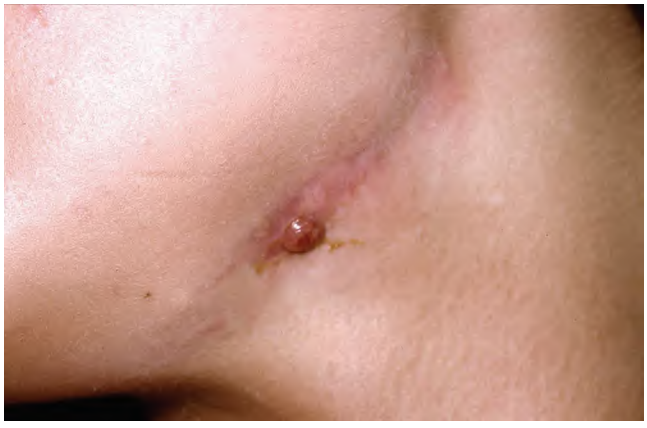
Occasionally, such infections are discovered during a routine oral examination after detection of a parulis or drainage through a large carious defect (Figs. 3-38 and 3-39). If the drainage site becomes blocked, then signs and symptoms of the abscess frequently become evident in a short time. On occasion, periapical infections can spread through the bloodstream and result in systemic symptoms, such as fever, lymphadenopathy, and malaise. The risk of dissemination appears to be less for periapical abscesses that drain freely.

Histopathologic Features

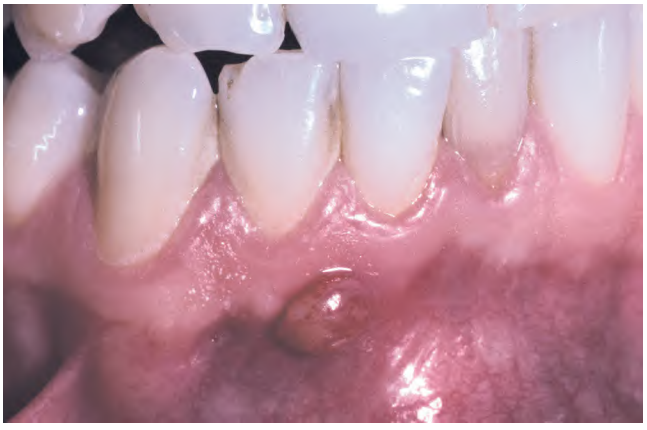
Biopsy specimens from pure abscesses are uncommon because the material is in liquid form. Abscesses consist of a sea of polymorphonuclear leukocytes often intermixed with inflammatory exudate, cellular debris, necrotic material, bacterial colonies, or histiocytes (Fig. 3-40). Phoenix abscesses can maintain a soft tissue component; they present as subacutely inflamed periapical granulomas or cysts intermixed with areas of significant abscess formation. In these



• **Fig. 3-36 Periapical Abscess. A,** Same patient as depicted in Fig. 3-34. None of the incisors demonstrates obvious periapical radiolucency. (The large radiolucency at the top is the anterior portion of the maxillary sinus.) **B,** Gutta-percha point revealed that the right maxillary incisor was the source of the infection.



• **Fig. 3-37 Cutaneous Sinus.** Erythematous, sensitive, and exophytic mass of granulation tissue of the skin inferior to the left body of the mandible.

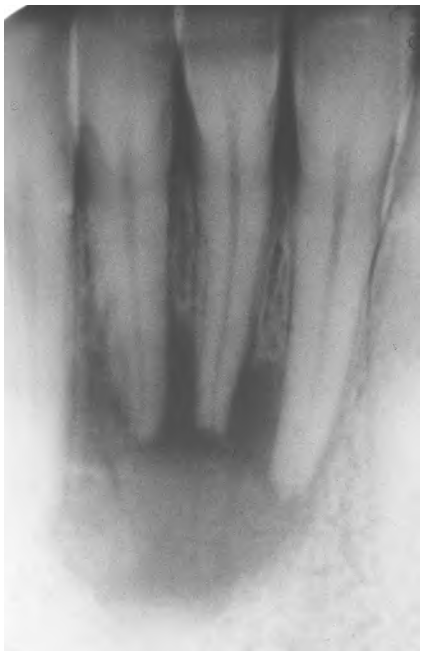


• **Fig. 3-38 Parulis.** Asymptomatic yellow-red nodule of the anterior mandibular alveolar mucosa. The adjacent teeth were asymptomatic and appeared clinically normal.

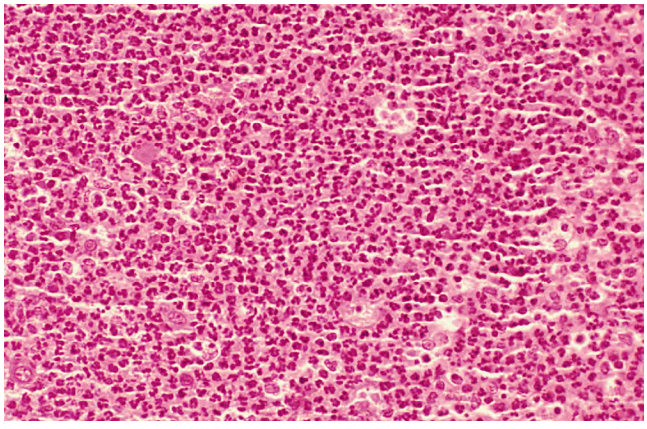
cases the pathologist typically diagnoses the primary lesion but comments about the abscess formation.

Treatment and Prognosis

Treatment of the patient with a periapical abscess consists of drainage and elimination of the focus of infection. Those abscesses associated with a patent sinus tract may be asymptomatic but, nevertheless, should be treated. With localized periapical abscesses, the signs and symptoms typically diminish significantly within 48 hours of initiation of appropriate drainage. When the abscess causes clinical expansion of the bone or soft tissue adjacent to the apex of the affected tooth, incisional drainage of the swelling should be considered because this technique appears to be associated with more rapid resolution of the inflammatory process when compared with drainage through the root canal. If the affected tooth is extruded, then reduction of the occlusion is recommended because chronic occlusal trauma has been shown to delay resolution of the inflammatory process. Unless contraindicated, treatment with NSAIDs usually is appropriate preoperatively, immediately postoperatively, and for subsequent pain control. Typically, use of antibiotic medications for a well-localized and easily drained periapical abscess in a healthy patient is unnecessary. Antibiotic coverage should be reserved for the medically compromised and patients with significant cellulitis (see next section) or clinical evidence of dissemination (i.e., fever,



• **Fig. 3-39 Periapical Abscess.** Same patient as depicted in Fig. 3-38. Periapical radiolucency associated with the nonvital mandibular lateral incisor.



• **Fig. 3-40 Periapical Abscess.** Sheet of polymorphonuclear leukocytes intermixed with scattered histiocytes.

lymphadenopathy, malaise). Once the infection has been resolved by extraction or appropriate endodontic therapy, the affected bone typically heals.

Usually, a sinus tract resolves spontaneously after the offending tooth is extracted or endodontically treated. Sinus tracts that persist are thought to contain sufficient infectious material along the fistulous tract to maintain the surface granulation tissue, and surgical removal with curettage of the tract is required for resolution.

◆ CELLULITIS

If an abscess is not able to establish drainage through the surface of the skin or into the oral cavity, it may spread diffusely through fascial planes of the soft tissue. This acute and edematous spread of an acute inflammatory process is termed **cellulitis.** Although cellulitis may occur in otherwise healthy individuals, there is an increased prevalence in patients with variety of medical conditions, such as use of corticosteroid or cytotoxic medications, malignancy, diabetes mellitus, or immunosuppressive disorders including neutropenia, aplastic anemia, and acquired immunodeficiency syndrome (AIDS). Although numerous patterns of cellulitis can be seen from the spread of dental infections, two especially dangerous forms warrant further discussion: (1) **Ludwig angina** and (2) **cavernous sinus thrombosis.**

Ludwig angina, named after the German physician who described the seriousness of the disorder in 1836, refers to cellulitis of the submandibular region. Angina comes from the Latin word *angere,* which means *to strangle* (an apt term, considering the clinical features described in the following section). In approximately 70% of cases, Ludwig angina develops from spread of an acute infection from the lower molar teeth. Other situations associated with this clinical presentation are peritonsillar or parapharyngeal abscesses, tongue piercing, oral lacerations, fractures of the mandible, or submandibular sialadenitis.

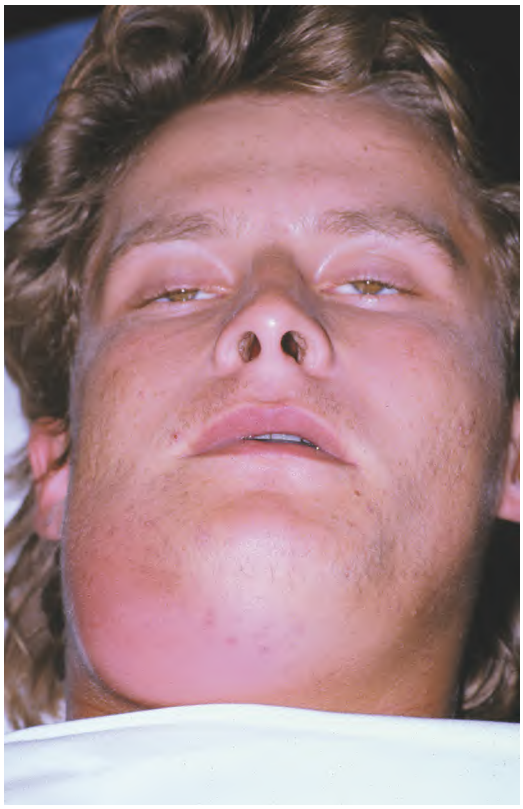
The cavernous sinus is a group of thin-walled veins that are located lateral to the sella turcica and medial to the temporal bone. The trochlear and oculomotor nerves and the maxillary and ophthalmic branches of the trigeminal nerve course through the area. In addition, the internal carotid artery and abducens nerve travel within the sinus. The sinus receives venous drainage from the orbit via the superior and inferior ophthalmic veins. Infection of the sinus can produce a variety of clinical symptoms related to the numerous anatomic structures that course through this site.

Cavernous sinus thrombosis can occur via an anterior or posterior pathway. Infection from the maxillary anterior teeth can perforate the facial maxillary bone and spread to the canine space. A septic thrombus develops in the valveless facial veins located in this space, and retrograde propagation occurs from the angular vein to the inferior ophthalmic vein through the inferior orbital fissure into the cavernous sinus. The posterior pathway is followed by infections originating from maxillary premolar or molar teeth, which demonstrate buccal or infratemporal space involvement that may spread via the emissary veins from the pterygoid venous plexus to the inferior petrosal sinus and into the cavernous sinus. Overall, cavernous sinus thrombosis is relatively uncommon, and dental infections are responsible in approximately 10% of the cases.

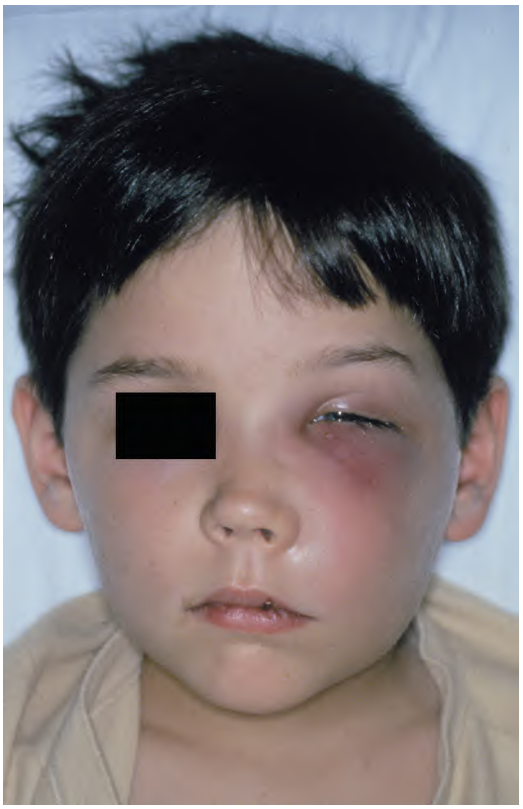
Clinical Features

Ludwig Angina

Ludwig angina is an aggressive and rapidly spreading cellulitis that involves the sublingual, submandibular, and submental spaces bilaterally. Once the infection enters the submandibular space, it may extend to the lateral pharyngeal space and then to the retropharyngeal space. This extension may result in spread to the mediastinum with several serious consequences.



• **Fig. 3-41 Ludwig Angina.** Soft tissue swelling of the right submandibular region. (Courtesy of Dr. Brian Blocher.)



• **Fig. 3-42 Cellulitis Involving Canine Space.** Erythematous and edematous enlargement of the left side of the face with involvement of the eyelids and conjunctiva. Patients with odontogenic infections involving the canine space are at risk for cavernous sinus thrombosis. (Courtesy of Dr. Richard Ziegler.)

Ludwig angina creates massive swelling of the neck that often extends close to the clavicles (Fig. 3-41). Involvement of the sublingual space results in elevation, posterior enlargement, and protrusion of the tongue **(woody tongue),** which can compromise the airway. Submandibular space spread causes enlargement and tenderness of the neck above the level of the hyoid bone **(bull neck).** Although initially unilateral, spread to the contralateral neck typically occurs. Pain in the neck and floor of mouth may be seen in addition to restricted neck movement, dysphagia, dysphonia, dysarthria, drooling, and sore throat. Involvement of the lateral pharyngeal space can cause respiratory obstruction secondary to laryngeal edema. Tachypnea, dyspnea, tachycardia, stridor, restlessness, and the patient's need to maintain an erect position suggest airway obstruction. Fever, chills, leukocytosis, and an elevated sedimentation rate may be seen. Classically, obvious collections of pus are not present.

Cavernous Sinus Thrombosis

Cavernous sinus thrombosis appears as an edematous periorbital enlargement with involvement of the eyelids and conjunctiva. In cases involving the canine space, swelling is also typically present along the lateral border of the nose and may extend up to the medial aspect of the eye and periorbital area (Fig. 3-42). Protrusion and fixation of the eyeball often are evident, in addition to induration and swelling of the adjacent forehead and nose. Pupil dilation, lacrimation, photophobia, and loss of vision may occur. Pain over the eye and along the distribution of the ophthalmic and maxillary branches of the trigeminal nerve often is present. Proptosis, chemosis, and ptosis are noted in greater than 90% of affected patients. The cavernous sinuses freely communicate via the intercavernous sinus. Although many cases are initially unilateral, without appropriate therapy, the infection may spread to the contralateral side.

Fever, chills, headache, sweating, tachycardia, nausea, and vomiting can occur. With progression, signs of central nervous system (CNS) involvement develop. Meningitis, tachycardia, tachypnea, irregular breathing, stiffening of the neck, and deepening stupor with or without delirium indicate advanced toxemia and meningeal involvement. Occasionally, brain abscesses may result.

Treatment and Prognosis

Ludwig Angina

Treatment of Ludwig angina centers around two major priorities: maintenance of the airway and resolution of the infection. The choice of airway maintenance varies according to the severity of the obstruction. Choices include observation, orotracheal intubation, fiber-optic nasotracheal intubation, and tracheotomy. Orotracheal intubation often is very difficult because of the presence

of trismus and swollen soft tissues. On occasion, cricothyroidotomy is performed instead of a tracheostomy because of a perceived lower risk of spreading the infection to the mediastinum.

Resolution of the infection involves elimination of the original focus of infection and intravenous (IV) antibiotic therapy. Penicillin with or without clindamycin or metronidazole frequently is the initial choice with culture and sensitivity testing used to guide final therapy. Although controversial, corticosteroids are prescribed by some clinicians to reduce swelling and augment antibiotic penetration.

Although once an essential component of the treatment, surgical decompression of the cellulitis has been reserved by many clinicians for those patients who are nonresponsive to the antibiotics or demonstrate evidence of localized abscess formation. In spite of this, others believe decompression should be performed in all cases and is associated with a reduced hospital stay. Although drainage frequently does not produce significant pus, copious amounts of edema fluid often drain from the surgical excisions.

Before the use of modern antibiotic medications, the mortality from Ludwig angina often exceeded 50%. Although this rate has been reduced to less than 10%, deaths still occur as the result of complications such as pericarditis, pneumonia, mediastinitis, sepsis, empyema, and respiratory obstruction.

Cavernous Sinus Thrombosis

The therapeutic cornerstones for cavernous sinus thrombosis secondary to dental infections are surgical drainage combined with high-dose antibiotic medications similar to those administered for patients with Ludwig angina. The offending tooth should be extracted, and drainage is required if fluctuance is present. Administration of systemic corticosteroid drugs is indicated only in patients who have developed pituitary insufficiency in advanced cases of cavernous sinus thrombosis. Some investigators also prescribe anticoagulant medications to prevent thrombosis and septic emboli; conversely, others believe that thrombosis limits the infection and that the use of anticoagulant drugs may promote hemorrhagic lesions in the orbit and brain.

In older series the mortality rate approached 75%. Even with current medical advances and modern antibiotic medications, the mortality rate remains at approximately 30% with fewer than 40% of patients achieving full recovery.

◆ OSTEOMYELITIS

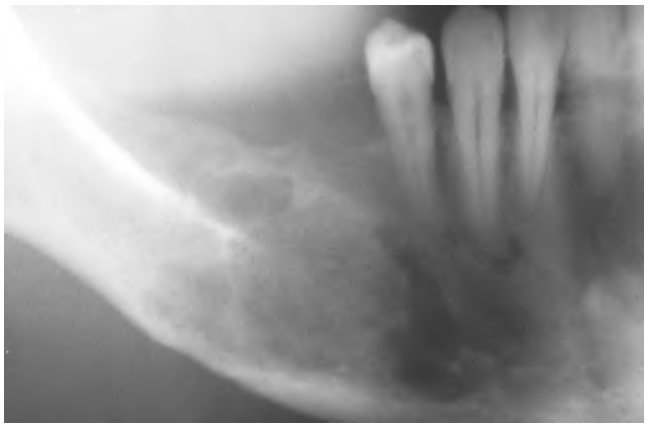
Osteomyelitis is an acute or chronic inflammatory process in the medullary spaces or cortical surfaces of bone that extends away from the initial site of involvement. The term *osteomyelitis* arose from the ancient Greek words *osteon* (bone) and *muelinos* (marrow) and literally implies infection of the medullary segments of bone. This section describes the classic pattern of osteomyelitis.

The vast majority of osteomyelitis cases are caused by bacterial infections and result in an expanding lytic destruction of the involved bone, with suppuration and sequestra formation. Many believe that this condition is more appropriately termed *suppurative osteomyelitis, bacterial osteomyelitis,* or *secondary osteomyelitis*. This pattern of osseous pathosis is in contrast to an ill-defined group of idiopathic inflammatory disorders of bone that do not respond consistently to antibacterial medications and typically demonstrate ultimate sclerosis of bone without suppuration or sequestra formation. This second pattern of inflammatory bone disease is most appropriately termed *primary chronic osteomyelitis* but often is included under the term *diffuse sclerosing osteomyelitis*. This disorder and several other patterns of inflammatory bone disease (e.g., focal sclerosing osteomyelitis, proliferative periostitis, and alveolar osteitis) are unique and are covered separately later in the chapter. Osteoradionecrosis is excluded from this discussion because this is primarily a problem of hypoxia, hypocellularity, and hypovascularity in which the presence of bacteria represents a secondary colonization of nonhealing bone rather than a primary bacterial infection (see page 269). In addition, medication-related osteonecrosis represents another unique pattern that is discussed in a later chapter and appears more strongly related to altered bone metabolism (see page 271).

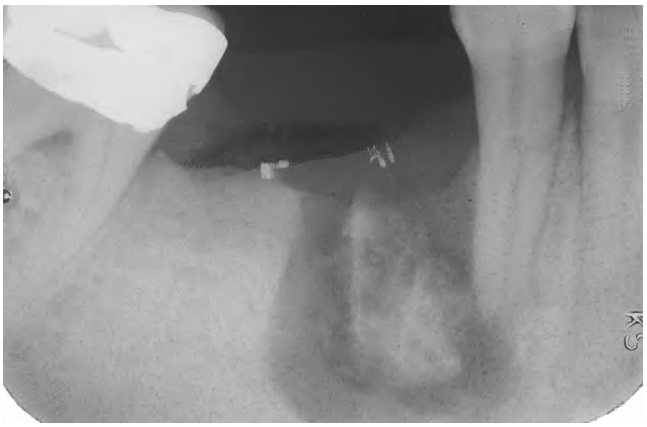
Suppurative osteomyelitis of the jaws is uncommon in developed countries, but it continues to be a source of significant difficulty in developing nations. In Europe and North America, most cases arise after odontogenic infections or traumatic fracture of the jaws. In addition, many cases reported in Africa occur in the presence of necrotizing ulcerative gingivitis (NUG) or noma.

Chronic systemic diseases, immunocompromised status, and disorders associated with decreased vascularity of bone appear to predispose people to osteomyelitis. Tobacco use, alcohol abuse, IV drug abuse, diabetes mellitus, exanthematous fevers, malaria, sickle cell anemia, malnutrition, malignancy, collagen vascular diseases, and AIDS have been associated with an increased frequency of osteomyelitis. In addition to radiation, several diseases (e.g., osteopetrosis, dysosteosclerosis, late Paget disease, end-stage cementoosseous dysplasia) may result in hypovascularized bone that is predisposed to necrosis and inflammation.

Acute suppurative osteomyelitis exists when an acute inflammatory process spreads through the medullary spaces of the bone and insufficient time has passed for the body to react to the presence of the inflammatory infiltrate. **Chronic suppurative osteomyelitis** exists when the defensive response leads to the production of granulation tissue, which subsequently forms dense scar tissue in an attempt to wall off the infected area. The encircled dead space acts as a reservoir for bacteria, and antibiotic medications have great difficulty reaching the site. This pattern begins to evolve about 1 month after the spread of the initial acute infection and results in a smoldering process that is difficult to manage unless the problem is approached aggressively.



• **Fig. 3-43 Acute Osteomyelitis.** Ill-defined area of radiolucency of the right body of the mandible.



• **Fig. 3-44 Acute Osteomyelitis with Sequestrum.** Radiolucency of the right body of the mandible with central radiopaque mass of necrotic bone. (Courtesy of Dr. Michael Meyrowitz.)

Clinical and Radiographic Features

Patients of all ages can be affected by osteomyelitis. There is a strong male predominance, approaching 75% in some reviews. Most cases involve the mandible due to its relatively poor vascular supply and dense cortical bone that is more susceptible to infection when compared to the maxilla. Maxillary disease becomes important primarily in pediatric patients and in cases that arise from NUG or noma (in African populations).

Acute Suppurative Osteomyelitis

Patients with acute osteomyelitis have signs and symptoms of an acute inflammatory process that has typically been less than 1 month in duration. Fever, leukocytosis, lymphadenopathy, significant sensitivity, and soft tissue swelling of the affected area may be present. Plain dental or panoramic radiographs may demonstrate an ill-defined radiolucency (Fig. 3-43), occasionally combined with widening of the periodontal ligament, loss of lamina dura, or loss of circumscription of the inferior alveolar canal or mental foramen. Periosteal new bone formation also may be seen in response to subperiosteal spread of the infection. This proliferation is more common in young patients and presents as a single-layered linear radiopaque line separated from the normal cortex by an intervening radiolucent band. Because plain radiographs require loss of up to 50% of bone mineral density to demonstrate an obvious pathosis, such films often may be unremarkable early in the course of infection. Scintigraphy and magnetic resonance imaging (MRI) demonstrate high sensitivity but low specificity. Conventional CT is a better choice due to its good combination of sensitivity and specificity. Being specially designed for imaging the gnathic hard tissues, cone-beam CT represents another excellent alterative with shorter scanning times and lower doses of radiation when compared to conventional CT. On occasion, paresthesia of the lower lip, drainage, or exfoliation of fragments of necrotic bone may be discovered. A fragment of necrotic bone that has separated from the adjacent vital bone is termed a **sequestrum.** Sequestra often exhibit spontaneous exfoliation (Fig. 3-44). On occasion, fragments of necrotic bone may become surrounded by new vital bone, and the dead bone in this situation is known as an **involucrum.**

Chronic Suppurative Osteomyelitis

If acute osteomyelitis is not resolved expeditiously, the entrenchment of **chronic osteomyelitis** occurs, or the process may arise primarily without a previous acute episode. Swelling, pain, sinus formation, purulent discharge, sequestrum formation, tooth loss, or pathologic fracture may occur. Patients may experience acute exacerbations or periods of decreased pain associated with chronic smoldering progression (Fig. 3-45).

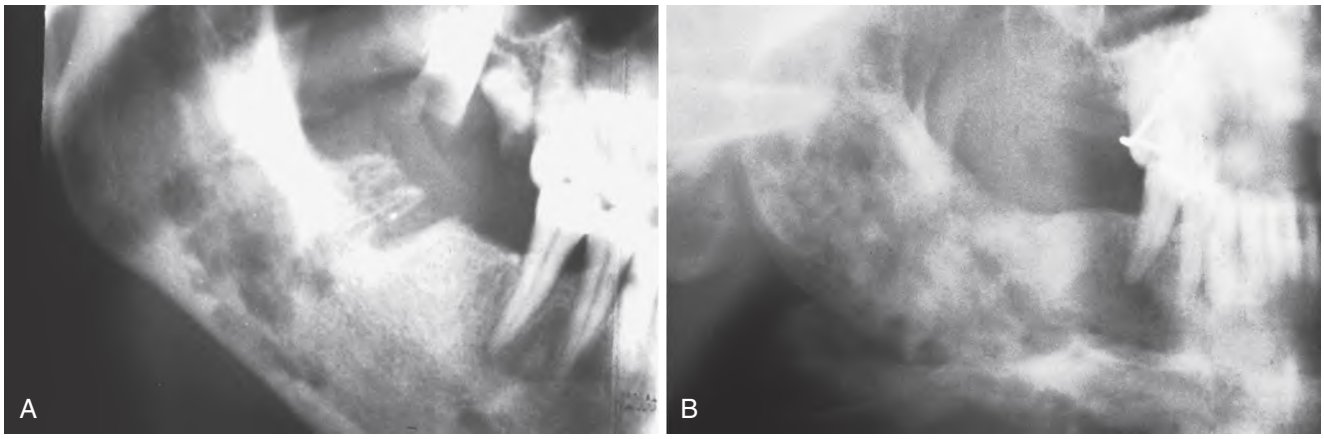
Radiographs reveal a patchy, ragged, and ill-defined radiolucency that may contain central radiopaque sequestra and be intermixed with zones of radiodensity. Less frequently, the infection may be predominantly osteosclerotic or occasionally almost totally osteolytic. The osseous change is continuous and may exhibit spread to the periosteum by direct extension. This is in contrast to primary chronic osteomyelitis, in which multifocal and separate areas of osteolysis are present within zones of sclerosis.

Because of an anatomic peculiarity, large portions of each jawbone receive their blood supply through multiple arterial loops originating from a single vessel. Involvement of this single feeder vessel can lead to necrosis of a large portion of the affected bone. Sequestration that has involved an entire quadrant of the jaw has been reported in long-standing cases of chronic osteomyelitis.

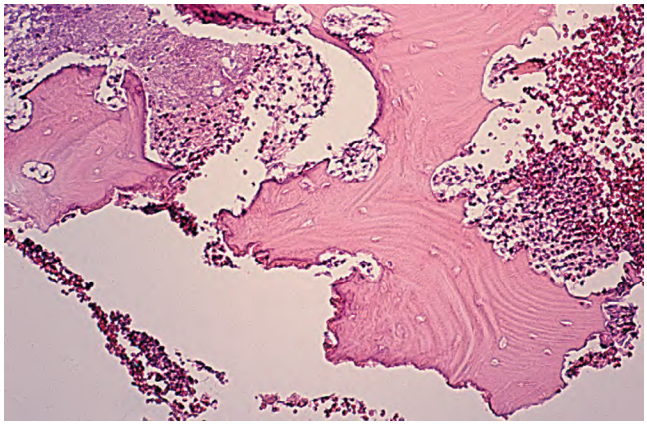
Histopathologic Features

Acute Suppurative Osteomyelitis

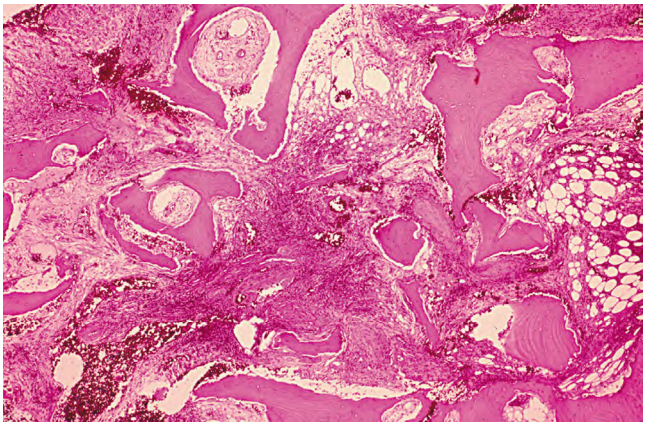
Generation of biopsy material from patients with acute osteomyelitis is not common because of the predominantly liquid content and lack of a soft tissue component. When submitted, the material consists predominantly of necrotic bone. The bone shows a loss of the osteocytes from their



• **Fig. 3-45 Chronic Osteomyelitis. A,** Ill-defined area of radiolucency of the right body of the mandible adjacent to a recent extraction site. **B,** After the initial intervention, the patient failed to return for follow-up because of lack of significant pain. An enlarged, ill-defined radiolucency of the right body of the mandible was discovered 2 years after the initial surgery. (Courtesy of Dr. Charles Waldron.)



• **Fig. 3-46 Acute Osteomyelitis.** Nonvital bone exhibits loss of the osteocytes from the lacunae. Peripheral resorption, bacterial colonization, and surrounding inflammatory response also can be seen.



• **Fig. 3-47 Chronic Osteomyelitis.** Chronically inflamed and reactive fibrous connective tissue filling the intertrabecular spaces.

lacunae, peripheral resorption, and bacterial colonization (Fig. 3-46). The periphery of the bone and the haversian canals contain necrotic debris and an acute inflammatory infiltrate consisting of polymorphonuclear leukocytes. The submitted material will be diagnosed as a sequestrum unless a good clinicopathologic correlation points to the appropriate diagnosis of acute osteomyelitis.

Chronic Suppurative Osteomyelitis

Biopsy material from patients with chronic osteomyelitis demonstrates a significant soft tissue component that consists of chronically or subacutely inflamed fibrous connective tissue filling the intertrabecular areas of the bone (Fig. 3-47). Scattered sequestra and pockets of abscess formation are common.

Treatment and Prognosis

Acute Suppurative Osteomyelitis

Therapy centers around surgical intervention to 1) resolve the source of infection, 2) establish drainage, 3) removal of obviously infected bone, and 4) obtain bacteriologic samples for culture and antibiotic sensitivity testing. While waiting on the bacteriologic evaluation, antibiotics are administered empirically, usually penicillin with metronidazole or clindamycin. Multiple procedures over days to weeks may be required for complete elimination of the infection and reconstruction of the gnathic defect.

Chronic Suppurative Osteomyelitis

Chronic osteomyelitis is difficult to manage medically, presumably because pockets of dead bone and organisms are protected from antibiotic drugs by the surrounding wall of fibrous connective tissue. Surgical intervention is mandatory. The antibiotic medications are similar to those used in the acute form but must be given intravenously in high doses.

The extent of the surgical intervention depends on the spread of the process; removal of all infected material down to good bleeding bone is mandatory in all cases. For small lesions, curettage, removal of necrotic bone, and

saucerization are sufficient. In patients with more extensive osteomyelitis, decortication or saucerization often is combined with transplantation of cancellous bone chips. In cases of persisting osteomyelitis, resection of the diseased bone followed by immediate reconstruction with an autologous graft is required. Weakened jawbones must be immobilized.

The goal of surgery is removal of all infected tissue. Persistence of chronic osteomyelitis is typically the result of incomplete removal of diseased tissue. On successful elimination of all infected material, resolution is expected. Adjunctive procedures (e.g., hyperbaric oxygen) are rarely necessary if thorough surgical curettage and sequestrectomy have been accomplished. In an attempt to remove all areas of necrotic bone thoroughly, tetracycline has been administered 48 hours in advance of surgery and used as a fluorescent marker of vital bone. At the time of surgery, necrotic bone will not fluoresce under the ultraviolet (UV) light of a Wood's lamp, indicating that it should be removed.

Management of persistent cases of chronic osteomyelitis often requires use of more sophisticated techniques. Scintigraphic techniques with technetium-99m (^{99m}Tc)-labeled phosphorus compounds can be used to evaluate the therapeutic response and progress of treatment. Hyperbaric oxygen is recommended primarily for the rare patient who does not respond to standard therapy or for disease arising in hypovascularized bone (e.g., osteoradionecrosis, osteopetrosis, Paget disease, and cemento-osseous dysplasia).

◆ DIFFUSE SCLEROSING OSTEOMYELITIS

Diffuse sclerosing osteomyelitis is an ill-defined, highly controversial, evolving area of dental medicine. This diagnosis encompasses a group of presentations that are characterized by pain, inflammation, and varying degrees of gnathic periosteal hyperplasia, sclerosis, and lucency. Included in this category are three different pathoses:

1. Diffuse sclerosing osteomyelitis
2. Primary chronic osteomyelitis
3. Chronic tendoperiostitis

In the purist's view, diffuse sclerosing osteomyelitis is different from primary chronic osteomyelitis and chronic tendoperiostitis. This term should be used only when an obvious infectious process directly is responsible for sclerosis of bone. In these cases, a chronic intraosseous bacterial infection creates a smoldering mass of chronically inflamed granulation tissue that incites sclerosis of the surrounding bone.

Primary chronic osteomyelitis often is confused with, but must be distinguished from, chronic suppurative osteomyelitis (secondary chronic osteomyelitis). In contrast to suppurative osteomyelitis, an association with a bacterial infection is not obvious, and suppuration and sequestration characteristically are absent. A number of causes have been proposed, such as an altered immune response to an organism of low virulence, but no single theory has received widespread acceptance. In contrast to suppurative osteomyelitis, a primary infectious cause cannot be proven, because many studies have been unable to culture organisms and the condition does not respond to long-term antibiotic therapy.

On occasion, gnathic lesions presenting as primary chronic osteomyelitis occur in patients with other significant systemic manifestations. **Chronic recurrent multifocal osteomyelitis (CRMO)** demonstrates involvement of multiple bones and is thought by many to represent a widespread variant of primary chronic osteomyelitis. **SAPHO syndrome** is closely related and an acronym for a complex clinical presentation that includes **S**ynovitis, **A**cne, **P**ustulosis, **H**yperostosis, and **O**steitis in which the osseous lesions mirror those of primary chronic osteomyelitis and CRMO. The cause of CRMO and SAPHO is unknown, but they possibly may arise in genetically predisposed individuals who develop an autoimmune disturbance secondary to exposure to dermatologic bacteria. Researchers theorize that an abnormal immune response to the microorganism cross-reacts with normal bone or joint structures, leading to the variety of clinical manifestations. The organism associated with acne, *Propionibacterium acnes,* has been recovered in bone biopsies of some affected patients.

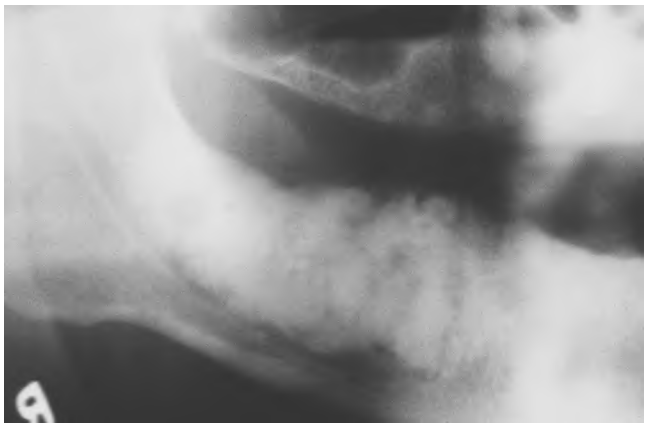
Although initially thought to be an obscure infectious process, the clinical presentation of **chronic tendoperiostitis** is similar to that of primary chronic osteomyelitis; today many clinicians believe it represents a reactive alteration of bone that is initiated and exacerbated by chronic overuse of the masticatory muscles, predominantly the masseter and digastric. In a large series of patients, parafunctional muscle habits (e.g., bruxism, clenching, nail biting, co-contraction, and inability to relax jaw musculature) were known or became evident during follow-up. In neurophysiologic studies, masseter inhibitory reflexes were abnormal in the vast majority of patients studied. The cause of chronic tendoperiostitis is controversial, and some investigators believe this disorder may represent a variation of primary chronic osteomyelitis, in which parafunctional muscle habits exacerbate the process but are not the initial cause.

Clinical and Radiographic Features

Diffuse Sclerosing Osteomyelitis

Diffuse sclerosing osteomyelitis is similar to the localized variant (condensing osteitis; see page 134); however, the disorder is also very different. It arises almost exclusively in adulthood, does not exhibit a sex predominance, and primarily occurs in the mandible. An increased radiodensity develops around sites of chronic infection (e.g., periodontitis, pericoronitis, and apical inflammatory disease) in a manner very similar to the increased radiodensity that may be seen surrounding areas of chronic suppurative osteomyelitis. Typically, the altered area is restricted to a single site but may be multifocal or extend to fill an entire quadrant.

The sclerosis centers on the crestal portions of the tooth-bearing alveolar ridge and does not appear to originate in the areas of attachment of the masseter or digastric muscle (Fig. 3-48). The radiodensities do not develop from



• **Fig. 3-48 Diffuse Sclerosing Osteomyelitis.** Diffuse area of increased radiodensity of the right body of the mandible in the tooth-bearing area. No other quadrants were involved. (Courtesy of Dr. Louis M. Beto.)

previously radiolucent fibro-osseous lesions and do not exhibit the predilection for black females, as is found in those patients with florid cemento-osseous dysplasia. Pain and swelling are not typical.

Primary Chronic Osteomyelitis

Primary chronic osteomyelitis is most commonly discovered as an isolated process that typically is localized to the mandible. Extragnathic evidence of SAPHO syndrome or CRMO is seen much less frequently. The onset of symptoms tends to demonstrate two peaks, one in adolescence and the other in adults after the fifth decade of life. Affected patients have recurrent episodes of pain, swelling, local induration, and limited mouth opening that is not associated with any obvious dental infection. During periods of disease activity, regional lymphadenopathy and reduced sensation in the distribution of the inferior alveolar nerve may be present. Absence of fever, purulence, sequestration, and sinus formation are characteristic. The lack of an obvious association with an odontogenic infection and the nonsuppurative presentation clearly separate this condition from chronic suppurative osteomyelitis.

In the early stages of primary chronic osteomyelitis, radiographs tend to demonstrate a mixed pattern, with areas of radiolucent osteolysis intermingled with zones of sclerosis. In contrast to the pattern noted in CT images of suppurative osteomyelitis, the osteolytic areas are not continuous and alternate with zones of sclerosis. The affected area of the bone typically is thickened and demonstrates a periosteal proliferation that is more solid than the typical laminated proliferative periostitis of inflammatory origin. Facial asymmetry is not uncommon and often takes years to resolve secondary to slow remodeling. Over time, the affected area becomes predominantly sclerotic, but during subsequent periods of disease activity, new foci of osteolysis and cortical bone destruction appear. These newly affected areas subsequently undergo sclerosis, awaiting the next cycle of disease activity. With disease progression, the clinical symptoms typically diminish and the affected bone demonstrates progressive sclerosis and a reduction in the volume. Radiolucent osteolytic areas may remain, but they tend to be relatively small and widely scattered. Overall, the predominant radiographic alteration of primary chronic osteomyelitis is medullary sclerosis, a pattern that is noted invariably in affected patients. Skeletal scintigraphy demonstrates significant uptake in the affected areas and should be performed in all patients in an effort to rule out extragnathic involvement.

CRMO and SAPHO Syndrome

CRMO and SAPHO syndrome appear closely related, and many believe that CRMO represents the pediatric variant of SAPHO. CRMO presents in childhood with pain and swelling of multiple bones, classically the extremities. Affected bones typically demonstrate hyperostosis with osteitis that is associated with negative microbiologic cultures and lack of response to antibiotics. Many patients demonstrate concurrent or future neutrophilic skin diseases, such as palmoplantar pustulosis, severe acne, hidradenitis suppurativa, psoriasis, Sweet syndrome, or pyoderma gangrenosum. The dermatologic involvement may be absent, appear after some delay, or be so subtle as to escape detection. In contrast, SAPHO usually is noted in adults, classically affects the axial skeleton (anterior chest wall), and more frequently demonstrates concurrent neutrophilic skin lesions. Gnathic involvement has been reported in both CRMO and SAPHO, mandating full bone scan in any patient with an unexplained primary chronic osteomyelitis. In contrast to bacterial osteomyelitis, the osteolytic areas are scattered randomly within areas of sclerotic bone. Periosteal new bone formation is common but not related to cortical bone perforation. Investigation of the entire skeleton by bone scintigraphy classically reveals involvement of multiple sites.

In early gnathic lesions, diffuse osteolytic zones are more prominent than sclerosis, and the affected bone is enlarged because of significant production of periosteal new bone. With time, the bone becomes more sclerotic and decreases in size because of diminished periosteal apposition, while the osteolytic zones become smaller and fewer. External bone resorption and deformity of the mandible are characteristic in older lesions.

Chronic Tendoperiostitis

Although the mean age of occurrence is 40 years, chronic tendoperiostitis may occur in people of all ages. There is no sex predilection. Recurrent pain, swelling of the cheek, and trismus are classic symptoms. Suppuration and an associated infectious cause are not found. Microbiologic cultures are typically negative, with the lesions failing to respond to appropriate antibiotic medications. Uncommon spontaneous resolution with development of radiographic normalcy has been noted.

In most instances, the sclerosis is limited to a single quadrant and centers on the anterior region of the

mandibular angle and posterior portion of the mandibular body (i.e., attachment of the masseter muscle). Occasionally, the cuspid and premolar region and the anterior mandible (i.e., attachment of the digastric muscle) may be involved. Relatively radiolucent zones are apparent within the areas of radiodensity, but histopathologic examination reveals only dense bone, formation of reactive bone, and relatively few signs of inflammation. The inferior border of the mandibular body is typically affected, and significant erosion of the inferior border appears just anterior to the angle of the mandible.

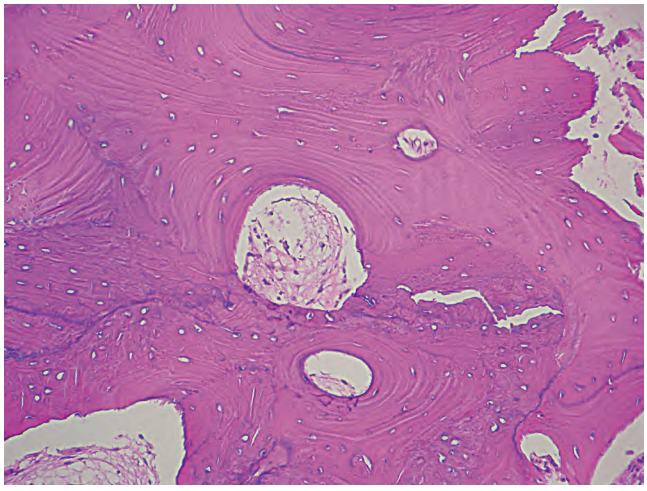
Histopathologic Features

Diffuse Sclerosing Osteomyelitis

Diffuse sclerosing osteomyelitis demonstrates sclerosis and remodeling of bone. The haversian canals are scattered widely and little marrow tissue can be found. Although the sclerosis occurs adjacent to areas of inflammation, the bone is not typically intermixed with a significant inflammatory soft tissue component. If the adjacent inflammatory process extends into the sclerotic bone, then necrosis often occurs. The necrotic bone separates from the adjacent vital tissue and becomes surrounded by subacutely inflamed granulation tissue. Secondary bacterial colonization often is visible.

Primary Chronic Osteomyelitis, CRMO, and SAPHO Syndrome

Similar histopathologic features are seen in primary chronic osteomyelitis, SAPHO syndrome, and CRMO. In the areas of sclerosis, numerous irregular trabeculae of pagetoid bone are present and demonstrate extensive evidence of remodeling with prominent reversal lines, osteoblastic rimming, and focal areas of osteoclastic activity (Fig. 3-49). Intertrabecular fibrosis is present, with scattered lymphocytes and plasma cells. Present in many, but not all examples, are foci of microabscess formation, hyalinization around small blood vessels, and subperiosteal bone formation. The microabscesses have been correlated with the osteolytic foci noted during active phases of the disease. In obvious contrast to chronic suppurative osteomyelitis, bone necrosis, bacterial colonization, and frank purulence are absent.



• **Fig. 3-49 Primary Chronic Osteomyelitis.** Trabeculae of sclerotic, pagetoid bone showing numerous resting and reversal lines.

Chronic Tendoperiostitis

Chronic tendoperiostitis demonstrates sclerosis and remodeling of the cortical and subcortical bone with a resultant increase in bone volume. If chronic inflammatory cells are present, then they are located in cortical resorption defects and the subcortical bone adjacent to sites of muscle insertion.

Treatment and Prognosis

Diffuse Sclerosing Osteomyelitis

Diffuse sclerosing osteomyelitis is treated best through resolution of the adjacent foci of chronic infection. After resolution of the infection, the sclerosis remodels in some patients but remains in others. The persistent sclerotic bone is hypovascular, does not exhibit typical remodeling, and is very sensitive to inflammation. The patient and the clinician should work together to avoid future problems with periodontitis or apical inflammatory disease. With long-term alveolar resorption after denture placement, the altered bone does not exhibit typical resorption and exposure with secondary osteomyelitis can develop. These secondary lesions can be treated in the same way as a primary acute or chronic osteomyelitis (see page 130).

Primary Chronic Osteomyelitis, CRMO, and SAPHO Syndrome

Even with significant surgical and medical intervention, the disease course is characterized by flares separated by partial remissions. Most treatments directed toward elimination of infection have been proven ineffective. Long-term antibiotic treatment with or without hyperbaric oxygen therapy has not produced consistent long-term success. Surgical decortication has decreased the intensity and frequency of symptoms but has failed to resolve the process totally. Because of inconsistent results from surgical intervention, extensive surgery is contraindicated, especially in young, growing patients. Corticosteroid medications, NSAIDs, calcitonin, and tumor necrosis factor-α antagonists have been reported to relieve symptoms but usually are associated with incomplete resolution. In a number of publications, IV administration of bisphosphonates has shown significant therapeutic benefits with reduction of symptoms and radiographic resolution of bony abnormalities. In spite of this, recurrences have been noted, often leading to additional therapeutic interventions.

Chronic Tendoperiostitis

Treatment of chronic tendoperiostitis as a form of osteomyelitis has been most unsatisfactory. Large series of patients have been treated with antibiotic medications, explorations, intraoral decortication, implantation of gentamicin beads, hyperbaric oxygen, and corticosteroid drugs with no significant effect. Treatment directed toward resolution of muscle

overuse has resulted in significantly decreased symptoms in most patients and total resolution in a minority. Therapeutic approaches include the following:

- Muscular relaxation instructions (soft diet, avoidance of parafunctional habits)
- Rotation exercises
- Occlusal splint therapy
- Myofeedback
- Muscle relaxant drugs (e.g., diazepam)

◆ CONDENSING OSTEITIS (FOCAL SCLEROSING OSTEOMYELITIS)

Localized areas of bone sclerosis associated with the apices of teeth with pulpitis (from large carious lesions or deep coronal restorations) or pulpal necrosis are termed **condensing osteitis.** The association with an area of inflammation is critical, because these lesions can resemble several other intrabony processes that produce a somewhat similar pattern.

Clinical and Radiographic Features

This secondary sclerosis of bone is seen most frequently in children and young adults but also can occur in older adults. The classic alteration consists of a localized, usually uniform zone of increased radiodensity adjacent to the apex of a tooth that exhibits a thickened periodontal ligament (PDL) space or an apical inflammatory lesion (Fig. 3-50). Clinical expansion should not be present. Most cases occur in the premolar and molar areas of the mandible, and the dental pulp of the involved tooth demonstrates pulpitis or necrosis. The lesion does not exhibit a radiolucent border, as is seen in cases of **focal cemento-osseous dysplasia** (see page 597), although an adjacent radiolucent inflammatory lesion may be present. In addition, the radiopacity is not separated from the apex as would be seen in **idiopathic osteosclerosis** (see page 579).

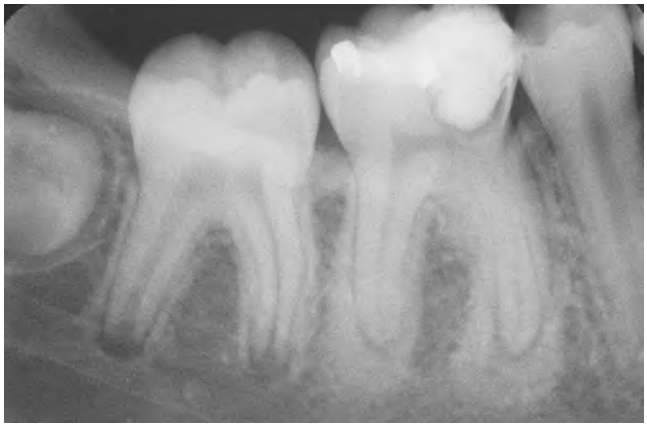
Treatment and Prognosis

Treatment of the patient with condensing osteitis consists of resolution of the odontogenic focus of infection. After extraction or appropriate endodontic therapy of the involved tooth, approximately 85% of cases of condensing osteitis will regress, either partially or totally. Typically, resolution of the lesion is associated with normalization of the associated periodontal membrane. If the lesion persists and the periodontal membrane remains wide, then reevaluation of the endodontic therapy should be considered. A residual area of condensing osteitis that remains after resolution of the inflammatory focus is termed a *bone scar* (Fig. 3-51). Root resorption has been noted during orthodontics if the sclerotic bone is the path of tooth movement.

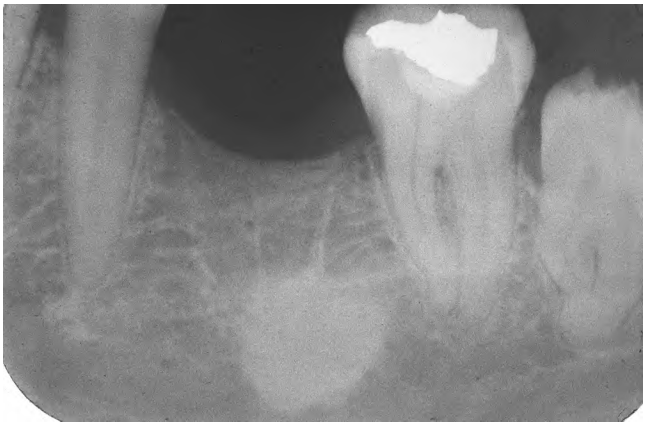
◆ OSTEOMYELITIS WITH PROLIFERATIVE PERIOSTITIS (PERIOSTITIS OSSIFICANS)

Bone formation within a periosteal reaction is a common finding that occurs in a wide variety of intraosseous pathoses and in all age groups. Causes of periosteal new bone formation include osteomyelitis, trauma, cysts, infantile cortical hyperostosis, fluorosis, avitaminosis C, hypertrophic osteoarthropathy, congenital syphilis, and neoplasms (such as, Ewing sarcoma, Langerhans cell histiocytosis, and osteogenic sarcoma). Of these, osteomyelitis and malignant neoplasms are associated most frequently with formation of bone within a periosteal reaction.

In 1893 a Swiss physician, Carl Garrè, reported in the German literature on patterns of acute osteomyelitis. Since that time, numerous articles have been written that associate Garrè's report with a form of inflammatory periosteal hyperplasia demonstrating an onionskin-like reduplication of the cortical plate. (In these subsequent articles, Garrè's name was misspelled consistently as Garré, with an incorrect accent designation.) However, Garrè did not have any pathologic specimens for microscopic examination, and



• **Fig. 3-50 Condensing Osteitis.** Increased areas of radiodensity surrounding the apices of the nonvital mandibular first molar.



• **Fig. 3-51 Bone Scar.** Residual area of increased radiodensity in the area of extraction of the mandibular first molar. (Courtesy of Dr. Walter Blevins.)

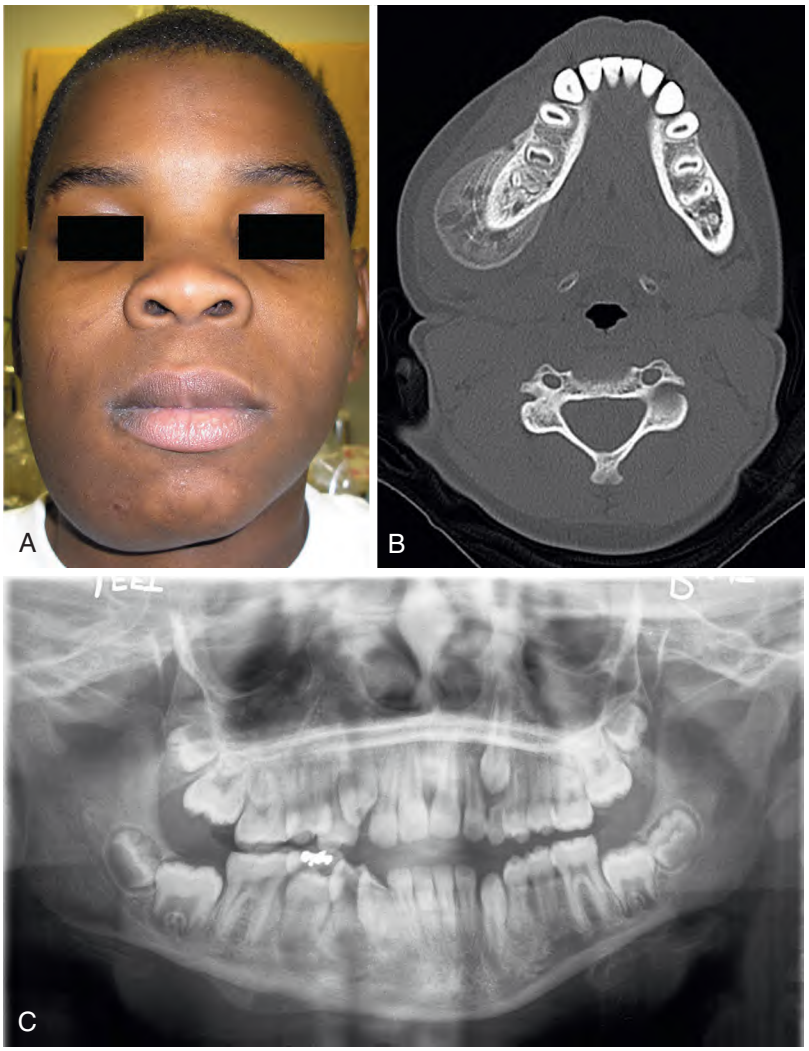
Roentgen did not discover x-rays until 2 years after Garrè's publication. Nowhere in the original publication is there any mention of periostitis, periosteal duplication, or "onion-skinning." Although the term *Garrè osteomyelitis* often is used synonymously for this condition, it is an improper designation that should be disassociated with the entity described in the text that follows.

Clinical and Radiographic Features

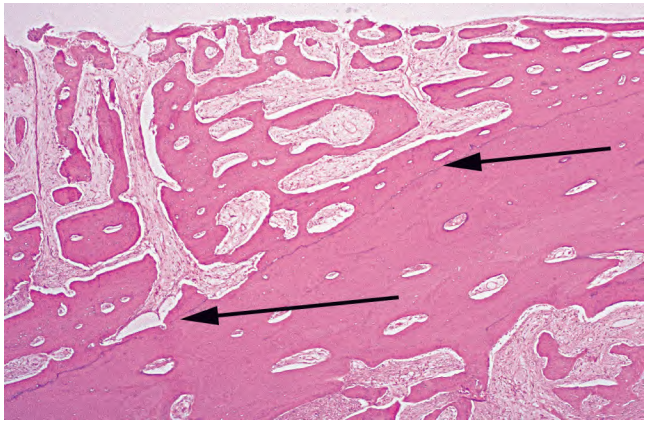
Proliferative periostitis represents a periosteal reaction to the presence of inflammation. The affected periosteum forms several rows of reactive vital bone that parallel each other and expand the surface of the altered bone. Affected patients tend to be primarily children and young adults, with a mean age of 13 years. No sex predominance is noted.

As expected, the most frequent cause is dental caries with associated periapical inflammatory disease, although lesions have been reported secondary to periodontal infections, fractures, buccal bifurcation cysts, and nonodontogenic infections. Most cases arise in the premolar and molar area of the mandible. The hyperplasia is located most frequently along the lower border of the mandible, but buccal cortical involvement also is common. Isolated lingual cortical enlargement is infrequent. Most cases are unifocal, although multiple quadrants may be affected.

Appropriate radiographs demonstrate radiopaque laminations of bone that roughly parallel each other and the underlying cortical surface (Fig. 3-52). The laminations vary from 1 to 12 in number, and radiolucent separations often are present between the new bone and the original cortex. Less frequently, the new bone formation exhibits consolidation and contains numerous fine bony projections that radiate perpendicular from the underlying and intact periosteum. Within the new bone, areas of small sequestra or osteolytic radiolucencies may be found.



• **Fig. 3-52 Proliferative Periostitis. A,** Firm swelling of the lateral and inferior border of the right mandible that arose after traumatic injury. **B,** Computed tomography (CT) image demonstrating new periosteal bone growth with onionskin laminations. **C,** Panoramic radiograph exhibiting new periosteal bone formation along the right inferior border of the mandible. (Courtesy of Drs. Sherif Mekhail and Benjamin Lin.)



• **Fig. 3-53 Proliferative Periostitis.** Interconnecting trabeculae of new bone formation *(top left)* extending from the original cortical surface *(delineated by arrows).*

Because of difficulty in proper angulation and problems related to superimposition of the underlying bone, CT scanning has proved to be consistently superior to conventional radiography in demonstrating proliferative periostitis. On plain films, the alterations are typically seen best on a panoramic or lateral oblique radiograph. If lateral oblique radiographs fail to demonstrate the lesion, then occlusal views and, less frequently, posteroanterior radiographs may be successful.

Histopathologic Features

Usually, biopsy is not required unless the clinical diagnosis is in question. Specimens often reveal parallel rows of highly cellular and reactive woven bone in which the individual trabeculae are frequently oriented perpendicular to the surface. The trabeculae sometimes form an interconnecting meshwork of bone or are scattered more widely, resembling the pattern seen in immature fibrous dysplasia (Fig. 3-53). Between the cellular trabeculae, relatively uninflamed fibrous connective tissue is evident. Sequestra, if included, demonstrate the typical features of bone necrosis (see Osteomyelitis, page 129).

Treatment and Prognosis

Most cases of proliferative periostitis of the jaws are associated with periapical inflammatory lesions, and treatment in these cases (either extraction of the offending tooth or appropriate endodontic therapy) is directed toward eliminating the source of the infection. After the focus of infection has been eliminated and inflammation has resolved, the layers of bone will consolidate in 6 to 12 months as the overlying muscle action helps to remodel the bone to its original state.

If a unifocal periosteal reaction similar to proliferative periostitis appears in the absence of an obvious source of inflammation, biopsy is recommended because several neoplastic conditions can result in a similar pattern.

◆ ALVEOLAR OSTEITIS (DRY SOCKET; FIBRINOLYTIC ALVEOLITIS)

After extraction of a tooth, a blood clot is formed at the site, with eventual organization of the clot by granulation tissue, gradual replacement by coarse fibrillar bone, and, finally, replacement by mature bone. Premature fibrinolysis of the initial clot is thought to be responsible for the clinical condition known as **alveolar osteitis.** Factors deemed to be associated with an increased prevalence include oral contraceptive use, tobacco use, preoperative infection, difficult extraction, inexperienced surgeons, surgical flap design (envelope flap rather than modified triangular flap), use of a local anesthetic with vasoconstrictor, and inadequate postoperative irrigation.

Clinical Features

The frequency of alveolar osteitis is higher in the mandible and the posterior areas. After oral contraceptive use is taken into account, there does not appear to be a significant sex predilection. The prevalence is between 1% and 3% of all extractions, but it increases to 25% to 30% for impacted mandibular third molars. The frequency appears to be decreased when impacted teeth are removed prophylactically rather than for pericoronitis. The overall prevalence is highest between 20 and 40 years of age (when the majority of teeth are extracted), although the likelihood of developing alveolar osteitis appears greatest for extractions in the 40- to 45-year-old age group.

The affected extraction site is filled initially with a dirty gray clot that is lost and leaves a bare bony socket **(dry socket).** The detection of the bare socket may be hindered by partial retention of the clot or by overlying inflamed tissue that covers the site. The diagnosis is confirmed by probing of the socket, which reveals exposed and extremely sensitive bone. Typically, severe pain, foul odor, and (less frequently) swelling and lymphadenopathy develop 3 to 4 days after extraction of the tooth. On occasion, the pain radiates from the socket to the ipsilateral ear, temporal region, or eye. Rarely, trismus also may be noted. The signs and symptoms may last from 10 to 40 days.

Treatment and Prognosis

On evaluation of the patient complaining of postextraction pain, a radiograph should be taken of the affected area to rule out the possibility of a retained root tip or a foreign body. All sutures should be removed. The socket is irrigated with warm saline, followed by thorough clinical inspection of the socket for any unexpected pathosis. Curettage of the socket is not recommended, because this typically increases the associated pain. Potent oral analgesics should be prescribed, and the patient should be given a plastic syringe with instructions to keep the socket clean via home irrigation with a chlorhexidine or saline solution. This irrigation

should continue until debris no longer collects within the healing socket (usually 3 to 4 weeks).

Use of an obtundent and antiseptic dressing, such as iodoform gauze containing eugenol, is controversial. Although the dressing may reduce the symptoms and help keep out food debris, many believe the dressing acts as foreign material and delays healing of the extraction socket. If a dressing is used, then it should be changed every 24 hours for the first 3 days, then every 2 to 3 days until granulation tissue covers the exposed bone. The dressing should be discontinued as soon as the patient is pain free. After that time, the patient should be given a plastic syringe with instructions for home irrigation.

Many investigators have studied preventive measures for alveolar osteitis including systemic and topical antibiotics, cessation of smoking the day before and after surgery, copious surgical irrigation, and antifibrinolytic agents. Any topical antibiotic should not be in an ointment form, because such use has resulted in chronic foreign body reactions (e.g., myospherulosis) (see page 297).

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4 Periodontal Diseases

In this textbook of oral and maxillofacial pathology, the discussion of periodontal diseases is limited appropriately in scope. However, several fine textbooks are available on periodontology and can provide the reader with more information on the background, microbiology, clinical presentations, diagnostic procedures, and current therapies used to treat these diseases.

GINGIVITIS

Gingivitis refers to inflammation limited to the soft tissues that surround the teeth. It does not include the inflammatory processes that may extend into the underlying alveolar ridge, periodontal ligament, or cementum. A similar pattern of inflammation has noted in the mucosa surrounding implants and has been termed **peri-implant mucositis.** The primary types of gingivitis are listed in Box 4-1. This part of the text concentrates on the plaque-related types. **Necrotizing ulcerative gingivitis (NUG), medication-influenced gingivitis,** and a specific type of allergic gingivitis **(plasma cell gingivitis)** are presented later in this chapter. Additional forms of allergic gingivitis are discussed in Chapter 9. The gingivitis associated with specific infections (e.g., herpes simplex, and human immunodeficiency virus [HIV]) is discussed in Chapters 5 and 7. The gingiva is a frequent site of involvement in several of the dermatologic vesiculoerosive diseases; these are well described in Chapter 16.

Clinical Features

Most cases of gingivitis occur from lack of proper oral hygiene, which leads to the accumulation of dental plaque and calculus; however, many other factors can affect the gingiva's susceptibility to the oral flora. The frequency of gingivitis is high in all age groups. Clinically detectable inflammatory changes of the gingiva begin in childhood and increase with age. With similar amounts of dental plaque, the severity of gingivitis is greater in adults than in prepubertal children. Around the time of puberty, there is a period of increased susceptibility to gingivitis **(puberty gingivitis),** with the peak prevalence of involvement occurring between the ages of 9 and 14 years. Between the ages of 11 and 17 years, the frequency declines; then a slow increase is seen until the prevalence approaches 100% in the sixth decade of life.

In most age groups, females demonstrate a lower frequency of gingivitis than do males (although females have periods of increased susceptibility). This may be due more to better oral hygiene in females than to a physiologic difference between the sexes. In addition to the years of puberty, females exhibit a greater susceptibility to gingivitis when they are exposed to the high levels of progesterone associated with pregnancy or some forms of oral contraceptives.

A number of other systemic factors have been shown to increase the frequency of gingivitis and are listed in Box 4-2. In contrast, smoking and use of many antibiotic drugs, corticosteroid medications, and nonsteroidal antiinflammatory drugs (NSAIDs) have been correlated with a reduced gingival response to plaque. Various local factors that can be related to gingivitis are shown in Box 4-3.

Injury to the gingiva from mastication, oral hygiene techniques, or other habits may result in a breach of the oral mucosa, with secondary infection from the local flora. Most such injuries result in transient areas of erythema. However, if the trauma follows a chronic pattern, then areas of persistently swollen, erythematous gingiva may result. Patients who are mouth breathers or demonstrate incomplete lip closure can display a unique pattern of gingivitis in which the anterior facial gingiva is smooth, swollen, and red (Fig. 4-1).

Susceptibility to plaque-related gingivitis appears to vary within the population, and the individual traits seem to determine the severity of gingivitis, independent of the degree of plaque accumulation. In addition, evidence suggests that susceptibility to gingivitis appears linked to susceptibility to future development of periodontitis.

Inflammation of the gingiva may be localized or generalized. The involved area may be diffuse or confined to the free gingival margins **(marginal gingivitis)** (Fig. 4-2) or the interdental papillae **(papillary gingivitis).** The earliest signs of gingivitis include a loss of stippling plus bleeding on gentle probing. Healthy gingiva is coral pink; with inflammation, the involved gingiva becomes light red. With progression, the area becomes redder and edematous. As the process becomes entrenched, the involved gingiva becomes brighter red or magenta; the gingiva often demonstrates

• BOX 4-1 Types of Gingivitis

- Plaque-related gingivitis
- Necrotizing ulcerative gingivitis (NUG)
- Medication-influenced gingivitis
- Allergic gingivitis
- Specific infection-related gingivitis
- Dermatosis-related gingivitis

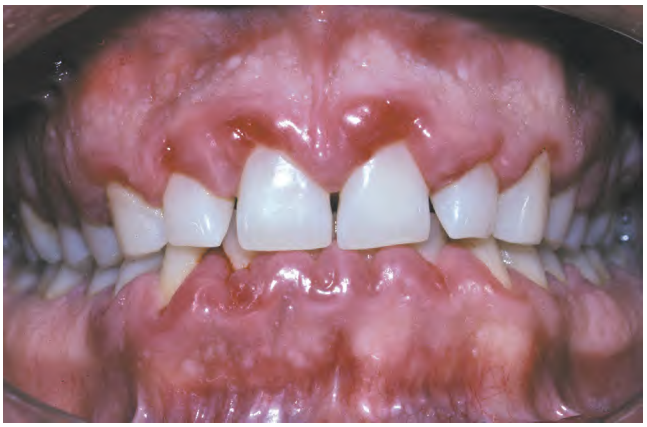
• BOX 4-2 Systemic Factors Associated with Gingivitis

1. Hormonal changes
   - Puberty
   - Pregnancy
   - Oral contraceptive use
2. Stress
3. Substance abuse
4. Poor nutrition
   - Ascorbate (vitamin C) deficiency (see page 770)
5. Certain medications (see page 148)
   - Phenytoin
   - Calcium channel blockers
   - Cyclosporine
6. Diabetes mellitus (see page 785)
7. Down syndrome
8. Immune dysfunction
9. Heavy-metal poisoning (see page 286)

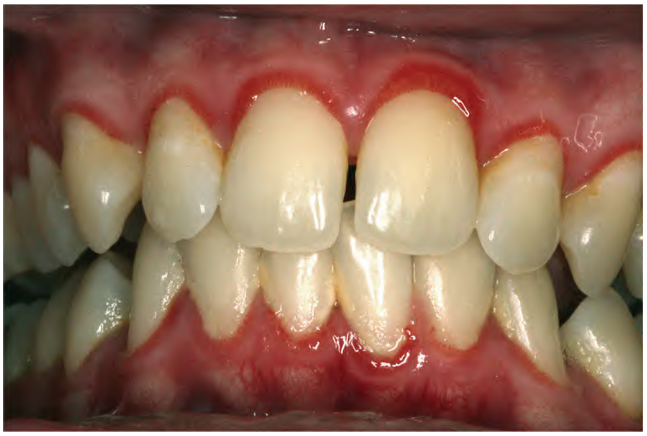
• BOX 4-3 Local Factors Associated with Gingivitis

1. Local trauma
2. Tooth crowding with overlapping
3. Dental anomalies
   - Enamel pearls (see page 85)
   - Enamel and radicular grooves
4. Tooth fracture
5. Dental caries
6. Gingival recession
7. High frenum attachments
8. Iatrogenic factors
   - Overhanging restorations
   - Removable prostheses
   - Orthodontic appliances
9. Inadequate lip closure
10. Mouth breathing

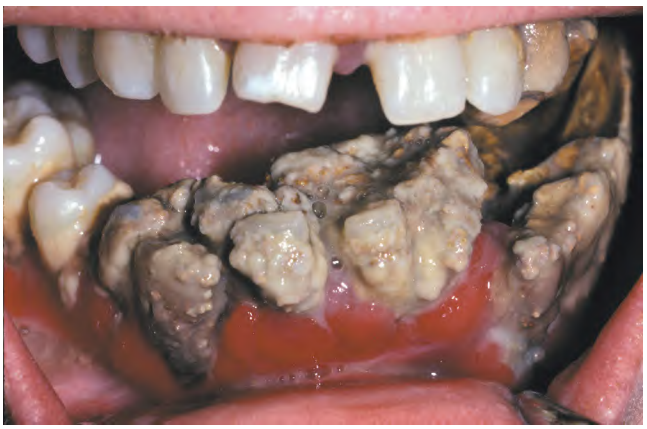
margins that may be blunted, receded, or hyperplastic (Fig. 4-3). When chronic inflammation causes significant enlargement because of edema or fibrosis, the process is termed **chronic hyperplastic gingivitis** (Fig. 4-4). Bleeding occurs easily, and exudate can be seen in the gingival sulcus. A localized tumorlike proliferation of subacutely inflamed granulation tissue, known as a **pyogenic granuloma** (see page 483), can develop on the gingiva of patients with severe gingivitis (Fig. 4-5).



• Fig. 4-1 Mouth Breathing–Related Gingivitis. Slick, swollen, and red gingivitis of the anterior facial gingiva secondary to chronic mouth breathing.



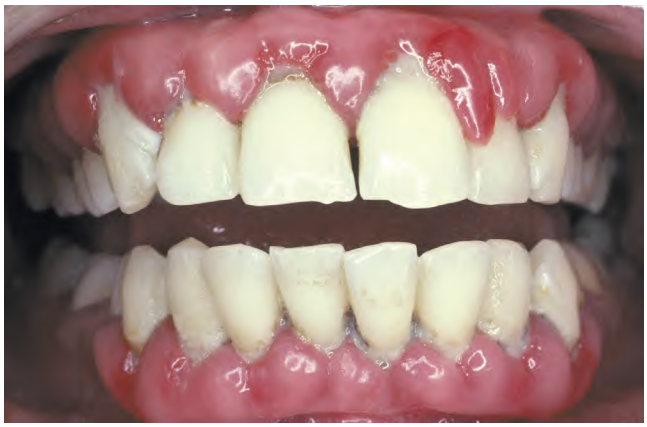
• Fig. 4-2 Marginal Gingivitis. Diffuse erythematous alteration of the free gingival margins.



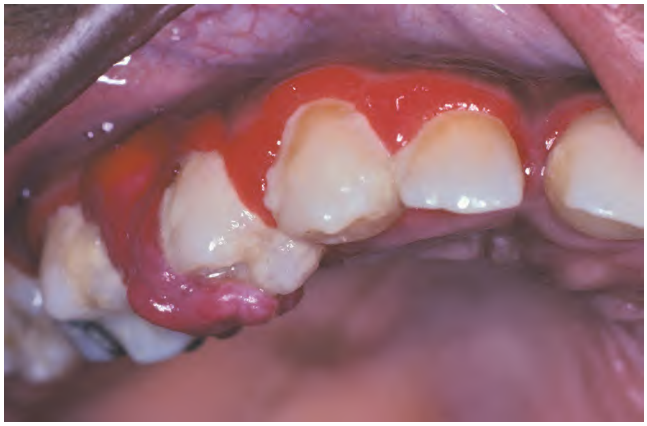
• Fig. 4-3 Chronic Gingivitis. Bright-red gingiva is blunted, receded, and hyperplastic secondary to a total lack of oral hygiene. Note the extensive calculus buildup.

Histopathologic Features

Incipient gingivitis demonstrates a light inflammatory infiltrate consisting of polymorphonuclear leukocytes that accumulate in the connective tissue adjacent to the sulcular



• **Fig. 4-4 Chronic Hyperplastic Gingivitis.** Diffuse erythema and enlargement of marginal and papillary gingiva.



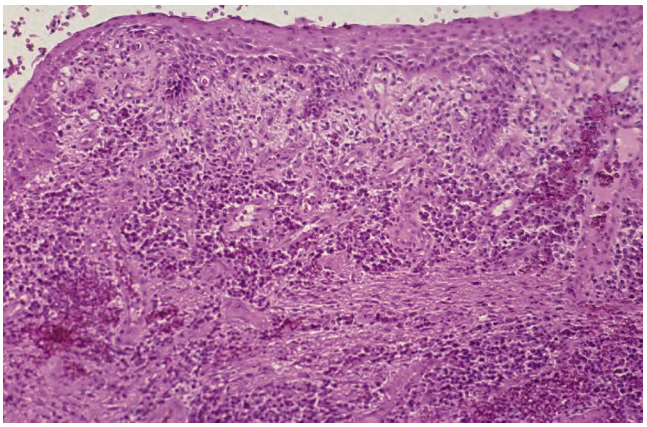
• **Fig. 4-5 Hyperplastic Gingivitis with Pyogenic Granuloma.** Diffuse erythematous enlargement of marginal and papillary gingiva with hemorrhagic, tumorlike proliferation (which arose during pregnancy) between the maxillary bicuspid and first molar.

epithelium. With progression, the infiltrate becomes more intense and demonstrates a mixture of lymphocytes, plasma cells, and acute inflammatory cells (Fig. 4-6). Areas of fibrosis, hyperemia, edema, and hemorrhage may be present.

Treatment and Prognosis

Although periodontitis always is preceded by gingivitis, most areas of gingivitis remain stable for years, and the number of affected sites that convert to periodontitis is small. In spite of this, optimal gingival health should be the goal of all clinicians and their patients. Even when attachment loss is not evident and the alterations appear restricted to the gingival soft tissues, proactive interventions are recommended to eliminate these areas of persistent pathosis during the early stages of disease.

Treatment of gingivitis consists of elimination (if possible) of any known cause of increased susceptibility and improvement in oral hygiene to decrease the dental plaque responsible for the inflammatory alterations. A further discussion of dental plaque and its relationship to gingival inflammation is presented in the discussion of periodontitis



• **Fig. 4-6 Chronic Gingivitis.** Sulcular epithelium with exocytosis overlying connective tissue that contains inflammatory infiltrate consisting of lymphocytes, plasma cells, and polymorphonuclear leukocytes.

(see page 153). Most self-administered plaque control programs are ineffective unless periodic professional reinforcement also is provided. Research has shown that few individuals have the physical skills and motivation necessary to obtain and maintain ultimate oral hygiene. An analysis of multiple clinical trials revealed that use of a mechanical toothbrush was associated with plaque reduction of less than 50%. Although rotation/oscillation-powered brushes have demonstrated the ability to remove an increased percentage of plaque, the best toothbrush remains the one that gets into the mouth. Brushing fails to clean the interdental areas and should be supplemented by other cleaning aids, such as specialized wood sticks (not toothpicks), dental floss, or interdental brushes.

Mechanical removal of dental plaque can be aided by the use of numerous chemical agents, such as mouth rinses with chlorhexidine or essential oils, or dentifrices containing triclosan or stannous fluoride. On occasion, hyperplastic and fibrotic gingiva may have to be recontoured surgically to achieve total resolution of the altered anatomy after improvements in hygiene have been made. If the gingivitis does not resolve after improved plaque control and elimination of obvious contributing factors, then the patient should be evaluated for underlying systemic disorders that could be contributing to the process.

◆ LOCALIZED JUVENILE SPONGIOTIC GINGIVAL HYPERPLASIA (LOCALIZED JUVENILE SPONGIOTIC GINGIVITIS)

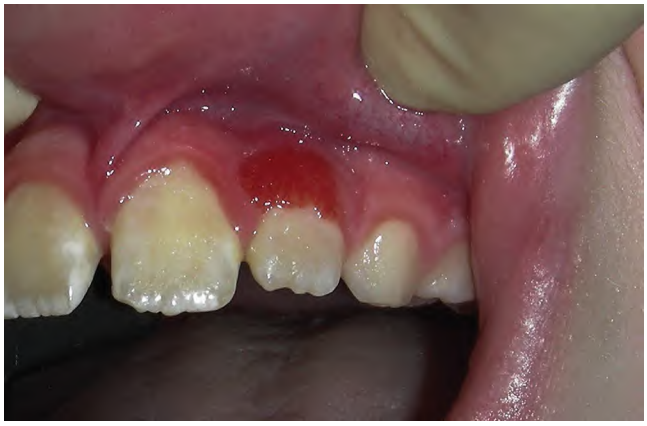
Localized juvenile spongiotic gingival hyperplasia is a clinically and histopathologically distinctive gingival pathosis that was initially described in 2007. Although the disorder is idiopathic, it has been suggested that the alteration represents an isolated patch of exteriorized junctional or sulcular epithelium that may be altered secondarily by local factors, such as mouth breathing. The changes do not

appear plaque-related and fail to respond to improved oral hygiene.

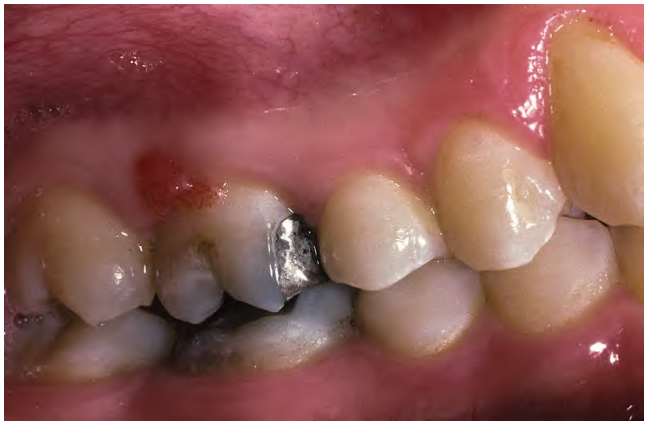
Prior to the initial description, some of these cases were designed as puberty gingivitis, but several features dispute this contention. Numerous examples have been reported in prepubescent children and, in contrast to puberty gingivitis, the lesions do not respond to improved oral hygiene. Additionally, an absence of estrogen and progesterone receptors has been documented in these lesions.

Clinical Features

The most common presentation of localized juvenile spongiotic gingival hyperplasia is a small bright red velvety or papillary alteration that often bleeds easily upon manipulation (Fig. 4-7). The facial gingiva overlying the root is affected most frequently, but involvement of the interproximal areas also may occur. Although the lesion typically is sessile, some examples may be very pedunculated with occasional extension into the gingival sulcus (Fig. 4-8). Although the lesion has been diagnosed in adulthood, the vast majority occurs under 20 with a median age of 12 years. The alteration demonstrates a strong predilection for the maxillary anterior facial gingiva with a female predominance. Although occasional multifocal involvement may be seen, most examples are isolated. The natural history of the lesion is difficult to ascertain due to therapeutic removal, but several examples have been noted for 2 to 3 years prior to excision.



• Fig. 4-7 Localized Juvenile Spongiotic Gingival Hyperplasia. Bright red velvety alteration of maxillary facial gingiva in 9-year-old male. (Courtesy of Dr. Tom Ocheltree.)



• Fig. 4-8 Localized Juvenile Spongiotic Gingival Hyperplasia. Red, papillary, and pedunculated lesion with a stalk that extends into the gingival sulcus in a 28-year-old female.

Histopathologic Features

Microscopically, the epithelium is variably hyperplastic and demonstrates a pebbly to papillary surface. Prominent intercellular edema (spongiosis) and exocytosis by neutrophils are noted consistently. Histopathologically, the epithelium is remarkably similar to junctional or sulcular areas. Upon immunoperoxidase evaluation, the epithelium demonstrates a reactivity pattern to CK19 that mimics sulcular epithelium and is not typical of the facial gingiva. The associated stroma reveals vasodilation with congestion and a mixed inflammatory cellular infiltrate.

Treatment and Prognosis

The vast majority of the reported examples have been excised conservatively with a recurrence rate that varies from 6% to 16.7%. Although the lesion may persist for years, the possibility of spontaneous resolution is likely because the process is reported infrequently in adults.

◆ NECROTIZING ULCERATIVE GINGIVITIS (VINCENT INFECTION; TRENCH MOUTH)

Necrotizing ulcerative gingivitis (NUG) has a distinctive pattern of gingival pathologic changes that have been recognized for hundreds of years. Until recently, the name of this process has been preceded by the term *acute* (i.e., ANUG); however, several investigators have discontinued the use of this word, because there is no chronic form of the disease. In the 1890s the French physician Jean Hyacinthe Vincent identified a fusiform bacterium, *Bacillus fusiformis* (currently *Fusobacterium nucleatum*), and a spirochete, *Borrelia vincentii,* after microscopic examination of plaque samples from affected sites. Vincent believed that the fusiform bacteria were principally responsible for the condition, and the spirochetes mainly were saprophytic opportunists. The spirochete and fusiform bacterium association remains true today, but more sophisticated techniques have implicated *Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis, Treponema spp.,* and *Selenomonas spp.* Although the association with bacteria is strong, controversial research has suggested that viruses, such as cytomegalovirus, Epstein-Barr virus, and herpes simplex, may contribute to the onset and progression of the process.

The infection frequently occurs in the presence of psychologic stress. People in military service exhibit an increased frequency of NUG; the disorder was so common in the

battlefield trenches during World War I that the nickname *trench mouth* became well known.

In addition to stress, other factors have been related to an increased frequency of NUG:

- Immunosuppression
- Smoking
- Local trauma
- Poor nutritional status
- Poor oral hygiene
- Inadequate sleep
- Recent illness

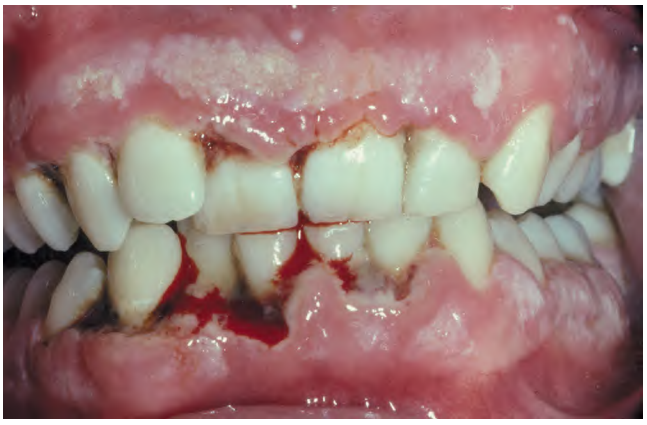
A number of medications have been reported to cause agranulocytosis, a condition that may clinically present initially as NUG. A thorough investigation of all currently utilized medications appears prudent and may lead to discovery of a significant associated immunosuppression. In addition, the immunocompromised status associated with acquired immunodeficiency syndrome (AIDS) (see page 239) or infectious mononucleosis (see page 229) has been related to the development of NUG. The list of predisposing factors clearly supports the association between a depressed systemic immunity and the appearance of the disorder.

Clinical Features

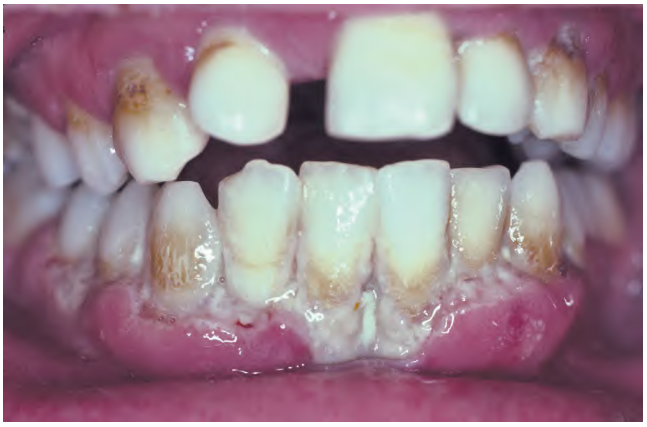
NUG may occur at any age; however, when encountered in the United States or Europe, it is seen most frequently in young and middle-aged adults. Several publications have reported a higher frequency in whites. The prevalence in the normal population is less than 0.1%; however, in stressed populations (e.g., military recruits) the frequency increases up to 7%. In developing countries, NUG typically occurs in very young children suffering from malnutrition.

In a classic case of NUG, the interdental papillae are highly inflamed, edematous, and hemorrhagic. Typically, the affected papillae are blunted and demonstrate areas of "punched-out," craterlike necrosis that are covered with a gray pseudomembrane (Fig. 4-9). Early cases may be missed easily because the ulceration initially involves only the tip of the interdental papilla. A fetid odor, exquisite pain, spontaneous hemorrhage, and accumulations of necrotic debris usually are noted. Although a bad odor is not always noted, its absence in a patient without predisposing factors should raise concern for other pathoses, such as gonorrhea (see page 174). Occasional ancillary clinical features include lymphadenopathy, fever, and malaise. The process sometimes can lead to a loss of attachment and the development of associated periodontitis **(necrotizing ulcerative periodontitis)** or spread to adjacent soft tissue **(necrotizing ulcerative mucositis, necrotizing stomatitis)** (Fig. 4-10). If the necrotizing infection extends through the mucosa to the skin of the face, then it is typically termed *noma* **(cancrum oris)** (see page 181).

Several investigators have suggested that NUG, necrotizing ulcerative periodontitis (NUP), and necrotizing stomatitis are one disease process termed **necrotizing gingivostomatitis.** Evidence presented by numerous authors has shown the diseases to be similar clinically, histopathologically, and bacteriologically, with the only differences being underlying systemic factors and anatomic extension of the necrosis.



• **Fig. 4-9 Necrotizing Ulcerative Gingivitis (NUG).** Gingiva is friable and hemorrhagic with necrosis of the interdental papillae.



• **Fig. 4-10 Necrotizing Ulcerative Mucositis.** Gingiva exhibits epithelial necrosis that has extended between the adjacent interdental papillae and apically to the alveolar mucosa junction.

Histopathologic Features

The histopathologic features of NUG are not specific. Typically, affected gingival papillae demonstrate surface ulceration that is covered by a thickened fibrinopurulent membrane. The underlying lamina propria demonstrates an intense acute or mixed inflammatory infiltrate and extensive hyperemia. In nonulcerated affected epithelium, often a loss of the typical surface keratinization occurs. Necrotic material and extensive bacterial colonization often are included in the material submitted for microscopic examination.

Treatment and Prognosis

In contrast to most forms of periodontal disease, NUG typically demonstrates quick resolution after removal of the bacterial challenge. Even with conservative therapy, regeneration of the affected gingiva is normally seen. The affected

area is treated best with débridement by scaling, curettage, or ultrasonic instrumentation (except when contraindicated, as in HIV-positive patients). Topical or local anesthetic often is required before the clinician can débride the tissues adequately. Frequent rinses with chlorhexidine, warm saltwater, or diluted hydrogen peroxide are beneficial in increasing the therapeutic response. Antibiotic medications (metronidazole and penicillin have been suggested as the drugs of choice) are a useful adjunct, especially in the presence of fever or lymphadenopathy.

Treatment should include instructions on oral hygiene and patient motivation; identification and resolution of any predisposing factors also are advantageous. Supportive therapy (e.g., rest, appropriate fluid intake, and soft nutritious diet) and smoking cessation often improve the clinical response. Follow-up appointments are necessary to reinforce the home care instructions and to rule out a recurrence of the process. In cases resistant to treatment, further evaluation to rule out HIV infection or infectious mononucleosis is prudent.

The clinician must be ever vigilant in the search for other signs and symptoms of immunosuppression. Subtle palatal candidiasis or HIV-related oral hairy leukoplakia (see page 242) can be overlooked easily in a patient with NUG. Appropriate attention must be directed toward the oral soft tissue examination, especially in patients with infections such as NUG that are related to immunosuppression. In addition, a thorough investigation of underlying causes of immunosuppression should be performed on patients whose conditions are resistant to normal therapy.

◆ PLASMA CELL GINGIVITIS (ATYPICAL GINGIVOSTOMATITIS)

A distinctive pattern of gingival inflammation, **plasma cell gingivitis,** was brought to the attention of health care practitioners during the late 1960s and early 1970s. A rash of cases occurred during that time, and most appear to have been related to a hypersensitivity to a component of chewing gum. Since that time, the number of cases has dwindled, but similar gingival alterations are reported occasionally.

Although the association with chewing gum has decreased, allergy still is responsible for many reported cases. A brand of herbal toothpaste, a specific type of mint candy, and peppers used for cooking have all been implicated in more recent reports. The list of allergens appears to be variable, and a thorough evaluation often is required to rule out an allergic cause.

Clinical Features

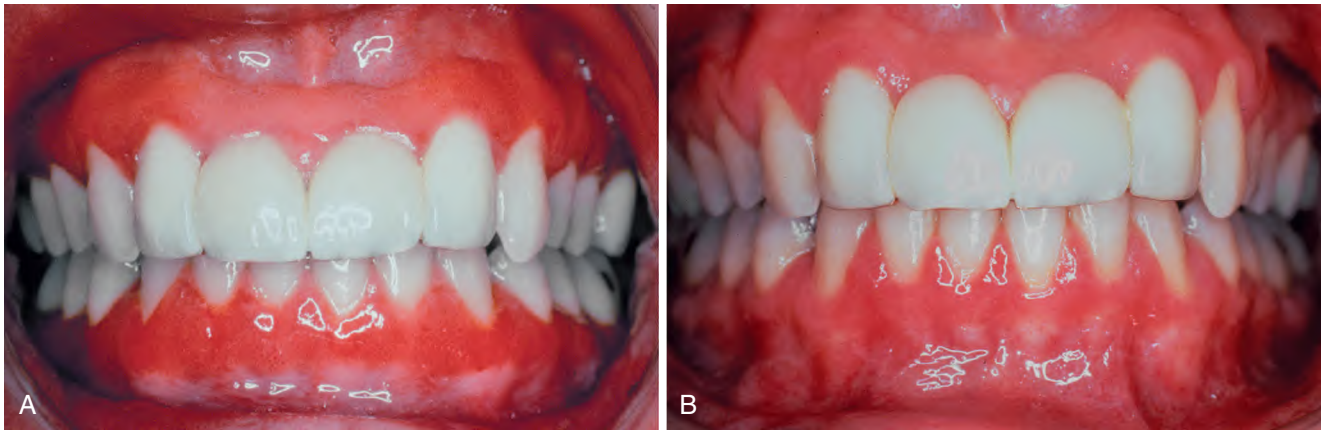
Patients with plasma cell gingivitis experience a rapid onset of sore mouth, which often is intensified by dentifrices and hot or spicy foods. The entire free and attached gingiva demonstrates a diffuse enlargement with bright erythema and loss of normal stippling (Fig. 4-11). Extension onto the palate can occur, and edentulous areas typically exhibit less intense changes. On occasion, a similar localized gingival and vestibular alteration can occur from topical placement of a material that elicits a similar plasmacytic inflammatory reaction.

Additional sites of involvement may be seen, or the changes may be localized to the gingiva. In the chewing gum–related cases of the early 1970s, involvement of the lips and tongue was typical. The lips were dry, atrophic, occasionally fissured, and angular cheilitis was frequent. Tongue involvement resulted in erythematous enlargement with furrows, mild crenation, and loss of the typical dorsal coating.

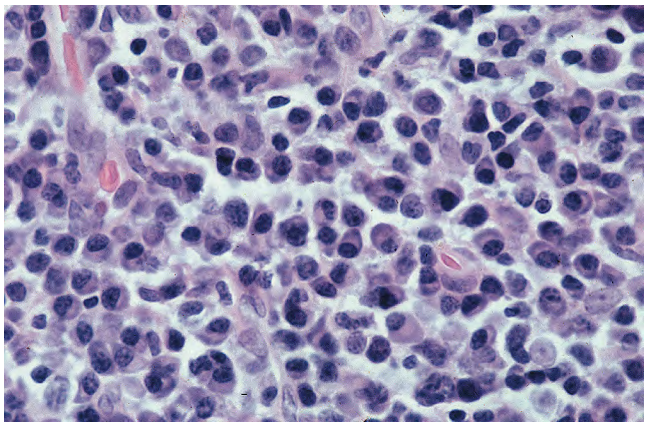
More recent reports have described lesions often isolated to the gingiva without the classic lip and tongue involvement seen in the past. A larger percentage of these cases are idiopathic, and occasional extraoral involvement of sites such as the supraglottic region occurs.

Histopathologic Features

The cases of classic plasma cell gingivitis of the 1970s demonstrated psoriasiform hyperplasia and spongiosis of the



• **Fig. 4-11 Plasma Cell Gingivitis. A,** Diffuse, bright-red enlargement of the free and attached gingiva. **B,** Same patient as depicted in **A** after elimination of the inciting allergen.



• **Fig. 4-12 Plasma Cell Gingivitis.** High-power photomicrograph exhibiting a dense inflammatory infiltrate consisting predominantly of plasma cells with scattered lymphocytes.

surface epithelium with intense exocytosis and neutrophilic microabscesses. The underlying lamina propria contains numerous dilated vascular channels and an extremely dense chronic inflammatory infiltrate that is composed predominantly of plasma cells (Fig. 4-12). The more recent cases are similar but often demonstrate less involvement of the surface epithelium and a less dense underlying plasmacytic infiltrate.

Investigation of the clonality of the plasma cell infiltrate may be necessary to rule out the possibility of a monoclonal plasma cell neoplasm. All allergic and idiopathic cases of plasma cell gingivitis demonstrate a polyclonal mixture of plasma cells and a normal profile on plasma immunoelectrophoresis.

It must be remembered that an identical dense infiltrate of plasma cells can be seen in plaque-related gingival hyperplasia and chronic periodontitis. The diagnosis depends on a strong clinical and histopathologic correlation in which the changes are associated with a rapid onset of sore mouth and do not resolve with improved oral hygiene. Reports of this entity that do not fulfill the diagnostic criteria still can be found in the dental and medical literature. Review of the original 1971 publication may be helpful for those contemplating the diagnosis.

Treatment and Prognosis

All patients with plasma cell gingivitis should be instructed to keep a complete dietary history with records of everything taken into the mouth (e.g., foods, dentifrice, mouthwash, tobacco, alcohol, chewing gum, candy, and medications). Possible allergens should be eliminated in an attempt to discover the underlying cause. If an easy answer is not apparent, then extensive allergy testing and an elimination diet can be undertaken.

Many patients in whom no underlying cause could be discovered have been treated with topical or systemic immunosuppressive medications with variable results. Betamethasone rinses, fluocinonide gel, topical triamcinolone, and topical fusidic acid are several of the reported choices. In spite of all the evaluations and therapeutic interventions, some patients do not respond to treatment, and no cause for the disease can be identified.

◆ GRANULOMATOUS GINGIVITIS

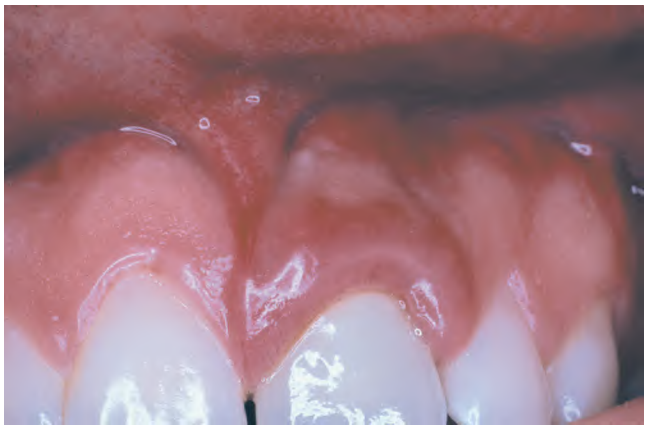
The presence of oral soft tissue alterations in association with histopathologic evidence of noncaseating granulomatous inflammation is termed **orofacial granulomatosis** (see page 312). Gingival involvement is noted in approximately 25% of affected patients and is designated **granulomatous gingivitis.** After a thorough microscopic examination for foreign material and special stains for fungal and mycobacterial infection have ruled out those entities, an extended search for a possible trigger often follows.

Several investigators have reported granulomatous gingival lesions caused by the introduction of dental materials into the connective tissue deep to the sulcular epithelium. As more cases have been reported, it has become evident that the associated inflammatory reaction often is not granulomatous and may mimic gingival lichen planus or create a nonspecific pattern of chronic or subacute mucositis. These lesions have been termed **foreign body gingivitis** and are thought to arise when damage to the sulcular epithelium during restorative or oral hygiene procedures allows the introduction of foreign material into the gingival tissues. Although the foreign material may be obvious, often it is smaller than 1 μm in diameter and so fine that it could be overlooked.

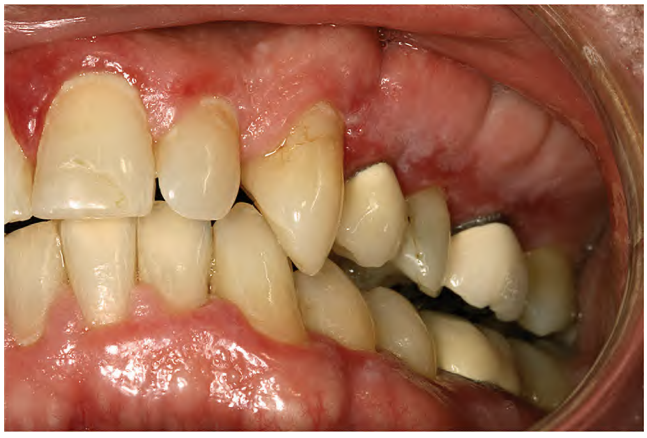
In a review of 85 cases of foreign body gingivitis, energy-dispersive radiographic microanalysis revealed 21 different elements embedded with the gingival soft tissues. The most common elements were silver, aluminum, silicon, tin, sulfur, copper, calcium, phosphorus, and iron. Elements compatible with fine particles of amalgam dust were identified most often. Particles consistent with corundum or silica also were common (sandpaper disks, polishing paste, toothpaste, and possibly restorative filling material). Materials implicated less frequently include dust from tungsten carbide burs, composite material, endodontic sealer components, and temporary cement. This investigation demonstrates that the presumed causative agents are diverse and can originate from a wide variety of dental materials.

Clinical Features

Both foreign body gingivitis and nonspecific granulomatous gingivitis may occur at any age; however, they are most frequently encountered in adulthood. The lesions may be solitary or multifocal, typically with a diameter less than 2 cm. The affected areas appear as red or red-and-white macules, which most frequently involve the interdental papillae but also may occur along the marginal gingiva (Figs. 4-13 and 4-14). On occasion, significant gingival hyperplasia may be present in a localized or generalized pattern. Pain or sensitivity is a common finding, and the lesions persist despite conventional therapy and rigorous



• **Fig. 4-13 Granulomatous Gingivitis.** Localized enlarged and erythematous gingiva associated with the maxillary left central incisor. The alterations developed shortly after placement of a porcelain-fused-to-metal (PFM) full crown and were not responsive to conservative local therapy. (Courtesy of Dr. Timothy L. Gutierrez.)



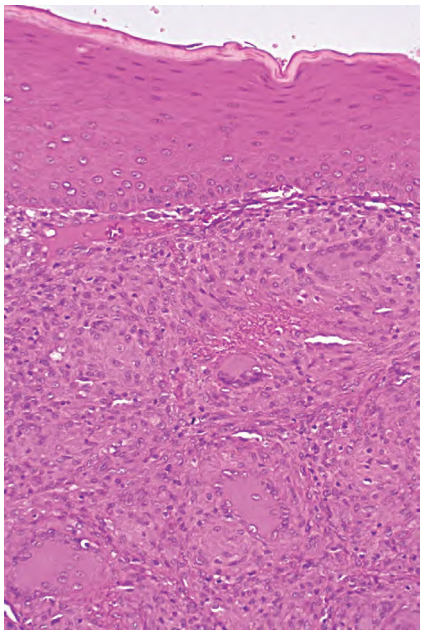
• **Fig. 4-14 Foreign Body Gingivitis.** Red, atrophic mucosa of the left maxillary facial gingiva. The alterations arose following placement of two porcelain-fused-to-metal (PFM) crowns. Biopsy revealed lichenoid mucositis with intermixed fragments of foreign material.

oral hygiene. The process can be seen adjacent to clinically normal teeth or next to teeth with restorations.

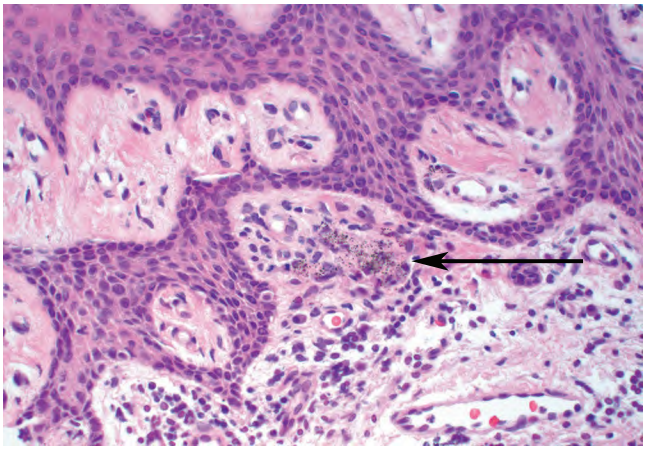
Frequently, foreign body gingivitis creates areas of erythematous and atrophic mucositis that closely resemble gingival lichen planus. A good clinicopathologic correlation often is beneficial in arriving at the correct diagnosis. A diagnosis of gingival lichen planus should be viewed with suspicion in a patient who does not have extragingival involvement or if the gingival changes are somewhat localized and nonmigrating. In such cases, a request to the pathologist for a thorough search for foreign material is prudent.

Histopathologic Features

A biopsy specimen of granulomatous gingivitis demonstrates focal collections of histiocytes intermixed with an intense lymphocytic infiltrate (Fig. 4-15). On occasion, well-formed histiocytic granulomas with multinucleated giant cells are seen. Special stains for organisms should be



• **Fig. 4-15 Granulomatous Gingivitis.** Focal collection of histiocytes, lymphocytes, and multinucleated giant cells within the superficial lamina propria of the gingiva.



• **Fig. 4-16 Foreign Body Gingivitis.** Particles of pigmented foreign material *(arrow)* intermixed with lymphocytes and plasma cells.

negative. If foreign material is reported, then the clinician should consider the possibility of foreign body gingivitis.

In the previously mentioned review of 85 cases of foreign body gingivitis, granulomatous inflammation was present in approximately 20%. In the remainder, the inflammatory infiltrate was dominated by lymphocytes, intermixed with plasma cells and macrophages (Fig. 4-16). In some cases, neutrophils were noted along with the chronic inflammatory cellular infiltrate. Not infrequently, the mucositis was lichenoid with degeneration of the basal cell layer of the epithelium and a superficial bandlike inflammatory cell infiltrate in the superficial lamina propria. Because the immune reaction in lichen planus tends to be composed primarily of lymphocytes, the presence of significant numbers of plasma cells, histiocytes, or neutrophils in the absence of plaque-related gingivitis should suggest a

thorough search for subtle foreign material. In many cases, the foreign material is subtle and discovered only with a high index of suspicion and after a thorough search. To ensure that any foreign material is not an artifact introduced during processing, it should be present in multiple sections.

Treatment and Prognosis

When all of the histopathologic and clinical investigations have been performed, the final differential diagnosis of granulomatous gingivitis usually is narrowed down to a localized form of orofacial granulomatosis or a foreign body reaction. Without definitive demonstration of foreign material, a complete physical evaluation for disorders known to be associated with orofacial granulomatosis is appropriate (see page 312).

Surgical excision of the affected tissue is the therapy of choice for those cases related to foreign material if the process is sufficiently symptomatic. In persistently atrophic or erosive areas of foreign body gingivitis, overlaying the damaged area with a graft from a healthy gingival donor site may be a better option than complete excision. In an attempt to prevent future introduction of iatrogenic foreign material, clinicians should use care during restorative and oral hygiene procedures that might introduce foreign material into a surgical wound. In addition, dental prophylaxis should be delayed for 2 days after scaling, root planing, and curettage procedures. Patients who do not respond to surgical removal and have recurrences of granulomatous gingivitis despite cautious dental care probably should be classified as having orofacial granulomatosis and managed accordingly.

◆ DESQUAMATIVE GINGIVITIS

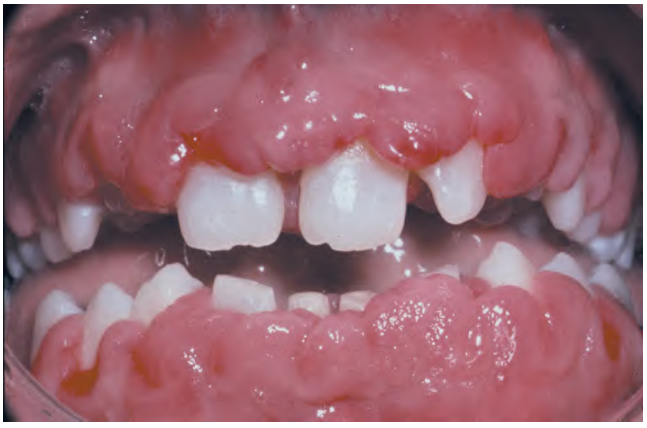
Desquamative gingivitis is a clinical term for gingiva that demonstrates superficial peeling of the epithelium characterized by formation and rupture of mucosal vesicles. The process almost always represents a manifestation of one of several different vesiculoerosive diseases, usually mucous membrane pemphigoid. Some clinicians broaden the definition to include patients with atrophic and erosive gingival lesions without true peeling of the epithelium. In such cases, lichen planus is diagnosed most frequently. Other diagnoses that are made less frequently include linear IgA disease, pemphigus vulgaris, epidermolysis bullosa acquisita, systemic lupus erythematosus (SLE), chronic ulcerative stomatitis, and paraneoplastic pemphigus. The gingival manifestations of these mucosal and dermatologic diseases are described in greater detail in Chapter 16, so further discussion here is not warranted.

◆ DRUG-RELATED GINGIVAL HYPERPLASIA (DRUG-RELATED GINGIVAL OVERGROWTH)

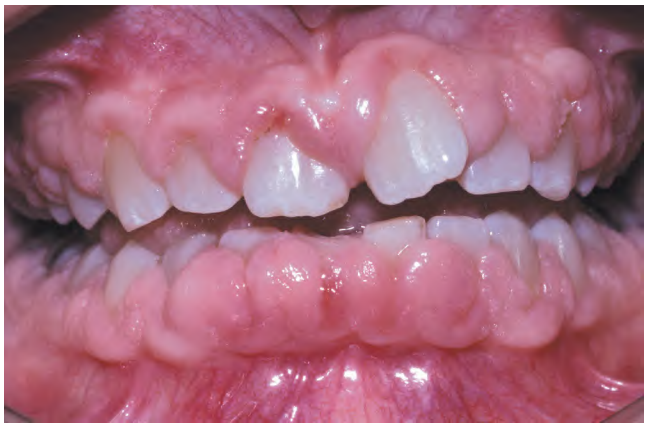
Drug-related gingival hyperplasia refers to an abnormal growth of the gingival tissues secondary to use of a systemic medication. A list of medications reported to be associated with gingival hyperplasia is provided in Box 4-4. Of these medications, a strong association has been noted only with cyclosporine (Fig. 4-17), phenytoin, and nifedipine (Fig. 4-18). In addition to nifedipine, a definitive but much weaker association has been documented with other calcium channel-blocking agents, such as diltiazem, amlodipine, and verapamil. In the remainder of these agents, the prevalence is much lower or the association is weak or anecdotal. A number of calcium channel blockers exist that have not been associated with gingival hyperplasia and may represent safer alternatives. As new drugs are developed, the list of offending medications may grow. Cyclosporine is known to be associated with hypertension, often leading to utilization of a calcium channel blocker. When cyclosporine and

• BOX 4-4 Medications Reported to be Associated with Gingival Hyperplasia

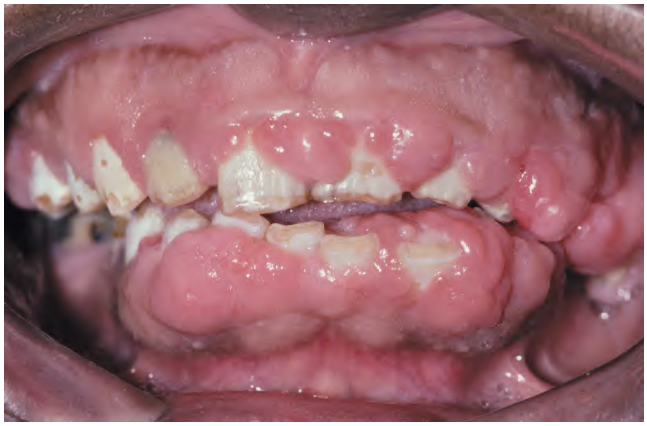
- Anticonvulsants
  - Carbamazepine
  - Ethosuximide
  - Ethotoin
  - Felbamate
  - Mephenytoin
  - Methsuximide
  - Phenobarbital
  - Phensuximide
  - Phenytoin
  - Primidone
  - Sodium valproate
  - Vigabatrin
- Calcium channel blockers
  - Amlodipine
  - Bepridil
  - Diltiazem
  - Felodipine
  - Nifedipine
  - Nitrendipine
  - Verapamil
- Cyclosporine
- Erythromycin
- Oral contraceptives



• Fig. 4-17 Cyclosporine-Related Gingival Hyperplasia. Diffuse, erythematous, and fibrotic gingival hyperplasia.



• **Fig. 4-18 Nifedipine-Related Gingival Hyperplasia.** Diffuse, fibrotic gingival hyperplasia after 1 month of intensive oral hygiene. Significant erythema, edema, and increased enlargement were present before intervention.

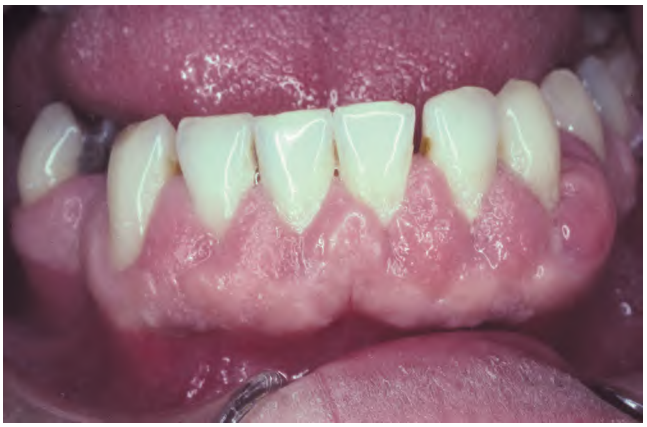


• **Fig. 4-19 Cyclosporine- and Nifedipine-Related Gingival Hyperplasia.** Dramatic gingival hyperplasia in a patient using two drugs associated with gingival enlargement.

nifedipine are used concurrently, the severity of the associated hyperplasia often is increased (Fig. 4-19).

The prevalence of these hyperplasias varies widely; however, as reported in one critical review of the literature, the prevalence related to use of phenytoin is approximately 50%. Cyclosporine and nifedipine each produce significant changes in about 25% of patients treated. Whether there is a relationship between the particular dose and the risk or severity of the hyperplasia is a controversial issue. Investigators have suggested that susceptibility to cyclosporine gingival hyperplasia is associated with certain histocompatibility antigen (HLA) types, whereas other HLA types appear to protect against hyperplasia. Whether similar correlations exist for the other forms of medication-associated gingival hyperplasia is unknown.

The degree of gingival enlargement appears to be related significantly to the patient's susceptibility and the level of oral hygiene. In observations of patients with excellent oral hygiene, gingival overgrowth (as ascertained by pseudopocket formation) is reduced dramatically or not present. Even with good oral hygiene, however, some degree of gingival enlargement can be discovered in susceptible individuals, although in many cases the changes are difficult to detect. Rigorous oral hygiene often can limit the severity to clinically insignificant levels. Of the medications discussed, cyclosporine appears to be the least responsive to the institution of a rigorous program of oral hygiene; even with this medication, however, the elimination of gingival inflammation results in noticeable clinical improvement. In addition, the degree of drug-associated gingival hyperplasia appears to be markedly higher in smokers.



• **Fig. 4-20 Mild Phenytoin-Related Gingival Hyperplasia.** Gingival enlargement present predominantly in the interdental papillae.

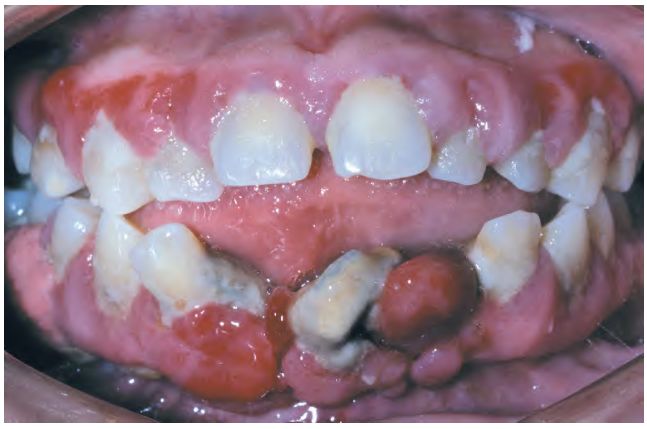
Clinical Features

Because young patients use phenytoin most often, the gingival hyperplasia it induces is primarily a problem in people younger than age 25. Cases related to the calcium channel blockers occur mainly in middle-aged or older adults. Cyclosporine is used over a broad age range, and this correlates with the age of reported hyperplasia. A greater risk for gingival hyperplasia occurs when the drug is used in children, especially adolescents. No sex or race predilection is present.

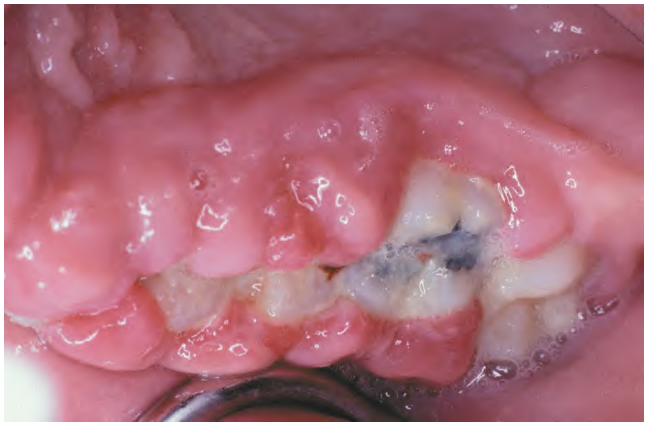
After 1 to 3 months of drug use, the enlargements originate in the interdental papillae and spread across the tooth surfaces (Fig. 4-20). The anterior and facial segments are the most frequently involved areas. In extensive cases, the hyperplastic gingiva can cover a portion (or all) of the crowns of many of the involved teeth (Figs. 4-21 and 4-22). Extension lingually and occlusally can interfere with speech and mastication. Edentulous areas generally are not affected, but significant hyperplasia under poorly maintained dentures and around implants has been noted (Fig. 4-23).

Nongingival soft tissue growths that resemble pyogenic granulomas have been reported in allogeneic bone marrow transplant recipients who are receiving cyclosporine for graft-versus-host disease (GVHD) (Fig. 4-24). It is thought that cyclosporine triggers the proliferations in areas chronically inflamed by GVHD.

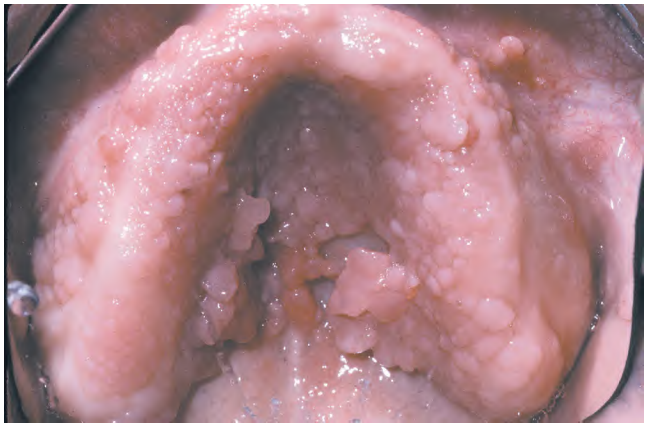
In the absence of inflammation, the enlarged gingiva is normal in color and firm, with a surface that may be smooth, stippled, or granular. With inflammation, the



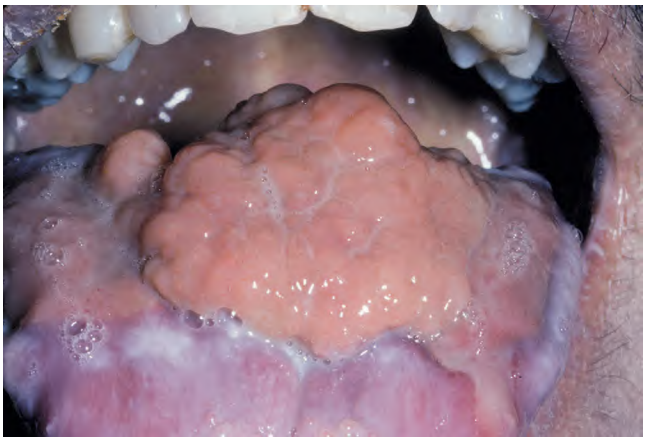
• **Fig. 4-21 Phenytoin-Related Gingival Hyperplasia.** Significant erythematous gingival hyperplasia is covering portions of the crowns of numerous teeth.



• **Fig. 4-22 Phenytoin-Related Gingival Hyperplasia.** Significant gingival hyperplasia almost totally covers the crowns of the posterior maxillary dentition. (Courtesy of Dr. Ann Drummond and Dr. Timothy Johnson.)



• **Fig. 4-23 Phenytoin-Related Palatal Hyperplasia.** Extensive hyperplasia of palatal mucosa in an edentulous patient with poor denture hygiene.



• **Fig. 4-24 Nongingival Cyclosporine Hyperplasia.** Exophytic and granulomatous-appearing mass of the dorsal surface of the tongue that arose in a bone marrow transplant patient who was receiving cyclosporine for graft-versus-host disease (GVHD).

affected gingiva often becomes dark red and edematous, with a surface that is friable, bleeds easily, and occasionally is ulcerated. Pyogenic granuloma-like enlargements occasionally are seen in the presence of heavy inflammation.

Histopathologic Features

Upon histopathologic examination, the overlying surface epithelium may demonstrate elongation of the rete ridges, with long extensions into the underlying stroma. The lamina propria exhibits an increased amount of fibrous connective tissue that demonstrates a normal density of fibroblasts. In patients with secondary inflammation, there is increased vascularity and a chronic inflammatory cellular infiltrate that most frequently consists of lymphocytes and plasma cells. In patients with pyogenic granuloma-like overgrowths, the proliferations often demonstrate an increased vascularity and significant subacute inflammation.

Treatment and Prognosis

Discontinuation of the offending medication by the attending physician often results in cessation, and possibly some regression, of the gingival enlargement; even substitution of one medication for another in the same class may be beneficial. Often the response to medication substitution is not immediate. If the drug use is mandatory, then professional cleaning, frequent reevaluations, and home plaque control are important. Antiplaque agents, such as chlorhexidine, have been beneficial in the prevention of plaque buildup and the associated gingival hyperplasia.

Systemic or topical folic acid has been shown to ameliorate the gingival hyperplasia in some cases. In addition, several authors have documented significant resolution of cyclosporine-related gingival hyperplasia after a short course of metronidazole, azithromycin, or roxithromycin. Azithromycin also may be beneficial in resolving gingival hyperplasia related to nifedipine and phenytoin.

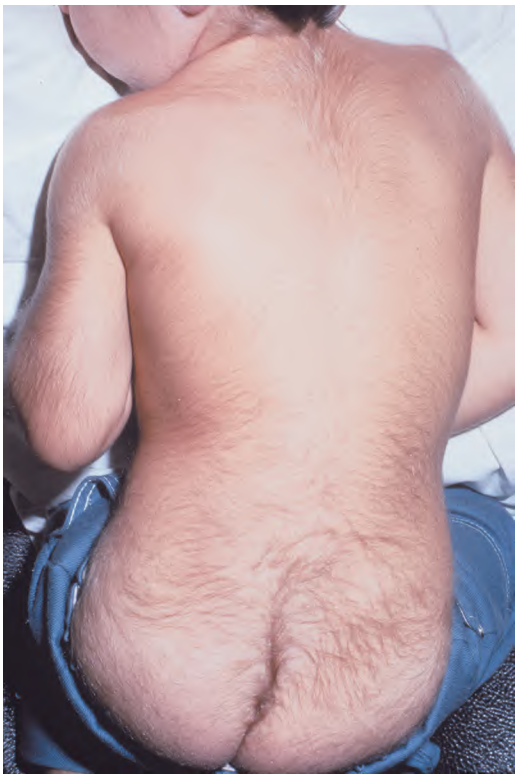
Although gingival hyperplasia is associated with increased probing depths, some investigators do not believe this necessarily leads to exaggerated attachment loss or an increased loss of teeth. Therefore, some clinicians exercise watchful waiting and do not perform invasive therapy without evidence of attachment loss, inappropriate aesthetics, or disruption of speech or mastication. When objectionable alterations are noted and all other interventions fail to achieve significant resolution, eradication of the excess gingival tissues remains the treatment of choice. Recurrence is not uncommon, however, especially in patients with inadequate oral hygiene.

◆ GINGIVAL FIBROMATOSIS (FIBROMATOSIS GINGIVAE; ELEPHANTIASIS GINGIVAE)

Gingival fibromatosis is a slowly progressive gingival enlargement caused by a collagenous overgrowth of the gingival fibrous connective tissue. In spite of the name, this disorder bears no relationship to the hypercellular and neoplastic fibromatoses that can occur in soft tissue and bone (see pages 481 and 613). Gingival fibromatosis is a rare condition with an estimated prevalence of 1:750,000.

Gingival fibromatosis may be familial or idiopathic. Other findings sometimes seen in conjunction with gingival fibromatosis include hypertrichosis (Fig. 4-25), generalized aggressive periodontitis, epilepsy, intellectual disability, sensorineural deafness, hypothyroidism, chondrodystrophia, and growth hormone deficiency. The familial variations may occur as an isolated finding or in association with one of several hereditary syndromes. Box 4-5 lists the syndromes that often have been associated with gingival fibromatosis.

In most cases of isolated gingival fibromatosis, an autosomal dominant pattern of inheritance is seen; however, autosomal recessive examples also have been noted. Incomplete penetrance and variable expressivity are seen. The phenotype of hereditary gingival fibromatosis demonstrates significant genetic heterogeneity with the existence of at least five genes that are responsible for similar patterns of clinical presentation.



• **Fig. 4-25 Hypertrichosis in Association with Gingival Fibromatosis.** Dramatically increased body hair of the back and buttocks in a patient with gingival fibromatosis. (Courtesy of Dr. George Blozis.)

• BOX 4-5 Syndromes Associated with Gingival Fibromatosis

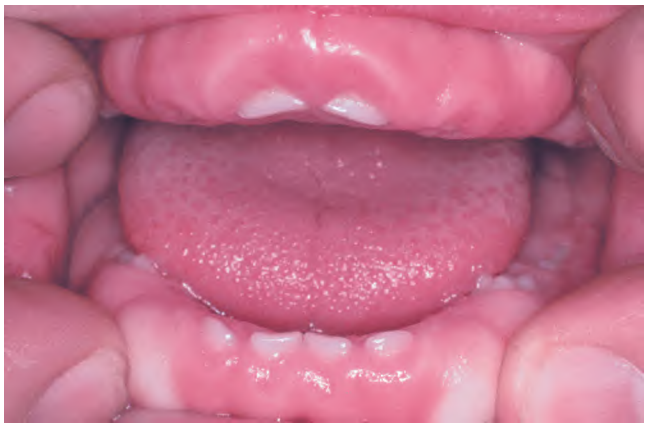
- Byars-Jurkiewicz syndrome
- Costello syndrome
- Cross syndrome
- Infantile systemic hyalinosis
- Jones-Hartsfield syndrome
- Murray-Puretic-Drescher syndrome
- Ramon syndrome
- Rutherford syndrome
- Zimmerman-Laband syndrome

Clinical Features

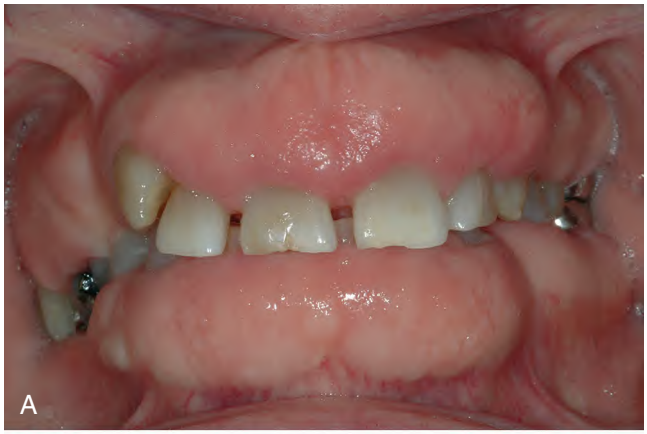
In most instances, the enlargement begins before age 20 and often is correlated with the eruption of the deciduous or permanent teeth (Fig. 4-26). Most investigators believe that the presence of teeth probably is necessary for the condition to occur. In spite of this, rare patterns can present in infancy or even at birth. After the process has begun, it can overgrow the associated teeth and even interfere with lip closure. Failure or delay in eruption, or altered position of the erupted teeth, may be evident (Fig. 4-27). In some instances, a tooth may have erupted into a normal position, but the fibrous connective tissue continues to cover the crown and prevent visualization.

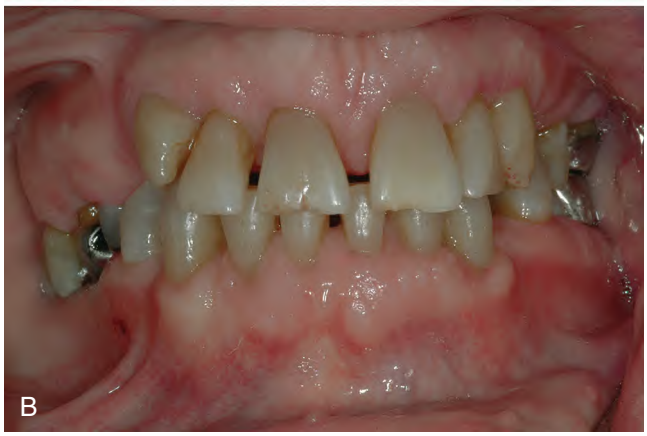
The gingival changes may be generalized or localized to one or more quadrants. Either jaw may be involved, but the maxilla is affected more frequently and demonstrates a greater degree of enlargement. Palatal surfaces are typically increased in thickness more than the buccal side. Typically, extension past the alveolar mucosal junction into the mucobuccal fold is not seen, but palatal extensions can cause significant distortion of the contour of the palate and, at times, almost can meet in the midline.

In localized cases, the hyperplasia may involve a group of teeth and remain stable or, at a later date, may extend to other segments of one or both jaws. One distinctive and not uncommon pattern involves the posterior maxillary alveolar ridge. In this pattern, the hyperplastic tissue forms



• **Fig. 4-26 Gingival Fibromatosis.** A young child with cheeks retracted by the parent. Note erythematous gingival hyperplasia arising in association with erupting deciduous dentition. (Courtesy of Dr. George Blozis.)

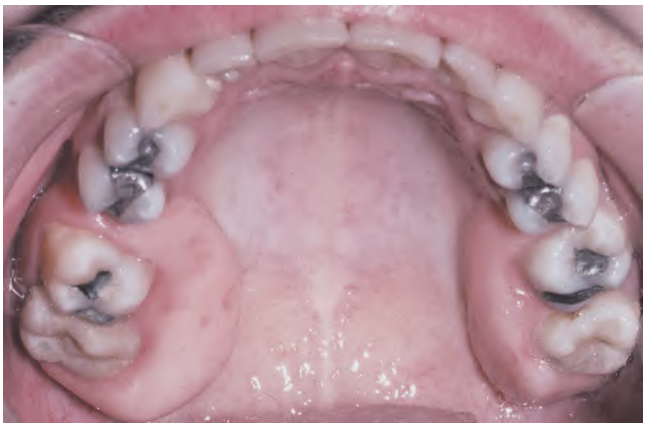




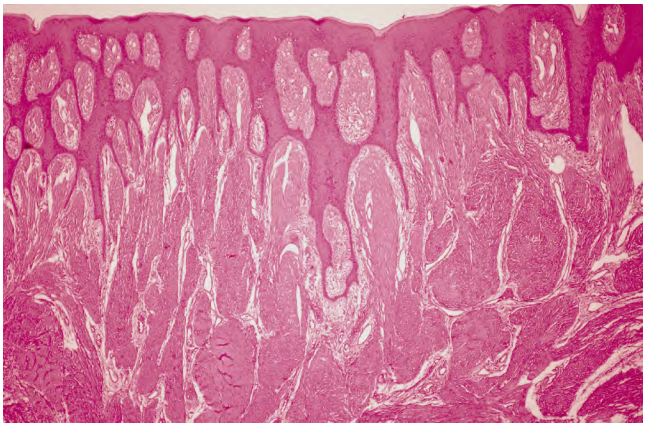
• **Fig. 4-27 Gingival Fibromatosis. A,** Dense fibrotic enlargement of the gingiva, which results in flaring of the dentition and open contact points. **B,** Same patient following surgical reduction of the excess fibrotic gingival tissue.

bilaterally symmetrical enlargements that extend posteriorly and palatally from the posterior alveolar ridges (Fig. 4-28). Less commonly, the overgrowth also may be isolated to the facial gingiva of the lower molars.

The gingiva is firm, normal in color, and covered by a surface that is smooth or finely stippled. In older patients,



• **Fig. 4-28 Localized Gingival Fibromatosis.** Bilateral and symmetrical fibrotic enlargements of the palatal surfaces of the posterior maxillary alveolar ridges.



• **Fig. 4-29 Gingival Fibromatosis.** Surface stratified squamous epithelium exhibiting long, thin rete ridges and underlying dense, fibrous connective tissue.

the surface may develop numerous papillary projections. The frenular attachments may appear to divide the gingival tissues of the alveolar ridge into lobules. Associated clinical problems include poor aesthetics, prolonged retention of deciduous teeth, abnormal occlusion, inadequate lip closure, and difficulty in eating and speaking.

Histopathologic Features

The enlargements of gingival fibromatosis consist of dense hypocellular, hypovascular collagenous tissue, which forms numerous interlacing bundles that generally are arranged mostly in a parallel pattern. The surface epithelium often is acanthotic and exhibits long, thin rete ridges that extend deeply into the underlying fibrous connective tissue (Fig. 4-29). Inflammation is absent to mild. On occasion, scattered islands of odontogenic epithelium, foci of dystrophic calcification, or areas of osseous metaplasia may be seen.

Treatment and Prognosis

Mild cases often respond to scaling and root planing followed by close professional follow-up. For more advanced gingival thickening, conservative surgical removal is indicated. The rate of recurrence following excision is reduced if the removal is delayed until full eruption of the permanent dentition. In spite of this, local and psychological benefits often exceed the downside of recurrence, warranting earlier removal. Although recurrence is common in dentulous patients, a rigorous program of oral hygiene often slows regrowth. In severe cases, selective extraction of teeth and gingivectomy often are required to achieve a normal gingival morphology.

◆ PERIODONTITIS

Periodontitis refers to an inflammation of the gingival tissues in association with some loss of both the attachment of the periodontal ligament and bony support. With progressive loss of attachment, significant destruction of the periodontal ligament and adjacent alveolar bone can occur. Apical migration of the crevicular epithelium along the root surface results in the formation of periodontal pockets. Loosening and eventual loss of teeth are possible.

For more than a century, the presence of the disease has been correlated with the accumulation of dental plaque on the tooth and under the gingiva. In spite of this, some patients demonstrate extensive dental plaque but do not develop destructive lesions of the periodontium. Many investigators now believe that periodontitis represents a *microbial-shift disease*. Dramatic differences exist in the content of dental plaque in areas of healthy and diseased periodontium. Healthy sites are colonized primarily by facultative gram-positive organisms, whereas plaque within areas of active periodontitis contains anaerobic and microaerophilic gram-negative flora. Of the more than 500 types of bacteria that may reside in the oral cavity, only a few have been related to periodontitis, and the specific types often correlate with the clinical patterns of periodontitis. Chronic periodontitis is associated strongly with *Treponema denticola, Tannerella forsythensis,* and *Porphyromonas gingivalis.* Additional organisms frequently thought to be involved include *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans), Prevotella intermedia, Campylobacter rectus,* and *Fusobacterium nucleatum.* Although controversial, some investigators also have suggested that human cytomegalovirus and other herpesviruses could play a contributing role.

The pathogenic organisms exist in an organized community termed a **biofilm.** Bacteria growing in biofilms are relatively protected from normal host defenses and exhibit an increased resistance to locally or systemically administered antibiotic medications. Lipopolysaccharides released from the biofilms are thought to trigger release of catabolic inflammatory mediators that lead to the loss of attachment. Mechanical disruption of this organized bacterial biofilm may be an important factor associated with successful treatment of periodontitis.

The presence of pathogenic bacteria is essential but insufficient to produce periodontitis. Although mild-to-moderate periodontitis is present in the majority of adults, only 10% to 15% of the population develops severe, generalized disease. The variation of susceptibility to periodontitis appears related to genetic influences on host response, with 50% of the risk for chronic periodontitis attributed to heredity, 20% to tobacco abuse, and another 20% to colonization by specific pathogenic bacteria.

The classification of periodontitis, as delineated by the American Academy of Periodontology, is listed in Box 4-6. In 1999, this classification underwent significant revision with consolidation of many previously distinct disorders. The concept of "early-onset periodontitis" and all of its subdivisions has been reclassified as **aggressive periodontitis.** The following text concentrates on the chronic form of periodontitis; a later section discusses the aggressive forms of periodontitis. From this list it should be clear that periodontitis represents a heterogeneous group of disorders.

Periodontitis associated with systemic disease is not rare, and Box 4-7 lists many of the disorders that may be associated with a premature loss of periodontal attachment. **Necrotizing ulcerative periodontitis (NUP)** represents the loss of attachment that often occurs in association with necrotizing ulcerative gingivitis (NUG) (see page 143). This form has been correlated with aggressive invasion by a number of spirochetes and *Prevotella intermedia.*

Clinical and Radiographic Features

Chronic Periodontitis

With the decline in caries, **chronic periodontitis** has become the primary cause of tooth loss in patients older than 35 years of age. The disorder demonstrates an increased prevalence in males, although researchers believe that much of this effect is related to poorer oral hygiene and

• BOX 4-6 Classification of Periodontitis

1. Chronic periodontitis
   - Localized
   - Generalized
2. Aggressive periodontitis
   - Localized
   - Generalized
3. Periodontitis as a manifestation of systemic diseases
   - Associated with hematologic disorders
   - Associated with genetic disorders
   - Not otherwise specified
4. Necrotizing periodontal diseases
   - Necrotizing ulcerative gingivitis (NUG)
   - Necrotizing ulcerative periodontitis (NUP)
5. Abscesses of the periodontium
   - Gingival abscess
   - Periodontal abscess
   - Pericoronal abscess (in association with pericoronitis)
6. Periodontitis associated with endodontic lesions

• BOX 4-7 Systemic Disorders with Premature Attachment Loss

1. Acatalasia
2. Acrodynia
3. Acquired immunodeficiency syndrome (AIDS)
4. Blood dyscrasias
   - Leukemia
   - Agranulocytosis
   - Cyclic neutropenia
5. Chédiak-Higashi syndrome
6. Cohen syndrome
7. Crohn disease
8. Diabetes mellitus
9. Dyskeratosis congenita
10. Ehlers-Danlos syndrome, types IV and VIII
11. Glycogen storage disease
12. Haim-Munk syndrome
13. Hemochromatosis
14. Hypophosphatasia
15. Kindler syndrome
16. Langerhans cell disease
17. Leukocyte dysfunctions with associated extraoral infections
18. Oxalosis
19. Papillon-Lefèvre syndrome
20. Sarcoidosis
21. Trisomy 21

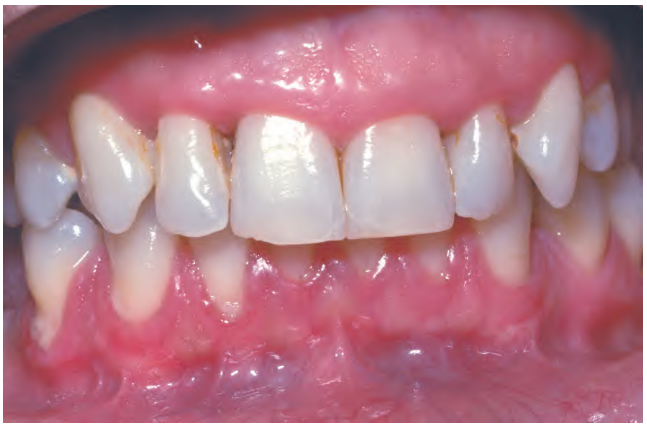
dental-visit behavior. In addition, an increased prevalence of chronic periodontitis is associated with the following:

- Advancing age
- Smoking
- Diabetes mellitus
- Osteoporosis
- HIV infection
- Lower socioeconomic level

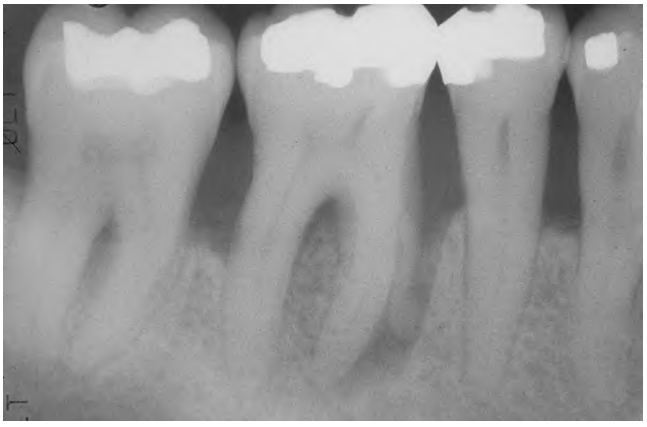
Local factors also may predispose patients to isolated periodontal defects; these include tooth shape and alignment, presence and quality of dental restorations, poor interdental contact, calculus formation, subgingival dental caries, traumatic occlusion, and abnormal alveolar bone or gingival anatomy.

Conversely, it appears that the presence of significant periodontitis may place patients at risk for an increased prevalence or greater severity of certain medical disorders. Although controversial, periodontitis has been associated with an elevated risk for coronary artery disease, stroke, progressive diabetes mellitus, respiratory diseases, and delivery of low–birth weight babies. Although strong direct associations have been documented, the epidemiology is difficult to interpret because of the additional risk factors associated with both conditions. For example, cardiovascular disease has been related to periodontitis, but the nature of this association is cloudy because both are strongly associated with smoking.

In chronic periodontitis, no abnormalities of the immune system typically are found. Periodontitis begins in youth and early adulthood, takes years to decades to progress, and includes cyclic patterns of exacerbation and remission. The assumption that periodontitis is a disease of aging has been challenged, and most believe the increased periodontal destruction observed in older adults reflects a lifetime of disease accumulation rather than an age-specific disease.

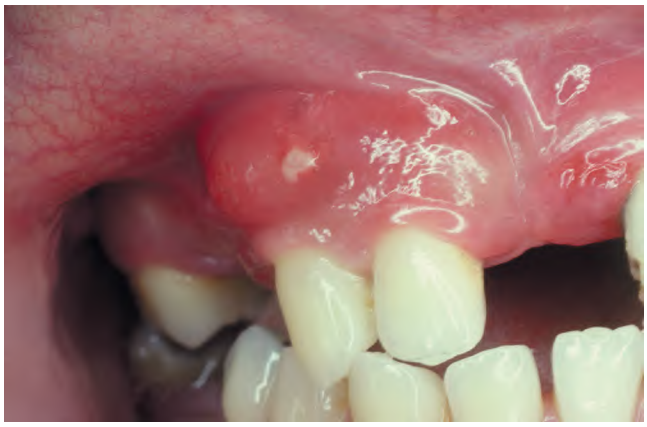


• Fig. 4-30 Adult Periodontitis. Diffuse gingival erythema with blunting and apical positioning of the gingival margins. (Courtesy of Dr. Samuel Jasper.)



• Fig. 4-31 Advanced Adult Periodontitis. Generalized horizontal bone loss with an isolated vertical defect involving the mesial root of the first molar.

In patients with periodontitis, gingivitis is present and precedes the development of significant periodontal lesions. Although many sites may demonstrate gingivitis and do not progress to attachment loss, lifelong local measures directed against sites of gingivitis represent an effective approach for prevention of chronic periodontitis. As loss of attachment occurs, blunting and apical positioning of the gingival margins typically are present (Fig. 4-30). Periodontal disease is present when a loss of attachment can be demonstrated through the use of a periodontal probe. In the absence of significant gingival hyperplasia, a measurement of pocket depths greater than 3 to 4 mm indicates destruction of the periodontal ligament and resorption of adjacent alveolar bone; however, clinical attachment loss is the best measurement of accumulated periodontal destruction and represents the diagnostic gold standard. High-quality dental radiographs exhibit a decreased vertical height of the bone surrounding the affected teeth (Fig. 4-31). With advanced bone



• **Fig. 4-32 Periodontal Abscess.** Localized erythematous gingival enlargement with central purulent drainage.

loss, tooth mobility is present. Although to date there are no confirmed biomarkers for periodontal disease, ongoing research is attempting to analyze saliva for genomic and microbial markers for the early diagnosis of periodontitis.

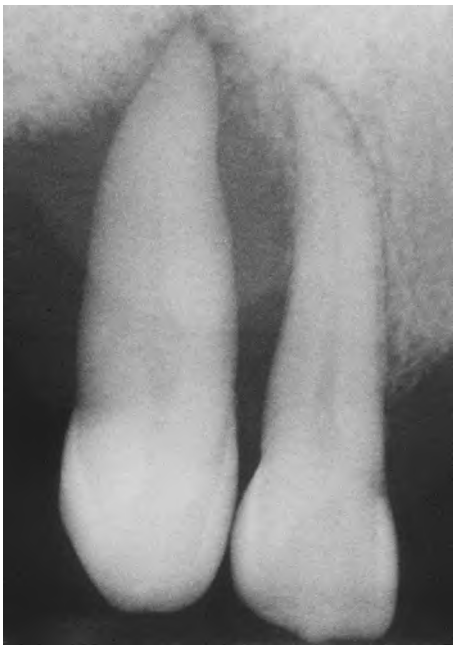
Necrotizing Ulcerative Periodontitis

NUP has symptoms similar to NUG (see page 143), but it also demonstrates loss of clinical attachment and alveolar bone. This destructive form of periodontitis may arise within a zone of preexisting periodontitis, or it may represent a sequela of a single or multiple episodes of NUG. Many believe that NUG and NUP represent different stages of the same infection. Patients affected with this pattern frequently are younger than most patients affected with chronic periodontitis and often demonstrate immunosuppression or malnutrition.

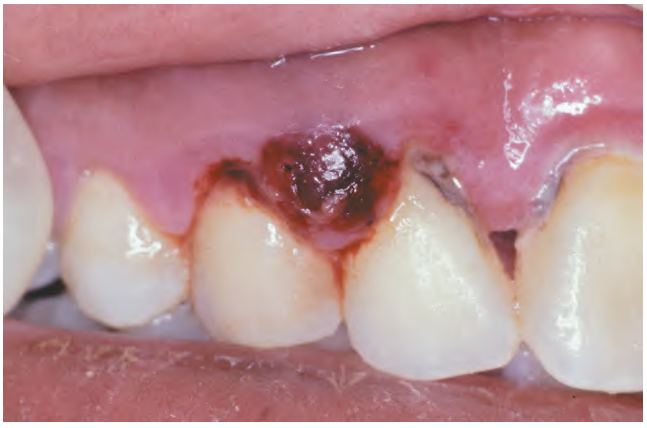
Periodontal Abscess

A **periodontal abscess** (Figs. 4-32 and 4-33) is a localized purulent infection of the gingiva with involvement of the adjacent periodontal attachment and alveolar bone. On occasion, an abscess may be localized to the marginal or interdental gingiva without involvement of the adjacent periodontal ligament or alveolar bone. This lesion is termed a **gingival abscess** and often is secondary to plaque or foreign material that has become entrapped in the gingival sulcus.

A periodontal abscess often arises in a preexisting periodontal lesion and usually is precipitated by alterations in the subgingival flora, host resistance, or both. Factors frequently associated with abscess formation are closure of the entrance into a periodontal pocket, furcation involvement, or diabetes. Many cases arise in patients actively undergoing periodontal therapy, perhaps because of incomplete removal of deep calculus with microbial penetration of the soft tissue surrounding the pocket or premature sealing of the coronal opening to the pocket. Other factors involved less frequently are trauma and anatomic dental anomalies, such as enamel pearls (see page 85) and dens invaginatus (see page 82). Most cases arise in adults; periodontal abscesses in children



• **Fig. 4-33 Periodontal Abscess.** Same patient as depicted in Fig. 4-32. Note extensive loss of bone support associated with the maxillary cuspid.

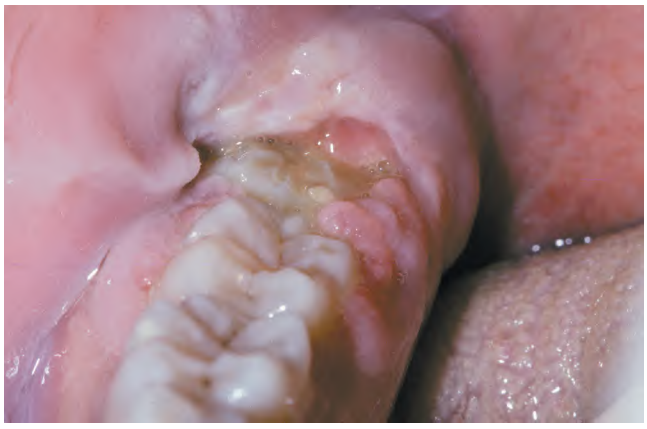


• **Fig. 4-34 Periodontal Abscess.** Dark-red and hemorrhagic enlargement of the interdental papilla between the maxillary right lateral incisor and cuspid.

are rare and most frequently the result of a foreign body that has been introduced into previously healthy periodontal tissues.

A periodontal abscess appears as a zone of gingival enlargement along the lateral aspect of a tooth. The involved gingiva may be erythematous and edematous with a slick, red surface, or it may be hemorrhagic with a dark-red coloration (Fig. 4-34). Common symptoms include the following:

- Throbbing pain
- Extreme sensitivity to palpation of the affected gingiva
- Sensitivity, mobility, or extrusion of the adjacent tooth
- Foul taste
- Lymphadenopathy
- Fever, leukocytosis, and malaise (occasionally)



• **Fig. 4-35 Pericoronitis.** Painful erythematous enlargement of the soft tissues overlying the crown of the partially erupted right mandibular third molar.

Probing or gentle pressure on the affected gingiva often results in the expression of pus from the sulcus. The abscess may drain through an overlying sinus tract. With drainage, the abscess becomes asymptomatic but can demonstrate acute exacerbations if the mucosa heals over and the pressure builds again. Radiographs often demonstrate bone loss associated with the previous periodontal defect or additional radiolucency secondary to the current acute process. In some cases, the infection can spread into the periapical region and create a combined periodontal-endodontic lesion.

Pericoronitis

Pericoronitis is an inflammatory process that arises within the tissues surrounding the crown of a partially erupted tooth. The inflammatory reaction often arises when food debris and bacteria are present beneath the gingival flap overlying the crown. Other predisposing factors include stress and upper respiratory infections, especially tonsillitis or pharyngitis.

These gingival flaps can exhibit long periods of chronic inflammation without symptoms. If the debris and bacteria become entrapped deep within the gingival flap, then abscess formation develops. Abscess development is seen most frequently in association with the mandibular third molars, and the predominant symptoms are extreme pain in the area, a foul taste, and inability to close the jaws. The pain may radiate to the throat, ear, or floor of the mouth. The affected area is erythematous and edematous, and the patient often has lymphadenopathy, fever, leukocytosis, and malaise (Fig. 4-35). NUG-like necrosis may develop in areas of persistent pericoronitis.

Histopathologic Features

When soft tissue from areas of periodontitis is examined microscopically, gingivitis is present and the crevicular epithelium lining the pocket is hyperplastic with extensive exocytosis of acute inflammatory cells. The adjacent connective tissue exhibits an increased vascularity and contains an inflammatory cellular infiltrate consisting predominantly of lymphocytes and plasma cells, but with a variable number of polymorphonuclear leukocytes. Frequently, large colonies of microorganisms, representing plaque and calculus, are noted.

Treatment and Prognosis

Periodontitis

Initial attention must be directed toward elimination of any existing risk factors. Once these influences have been managed, the treatment of periodontitis is directed toward stopping the loss of attachment. The foremost goal of this process is the elimination of the pathogenic bacterial plaque. Scaling, root planing, and curettage can be used to treat early periodontal lesions. In deeper pockets, a surgical flap may be required to gain access to the tooth for necessary débridement. At this time, the underlying bone may be recontoured (if necessary) to aid in the resolution of the periodontal pocket.

In some bony defects, regeneration of the attachment can be attempted through interdental denudation or the placement of autogenous bone grafts, allografts, or alloplastic materials. Often these grafts are used in conjunction with materials, such as polytetrafluoroethylene, in an attempt to achieve guided tissue regeneration in moderate-to-advanced periodontal defects.

Because of the chronic nature of periodontitis, antibiotic medications generally are not used except in patients who do not respond to conventional therapy. When required, tetracycline or metronidazole is used most frequently. Several studies also suggest that NSAIDs may help slow the progression of bone loss in some cases of destructive periodontitis.

Several forms of local antibiotic delivery have been developed. The antibiotic drugs are placed directly into sites of refractory periodontitis and consist of gels, ointments, nonresorbable fibers, and resorbable polymers. These antibiotic agents represent an adjunct to scaling and root planing and should be limited to sites that are resistant to conventional therapy alone.

In many cases, the prognosis for chronic periodontitis correlates directly with the patient's desire to maintain oral health. Long-term studies show that periodontal health can be maintained after appropriate periodontal therapy if a program of rigorous oral hygiene and professional care is established. Bacterial morphotypes return to pretreatment levels 42 days after professional prophylaxis, but pathogenic complexes capable of inducing attachment loss require approximately 3 months to be reestablished functionally. In patients with less-than-optimal oral hygiene or with isolated defects that cannot be self-cleaned, a loss of attachment can be prevented if professional scaling and root planing are performed at 3-month intervals.

Destructive periodontal disease that is nonresponsive to normal therapy in compliant patients is termed **refractory periodontitis.** In such cases the patient should be reevaluated closely for any predisposing risk factors (such as, smoking) or systemic diseases known to be associated with

an increased prevalence of periodontitis (such as, diabetes). Subgingival microbial cultures can be obtained to assist in selection of an appropriate antibiotic intervention. Antimicrobial therapy may be combined with more frequent periodontal maintenance therapy and stronger reinforcement of the patient's oral hygiene techniques.

Necrotizing Ulcerative Periodontitis

Once any underlying influence (e.g., immunosuppression, malnutrition) has been resolved, NUP often responds well to irrigation, débridement of the necrotic areas, effective oral hygiene measures, and administration of systemic antibiotic medications. Failure to respond to standard therapy mandates a thorough physical evaluation to rule out the possibility of an underlying disease.

Periodontal Abscess

A gingival or periodontal abscess is treated by drainage through the sulcus or by an incision through the overlying mucosa. Thorough cleansing of the area with removal of all foreign material, plaque, and calculus should be performed. Penicillin or other antibiotic drugs are prescribed when a fever is present. Analgesic agents are prescribed, and the patient receives a soft diet, is told to use warm saltwater rinses, and is instructed to return each day until the symptoms have resolved. After the acute phase has passed, the patient is treated for any underlying chronic pathologic periodontal condition.

Pericoronitis

Acute pericoronitis is treated with gentle antiseptic lavage under the gingival flap to remove gross food debris and bacteria. Systemic antibiotic agents are used if a fever or general symptoms are noted. The patient is instructed to use warm saltwater rinses and to return in 24 hours. Once the acute phase has subsided, the tooth can be extracted if long-term maintenance is contraindicated. If tooth retention is desirable, then the overlying gingival flap is removed surgically, which is followed by elimination of all food debris and bacterial colonies by thorough curettage.

◆ AGGRESSIVE PERIODONTITIS

Although periodontitis is much more frequent in older adults, it also can be a significant problem in children and young adults. Before the 1999 reclassification by the American Academy of Periodontology, destructive periodontal disease in younger patients was termed **early-onset periodontitis** and subdivided into **prepubertal**, **localized juvenile, generalized juvenile,** and **rapidly progressing** forms of periodontitis. The "early-onset" designation was discontinued during the 1999 workshop because the term was deemed too restrictive.

The 1999 workshop concluded that the most logical classification system should not be age dependent or require knowledge of rates of progression. In general, the new designation of **localized aggressive periodontitis** replaces the older term, **localized juvenile periodontitis,** whereas **generalized aggressive periodontitis** supersedes **generalized juvenile periodontitis.** The pattern previously designated as **prepubertal periodontitis** has been associated with a systemic leukocyte dysfunction termed *leukocyte adhesion deficiency syndrome.* This disease currently is classified as one of the forms of periodontitis presenting as a manifestation of a systemic disease.

By definition, aggressive periodontitis occurs in otherwise healthy people; there should be no association with a systemic disease process. In keeping with this definition, the diagnosis is one of exclusion, and all systemic disorders known to be related to premature loss of attachment (see Box 4-7) should be ruled out before the definitive diagnosis is made.

Researchers believe that aggressive periodontitis represents a number of different pathoses that have been grouped together because of similar clinical presentations. The majority of patients with aggressive periodontitis have a demonstrable neutrophil dysfunction but without systemic manifestations. Although this is a controversial topic, several investigators have suggested that aggressive periodontitis requires specific bacterial flora and the presence of a selective immune dysfunction that allows these pathogens to flourish. This unique pattern of immune alteration may explain the failure to defend appropriately against certain periodontal pathogens without exhibiting systemic signs of immunodeficiency. Familial aggregation of patients with aggressive periodontitis is noted and suggests an underlying genetic foundation. In all likelihood, aggressive periodontitis is genetically heterogeneous, meaning the mutation of any one of several different gene loci can result in the disease.

Clinical and Radiographic Features

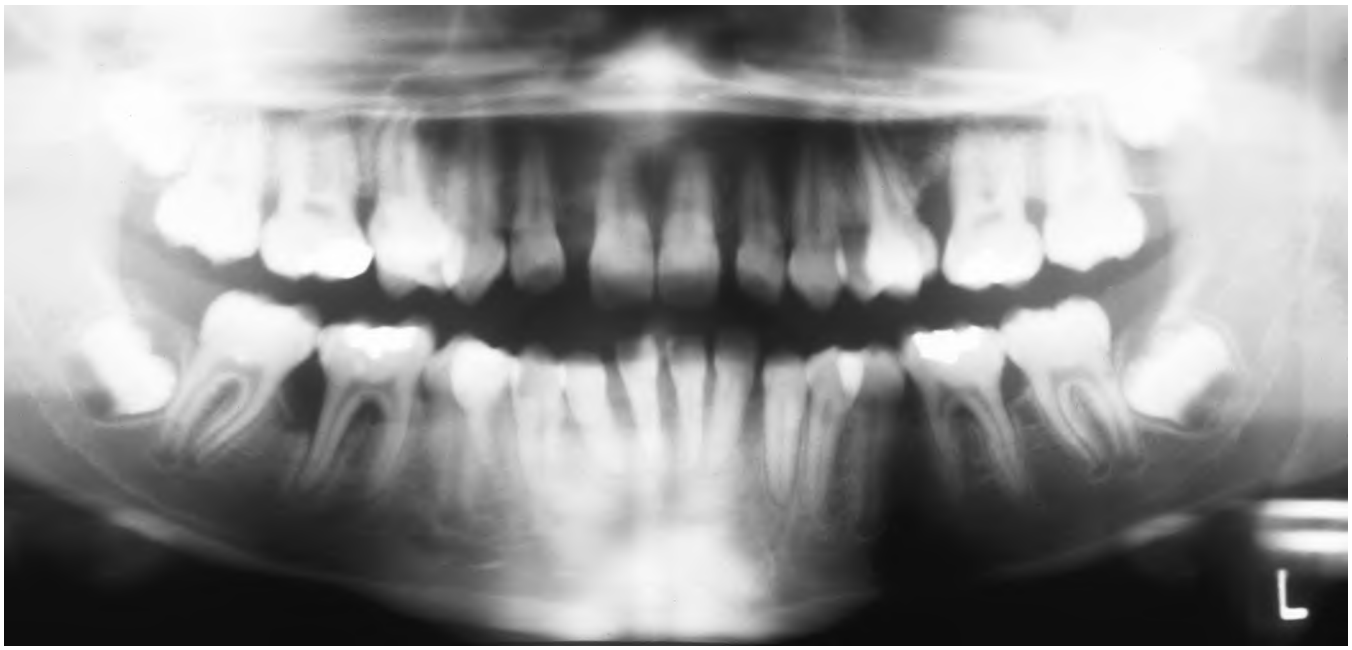
Localized Aggressive Periodontitis

As previously stated, aggressive periodontitis can be localized or generalized. **Localized aggressive periodontitis** typically begins around the ages of 11 to 13 years and has a strong familial tendency. The following specific features have been delineated by the American Academy of Periodontology:

- Circumpubertal onset
- Robust serum antibody response to infecting agents
- Attachment loss localized to the first molars and incisors, with involvement of no more than two teeth other than the first molars and incisors

This form may appear to localize around the first molars and the incisors, possibly because these teeth have been erupted for the longest duration (Fig. 4-36). In numerous clinical studies, minimal supragingival plaque or calculus has been documented; however, this finding has been disputed. The rate of bone destruction is three to five times faster than that seen in chronic periodontitis.

In the first molar regions, radiographs reveal vertical bone resorption that often is bilateral and symmetrical. In classic cases an arc-shaped zone of bone loss extends from the distal aspect of the second bicuspid to the mesial aspect



• **Fig. 4-36 Localized Aggressive Periodontitis.** Loss of bone support in the area of the first molars and incisors of both maxillary and mandibular arches in a 14-year-old patient.

of the second molar. Similar involvement is apparent around the anterior teeth. Tooth migration and mobility are common. If untreated, then the process often continues until the teeth are exfoliated. In about one-third of patients affected with localized aggressive periodontitis, progression to more generalized disease occurs.

Of all the pathogens in dental plaque, *A. actinomycetemcomitans* appears to be predominant in localized aggressive periodontitis. This bacterium is present in disease sites in more than 90% of cases. Its ability to invade gingival tissue has created difficulties in mechanical eradication. Knowledge of its importance to the disease process has led to remarkable advances in therapy.

Generalized Aggressive Periodontitis

Generalized aggressive periodontitis may not represent a distinct disease entity but, rather, may occur in a collection of young adults with advanced periodontal disease. Many cases may represent localized aggressive periodontitis that has become more generalized with time; other cases initially demonstrate generalized disease. As with the localized variant, a significant percentage of cases demonstrate neutrophil dysfunction. The American Academy of Periodontology recognizes the following features:

- Usually diagnosed in patients younger than 30 years old but may occur at any age
- Poor serum antibody response to infecting agents
- Pronounced episodic destruction of periodontal attachment and alveolar bone
- Generalized loss of attachment that must affect at least three teeth other than the first molars and incisors

Most affected patients are between the ages of 12 and 32. In contrast to many examples of the localized variant, heavy plaque, calculus, and marked gingival inflammation may be present. Compared with the localized variant, more teeth are affected and the bone loss is not restricted to specific areas of the jaws.

Although the localized pattern is associated primarily with *A. actinomycetemcomitans,* the pathogens active in the generalized variant are more complex, more closely aligned to chronic periodontitis, and also involve such organisms as *Prevotella intermedia, Porphyromonas gingivalis, Tannerella forsythensis, Fusobacterium nucleatum, Campylobacter rectus,* and *Treponema denticola.* As mentioned in the discussion of periodontitis (see page 153), an association with a number of viruses has been suggested by some, but disputed by others. In patients whose disease progresses from the localized to generalized pattern, the associated periodontal pathogens often become more diverse as the patient ages and the disease becomes more widespread.

Histopathologic Features

The microscopic examination of granulation tissue removed from sites of aggressive periodontitis does not differ dramatically from that seen in chronic periodontitis. In spite of this, initial histopathologic examination of the material removed from active sites of disease is important to rule out the possibility of other disease processes, such as Langerhans cell histiocytosis (see page 550). The definitive diagnosis centers on the clinical, radiographic, histopathologic, and microbiologic findings combined with the family history and leukocyte function tests.

Treatment and Prognosis

Unlike the treatment used for patients with chronic periodontitis, scaling and root planing alone do not

stop progression of aggressive periodontitis. The defects in leukocyte function, in addition to the invasive capabilities of the involved pathogenic organisms, mandate the use of antibiotics in combination with mechanical removal of subgingival plaque and inflamed periodontal tissues. Although tetracycline, amoxicillin and clavulanate potassium, minocycline, and erythromycin can be used in selected patients, the combination of high-dose (500 mg three times per day) amoxicillin and metronidazole has been shown to be most effective in controlling the involved periodontal pathogens, especially *A. actinomycetemcomitans.* The effectiveness of the antibiotics appears to be improved if initiated immediately after scaling and root planing. Continued therapy often is predicated on microbiologic testing to ensure selection of the most appropriate antimicrobial agent. Some investigators have claimed better results if the scaling and root planing are completed within a 24-hour period, rather than treating a quadrant at a time over an extended period. Reinfection of previously cleaned areas by organisms from untreated sites is thought to worsen the response to therapy. Use of local anti-infective agents, such as chlorhexidine, for 2 weeks after the initial débridement has proven to be beneficial in many individuals. Patients with active disease may be at increased risk for adverse peri-implant gingival infection. Some clinicians delay implant placement in patients with the localized type because the disease process often stabilizes with age.

A reevaluation with professional prophylaxis is performed once a month for 6 months and then every 3 months thereafter. Specimens for anaerobic cultures are obtained at each 3-month recall. Patients with refractory disease or significant colonization by pathogenic organisms receive additional courses of appropriate antibiotics. Long-term follow-up is mandatory because of the possibility of reinfection or incomplete elimination of the organisms. The presence of deep residual pockets is associated with disease progression. In such circumstances, periodontal surgery often is performed to eliminate these defects. This intervention is directed at any pocket consistently deeper than 5 mm and typically is performed after 2 to 6 months of nonsurgical therapy.

Dental practitioners should alert proband patients with aggressive periodontitis of the possible genetic transmission of the disease process. In general, patients diagnosed with localized aggressive periodontitis typically exhibit relatively stable disease, whereas those initially diagnosed with generalized involvement often continue to lose periodontal attachment and teeth. Patients who present for therapy with advanced clinical attachment loss tend to demonstrate a worse prognosis and respond less reliably to therapy. Smoking and psychosocial stress are related to a worse prognosis and are thought possibly to alter immune function and the susceptibility to infections.

◆ PAPILLON-LEFÈVRE SYNDROME

In 1924, Papillon and Lefèvre initially described the syndrome that bears their names. This autosomal recessive disorder predominantly demonstrates oral and dermatologic manifestations; similar dermatologic changes can be seen in the absence of oral findings **(Unna-Thost syndrome, Howell-Evans syndrome, Vohwinkel syndrome, Gamborg Nielsen syndrome,** and **mal de Meleda).** Because of the autosomal recessive inheritance pattern, the parents typically are not affected; consanguinity is noted in approximately one-third of cases.

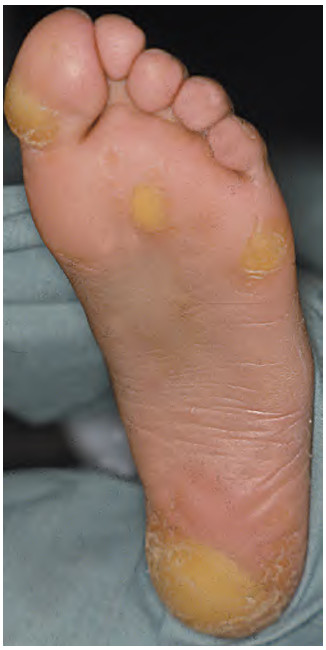
Genetic studies of patients with Papillon-Lefèvre syndrome have mapped the major gene locus to chromosome 11q14-q21 and revealed mutation and loss of function of the *cathepsin C* gene. This gene is important in the structural growth and development of the skin and is critical for appropriate immune response of myeloid and lymphoid cells. Researchers believe that the loss of appropriate function of the *cathepsin C* gene results in an altered immune response to infection. In addition, the altered gene may affect the integrity of the junctional epithelium surrounding the tooth.

A closely related disease, **Haim-Munk syndrome,** also exhibits palmoplantar keratosis, progressive periodontal disease, recurrent skin infections, and several skeletal malformations. In this syndrome, the skin manifestations are more severe and the periodontal disease is milder. Studies have demonstrated that Haim-Munk syndrome and many examples of prepubertal periodontitis also exhibit mutation of the *cathepsin C* gene and represent allelic variants of the mutated gene responsible for Papillon-Lefèvre syndrome.

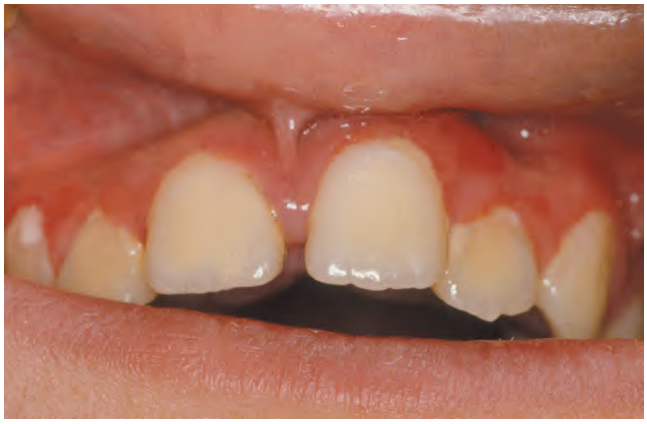
Clinical and Radiographic Features

Papillon-Lefèvre syndrome exhibits a prevalence of one to four per million people in the population, and carriers are thought to be present in two to four per thousand persons. In most cases, the dermatologic manifestations become clinically evident in the first 3 years of life. Diffuse transgredient (first occurs on the palms and soles and then spreads to the dorsa of the hands and feet) palmar-plantar keratosis develops, with occasional reports of diffuse follicular hyperkeratosis, nail dystrophy, hyperhidrosis, and keratosis on the elbows and knees (Fig. 4-37). Other less common sites of involvement include the legs, thighs, dorsal surface of the fingers and toes, and (rarely) the trunk. Although the appearance of the dermatologic manifestations is variable, the lesions typically present as white, light-yellow, brown, or red plaques and patches that develop crusts, cracks, or deep fissures.

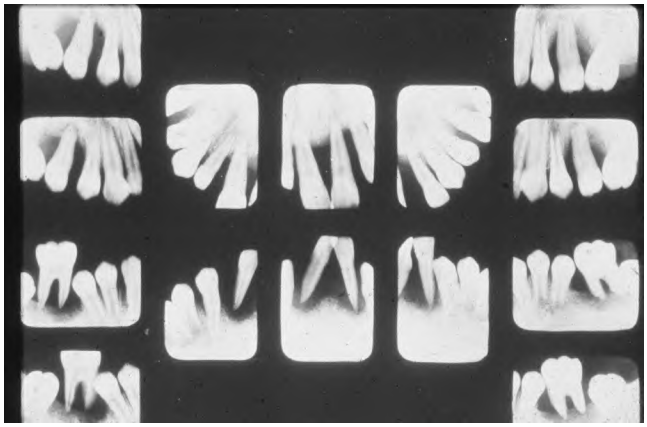
The oral manifestations consist of dramatically advanced periodontitis that is seen in both the deciduous and the permanent dentitions. Upon eruption of the deciduous teeth, diffuse hemorrhagic and hyperplastic gingivitis develops in association with rapid loss of periodontal attachment (Fig. 4-38). The extensive loss of osseous support often results in teeth that radiographically appear to be floating in soft tissue (Fig. 4-39). At 4 to 5 years of age, all primary teeth typically have been lost or extracted. Once edentulous, the gingiva returns to a normal state of health until eruption



• **Fig. 4-37 Papillon-Lefèvre Syndrome.** Plantar keratosis of the foot.



• **Fig. 4-38 Papillon-Lefèvre Syndrome.** Generalized erythematous gingivitis.



• **Fig. 4-39 Papillon-Lefèvre Syndrome.** Multifocal sites of bone loss in all four quadrants. (From Giansanti JS, Hrabak RP, Waldron CA: Palmoplantar hyperkeratosis and concomitant periodontal destruction [Papillon-Lefèvre syndrome], *Oral Surg Oral Med Oral Pathol* 36:40, 1973.)

of the permanent dentition restarts the cycle of rapidly progressive periodontal disease. By age 15, all of the permanent teeth have been lost in most affected individuals. Although other pathogenic bacteria have been isolated from sites of active disease, *A. actinomycetemcomitans* has been related directly to the periodontal destruction.

In addition to the dermatologic and oral manifestations, numerous investigators have documented less frequent findings. Impaired somatic development and ectopic calcifications of the falx cerebri and choroid plexus have been reported, in addition to an increased susceptibility to infections beyond the oral cavity. Pyoderma, furunculosis, pneumonia, hepatic abscesses, and other infections have been documented.

Histopathologic Features

Once again, the histopathologic features of Papillon-Lefèvre syndrome are similar to those seen in chronic periodontitis and are not specific. Submitted tissue often contains hyperplastic crevicular epithelium with exocytosis. The underlying connective tissue exhibits increased vascularity and a mixed inflammatory cellular infiltrate consisting predominantly of plasma cells intermixed with polymorphonuclear leukocytes, lymphocytes, and histiocytes. Initially, histopathologic examination is recommended to rule out other pathologic causes of the periodontal destruction.

Treatment and Prognosis

Skin lesions in these patients have been treated most successfully using systemic retinoids, such as etretinate, acitretin, and isotretinoin. This approach has resulted in remarkable improvement with complete clearance in the majority of patients. Surprisingly, a few authors have reported improvement of the associated periodontal disease during periods of retinoid use, but others have disputed this claim. Possible adverse reactions caused by retinoid administration include angular cheilitis, dry lips, hair loss, arthralgia, tendinous and ligamentous calcifications, and teratogenicity. In an attempt to avoid these drug-related adverse reactions, patients with mild dermatologic manifestations often are treated with topical lubricants, keratolytic agents (salicylic or lactic acid), corticosteroids, or antibiotics.

Attempts at resolution of the periodontal disease often have been frustrating. In spite of extensive periodontal therapy and antibiotic agents, in many patients the disease progresses until all teeth are lost. However, several investigators have reported a cessation of attachment loss, and two different treatment approaches have been used.

Despite the use of numerous antibiotic medications, several reports document a difficulty in resolution of the infection associated with teeth that already exhibit attachment loss. Some clinicians recommend extraction of all deciduous teeth to eliminate the periodontal pathogens and reduce the risk of transmitting these organisms to the permanent dentition. Following eruption of the permanent

teeth, antibiotics are utilized in an attempt to prevent redevelopment of periodontitis.

The second approach revolves around a direct attack against *A. actinomycetemcomitans.* Therapy with high-dose amoxicillin and metronidazole has proven effective when combined with extraction of severely affected teeth, high patient compliance, and strong supportive periodontal therapy. In clinical studies, the progression of attachment loss of the erupted dentition and the periodontal destruction of the teeth that erupt after the initiation of therapy were slowed dramatically. Rigorous oral hygiene, chlorhexidine mouth rinses, frequent professional prophylaxis, and periodic appropriate antibiotic therapy are necessary for long-term maintenance.

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5 Bacterial Infections

IMPETIGO

Impetigo is a superficial infection of the skin that is caused by *Staphylococcus aureus,* alone or in combination with *Streptococcus pyogenes (*group A, β-hemolytic). Two main patterns are seen. Seventy percent of the cases are **nonbullous impetigo,** which typically demonstrates a mixture of *S. aureus* and *S. pyogenes.* **Bullous impetigo** is less common and predominantly caused by *S. aureus.* The term *impetigo* is derived from a Latin word meaning "attack" because of its common presentation as a scabbing eruption. Intact epithelium normally is protective against infection; therefore, many cases arise in damaged skin, such as preexisting dermatitis, cuts, abrasions, or insect bites. Secondary involvement of an area of dermatitis has been termed **impetiginized dermatitis.** An increased prevalence is associated with debilitating systemic conditions, such as human immunodeficiency virus (HIV) infection, type 2 diabetes mellitus, or dialysis.

Clinical Features

Nonbullous impetigo (impetigo contagiosa) is the more prevalent pattern and occurs most frequently on the legs, with less common involvement noted on the trunk, scalp, or face. The facial lesions usually develop around the nose and mouth. In many patients with facial involvement, the pathogenic bacteria are harbored in the nose and spread onto the skin into previously damaged sites, such as scratches or abrasions. Often, facial lesions will have a linear pattern that corresponds to previous fingernail scratches. The infection is more prevalent in school-aged children but also may be seen in adults. The peak occurrence is during the summer or early fall in hot, moist climates. Impetigo is contagious and easily spread in crowded or unsanitary living conditions.

Nonbullous impetigo initially appears as red macules or papules, with the subsequent development of fragile vesicles. These vesicles quickly rupture and become covered with a thick, amber crust (Fig. 5-1). The crusts are adherent and have been described as "cornflakes glued to the surface." Some cases may be confused with exfoliative cheilitis (see page 278) or recurrent herpes simplex (see page 220). Pruritus is common, and scratching often causes the lesions to spread (Fig. 5-2). Lymphangitis, cellulitis, fever, anorexia, and malaise are uncommon, although leukocytosis occurs in about half of affected patients.

In an infrequent pattern of impetigo termed **ecthyma,** the central area of the crust becomes necrotic and forms a deep indurated ulceration. This lesion heals slowly and often is associated with a permanent scar.

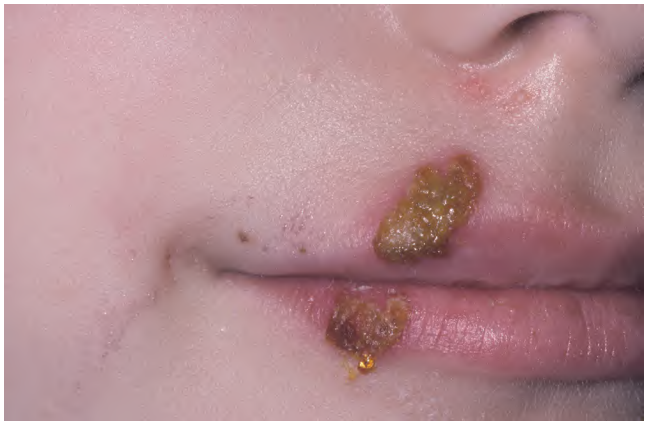
Due to its strong association with *S. aureus*, **bullous impetigo** also has been termed **staphylococcal impetigo.** Like the nonbullous form, it most frequently affects the extremities, trunk, and face. Infants and newborns are infected most commonly, but the disease also may occur in children and adults. The lesions are characterized by superficial vesicles that rapidly enlarge to form larger flaccid bullae. Initially, the bullae are filled with clear serous fluid, but the contents of the bullae quickly become more turbid and eventually purulent. Although the bullae may remain intact, they usually rupture and develop a thin brown crust that some describe as "lacquer." Weakness, fever, and diarrhea may be seen. Lymphadenopathy and cellulitis are unusual complications. Meningitis and pneumonia are very rare but may lead to serious complications, even death.

Diagnosis

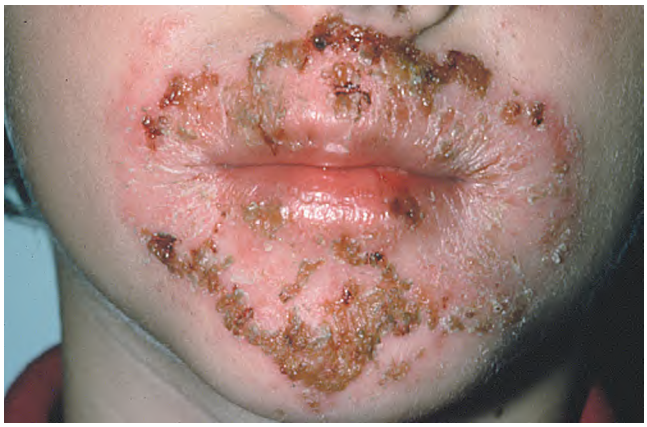
A strong presumptive diagnosis normally can be made from the clinical presentation. When the diagnosis is not obvious clinically or the infection fails to respond to standard therapy within 7 days, the definitive diagnosis requires isolation of *S. aureus* or *S. pyogenes* from cultures of involved skin.

Treatment and Prognosis

For patients with nonbullous impetigo involving only a small area with few lesions, topical mupirocin or fusidic acid (available in Canada and Europe, not in the United States) has been shown to be effective. Although uncommon, increasing reports of resistance to these medications are appearing, especially in infections associated with methicillin-resistant *S. aureus* (MRSA). In such cases, utilization of topical retapamulin has been proven effective in many patients. Removal of the crusts with a clean cloth soaked in warm soapy water is recommended before application of topical therapy, rather than placing the medication on inert,



• **Fig. 5-1 Impetigo.** Amber crusts of the skin and vermilion border of the lips.



• **Fig. 5-2 Impetigo.** Scaly and amber-colored crusts of the perioral skin.

dried, exfoliating skin. For bullous or more extensive lesions, topical antibiotic drugs often are insufficient; the treatment of choice is a 1-week course of a systemic oral antibiotic. The best antibiotic is one that is effective against both *S. pyogenes* and penicillin-resistant *S. aureus*. Cephalexin, dicloxacillin, flucloxacillin, and amoxicillin-clavulanic acid represent good current choices. In communities frequented with MRSA, therapy with agents such as trimethoprim/sulfamethoxazole, clindamycin, tetracycline, or fluoroquinolones is recommended. If left untreated, then the lesions often enlarge slowly and spread. Serious complications, such as acute glomerulonephritis, are rare but possible in prolonged cases. Inappropriate diagnosis and treatment with topical corticosteroids may produce resolution of the surface crusts, but infectious, red, raw lesions remain.

◆ ERYSIPELAS

Erysipelas is a superficial skin infection most commonly associated with β-hemolytic streptococci (usually group A, such as *S. pyogenes,* but occasionally other groups, such as group C, B, or G). Other organisms, such as *Staphylococcus aureus,* have been isolated from the lesions, but it is unclear if these bacteria are causative or a contaminant. The infection rapidly spreads through the lymphatic channels, which become filled with fibrin, leukocytes, and streptococci. Although also associated with ergotism, the term *Saint Anthony's fire* has been used to describe erysipelas. Because the French House of St. Anthony, an eleventh-century hospital, had fiery red walls similar to the color of erysipelas, the term *Saint Anthony's fire* was used to describe this disease. Today, classical facial erysipelas is a rare and often forgotten diagnosis. At times, the appropriate diagnosis has been delayed because of confusion with facial cellulitis from dental infections.

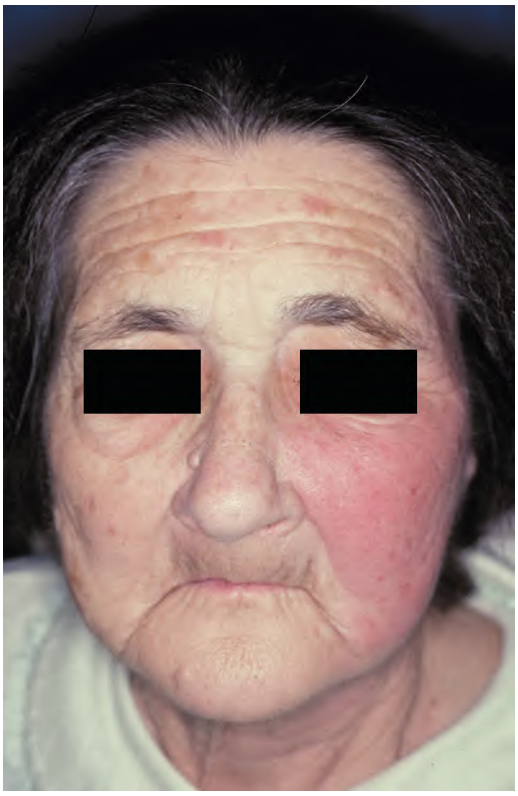
Clinical Features

Erysipelas tends to occur primarily in young and older adult patients or in those who are debilitated, diabetic, immunosuppressed, obese, or alcoholic. Patients who have areas of chronic lymphedema or large surgical scars (such as, postmastectomy or saphenous venectomy) also are susceptible to this disease. The infection may occur anywhere on the skin, especially in areas of previous trauma. The most commonly affected site is the leg in areas affected by tinea pedis (athlete's foot). The face, arm, and upper thigh also frequently are infected. In facial erysipelas, an increased prevalence is noted in the winter and spring months, whereas summer is the peak period of involvement of the lower extremities.

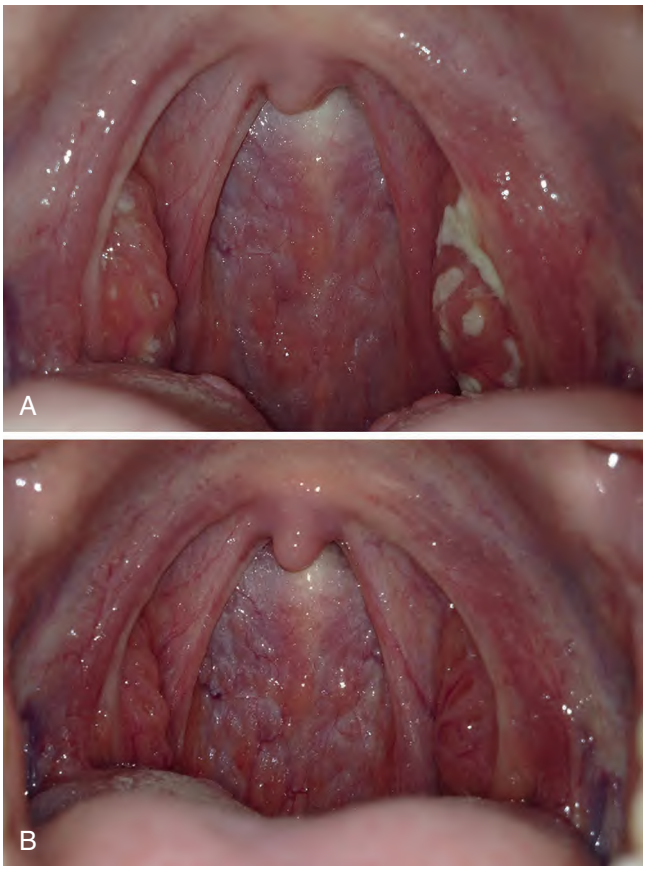
When lesions occur on the face, they normally appear on the cheeks, eyelids, and bridge of the nose, at times producing a butterfly-shaped lesion that may resemble lupus erythematosus (see page 740). If the eyelids are involved, then they may become edematous and shut, thereby resembling angioedema (see page 326). The affected area is painful, bright red, well-circumscribed, swollen, indurated, and warm to the touch (Fig. 5-3). Often the affected skin will demonstrate a surface texture that resembles an orange peel *(peau d'orange).* High fever and lymphadenopathy often are present. Lymphangitis, leukocytosis, nausea, and vomiting occur infrequently. Diagnostic confirmation is difficult because cultures usually are not beneficial.

Treatment and Prognosis

The treatment of choice is penicillin. Alternative antibiotic drugs include macrolides (such as, erythromycin), cephalosporins (such as, cephalexin), and fluoroquinolones (such as, ciprofloxacin). On initiation of therapy, the area of skin involvement often enlarges, probably secondary to the release of toxins from the dying streptococci. A rapid resolution is noted within 48 hours. Without appropriate therapy, possible complications include abscess formation, gangrene, necrotizing fasciitis, toxic shock syndrome with possible multiple organ failure, thrombophlebitis, acute glomerulonephritis, septicemia, endocarditis, and death. Recurrences may develop in the same area, most likely in a previous zone of damaged lymphatics or untreated athlete's foot. With repeated recurrences, permanent and disfiguring



• **Fig. 5-3 Erysipelas.** Red, swollen area of the left cheek. (Courtesy of Dr. Arthur Gonty.)



• **Fig. 5-4 Tonsillitis. A,** Hyperplastic pharyngeal tonsils with yellowish exudate of crypts. **B,** Same patient following successful therapy with amoxicillin/clavulanic acid. (Courtesy of Dr. Molly Housley.)

enlargements may result. In cases with multiple recurrences, prophylaxis with oral penicillin has been used.

◆ STREPTOCOCCAL TONSILLITIS AND PHARYNGITIS

Tonsillitis and **pharyngitis** are extremely common and may be caused by many different organisms. The most common causes are group A, β-hemolytic streptococci, adenoviruses, enteroviruses, influenza, parainfluenza, and Epstein-Barr virus. Although a virus causes the majority of pharyngitis cases, infection with group A streptococci is responsible for 20% to 30% of acute pharyngitis cases in children and 5% to 15% of cases in adults. Spread is typically by person-to-person contact through respiratory droplets or oral secretions, with a short incubation period of 2 to 5 days.

Clinical Features

Although the infection can occur at any age, the greatest prevalence occurs in children 5 to 15 years old, with most cases in temperate climates arising in the winter or early spring. The signs and symptoms of **tonsillitis** and **pharyngitis** vary from mild to intense. Common findings include sudden onset of sore throat, temperature of 101° to 104° F, dysphagia, tonsillar hyperplasia, redness of the oropharynx and tonsils, palatal petechiae, cervical lymphadenopathy, and a yellowish tonsillar exudate that may be patchy or confluent (Fig. 5-4). Other occasional findings include a "beefy" red and swollen uvula, excoriated nares, and a scarlatiniform rash (see next topic). Systemic symptoms, such as headache, malaise, anorexia, abdominal pain, and vomiting, may be noted, especially in younger children. Conjunctivitis, coryza (rhinorrhea), cough, hoarseness, discrete ulcerative lesions, anterior stomatitis, absence of fever, a viral exanthem, and diarrhea typically are associated with the viral infections and normally are not present in streptococcal pharyngotonsillitis.

Diagnosis

Although the vast majority of pharyngitis cases are caused by a viral infection, reviews have shown that about 70% of adults in the United States receive antibiotic therapy. In an attempt to minimize overuse, antibiotics should not be prescribed without confirmation of bacterial infection. Except for very rare infections, such as *Corynebacterium diphtheriae* (see page 168) and *Neisseria gonorrhoeae* (see page 174), antibiotics are of no benefit for acute pharyngitis except for those related to group A streptococci.

Patients exhibiting features strongly suggestive of a viral infection (see previous section) should not receive antibiotic

therapy or microbiologic testing for streptococcal infection. Because the clinical features of streptococcal pharyngitis overlap those of viral origin, the diagnosis cannot be based solely on clinical features; however, laboratory testing of all patients with sore throat cannot be justified. Diagnostic testing is recommended only for those patients with clinical and epidemiologic findings that suggest streptococcal infection or for those in close contact with a well-documented case. Although less sensitive than throat culture, rapid antigen detection testing provides quick results and exhibits good sensitivity and specificity. If negative results are obtained in children, then confirmatory throat cultures should be performed.

Treatment and Prognosis

Streptococcal pharyngitis usually is self-limited and resolves spontaneously within 3 to 4 days after onset of symptoms. In addition to reducing the localized morbidity of the infection, including the possibility of peritonsillar abscess formation, the main goal of therapy is to prevent development of systemic complications, such as acute rheumatic fever and acute glomerulonephritis. Initiation of appropriate therapy within the first 9 days after development of the pharyngitis prevents rheumatic fever. Patients are considered noncontagious 24 hours after initiation of appropriate antibiotic therapy.

The oral antibiotic of choice for group A streptococci is either penicillin V or amoxicillin. Other choices for penicillin-allergic patients include azithromycin, clindamycin, cephalosporins (such as, cefadroxil or cephalexin), and macrolides (such as, erythromycin or clarithromycin).

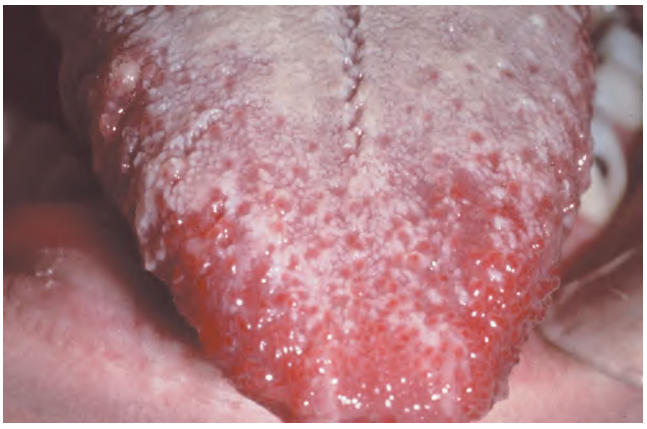
◆ SCARLET FEVER (SCARLATINA)

Scarlet fever is a systemic infection produced by group A, β-hemolytic streptococci. The disease begins as a streptococcal tonsillitis with pharyngitis in which the organisms elaborate an erythrogenic toxin that attacks the blood vessels and produces the characteristic skin rash. The condition occurs in susceptible patients who do not have antitoxin antibodies. The incubation period ranges from 1 to 7 days, and the significant clinical findings include fever, enanthem, and exanthem.

Clinical Features

Scarlet fever is most common in children from the ages of 3 to 12 years. The enanthem of the oral mucosa involves the tonsils, pharynx, soft palate, and tongue (see discussion of streptococcal pharyngotonsillitis in previous section). The tonsils, soft palate, and pharynx become erythematous and edematous, and the tonsillar crypts may be filled with a yellowish exudate. In severe cases, the exudates may become confluent and can resemble diphtheria (see page 168).

Scattered petechiae may be seen on the soft palate in up to 10% of affected patients. During the first 2 days, the dorsal surface of the tongue demonstrates a white coating through which only the fungiform papillae can be seen; this has been called **white strawberry tongue** (Fig. 5-5). By the fourth or fifth day, **red strawberry tongue** develops when the white coating desquamates to reveal an erythematous dorsal surface with hyperplastic fungiform papillae.



• **Fig. 5-5 Scarlet Fever.** Dorsal surface of the tongue exhibiting white coating in association with numerous enlarged and erythematous fungiform papillae (white strawberry tongue).

Classically, in untreated cases, fever develops abruptly around the second day. The patient's temperature peaks at approximately 103° F and returns to normal within 6 days. Abdominal pain, headache, malaise, nausea, and vomiting frequently are present. The exanthematous rash develops within the first 2 days and becomes widespread within 24 hours. The classic rash of scarlet fever is distinctive and often is described as a "sunburn with goose pimples." Pinhead punctate areas that are normal in color project through the erythema, giving the skin of the trunk and extremities a sandpaper texture. The rash is more intense in areas of pressure and skin folds. Often, transverse red streaks, known as **Pastia lines,** occur in the skin folds secondary to the capillary fragility in these zones of stress. In contrast, the skin of the face usually is spared or may demonstrate erythematous cheeks with circumoral pallor.

The rash usually clears within 1 week, and then a period of desquamation of the skin occurs. This scaling begins on the face at the end of the first week and spreads to the rest of the skin by the third week, with the extremities being the last affected. The desquamation of the face produces small flakes; the skin of the trunk comes off in thicker, larger flakes. This period of desquamation may last from 3 to 8 weeks.

Diagnosis

Throat culture is the standard for the diagnosis of streptococcal pharyngitis and scarlet fever. Although less sensitive than throat culture, rapid antigen detection testing provides quick results and exhibits good sensitivity and specificity. If negative results are obtained in children, then confirmatory throat cultures should be performed.

Treatment and Prognosis

Treatment of scarlet fever and the associated streptococcal pharyngitis is necessary to prevent the possibility of complications, such as peritonsillar or retropharyngeal abscess, sinusitis, or pneumonia. Late complications are rare and include otitis media, acute rheumatic fever, glomerulonephritis, arthralgia, meningitis, and hepatitis. The oral antibiotic of choice for group A streptococci is either penicillin V or amoxicillin. Other choices for penicillin-allergic patients include azithromycin, clindamycin, cephalosporins (such as, cefadroxil or cephalexin), and macrolides (such as, erythromycin or clarithromycin). Ibuprofen can be used to reduce the fever and relieve the associated discomfort. The fever and symptoms show dramatic improvement within 48 hours after the initiation of treatment. With appropriate therapy, the prognosis is excellent.

◆ TONSILLAR CONCRETIONS AND TONSILLOLITHIASIS

Anatomically, the pharyngeal tonsils demonstrate numerous deep, twisted, and epithelial-lined invaginations. The tonsillar crypts function to increase the surface area for interaction between the immune cells within the lymphoid tissue and the oral environment. These convoluted crypts commonly are filled with desquamated keratin and foreign material with secondary bacterial colonization. The contents of the invaginations often become compacted and form a mass of foul-smelling material known as a **tonsillar concretion.** Occasionally, the condensed necrotic debris and bacteria undergo dystrophic calcification and form a **tonsillolith.** These structures have been shown to contain a living biofilm of densely packed bacteria demonstrating a diversity of rods, cocci, and filamentous organisms embedded within an extracellular matrix.

Clinical and Radiographic Features

Tonsillar concretions and tonsilloliths are not uncommon. The affected tonsil demonstrates one or more enlarged crypts filled with yellow debris that varies in consistency from soft to friable to fully calcified. In contrast to acute tonsillitis, the surrounding tonsillar tissue is not acutely painful, dramatically inflamed, or significantly edematous. Tonsilloliths can develop over a wide age range, from childhood to old age, with a mean patient age in the early 40s. Men are affected twice as frequently as women. These calcifications vary from small clinically insignificant lesions to massive calcifications more than 14 cm in length. Tonsilloliths may be single or multiple, and bilateral cases have been reported.

Although many tonsillar concretions and tonsilloliths are asymptomatic, these calcifications can promote recurrent tonsillar infections and may lead to pain, abscess formation, ulceration, dysphagia, chronic sore throat, irritable cough, or otalgia. Halitosis is a common complaint and not surprising because several of the bacteria within the associated biofilm are known to produce hydrogen sulfide and methyl mercaptan, both of which are associated strongly with oral malodor. Occasionally, patients report a dull ache or a sensation of a foreign object in the throat that is relieved on removal of the tonsillar plug. In patients with large stones, clinical examination often reveals a hard, yellow submucosal mass of the affected tonsil. In older adult patients, large tonsilloliths can be aspirated and produce significant pulmonary complications. Most frequently, tonsilloliths are discovered on panoramic radiographs as radiopaque objects superimposed on the midportion of the mandibular ramus (Fig. 5-6).

Diagnosis

A strong presumptive diagnosis can be made through a combination of the clinical and radiographic features. After detection on a panoramic radiograph, if further diagnostic confirmation of tonsilloliths is deemed necessary, then their presence can be confirmed with computed tomography (CT), magnetic resonance imaging (MRI), or the demonstration of the calculi on removal of the affected tonsil.

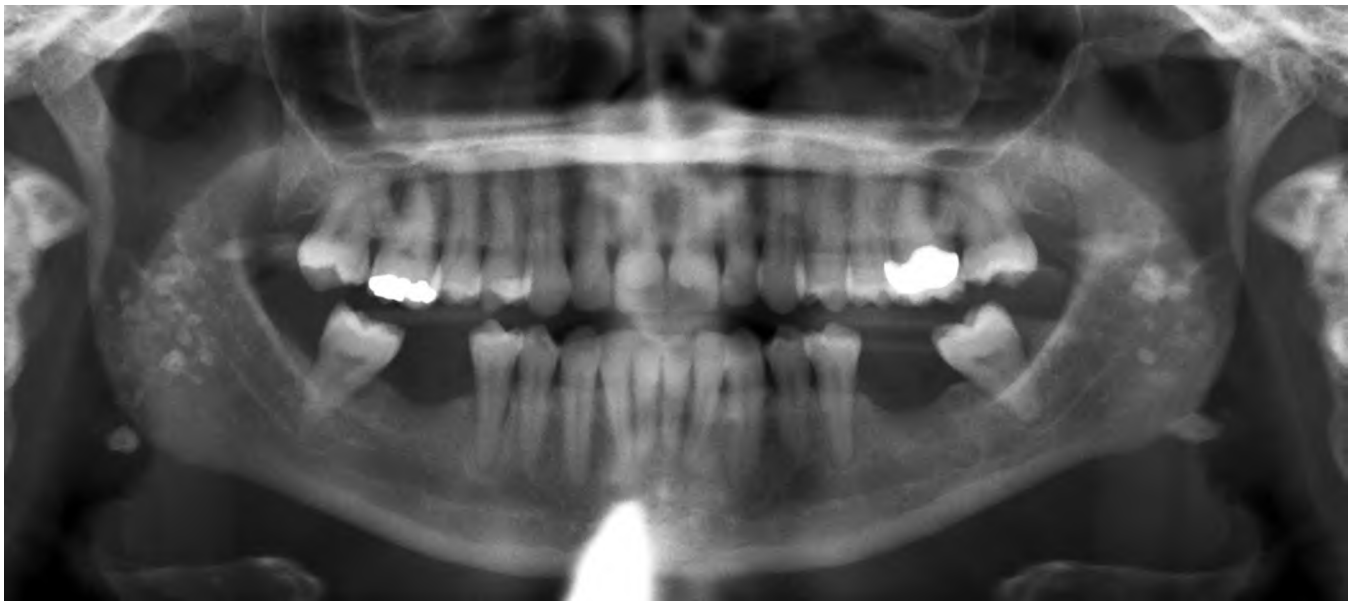
Treatment and Prognosis

Tonsilloliths discovered incidentally during evaluation of a panoramic radiograph often are not treated unless associated with significant tonsillar hyperplasia or clinical symptoms. Affected individuals occasionally try to remove tonsillar concretions with instruments, such as straws, toothpicks, and dental instruments. Such therapy has the potential to damage the surrounding tonsillar tissue and should be discouraged. Patients should be educated to attempt removal by gargling warm salt water or using pulsating jets of water.

Superficial calculi can be enucleated or curetted; deeper tonsilloliths require local excision. Redevelopment of removed concretions is common. Laser or Coblation cryptolysis has been utilized successfully to reduce the extent of the tonsillar invaginations and stop the redevelopment of the concretions. If evidence of associated chronic tonsillitis is seen, then tonsillectomy provides definitive therapy.

◆ DIPHTHERIA

Diphtheria is a life-threatening infection most commonly produced by *Corynebacterium diphtheriae. C. ulcerans* and *C. pseudotuberculosis* are less common causes and usually discovered in individuals exhibiting contact with farm animals or dairy products. The disease initially was described in 1826, and *C. diphtheriae* (also termed *Klebs-Löffler bacillus*) was discovered by Klebs in 1883 and isolated in pure culture by Löffler in 1884. Humans are the sole reservoir, and the infection is acquired through contact with an infected person or carrier. The bacterium produces a lethal exotoxin that causes tissue necrosis, thereby providing



• **Fig. 5-6 Tonsilloliths.** Cluster of radiopacities noted bilaterally in the midportion of the ascending ramus. (Courtesy of Dr. Kim Nichols.)

nutrients for further growth and leading to peripheral spread. The first effective antitoxin was discovered by the German physician, Emil von Behring, who was awarded the first Nobel Prize in medicine for this work. The antitoxin has been available since 1913, and immunization has been widespread in North America since 1922.

Widespread vaccination led to a dramatically decreased prevalence of the infection until the 1990s when collapse of the Soviet Union produced inconsistent vaccination and localized outbreaks. The epidemic began in Moscow and spread to involve all of the newly independent states of the former Soviet Union. During this outbreak, more than 150,000 cases were reported with approximately 4500 deaths. The process finally was controlled by administration of vaccine to all children, adolescents, and adults (regardless of immunization histories).

In addition to this epidemic, infections may occur in people who are immunosuppressed or who have failed to receive booster injections as required. Isolated outbreaks still are reported in the urban poor and Native American populations of North America. Occasional reports from industrialized nations continue to document individuals who have returned home after contracting the infection while visiting a developing country.

Clinical Features

The signs and symptoms of diphtheria arise 1 to 5 days after exposure to the organism. The initial systemic symptoms, which include low-grade fever, headache, malaise, anorexia, sore throat, and vomiting, arise gradually and may be mild. Although skin wounds may be involved, the infection predominantly affects mucosal surfaces and may produce exudates of the nasal, tonsillar, pharyngeal, laryngotracheal, conjunctival, or genital areas. Involvement of the nasal cavity often is accompanied with prolonged mucoid or hemorrhagic discharge. The oropharyngeal exudate begins on one or both tonsils as a patchy, yellow-white, thin film that thickens to form an adherent gray covering. With time, the membrane may develop patches of green or black necrosis. The superficial epithelium is an integral portion of this exudate, and attempts at removal are difficult and may result in bleeding. The covering may continue to involve the entire soft palate, uvula, larynx, or trachea, resulting in stridor and respiratory difficulties. Palatal perforation has rarely been reported. Rarely, the lesions have been isolated to the oral cavity.

The severity of the infection correlates with the spread of the membrane. Local obstruction of the airway can be lethal. Involvement of the tonsils leads to significant cervical lymphadenopathy, which often is associated with an edematous neck enlargement known as *bull neck.* Toxin-related paralysis may affect oculomotor, facial, pharyngeal, diaphragmatic, and intercostal muscles. The soft palatal paralysis can lead to nasal regurgitation during swallowing. Oral or nasal involvement has been reported to spread to the adjacent skin of the face and lips.

Cutaneous diphtheria can occur anywhere on the body and is characterized by chronic skin ulcers that frequently are associated with infected insect bites and also may harbor other pathogens, such as *S. aureus* or *S. pyogenes.* These skin lesions can arise even in vaccinated patients and typically are not associated with systemic toxic manifestations. When contracted by travelers from developed nations, the diagnosis often is delayed because of the nonspecific clinical presentation and a low index of suspicion. The cutaneous lesions represent an important reservoir of infection and can lead to more typical and lethal diphtheria in unprotected contacts.

Although bacteremia is rare, circulating toxin can result in systemic complications, such as myocarditis, neuropathy,

thrombocytopenia, proteinuria, and renal failure. Myocarditis and neurologic difficulties are seen most frequently and usually are discovered in patients with severe nasopharyngeal diphtheria. Myocarditis may exhibit as progressive weakness and dyspnea or lead to acute congestive heart failure. Neuropathy is not uncommon in patients with severe diphtheria, and palatal paralysis is the most commonly seen manifestation. A peripheral polyneuritis resembling Guillain-Barré syndrome also may occur.

Diagnosis

Although the clinical presentation can be distinctive in severe cases, laboratory confirmation should be sought in all instances. Although culture remains the diagnostic gold standard, a polymerase chain reaction (PCR) analysis has become available and has reduced the time required to confirm the diagnosis. Except in the midst of an epidemic, the diagnosis can be difficult due to the rarity of the infection and the inexperience of many physicians with the disease.

Treatment and Prognosis

Treatment of the patient with diphtheria should be initiated at the time of the clinical diagnosis and should not be delayed until the results of the culture are received. Antitoxin should be administered in combination with antibiotics to prevent further toxin production, to stop the local infection, and to prevent transmission. Erythromycin, procaine penicillin, or intravenous (IV) penicillin may be used. Most patients are no longer infectious after 4 days of antibiotic therapy, but some may retain vital organisms. The patient is not considered to be cured until three consecutive negative culture specimens are obtained.

Because the antitoxin neutralizes only circulating toxin that is not bound to tissue, prompt administration is critical. This factor stresses the need for maintaining local stocks that have not reached their expiration date.

Before the development of the antitoxin, the mortality rate approached 50%, usually from cardiac or neurologic complications. The current mortality rate is less than 5%, but the outcome is unpredictable. Development of myocarditis is an important predictor of mortality.

Deaths still occur in the United States because of delays in therapy secondary to lack of suspicion. With worldwide travel and visitors from across the globe, prevention is paramount. Even in those vaccinated as children, it must be remembered that a booster inoculation is required every 10 years. Currently, the inoculation has been combined into the *Tdap vaccine* that includes tetanus, diphtheria, and pertussis.

◆ SYPHILIS (LUES)

Syphilis is a worldwide chronic infection produced by *Treponema pallidum*. The organism is extremely vulnerable to drying; therefore, the primary modes of transmission are sexual contact or from mother to fetus. Humans are the only proven natural host for syphilis.

After the advent of penicillin therapy in the 1940s, the prevalence of syphilis slowly decreased for many years but often demonstrated peaks and troughs associated with sexual activity during that era. A peak occurred during the "sexual revolution" of the 1960s, but fear of acquired immunodeficiency syndrome (AIDS) in 2000 led to the fewest reported cases of primary and secondary syphilis since reporting began in 1941. As more effective therapy for AIDS has been developed, sexual activity has changed once again with an increasing prevalence of sexually transmitted diseases being reported, primarily as a result of increases among men who have sex with men (MSM).

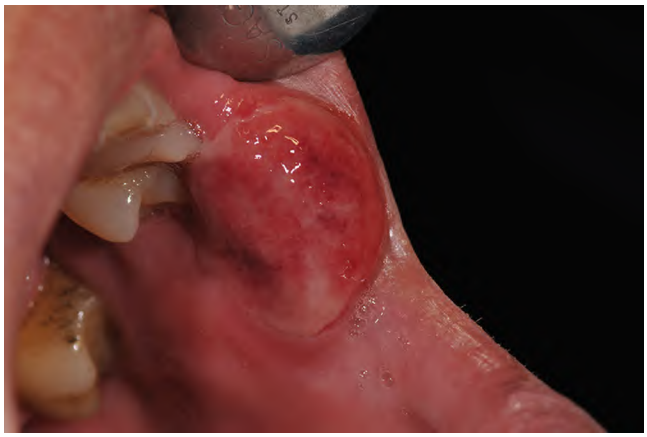
Oral sex is thought to have played an increasingly important contribution to the recent surge in a number of sexually transmitted diseases in MSM. Because the risk of HIV transmission through oral sex is lower than the rate associated with vaginal or anal sex, many falsely believed that unprotected oral sex was a safe or no-risk sexual practice and represented a good replacement for other higher-risk behaviors.

In patients with syphilis, the infection undergoes a characteristic evolution that classically proceeds through three stages. A syphilitic patient is highly infectious only during the first two stages, but pregnant women also may transmit the infection to the fetus during the latent stage. Maternal transmission during the first two stages of infection almost always results in miscarriage, stillbirth, or an infant with congenital malformations. The longer the mother has had the infection, the less the chance of fetal infection. Infection of the fetus may occur at any time during pregnancy, but the stigmata do not begin to develop until after the fourth month of gestation. The clinical changes secondary to the fetal infection are known as **congenital syphilis.** Oral syphilitic lesions are uncommon but may occur in any stage. Due to the rarity of oral lesions and the nonspecific microscopic pattern, appropriate histopathologic diagnosis easily can be missed by pathologists inexperienced with the pathosis.

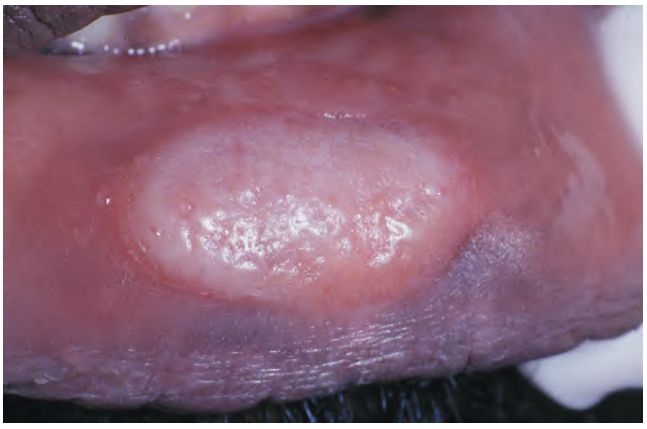
Clinical Features

Primary Syphilis

Primary syphilis is characterized by the **chancre** that develops at the site of inoculation, becoming clinically evident 3 to 90 days after the initial exposure. Most chancres are solitary and begin as papular lesions that develop a central ulceration. Approximately 85% arise in the genital areas, whereas 10% are anal, 4% are oral, and the remaining 1% is discovered in other extragenital locations. Oral lesions are seen most commonly on the lip, but other sites include the buccal mucosa, tongue, palate, gingiva, and tonsils (Fig. 5-7). The upper lip is affected more frequently in males, whereas lower lip involvement is predominant in females. Some believe this selective labial distribution may reflect the surfaces most actively involved during fellatio and cunnilingus. The oral lesion appears as a painless, clean-based



• **Fig. 5-7 Chancre of Primary Syphilis.** Erythematous and ulcerated mass of the right anterior buccal mucosa. (Courtesy of Dr. Benjamin Martinez.)



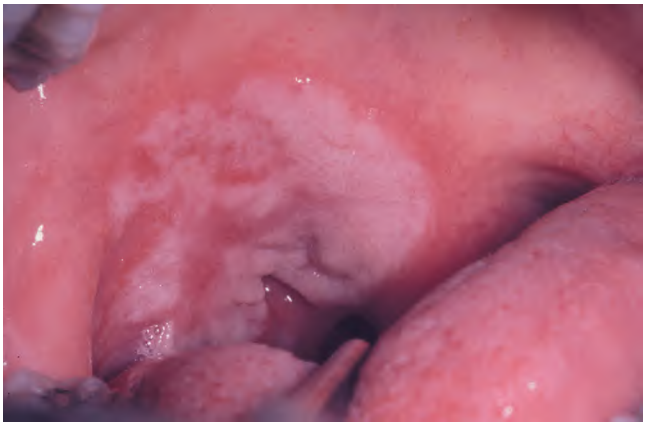
• **Fig. 5-8 Mucous Patch of Secondary Syphilis.** Circumscribed white plaque on the lower labial mucosa. (Courtesy of Dr. Pete Edmonds.)

ulceration or, rarely, as a vascular proliferation resembling a pyogenic granuloma. Regional lymphadenopathy, which may be bilateral, is seen in most patients. At this time, the organism is spreading systemically through the lymphatic channels, setting the stage for future progression. If untreated, then the initial lesion heals within 3 to 8 weeks.

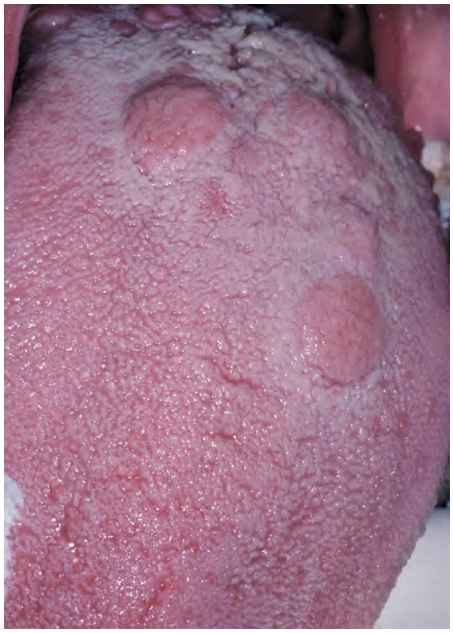
Secondary Syphilis

The next stage is known as *secondary* (disseminated) *syphilis* and is discovered clinically 4 to 10 weeks after the initial infection. The lesions of secondary syphilis may arise before the primary lesion has resolved completely. During secondary syphilis, systemic symptoms often arise. The most common are painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever, and musculoskeletal pain. A consistent sign is a diffuse, painless, maculopapular cutaneous rash, which is widespread and can even affect the palmar and plantar areas. The rash also may involve the oral cavity and appear as red, maculopapular areas. Although the skin rash may result in areas of scarring and hyperpigmentation or hypopigmentation, it heals without scarring in the vast majority of patients.

In addition, roughly 30% of patients have focal areas of intense exocytosis and spongiosis of the oral mucosa, leading to zones of sensitive whitish mucosa known as **mucous patches** (Figs. 5-8 and 5-9). Occasionally, several adjacent patches can fuse and form a serpentine or snail-track pattern. Subsequently, superficial epithelial necrosis may occur, leading to sloughing and exposure of the underlying raw connective tissue. These may appear on any mucosal surface but are found commonly on the tongue, lip, buccal mucosa, and palate. Elevated mucous patches also may be centered over the crease of the oral commissure and have been termed **split papules.** Occasionally, papillary lesions that may resemble viral papillomas arise during this time and are known as **condylomata lata.** Although these lesions typically occur in the genital or anal regions, rare oral examples occur (Fig. 5-10). In contrast to the isolated chancre noted



• **Fig. 5-9 Mucous Patch of Secondary Syphilis.** Irregular thickened white plaque of the right soft palate.



• **Fig. 5-10 Condyloma Lata.** Multiple indurated and slightly papillary nodules on the dorsal tongue. (Courtesy of Dr. Karen Novak.)

in the primary stage, multiple lesions are typical of secondary syphilis. Spontaneous resolution usually occurs within 3 to 12 weeks; however, relapses may occur during the next year.

Tertiary Syphilis

After the second stage, patients enter a period in which they are free of lesions and symptoms, known as **latent syphilis.** This period of latency may last from 1 to 30 years; then the third stage known as *tertiary syphilis* develops in approximately 30% of affected individuals. This stage includes the most serious of all complications. The vascular system can be affected significantly through the effects of the earlier arteritis. Aneurysm of the ascending aorta, left ventricular hypertrophy, aortic regurgitation, and congestive heart failure may occur. Involvement of the central nervous system (CNS) may result in tabes dorsalis, general paralysis, psychosis, dementia, paresis, and death. Ocular lesions such as iritis, choroidoretinitis, and Argyll Robertson pupil may occur. Argyll Robertson pupils constrict upon focusing, but they fail to respond to bright light (nicknamed "prostitute's pupil" because they accommodate but do not react). Less significant, but more characteristic, are scattered foci of granulomatous inflammation, which may affect the skin, mucosa, soft tissue, bones, and internal organs. This active site of granulomatous inflammation, known as a **gumma,** appears as an indurated, nodular, or ulcerated lesion that may produce extensive tissue destruction. Intraoral lesions usually affect the palate or tongue. When the palate is involved, the ulceration frequently perforates through to the nasal cavity (Fig. 5-11). The tongue may be involved diffusely with gummata and appear large, lobulated, and irregularly shaped. This lobulated pattern is termed **interstitial glossitis** and is thought to be the result of contracture of the lingual musculature after healing of gummas. Diffuse atrophy and loss of the dorsal tongue papillae produce a condition called **luetic glossitis.** In the past, this form of atrophic glossitis was thought to be precancerous, but several more recent publications dispute this concept.

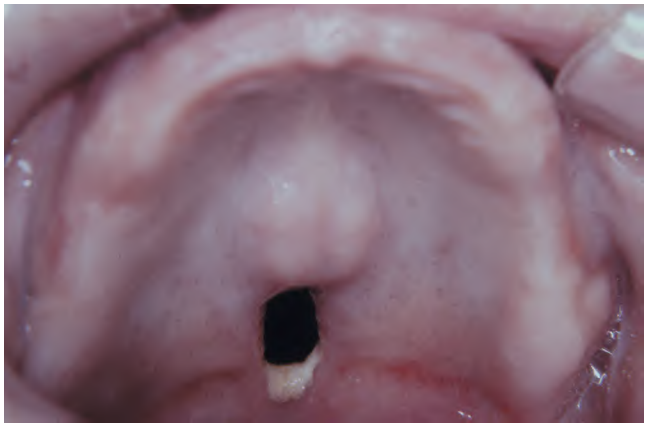


Fig. 5-11 Tertiary Syphilis. Perforation of the hard palate. (Courtesy of Dr. George Blozis.)

Congenital Syphilis

In 1858, Sir Jonathan Hutchinson described the changes found in congenital syphilis and defined the following three pathognomonic diagnostic features, known as **Hutchinson triad:**

- Hutchinson teeth
- Ocular interstitial keratitis
- Eighth nerve deafness

Like many diagnostic triads, few patients exhibit all three features. In addition to Hutchinson triad, a number of other alterations may be seen, such as saddle-nose deformity, high-arched palate, frontal bossing, hydrocephalus, intellectual disability, gummas, and neurosyphilis. Table 5-1 delineates the prevalence rates of the stigmata of congenital syphilis in a cohort of affected patients.

Infants infected with syphilis can display signs within 2 to 3 weeks of birth. These early findings include growth impairment, fever, jaundice, anemia, hepatosplenomegaly, rhinitis, rhagades (circumoral radial skin fissures), and desquamative maculopapular, ulcerative, or vesiculobullous skin eruptions. Untreated infants who survive often develop tertiary syphilis with damage to the bones, teeth, eyes, ears,

TABLE 5-1 Stigmata of Congenital Syphilis

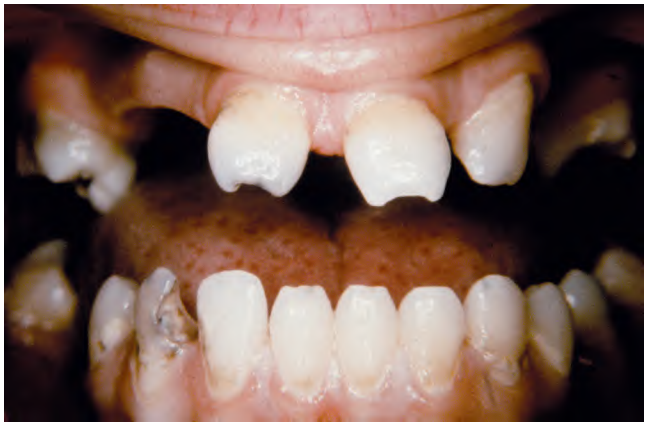
Stigmata of Congenital Syphilis*	Number of Patients	Percentage Affected
Frontal bossing	235	86.7
Short maxilla	227	83.8
High-arched palate	207	76.4
Saddle nose	199	73.4
Mulberry molars	176	64.9
Hutchinson incisors	171	63.1
Higoumenaki sign†	107	39.4
Relative prognathism of mandible	70	25.8
Interstitial keratitis	24	8.8
Rhagades‡	19	7.0
Saber shin§	11	4.1
Eighth nerve deafness	9	3.3
Scaphoid scapulae‖	2	0.7
Clutton joint¶	1	0.3

Modified from Fiumara NJ, Lessel S: Manifestations of late congenital syphilis: an analysis of 271 patients, *Arch Dermatol* 102:78-83, 1970.
*In a cohort of 271 patients
†Enlargement of clavicle adjacent to the sternum
‡Premature perioral fissuring
§Anterior bowing of tibia as a result of periostitis
‖Concavity of vertebral border of the scapulae
¶Painless synovitis and enlargement of joints, usually the knee

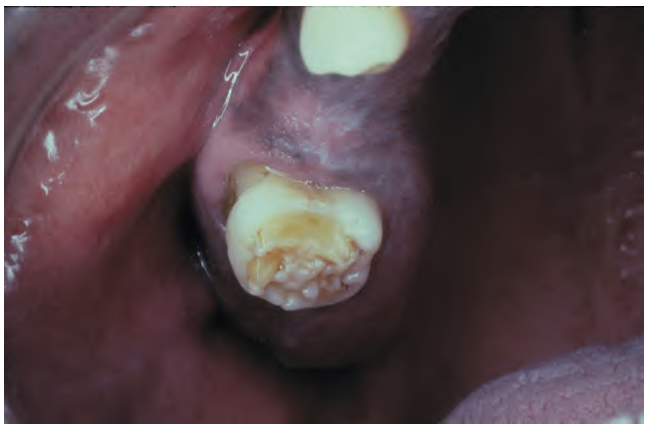
and brain. It is these findings that were described well by Hutchinson.

The infection alters the formation of both the anterior teeth **(Hutchinson incisors)** and the posterior dentition **(mulberry molars, Fournier molars, Moon molars).** Hutchinson incisors exhibit their greatest mesiodistal width in the middle third of the crown. The incisal third tapers to the incisal edge, and the resulting tooth resembles a straight-edge screwdriver (Fig. 5-12). The incisal edge often exhibits a central hypoplastic notch. Mulberry molars taper toward the occlusal surface with a constricted grinding surface. The occlusal anatomy is abnormal, with numerous disorganized globular projections that resemble the surface of a mulberry (Fig. 5-13).

Worldwide, the prevalence of congenital syphilis has increased fourfold to fivefold over the last 10 years. The World Health Organization (WHO) has stated that the number of congenital syphilis cases worldwide now equals the prevalence of neonatal AIDS, but this problem has received very little attention globally.



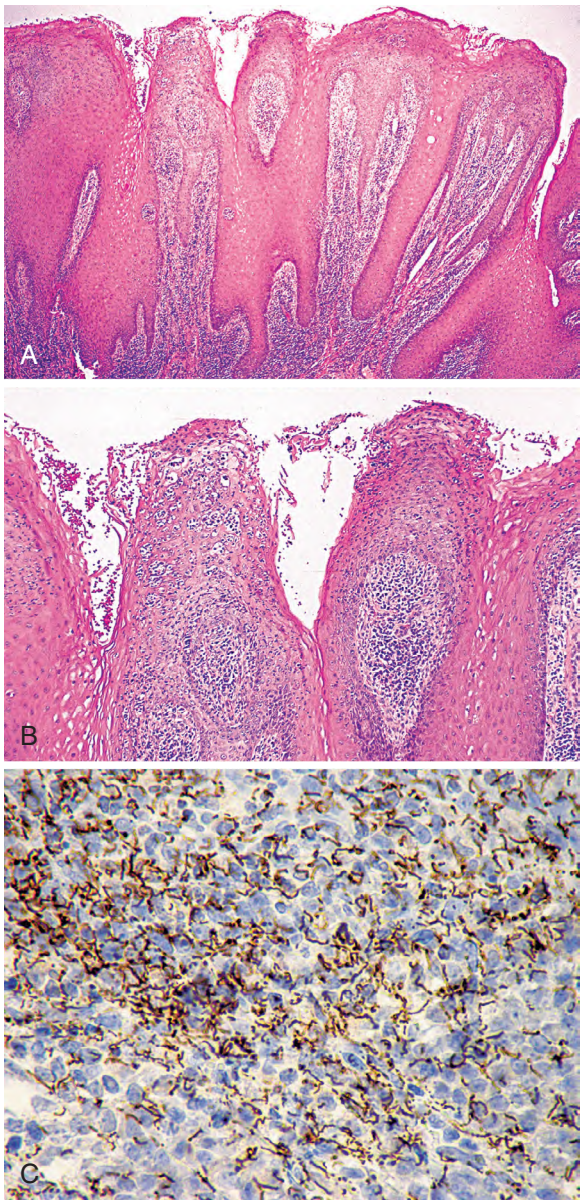
• **Fig. 5-12 Hutchinson Incisors of Congenital Syphilis.** Dentition exhibiting crowns tapering toward the incisal edges. (From Halstead CL, Blozis GG, Drinnan AJ, et al: *Physical evaluation of the dental patient,* St Louis, 1982, Mosby.)



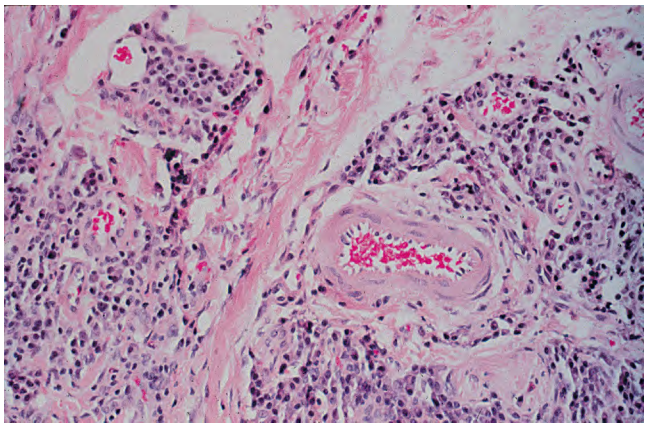
• **Fig. 5-13 Mulberry Molar of Congenital Syphilis.** Maxillary molar demonstrating occlusal surface with numerous globular projections.

Histopathologic Features

The histopathologic picture of the oral lesions in the syphilitic patient is not specific. During the first two stages, the pattern is similar. The surface epithelium is ulcerated in primary lesions and may be ulcerated or hyperplastic in the secondary stage. Extensive exocytosis typically is noted and represents a major clue to the diagnosis (Fig. 5-14). The underlying lamina propria exhibits an intense chronic inflammatory cellular infiltrate composed predominantly of lymphocytes and plasma cells, which is noted primarily in



• **Fig. 5-14 Secondary Syphilis, Condyloma Lata. A,** Low-power photomicrograph of biopsy from patient in Fig. 5-10, which shows papillary epithelial hyperplasia and a heavy plasmacytic infiltrate in the connective tissue. **B,** High-power view showing intense exocytosis of neutrophils into the epithelium. **C,** Immunoperoxidase reaction for *Treponema pallidum* demonstrating numerous spirochetes in the epithelium.



• **Fig. 5-15 Primary Syphilis.** A chronic perivascular inflammatory infiltrate of plasma cells and lymphocytes. (Courtesy of Dr. John Metcalf.)

the superficial stroma and around deeper vascular channels (Fig. 5-15). Although the presence of plasma cells is commonplace within ulcerations and areas of oral mucositis, the combination of heavy exocytosis and an underlying dense lymphoplasmacytic infiltrate often raises the index of suspicion to a level that supports search for the organism. The use of special silver impregnation techniques, such as Warthin-Starry or Steiner stains, or immunoperoxidase reactions directed against the organism often show scattered corkscrew-like spirochetal organisms that frequently are found most easily within the surface epithelium and at the interface between the epithelium and the superficial stroma (see Fig. 5-14, *C*). The organism also can be detected in tissue through direct fluorescent antibody or nucleic acid amplification testing.

Oral tertiary lesions typically exhibit surface ulceration, with peripheral pseudoepitheliomatous hyperplasia. The underlying inflammatory infiltrate usually demonstrates foci of granulomatous inflammation with well-circumscribed collections of histiocytes and multinucleated giant cells. Even with special stains, the organisms are hard to demonstrate in the third stage; researchers believe the inflammatory response is an immune reaction, rather than a direct response to *T. pallidum.*

Diagnosis

The diagnosis of syphilis can be confirmed by demonstrating the spiral organism by biopsy or dark-field examination of a smear of an active lesion. False-positive results in smears are possible in the oral cavity because of morphologically similar oral inhabitants, such as *Treponema microdentium, T. macrodentium,* and *T. mucosum.* Demonstration of the organism on a smear or in biopsy material should be confirmed through the use of specific immunofluorescent antibodies, nucleic acid amplification testing, or serologic evaluation.

Several nonspecific and not highly sensitive serologic screening tests for syphilis are available. These include the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR). After the first 3 weeks of infection, the screening tests are strongly positive throughout the first two stages. After the development of latency, the positivity generally subsides with time. As part of appropriate prenatal care, all pregnant women should receive one of the nonspecific screening tests. Because these tests typically are negative in the early primary stage and also may be falsely negative in immunosuppressed patients (such as, AIDS), tissue identification of the organism is critical in many patients.

Specific and highly sensitive serologic tests for syphilis also are available. These include the fluorescent treponemal antibody absorption (FTA-ABS), *T. pallidum* hemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA), and microhemagglutination assay for antibody to *T. pallidum* (MHA-TP). These test results remain positive for life. This lifelong persistence of positivity limits their usefulness in the diagnosis of a second incidence of infection. Therefore, in cases of possible reinfection, the organisms should be demonstrated within the tissue or exudates.

Treatment and Prognosis

The treatment for syphilis necessitates an individual evaluation and a customized therapeutic approach. The treatment of choice is penicillin. The dose and administration schedules vary according to the stage, neurologic involvement, and immune status. For primary, secondary, or early latent syphilis, a single dose of parenteral long-acting benzathine penicillin G is given. For late latent or tertiary syphilis, intramuscular penicillin is administered weekly for 3 weeks. For the patient with a true penicillin allergy, doxycycline is second-line therapy, although tetracycline, erythromycin, and ceftriaxone also have demonstrated antitreponemal activity.

Even in patients who obtain a clinical and serologic "cure" with penicillin, it must be remembered that *T. pallidum* can escape the lethal effects of the antibiotic when the organism is located within the confines of lymph nodes or the CNS. Therefore, antibiotic therapy may not always result in a total cure in patients with neurologic involvement but may arrest only the clinical presentations of the infection. Patients with immunosuppression, such as those with AIDS, may not respond appropriately to standard antibiotic regimens, and numerous reports have documented a continuation to neurosyphilis despite seemingly appropriate single-dose therapy.

◆ GONORRHEA

Gonorrhea, a sexually transmitted disease that is produced by *Neisseria gonorrhoeae,* represents the most common reportable bacterial infection in the United States with an estimated 700,000 to 800,000 persons infected each year. The disease is epidemic, especially in urban areas;

worldwide, millions of people are infected each year. The rate in the United States remains the highest of any industrialized country, and certain segments of the population, such as those with a low socioeconomic or education level, injecting drug users, prostitutes, homosexual men, and military personnel, remain at high risk. In contrast to many other sexually transmitted diseases, women are affected slightly more frequently than men.

Clinical Features

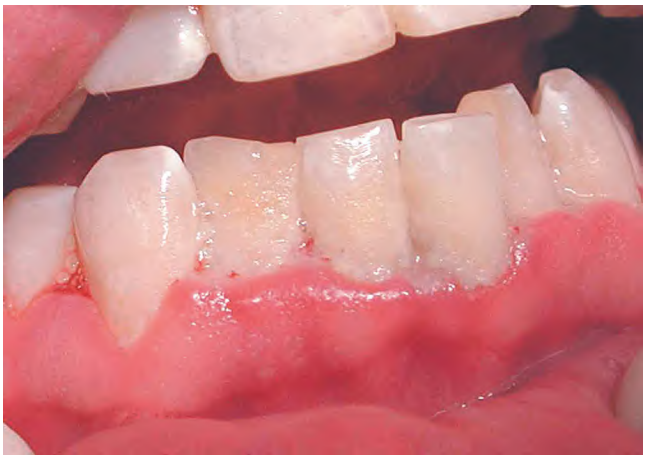
The infection is spread through sexual contact, and most lesions occur in the genital areas. Indirect infection is rare because the organism is sensitive to drying and cannot penetrate intact stratified squamous epithelium. The incubation period is typically 2 to 5 days. Affected areas often demonstrate significant purulent discharge, but approximately 10% of men and up to 80% of women who contract gonorrhea are asymptomatic.

In men, the most frequent site of infection is the urethra, resulting in purulent discharge and dysuria. Less common primary sites include the anorectal and pharyngeal areas. The cervix is the primary site of involvement in women, and the chief complaints are increased vaginal discharge, intermenstrual bleeding, genital itching, and dysuria. The organism may ascend to involve the uterus and ovarian tubes leading to **pelvic inflammatory disease (PID)** with long-term complications that include ectopic pregnancies or infertility from tubal obstruction.

Between 0.5% and 3.0% of untreated patients with gonorrhea will have disseminated gonococcal infections from systemic bacteremia. The most common signs of dissemination are myalgia, arthralgia, polyarthritis, and dermatitis. In 75% of patients with disseminated disease, a characteristic skin rash develops. The dermatologic lesions consist of discrete papules and pustules that often exhibit a hemorrhagic component and occur primarily on the extremities. Less common alterations secondary to gonococcal septicemia include fever, endocarditis, pericarditis, meningitis, and oral mucosal lesions of the soft palate and oropharynx, which are similar to aphthous ulcerations.

Most cases of oral gonorrhea appear to be a result of fellatio, although oropharyngeal gonorrhea may be the result of gonococcal septicemia, kissing, or cunnilingus. The majority of cases are reported in women or homosexual men, with the most common sites being the pharynx, tonsils, and uvula. Although pharyngeal gonorrhea usually is asymptomatic, a mild-to-moderate sore throat may occur and be accompanied by nonspecific, diffuse oropharyngeal erythema. Involved tonsils typically demonstrate edema and erythema, often with scattered, small punctate pustules.

Although most cases of pharyngeal infection resolve spontaneously without adverse sequelae, new findings suggest the infection has important implications, which strongly support the need for treatment to reduce the potential for spreading the infection. Research also has suggested that pharyngeal involvement may play an important role in the development of antibiotic resistance. Several studies have shown that *N. gonorrhoeae* may undergo mutation by acquiring genetic material from other *Neisseria* species that frequent the throat. This has led many to recommend periodic pharyngeal screening for high-risk groups, such as men who have sex with men (MSM) and commercial sex workers.



• **Fig. 5-16 Gonorrhea.** Necrosis, purulence, and hemorrhage of the anterior mandibular gingiva. (From Williams LN: The risks of oral-genital contact: a case report, *Gen Dent* 50:282-284, 2002. Published with permission by the Academy of General Dentistry. Copyright 2002 by the American Academy of General Dentistry. All rights reserved.)

Rarely, lesions have been reported in the anterior portion of the oral cavity, with areas of infection appearing erythematous, pustular, erosive, or ulcerated. Occasionally, the infection may simulate **necrotizing ulcerative gingivitis (NUG),** but some clinicians have reported that the typical fetor oris is absent, providing an important clue to the actual cause (Fig. 5-16). Submandibular or cervical lymphadenopathy may be present.

During birth, infection of an infant's eyes can occur from an infected mother who may be asymptomatic. This infection is called **gonococcal ophthalmia neonatorum** and can rapidly cause perforation of the globe of the eye and blindness. Common signs of infection include significant conjunctivitis and a mucopurulent discharge from the eye.

Diagnosis

In males with a urethral discharge, a Gram stain of the purulent material can be used to demonstrate gram-negative diplococci within the neutrophils; additional testing usually is not indicated. Although Gram stains may be beneficial in women, confirmation of the diagnosis is recommended by culture of endocervical swabs if conditions are adequate to maintain viability of the organisms. A number of other diagnostic studies have been available for many years. Nucleic acid amplification tests (NAATs) amplify and detect *N. gonorrhoeae*–specific DNA or RNA sequences and are recommended for the diagnosis when conditions are not adequate to maintain the viability of the organisms. In spite of the

availability of NAATs, culture remains the preferred diagnostic method for diagnosis of oropharyngeal infections.

Treatment and Prognosis

Treatment has been complicated due to the development of antibiotic resistance by *N. gonorrhoeae*. Only one class of antibiotics, the cephalosporins, is thought sufficiently efficacious by the Centers for Disease Control and Prevention (CDC). In addition, coinfection by *Chlamydia trachomatis* is common, leading to a suggested therapy that is effective against both organisms. The currently recommended regimen is intramuscular ceftriaxone combined with oral azithromycin or doxycycline. Rescreening is recommended 1 to 2 months after therapy. The most common cause for treatment failure is reexposure to infected partners, who often are asymptomatic; therefore, the treatment of all recent sexual partners is recommended. Truly resistant infections should be cultured with antimicrobial testing and selection of an appropriate alternate antibiotic. Prophylactic ophthalmic erythromycin, tetracycline, or silver nitrate is applied to the newborn's eyes to prevent the occurrence of gonococcal ophthalmia neonatorum.

TUBERCULOSIS

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Worldwide, it is estimated that 2 billion people (one-third of the population) are infected. Each year approximately 8 million additional individuals become infected, with 2 to 3 million deaths annually attributed to TB. Worldwide, the prevalence of the infection declined with the introduction of effective antimicrobials, but in recent years it has demonstrated an increased frequency that appears to be associated with emergence of AIDS and drug-resistant strains. However, in the United States during 2012, the annual incidence declined 6.1%, which was the 20th consecutive year of declining rates. The rate of TB in foreign-born individuals in the US was 11.5 times higher than US-born persons.

Nontuberculous mycobacterial disease can occur from a variety of organisms. Before the tuberculin testing of dairy herds, many cases arose from the consumption of milk infected with *Mycobacterium bovis.* Except for HIV-infected individuals, most other cases of nontuberculous mycobacterial disease appear as localized chronic cervical lymphadenitis in otherwise healthy children. In patients with AIDS (see page 239), *Mycobacterium avium-intracellulare* is a common cause of opportunistic infections.

Infection must be distinguished from active disease. **Primary tuberculosis** occurs in previously unexposed people and almost always involves the lungs. Most infections are the result of direct person-to-person spread through airborne droplets from a patient with active disease. The organism initially elicits a nonspecific, chronic inflammatory reaction. In most individuals, the primary infection results only in a localized, fibrocalcific nodule at the initial site of involvement. However, viable organisms may be present in these nodules and remain dormant for years to life.

Only about 5% to 10% of patients with TB progress from infection to active disease, and an existing state of immunosuppression often is responsible. In rare instances, active TB may ensue directly from the primary infection. However, active disease usually develops later in life from a reactivation of organisms in a previously infected person. This reactivation is typically associated with compromised host defenses and is called **secondary tuberculosis.** Diffuse dissemination through the vascular system may occur and often produces multiple small foci of infection that grossly and radiographically resemble millet seeds, resulting in the nickname, **miliary tuberculosis.** Secondary TB often is associated with immunosuppressive medications, diabetes, old age, poverty, and crowded living conditions. AIDS represents one of the strongest known risk factors for progression from infection to disease.

Clinical and Radiographic Features

Primary TB usually is asymptomatic. Occasionally, fever and pleural effusion may occur.

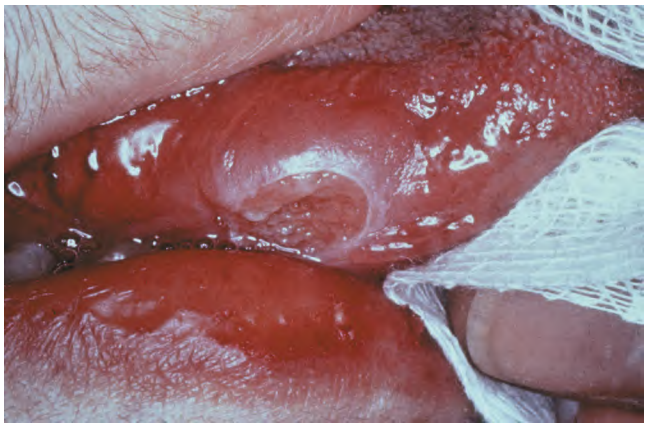
Classically, the lesions of secondary TB are located in the apex of the lungs but may spread to many different sites by expectorated infected material or through the lymphatic or vascular channels. Typically, patients have a low-grade fever, malaise, anorexia, weight loss, and night sweats. With pulmonary progression, a productive cough develops, often with hemoptysis or chest pain. Progressive TB may lead to a wasting syndrome that, in the past, was termed **consumption,** because it appeared that the patient's body was being consumed or destroyed.

Extrapulmonary TB is seen and represents an increasing proportion of the currently diagnosed cases. In patients with AIDS, more than 50% will have extrapulmonary lesions. Any organ system may be involved, including the lymphatic system, skin, skeletal system, CNS, kidneys, and gastrointestinal tract. Involvement of the skin may develop and has been called **lupus vulgaris.**

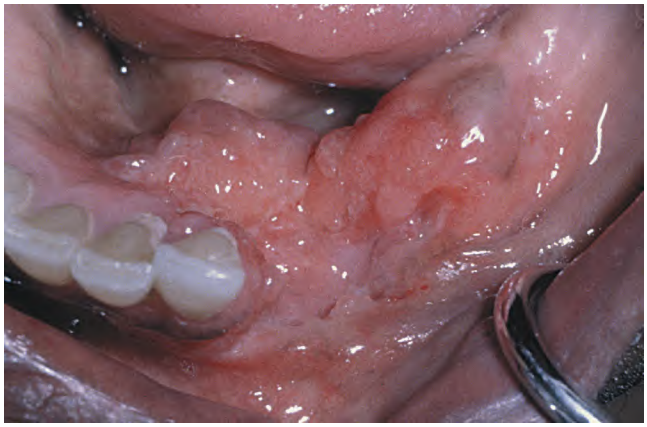
Head and neck involvement may occur. The most common extrapulmonary sites in the head and neck are the cervical lymph nodes followed by the larynx and middle ear. Much less common sites include the nasal cavity, nasopharynx, oral cavity, parotid gland, esophagus, and spine.

Oral lesions of TB are uncommon. The most common presentations for oral involvement are chronic ulcerations or swellings (Fig. 5-17). Less frequent findings include nonhealing extraction sockets, areas of mucosal granularity, or diffuse zones of inflammation (Fig. 5-18). Chronic tongue ulcerations are seen most frequently and followed closely in prevalence by mandibular swellings associated with intrabony involvement. Other affected sites in order of decreasing frequency include the gingiva, lips, buccal mucosa, soft palate, and hard palate.

Often oral ulcerative lesions of TB coexist with palpable lymph nodes. Although this combination most strongly



• **Fig. 5-17 Tuberculosis (TB).** Chronic mucosal ulceration of the ventral surface of the tongue on the right side. (Reprinted with permission from the American Dental Association.)

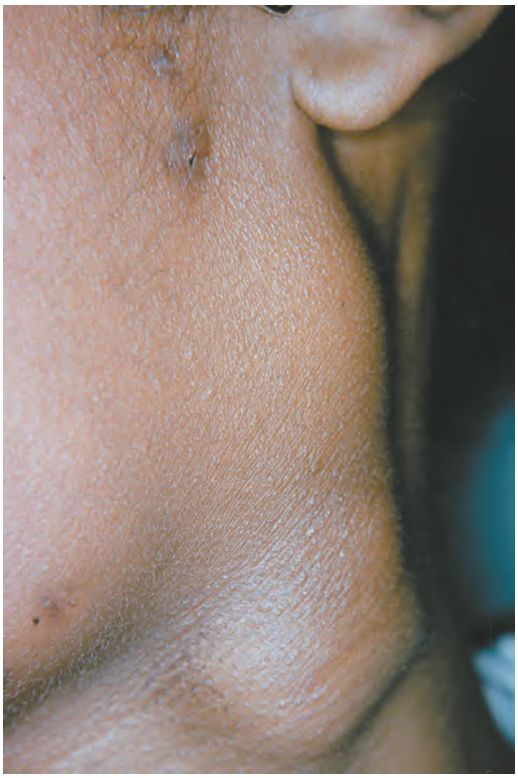


• **Fig. 5-18 Tuberculosis (TB).** Area of granularity and ulceration of the lower alveolar ridge and floor of mouth. (Courtesy of Dr. Brian Blocher.)

suggests squamous cell carcinoma, the possibility of TB also must be considered, especially in younger patients and those who reside in geographic areas with a high prevalence of the infection.

The majority of the oral lesions represent secondary infection from the initial pulmonary foci, occurring most frequently in middle-aged adults. It is unclear whether these lesions develop from hematogenous spread or from exposure to infected sputum. The reported prevalence of clinically evident oral lesions varies from 0.5% to 5.0%. The discovery of pulmonary TB as a result of the investigation of oral lesions occurs but is unusual. Primary oral TB without pulmonary involvement is rare and is more common in children and adolescents.

Nontuberculous mycobacterial infections from contaminated milk currently are rare in the industrialized world because of pasteurization of milk, as well as rapid identification and elimination of infected cows. Drinking contaminated milk can result in a form of mycobacterial infection known as **scrofula.** Scrofula is characterized by enlargement of the oropharyngeal lymphoid tissues and cervical lymph nodes (Fig. 5-19). On occasion, the involved nodes may



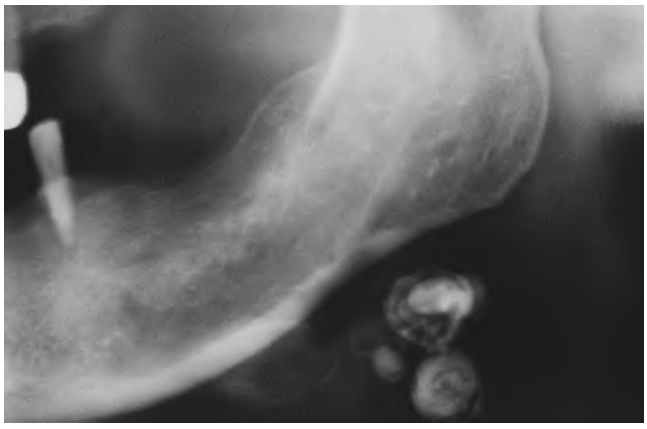
• **Fig. 5-19 Tuberculosis (TB).** Enlargement of numerous cervical lymph nodes. (Courtesy of Dr. George Blozis.)

• **Fig. 5-20 Tuberculosis (TB).** Submandibular fistula secondary to involvement of underlying cervical lymph nodes.

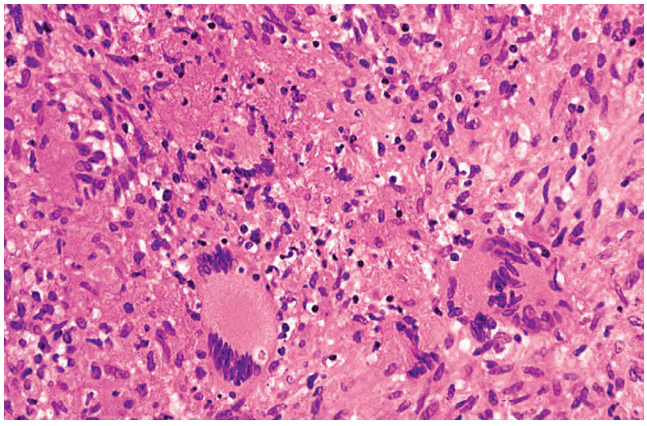
develop significant caseous necrosis and form numerous sinus tracts through the overlying skin (Fig. 5-20). In addition, areas of nodal involvement may radiographically appear as calcified lymph nodes that may be confused with sialoliths (Fig. 5-21). Pulmonary involvement is unusual in patients with scrofula.

Histopathologic Features

The cell-mediated hypersensitivity reaction is responsible for the classic histopathologic presentation of TB. Areas of infection demonstrate the formation of granulomas, which



• **Fig. 5-21 Tuberculosis (TB).** Multiple calcified cervical lymph nodes.

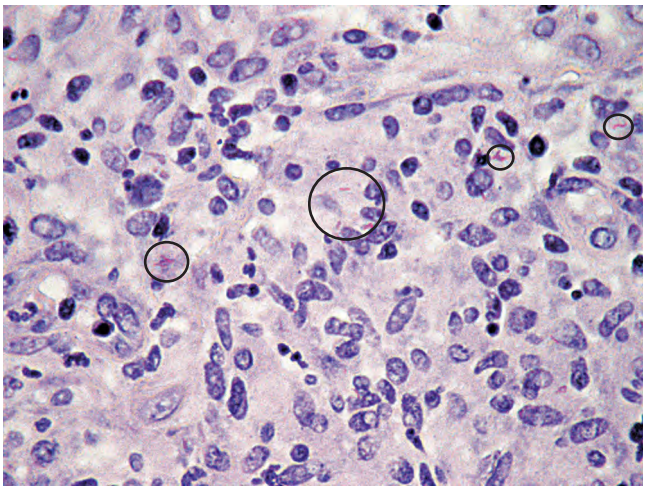


• **Fig. 5-22 Tuberculosis (TB).** Histopathologic presentation of the same lesion depicted in Fig. 5-18. Sheets of histiocytes are intermixed with multinucleated giant cells and areas of necrosis.

are circumscribed collections of epithelioid histiocytes, lymphocytes, and multinucleated giant cells, often with central caseous necrosis (Fig. 5-22). The nuclei of the giant cells frequently are arranged along the periphery of the cell in a horseshoe or ring shape *(Langhans giant cells).* In a person with TB, one of these granulomas is called a **tubercle.** Special stains, such as the Ziehl-Neelsen or other acid-fast stains, are utilized to demonstrate the mycobacteria (Fig. 5-23). A newer technique, fluorescence microscopy of auramine-rhodamine stains, is employed by many institutions in an attempt to increase the ease of finding the organisms. Because of the relative scarcity of the organisms within tissue, the special stains successfully demonstrate the organism in only 27% to 60% of cases. Therefore, a negative result does not completely rule out the possibility of TB.

Diagnosis

Approximately 2 to 4 weeks after initial exposure, a cell-mediated hypersensitivity reaction to tubercular antigens develops. This reaction is the basis for the purified protein derivative (PPD) skin test (i.e., tuberculin skin test), which uses a filtered precipitate of heat-sterilized broth cultures of



• **Fig. 5-23 Tuberculosis (TB).** Acid-fast stain of specimen depicted in Fig. 5-22 exhibiting scattered mycobacterial organisms presenting as small red rods.

M. tuberculosis. Positivity runs as high as 80% in developing nations; only 5% to 10% of the population in the United States is positive. A positive tuberculin skin test result indicates exposure to the organism and does not distinguish infection from active disease. A negative tuberculin skin test result does not totally rule out the possibility of TB. False-negative reactions have been documented in older adults; the immunocompromised; patients with sarcoidosis, measles, or Hodgkin lymphoma; and when the antigen was placed intradermally. The false-negative rate may be as high as 66% in patients with AIDS.

Special mycobacterial stains and culture of infected sputum or tissue must be used to confirm the diagnosis of active disease. Even if detected with special stains, identification of the organism by culture is appropriate. This identification is important because some forms of nontuberculous mycobacteria have a high level of resistance to traditional antituberculous therapy and frequently require surgical excision. Because 4 to 6 weeks may be required to identify the organism in culture, antituberculous therapy often is initiated before definitive classification. PCR also is used to identify *M. tuberculosis* DNA and speeds the diagnosis without the need to await culture results.

Treatment and Prognosis

M. tuberculosis can mutate and develop resistance to single-agent medications. To combat this ability, multiagent therapy is the treatment of choice for an active infection, and treatment usually involves two or more active drugs for several months to years. A frequently used protocol consists of an 8-week course of pyrazinamide, isoniazid, rifampin, and ethambutol, followed by a 16-week course of isoniazid and rifampin. With an alteration of doses and the administration schedule, the response to therapy in patients with AIDS has been good, but relapses and progression of infection have been seen.

A different protocol termed *chemoprophylaxis* is used for patients who have a positive PPD skin test but no signs or symptoms of active disease. Although this situation does not mandate therapy, several investigators have demonstrated the value of therapy, especially in young individuals. **Bacillus Calmette-Guérin (BCG) vaccine** for TB is available to approximately 85% of the global population, but its use is restricted in the United States because of a controversy related to its effectiveness.

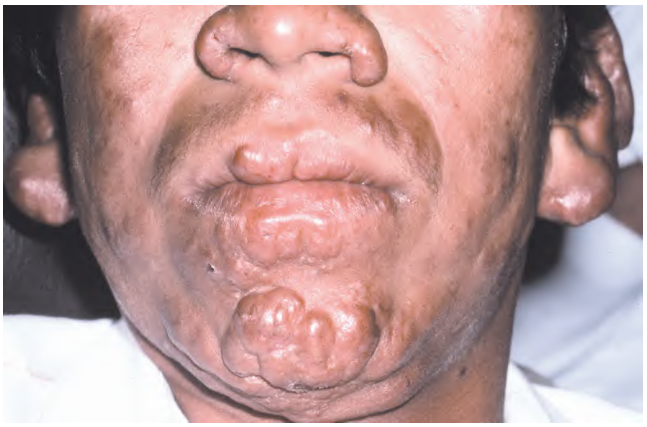
LEPROSY (HANSEN DISEASE)

Leprosy is a chronic infectious disease produced by *Mycobacterium leprae.* Because of worldwide efforts coordinated by the World Health Organization (WHO), a dramatic decrease in the prevalence of leprosy has been seen over the past 15 years. However, leprosy remains a public health problem in many areas of the world. Approximately 80% of all currently reported cases are noted in seven countries: Brazil, India, Indonesia, Madagascar, Myanmar, Nepal, and Nigeria.

The organism has a low infectivity, and exposure rarely results in clinical disease. Small endemic areas of infection are present in Louisiana and Texas, but most patients in the United States have been infected abroad. Many believe that the organism requires a cool host body temperature for survival. Although the exact route of transmission is not known, the high number of organisms in nasal secretions suggests that in some cases the initial site of infection may be the nasal or oropharyngeal mucosa. Although humans are considered the major host, other animals (e.g., armadillo, chimpanzee, and mangabey monkey) may be additional possible reservoirs of infection.

For decades, leprologists have believed the bacillus is highly temperature dependent and produces lesions primarily in cooler parts of the body, such as the skin, nasal cavity, and palate. This concept has been questioned because the organism may be seen in significant numbers at sites of core body temperature, such as the liver and spleen. Recently, one investigator mapped common sites of oral involvement and compared this pattern to a map of the local temperature. This comparison demonstrated that the oral lesions tend to occur more frequently in the areas of the mouth with a lower surface temperature. The temperature-dependent theory of leprosy infection remains an area of interest and controversy.

A variety of disease severity is seen. Two main clinical presentations are noted at opposite ends of the spectrum, and these are related to the immune reaction to the organism. The first, called **tuberculoid leprosy,** develops in patients with a high immune reaction. Typically, the organisms are not found in skin biopsy specimens, skin test results to heat-killed organisms (lepromin) are positive, and the disease usually is localized. The second form, **lepromatous leprosy,** is seen in patients who demonstrate a reduced cell-mediated immune response. These patients exhibit numerous organisms in the tissue, do not respond to lepromin skin tests, and exhibit diffuse disease. Many patients present with intermediate disease that can be divided into three subgroups: borderline-tuberculoid, borderline-borderline, and borderline-lepromatous. Active disease progresses through stages of invasion, proliferation, ulceration, and resolution with fibrosis. The incubation period is prolonged, with an average of 2 to 5 years for the tuberculoid type and 8 to 12 years for the lepromatous variant.



• **Fig. 5-24 Multibacillary (Lepromatous) Leprosy.** Numerous thickened facial nodules.

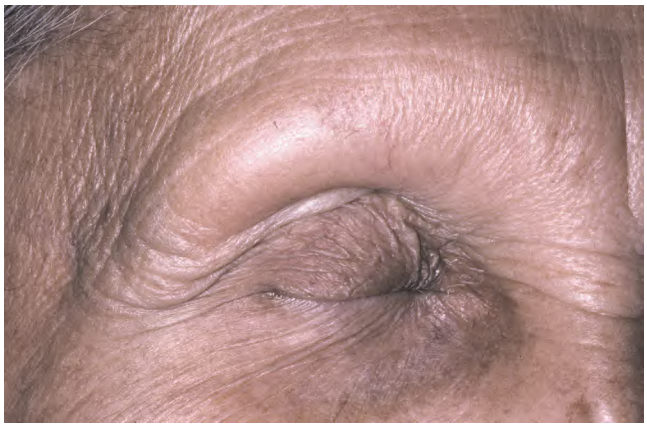
Clinical Features

Because laboratory services such as skin smears often are not available, patients increasingly are being classified on clinical grounds using the number of lesions (primarily skin) and the number of body areas affected.

Tuberculoid leprosy exhibits a small number of well-circumscribed, hypopigmented skin lesions. Nerve involvement usually results in anesthesia of the affected skin, often accompanied by a loss of sweating. Oral lesions are rare in this variant.

Lepromatous leprosy begins slowly with numerous, ill-defined, hypopigmented macules or papules on the skin that, with time, become thickened (Fig. 5-24). The face is a common site of involvement, and the skin enlargements can lead to a distorted facial appearance **(leonine facies).** Hair, including the eyebrows and lashes, often is lost (Fig. 5-25). Nerve involvement leads to a loss of sweating and decreased light touch, pain, and temperature sensors. This sensory loss begins in the extremities and spreads to most of the body. Nasal involvement results in nosebleeds, stuffiness, and a loss of the sense of smell. The hard tissue of the floor, septum, and bridge of the nose may be affected. Collapse of the bridge of the nose is considered pathognomonic.

The reported prevalence of oral lesion varies from a complete absence of lesions to 60%. A number of authors believe many reports document an artificially high frequency of oral lesions due to a failure to prove an association with the infection. Well-documented oral lesions occur predominantly in lepromatous leprosy and are rare in the tuberculoid and borderline variants.

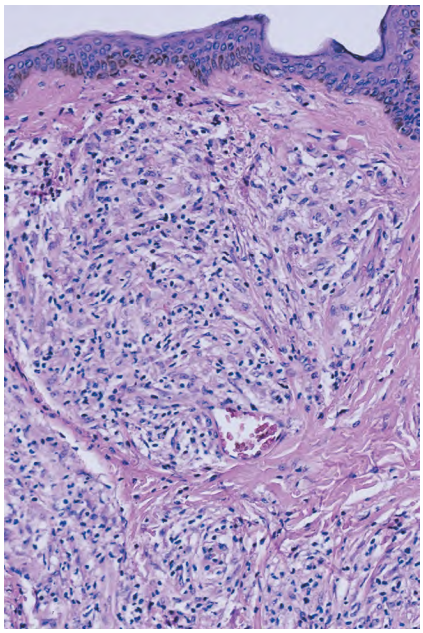


• **Fig. 5-25 Multibacillary (Lepromatous) Leprosy.** Loss of eyebrows and eyelashes.

The WHO mapped the frequency and distribution of oral lesions in leprosy patients. The sites that are cooled by the passage of air appear to be affected most frequently. The locations affected in order of frequency are the hard palate, soft palate, facial maxillary gingiva, tongue, lips, palatal gingiva, mandibular gingiva, and buccal mucosa. Affected soft tissue initially appears as yellowish to red, sessile, firm, enlarging papules that develop ulceration and necrosis, followed by attempted healing by secondary intention. Continuous infection of an area can lead to significant scarring and loss of tissue. Complete loss of the uvula and fixation of the soft palate may occur. The lingual lesions appear primarily in the anterior third and often begin as areas of erosion, which may develop into large nodules. Infection of the lip can result in significant macrocheilia, which can be confused clinically and microscopically with cheilitis granulomatosa (see page 313).

Direct infiltration of the inflammatory process associated with lepromatous leprosy can destroy the bone underlying the areas of soft tissue involvement. Often the infection creates a unique pattern of facial destruction that has been termed **facies leprosa** and demonstrates a triad of lesions consisting of atrophy of the anterior nasal spine, atrophy of the anterior maxillary alveolar ridge, and endonasal inflammatory changes. Involvement of the anterior maxilla can result in significant bone erosion with loss of the teeth in this area. Maxillary involvement in children can affect the developing teeth and produce enamel hypoplasia and short tapering roots. Dental pulp infection can lead to internal resorption or pulpal necrosis. Teeth with pulpal involvement may demonstrate a clinically obvious red discoloration of the crown. The cause of the discoloration is unknown but appears to be related to intrapulpal vascular damage secondary to the infection. Granulomatous involvement of the nasal cavity can erode through the palatal tissues and result in perforation.

Involvement of peripheral nerves is common, with leprosy considered one of the most common causes of treatable peripheral neuropathy in the world. The facial and trigeminal nerves can be involved with the infectious process. Facial paralysis may be unilateral or bilateral. Sensory deficits may affect any branch of the trigeminal nerve, but the maxillary division is the most commonly affected. In addition to sensory deficits, reports of disease-related orofacial pain may be confused with temporomandibular joint discomfort or tooth-related pain.



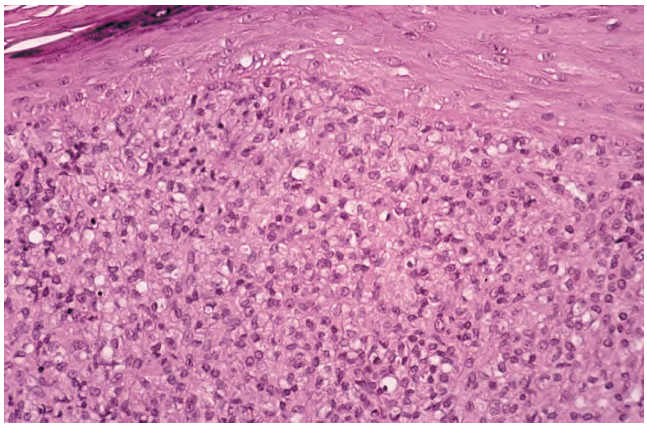
• **Fig. 5-26 Paucibacillary (Tuberculoid) Leprosy.** Well-formed granulomatous inflammation demonstrating clusters of lymphocytes and histiocytes.

Histopathologic Features

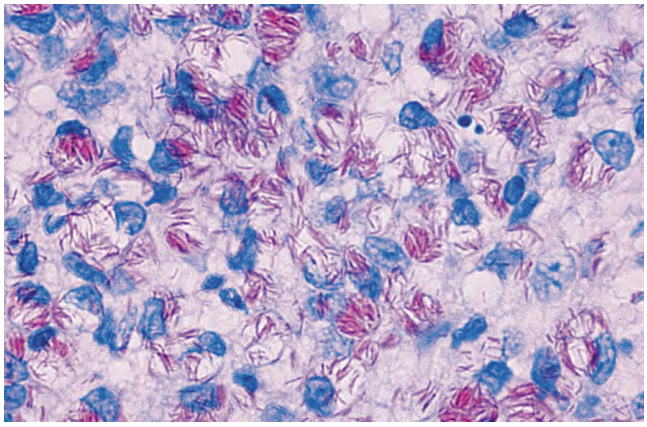
Biopsy specimens of tuberculoid leprosy typically reveal granulomatous inflammation with well-formed clusters of epithelioid histiocytes, lymphocytes, and multinucleated giant cells (Fig. 5-26). A paucity of organisms exists; when present, they can be demonstrated only when stained with acid-fast stains, such as the Fite method. Lepromatous leprosy demonstrates no well-formed granulomas; the typical finding is sheets of lymphocytes intermixed with vacuolated histiocytes known as **lepra cells** (Fig. 5-27). Unlike tuberculoid leprosy, an abundance of organisms can be demonstrated with acid-fast stains in the lepromatous variant (Fig. 5-28). It has been reported that the organism can be found with special stains in 100% of lepromatous leprosy cases, 75% of borderline cases, and only 5% of tuberculoid cases.

Diagnosis

The definitive diagnosis is based on the clinical presentation and supported by the demonstration of acid-fast organisms on a smear or in the tissue. The organism cannot be cultivated on artificial media, but *M. leprae* can be identified by using molecular biologic techniques. No reliable test is available to determine whether a person has been exposed



• **Fig. 5-27 Multibacillary (Lepromatous) Leprosy.** Sheets of lymphocytes and histiocytes exhibiting scattered vacuolated lepra cells.



• **Fig. 5-28 Multibacillary (Lepromatous) Leprosy.** Acid-fast stain exhibiting numerous small mycobacterial organisms seen individually and in clusters.

to *M. leprae* without developing the disease; this creates difficulties in establishing the diagnosis and determining the prevalence of the infection.

Treatment and Prognosis

For therapeutic purposes, the WHO has developed a simple classification system based upon the bacterial index noted upon biopsy. Those with an index less than 2+ are termed **paucibacillary,** whereas those greater than 2+ are designated **multibacillary.** Paucibacillary patients present clinically as tuberculoid or borderline-tuberculoid variants; multibacillary patients include borderline-borderline, borderline-lepromatous, and lepromatous variants. Patients with multibacillary leprosy receive a combination of rifampicin, clofazimine, and dapsone, whereas those presenting with paucibacillary leprosy receive rifampicin and dapsone. Use of dapsone or rifampicin alone has resulted in development of resistance to that respective drug. Since the introduction of multidrug therapy in 1981, an estimated 15 million patients have been cured, and disabilities have been prevented in another 2 to 3 million individuals. One of the major reasons for the decreasing prevalence of leprosy is the provision of an uninterrupted supply of free, high-quality medications in calendar blister packs to all patients regardless of the living conditions or remoteness of the location.

◆ NOMA (CANCRUM ORIS; OROFACIAL GANGRENE; GANGRENOUS STOMATITIS; NECROTIZING STOMATITIS)

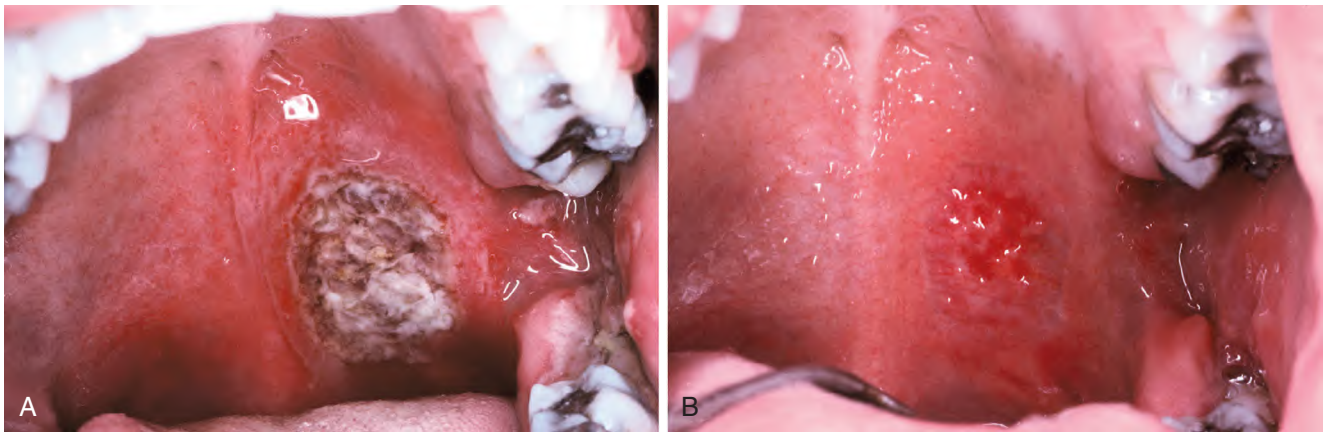
The term **noma** is derived from the Greek word *nomein,* meaning *to devour.* Noma is a rapidly progressive, polymicrobial, opportunistic infection caused by components of the normal oral flora that become pathogenic during periods of compromised immune status. *Fusobacterium necrophorum* and *Prevotella intermedia* are thought by many to be key players in the process and interact with one or more other bacterial organisms of which the most commonly implicated are *Actinomyces pyogenes, Bacillus cereus, Bacteroides fragilis, Fusobacterium nucleatum,* and *Prevotella melaninogenica*. Culture is thought to underestimate the variety of organisms involved due to the difficulties in growing many of these fastidious bacteria. Studies utilizing PCR for bacterial gene sequences have failed to identify a specific causative organism because the plausible bacteria were noted in both affected and healthy subjects.

The reported predisposing factors include the following:

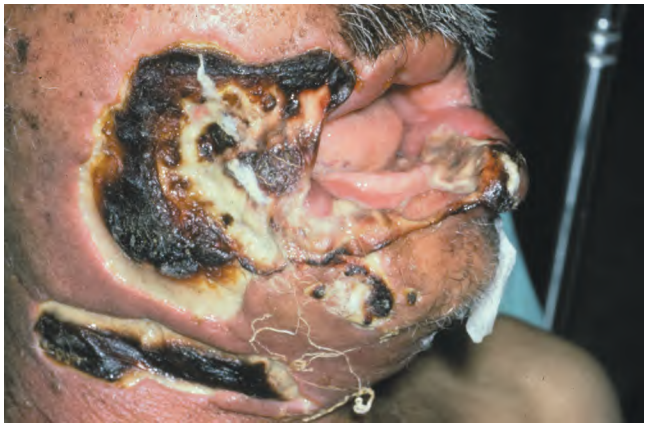
- Poverty
- Malnutrition or dehydration
- Poor oral hygiene
- Poor sanitation
- Unsafe drinking water
- Proximity to unkempt livestock
- Recent illness
- Malignancy
- An immunodeficiency disorder, including AIDS

In many cases a recent debilitating illness appears to set the stage for the development of noma. Measles most frequently precedes development of noma; other common but less frequent predisposing illnesses include herpes simplex, varicella, scarlet fever, malaria, tuberculosis, gastroenteritis, and bronchopneumonia. Cases associated with malignancies (e.g., leukemia) are not rare. In many instances, the infection begins as necrotizing ulcerative gingivitis (NUG) (see page 143), and several investigators believe that noma is merely an extension of the same process. Because the disease usually is well advanced at the time of initial presentation, descriptions of the initial stages of the disease are sketchy.

In the developed world, noma has virtually disappeared except for an occasional case related to immunosuppressive conditions, such as HIV infection, severe combined immunodeficiency syndrome, or intense immunosuppressive therapy. The World Health Organization (WHO) estimates the global yearly incidence to be approximately 140,000. This number is thought by many to be a gross underestimation because less than 15% of acute cases present for therapy.



• **Fig. 5-29 Necrotizing Ulcerative Mucositis. A,** Large area of soft tissue necrosis of the posterior soft palate on the left side. **B,** Healing site of necrotizing mucositis 6 days after initiation of tetracycline therapy.



• **Fig. 5-30 Noma.** Extensive blackish orofacial necrosis of the right cheek in an immunocompromised patient.

Clinical Features

Noma usually arises in children from 1 to 10 years of age, although it also can occur in adults with a major debilitating disease (e.g., diabetes mellitus, leukemia, lymphoma, or HIV infection). The infection often begins on the gingiva as NUG, which may extend either facially or lingually to involve the adjacent soft tissue and form areas called **necrotizing ulcerative mucositis.** Zones of necrosis also may develop in soft tissue not contiguous with the gingiva, particularly in areas of trauma (Fig. 5-29). The necrosis can extend into deeper tissues; over the next few days, zones of blue-black discoloration of the overlying skin surface may develop (Fig. 5-30). Often the necrotic zone is cone shaped, with a small point of cutaneous necrosis overlying a larger zone of oral mucosal destruction. Unlike other infections, the process does not follow tissue planes and tends to spread through anatomic barriers, such as muscle. These discolored zones break down into areas of yellowish necrosis that also frequently spreads into adjacent bone, with large areas of osteomyelitis possible. In most instances the necrotic area is well defined and unilateral. Fetid odor, significant pain, fever, malaise, tachycardia, increased respiratory rate, anemia, leukocytosis, and regional lymphadenopathy are typical. Additional lesions also may occur in distant sites, such as the scalp, neck, ear, shoulders, chest, perineum, and vulva.

Treatment and Prognosis

In addition to using appropriate antibiotics to treat noma, the clinician must direct therapeutic attention not only to local wound care but also toward correcting the inadequate nutrition, hydration, and electrolyte imbalances. Penicillin and metronidazole are the first-line therapeutic antibiotics for necrotizing stomatitis. Conservative débridement of gross necrotic areas is recommended, but aggressive removal is contraindicated because it does not stop the extension of the process and compounds the reconstruction problems.

Without therapy, only 10% to 20% of affected patients survive. With appropriate intervention, the survival is greater than 90%. Common causes of death include infectious complications, such as pneumonia, diarrhea, and septicemia. Noma infection can cause significant morbidity when it is not fatal. Facial disfigurement that affects the patient's future growth and development is not rare. Reconstruction often is extremely challenging and should be delayed until healing is complete.

◆ ACTINOMYCOSIS

Although the term **actinomycosis** seems to imply a fungal infection, it is an infection of filamentous, branching, gram-positive anaerobic bacteria. Actinomycetes are normal saprophytic components of the oral flora. Documented sites of colonization in healthy patients include the tonsillar crypts, dental plaque and calculus, carious dentin, bone sequestra, salivary calculi, gingival sulci, and periodontal pockets. The colonies within the tonsillar crypts may form concretions and become large enough for the patient to feel the firm plugs within the crypts (see page 168). In surveys of documented actinomycosis, *Actinomyces israelii* is the causative organism in the majority, with *A. viscosus* being a close

second. Much less frequent causes of the infection are *A. naeslundii, A. odontolyticus, A. meyeri, A. pyogenes, A. viscosus,* and *A. bovis,* along with *Arachnia propionica* and *Bifidobacterium dentium.* In most such cases, the primary organism is combined synergistically with streptococci and staphylococci.

Clinical Features

Actinomycosis may be either an acute, rapidly progressing infection or a chronic, slowly spreading lesion that is associated with fibrosis. Approximately 55% of cases of actinomycosis are diagnosed in the cervicofacial region, with 25% occurring in the abdominal and pelvic region and 15% in the pulmonary system. The remaining 5% exhibits a variety of patterns, such as superficial skin infections, or infections of the genitourinary region (often linked to use of intrauterine contraceptive devices).

The suppurative reaction of the infection may discharge large yellowish flecks that represent colonies of the bacteria called **sulfur granules.** Although common, sulfur granules are not present invariably. In addition, another infection that also can produce sulfur granules and mimic actinomycosis is **botryomycosis,** an unrelated process that represents an unusual host reaction to *S. aureus* and other bacteria.

In the cervicofacial region, the organism typically enters tissue through an area of prior trauma, such as a soft tissue injury, periodontal pocket, nonvital tooth, extraction socket, or infected tonsil. The infection does not spread along the typical fascial planes and usually disregards the normal lymphatic and vascular routes. Direct extension through soft tissue is seen, and lymph nodes become involved only if they are in the path of the process. The classic description is of a "wooden" indurated area of fibrosis, which ultimately forms a central, softer area of abscess. The infection may extend to the surface, forming a sinus tract (Fig. 5-31). Pain often is minimal. The soft tissues of the submandibular, submental, and cheek areas are common areas of involvement, with the area overlying the angle of the mandible being the most frequently affected site.

Localized abscesses without the associated chronic fibrosing reaction have been reported in soft tissue that has received minor trauma. The tongue is the most frequently mentioned site, but any oral mucosal location is possible. Involvement of the tonsillar crypts may produce infectious symptoms; in most cases, however, the primary change is one of variable hyperplasia. Tonsillar hyperplasia thought to be secondary to actinomycotic infestation of the crypts does not appear responsive to antibiotics, probably because of the superficial location of the bacterial colonies. Tonsillectomy is generally the most effective treatment for this situation.

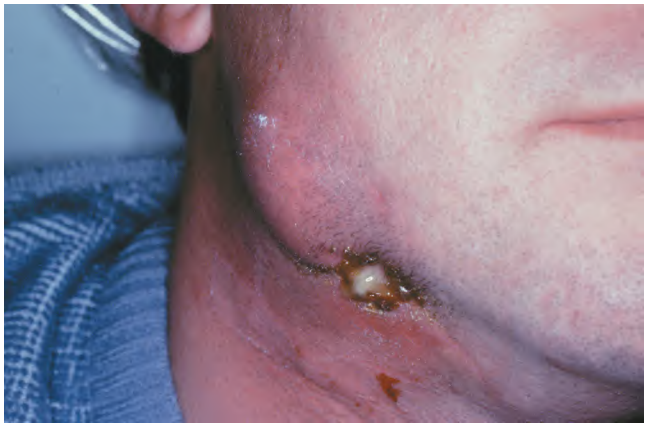
Salivary gland involvement also is not unusual. Intraductal colonization by the organism may lead to infections in both the submandibular and parotid glands, resulting in abscess formation in the submandibular and masseter spaces, respectively. In addition, more localized infections occur in minor salivary gland ducts, which also may demonstrate mucous plugs or sialoliths.

Actinomycotic osteomyelitis of the mandible and maxilla has been reported. Trauma, periodontal infections, nonvital teeth, and extraction sites have all provided access. Ill-defined areas of radiolucency, often surrounded by radiopacity, may be found with or without involvement of the overlying soft tissue.

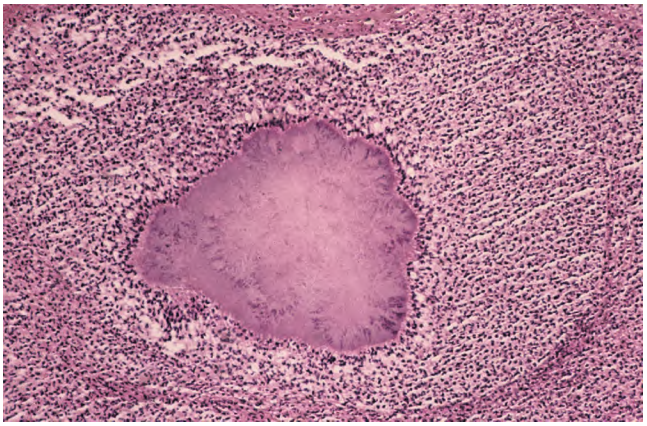
Intrabony colonization of dentigerous cysts without other significant clinical or radiographic spread has been reported. Periapical inflammatory lesions involved by the bacteria can result in lesions that are difficult to resolve with standard endodontic treatment, but such lesions typically remain localized and do not evolve into invasive cervicofacial actinomycosis.

Histopathologic Features

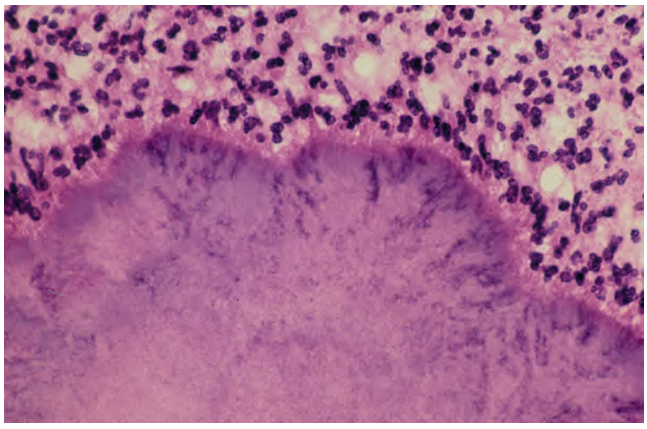
The tissue removed from areas of active infection demonstrates a peripheral band of fibrosis encasing a zone of chronically inflamed granulation tissue surrounding large collections of polymorphonuclear leukocytes and, with luck, colonies of organisms (Fig. 5-32). The colonies consist



• **Fig. 5-31 Actinomycosis.** Draining fistula of the right submandibular area.



• **Fig. 5-32 Actinomycosis.** Colony of actinomycotic organisms surrounded by polymorphonuclear leukocytes.



• **Fig. 5-33 Actinomycosis.** Actinomycotic colony exhibiting club-shaped filaments arranged in a radiating rosette pattern.

of club-shaped filaments that form a radiating rosette pattern (Fig. 5-33). With hematoxylin and eosin (H&E) stains, the central core stains basophilic and the peripheral portion is eosinophilic. Methenamine silver stains demonstrate the organisms well. If the colonies of actinomycetes become displaced from the exudate, then a rim of neutrophils typically clings to the periphery of the organisms.

Diagnosis

The diagnosis of actinomycosis is achieved ideally by culture, but less than 50% of cases are positive because of the overgrowth of associated bacteria, prior antibiotic therapy, or improper anaerobic media conditions. Lacking positive culture results, a strong presumptive diagnosis can be obtained through a demonstration of the typical colonies in lesional biopsy material. The material for culture and histopathologic examination typically is obtained during surgical exploration, with fine-needle aspiration being a satisfactory substitute in many cases. Sulfur granules in infections other than actinomycosis are so rare that their demonstration strongly supports the diagnosis. If desired, then fluorescein-conjugated antiserum can be used on the granules to specifically identify the *Actinomyces* species.

Treatment and Prognosis

The treatment of choice for actinomycosis in chronic fibrosing cases is prolonged high doses of antibiotics in association with abscess drainage and excision of the sinus tracts. A high antibiotic concentration is required to penetrate larger areas of suppuration and fibrosis. Although penicillin remains the standard of care with no documented *in vivo* resistance, some clinicians believe amoxicillin represents a better first-choice antibiotic. Other investigators have demonstrated *in vitro* resistance to penicillin and recommend tetracycline, which is as effective as penicillin and is the drug of choice for patients with a known allergy to penicillin. Early cervicofacial actinomycosis typically responds to a 5- to 6-week course of penicillin; patients with deep-seated infections may require up to 12 months.

In cases of osteomyelitis caused by actinomycetes, antibiotic therapy alone often is associated with persistent disease. Adequate débridement appears to be the cornerstone of therapy and ultimately determines the success of the subsequent antibiotic treatment. When combined with appropriate surgery, a 3-month course of penicillin usually is curative. In resistant cases, repeated débridement should be combined with cultures to direct future antibiotic therapy. Care should be taken to ensure that colonization of bony sequestra by actinomycotic colonies is not mistaken for invasive actinomycotic osteomyelitis.

Several authors have indicated that localized acute actinomycotic infections may be treated more conservatively than the deep, chronic cases of actinomycosis. Localized periapical and pericoronal actinomycosis, tongue abscesses, and focal subacute sialadenitis with intraductal involvement frequently respond well to surgical removal of infected tissue. It appears best to reserve antibiotics for patients in whom the microorganisms invade the surrounding structures and spread through the soft tissues.

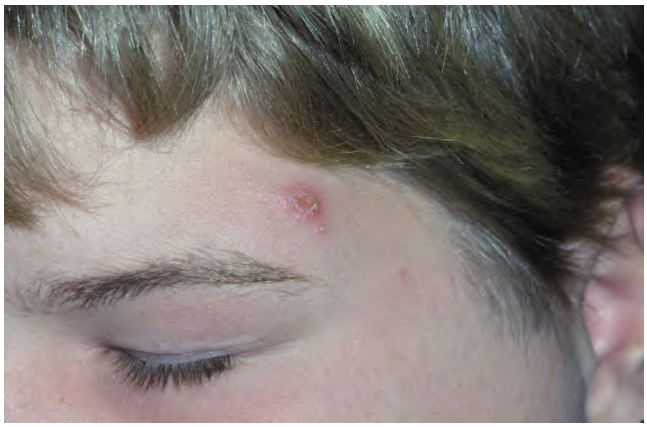
◆ CAT-SCRATCH DISEASE

Cat-scratch disease is an infectious disorder that begins in the skin but classically spreads to the adjacent lymph nodes. This infection is the most common cause of chronic regional lymphadenopathy in children, with an estimated 22,000 cases occurring annually in the United States. This disease has been recognized since 1931, but the definitive cause was not determined until the 1980s. Isolation and culture of the organism were finally achieved in 1988. The causative organism was initially named *Rochalimaea henselae* but was reclassified as *Bartonella henselae* when the genera *Bartonella* and *Rochalimaea* were combined.

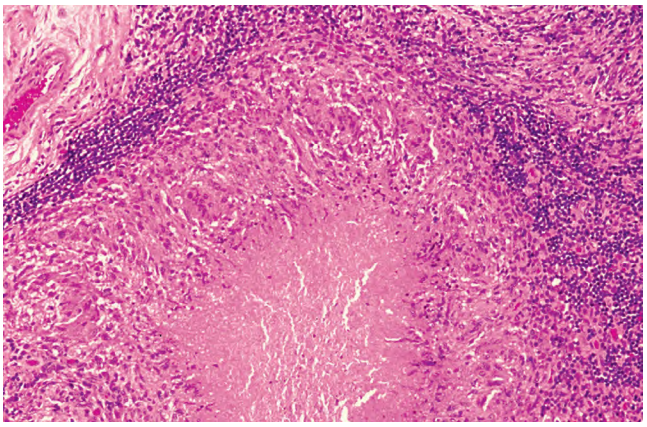
Almost all cases arise after contact with a cat. The spread of the infection between cats appears to occur through cat fleas. The organism becomes an intraerythrocytic parasite and may be transmitted to humans via saliva or from a scratch. Infection from other sources is highly unlikely, but the disease rarely has been described via dogs, monkeys, porcupine quills, and thorns. Person-to-person transmission has not been documented.

Clinical Features

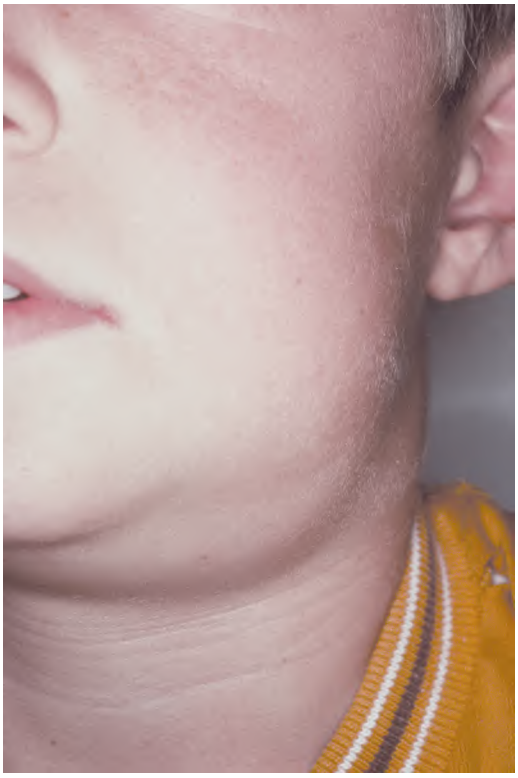
Eighty percent of the cases occur in patients younger than 21 years of age. Cat-scratch disease begins as a papule that develops in 3 to 14 days along the initial scratch line (Fig. 5-34). The lesion typically progresses through erythematous, vesicular, and papular-crusted stages with resolution usually occurring within 1 to 3 weeks. About the time the skin lesion heals, lymph node changes arise and may be accompanied by fever or malaise (Fig. 5-35). In about half of the cases, a single node is involved. Multiple regional nodes are affected in about 20%, and nodal enlargement is



• **Fig. 5-34 Cat-Scratch Disease.** Papule that developed at initial site of injury.



• **Fig. 5-36 Cat-Scratch Disease.** Intranodal area of necrosis surrounded by a band of epithelioid histiocytes and lymphocytes.



• **Fig. 5-35 Cat-Scratch Disease.** Submandibular lymphadenopathy has developed after initial trivial injury to skin. (Courtesy of Dr. George Blozis.)

discovered in multiple sites in about 33%. Suppuration is noted in approximately 10% of affected patients. The most frequently affected nodes are those in the head and neck, axillary, epitrochlear, and groin regions.

Although the vast majority of affected patients present with typical cat-scratch disease as described above, a variety of systemic manifestations may be seen. Of these, prolonged fever of unknown origin and hepatosplenic disease are the most common. Less common problems include cardiac, hematologic, neurologic, ocular, orthopedic, and pulmonary manifestations. Although necrotizing granulomas usually are noted in immunocompetent patients, vasoproliferative disorders, such as **bacillary angiomatosis** or **bacillary peliosis hepatis** (a specific form of hepatosplenic *Bartonella* disease) may be seen in immunocompromised patients. Bacillary angiomatosis is an unusual subcutaneous vascular proliferation that has been recognized in patients with AIDS. The affected areas often resemble Kaposi sarcoma (see page 244) and appear as variable numbers of red-to-purple skin lesions. These may be macular, papular, or pedunculated and exhibit a widespread distribution on the skin. Pain and tenderness are common. The larger lesions are friable and bleed easily.

Histopathologic Features

The involved lymph nodes are enlarged as a result of significant cortical hyperplasia, which classically contains areas of stellate suppurative necrosis surrounded by a band of histiocytes and neutrophils (Fig. 5-36). Upon Warthin-Starry stains or the Brown-Hopps method of Gram staining, cat-scratch bacilli usually are found in areas without significant necrosis. As the disease progresses and necrosis increases, the organisms become more difficult to identify. A commercially available monoclonal antibody against *B. henselae* has been used to demonstrate the organisms via immunoperoxidase techniques on paraffin-embedded material. Upon immunostaining, the organisms are highlighted dramatically, an important advance over the previous special stains.

Bacillary angiomatosis reveals lobular proliferations of small blood vessels in an edematous to fibrotic stroma. The supporting connective tissue typically demonstrates a significant number of neutrophils and leukocytoclasis, important clues to the diagnosis. Also present are variably sized amphophilic and granular aggregates that upon Warthin-Starry staining prove to be masses of the causative bacteria.

Diagnosis

Today the diagnosis of cat-scratch disease usually is established by a combination of clinical and serologic criteria.

Histopathology can confirm the clinical diagnosis but involves an invasive procedure. In patients with a suggestive clinical presentation, the diagnosis usually is confirmed by negative evaluations for other common causes of adenopathy, combined with positive serology. The most widely used tests are an indirect fluorescent assay (IFA) or enzyme-linked immunosorbent assay (ELISA) for detecting antibodies to *B. henselae*. PCR techniques also are available but are not widely used due to low sensitivity.

Treatment and Prognosis

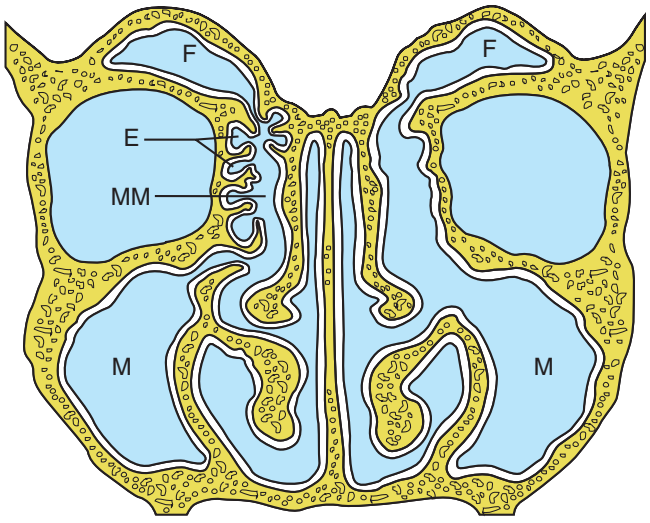
Cat-scratch disease is a self-limiting condition and normally resolves within 4 months. The use of local heat, analgesics, and aspiration of the node on suppuration is the typical pattern of therapy. If persistent discomfort makes nodal aspiration necessary, then drainage should be achieved with a needle that is tunneled into the node laterally through normal skin 1 to 2 cm away from the lesion. Incision directly into the node could result in a chronic draining sinus.

Although the organism has demonstrated sensitivity to a number of antibiotics in culture, the results in immunocompetent patients have been inconsistent and difficult to evaluate because the disease is self-limited in most cases. Antibiotics typically are reserved for those cases that demonstrate a prolonged course or severe involvement. Use of antibiotic drugs in patients with AIDS and bacillary angiomatosis has produced dramatic resolution within 2 days. Although a number of medications have been used successfully, the primary antibiotics used for cat-scratch disease or bacillary angiomatosis are azithromycin, erythromycin, doxycycline, rifampin, ciprofloxacin, and gentamicin.

◆ SINUSITIS

Sinusitis is one of the most common health complaints in the United States with an associated annual incidence of 20 million doctor visits. To understand the problem, the clinician must first have some knowledge of sinus anatomy. Adults have bilateral maxillary, frontal, sphenoid, ethmoid, and mastoid sinuses. Except for the mastoid sinuses, these cavities drain into the nose through openings called **ostia.** The frontal, sphenoid, and maxillary sinuses must drain through the middle meatus. In addition, the ethmoids are located bilaterally in this area of the nose and present as a labyrinth of 3 to 15 small sinuses, which drain through smaller ostia. The ostiomeatal complex, with its numerous narrow openings (Fig. 5-37), is the key to sinus disease, because it is the primary nasal site for the deposition of foreign matter from inspired air.

Normal sinuses are lined by pseudostratified columnar epithelium with cilia. The cilia are necessary to move the sinus secretions toward the ostia. Gravity also is beneficial in removing the secretions, except in the maxillary sinus where there is a superior location of the ostial opening and, therefore, the ciliary apparatus becomes even more important.



• **Fig. 5-37 The Paranasal Sinuses.** Illustration demonstrating the ostiomeatal complex and its importance to appropriate sinus drainage. The left side demonstrates the typical narrow middle meatus through which all sinus drainage must pass. The right side reveals enlargement of the middle meatus, such as that achieved through corrective endoscopic surgery. *M,* Maxillary sinus; *F,* frontal sinus; *E,* ethmoid sinuses; *MM,* middle meatus.

For a long time, researchers believed that primary inflammation of the lining of the maxillary antrum was the major cause of sinusitis; however, advances have demonstrated that most sinus disease begins from a blockage of the ostiomeatal complex that disrupts normal drainage, decreases ventilation, and precipitates disease. Less common localized sinus infections can occur from focal areas of inflammation within a single sinus, such as a dental infection affecting the maxillary sinus.

Most acute sinusitis cases are viral in origin and arise shortly after an upper respiratory tract infection. In contrast, most examples of chronic sinusitis are bacterial. All of the sinuses contain bacteria. With bacteria already present in the sinuses, changes as minor as a slight mucosal thickening in the ostiomeatal complex can lead to improper sinus drainage and infection. The most common predisposing factors for chronic sinusitis are a recent upper respiratory viral infection, allergic rhinitis, or an adjacent odontogenic infection.

Historically, 10% to 12% of maxillary sinusitis cases were thought to arise from an odontogenic source, but many current investigators believe the prevalence is closer to 30%. Common causes include periapical or periodontal infection from the maxillary teeth, dental trauma, or iatrogenic causes, such as dental extractions, maxillary osteotomies, or placement of dental implants. In such cases, therapy requires resolution of the odontogenic pathosis in addition to management of the sinus infection.

In otherwise healthy patients, the most common bacterial organisms cultured from acute sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis. Chronic sinusitis* is defined as recurring episodes of acute sinusitis or symptomatic sinus disease lasting longer than 3

months. In these cases, the bacteria tend to be anaerobes and are most frequently *Streptococcus, Bacteroides,* or *Veillonella* spp. When sinusitis arises secondary to an odontogenic infection, the causative organisms are usually those that predominate in periodontal or endodontic infections and include bacteria, such as *Peptostreptococcus* spp., *Fusobacterium* spp., *Prevotella* spp., *Bacteroides* spp., and *Porphyromonas* spp.

Infrequently, in an environment of chronic sinusitis, an area of dystrophic calcification **(antrolith)** may develop and be detected radiographically. The nidus for this calcification may be endogenous from materials, such as inflamed mucus, pus, or clots. In other cases the source may be exogenous from tooth roots or foreign bodies, such as dental materials, vegetable matter, paper, glass, and stone. Focal antral calcification also has been seen in sinuses filled with a fungal ball of *Aspergillus fumigatus* (noninvasive mycetoma) (see page 210). A sinus that is unresponsive to therapy and exhibits focal antrolith formation within a diffuse soft tissue opacification is highly suggestive of noninvasive aspergillosis.

Clinical and Radiographic Features

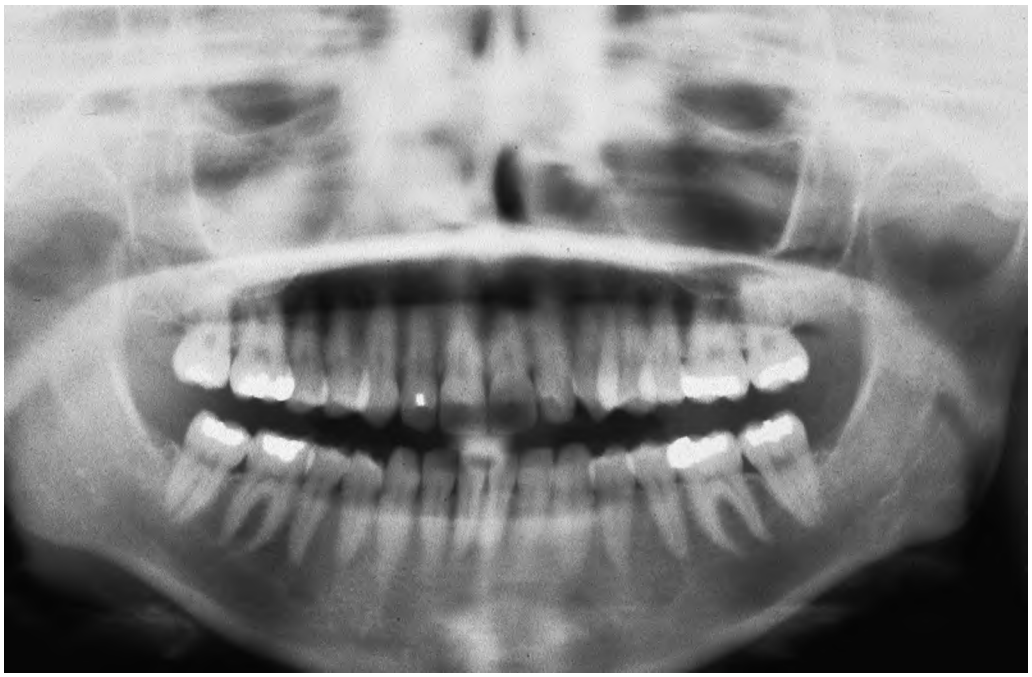
Presenting symptoms of acute sinusitis in adults include headache, fever, and facial pain over the affected sinus. Anorexia, photophobia, and malaise also may be seen. Anterior nasal or posterior pharyngeal discharge is present; it may be thick or thin in consistency and appear clear, mucoid, or purulent. Children, with their less complex sinuses, typically have only persistent cough, fever, and purulent rhinorrhea. Localized involvement of the maxillary sinus can occur as pain over the cheekbone, toothache, periorbital pain, or temporal headache. Maxillary sinusitis is associated with increased pain when the head is held upright and less discomfort when the patient is supine.

Chronic sinusitis is less diagnostic, and radiographic imaging becomes more important. Frequent complaints include facial pressure, pain, or a sensation of obstruction. In some cases, nonspecific symptoms, such as headache, sore throat, lightheadedness, or generalized fatigue, also may be present or even dominate. Radiographically, the involved sinus has a cloudy, increased density (Fig. 5-38).

At times, sinusitis can be confused with an odontogenic infection. In such cases, close examination of periapical radiographs, a thorough periodontal examination, and assessment of tooth vitality often may point to an odontogenic infection. A sinus infection should be strongly considered when patients complain of pain from several teeth, demonstrate tenderness over one or both of the maxillary sinuses, exhibit nasal congestion, or have a nasal discharge accompanied by a foul odor, fever, and headache.

In addition to the patient's symptoms, the diagnosis in the past often was made by procedures (such as, transillumination) and by plain radiographs (such as, the Waters, Caldwell-Luc, lateral, and submental vertex views). Today, when the diagnosis is in question, many clinicians use nasal endoscopy, CT, or cone beam CT. Areas of infection and sites of improper drainage will be found. These techniques not only confirm the diagnosis but also pinpoint the primary pathologic alteration that led to the obstructive sinusitis.

An antrolith appears radiographically as a radiodense focus within the sinus. The calcification often is seen in association with a thickening of the antral lining or diffuse clouding of the affected sinus.



• **Fig. 5-38 Sinusitis.** Cloudy right maxillary antrum.

Treatment and Prognosis

Treatment options for acute sinusitis include moisturizing sprays, decongestants, mucolytics, corticosteroids, antibiotics, or mechanical intervention, such as sinus puncture or lavage. Although acute sinusitis is usually a self-limiting disease, antibiotics frequently are prescribed. Most cases are viral in origin and resolve within 2 weeks, with or without antibiotic therapy. A Cochrane meta-analysis demonstrated a small benefit associated with antibiotic therapy, but this appeared to be overshadowed by adverse effects, such as diarrhea, abdominal pain, and vomiting.

If antibiotics are used, the first-line therapy for acute sinusitis in otherwise healthy patients is amoxicillin. Doxycycline or clarithromycin are alternatives for patients allergic to penicillin. If amoxicillin is associated with a poor clinical response, other choices include azithromycin, cefoxitin, ceftriaxone, cephalexin, clindamycin, and moxifloxacin. The choice of antibiotics should be guided by local resistance patterns and by appropriately collected cultures.

In otherwise healthy adult patients, chronic sinusitis that is not responsive to typical medical management often is corrected surgically. When located in the maxillary sinus, such invasive therapy should be performed only after a thorough examination to rule out an association with an adjacent odontogenic infection. On occasion, a clinical dental evaluation with plain films will fail to discover the origin. If a high index of suspicion exists, CT often proves beneficial in highlighting the associated focus of infection.

Nasal endoscopy has shown that sinusitis is a disease of obstruction and that mucosal inflammation is usually a secondary development. Functional endoscopic sinus surgery enlarges the ostial openings and corrects blockages in the ostiomeatal complex, often with a rapid resolution of the signs and symptoms (see Fig. 5-37). The surgery is delicate because it extends close to the orbit and the CNS. Each patient's unique anatomy should be evaluated carefully by CT and nasal endoscopy before surgery.

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6 Fungal and Protozoal Diseases

CANDIDIASIS

Infection with the yeastlike fungal organism *Candida albicans* is termed **candidiasis** or, as the British prefer, **candidosis.** An older name for this disease is *moniliasis;* the use of this term should be discouraged because it is derived from the archaic designation *Monilia albicans*. Other members of the *Candida* genus, such as *C. tropicalis, C. krusei, C. parapsilosis,* and *C. guilliermondii,* may also be found intraorally, but they rarely cause disease.

Like many other pathogenic fungi, *C. albicans* may exist in two forms—a trait known as **dimorphism.** The yeast form of the organism is believed to be relatively innocuous, but the hyphal form is usually associated with invasion of host tissue.

Candidiasis is by far the most common oral fungal infection in humans and has a variety of clinical manifestations, making the diagnosis difficult at times. In fact, *C. albicans* may be a component of the normal oral microflora, with as many as 30% to 50% of people simply carrying the organism in their mouths without clinical evidence of infection. This rate of carriage has been shown to increase with age, and *C. albicans* can be recovered from the mouths of nearly 60% of dentate patients older than 60 years who have no sign of oral mucosal lesions. At least three general factors may determine whether clinical evidence of infection exists:

1. The immune status of the host
2. The oral mucosal environment
3. The strain of *C. albicans*

In the past, candidiasis was considered to be only an opportunistic infection, affecting individuals who were debilitated by another disease. Certainly, such patients make up a large percentage of those with candidal infections today. However, now clinicians recognize that oral candidiasis may develop in people who are otherwise healthy. As a result of this complex host and organism interaction, candidal infection may range from mild, superficial mucosal involvement seen in most patients to fatal, disseminated disease in severely immunocompromised patients. This chapter focuses on those clinical presentations of candidiasis that affect the oral mucosa.

Clinical Features

Candidiasis of the oral mucosa may exhibit a variety of clinical patterns, which are summarized in Table 6-1. Many patients display a single pattern, although some individuals exhibit more than one clinical form of oral candidiasis.

Pseudomembranous Candidiasis

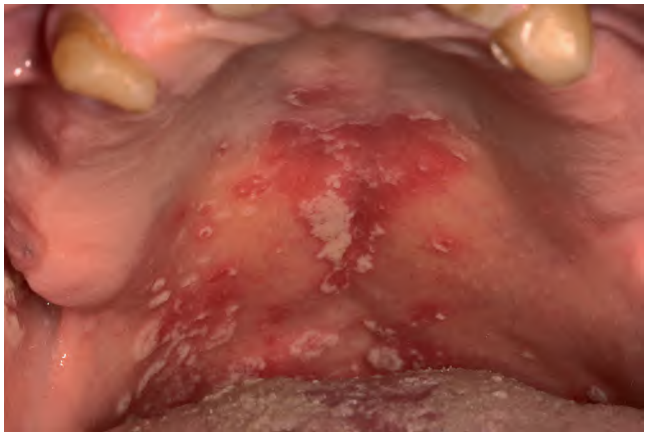
The best recognized form of candidal infection is **pseudomembranous candidiasis.** Also known as *thrush,* pseudomembranous candidiasis is characterized by the presence of adherent white plaques that resemble cottage cheese or curdled milk on the oral mucosa (Figs. 6-1 and 6-2). The white plaques are composed of tangled masses of hyphae, yeasts, desquamated epithelial cells, and debris. Scraping them with a tongue blade or rubbing them with a dry gauze sponge can remove these plaques. The underlying mucosa may appear normal or erythematous. If bleeding occurs, then the mucosa has probably also been affected by another process, such as erosive lichen planus or cancer chemotherapy.

Pseudomembranous candidiasis may be initiated by exposure of the patient to broad-spectrum antibiotics (thus eliminating competing bacteria) or by impairment of the patient's immune system. The immune dysfunctions seen in leukemic patients (see page 547) or those infected with human immunodeficiency virus (HIV) (see page 241) are often associated with pseudomembranous candidiasis. Infants may also be affected, ostensibly because of their underdeveloped immune systems. Antibiotic exposure is typically responsible for an acute (rapid) expression of the condition; immunologic problems usually produce a chronic (slow-onset, long-standing) form of pseudomembranous candidiasis.

Symptoms, if present at all, are usually relatively mild, consisting of a burning sensation of the oral mucosa or an unpleasant taste in the mouth, variably described as salty or bitter. Sometimes patients complain of "blisters," when in fact they feel the elevated plaques rather than true vesicles. The plaques are characteristically distributed on the buccal mucosa, palate, and dorsal tongue.

TABLE 6-1 Clinical Forms of Oral Candidiasis

Clinical Type	Appearance and Symptoms	Common Sites	Associated Factors and Comments
Pseudomembranous (thrush)	Creamy-white plaques, removable; burning sensation, foul taste	Buccal mucosa, tongue, palate	Antibiotic therapy, immunosuppression
Erythematous	Red macules, burning sensation	Posterior hard palate, buccal mucosa, dorsal tongue	Antibiotic therapy, xerostomia, immunosuppression, idiopathic
Central papillary atrophy (median rhomboid glossitis)	Red, atrophic mucosal areas; asymptomatic	Midline posterior dorsal tongue	Idiopathic, immunosuppression
Chronic multifocal	Red areas, often with removable white plaques; burning sensation, asymptomatic	Posterior palate, posterior dorsal tongue, angles of mouth	Immunosuppression, idiopathic
Angular cheilitis	Red, fissured lesions; irritated, raw feeling	Angles of mouth	Idiopathic, immunosuppression, loss of vertical dimension
Denture stomatitis (chronic atrophic candidiasis, denture sore mouth)	Red, asymptomatic	Confined to palatal denture-bearing mucosa	Probably not true infection; denture often is positive on culture but mucosa is not
Hyperplastic (candidal leukoplakia)	White plaques that are not removable; asymptomatic	Anterior buccal mucosa	Idiopathic, immunosuppression; care must be taken not to confuse this with other keratotic lesions with superimposed candidiasis
Mucocutaneous	White plaques, some of which may be removable; red areas	Tongue, buccal mucosa, palate	Rare; inherited or sporadic idiopathic immune dysfunction
Endocrine-candidiasis syndromes	White plaques, most of which are not removable	Tongue, buccal mucosa, palate	Rare; endocrine disorder develops after candidiasis



• **Fig. 6-1 Pseudomembranous Candidiasis.** Multiple white plaques overlying erythematous mucosal change on the soft palate.

Erythematous Candidiasis

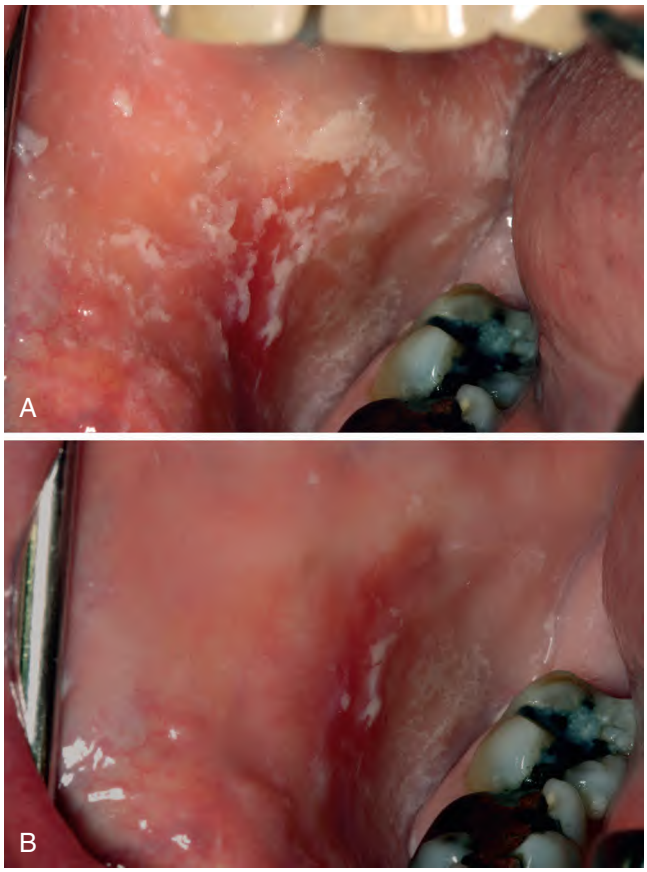
In contrast to the pseudomembranous form, patients with erythematous candidiasis either do not show white flecks, or a white component is not a prominent feature. Erythematous candidiasis is undoubtedly more common than pseudomembranous candidiasis, although it is often overlooked clinically. Several clinical presentations may be seen. **Acute atrophic candidiasis,** or "antibiotic sore mouth," typically follows a course of broad-spectrum antibiotic therapy. Patients often complain that the mouth feels as if a hot beverage had scalded it. This burning sensation is usually accompanied by a diffuse loss of the filiform papillae of the dorsal tongue, resulting in a reddened, "bald" appearance of the tongue (Fig. 6-3). Burning mouth syndrome (see page 807) frequently manifests with a scalded sensation of the tongue; however, the tongue appears normal in that condition. Patients who suffer from xerostomia for any reason (e.g., pharmacologic, postradiation therapy, or Sjögren syndrome) have an increased prevalence of erythematous candidiasis that is commonly symptomatic as well.

Other forms of erythematous candidiasis are usually asymptomatic and chronic. Included in this category is the condition known as **central papillary atrophy** of the tongue, or **median rhomboid glossitis.** In the past, this was thought to be a developmental defect of the tongue, occurring in 0.01% to 1.00% of adults. The lesion was

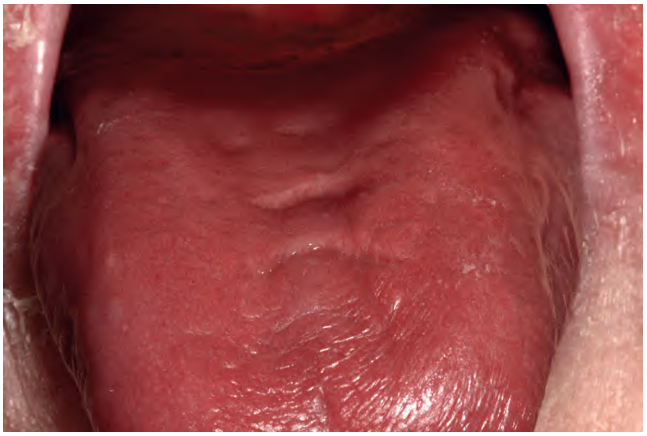
supposed to have resulted from a failure of the embryologic tuberculum impar to be covered by the lateral processes of the tongue. Theoretically, the prevalence of central papillary atrophy in children should be identical to that seen in adults; however, in one study in which 10,000 children were examined, not a single lesion was detected. Other investigators have noted a consistent relationship between the lesion and *C. albicans,* and similar lesions have been induced experimentally on the dorsal tongues of rats.

Clinically, central papillary atrophy appears as a well-demarcated erythematous zone that affects the midline, posterior dorsal tongue and often is asymptomatic (Fig. 6-4). The erythema is due in part to the loss of the filiform papillae in this area. The lesion is usually symmetrical, and its surface may range from smooth to lobulated. Often the mucosal alteration resolves with antifungal therapy, although occasionally only partial resolution can be achieved.

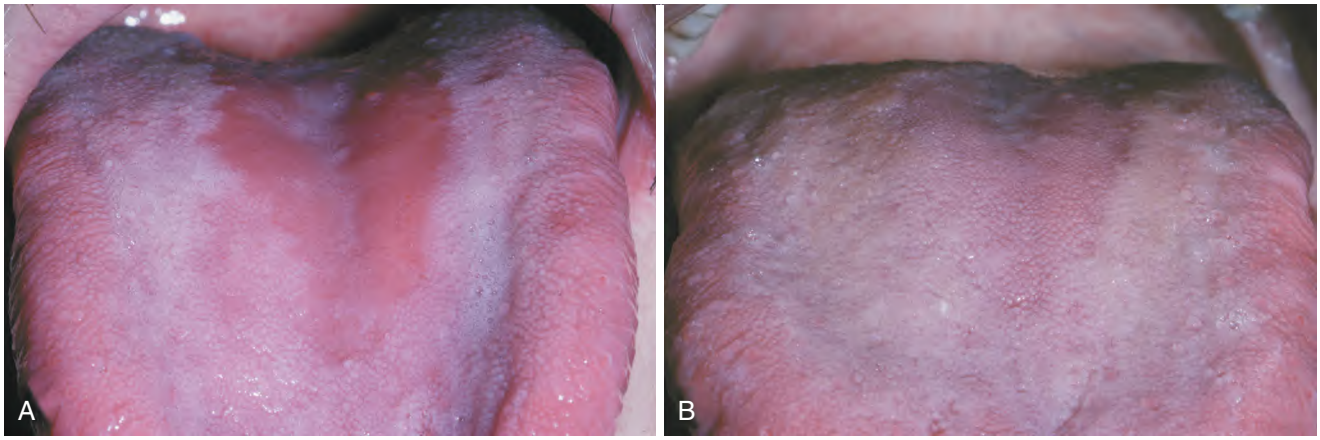
Some patients with central papillary atrophy may also exhibit signs of oral mucosal candidal infection at other sites. This presentation of erythematous candidiasis has been termed **chronic multifocal candidiasis.** In addition to the dorsal tongue, the sites that show involvement include the junction of the hard and soft palate and the angles of the mouth. The palatal lesion appears as an erythematous area that, when the tongue is at rest, contacts the dorsal tongue lesion, resulting in what is called a "kissing lesion" because of the intimate proximity of the involved areas (Fig. 6-5).



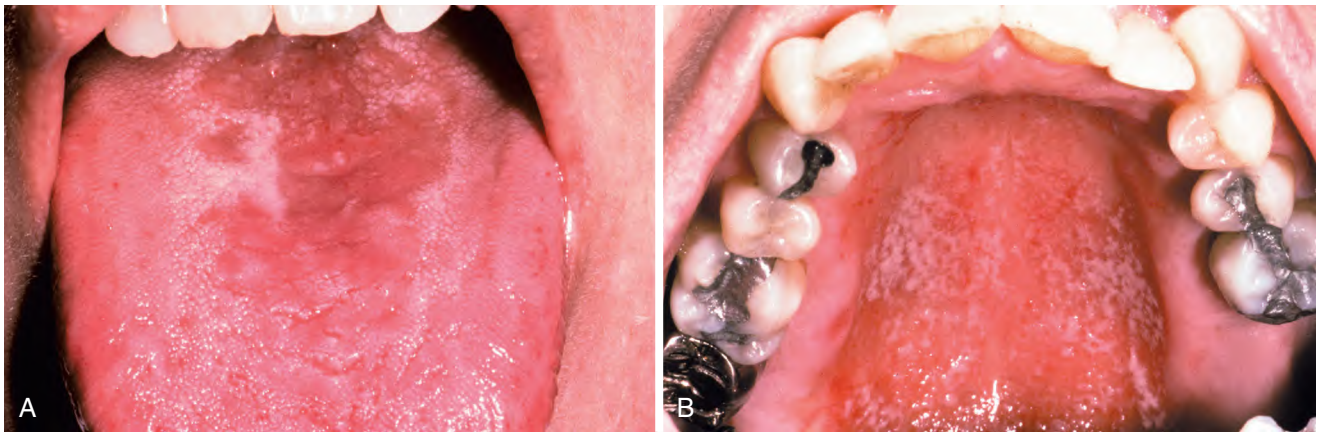
• **Fig. 6-2 Pseudomembranous Candidiasis. A,** White plaques on an erythematous base, characteristic of pseudomembranous candidiasis. **B,** Removal of several of the pseudomembranous plaques reveals a mildly erythematous mucosal surface but no evidence of bleeding.



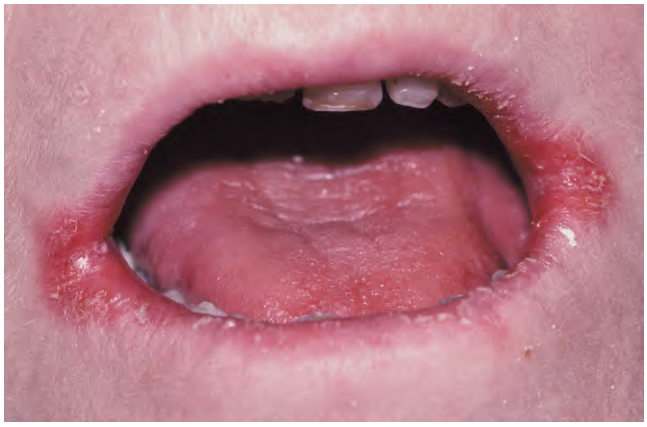
• **Fig. 6-3 Erythematous Candidiasis.** The diffuse erythema with a smooth atrophic appearance of the dorsal tongue represents erythematous candidiasis.



• **Fig. 6-4 Erythematous Candidiasis. A,** Severe presentation of central papillary atrophy. In this patient, the lesion was asymptomatic. **B,** Marked regeneration of the dorsal tongue papillae occurred 2 weeks after antifungal therapy with fluconazole.



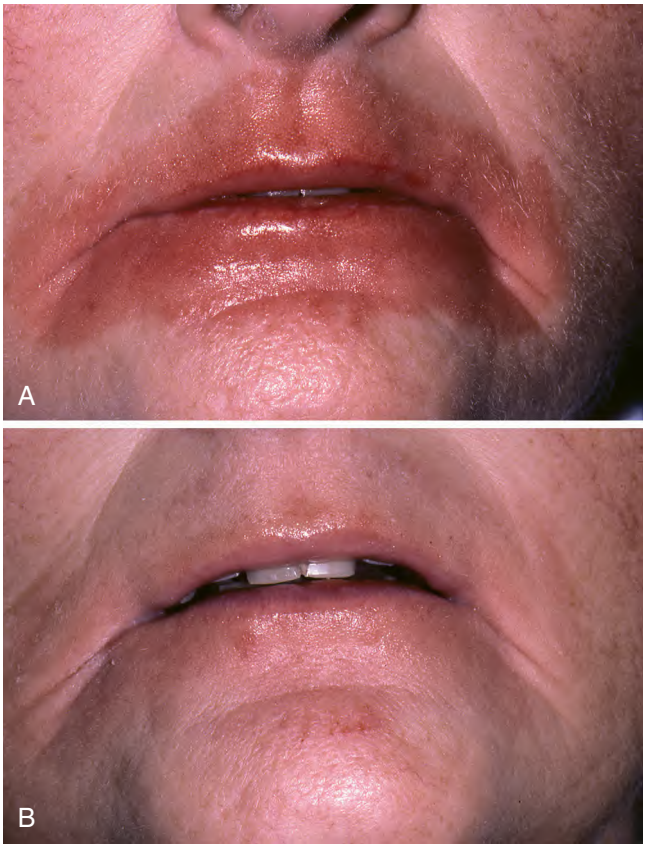
• **Fig. 6-5 Candidiasis. A,** Multifocal oral candidiasis characterized by central papillary atrophy of the tongue and other areas of involvement. **B,** Same patient showing a "kissing" lesion of oral candidiasis on the hard palate.



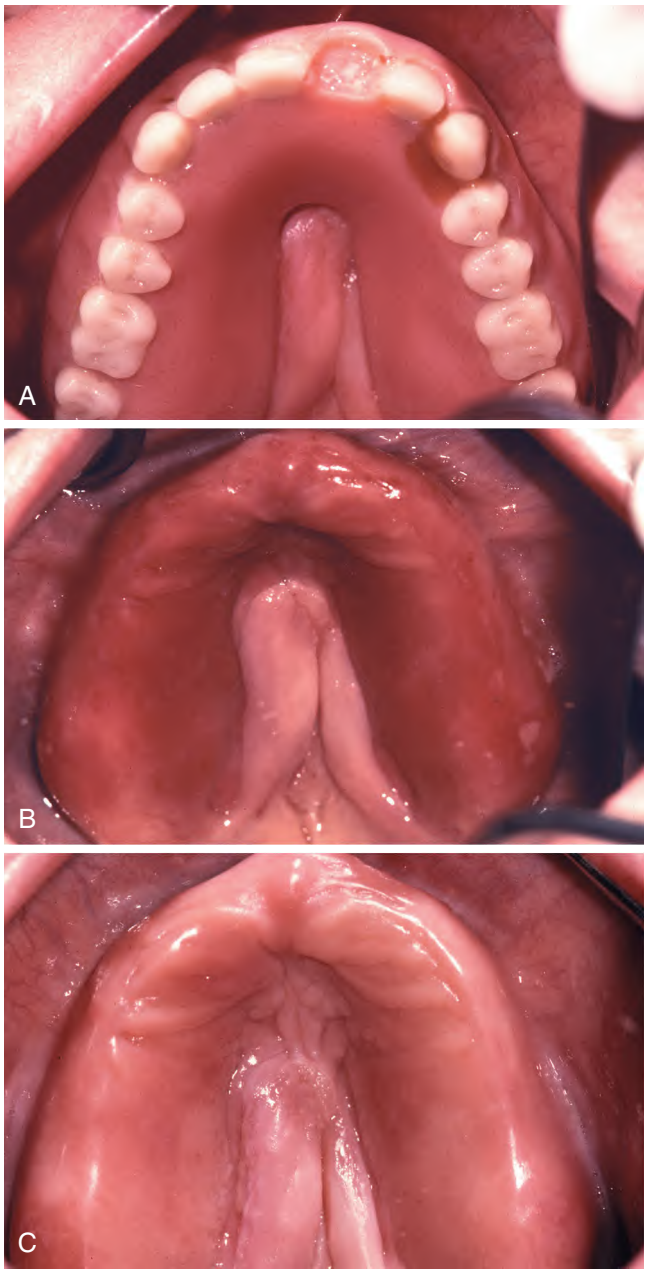
• **Fig. 6-6 Angular Cheilitis.** Characteristic lesions appear as fissured, erythematous alterations of the skin at the corners of the mouth.

The involvement of the angles of the mouth **(angular cheilitis, perlèche)** is characterized by erythema, fissuring, and scaling (Fig. 6-6). Sometimes this condition is seen as a component of chronic multifocal candidiasis, but it often occurs alone, typically in an older person with reduced vertical dimension of occlusion and accentuated folds at the corners of the mouth. Saliva tends to pool in these areas, keeping them moist and thus favoring a yeast infection. Patients often indicate that the severity of the lesions waxes and wanes. Microbiologic studies have indicated that 20% of these cases are caused by *C. albicans* alone, 60% are due to a combined infection with *C. albicans* and *Staphylococcus aureus,* and 20% are associated with *S. aureus* alone. Infrequently, the candidal infection more extensively involves the perioral skin, usually secondary to actions that keep the skin moist (e.g., chronic lip licking, thumb sucking, chronic use of petrolatum-based salves), creating a clinical pattern known as **cheilocandidiasis** (Fig. 6-7). Other causes of exfoliative cheilitis often must be considered in the differential diagnosis (see page 278).

Denture stomatitis should be mentioned because it is often classified as a form of erythematous candidiasis, and some authors may use the term *chronic atrophic candidiasis* synonymously. This condition is characterized by varying degrees of erythema, sometimes accompanied by petechial hemorrhage, localized to the denture-bearing areas of a maxillary removable dental prosthesis (Figs. 6-8 and 6-9).

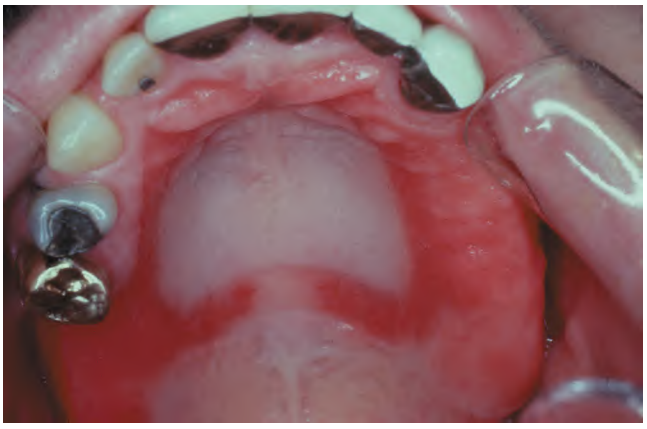


• **Fig. 6-7 Cheilocandidiasis. A,** Candidal infection of the perioral skin caused by use of a petrolatum-based product. The condition started as angular cheilitis, but the patient continuously applied petroleum jelly to the corners of the mouth and perioral skin, sealing moisture into the keratin layer of the epidermis, thereby allowing the candidal organisms to thrive. **B,** Two weeks after discontinuing the petroleum jelly and using topical iodoquinol with triamcinolone.



• **Fig. 6-8 Denture Stomatitis. A,** Maxillary denture with incomplete palatal vault associated with midline tissue hyperplasia. **B,** Mucositis corresponds to the outline of the prosthesis. **C,** Resolution of mucositis after antifungal therapy and appropriate denture cleansing.

Although the clinical appearance can be striking, the process is rarely symptomatic. Usually the patient admits to wearing the denture continuously, removing it only periodically to clean it. Whether this represents actual infection by *C. albicans* or is simply a tissue response by the host to the various microorganisms living beneath the denture remains controversial. The clinician should also rule out the possibility that this reaction could be caused by improper design of the denture (which could cause unusual pressure on the mucosa), allergy to the denture base, or inadequate curing of the denture acrylic.



• **Fig. 6-9 Denture Stomatitis.** Denture stomatitis, not associated with *Candida albicans,* confined to the denture-bearing mucosa of a maxillary partial denture framework.

• **Fig. 6-10 Denture Stomatitis.** This Sabouraud agar slant has been streaked with swabs obtained from erythematous palatal mucosa *(left side of the slant)* and the tissue-bearing surface of the denture *(right side of the slant).* Extensive colonization of the denture is demonstrated, whereas little evidence of yeast associated with the mucosa is noted.

Although *C. albicans* is often associated with this condition, biopsy specimens of denture stomatitis seldom show candidal hyphae actually penetrating the keratin layer of the host epithelium. Therefore, this lesion does not meet one of the main defining criteria for the diagnosis of infection—host tissue invasion by the organism. Furthermore, if the palatal mucosa and tissue-contacting surface of the denture are swabbed and separately streaked onto a Sabouraud agar slant, then the denture typically shows much heavier colonization by yeast (Fig. 6-10).

Chronic Hyperplastic Candidiasis (Candidal Leukoplakia)

In some patients with oral candidiasis, there may be a white patch that cannot be removed by scraping; in this case the term *chronic hyperplastic candidiasis* is appropriate. This form of candidiasis is the least common and is also somewhat controversial. Some investigators believe that this condition simply represents candidiasis that is superimposed on a

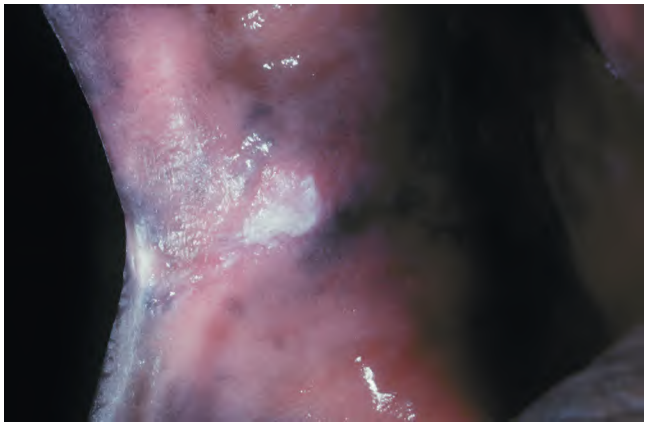
preexisting leukoplakic lesion, a situation that may certainly exist at times. In some instances, however, the candidal organism alone may be capable of inducing a hyperkeratotic lesion. Such lesions are usually located on the anterior buccal mucosa and cannot clinically be distinguished from a routine leukoplakia (Fig. 6-11). Often the leukoplakic lesion associated with candidal infection has a fine intermingling of red and white areas, resulting in a speckled leukoplakia (see page 359). Such lesions may have an increased frequency of epithelial dysplasia histopathologically.

The diagnosis is confirmed by the presence of candidal hyphae associated with the lesion and, more importantly, by complete resolution of the lesion after antifungal therapy (Fig. 6-12).

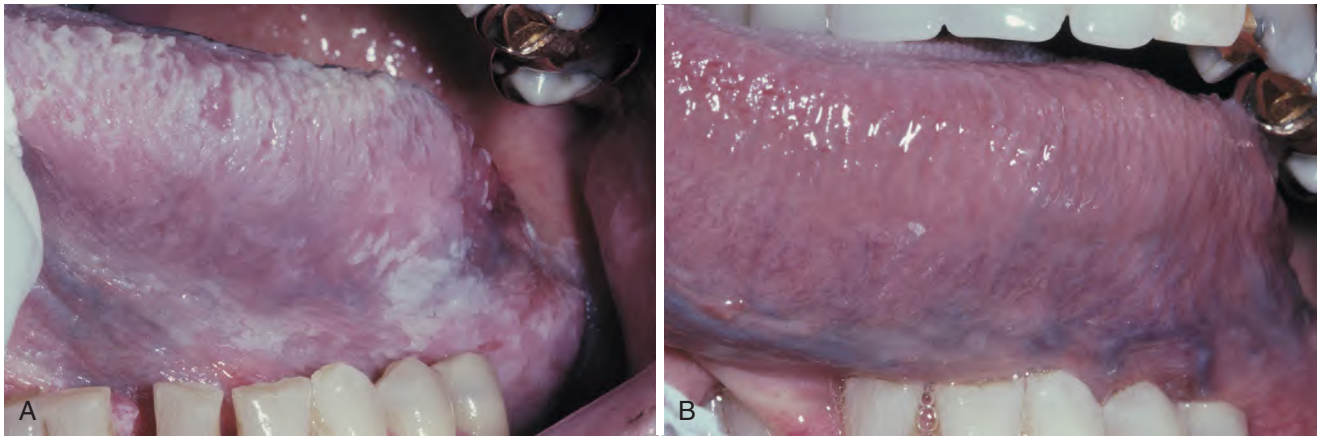
Mucocutaneous Candidiasis

Severe oral candidiasis may also be seen as a component of a relatively rare group of immunologic disorders known as *mucocutaneous candidiasis.* Several distinct immunologic dysfunctions have been identified, and the severity of the candidal infection correlates with the severity of the immunologic defect. Most cases are sporadic, although an autosomal recessive pattern of inheritance has been identified in some families. Several recent studies have suggested that the cytokine IL-17 is critical in mucosal immunity related to *C. albicans*, and mutations of the gene responsible for producing this cytokine result in mucocutaneous candidiasis. The immune problem usually becomes evident during the first few years of life, when the patient begins to have candidal infections of the mouth, nails, skin, and other mucosal surfaces. The oral lesions are usually described as thick, white plaques that typically do not rub off (essentially chronic hyperplastic candidiasis), although the other clinical forms of candidiasis may also be seen.

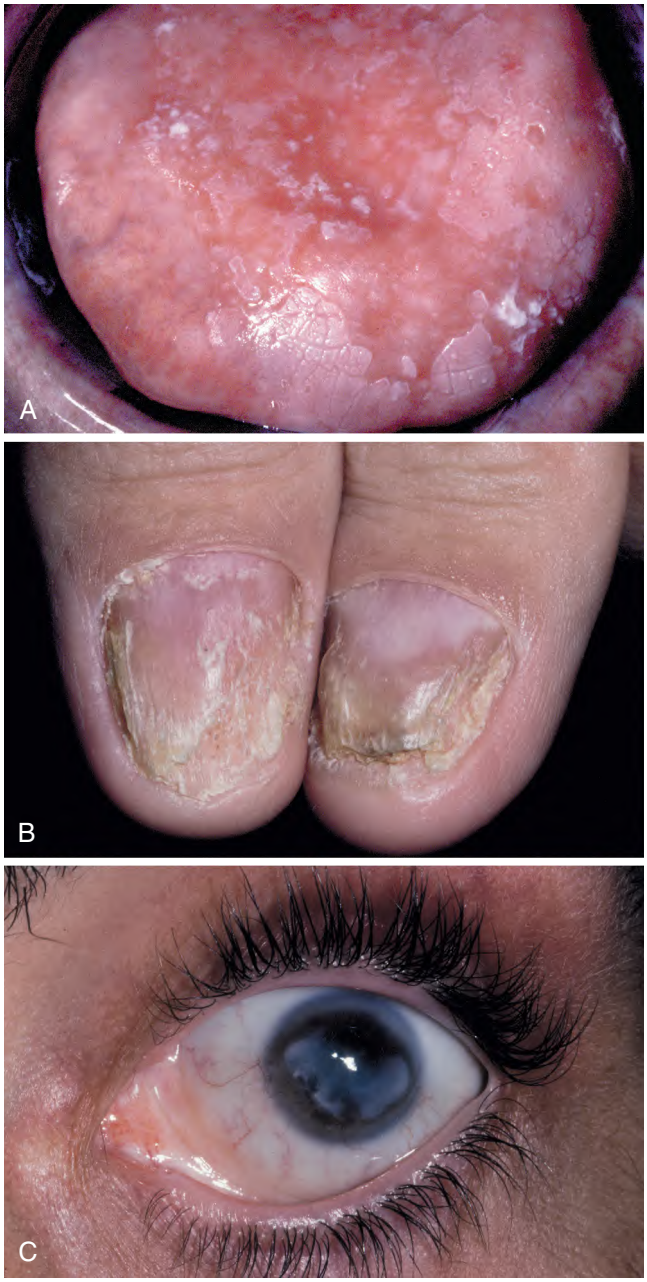
In some patients with mucocutaneous candidiasis, mutations in the autoimmune regulator (AIRE) gene have been documented, with the resultant formation of autoantibodies directed against the person's own tissues (Fig. 6-13). In most instances, the immunologic attack is directed against the endocrine glands; however, the reasons for this tissue specificity are currently unclear. Autoimmune destruction of the T-lymphocytes that produce interleukin-17 (IL-17) and IL-22 appears to be responsible for the candidal infections seen in these individuals. Young patients with mucocutaneous candidiasis should be evaluated periodically because any one of a variety of endocrine abnormalities (i.e., **endocrine-candidiasis syndrome**, **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome/autoimmune polyendocrinopathy syndrome, type 1**), as well as iron-deficiency anemia, may develop in addition to the candidiasis. These endocrine disturbances include hypothyroidism, hypoparathyroidism, hypoadrenocorticism (Addison disease), and diabetes mellitus. Typically, the endocrine abnormality develops months or even years after the onset of the candidal infection. One



• **Fig. 6-11 Hyperplastic Candidiasis.** This lesion of the anterior buccal mucosa clinically resembles a leukoplakia, because it is a white plaque that cannot be removed by rubbing. With antifungal therapy, such a lesion should resolve completely.



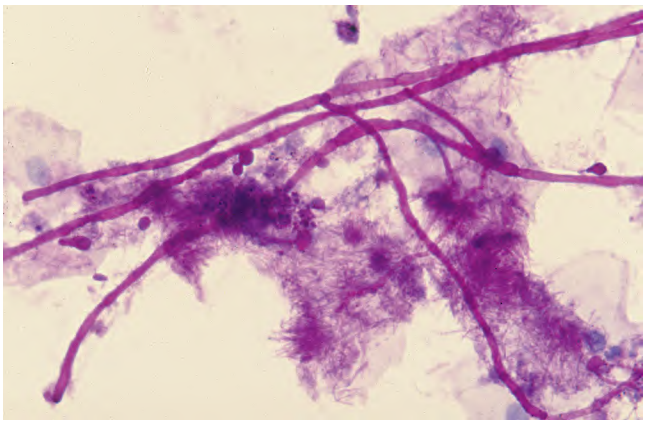
• **Fig. 6-12 Hyperplastic Candidiasis. A,** These diffuse white plaques clinically appear as leukoplakia, but they actually represent an unusual presentation of hyperplastic candidiasis. **B,** Treatment with clotrimazole oral troches shows complete resolution of the white lesions within 2 weeks, essentially confirming the diagnosis of hyperplastic candidiasis. If any white mucosal alteration had persisted, a biopsy of that area would have been mandatory.



• **Fig. 6-13 Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) Syndrome. A,** Erythematous candidiasis diffusely involving the dorsal tongue of a 32-year-old man. **B,** Same patient showing nail dystrophy. **C,** Corneal keratopathy is also noted. Patient had a history of the onset of hypoparathyroidism and hypoadrenocorticism, which were both diagnosed in the second decade of life.

recent study has documented increased prevalence of oral and esophageal carcinoma in this condition, with these malignancies affecting approximately 10% of adults with APECED syndrome. This finding represents another justification for periodic reevaluation of these individuals.

Interestingly, the candidal infection remains relatively superficial rather than disseminating throughout the body. Both the oral lesions and any cutaneous involvement (usually presenting as roughened, foul-smelling cutaneous plaques and nodules) can be usually controlled with continuous use of relatively safe systemic antifungal drugs. As with any long-term antibiotic treatment, development of drug-resistant organisms can occur, however.



• **Fig. 6-14 Candidiasis.** This cytologic preparation demonstrates tubular-appearing fungal hyphae and ovoid yeasts of *Candida albicans*. (Periodic acid-Schiff [PAS] stain.)

Histopathologic Features

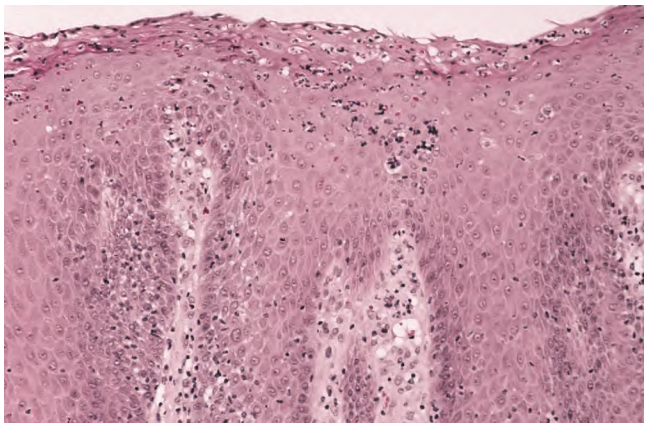
The candidal organism can be seen microscopically in either an exfoliative cytologic preparation or in tissue sections obtained from a biopsy specimen. On staining with the periodic acid-Schiff (PAS) method or the Grocott-Gomori methenamine silver (GMS) method, the candidal hyphae and yeasts can be readily identified (Fig. 6-14). Both techniques stain carbohydrates, contained in abundance by fungal cell walls; the organisms appear bright-magenta with the PAS stain or black with the GMS stain. To make a diagnosis of candidiasis, one must be able to see hyphae or pseudohyphae (which are essentially elongated yeast cells). These hyphae are approximately 2 µm in diameter, vary in their length, and may show branching. Often the hyphae are accompanied by variable numbers of yeasts, squamous epithelial cells, and inflammatory cells.

A 10% to 20% potassium hydroxide (KOH) preparation may also be used to rapidly evaluate specimens for the presence of fungal organisms. With this technique, the KOH lyses the background of epithelial cells, allowing the more resistant yeasts and hyphae to be visualized.

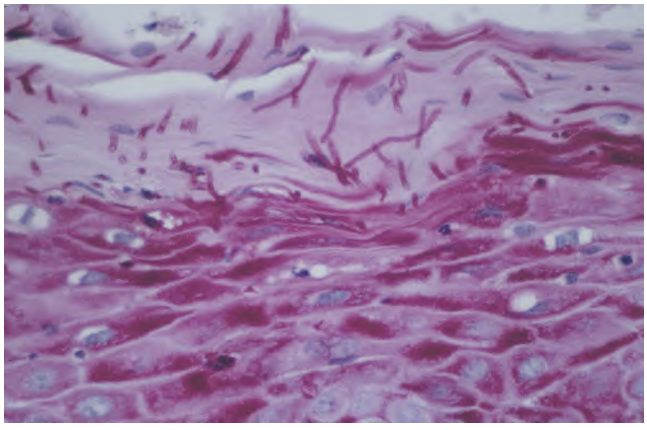
The disadvantages of the KOH preparation include the following:

- Lack of a permanent record
- Greater difficulty in identifying the fungal organisms, compared with PAS staining
- Inability to assess the nature of the epithelial cell population with respect to other conditions, such as epithelial dysplasia or pemphigus vulgaris

The histopathologic pattern of oral candidiasis may vary slightly, depending on which clinical form of the infection has been submitted for biopsy. The features that are found in common include an increased thickness of parakeratin



• **Fig. 6-15 Candidiasis.** This medium-power photomicrograph shows a characteristic pattern of parakeratosis, neutrophilic microabscesses, a thickened spinous layer, and chronic inflammation of the underlying connective tissue associated with long-standing candidal infection of the oral mucosa.



• **Fig. 6-16 Candidiasis.** This high-power photomicrograph shows the tubular hyphae of *Candida albicans* embedded in the parakeratin layer. (Periodic acid-Schiff [PAS] stain.)

on the surface of the lesion in conjunction with elongation of the epithelial rete ridges (Fig. 6-15). Typically, a chronic inflammatory cell infiltrate can be seen in the connective tissue immediately subjacent to the infected epithelium, and small collections of neutrophils (microabscesses) are often identified in the parakeratin layer and the superficial spinous cell layer near the organisms (Fig. 6-16). The candidal hyphae are embedded in the parakeratin layer and rarely penetrate into the viable cell layers of the epithelium unless the patient is extremely immunocompromised.

Diagnosis

The diagnosis of candidiasis is usually established by the clinical signs in conjunction with exfoliative cytologic examination. Although a culture can definitively identify the organism as *C. albicans,* this process may not be practical in most office settings. The cytologic findings should demonstrate the hyphal phase of the organism, and antifungal therapy can then be instituted. If the lesion is clinically suggestive of chronic hyperplastic candidiasis but does not respond to antifungal therapy, then a biopsy should be performed to rule out the possibility of *C. albicans* superimposed on epithelial dysplasia, squamous cell carcinoma, or lichen planus.

The definitive identification of the organism can be made by means of culture. A specimen for culture is obtained by rubbing a sterile cotton swab over the lesion and then streaking the swab on the surface of a Sabouraud agar slant. *C. albicans* will grow as creamy, smooth-surfaced colonies after 2 to 3 days of incubation at room temperature.

Treatment and Prognosis

Several antifungal medications have been developed for managing oral candidiasis, each with its advantages and disadvantages (Table 6-2).

Polyene Agents

Nystatin

In the 1950s, the polyene antibiotic nystatin was the first effective treatment for oral candidiasis. Nystatin is formulated for oral use as a suspension or pastille (lozenge). Many patients report that nystatin has a very bitter taste, which may reduce patient compliance; therefore, the taste has to be disguised with sucrose and flavoring agents. If the candidiasis is due to xerostomia, the sucrose content of the nystatin preparation may contribute to xerostomia-related caries in these patients. The gastrointestinal tract poorly absorbs nystatin and the other polyene antibiotic, amphotericin; therefore, their effectiveness depends on direct contact with the candidal organisms. This necessitates multiple daily doses so that the yeasts are adequately exposed to the drug. Nystatin combined with triamcinolone acetonide cream or ointment can be applied topically and is effective for angular cheilitis that does not have a bacterial component.

Amphotericin B

For many years in the United States, the use of amphotericin B was restricted to intravenous (IV) treatment of life-threatening systemic fungal infections. This medication subsequently became available as an oral suspension for the management of oral candidiasis. Unfortunately, the interest in this formulation of the drug was scant, and it is no longer marketed in the United States.

Imidazole Agents

The imidazole-derived antifungal agents were developed during the 1970s and represented a major step forward in the management of candidiasis. The two drugs of this group that are used most frequently are clotrimazole and ketoconazole.

Clotrimazole

Like nystatin, clotrimazole is not well absorbed and must be administered several times each day. It is formulated as a pleasant-tasting troche (lozenge) and produces few side

effects. The efficacy of this agent in treating oral candidiasis can be seen in Fig. 6-12. Clotrimazole cream is also effective treatment for angular cheilitis, because this drug has antibacterial and antifungal properties.

Ketoconazole

Ketoconazole was the first antifungal drug that could be absorbed across the gastrointestinal tract, thereby providing systemic therapy by an oral route of administration. The single daily dose was much easier for patients to use; however, several disadvantages have been noted. Patients must not take antacids or H_2-blocking agents, because an acidic environment is required for proper absorption. If a patient is to take ketoconazole for more than 2 weeks, then liver function studies are recommended because approximately 1 in 10,000 individuals experience idiosyncratic liver toxicity from the agent. For this reason, the US Food and Drug Administration has stated that ketoconazole should not be used as initial therapy for routine oral candidiasis. Furthermore, ketoconazole has been implicated in drug interactions with macrolide antibiotics (e.g., erythromycin), which may produce potentially life-threatening cardiac arrhythmias.

Triazoles

The triazoles are among the more recently developed antifungal drugs. Both fluconazole and itraconazole have been approved for treating candidiasis in the United States.

Fluconazole

Fluconazole appears to be more effective than ketoconazole; it is well absorbed systemically, and an acidic environment is not required for absorption. A relatively long half-life allows for once-daily dosing, and liver toxicity is rare at the doses used to treat oral candidiasis. Some reports have suggested that fluconazole may not be appropriate for long-term preventive therapy because resistance to the drug seems to develop in some instances. Known drug interactions include a potentiation of the effects of phenytoin (Dilantin), an antiseizure medication; warfarin compounds (anticoagulants); and sulfonylureas (oral hypoglycemic agents). Other drugs that may interact with fluconazole are summarized in Table 6-2.

Itraconazole

Itraconazole has proven efficacy against a variety of fungal diseases, including histoplasmosis, blastomycosis, and fungal conditions of the nails. Recently, itraconazole solution was approved for management of oropharyngeal candidiasis, and this appears to have an efficacy equivalent to clotrimazole and fluconazole. As with fluconazole, significant drug interactions are possible, and itraconazole is contraindicated for patients taking erythromycin, triazolam, and midazolam. (See Table 6-2 for other potential drug interactions.)

Posaconazole

This relatively new triazole compound has been shown to be effective in the management of oropharyngeal candidiasis in patients with HIV infection. Given the cost of this drug and the proven effectiveness of other, less expensive, oral antifungal agents, the use of this medication for treatment of routine oral candidiasis would be difficult to justify.

Echinocandins

This new class of antifungal drugs acts by interfering with candidal cell wall synthesis. The formation of β-1,3-glucan, which is a principal component of the candidal cell wall, is disrupted and results in permeability of the cell wall with subsequent demise of the candidal organism. These medications are not well absorbed; consequently they must be administered intravenously and are reserved for more life-threatening candidal infections. Examples include caspofungin, micafungin, and anidulafungin.

Other Antifungal Agents

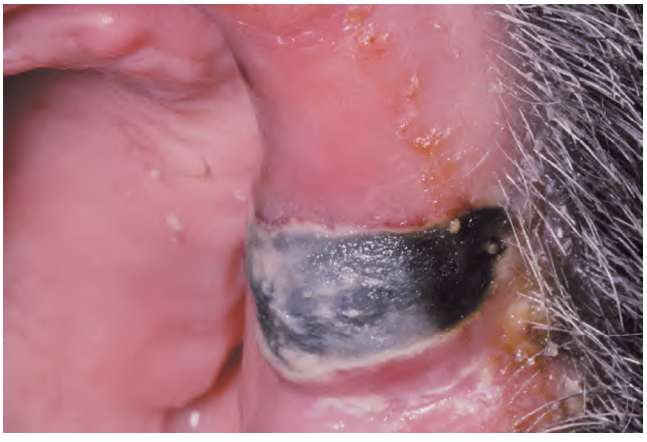
Iodoquinol

Although not strictly an antifungal drug, iodoquinol has antifungal and antibacterial properties. When compounded in a cream base with a corticosteroid, this material is very effective as topical therapy for angular cheilitis.

In most cases, oral candidiasis is an annoying superficial infection that is easily resolved by antifungal therapy. If infection should recur after treatment, then a thorough investigation of potential factors that could predispose to candidiasis, including immunosuppression, may be necessary. In only the most severely compromised patient will candidiasis cause deeply invasive disease (Fig. 6-17).

◆ HISTOPLASMOSIS

Histoplasmosis, the most common systemic fungal infection in the United States, is caused by the organism *Histoplasma capsulatum.* Like several other pathogenic fungi, *H. capsulatum* is dimorphic, growing as a yeast at body temperature in the human host and as a mold in its natural



• **Fig. 6-17 Candidiasis.** This necrotic lesion of the upper lip developed in a man with uncontrolled type I diabetes mellitus. Biopsy and culture showed a rare example of invasive oral infection by *Candida albicans*.

TABLE 6-2 Antifungal Medications

Generic Name	Trade Name	Indications	Dosage
Nystatin	Mycostatin pastilles Mycostatin oral suspension	Oral candidiasis	One or two pastilles (200,000-400,000 units) dissolved slowly in the mouth 4 to 5 times daily for 10 to 14 days
Clotrimazole	Mycelex oral troches	Oral candidiasis	Dissolve 1 troche (10 mg) slowly in the mouth, 5 times daily for 10 to 14 days
Ketoconazole	Nizoral tablets	Oral candidiasis Blastomycosis Coccidioidomycosis Histoplasmosis Paracoccidioidomycosis	Not to be used as initial therapy for oral candidiasis One tablet (200 mg) daily for 1 to 2 weeks for candidiasis Minimum treatment period for systemic mycoses is 6 months
Fluconazole	Diflucan tablets	Oral candidiasis Cryptococcal meningitis	For oral candidiasis: two tablets (200 mg) on day 1 and then one tablet (100 mg) daily for 1 to 2 weeks
Itraconazole	Sporanox capsules	Blastomycosis Histoplasmosis Aspergillosis refractory to amphotericin B therapy	For blastomycosis and histoplasmosis: two capsules (200 mg) daily, increasing by 100-mg increments up to 400 mg daily in divided doses if no clinical response is noted For aspergillosis: 200 to 400 mg daily For life-threatening situations: loading dose of 200 mg t.i.d. for first 3 days, then dose can be reduced Treatment should continue for at least 3 months for all of the above
Itraconazole	Sporanox oral solution	Oral candidiasis	10 mL (100 mg) vigorously swished in the mouth and swallowed, twice daily for 1 to 2 weeks
Amphotericin B	Fungizone oral suspension	Oral candidiasis	1 mL (100 mg) rinse and hold in the mouth for as long as possible, q.i.d., p.c., and h.s. for 2 weeks

h.s., Hora somni (at bedtime); *p.c.,* post cibum (after meals); *q.i.d.,* quarter in die (four times a day); *t.i.d.,* ter in die (three times a day).

environment. Humid areas with soil enriched by bird or bat excrement are especially suited to the growth of this organism. This habitat preference explains why histoplasmosis is seen endemically in fertile river valleys, such as the region drained by the Ohio and Mississippi Rivers in the United States. Airborne spores of the organism are inhaled, pass into the terminal passages of the lungs, and germinate.

Approximately 500,000 new cases of histoplasmosis are thought to develop annually in the United States. Other parts of the world, such as Central and South America, Europe, and Asia, also report numerous cases. Epidemiologic studies in endemic areas of the United States suggest that 80% to 90% of the population in these regions has been infected.

Clinical and Radiographic Features

Most cases of histoplasmosis produce either no symptoms or such mild symptoms that the patient does not seek medical treatment. The expression of disease depends on the quantity of spores inhaled, the immune status of the host, and perhaps the strain of *H. capsulatum.* Most individuals who become exposed to the organism are relatively healthy and do not inhale a large number of spores; therefore, they

Side Effects/Adverse Reactions	Drug Interactions
Nausea, diarrhea, vomiting with large doses	None known
Mild elevations of liver enzymes in 15% of patients Periodic assessment of liver function in patients with hepatic impairment Nausea, vomiting	No significant drug interactions
Serious hepatotoxicity in 1:10,000 patients Monitoring of liver function is indicated for patients with preexisting hepatic problems, patients who develop symptoms of hepatic failure, or patients treated for more than 28 days Serum testosterone is lowered Nausea, vomiting Anaphylaxis	Serious and/or life-threatening interactions with erythromycin Metabolism of cyclosporine, tacrolimus, methylprednisolone, midazolam, triazolam, coumarin-like drugs, phenytoin, and rifampin may be altered
Rare cases of hepatotoxicity, ranging from mild transient elevation of liver enzymes to hepatic failure Headache, nausea, vomiting, abdominal pain, diarrhea	Clinically or potentially significant side effects have been noted with the following medications: oral hypoglycemic agents, coumarin-like drugs, phenytoin, cyclosporine, rifampin, theophylline, rifabutin, and tacrolimus
Rare cases of hepatoxicity Liver function should be monitored in patients with preexisting hepatic problems on therapy for more than 1 month Nausea, diarrhea, vomiting	Serious and/or life-threatening interactions with erythromycin, pimozide, quinidine, oral triazolam, and oral midazolam Lovastatin and simvastatin should be discontinued Increased plasma concentrations may be seen with warfarin, ritonavir, indinavir, vinca alkaloid agents, diazepam, cyclosporine, dihydropyridine medications, tacrolimus, digoxin, and methylprednisolone
Rare cases of hepatotoxicity Liver function should be monitored in patients with preexisting hepatic problems on therapy for more than 1 month Nausea, diarrhea, vomiting	Serious and/or life-threatening interactions with erythromycin, oral triazolam, and oral midazolam, Lovastatin and simvastatin should be discontinued
Rash, gastrointestinal symptoms	No significant drug interactions

have either no symptoms or they have a mild, flulike illness for 1 to 2 weeks. The inhaled spores are ingested by macrophages within 24 to 48 hours, and specific T-lymphocyte immunity develops in 2 to 3 weeks. Antibodies directed against the organism usually appear several weeks later. With these defense mechanisms, the host is usually able to destroy the invading organism, although sometimes the macrophages simply surround and confine the fungus so that viable organisms can be recovered years later. Thus patients who formerly lived in an endemic area may have acquired the organism and later express the disease at some other geographic site if they become immunocompromised.

Acute histoplasmosis is a self-limited pulmonary infection that probably develops in only about 1% of people who are exposed to a low number of spores. With a high concentration of spores, as many as 50% to 100% of individuals may experience acute symptoms. These symptoms (e.g., fever, headache, myalgia, nonproductive cough, and anorexia) result in a clinical picture similar to that of influenza. Patients are usually ill for 2 weeks, although calcification of the hilar lymph nodes may be detected as an incidental finding on chest radiographs years later.

Chronic histoplasmosis also primarily affects the lungs, although it is much less common than acute histoplasmosis.

The chronic form usually affects older, emphysematous, white men or immunosuppressed patients. Clinically, it appears similar to tuberculosis. Patients typically exhibit cough, weight loss, fever, dyspnea, chest pain, hemoptysis, weakness, and fatigue. Chest roentgenograms show upper-lobe infiltrates and cavitation.

Disseminated histoplasmosis is even less common than the acute and chronic types. It occurs in 1 of 2000 to 5000 patients who have acute symptoms. This condition is characterized by the progressive spread of the infection to extrapulmonary sites. It usually occurs in either older, debilitated, or immunosuppressed patients. In some areas of the United States, 2% to 10% of patients with **acquired immunodeficiency syndrome (AIDS)** (see page 251) develop disseminated histoplasmosis. Patients who are being treated with a tumor necrosis factor-alpha (TNF-α) inhibitor (such as, infliximab, etanercept, or adalimumab) and who live in endemic geographic regions also are at risk for disseminated disease, probably due to reactivation of the organism. Tissues that may be affected include the spleen, adrenal glands, liver, lymph nodes, gastrointestinal tract, central nervous system (CNS), kidneys, and oral mucosa. Adrenal involvement may produce hypoadrenocorticism **(Addison disease)** (see page 784).

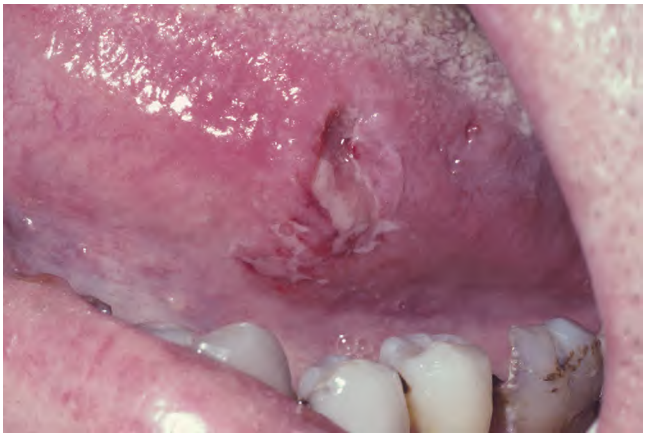
Most oral lesions of histoplasmosis occur with the disseminated form of the disease. The most commonly affected sites are the tongue, palate, and buccal mucosa. The condition usually appears as a solitary, variably painful ulceration of several weeks' duration; however, some lesions may appear erythematous or white with an irregular surface (Fig. 6-18). The ulcerated lesions have firm, rolled margins, and they may be indistinguishable clinically from a malignancy (Fig. 6-19).

Histopathologic Features

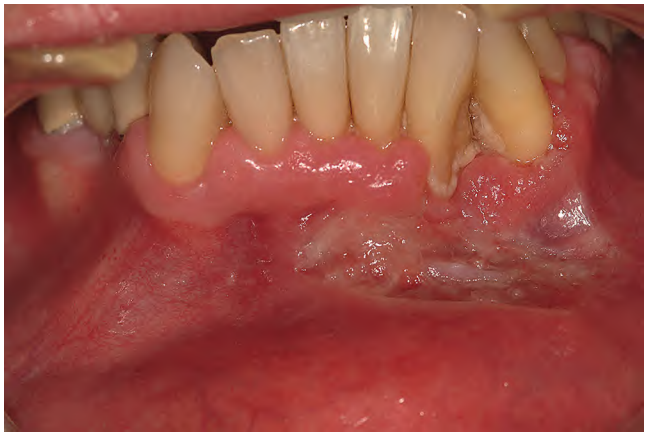
Microscopic examination of lesional tissue shows either a diffuse infiltrate of macrophages or, more commonly, collections of macrophages organized into granulomas (Fig. 6-20). Multinucleated giant cells are usually seen in association with the granulomatous inflammation. The causative organism can be identified with some difficulty in the routine hematoxylin and eosin (H&E)-stained section; however, special stains, such as the PAS and Grocott-Gomori methenamine silver methods, readily demonstrate the characteristic 1- to 3-μm yeasts of *H. capsulatum* (Fig. 6-21).

Diagnosis

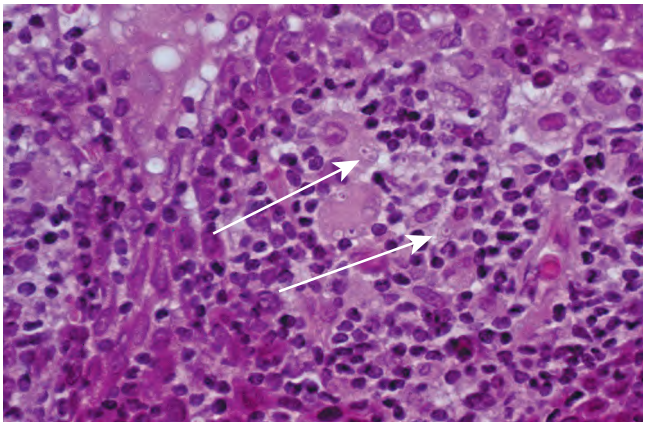
The diagnosis of histoplasmosis can be made by histopathologic identification of the organism in tissue sections or by culture. Other helpful diagnostic studies include serologic testing in which antibodies directed against *H. capsulatum* are demonstrated and antigen produced by the yeast is identified.



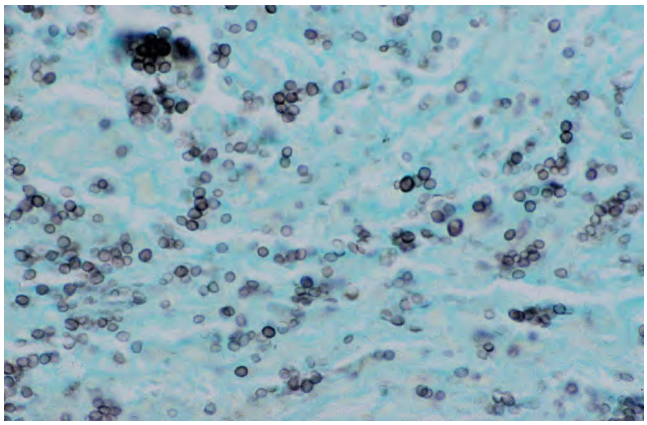
• **Fig. 6-19 Histoplasmosis.** This chronic ulceration of the ventral and lateral tongue represents an oral lesion of histoplasmosis that had disseminated from the lungs. The lesion clinically resembles carcinoma; because of this high-risk site, biopsy is mandatory.



• **Fig. 6-18 Histoplasmosis.** This ulcerated granular lesion involves the mandibular labial vestibule and is easily mistaken clinically for carcinoma. Biopsy established the diagnosis. (Courtesy of Dr. John Werther.)



• **Fig. 6-20 Histoplasmosis.** This medium-power photomicrograph shows scattered epithelioid macrophages admixed with lymphocytes and plasma cells. Some macrophages contain organisms of *Histoplasma capsulatum (arrows)*.



• **Fig. 6-21 Histoplasmosis.** This high-power photomicrograph of a tissue section readily demonstrates the small yeasts of *Histoplasma capsulatum*. (Grocott-Gomori methenamine silver stain.)

Treatment and Prognosis

Acute histoplasmosis, because it is a self-limited process, generally warrants no specific treatment other than supportive care with analgesic and antipyretic agents. Often the disease is not treated because the symptoms are so nonspecific and the diagnosis is not readily evident.

Patients with chronic histoplasmosis require treatment, despite the fact that up to half of them may recover spontaneously. Often the pulmonary damage is progressive if it remains untreated, and death may result in up to 20% of these cases. For severe cases of chronic histoplasmosis, the treatment of choice is IV administration of one of the lipid preparations of amphotericin B, which are significantly less toxic than standard formulations of amphotericin B deoxycholate. Itraconazole may be used in nonimmunosuppressed patients because it is associated with even fewer side effects and is less expensive, but this medication requires daily dosing for at least 3 months. Although fluconazole has been used for treatment of histoplasmosis, this agent appears to be less effective than itraconazole and less likely to produce a desired therapeutic response.

Disseminated histoplasmosis occurring in an immunesuppressed individual is a very serious condition that results in death in 80% to 90% of patients if they remain untreated. One of the lipid preparations of amphotericin B is indicated for such patients; once the life-threatening phase of the disease is under control, daily itraconazole is necessary for 6 to 18 months. Despite therapy, however, a mortality rate of 7% to 23% is observed. Itraconazole alone may be used if the patient is nonimmunocompromised and has relatively mild to moderate disease; however, the response rate is slower than for patients receiving amphotericin B, and the relapse rate may be higher.

◆ BLASTOMYCOSIS

Blastomycosis is a relatively uncommon disease caused by the dimorphic fungus known as *Blastomyces dermatitidis*. Although the organism is rarely isolated from its natural habitat, it seems to prefer rich, moist soil, where it grows as a mold. Much of the region in which it grows overlaps the territory associated with *H. capsulatum* (affecting the eastern half of the United States). The range of blastomycosis extends farther north, however, including Wisconsin, Minnesota, and the Canadian provinces surrounding the Great Lakes. Sporadic cases have also been reported in Africa, India, Europe, and South America. By way of comparison, histoplasmosis appears to be at least ten times more common than blastomycosis. In some series of cases, a prominent adult male predilection has been noted, often with a male-to-female ratio as high as 9:1. Although some researchers have attributed this to the greater degree of outdoor activity (e.g., hunting, fishing) by men in areas where the organism grows, others have noted that these series were typically reported from VA hospital data, which has an inherent male bias. The occurrence of blastomycosis in immunocompromised patients is relatively rare.

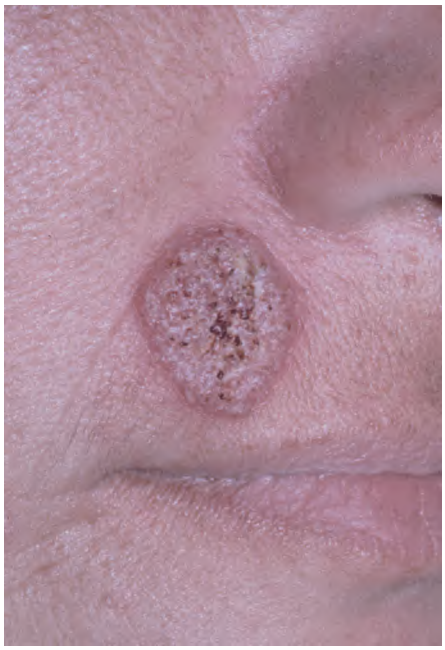
Clinical and Radiographic Features

Blastomycosis is almost always acquired by inhalation of spores, particularly after a rain. The spores reach the alveoli of the lungs, where they begin to grow as yeasts at body temperature. In most patients, the infection is probably halted and contained in the lungs, but it may become hematogenously disseminated in a few instances. In order of decreasing frequency, the sites of dissemination include skin, bone, prostate, meninges, oropharyngeal mucosa, and abdominal organs.

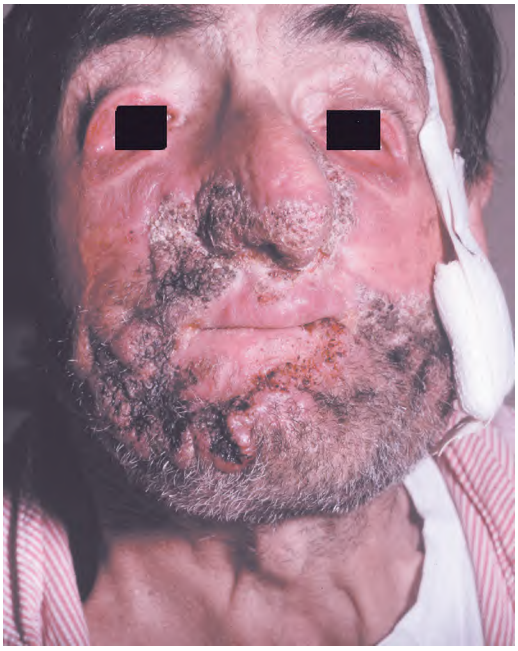
Although most cases of blastomycosis are either asymptomatic or produce only very mild symptoms, patients who do experience symptoms usually have pulmonary complaints. **Acute blastomycosis** resembles pneumonia, characterized by high fever, chest pain, malaise, night sweats, and productive cough with mucopurulent sputum. Rarely, the infection may precipitate life-threatening adult respiratory distress syndrome.

Chronic blastomycosis is more common than the acute form, and it may mimic tuberculosis; both conditions are often characterized by low-grade fever, night sweats, weight loss, and productive cough. Chest radiographs may appear normal, or they may demonstrate diffuse infiltrates or one or more pulmonary or hilar masses. Unlike the situation with tuberculosis and histoplasmosis, calcification is not typically present. Cutaneous lesions usually represent the spread of infection from the lungs, although occasionally they are the only sign of disease. Such lesions begin as erythematous nodules that enlarge, becoming verrucous or ulcerated (Figs. 6-22 and 6-23).

Oral lesions of blastomycosis may result from either extrapulmonary dissemination or local inoculation with the organism. These lesions may have an irregular, erythematous or white intact surface, or they may appear as ulcerations with irregular rolled borders and varying degrees of pain (Figs. 6-24 and 6-25). Clinically, because the lesions



• **Fig. 6-22 Blastomycosis.** This granular erythematous plaque of cutaneous blastomycosis has affected the facial skin. (Courtesy of Dr. William Welton.)

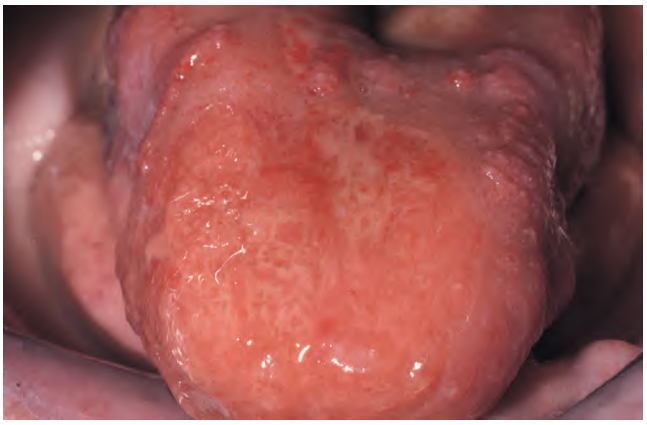


• **Fig. 6-23 Blastomycosis.** Severe cutaneous infection by *Blastomyces dermatitidis.* (Courtesy of Dr. Emmitt Costich.)

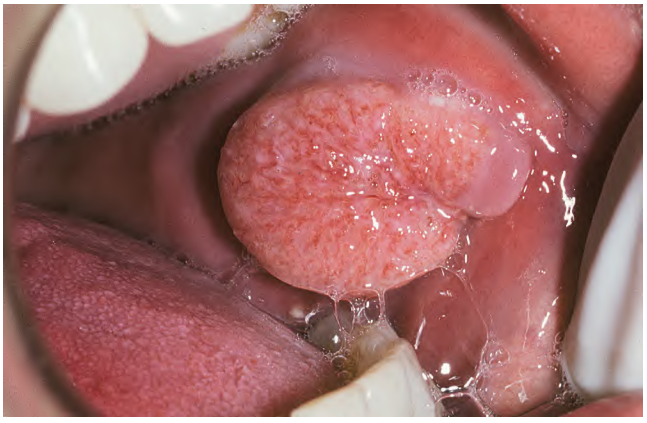
resemble squamous cell carcinoma, biopsy and histopathologic examination are required.

Histopathologic Features

Histopathologic examination of lesional tissue typically shows a mixture of acute inflammation and granulomatous inflammation surrounding variable numbers of yeasts. These organisms are 8 to 20 µm in diameter. They are



• **Fig. 6-24 Blastomycosis.** These irregular ulcerations of the tongue represent blastomycosis. Direct inoculation was thought to have occurred from the patient's habit of chewing dried horse manure ("Kentucky field candy"), in which the organism was probably growing.

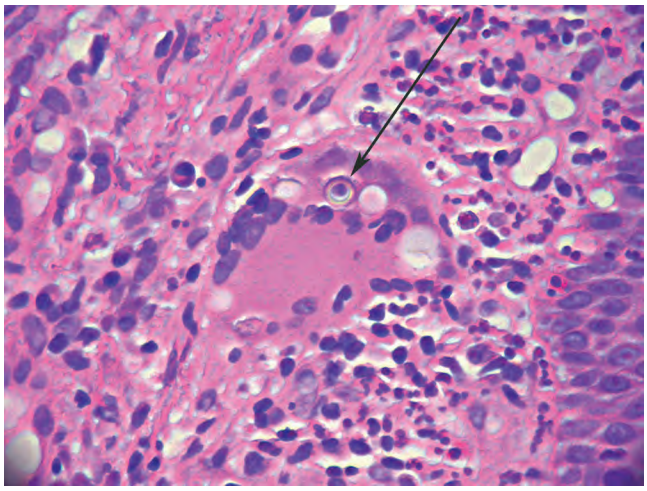


• **Fig. 6-25 Blastomycosis.** Granular exophytic and indurated mass on the buccal mucosa.

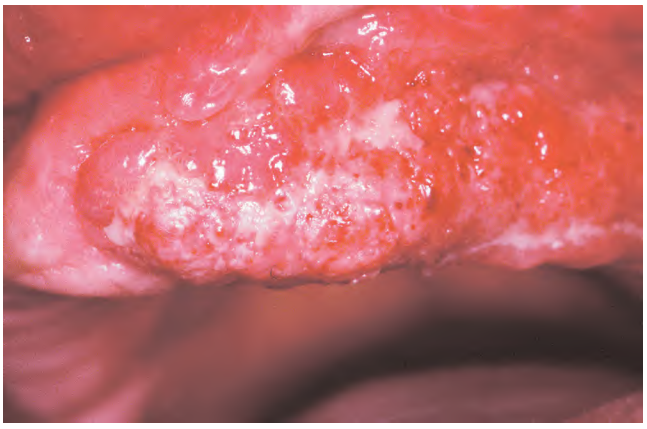
characterized by a doubly refractile cell wall (Fig. 6-26) and a broad attachment between the budding daughter cell and the parent cell. Like many other fungal organisms, *B. dermatitidis* can be detected more easily using special stains, such as the Grocott-Gomori methenamine silver and PAS methods. Identification of these organisms is especially important, because this infection often induces a benign reaction of the overlying epithelium in mucosal or skin lesions called **pseudoepitheliomatous (pseudocarcinomatous) hyperplasia.** Because this benign elongation of the epithelial rete ridges may look like squamous cell carcinoma at first glance under the microscope, careful inspection of the underlying inflamed lesional tissue is mandatory.

Diagnosis

Rapid diagnosis of blastomycosis can be performed by microscopic examination of either histopathologic sections or an alcohol-fixed cytologic preparation. The most rapid means of diagnosis, however, is the KOH preparation, which may be used for examining scrapings from a suspected lesion. The most accurate method of identifying *B. dermatitidis* is by obtaining a culture specimen from



• **Fig. 6-26 Blastomycosis.** This high-power photomicrograph shows the large yeasts of *Blastomyces dermatitidis (arrow)* within a multinucleated giant cell.



• **Fig. 6-27 Paracoccidioidomycosis.** This granular, erythematous, and ulcerated lesion of the maxillary alveolus represents infection by *Paracoccidioides brasiliensis*. (Courtesy of Dr. Ricardo Santiago Gomez.)

sputum or fresh biopsy material and growing the organism on Sabouraud agar. This is a slow technique, however, sometimes taking as long as 3 to 4 weeks for the characteristic mycelium-to-yeast conversion to take place. A specific DNA probe has been developed, allowing immediate identification of the mycelial phase that usually appears by 5 to 7 days in culture. Serologic studies and skin testing are usually not helpful because of lack of reactivity and specificity.

Treatment and Prognosis

As stated previously, most patients with blastomycosis are asymptomatic or have only mild symptoms, so treatment may not be given because the disease is often not suspected. In the case of documented symptomatic acute or chronic pulmonary blastomycosis, itraconazole should be prescribed for mild to moderate disease, whereas systemic amphotericin B is indicated for severe cases.

Immunosuppressed patients or those with extrapulmonary lesions also need treatment with amphotericin B, followed by 6 to 12 months of itraconazole. Although ketoconazole and fluconazole are active against *B. dermatitidis,* these drugs have been shown to be less effective than itraconazole.

Disseminated blastomycosis occurs in only a small percentage of infected patients and, with proper treatment, the outlook for the patient is reasonably good. Still, mortality rates ranging from 4% to 22% have been described over the past 20 years, with men, blacks, and patients with HIV infection tending to have less favorable outcomes.

◆ PARACOCCIDIOIDOMYCOSIS (SOUTH AMERICAN BLASTOMYCOSIS)

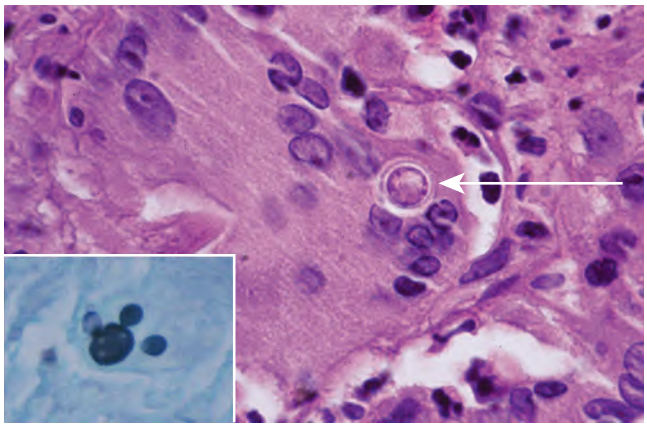
Paracoccidioidomycosis is a deep fungal infection that is caused by *Paracoccidioides brasiliensis*. The condition is seen most frequently in patients who live in either South America (primarily Brazil, Colombia, Venezuela, Uruguay, and Argentina) or Central America. However, immigrants from those regions and visitors to those areas can acquire the infection. Within some endemic areas, the nine-banded armadillo has been shown to harbor *P. brasiliensis* (similar to the situation seen with leprosy) (see page 179). Although there is no evidence that the armadillo directly infects humans, it may be responsible for the spread of the organism in the environment.

Paracoccidioidomycosis has a distinct predilection for males, with a 15:1 male-to-female ratio typically reported. This striking difference is thought to be attributable to a protective effect of female hormones (because β-estradiol inhibits the transformation of the hyphal form of the organism to the pathogenic yeast form). This theory is supported by the finding of an equal number of men and women who have antibodies directed against the yeast.

Clinical Features

Patients with paracoccidioidomycosis are typically middle-aged at the time of diagnosis, and most are employed in agriculture. Most cases of paracoccidioidomycosis are thought to appear initially as pulmonary infections after exposure to the spores of the organism. Although infections are generally self-limiting, *P. brasiliensis* may spread by a hematogenous or lymphatic route to a variety of tissues, including lymph nodes, skin, and adrenal glands. Adrenal involvement often results in hypoadrenocorticism **(Addison disease)** (see page 784).

Oral lesions are frequently observed and appear as mulberry-like ulcerations that most commonly affect the alveolar mucosa, gingiva, and palate (Fig. 6-27). The lips, tongue, oropharynx, and buccal mucosa are also involved in a significant percentage of cases. In most patients with oral lesions, more than one oral mucosal site is affected.



• **Fig. 6-28 Paracoccidioidomycosis.** This high-power photomicrograph shows a large yeast of *Paracoccidioides brasiliensis (arrow)* within the cytoplasm of a multinucleated giant cell. A section stained with the Grocott-Gomori methenamine silver method *(inset)* illustrates the characteristic "Mickey Mouse ears" appearance of the budding yeasts. (Courtesy of Dr. Ricardo Santiago Gomez.)

Histopathologic Features

Microscopic evaluation of tissue obtained from an oral lesion may reveal pseudoepitheliomatous hyperplasia in addition to ulceration of the overlying surface epithelium. *P. brasiliensis* elicits a granulomatous inflammatory host response that is characterized by collections of epithelioid macrophages and multinucleated giant cells (Fig. 6-28). Scattered, large (up to 30 μm in diameter) yeasts are readily identified after staining of the tissue sections with the Grocott-Gomori methenamine silver or PAS method. The organisms often show multiple daughter buds on the parent cell, resulting in an appearance that has been described as resembling "Mickey Mouse ears" or the spokes of a ship's steering wheel ("mariner's wheel").

Diagnosis

Demonstration of the characteristic multiple budding yeasts in the appropriate clinical setting is usually adequate to establish a diagnosis of paracoccidioidomycosis. Specimens for culture can be obtained, but *P. brasiliensis* grows quite slowly.

Treatment and Prognosis

The method of management of patients with paracoccidioidomycosis depends on the severity of the disease presentation. Sulfonamide derivatives have been used since the 1940s to treat this infection. These drugs, such as trimethoprim/sulfamethoxazole, are still used today in many instances to treat mild-to-moderate cases, particularly in developing countries with limited access to the newer, more expensive antifungal agents. For severe involvement, IV amphotericin B is usually indicated. Non–life-threatening cases are best managed by oral itraconazole, although therapy may be needed for several months. Ketoconazole can also be used, although the side effects are typically greater than those associated with itraconazole.

◆ COCCIDIOIDOMYCOSIS (SAN JOAQUIN VALLEY FEVER; VALLEY FEVER; COCCI)

Recent molecular genetic studies have identified two species, *Coccidioides immitis* and *Coccidioides posadasii,* as the fungal organisms responsible for **coccidioidomycosis.** *C. immitis* grows saprophytically in the alkaline, semiarid, desert soil of the southwestern United States and Mexico, whereas *C. posadasii* is generally found in similar isolated arid regions in Central and South America, with some overlap in their ranges. As with several other pathogenic fungi, *C. immitis* and *C. posadasii* are dimorphic organisms, appearing as a mold in the natural environment of the soil and as a yeast in tissues of the infected host. Arthrospores produced by the mold become airborne and can be inhaled into the lungs of the human host, producing infection. Both *Coccidioides* species produce clinically identical signs and symptoms.

Coccidioidomycosis is confined to the Western hemisphere and is endemic throughout the desert regions of southwestern United States and Mexico; however, with modern travel taking many visitors to and from the Sunbelt, this disease can be encountered virtually anywhere in the world. It is estimated that 100,000 people are infected annually in the United States, although 60% of this group are asymptomatic.

Clinical Features

Even though most infections with *C. immitis* are asymptomatic, approximately 40% of infected patients experience a flulike illness and pulmonary symptoms within 1 to 3 weeks after inhaling the arthrospores. Fatigue, cough, chest pain, myalgias, and headache are commonly reported, lasting several weeks with spontaneous resolution in most cases. Occasionally, the immune response may trigger a hypersensitivity reaction that causes the development of an erythema multiforme–like cutaneous eruption (see page 723) or erythema nodosum. Erythema nodosum is a condition that usually affects the skin of the legs and is characterized by the appearance of multiple painful erythematous inflammatory nodules in the subcutaneous connective tissue. This hypersensitivity reaction occurring in conjunction with coccidioidomycosis is termed **valley fever**, and it resolves as the host cell–mediated immune response controls the pulmonary infection.

Chronic progressive pulmonary coccidioidomycosis is relatively rare. It mimics tuberculosis, with its clinical presentation of persistent cough, hemoptysis, chest pain, low-grade fever, and weight loss.

Disseminated coccidioidomycosis occurs when the organism spreads hematogenously to extrapulmonary sites.

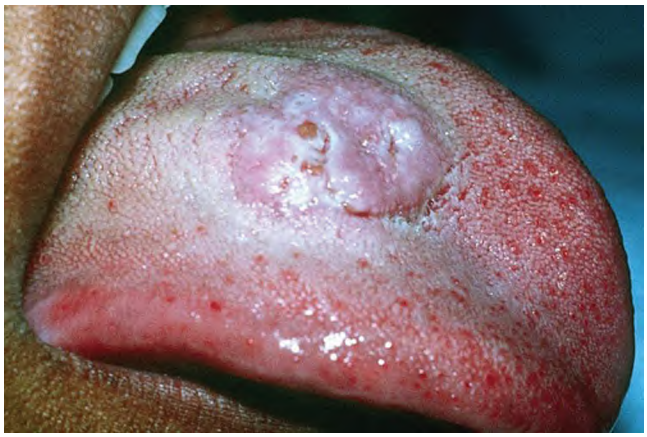


Fig. 6-29 Coccidioidomycosis. This ulcerated nodule involving the mid-dorsal tongue represents disseminated coccidioidomycosis. (Courtesy of Dr. Craig Fowler.)

This occurs in less than 1% of cases, but it is a more serious problem. The most commonly involved areas include skin, lymph nodes (including cervical lymph nodes), bone and joints, and the meninges. Immunosuppression greatly increases the risk of dissemination. The following groups are particularly susceptible:

- Patients taking large doses of systemic corticosteroids (e.g., organ transplant recipients)
- Patients who are being treated with cancer chemotherapy
- Patients who are being treated with TNF-α inhibitors
- Patients in the end stages of HIV infection
- Patients who are pregnant

Infants and older adult patients, both of whom may have suboptimally functioning immune systems, also may be at increased risk for disseminated disease. Persons of color (e.g., blacks, Filipinos, and Native Americans) also seem to have an increased risk, but it is unclear whether their susceptibility is due to genetic causes or socioeconomic factors, such as occupation or poor nutrition.

The cutaneous lesions may appear as papules, subcutaneous abscesses, verrucous plaques, and granulomatous nodules. Of prime significance to the clinician is the predilection for these lesions to develop in the area of the central face, especially the nasolabial fold. Oral lesions are distinctly uncommon, and these have been described as ulcerated granulomatous nodules (Fig. 6-29).

Histopathologic Features

Biopsy material shows large (20 to 60 μm), round spherules that may contain numerous endospores. The host response may be variable, ranging from a suppurative, neutrophilic infiltrate to a granulomatous inflammatory response. In some cases, the two patterns of inflammation are seen concurrently. Special stains, such as the PAS and Grocott-Gomori methenamine silver methods, enable the pathologist to identify the organism more readily.

Diagnosis

The diagnosis of coccidioidomycosis can be confirmed by culture or identification of characteristic organisms in biopsy material. If the organisms do not have a classic microscopic appearance, then *in situ* hybridization studies using specific complementary DNA probes for *C. immitis* can be performed to definitively identify the fungus. Cytologic preparations from bronchial swabbing or sputum samples may also reveal the organisms.

Serologic studies are helpful in supporting the diagnosis, and they may be performed at the same time as skin testing. Skin testing by itself may be of limited value in determining the diagnosis, because many patients in endemic areas have already been exposed to the organism and have positive test findings.

Treatment

The decision whether or not to treat a particular patient affected by coccidioidomycosis depends on the severity and extent of the infection and the patient's immune status. Relatively mild symptoms in an immunocompetent person do not warrant treatment. Amphotericin B is administered for the following groups:

- Immunosuppressed patients
- Patients with severe pulmonary infection
- Patients who have disseminated disease
- Patients who are pregnant
- Patients who appear to be in a life-threatening situation concerning the infection

For many cases of coccidioidomycosis, fluconazole or itraconazole is the drug of choice, usually given in high doses for an extended period of time. Although the response of the disease to these oral azole medications may be somewhat slower than that of amphotericin B, the side effects and complications of therapy are far fewer.

◆ CRYPTOCOCCOSIS

Cryptococcosis is a relatively uncommon fungal disease caused primarily by the yeast *Cryptococcus neoformans* in North America. This organism normally causes no problem in immunocompetent people, but it can be devastating to the immunocompromised patient. The incidence of cryptococcosis increased dramatically during the 1990s, primarily because of the AIDS epidemic. At that time, this was the most common life-threatening fungal infection in these patients. However, with the advent of combination antiretroviral therapy (cART) (see page 253), this complication has become less of a problem in the United States. In countries where the population cannot afford cART, cryptococcosis remains a significant cause of death for AIDS patients. The disease has a worldwide distribution because of its association with the pigeon (with the organism living in the deposits of excreta left by the birds). Unlike many other pathogenic fungi, *C. neoformans* grows as a yeast both in

the soil and in infected tissue. The organism usually produces a prominent mucopolysaccharide capsule that appears to protect it from host immune defenses.

The disease is acquired by inhalation of *C. neoformans* spores into the lungs, resulting in an immediate influx of neutrophils, which destroys most of the yeasts. Macrophages soon follow, although resolution of infection in the immunocompetent host ultimately depends on an intact cell-mediated immune system.

Over the past decade, molecular genetic studies have identified another species of *Cryptococcus,* designated *Cryptococcus gattii,* which had initially been thought to be a serotype of *C. neoformans.* This organism seems to be more capable of producing infection in otherwise normal immunocompetent individuals. Although *C. gattii* is more commonly found in tropical and subtropical environments, outbreaks have been documented in the Pacific Northwest in North America.

Clinical Features

Primary cryptococcal infection of the lungs is often asymptomatic; however, a mild flulike illness may develop. Patients complain of productive cough, chest pain, fever, and malaise. Most patients with a diagnosis of cryptococcosis have a significant underlying medical problem related to immune suppression (e.g., systemic corticosteroid therapy, cancer chemotherapy, malignancy, and AIDS). It is estimated that 5% to 10% of AIDS patients acquire this infection (see page 239).

Dissemination of the infection is common in these immunocompromised patients, and the most frequent site of involvement is the meninges, followed by skin, bone, and the prostate gland.

Cryptococcal meningitis is characterized by headache, fever, vomiting, and neck stiffness. In many instances, this is the initial sign of the disease.

Cutaneous lesions develop in 10% to 15% of patients with disseminated disease. These are of particular importance to the clinician, because the skin of the head and neck is often involved. The lesions appear as erythematous papules or pustules that may ulcerate, discharging a puslike material rich in cryptococcal organisms (Fig. 6-30).

Although oral lesions are relatively rare, they have been described either as craterlike, nonhealing ulcers that are tender on palpation or as friable papillary erythematous plaques. Dissemination to salivary gland tissue also has been reported rarely.

Histopathologic Features

Microscopic sections of a cryptococcal lesion generally show a granulomatous inflammatory response to the organism. The extent of the response may vary, however, depending on the host's immune status and the strain of the organism. The yeast appears as a round-to-ovoid structure, 4 to 6 μm in diameter, surrounded by a clear halo that represents the capsule. Staining with the PAS or Grocott-Gomori methenamine silver method readily identifies the fungus; moreover, a mucicarmine stain uniquely demonstrates its mucopolysaccharide capsule.

• **Fig. 6-30 Cryptococcosis.** These papules of the facial skin represent disseminated cryptococcal infection in a patient infected with human immunodeficiency virus (HIV). (Courtesy of Dr. Catherine Flaitz.)

Diagnosis

The diagnosis of cryptococcosis can be made by several methods, including biopsy and culture. Detection of cryptococcal polysaccharide antigen in the serum or cerebrospinal fluid is also useful as a diagnostic procedure.

Treatment and Prognosis

Management of cryptococcal infections can be very difficult because most of the affected patients have an underlying medical problem. Before amphotericin B was developed, cryptococcosis was almost uniformly fatal. For cryptococcal meningitis, a combination of systemic amphotericin B and another antifungal drug (flucytosine) is used initially for 2 weeks in most cases to treat this disease. Then, either fluconazole or itraconazole is given for an additional minimal period of 10 weeks. For relatively mild cases of pulmonary cryptococcosis, only fluconazole or itraconazole may be used. These drugs produce far fewer side effects than do amphotericin B and flucytosine, and they have proven to be important therapeutic tools for managing this type of infection.

◆ MUCORMYCOSIS (ZYGOMYCOSIS; PHYCOMYCOSIS)

Mucormycosis is an opportunistic, frequently fulminant, fungal infection that is caused by normally saprobic organisms of the subphylum Mucoromycotina, including such genera as *Absidia, Mucor, Rhizomucor,* and *Rhizopus.* The term *zygomycosis* is still used extensively in the literature, although recent molecular genetic studies have indicated

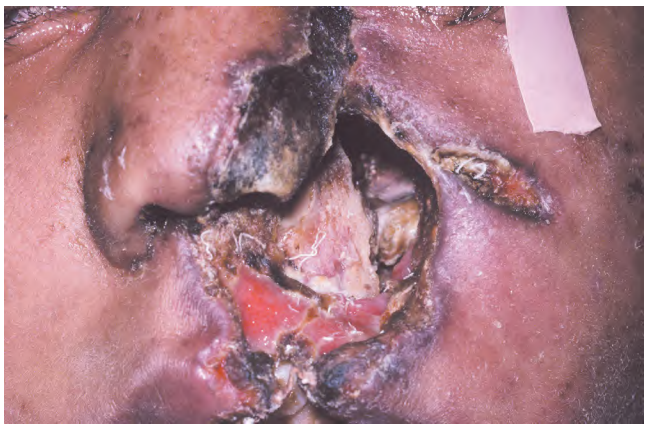
that the class Zygomycetes actually is comprised of several unrelated fungi. Mucoromycotina organisms are found throughout the world, growing in their natural state on a variety of decaying organic materials. Numerous spores may be liberated into the air and inhaled by the human host.

Mucormycosis may involve any one of several areas of the body, but the rhinocerebral form is most relevant to the oral health care provider. Mucormycosis is noted especially in insulin-dependent diabetics who have uncontrolled diabetes and are ketoacidotic; ketoacidosis inhibits the binding of iron to transferrin, allowing serum iron levels to rise. The growth of these fungi is enhanced by iron, and patients who are taking deferoxamine (an iron-chelating agent used in the treatment of diseases, such as thalassemia) are also at increased risk for developing mucormycosis. As with many other fungal diseases, this infection affects immunocompromised patients as well, including bone marrow transplant recipients, patients with AIDS, and those receiving systemic corticosteroid therapy. Only rarely has mucormycosis been reported in apparently healthy individuals in the oral region.

Clinical and Radiographic Features

The presenting symptoms of rhinocerebral mucormycosis may be exhibited in several ways. Patients may experience nasal obstruction, bloody nasal discharge, facial pain or headache, facial swelling or cellulitis, and visual disturbances with concurrent proptosis. Symptoms related to cranial nerve involvement (e.g., facial paralysis) are often present. With progression of disease into the cranial vault, blindness, lethargy, and seizures may develop, followed by death.

If the maxillary sinus is involved, the initial presentation may be seen as intraoral swelling of the maxillary alveolar process, the palate, or both. If the condition remains untreated, palatal ulceration may evolve, with the surface of the ulcer typically appearing black and necrotic. Massive tissue destruction may result if the condition is not treated (Figs. 6-31 and 6-32).

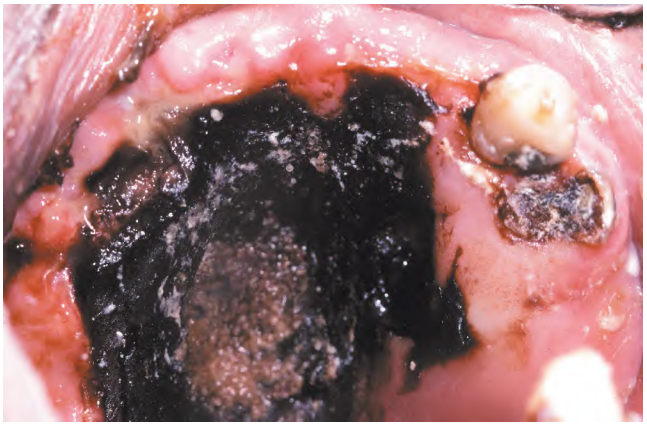


• **Fig. 6-31 Mucormycosis.** Diffuse tissue destruction involving the nasal and maxillary structures caused by a *Mucor* species. (Courtesy of Dr. Sadru Kabani.)

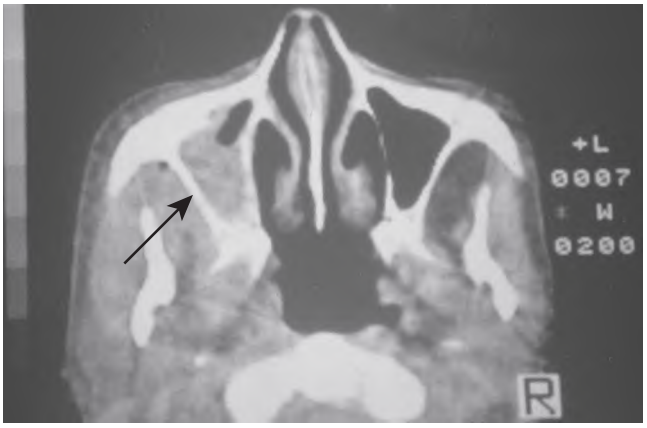
Radiographically, opacification of the sinuses may be observed in conjunction with patchy effacement of the bony walls of the sinuses (Fig. 6-33). Such a picture may be difficult to distinguish from that of a malignancy affecting the sinus area.

Histopathologic Features

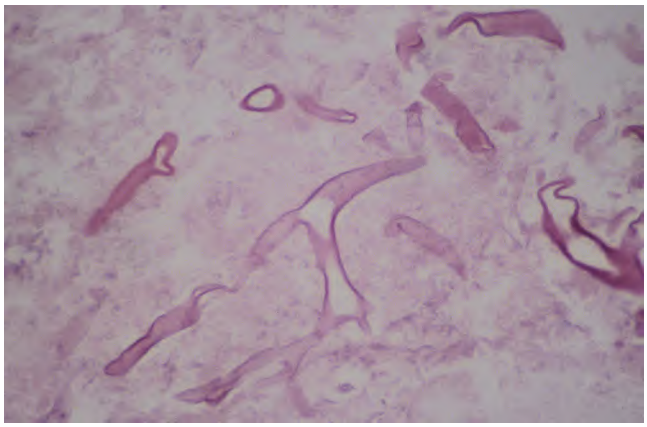
Histopathologic examination of lesional tissue shows extensive necrosis with numerous large (6 to 30 μm in diameter), branching, nonseptate hyphae at the periphery (Fig. 6-34). The hyphae tend to branch at 90-degree angles. The extensive tissue destruction and necrosis associated with this disease are undoubtedly attributable to the preference of the fungi for invasion of small blood vessels. This disrupts normal blood flow to the tissue, resulting in infarction and necrosis. A neutrophilic infiltrate usually predominates in the viable tissue, but the host inflammatory cell response to the infection may be minimal, particularly if the patient is immunosuppressed.



• **Fig. 6-32 Mucormycosis.** The extensive black, necrotic lesion of the palate represents mucormycotic infection that extended from the maxillary sinus in a patient with poorly controlled type I diabetes mellitus. (Courtesy of Dr. Michael Tabor.)



• **Fig. 6-33 Mucormycosis.** This computed tomography (CT) scan demonstrates the opacification of the left maxillary sinus *(arrow).*



• **Fig. 6-34 Mucormycosis.** This high-power photomicrograph shows the large, nonseptate fungal hyphae characteristic of the mucormycotic organisms.

Diagnosis

Diagnosis of mucormycosis is usually based on the histopathologic findings. Because of the grave nature of this infection, appropriate therapy must be instituted in a timely manner (often without the benefit of definitive culture results).

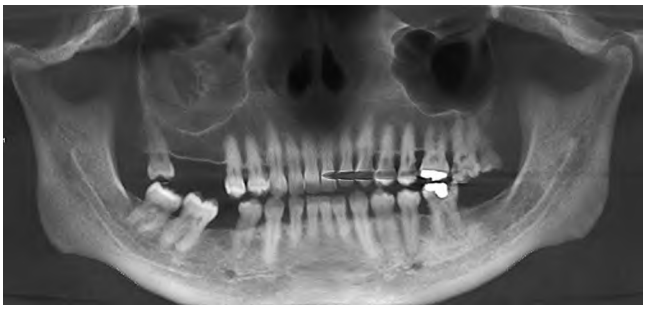
Treatment and Prognosis

Successful treatment of mucormycosis consists of rapid accurate diagnosis of the condition, followed by radical surgical débridement of the infected, necrotic tissue and systemic administration of high doses of one of the lipid formulations of amphotericin B. Magnetic resonance imaging (MRI) of the head may be useful in determining the extent of disease involvement so that surgical margins can be planned. Evaluation of frozen sections of curetted tissue, which has been stained with Calcofluor white and examined with fluorescence microscopy, can also be used to guide the extent of débridement. In addition, control of the patient's underlying disease (e.g., diabetic ketoacidosis) must be attempted.

Despite such therapy, the prognosis is usually poor, with approximately 40% to 50% of patients who develop rhinocerebral mucormycosis dying of their disease. Because their underlying systemic disease can usually be controlled, diabetic patients typically have a better prognosis than those who are immunosuppressed. If the patient survives, the massive tissue destruction that remains presents a challenge both functionally and aesthetically. Prosthetic obturation of palatal defects may be necessary.

◆ ASPERGILLOSIS

Aspergillosis is a fungal disease that is characterized by noninvasive and invasive forms. Noninvasive aspergillosis usually affects a normal host, appearing either as an allergic reaction or a cluster of fungal hyphae. Localized invasive infection of damaged tissue may be seen in a normal host, but a more extensive invasive infection is often evident in the immunocompromised patient. With the advent of intensive chemotherapeutic regimens, the AIDS epidemic, and both solid-organ and bone marrow transplantation, the prevalence of invasive aspergillosis has increased dramatically in the past 20 years. Patients with uncontrolled diabetes mellitus are also susceptible to *Aspergillus* spp. infections. Rarely, invasive aspergillosis has been reported to affect the paranasal sinuses of apparently normal immunocompetent individuals.



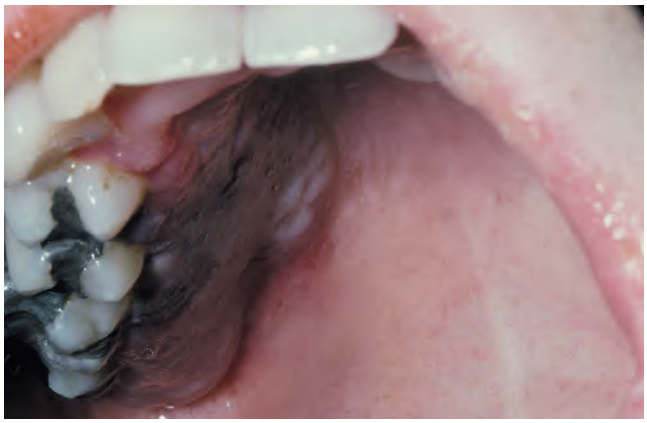
• **Fig. 6-35 Aspergillosis.** The opaque appearance of the right maxillary sinus is due to the presence of a fungus ball (aspergilloma). (Courtesy of Dr. Bart Farrell.)

Normally, the various species of the *Aspergillus* genus reside worldwide as saprobic organisms in soil, water, or decaying organic debris. Resistant spores are released into the air and inhaled by the human host, resulting in opportunistic fungal infection second in frequency only to candidiasis. Interestingly, most species of *Aspergillus* cannot grow at 37° C; only the pathogenic species have the ability to replicate at body temperature.

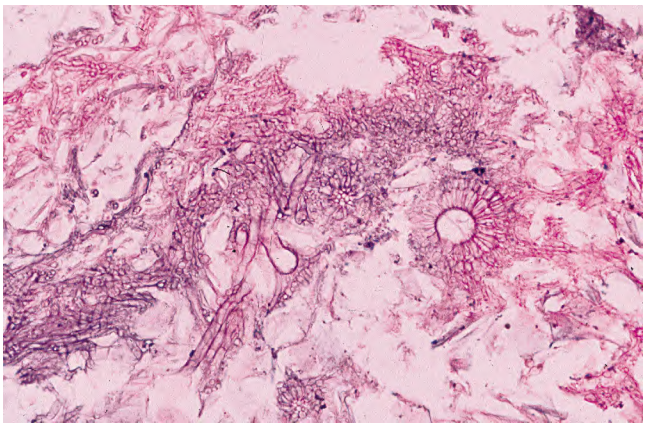
The two most commonly encountered species of *Aspergillus* in the medical setting are *A. flavus* and *A. fumigatus,* with *A. fumigatus* being responsible for most cases of aspergillosis. The patient may acquire such infections in the hospital (**"nosocomial"** infection), especially if remodeling or building construction is being performed in the immediate area. Such activity often stirs up the spores, which are then inhaled by the patient.

Clinical Features

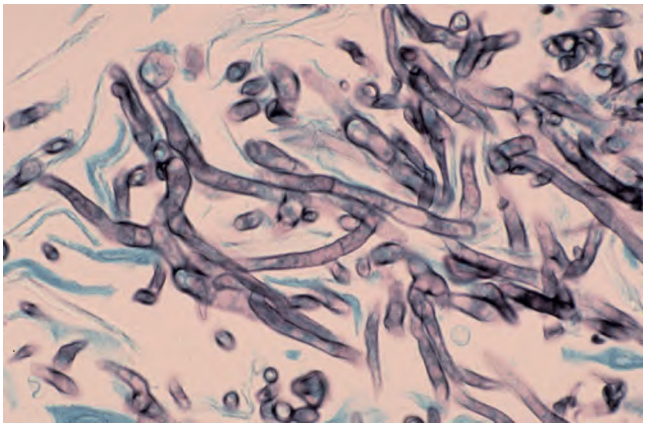
The clinical manifestations of aspergillosis vary, depending on the host immune status and the presence or absence of tissue damage. In the normal host, the disease may appear as an allergy affecting either the sinuses **(allergic fungal sinusitis)** or the bronchopulmonary tract. An asthma attack may be triggered by inhalation of spores by a susceptible person. Sometimes a low-grade infection becomes established in the maxillary sinus, resulting in a mass of fungal hyphae called a **fungus ball,** although **aspergilloma** and **mycetoma** are terms that are also sometimes used (Fig. 6-35). Occasionally, the mass will undergo dystrophic calcification, producing a radiopaque body called an **antrolith** within the sinus.



• **Fig. 6-36 Aspergillosis.** This young woman developed a painful purplish swelling of her hard palate after induction chemotherapy for leukemia.



• **Fig. 6-37 Aspergillosis.** This photomicrograph reveals fungal hyphae and a fruiting body of an *Aspergillus* species.



• **Fig. 6-38 Aspergillosis.** This high-power photomicrograph shows the characteristic septate hyphae of *Aspergillus* species. (Grocott-Gomori methenamine silver stain.)

Another presentation that may be encountered by the oral health care provider is aspergillosis after tooth extraction or endodontic treatment, especially in the maxillary posterior segments. Presumably, tissue damage predisposes the sinus to infection, resulting in symptoms of localized pain and tenderness accompanied by nasal discharge. Immunocompromised patients are particularly susceptible to oral aspergillosis, and some investigators have suggested that the portal of entry may be the marginal gingiva and gingival sulcus. Painful gingival ulcerations are initially noted, and peripherally the mucosa and soft tissue develops diffuse swelling with a gray or violaceous hue (Fig. 6-36). If the disease is not treated, extensive necrosis, which is seen clinically as a yellow or black ulcer, and facial swelling evolve.

Disseminated aspergillosis occurs principally in immunocompromised patients, particularly in those who have leukemia or who are taking high daily doses of corticosteroids. Such patients usually exhibit symptoms related to the primary site of inoculation: the lungs. The patient typically has chest pain, cough, and fever, but such symptoms are vague. Therefore, obtaining an early, accurate diagnosis may be difficult. Once the fungal organism obtains access to the bloodstream, infection can spread to such sites as the CNS, eye, skin, liver, gastrointestinal tract, bone, and thyroid gland.

Histopathologic Features

Tissue sections of invasive *Aspergillus* spp. lesions show varying numbers of branching, septate hyphae, 3 to 4 μm in diameter (Figs. 6-37 and 6-38). These hyphae show a tendency to branch at an acute angle and to invade adjacent small blood vessels. Occlusion of the vessels often results in the characteristic pattern of necrosis associated with this disease. In the immunocompetent host, a granulomatous inflammatory response—in addition to necrosis—can be expected. In the immunocompromised patient, however, the inflammatory response is often weak or absent, leading to extensive tissue destruction.

Noninvasive forms of aspergillosis have histopathologic features that differ from invasive aspergillosis, however. The fungus ball, for example, is characterized by a tangled mass of hyphae with no evidence of tissue invasion. Because the fungus ball develops in a paranasal sinus (where it is exposed to air), spore-bearing structures called *fruiting bodies* are formed (see Fig. 6-37). Allergic fungal sinusitis, on the other hand, histopathologically exhibits large pools of eosinophilic inspissated mucin with interspersed sheetlike collections of lymphocytes and eosinophils. Relatively few fungal hyphae are identified, and then only with careful examination after Grocott-Gomori methenamine silver staining.

Diagnosis

Although the diagnosis of fungal infection can be established by identification of hyphae within tissue sections, this finding is only suggestive of aspergillosis because other fungal organisms may appear similar microscopically. Ideally, the diagnosis should be supported by culture of the organism from the lesion; however, from a practical

standpoint, treatment may need to be initiated immediately to prevent the patient's demise. Culture specimens of sputum and blood are of limited value, because they are often negative despite disseminated disease.

Treatment and Prognosis

Treatment depends on the clinical presentation of aspergillosis. For immunocompetent patients with a noninvasive aspergilloma, surgical débridement may be all that is necessary. Patients who have allergic fungal sinusitis are treated with débridement and corticosteroid drugs. For localized invasive aspergillosis in the immunocompetent host, débridement followed by antifungal medication is indicated. Although systemic amphotericin B deoxycholate therapy was considered appropriate in the past, studies have shown that voriconazole, a triazole antifungal agent, is more effective for treating these patients. In one large series of patients with invasive aspergillosis, 71% of those treated with voriconazole were alive after 12 weeks of therapy, compared with 58% survival in the group who received standard amphotericin B treatment. For patients who cannot tolerate voriconazole, alternative drugs include liposomal amphotericin B or caspofungin. Immunocompromised patients who have invasive aspergillosis should be treated by aggressive débridement of necrotic tissue, combined with systemic antifungal therapy as described previously.

The prognosis for immunocompromised patients is much worse compared with immunocompetent individuals, particularly if the infection is disseminated. Even with appropriate therapy, only about one third of these patients survive. Because aspergillosis in the immunocompromised patient usually develops while the individual is hospitalized, particular attention should be given to the ventilation system in the hospital to prevent patient exposure to the airborne spores of *Aspergillus* spp.

◆ TOXOPLASMOSIS

Toxoplasmosis is a relatively common disease caused by the obligate intracellular protozoal organism *Toxoplasma gondii*. For normal, healthy adults, the organism poses no problems, and an estimated 16% to 23% of adults in the United States may have had asymptomatic infection, based on an epidemiologic study that examined serologic samples from more than 4000 randomized individuals. However, the prevalence of infection has considerable geographic variation around the world. Unfortunately, the disease can be devastating for the developing fetus or the immunocompromised patient. Other mammals, particularly members of the cat family, are vulnerable to infection, and cats are considered to be the definitive host. *T. gondii* multiplies in the intestinal tract of the cat by means of a sexual life cycle, discharging numerous oocysts in the cat feces. Another animal or human can ingest these oocysts, resulting in the production of disease.

Clinical Features

In the normal, immunocompetent individual, infection with *T. gondii* is often asymptomatic. If symptoms develop, they are usually mild and resemble infectious mononucleosis; patients may have a low-grade fever, cervical lymphadenopathy, fatigue, and muscle or joint pain. These symptoms may last from a few weeks to a few months, although the host typically recovers without therapy. Sometimes the lymphadenopathy involves one or more of the lymph nodes in the paraoral region, such as the buccal or submental lymph node. In such instances, the oral health care provider may discover the disease.

In immunosuppressed patients, toxoplasmosis may represent a new, primary infection or, more frequently, reactivation of previously encysted organisms. The principal groups at risk include the following:

- AIDS patients
- Transplant recipients
- Cancer patients

Manifestations of infection can include necrotizing encephalitis, pneumonia, and myositis or myocarditis. In the United States, it is estimated that from 3% to 10% of AIDS patients who are not being treated with combination antiretroviral therapy (cART) (see page 239) will experience CNS involvement. CNS infection is very serious. Clinically, the patient may complain of headache, lethargy, disorientation, and hemiparesis.

Congenital toxoplasmosis occurs when a non-immune mother contracts the disease during her pregnancy and the organism crosses the placental barrier, infecting the developing fetus. The potential effects of blindness, intellectual impairment, and delayed psychomotor development are most severe if the infection occurs during the first trimester of pregnancy.

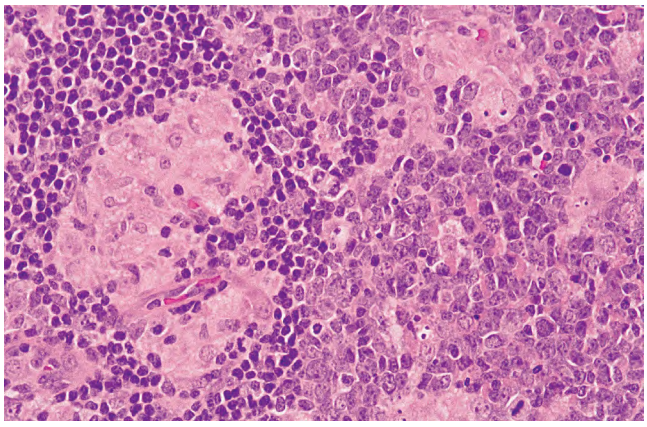
Histopathologic Features

Histopathologic examination of a lymph node obtained from a patient with active toxoplasmosis shows characteristic reactive germinal centers exhibiting an accumulation of eosinophilic macrophages. The macrophages encroach on the germinal centers and accumulate within the subcapsular and sinusoidal regions of the node (Fig. 6-39).

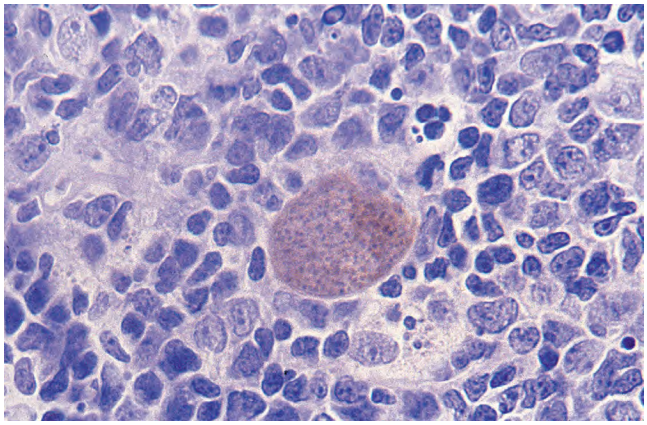
Diagnosis

The diagnosis of toxoplasmosis is usually established by identification of rising serum antibody titers to *T. gondii* within 10 to 14 days after infection. Immunocompromised patients, however, may not be able to generate an antibody response; therefore, the diagnosis may rest on the clinical findings and the response of the patient to therapy.

Biopsy of an involved lymph node may suggest the diagnosis, and the causative organisms can sometimes be detected immunohistochemically using antibodies directed against *T. gondii*–specific antigens (Fig. 6-40). The



• **Fig. 6-39 Toxoplasmosis.** This high-power photomicrograph shows an accumulation of eosinophilic macrophages within a lymph node. (Courtesy of Dr. John Kalmar.)



• **Fig. 6-40 Toxoplasmosis.** In this high-power photomicrograph, an encysted organism of toxoplasmosis is highlighted by an immunohistochemical study. (Courtesy of Dr. John Kalmar.)

diagnosis should also be confirmed by serologic studies, if possible.

Treatment and Prognosis

Most healthy adults with toxoplasmosis require no specific treatment because of the mild symptoms and self-limiting course. Perhaps more importantly, pregnant women should avoid situations that place them at risk for the disease. Handling or eating raw meat, eating raw, unpeeled fruits or vegetables, or cleaning a cat litter box should be avoided until after delivery. If exposure during pregnancy is suspected, treatment with a combination of sulfadiazine and pyrimethamine often prevents transmission of *T. gondii* to the fetus, although pyrimethamine is contraindicated in the first trimester due to its potential teratogenicity. Because these drugs act by inhibiting folate metabolism of the protozoan, folinic acid is given concurrently to help prevent hematologic complications in the patient. A similar drug regimen is used to treat immunosuppressed individuals with toxoplasmosis, although clindamycin may be substituted for sulfadiazine in managing patients who are allergic to sulfa drugs. Because most cases of toxoplasmosis in AIDS patients represent reactivation of encysted organisms, prophylactic administration of trimethoprim and sulfamethoxazole is generally recommended, particularly if the patient's CD4+ T-lymphocyte count is less than 100 cells/μL.

LEISHMANIASIS

Leishmaniasis is a protozoal infection that is transmitted to humans by the bite of certain species of sandfly. Both Old World and New World forms of the disease are recognized, and they are caused by different species of sandfly as well as different species of *Leishmania.* Although the disease has been reported on every continent except Australia and Antarctica, most of the cases are found in relatively few countries, particularly India (Bihar State), Afghanistan, Saudi Arabia, Syria, Algeria, Peru, and Brazil. Of course, because of international travel to these areas, leishmaniasis can be seen in virtually every corner of the earth.

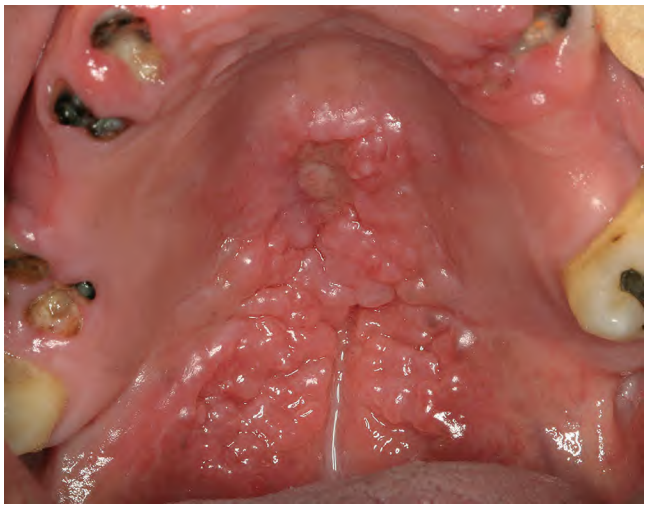
Dogs and other mammals are the primary reservoir for leishmaniasis, and in the mammalian host, the organism is an obligate intracellular parasite. When an infected animal is bitten by the female sandfly, macrophages containing the amastigote (lacking flagella) phase of the organism are ingested by the fly as it drinks the animal's blood. In the gut of the sandfly, the amastigote organisms develop into free-living promastigotes (having flagella). When the fly later bites a human (or another mammal), the promastigote organisms are injected into the subcutaneous tissues, where they are phagocytosed by macrophages, neutrophils, or dendritic cells. Once ingested, the promastigote transforms into an amastigote, which multiplies within the host cells, completing the parasitic cycle. Sometimes the replication is so pronounced that the phagocytic host cells ruptures, releasing amastigotes into the bloodstream, and causing infection of more host cells.

Clinical Features

Depending on the *Leishmania* species and the immune status of the human host, at least three presentations of disease are generally recognized:

- Cutaneous—either Old World or New World; New World cases caused by *Leishmania mexicana* complex
- Mucocutaneous—primarily New World; caused by *Leishmania braziliensis* complex
- Visceral ("kala-azar")—either Old World or New World; caused primarily by *Leishmania donovani* in the Old World; *Leishmania braziliensis* in the New World

Cutaneous leishmaniasis is by far the most common form of the disease. Individual lesions develop 3 to 6 weeks after the person is bitten, presenting as an elevated erythematous papule or nodule with a depressed, ulcerated center, often said to resemble a volcano. Such lesions persist for months but often eventually heal. Significant scarring is usually noted, however.



• **Fig. 6-41 Leishmaniasis.** Ulceration and granulomatous enlargement of the palatal mucosa in a patient with mucocutaneous leishmaniasis. (Courtesy of Dr. Ricardo Santiago Gomez.)

Mucocutaneous leishmaniasis is not as common as cutaneous leishmaniasis, but it is much more destructive. Most of the *Leishmania* species responsible for this form of the disease are found in South America. The skin of affected patients shows more diffuse involvement, characterized by scaly and ulcerative plaques and nodules. From several months to as long as 5 years later, mucosal involvement develops. Typically this begins with the nasal mucosa, but oral, pharyngeal, tracheal, and laryngeal mucosa often are involved eventually (Fig. 6-41). Perforation of the nasal septum or the hard and soft palate, as well as destruction of the alveolar bone, may be present. The extent of the damage may be so severe that it can be a life-threatening process.

Visceral leishmaniasis (also known as *kala-azar,* which is Hindi for "black fever") is characterized by grayish discoloration of the skin in some patients, hepatosplenomegaly, fever (usually related to pancytopenia), and weight loss. The severity of disease expression is undoubtedly related to the health of the patient prior to infection.

Histopathologic Features

The amastigote *Leishmania* organisms can be detected within the cytoplasm of histiocytes in touch preparations of infected tissue or in histopathologic sections. The protozoans may be seen in routine H&E-stained sections, but other stains such as Giemsa, Brown-Hopps (a tissue Gram stain), or Leishman methods may aid identification. In older, chronic lesions, the organisms may be sparse, making the diagnosis more challenging.

Diagnosis

Although the diagnosis of leishmaniasis often can be made on the cytologic or histopathologic findings, it is sometimes necessary to obtain tissue for culture or polymerase chain reaction (PCR) studies. These latter techniques are usually available only at specialized laboratories. Serologic studies can be difficult to interpret at times because many individuals in endemic areas have had exposure to the organism, although they may not have active disease.

Treatment and Prognosis

Since the 1920s, antimony compounds have been used to treat leishmaniasis, but these drugs often have significant side effects because they are heavy metals. Liposomal amphotericin B is ideally the drug of choice, but this less toxic compound is often too expensive for widespread use in developing countries. Most leishmaniasis patients receive treatment with pentavalent antimonial compounds, with the antiprotozoal drug pentamidine used for patients who cannot tolerate antimonial compounds. Attempts to develop a vaccine have not met with success.

The prognosis of leishmaniasis can be affected by both host factors (e.g., malnutrition and immune suppression) and organism factors, which are related to the *Leishmania* species responsible for infection. Without treatment, visceral leishmaniasis has an ominous prognosis and often results in death, whereas cutaneous leishmaniasis is typically a chronic, bothersome superficial infection. Mucocutaneous leishmaniasis has an intermediate course, although significant morbidity results from tissue destruction by the infection. All forms of leishmaniasis generally require weeks to months of therapy, and relapses are relatively common.

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7 Viral Infections

HUMAN HERPESVIRUSES

The human herpesvirus (HHV) family **(Herpetoviridae)** constitutes a large family of double-stranded DNA viruses. The best-known member of this family is **herpes simplex virus (HSV),** which includes HSV type 1 (HSV-1 or HHV-1) and HSV type 2 (HSV-2 or HHV-2). Other members of the HHV family include **varicella-zoster virus** (VZV or HHV-3), **Epstein-Barr virus** (EBV or HHV-4), **cytomegalovirus** (CMV or HHV-5), and more recently discovered members, HHV-6, HHV-7, and HHV-8. Humans are the only natural reservoir for these viruses, which are endemic worldwide.

The term **herpes** derives from the ancient Greek word meaning to creep or crawl, which apparently alludes to a tendency for spreading, latent, or recurrent infection. All eight types cause a primary infection and remain latent within specific cell types for the life of the individual. On reactivation, these viruses cause recurrent infections that may be symptomatic or asymptomatic. The viruses are shed in saliva or genital secretions, providing an avenue for infection of new hosts. Each type is known to transform cells in tissue culture, with several strongly associated with specific malignancies. The following sections concentrate on HSV, VZV, CMV and EBV. Much less is known about herpesvirus types 6, 7, and 8.

Human herpesvirus 6 (HHV-6) and **7 (HHV-7)** are closely related, usually transmitted by saliva or respiratory droplets, and exhibit infection rates close to 90% by age 5 in the United States. Primary infection usually is asymptomatic but may cause an acute febrile illness followed by an erythematous maculopapular eruption. This pattern of symptomatic primary infection—termed **roseola (exanthema subitum, sixth disease)**—most often is caused by HHV-6 but also may be caused by HHV-7. Both viruses may replicate in salivary glands and establish latency in CD4+ T lymphocytes or other cell types. Reactivation occurs most frequently in immunocompromised patients and can result in widespread multiorgan infection, including encephalitis, pneumonitis, bone-marrow suppression, and hepatitis.

Human herpesvirus 8 (HHV-8) is involved in the pathogenesis of **Kaposi sarcoma (KS)** (see page 520) and has been termed **Kaposi sarcoma–associated herpesvirus (KSHV).** In immunocompetent persons, primary infection usually is asymptomatic, with male-to-male sexual contact being the most common mode of transmission in Western countries. The virus is found without difficulty in saliva, suggesting another possible pattern of transmission. Associated symptoms, such as transient fever, lymphadenopathy, and arthralgias, are rarely reported. Circulating B lymphocytes appear to be the major cell of latency. In addition to Kaposi sarcoma, HHV-8 is associated with certain types of lymphoma and a benign lymphoid proliferation known as *Castleman disease.*

Interestingly, several studies have demonstrated genetic material from herpesviruses (including EBV, CMV, HHV-6, and HHV-7) in periapical inflammatory lesions and periodontitis. The significance of these findings is uncertain, although some investigators speculate that interactions between herpesviruses, bacteria, and the host immune response might play a role in the pathogenesis of such lesions.

HERPES SIMPLEX VIRUS

The two herpes simplex viruses are similar in structure and disease mechanisms but differ in antigenicity, anatomic site predilection, and epidemiology. Differences in envelope glycoproteins account for their distinct antigenicity. Nevertheless, there is potential for antibody cross-reactivity, and antibodies directed against one type may decrease the likelihood or severity of infection with the other type.

HSV-1 is spread predominantly through infected saliva or active perioral lesions and adapted best to the oral, facial, and ocular areas. The pharynx, intraoral mucosa, lips, eyes, and skin above the waist are involved most frequently. Genital HSV-1 infection is uncommon, although recent studies have shown an increase in the proportion of genital herpes caused by HSV-1 in developed nations. This trend has been attributed to an increase in oral-genital sexual behavior and lower rates of nonsexual HSV-1 acquisition in childhood.

HSV-2 is adapted best to the genital zones, is transmitted predominantly through sexual contact, and typically involves the genitalia and skin below the waist. Oral and

pharyngeal infection with HSV-2 is also possible but infrequent.

The natural history of HSV infection includes primary infection, latency, and recurrent infection. **Primary infection** refers to initial exposure of an individual without antibodies to the virus. Primary infection with HSV-1 typically occurs at a young age, often is asymptomatic, and usually does not cause significant morbidity. For symptomatic cases, the usual incubation period is 3 to 9 days. After primary infection is established, the virus is taken up by sensory nerves and transported to the associated sensory or, less frequently, autonomic ganglia where the virus remains in a latent state. The most common site of latency for HSV-1 is the trigeminal ganglion, but other possible sites include the nodose ganglion of the vagus nerve, dorsal root ganglia, and brain. The virus uses the axons of the sensory neurons to travel back and forth to the skin or mucosa.

Recurrent (secondary or **recrudescent) infection** occurs with reactivation of the virus. Old age, ultraviolet light, physical or emotional stress, fatigue, heat, cold, pregnancy, allergy, trauma, dental treatment, respiratory illnesses, fever, menstruation, systemic diseases, and malignancy have been associated with reactivation. Symptomatic recurrences are fairly common and affect the epithelium supplied by the sensory ganglion; however, reactivation with asymptomatic viral shedding greatly exceeds clinically evident recurrences. Spread to an uninfected host can occur from symptomatic, active lesions or asymptomatic viral shedding. In addition, the virus may spread to other sites in the same host to establish residency at the sensory ganglion of the new location. Based upon cultures of samples from otherwise healthy individuals, investigators have estimated that asymptomatic, oral HSV-1 shedding occurs in approximately 6% of the population on any given day. However, sensitive polymerase chain reaction (PCR) assays performed on oral samples obtained over several weeks suggest that at least 70% of the population sheds HSV-1 asymptomatically at least once a month.

Crowding and poor hygiene promote exposure to HSV-1. Furthermore, lower socioeconomic status correlates with earlier exposure. In developing countries, more than 50% of the population is exposed by 5 years of age, 95% by 15 years of age, and nearly 100% by 30 years of age. In contrast, upper socioeconomic groups in developed nations exhibit less than 20% exposure at 5 years of age and only 50% to 60% in adulthood. The low childhood exposure rate in privileged groups is followed by a second peak during the college years. The age of initial infection also affects the clinical presentation of symptomatic primary HSV-1 infection, with individuals infected at an early age tending to exhibit gingivostomatitis and those exposed later in life often demonstrating pharyngotonsillitis.

HSV-2 infection represents one of the most common sexually transmitted infections worldwide. In the United States, HSV-2 seroprevalence among individuals between 14 and 49 years of age is approximately 16% and has remained relatively stable in recent years. Exposure of those younger than age 14 is close to zero, and most initial infections occur between the ages of 15 and 35. Because many infected with HSV-2 refrain from sexual activity when active lesions are present, investigators believe that at least 70% of primary infections are contracted from individuals during asymptomatic viral shedding. Importantly, HSV-2 infection is associated with at least a twofold increase in risk for human immunodeficiency virus (HIV) infection (see page 239). Apparently, HSV-2 infection triggers a persistent microenvironment rich in immune cells that are susceptible to HIV infection.

In addition to clinically evident infections, HSV has been implicated in several noninfectious processes. More than 15% of cases of **erythema multiforme** are preceded by a symptomatic recurrence of HSV 3 to 10 days earlier (see page 723), and some investigators believe that up to 60% of mucosal erythema multiforme may be triggered by HSV. In some individuals, erythema multiforme outbreaks are frequent enough to warrant antiviral prophylaxis. An association with cluster headaches and several cranial neuropathies (e.g., Bell palsy [see page 801] and trigeminal sensory neuropathy) also has been proposed, but definitive proof is lacking.

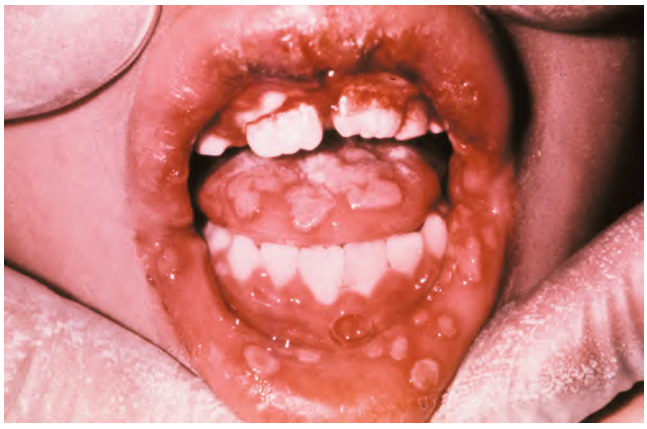
In a small subset of patients, asymptomatic release of HSV coincides with attacks of aphthous ulcerations (see page 303). In these cases, the ulcerations are not infected with the virus. Instead the virus may be responsible for the initiation of immune dysregulation, or the immune dysregulation that produces aphthae may allow the release of virions. Nevertheless, the association between HSV and aphthae is weak, and prophylactic antiviral therapy generally does not decrease the recurrence of aphthous stomatitis.

HSV also has been associated with oral carcinomas, but much of the evidence is circumstantial. HSV DNA has been extracted from some tumors but not others. HSV may aid carcinogenesis through the promotion of mutations, but its oncogenic role, if any, is uncertain.

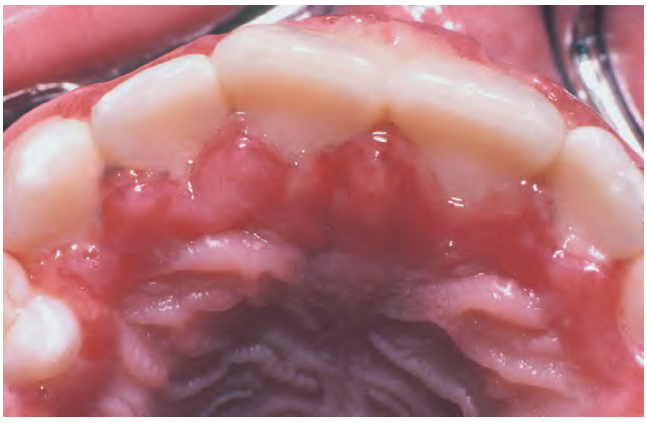
Clinical Features

Acute herpetic gingivostomatitis (primary herpes) is the most common pattern of symptomatic primary HSV infection, and more than 90% of cases are caused by HSV-1. Most affected individuals are between the ages of 6 months and 5 years, with the peak prevalence occurring between 2 and 3 years of age. However, occasional cases have been reported in patients over 60 years of age. Development before 6 months of age is rare because of protection by maternal anti-HSV antibodies. The onset is abrupt and often accompanied by anterior cervical lymphadenopathy, chills, fever (103° F to 105° F), nausea, anorexia, irritability, and sore mouth lesions. The manifestations vary from mild to severely debilitating.

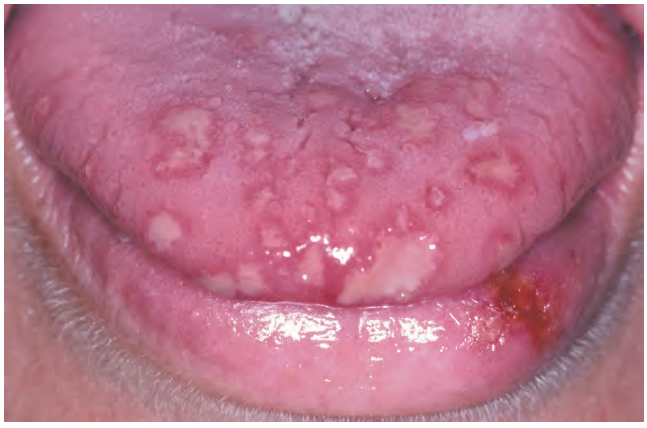
Initially the affected mucosa develops numerous pinhead vesicles, which rapidly collapse to form numerous small, red lesions. These lesions enlarge slightly and develop central ulceration covered by yellow fibrin (Fig. 7-1). Adjacent



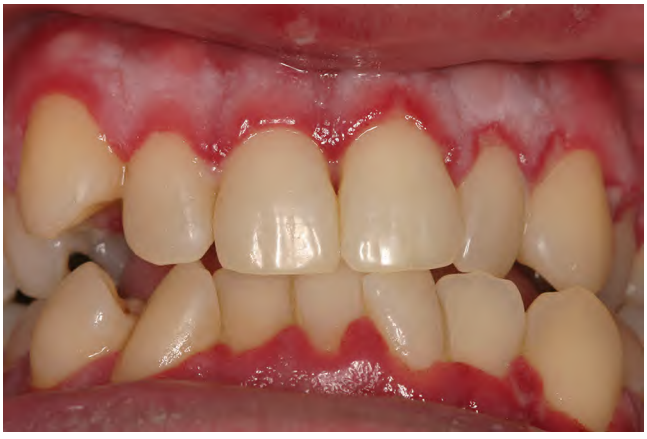
• **Fig. 7-1 Acute Herpetic Gingivostomatitis.** Widespread yellowish mucosal ulcerations. (Courtesy of Dr. David Johnsen.)



• **Fig. 7-3 Acute Herpetic Gingivostomatitis.** Painful, enlarged, and erythematous palatal gingiva.



• **Fig. 7-2 Acute Herpetic Gingivostomatitis.** Numerous coalescing, irregular, and yellowish ulcerations of the dorsal surface of the tongue.

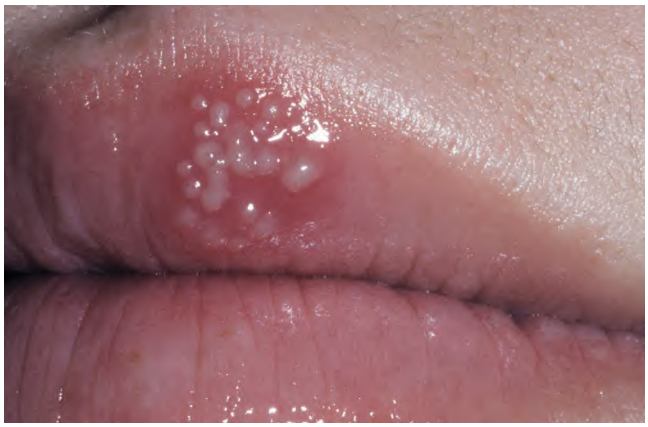


• **Fig. 7-4 Acute Herpetic Gingivostomatitis.** Painful, enlarged, and erythematous facial gingiva. Note erosions of the free gingival margin. (Courtesy of Dr. Gina Liford.)

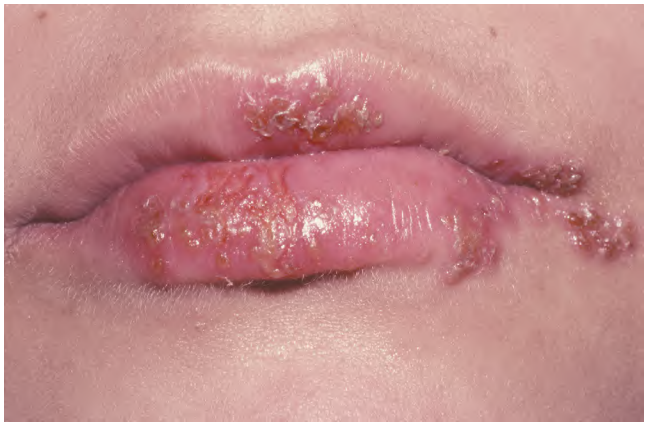
ulcerations may coalesce to form larger, shallow, irregular ulcerations (Fig. 7-2). Both the movable and attached oral mucosa can be affected, and the number of lesions is highly variable. In all cases, the gingiva is enlarged, painful, and extremely erythematous (Fig. 7-3). In addition, the affected gingiva often exhibits distinctive punched-out erosions along the midfacial free gingival margins (Fig. 7-4). It is not unusual for involvement of the labial mucosa to extend past the wet line to include the adjacent vermilion border. Satellite vesicles of the perioral skin are fairly common. Self-inoculation of the fingers, eyes, and genital areas can occur. Mild cases usually resolve within 5 to 7 days; severe cases may last 2 weeks. Rare complications include keratoconjunctivitis, esophagitis, pneumonitis, meningitis, and encephalitis.

As mentioned previously, primary infection in adults may cause **pharyngotonsillitis.** Sore throat, fever, malaise, and headache are the initial symptoms. Numerous small vesicles develop on the tonsils and posterior pharynx. The vesicles rapidly rupture to form shallow ulcers, which often coalesce and develop an overlying diffuse, gray-yellow exudate. Involvement of the oral mucosa anterior to Waldeyer ring occurs in less than 10% of cases. HSV appears to be a significant cause of pharyngotonsillitis in young adults who are from higher socioeconomic groups with previously negative test findings for HSV antibodies. Most cases are caused by HSV-1, but the proportion caused by HSV-2 is increasing. The clinical presentation closely resembles pharyngitis secondary to streptococci or infectious mononucleosis, making the true frequency difficult to determine.

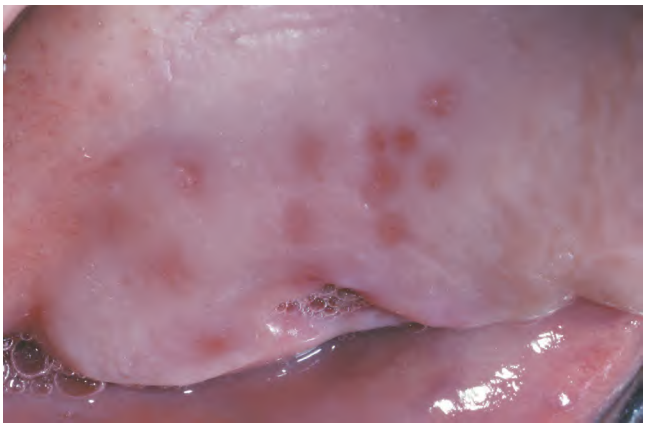
Recurrent herpes simplex infections (secondary herpes, recrudescent herpes) may occur either at the site of primary inoculation or in adjacent areas of surface epithelium supplied by the involved ganglion. The most common site of recurrence for HSV-1 is the vermilion border and adjacent skin of the lips. This is known as **herpes labialis** ("cold sore" or "fever blister"). Prevalence studies suggest that 15% to 45% of the United States population has a history of herpes labialis. In some patients, ultraviolet light or trauma can trigger recurrences. Prodromal signs and symptoms (e.g., pain, burning, itching, tingling, localized warmth, and erythema of the involved epithelium) arise 6 to 24 hours before the lesions develop. Multiple small, erythematous papules develop and form clusters of



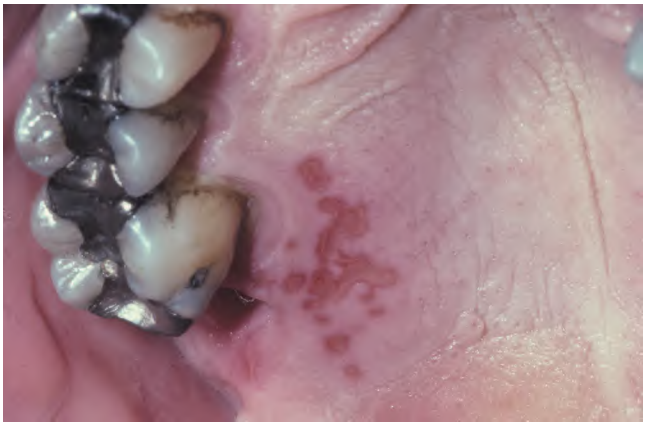
• **Fig. 7-5 Herpes Labialis.** Multiple fluid-filled vesicles on the lip vermilion.



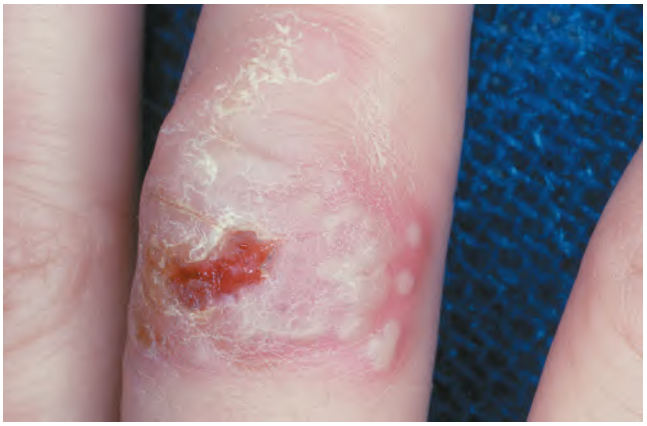
• **Fig. 7-6 Herpes Labialis.** Multiple sites of recurrent herpetic infection secondary to spread of viral fluid over cracked lips.



• **Fig. 7-7 Intraoral Recurrent Herpetic Infection.** Early lesions exhibiting as multiple erythematous macules on the hard palate. Lesions appeared a few days after extraction of a tooth.



• **Fig. 7-8 Intraoral Recurrent Herpetic Infection.** Multiple coalescing ulcerations on the hard palate.



• **Fig. 7-9 Herpetic Whitlow.** Recurrent herpetic infection of the finger.

fluid-filled vesicles (Fig. 7-5). The vesicles rupture and crust within 2 days. Healing usually occurs within 7 to 10 days. Symptoms are most severe in the first 8 hours, and most active viral replication is complete within 48 hours. Rupture of vesicles and the release of the virus-filled fluid may result in spreading of the lesions on lips previously cracked from sun exposure (Fig. 7-6). Recurrences are observed less commonly on the skin of the nose, chin, or cheek. The majority of those affected experience approximately two recurrences annually, but a small percentage may experience outbreaks that occur monthly or even more frequently.

On occasion, some lesions arise almost immediately after a known trigger and appear without any preceding prodromal symptoms. These rapidly developing recurrences tend to respond less favorably to treatment.

Recurrences also can affect the intraoral mucosa. In the immunocompetent patient, involvement is limited almost always to keratinized mucosa bound to bone (attached gingiva and hard palate). These sites often exhibit subtle changes, and the symptoms are less intense. The lesions begin as 1- to 3-mm vesicles that rapidly collapse to form a cluster of erythematous macules that may coalesce or slightly enlarge (Figs. 7-7 and 7-8). The damaged epithelium is lost, and a central yellowish ulceration develops. Healing occurs within 7 to 10 days.

Several less common presentations also exist. Primary or recurrent HSV infection of the fingers is known as **herpetic whitlow (herpetic paronychia)** (Fig. 7-9). This condition

may result from self-inoculation in children with orofacial HSV-1 infection or adults with genital HSV-2 infection. Before the uniform use of gloves, medical and dental personnel could infect their digits from contact with infected patients and represented the most commonly affected group. Recurrent digital infection may result in paresthesia and permanent scarring.

Cutaneous herpetic infections also can arise in areas of previous epithelial damage. Parents kissing skin injuries in children represent one vector. Wrestlers and rugby players also may contaminate areas of abrasion and develop lesions known as **herpes gladiatorum** or **scrumpox.** On occasion, herpes simplex has been spread over the bearded region of the face into minor injuries created by daily shaving, leading to a condition known as **herpes barbae.** Ocular involvement may occur by self-inoculation in children and, with multiple recurrences, may result in blindness. Patients with diffuse, chronic skin diseases, such as eczema, pemphigus, and Darier disease, may develop diffuse life-threatening HSV infection, known as **eczema herpeticum (Kaposi varicelliform eruption).** Newborns may become infected after delivery through a birth canal contaminated with HSV, usually HSV-2. Without treatment, there is a greater than 50% mortality rate.

HSV recurrence in immunocompromised hosts can be significant. Without proper immune function, recurrent herpes can persist, spread, and potentially be fatal. Skin lesions may continue to enlarge with formation of broad zones of superficial erosion. Likewise, herpes labialis may be severe, with extensive areas of involvement. Intraoral lesions usually begin on bound mucosa but often spread to unbound mucosa as well. The lesions may appear as brownish, necrotic epithelium raised above the surface of the adjacent intact epithelium. Typically, these areas are much larger than the usual pinhead lesions in immunocompetent patients. With continued enlargement, a zone of superficial necrosis or erosion with a distinctive circinate, raised, yellow border develops (Figs. 7-10 and 7-11). HSV infection in a chronic ulcer on the movable oral mucosa is ominous and should prompt thorough evaluation for possible immune dysfunction.

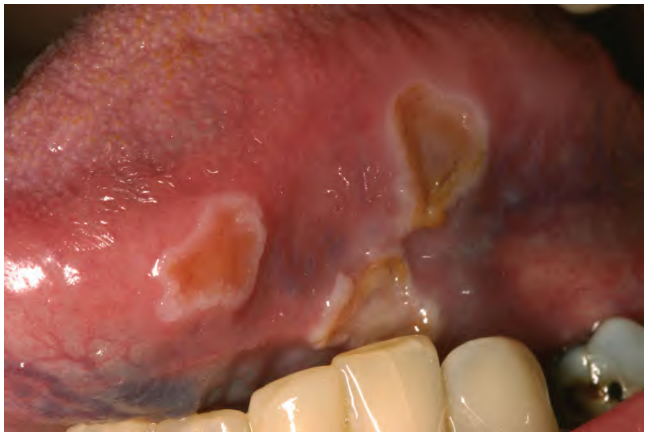
In addition, in patients with **acquired immunodeficiency syndrome (AIDS),** several authors have reported persistent oral ulcers that lack the distinctive curvilinear border, are nonspecific clinically, and may mimic aphthous ulcerations, necrotizing stomatitis, or ulcerative periodontal disease. Biopsy of persistent ulcers in patients with AIDS is mandatory and may reveal any of a number of infectious or neoplastic processes. Such ulcers may exhibit HSV infection, often combined with CMV (HHV-5) infection (see page 231).

Histopathologic Features

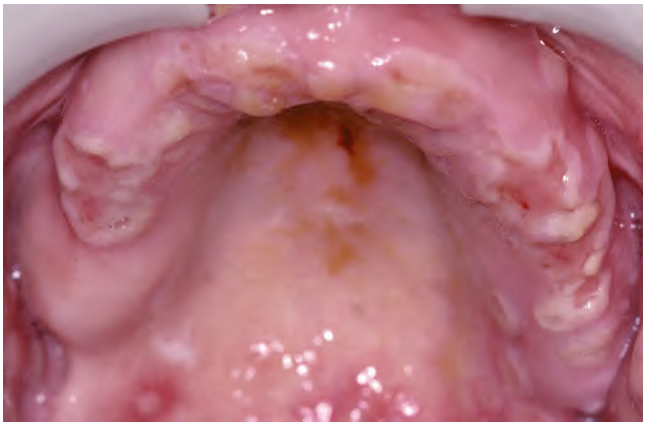
HSV-infected epithelial cells exhibit acantholysis, nuclear clearing, and nuclear enlargement (termed **ballooning degeneration**) (Fig. 7-12). The acantholytic epithelial cells may be referred to as **Tzanck cells.** (This term refers to free-floating epithelial cells in any intraepithelial vesicle and is not specific for herpes.) Nucleolar fragmentation occurs with a condensation of chromatin around the periphery of the nucleus. Multinucleated epithelial cells are formed by fusion between adjacent cells (see Fig. 7-12). Intercellular edema develops and leads to the formation of an intraepithelial vesicle (Fig. 7-13). Mucosal vesicles rupture rapidly; those on the skin often persist and become infiltrated by inflammatory cells. Once they have ruptured, the mucosal lesions demonstrate a surface fibrinopurulent membrane. Often at the edge of the ulceration or mixed within the fibrinous exudate are the scattered Tzanck or multinucleated epithelial cells.

Diagnosis

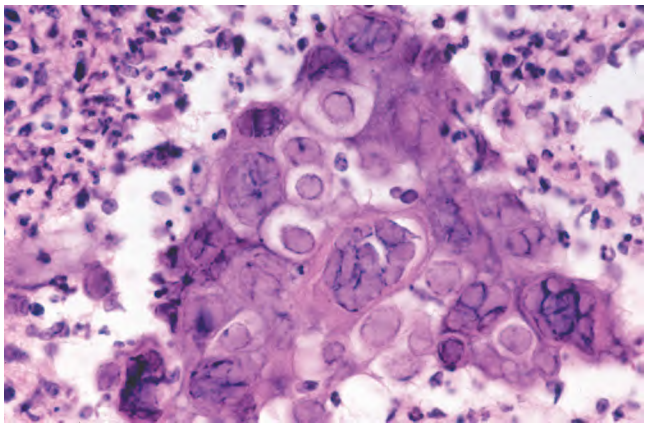
The clinician often can make a strong presumptive clinical diagnosis of HSV infection. However, on occasion, HSV



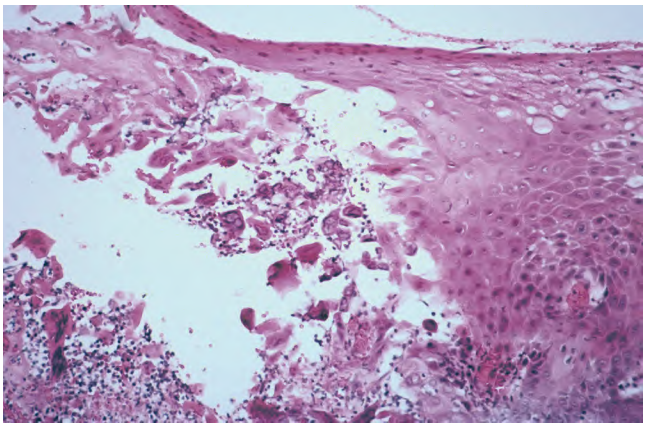
• **Fig. 7-10 Chronic Herpetic Infection.** Numerous mucosal erosions, each of which is surrounded by a slightly raised, yellow-white border, in a patient receiving systemic corticosteroid therapy for systemic sclerosis and rheumatoid arthritis.



• **Fig. 7-11 Chronic Herpetic Infection.** Numerous shallow herpetic erosions with raised, yellow and circinate borders on the maxillary alveolar ridge in an immunocompromised patient.



• **Fig. 7-12 Herpes Simplex.** Altered epithelial cells exhibiting ballooning degeneration, margination of chromatin, and multinucleation.



• **Fig. 7-13 Herpes Simplex.** Intraepithelial vesicle demonstrating acantholytic and virally altered epithelial cells.

infection can be confused with other diseases, and laboratory confirmation is desirable.

The traditional method for diagnosis is viral isolation from tissue culture inoculated with the fluid of intact vesicles. However, intact vesicles are rare in the oral cavity, and culture of ruptured oral lesions is unreliable because of the potential for contamination with saliva that may contain coincidentally released HSV from asymptomatic viral shedding. Another problem with viral culture is that up to 2 weeks may be required for a definitive result.

The most commonly used sampling methods for diagnosis are the cytologic smear and tissue biopsy, with the former being the least invasive and most cost-effective. Microscopic examination shows characteristic changes in infected epithelial cells. Only VZV produces similar changes, but these two infections usually can be differentiated on a clinical basis. If necessary, direct immunofluorescence, immunohistochemistry, *in situ* hybridization, or PCR may be performed for more definitive HSV detection and typing.

If diagnostic features of HSV are discovered in a biopsy of a persistent ulceration in an immunocompromised patient, additional studies for CMV should be performed to rule out coinfection. The histopathologic features of CMV can be missed easily, resulting in patients not receiving the most appropriate therapy.

Serologic testing is useful in documenting recent or past exposure to HSV and is used primarily in epidemiologic studies. HSV antibodies typically begin to appear 4 to 8 days after initial exposure. Confirmation of primary infection by serology requires a negative sample obtained within 3 days of initial presentation and a positive sample obtained approximately 4 weeks later.

Treatment and Prognosis

In the past, primary herpetic gingivostomatitis was treated only symptomatically; however, if administered early, antiviral medications can be beneficial. When acyclovir suspension is initiated during the first 3 symptomatic days and administered by a rinse-and-swallow technique 5 times daily for 5 days (children: 15 mg/kg up to the adult dose of 200 mg), significant acceleration of clinical resolution is seen. Once therapy is initiated, development of new lesions ceases. In addition, associated eating and drinking difficulties, pain, healing time, duration of fever, and viral shedding are shortened dramatically. In conjunction with acyclovir, additional medications—such as dyclonine hydrochloride spray, tetracaine hydrochloride lollipops (prepared by a compounding pharmacist), or nonsteroidal antiinflammatory drugs (NSAIDs)—may be used for more immediate pain relief. Viscous lidocaine and topical benzocaine should be avoided in pediatric patients because of reports of lidocaine-induced seizures in children and an association between topical benzocaine and methemoglobinemia. Patients also should be instructed to restrict contact with active lesions to prevent autoinoculation or spread to others.

Recurrent herpes labialis has been treated with everything from ether to voodoo; nothing has solved the problem for all patients. Acyclovir ointment in polyethylene glycol was the first topical antiviral formulation available. Acyclovir ointment has been of limited benefit for herpes labialis in immunocompetent patients, because its base is thought to prevent significant absorption. Subsequently, penciclovir cream became available in a base that allows increased absorption through the vermilion border. This formulation has produced reduction in healing time and pain by approximately 1 day. Although the best results are obtained if penciclovir cream is initiated during the prodrome, late application also has produced a measurable clinical benefit. Additional choices are acyclovir cream and over-the-counter 10% docosanol cream. All three of these creams are associated with statistically significant, albeit clinically minimal, reduction in healing time and pain, with penciclovir exhibiting the greatest efficacy and docosanol the least efficacy.

Systemic acyclovir and two newer medications, valacyclovir and famciclovir, demonstrate similar effectiveness against HSV. However, valacyclovir and famciclovir exhibit improved bioavailability and more convenient oral dosing

schedules. In particular, a valacyclovir regimen—consisting of 2 g during the prodrome followed by another 2 g 12 hours later—has been most successful in minimizing recurrences. The effects of this treatment are reduced significantly if it is not initiated during the prodrome. Although much less convenient, 400 mg of acyclovir taken five times daily for 5 days appears to produce similar results. For patients whose recurrences appear to be associated with dental procedures, a regimen of 2 g of valacyclovir taken twice on the day of the procedure and 1 g taken twice the next day may suppress or minimize an attack. In individuals with a known trigger that extends over a period of time (e.g., skiing or beach vacation), prophylactic short-term use of an antiviral (acyclovir, 400 mg twice daily; valacyclovir, 1 g daily; or famciclovir, 250 mg twice daily) has been shown to reduce the prevalence and severity of recurrences.

Long-term suppressive therapy with an antiviral medication typically is reserved for patients with more than six recurrences per year, HSV-triggered erythema multiforme, or an immunocompromised status. Over the past several decades, acyclovir-resistant strains of HSV have emerged, mainly among immunocompromised patients receiving long-term treatment or prophylaxis. In immunocompromised patients, the viral load tends to be high and replication is not suppressed completely by antiviral therapy, creating a favorable environment for generating drug-resistant mutants. Although resistance is seen primarily in immunocompromised patients, cavalier use of antiviral medications for mild cases of recurrent herpes infection probably is inappropriate.

The pain associated with intraoral secondary herpes usually is not intense, and many patients do not require treatment. Some studies have shown chlorhexidine to exert antiviral effects. In addition, acyclovir appears to function synergistically with chlorhexidine. Extensive clinical trials have not been performed, but chlorhexidine alone or in combination with acyclovir suspension may be beneficial for patients who desire or require therapy of intraoral lesions.

Immunocompromised hosts with HSV infection often require intravenous (IV) antiviral medications. Furthermore, severely immunosuppressed individuals, such as bone marrow transplant patients and those with AIDS, often need prophylactic oral acyclovir, valacyclovir, or famciclovir. Herpes lesions that do not respond to appropriate therapy within 5 to 10 days most likely are the result of resistant strains. At this point, the initial antiviral therapy should be repeated at an elevated dose. If this intervention fails, additional alternatives include IV trisodium phosphonoformate hexahydrate (foscarnet), IV cidofovir, and adenine arabinoside (vidarabine). Ulcerations that reveal coinfection with HSV and CMV respond well to ganciclovir, with foscarnet used in refractory cases. Although an effective vaccine for the closely related varicella virus initially was developed over 35 years ago, similar approaches against HSV have produced less satisfactory results. Research for a potential vaccine is ongoing.

◆ VARICELLA (CHICKENPOX)

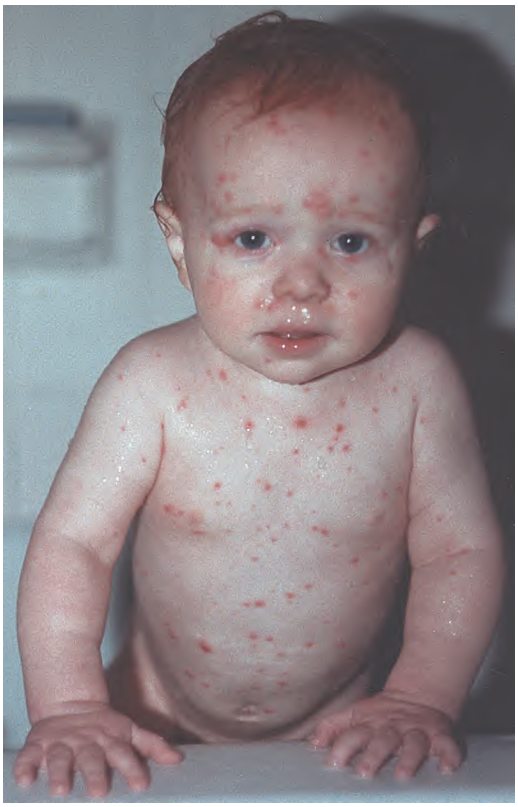
Varicella (chickenpox) represents primary infection with the varicella-zoster virus (VZV or HHV-3). Subsequently, latency ensues, and recurrence is possible as **herpes zoster** (see page 227), often after many decades. The virus may be spread through air droplets or direct contact with active lesions. In contrast to primary HSV infection, most cases of primary VZV infection are symptomatic. The incubation period is 10 to 21 days, with an average of 15 days.

In the pre-vaccine era, the annual incidence of chickenpox in the United States was approximately 4 million, with most cases arising in children younger than 10 years of age. However, since the introduction of universal varicella immunization in the United States in 1995, the incidence has declined across all age groups, and the age range of peak incidence has shifted to between 10 and 14 years. In surveillance areas with high vaccine coverage, the incidence of varicella decreased from 1995 to 2005 by approximately 90%; even further declines have occurred since 2006, when a two-dose vaccine regimen became routine. It is estimated that each year varicella vaccination prevents more than 3.5 million cases of chickenpox, 9,000 hospitalizations, and 100 deaths in the United States.

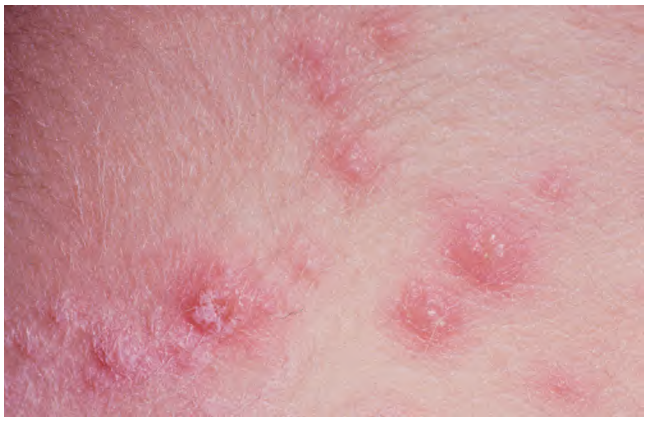
Clinical Features

Because of increasing varicella vaccination rates, the majority of new varicella cases now represent **breakthrough infection** (i.e., infection with wild-type virus in a previously immunized patient). A maculopapular, cutaneous rash with only a small number of lesions, few or no vesicles, low or no fever, and a shortened disease course of approximately 4 to 6 days are characteristic findings. The atypical presentation of breakthrough disease may be difficult to recognize. Patients are contagious until no new lesions appear within a 24-hour period, although transmission is less frequent with mild breakthrough infection compared with symptomatic infection in unimmunized individuals.

Among unimmunized individuals, the symptomatic phase of primary VZV infection usually begins with malaise, pharyngitis, and rhinitis. In older children and adults, additional symptoms (e.g., headache, myalgia, nausea, anorexia, and vomiting) occasionally are seen. This is followed by a characteristic, intensely pruritic exanthem. The rash begins on the face and trunk and spreads to the extremities. Each lesion rapidly progresses through stages of erythema, vesicle, pustule, and hardened crust (Figs. 7-14 and 7-15). The vesicular stage is the classic presentation. Each vesicle is surrounded by a zone of erythema and has been described as "a dewdrop on a rose petal." In contrast to herpes simplex, the lesions typically continue to erupt for 4 or more days. Old crusted lesions intermixed with newly formed, intact vesicles are commonplace. Affected individuals are contagious from 2 days before the exanthem until all the lesions crust. Fever usually is present during the active phase of the exanthem.

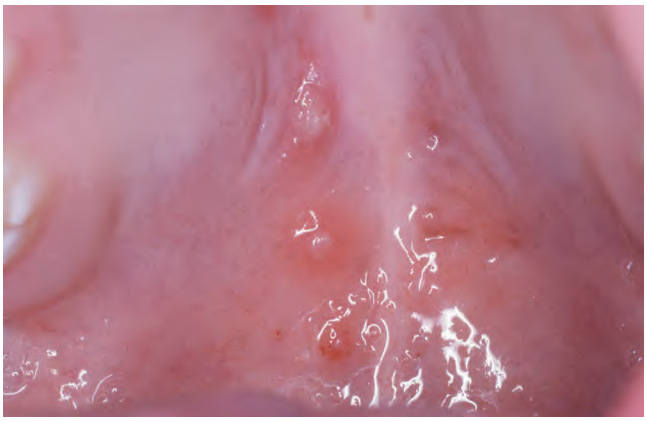


• **Fig. 7-14 Varicella.** Infant with diffuse erythematous and vesicular rash. (Courtesy of Dr. Sherry Parlanti.)



• **Fig. 7-15 Varicella.** Numerous vesicles with surrounding erythema and early crusting.

Perioral and oral manifestations are fairly common and may precede the skin lesions. The vermilion border and palate are involved most often, followed by the buccal mucosa. Occasionally, gingival lesions resemble those noted in primary HSV infection, but distinguishing between the two is not difficult because the lesions of varicella tend to be relatively painless. The lesions begin as 3- to 4-mm, white, opaque vesicles that rupture to form 1- to 3-mm ulcerations (Fig. 7-16). The prevalence and number of oral lesions correlate with the severity of extraoral infection. In mild cases, oral lesions are present in about one-third of affected individuals; often there are only one or two oral



• **Fig. 7-16 Varicella.** White opaque vesicles on the hard palate. (Courtesy of Tristan Neville.)

ulcers that heal within 1 to 3 days. On the other hand, patients with severe infections almost always have oral ulcerations, often numbering up to 30 and persisting for 5 to 10 days.

Infants, adults, and immunocompromised individuals are at increased risk for severe disease and complications. In addition, household members who become secondarily infected often suffer more severe disease than those initially infected.

In childhood, the most frequent complications of varicella are secondary skin infections, followed by encephalitis and pneumonia. In particular, secondary skin infection with group A, β-hemolytic streptococci may progress to necrotizing fasciitis, septicemia, toxic shock syndrome, or other life-threatening conditions. With enhanced public education and decreased use of aspirin in children, Reye syndrome (a potentially fatal condition characterized by acute encephalopathy, liver failure, and other major organ damage) is now rare.

The prevalence of complications in adults exceeds that in children. The most common and serious complication is pneumonitis, characterized by dry cough, tachypnea, dyspnea, hemoptysis, chest pain, and cyanosis. Other potential complications include pneumonia, encephalitis, gastrointestinal disturbance, and hematologic events (i.e., thrombocytopenia, pancytopenia, hemolytic anemia, sickle cell crisis). Central nervous system (CNS) involvement typically produces ataxia but also may result in headaches, drowsiness, convulsions, or coma. The risk of death is reported to be 15 times greater in adults compared with children, mostly because of an increased prevalence of encephalitis.

Infection during pregnancy can produce congenital or neonatal chickenpox. Involvement early in pregnancy can result in spontaneous abortion or congenital defects. When infection occurs before 20 weeks of gestation, the prevalence of congenital varicella syndrome is approximately 1% to 2%. In addition, infection of the mother close to delivery can result in severe neonatal infection caused by a lack of maternal antibodies.

Infection in immunocompromised patients also can be severe. Cutaneous involvement typically is extensive and may be associated with secondary bacterial infection, high fever, hepatitis, pneumonitis, pancreatitis, gastrointestinal obstruction, and encephalitis. Before effective antiviral therapy, the mortality rate in immunocompromised individuals was approximately 7%.

Histopathologic Features

The cytologic alterations are virtually identical to those described for HSV. The virus causes acantholysis, with formation of numerous free-floating Tzanck cells, which exhibit nuclear margination of chromatin and occasional multinucleation.

Diagnosis

Since the institution of universal vaccination in the United States, the annual incidence of typical varicella disease has decreased, whereas the incidence of atypical breakthrough disease has increased; consequently, the need for laboratory confirmation has grown. Confirmation can be obtained through demonstration of viral cytopathologic effects present within epithelial cells harvested from vesicular fluid. These cytologic changes are identical to those found in HSV infection, although correlation with the clinical findings may aid in distinguishing between HSV and VZV infection. The most definitive method for diagnosis is PCR performed on vesicular fluid, cells from the base of a lesion, or a scab from a resolving skin lesion. PCR is preferred over viral isolation in cell culture and direct fluorescent antibody assay, because it is more sensitive and allows for distinction between wild-type and vaccine strains of VZV. In addition, a diagnosis can be made retrospectively in immunocompetent hosts by demonstrating a fourfold or greater increase in VZV antibody titers between acute and convalescent serum samples; however, in vaccinated persons an increase of this magnitude may not be evident.

Treatment and Prognosis

Before antiviral medications became available, the treatment of varicella primarily was symptomatic. Warm baths with soap, baking soda, or colloidal oatmeal; application of calamine lotion; and systemic diphenhydramine still are used to relieve pruritus. Diphenhydramine lotions are not recommended because of reports of toxicity secondary to percutaneous absorption. Acetaminophen is the preferred antipyretic for childhood cases. In this age group, aspirin should be avoided because of the risk of Reye syndrome, and NSAIDs are discouraged because they have been associated with an increased risk for severe skin and soft tissue complications.

Peroral antiviral medications (such as, acyclovir, valacyclovir, and famciclovir) have been shown to reduce the duration and severity of infection if administered within 24 hours of the rash. Routine use of antiviral medications is not recommended in immunocompetent children with uncomplicated chickenpox. Instead, such therapy is reserved for those at risk for more severe disease, such as unvaccinated individuals over 12 years of age, patients with chronic cutaneous or pulmonary disease, patients receiving long-term salicylate therapy, and those receiving short, intermittent, or aerosolized courses of corticosteroids. In addition, some experts recommend antiviral therapy for individuals who contract the disease from a household member, because secondary household cases often are more severe than corresponding index cases. IV formulations are used in immunosuppressed patients or those exhibiting progressive, severe infection.

In patients who lack evidence of immunity and become exposed to VZV, postexposure immunization or purified varicella-zoster immune globulin administration may be considered. Postexposure vaccination is appropriate for nonimmune individuals 12 months or older. Ideally it should be administered within 3 days, although it may be given up to 5 days after exposure in order to prevent or modify disease. A second dose of vaccine should be administered at the age-appropriate interval following the first dose. Alternatively, for nonimmune individuals at high risk for severe disease or complications, purified varicella-zoster immune globulin (VariZIG) can be given postexposure. Individuals at elevated risk include immunocompromised patients, pregnant women, premature infants, and neonates whose mothers do not have evidence of immunity. VariZIG ideally should be administered as soon as possible, with the FDA approving administration up to 10 days postexposure.

In the United States, the FDA has approved a monovalent varicella virus vaccine (Varivax) as well as a quadrivalent measles, mumps, rubella, and varicella virus (MMRV) vaccine (ProQuad). Both vaccines are licensed for use in healthy children 12 months through 12 years of age, with the first dose of varicella-containing vaccine recommended at 12 through 15 months and a second dose at 4 through 6 years. Either MMRV vaccine or separate injections of measles, mumps, and rubella (MMR) vaccine and monovalent varicella vaccine may be administered to toddlers receiving their first dose; the latter method minimizes the generally small risk of vaccine-related febrile seizures in this age group. For the second dose, MMRV is preferred over separate injections of MMR and varicella virus vaccines. In addition, the monovalent varicella vaccine is licensed for routine use in individuals 13 years or older without evidence of immunity; in this age group, two doses separated by at least 28 days are recommended. Children, adolescents, and adults who have received only one dose of varicella virus vaccine as per past recommendations should receive a second "catch-up" dose.

The varicella virus vaccine is a live, attenuated virus that can be spread to individuals in close contact. Therefore, vaccine recipients who develop a rash should avoid contact with those at risk, such as immunocompromised or pregnant individuals.

HERPES ZOSTER (SHINGLES)

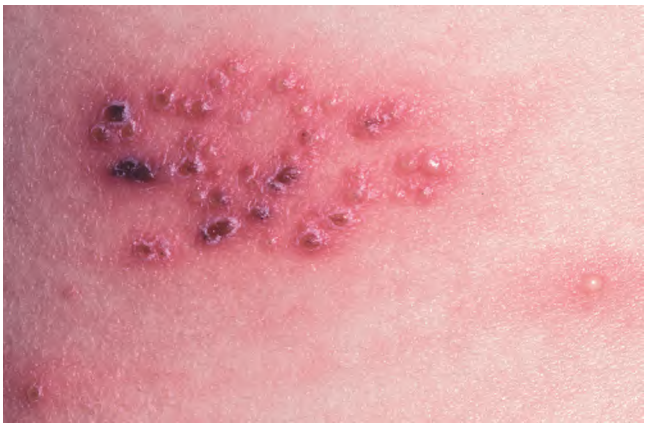
After primary infection with VZV (chickenpox), the virus is transported up the sensory nerves and establishes latency in the dorsal root ganglia. Clinically evident herpes zoster develops after reactivation of the virus, with involvement of the distribution of the affected sensory nerve. Unlike HSV, single rather than multiple recurrences are the rule. Herpes zoster occurs during the lifetime of approximately one in three individuals, and it is estimated that 1 million new episodes of herpes zoster occur annually in the United States. The prevalence of attacks increases with age, apparently due to age-related decline in cell-mediated immunity. The incidence is low among young people but increases dramatically after 50 years of age, with studies suggesting that as many as 50% of individuals who live to 85 years of age will be affected at some time. Immunosuppression, HIV infection, treatment with cytotoxic or immunosuppressive drugs, radiation, malignancy, old age, alcohol abuse, stress (emotional or physical), and dental manipulation are additional predisposing factors for reactivation.

The long-term impact of varicella virus vaccination on herpes zoster prevalence is controversial and presently under evaluation. Interestingly, it is possible to develop herpes zoster by reactivation of either the wild-type or vaccine-strain virus, although the risk for vaccine-strain zoster seems to be much lower than that for wild-type zoster.

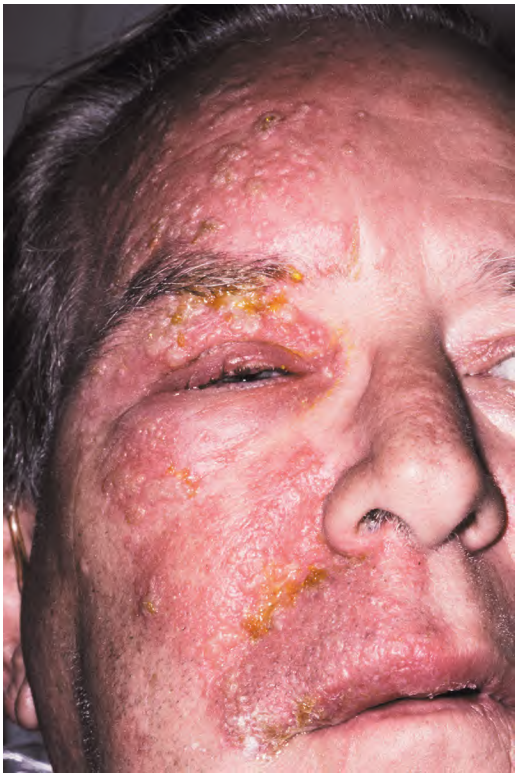
Clinical Features

The clinical features of herpes zoster can be grouped into three phases: prodrome, acute, and chronic. During initial viral replication, ganglionitis develops with resultant neuronal necrosis and severe neuralgia. This inflammatory reaction is responsible for the prodromal pain present in more than 90% of cases. As the virus travels down the nerve, the pain intensifies and has been described as burning, tingling, itching, boring, prickly, or knifelike. The pain develops in the area of epithelium innervated by the affected sensory nerve (dermatome) and may be accompanied by fever, malaise, and headache. Typically, one dermatome is affected, but involvement of two or more can occur. The thoracic dermatomes are affected in about two-thirds of cases. This prodromal pain normally precedes the acute phase rash by 1 to 4 days and, depending on which dermatome is affected, may masquerade as sensitive teeth, otitis media, migraine headache, myocardial infarction, or appendicitis.

The acute phase begins as the involved skin develops clusters of vesicles set on an erythematous base (Fig. 7-17). The lesions tend to follow the path of the affected nerve and terminate at the midline (Fig. 7-18). Within 3 to 4 days, the vesicles become pustular and ulcerate, with crusts developing after 7 to 10 days. The lesions are contagious until they crust, although the rate of VZV transmission from herpes zoster lesions is lower than that from varicella lesions. The exanthem typically resolves within 2 to 3 weeks in otherwise healthy individuals. On healing, scarring with hypopigmentation or hyperpigmentation is not unusual. Infrequently, there is dermatomal pain without development of a rash; this pattern is called **zoster sine herpete** (zoster without rash).

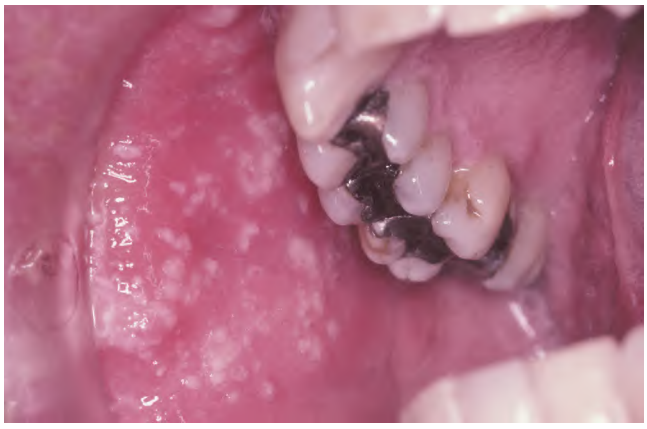


• **Fig. 7-17 Herpes Zoster.** Cluster of vesicles with surrounding erythema of the skin.



• **Fig. 7-18 Herpes Zoster.** Numerous crusting facial vesicles that extend to the midline.

Oral lesions occur with trigeminal nerve involvement and may be present on the movable or bound mucosa. The lesions often extend to the midline and frequently are accompanied by involvement of the skin overlying the affected quadrant. Like varicella, the individual lesions manifest as 1- to 4-mm vesicles or pustules that rupture to form shallow ulcerations (Fig. 7-19). The teeth in affected areas may develop pulpitis, pulpal necrosis, pulpal calcification, or root resorption. In addition, several reports have



• **Fig. 7-19 Herpes Zoster.** Numerous white opaque vesicles on the right buccal mucosa of the same patient depicted in Fig. 7-18.

documented significant bone necrosis with tooth loss. It is postulated that gnathic osteonecrosis may be secondary to extension of inflammation from affected nerves to adjacent blood vessels, leading to ischemic necrosis. The osteonecrosis may develop either during or following the exanthem, with reported lag periods as long as 150 days.

Ocular involvement is present in approximately 10% to 25% of cases and can cause significant morbidity, including permanent blindness. The ocular manifestations are highly variable and may arise from direct viral-mediated epithelial damage, neuropathy, immune-mediated damage, or secondary vasculopathy. Lesions on the tip of the nose (Hutchinson sign) indicate involvement of the nasociliary branch of the trigeminal nerve and an increased risk for severe ocular infection. In these cases, referral to an ophthalmologist is mandatory.

Reactivation of VZV in the geniculate ganglion may cause **Ramsay Hunt syndrome,** which is characterized by cutaneous lesions of the external auditory canal and involvement of the ipsilateral facial and auditory nerves. Affected individuals may exhibit facial paralysis as well as hearing deficits, vertigo, and other auditory and vestibular symptoms. In addition, some patients may develop loss of taste in the anterior two-thirds of the tongue. By using PCR or serology, investigators have detected active VZV infection in approximately 30% of patients thought to have Bell palsy (see page 801). Similar associations also have been demonstrated with HSV and EBV. These findings suggest an underlying viral cause for many cases of "idiopathic" facial paralysis.

Approximately 15% of patients progress to the chronic phase of herpes zoster (termed **postherpetic neuralgia**), which is characterized by persistent pain after resolution of the rash. In defining postherpetic neuralgia, there is a lack of consensus regarding the duration of pain persistence following the rash, although many investigators consider a minimum period of 1 to 3 months. Risk factors include female gender, older age, history of prodromal pain, moderate to severe rash and/or pain during the acute phase, and ophthalmic involvement. The pain is described as burning, throbbing, aching, itching, or stabbing, often with flares caused by light stroking or contact with clothing. Most of these neuralgias resolve within 1 year, with half of patients experiencing resolution after 2 months. Rare cases may last up to 20 years, and patients have been known to commit suicide because of the extreme pain. Although the cause is unknown, some investigators believe chronic VZV ganglionitis is responsible.

In rare cases, a potentially fatal ischemic stroke syndrome, termed **granulomatous angiitis,** may develop weeks to months after resolution of a zoster rash involving the trigeminal nerve distribution. This condition appears to result from direct extension of VZV and associated inflammation from the trigeminal ganglion to the internal carotid artery.

In immunocompromised individuals, herpes zoster is often severe, with an overall increased risk for complications. The cutaneous rash may become disseminated as a result of VZV viremia; in some cases, viremia may occur even without skin involvement. Potentially life-threatening complications include pneumonia, hepatitis, disseminated intravascular coagulopathy, and encephalitis. However, immunocompromised status does not appear to increase the risk for developing postherpetic neuralgia significantly.

Histopathologic Features

The active vesicles of herpes zoster are microscopically identical to those seen in the primary infection, varicella. For more information, see the previous sections regarding the histopathologic features of varicella and herpes simplex.

Diagnosis

Herpes zoster often is diagnosed from the clinical presentation, but laboratory testing may be necessary for atypical cases or exclusion of zosteriform recurrent HSV infection. Viral culture can provide confirmation. However, the results take at least 24 hours, and false negatives often occur because it is difficult to recover viable virus from cutaneous lesions. Cytologic smears demonstrate viral cytopathologic effects, as seen in varicella and HSV infection. A rapid diagnosis can be obtained by direct staining of cytologic smears with fluorescent monoclonal VZV antibodies. Molecular techniques, such as dot-blot hybridization and PCR, also can be used to detect VZV.

Treatment and Prognosis

Supportive therapy for herpes zoster may include antipruritics, such as diphenhydramine, and non-aspirin antipyretics. Skin lesions should be kept dry, clean, and, if possible, covered to prevent secondary infection; antibiotics may be administered to treat such secondary infections.

Prompt therapy with antiviral medications, such as acyclovir, valacyclovir, and famciclovir, has been found to accelerate healing of mucocutaneous lesions and reduce pain

during the acute phase. These medications are most effective if initiated within 72 hours after development of the first vesicle. Supplementation of antiviral agents with analgesics (such as, acetaminophen, NSAIDs, tramadol, and opioids), tricyclic antidepressants, antiepileptics (including gabapentin and pregabalin), or systemic corticosteroids may provide additional pain control.

Investigations regarding whether antiviral treatment administered alone or in combination with gabapentin during the acute phase may prevent or lessen the severity of postherpetic neuralgia have yielded variable results. Similarly, combination therapy with antivirals and corticosteroids may be helpful in the treatment of acute herpes zoster but does not appear to prevent postherpetic neuralgia.

In postherpetic neuralgia, tricyclic antidepressants, anticonvulsants (including gabapentin and pregabalin), and opioids may reduce pain. In addition, the FDA has approved the lidocaine patch, capsaicin patch, and capsaicin cream for the treatment of postherpetic neuralgia. However, the evidence in support of these topical therapies is of limited quality. Also, capsaicin—which is derived from peppers—may cause significant burning or stinging of the skin as a side effect. Nonpharmacologic treatments include nerve blocks and percutaneous electrical nerve stimulation, but there are few well-controlled studies to support these alternatives. Because postherpetic neuralgia often is difficult to treat, emphasis should be placed on herpes zoster prevention.

A herpes zoster vaccine (Zostavax) has been approved by the FDA for use in adults 50 years and older. However, because of concerns regarding adequate vaccine supply, the Centers for Disease Control and Prevention (CDC) have maintained their recommendation for routine herpes zoster vaccination in adults 60 years and older. Zostavax contains the same live, attenuated strain of VZV used in the varicella vaccines; however, it is 14 times more potent than Varivax, the monovalent varicella vaccine. Large-scale studies of Zostavax vaccination in older adults have shown an approximately 50% to 70% decrease in herpes zoster incidence and 67% decrease in postherpetic neuralgia incidence, with significantly reduced morbidity among those who do develop the disease. Because the zoster vaccine contains live, attenuated virus, it generally should not be administered to immunocompromised persons. However, vaccination of immunocompetent patients in anticipation of immunosuppressive therapy or disease states is appropriate.

◆ INFECTIOUS MONONUCLEOSIS (MONO; GLANDULAR FEVER; "KISSING DISEASE")

Infectious mononucleosis is a symptomatic disease resulting from exposure to Epstein-Barr virus (EBV or HHV-4). The infection usually occurs by intimate contact. Intrafamilial spread is common, and once a person is exposed, EBV remains in the host for life. Children usually become infected through contaminated saliva on fingers, toys, or other objects. Adults usually contract the virus through direct salivary transfer, such as shared straws or kissing, hence, the nickname "kissing disease." In developing nations, exposure usually occurs by age 3 and is universal by adolescence. In the United States, introduction to the virus often is delayed, with approximately 50% of college students lacking previous exposure. These unexposed adults become infected at a rate of 10% to 15% per year while in college. Infected children are typically asymptomatic, whereas young adults are at greatest risk for symptomatic disease. Similar mononucleosis syndromes may be produced by other pathogens, including cytomegalovirus (see page 231), HIV-1 (see page 239), and *Toxoplasma gondii* (see page 212).

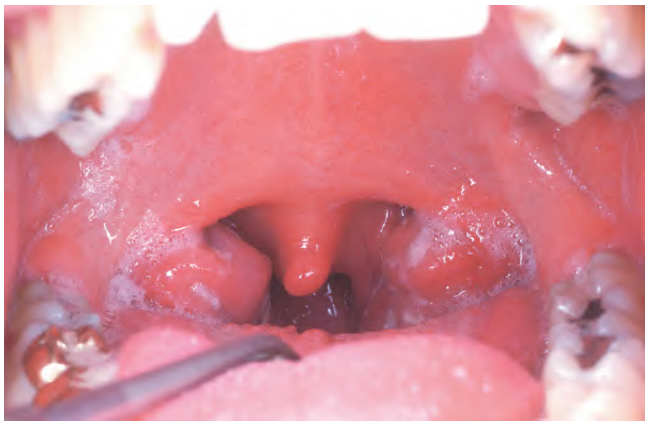
Besides infectious mononucleosis, EBV is associated with **oral hairy leukoplakia (OHL)** (see page 242), various lymphoproliferative disorders and lymphomas (most notably Burkitt lymphoma [see page 560]), nasopharyngeal carcinoma (see page 395), salivary lymphoepithelial carcinoma, some gastric carcinomas, possibly breast and hepatocellular carcinomas, and occasional smooth muscle tumors.

Clinical Features

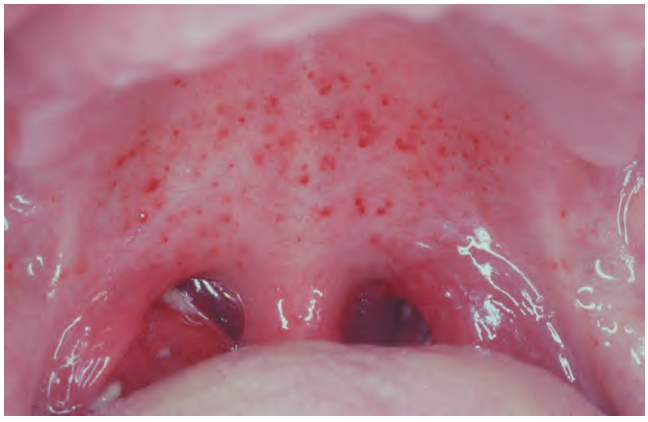
The clinical presentation varies by age. Most EBV infections in children are asymptomatic. In symptomatic children younger than 4 years, typical findings include fever, lymphadenopathy, pharyngitis, hepatosplenomegaly, and rhinitis or cough. Children 4 years and older are affected similarly but exhibit a much lower prevalence of hepatosplenomegaly, rhinitis, and cough. Most young adults experience fever, lymphadenopathy, pharyngitis, and tonsillitis. In adults older than 40 years, fever and pharyngitis are the predominant findings.

Complications are uncommon at any age but most frequently arise in children. Possible significant complications include splenic rupture, thrombocytopenia, autoimmune hemolytic anemia, aplastic anemia, neurologic problems, myocarditis, and hemophagocytic lymphohistiocytosis. The latter appears to be caused by massive activation of T lymphocytes and histiocytes and is often fatal without prompt treatment.

In classic infectious mononucleosis in a young adult, prodromal fatigue, malaise, and anorexia occur up to 2 weeks before the development of pyrexia. Fever may reach 104° F and last from 2 to 14 days. Prominent lymphadenopathy is noted in more than 90% of cases and typically appears as symmetrically enlarged and tender nodes, with frequent involvement of the posterior and anterior cervical chains. Enlargement of parotid lymphoid tissue rarely has been reported and can be associated with facial nerve palsy. More than 80% of affected young adults have oropharyngeal tonsillar enlargement, sometimes with diffuse surface exudates and secondary abscesses (Fig. 7-20). The lingual tonsils, which are located on the base of the tongue and extend from the circumvallate papillae to the epiglottis, can



• **Fig. 7-20 Infectious Mononucleosis.** Hyperplastic pharyngeal tonsils with yellowish crypt exudates. (Courtesy of Dr. George Blozis.)



• **Fig. 7-21 Infectious Mononucleosis.** Numerous petechiae of the soft palate. (Courtesy of Dr. George Blozis.)

become hyperplastic and compromise the airway. Rare fatalities have been reported from respiratory difficulties secondary to tonsillar hyperplasia, arytenoid hypertrophy, pharyngeal edema, and epiglottal swelling.

Oral lesions other than lymphoid enlargement also may be seen. Petechiae on the hard or soft palate are present in about 25% of patients (Fig. 7-21). The petechiae usually disappear within 24 to 48 hours. **Necrotizing ulcerative gingivitis (NUG)** (see page 143) also is fairly common. NUG-like pericoronitis (see page 156) and necrotizing ulcerative mucositis (see page 144) occur less frequently. Cases of NUG that are refractory to conventional therapy should be evaluated to rule out the possibility of EBV infection.

In less than 10% of classic infectious mononucleosis cases, patients experience fatigue persisting for several weeks to months. However, active EBV infection beyond 4 months is rare. Several investigators have attempted to associate EBV with a controversial symptom complex called **chronic fatigue syndrome,** characterized by profound fatigue lasting more than 6 months, pharyngitis, myalgias, arthralgias, headaches, lymphadenopathy, post-exertional malaise, unrestful sleep, and cognitive impairment. Nevertheless, current evidence does not support EBV as a specific cause of this condition, which likely may be triggered by a variety of illnesses or conditions.

Furthermore, some studies suggest that infectious mononucleosis increases the risk for developing multiple sclerosis later in life. However, whether EBV is a cause of multiple sclerosis or merely an innocent bystander remains highly controversial.

Diagnosis

The diagnosis of infectious mononucleosis commonly is based upon the clinical presentation combined with the presence of greater than 10% atypical lymphocytes on a peripheral blood smear and a positive heterophile antibody test. Heterophile antibodies are IgM antibodies that are directed against viral antigens and cross-react with sheep and horse erythrocytes. The Paul-Bunnell test and rapid slide agglutination (Monospot) assay are frequently used methods for detection of heterophile antibodies. More than 90% of infected young adults test positive for heterophile antibodies, but infected children younger than 4 years frequently test negative.

In suspected cases of EBV infection for which heterophile antibody testing is negative, EBV-specific antibody testing may be required. Indirect immunofluorescent assays can be performed during various stages of infection and resolution in order to quantify antibodies directed against viral capsid antigens (VCA) and EBV nuclear antigens (EBNA). Also, for immunocompromised patients or those with inconclusive serologic test results, real-time PCR may be useful.

Treatment and Prognosis

In most cases, infectious mononucleosis resolves within 4 to 6 weeks. NSAIDs can be used to minimize the most common symptoms. Adequate fluid intake and nutrition also are important. Patients with significant enlargement of the spleen should avoid contact sports to prevent the rare possibility of splenic rupture.

Tonsillar involvement may resemble streptococcal pharyngitis or tonsillitis (see page 166). However, ampicillin, amoxicillin, or other penicillins should be avoided because these antibiotics commonly cause nonallergic morbilliform skin rashes in patients with infectious mononucleosis.

Some clinicians advocate short-term corticosteroid administration in order to minimize acute symptoms. However, there is insufficient evidence from clinical studies to support the routine use of corticosteroid treatment for infectious mononucleosis. In addition, there is concern regarding an increased risk for complications, including encephalitis and myocarditis. In practice, most clinicians reserve corticosteroid treatment for management of severe complications, such as impending airway obstruction, hemolytic anemia, thrombocytopenia, or hemophagocytic lymphohistiocytosis. The latter also typically requires treatment with cyclosporine or etoposide.

Although antiviral medications, such as acyclovir, valacyclovir, and famciclovir, have been used successfully for temporary resolution of oral hairy leukoplakia (OHL), these medications do not demonstrate clinically obvious benefit for patients with infectious mononucleosis. These agents likely have an effect on viral replication; however, the main clinical manifestations of infectious mononucleosis appear to be secondary to the immune response to EBV-infected B lymphocytes and are not altered by this intervention.

◆ CYTOMEGALOVIRUS

Similar to other human herpesviruses, **cytomegalovirus** (CMV or HHV-5) may establish latency after initial infection and reactivate under certain conditions. CMV can reside latently in salivary gland cells, endothelium, macrophages, and lymphocytes. The virus can be found in most bodily fluids, including saliva, blood, urine, tears, respiratory secretions, genital secretions, and breast milk. Most clinically evident disease is found in neonates or immunosuppressed adults. In infants, the virus is contracted through the placenta, during delivery, or during breast-feeding. The next peak of transmission occurs during adolescence, predominantly from sexual contact. Transmission also has been documented through blood transfusion and organ transplantation. In the United States, seroprevalence is approximately 50% for individuals 6 to 49 years of age and greater than 90% for those older than 80 years. In addition to increasing age, other risk factors for CMV seropositivity include female gender, low socioeconomic status, household crowding, and foreign birthplace.

Clinical Features

At any age, almost 90% of CMV infections are asymptomatic. In clinically evident congenital and neonatal infection, typical features include jaundice, hepatosplenomegaly, cutaneous erythropoiesis, and thrombocytopenia (often with associated petechiae and purpura). CNS involvement may cause microcephaly, seizures, and mental and motor impairment. In addition, CMV infection represents the most common cause of nonhereditary sensorineural hearing loss, with infected infants often developing hearing loss at birth or later in childhood.

Among immunocompetent individuals, symptomatic acute CMV infection is rare and exhibits nonspecific features, ranging from an infectious mononucleosis-like presentation to lethal multiorgan involvement. CMV mononucleosis typically is characterized by fever, chills, sore throat, headache, and fatigue. Compared with classic EBV mononucleosis, this condition is much less commonly associated with exudative pharyngitis, lymphadenopathy, and hepatosplenomegaly. Other possible findings in symptomatic CMV infection include joint and muscle pain, abdominal pain, nonproductive cough, maculopapular rash, and diarrhea. Persistent fever of unknown origin may be the primary finding in some cases. Rarely, immunocompetent patients may develop acute sialadenitis diffusely involving the major and minor salivary glands. In such cases, xerostomia often is noted, and the affected glands are painful and enlarged. Unusual complications include myocarditis, pericarditis, pneumonitis, anterior uveitis, and meningitis.

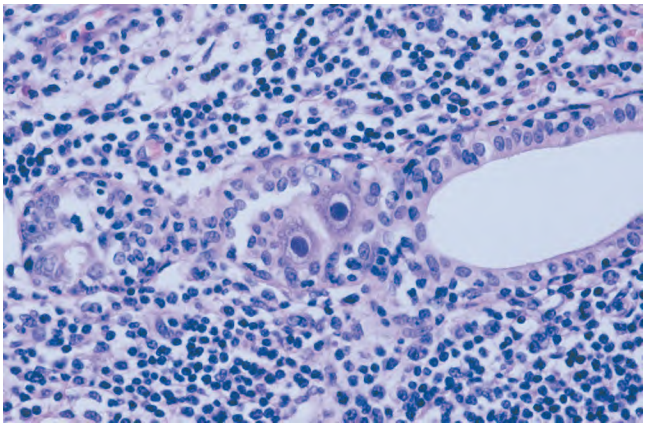
Clinically evident CMV involvement frequently arises in immunocompromised transplant patients. In some cases a temporary, mild fever is the only finding; in others, the infection becomes aggressive and is characterized by hepatitis, leukopenia, pneumonitis, gastroenteritis, and, more rarely, a progressive wasting syndrome.

Patients with AIDS (see page 239) also are at increased risk for symptomatic CMV disease, although a decrease in prevalence has been reported with the introduction of combination antiretroviral therapy (cART). The two most common manifestations of CMV infection in patients with AIDS are chorioretinitis and gastrointestinal involvement. The former may result in blindness, and the latter may cause bloody diarrhea or odynophagia.

Chronic oral ulcerations caused by CMV infection have been documented in association with HIV infection as well as other immunosuppressive conditions. Occasionally, chronic oral ulcerations in immunocompromised patients will demonstrate coinfection by CMV and HSV. In addition, neonatal CMV infection can produce developmental tooth defects. In a study of 118 people with a history of neonatal CMV infection, examination revealed tooth defects in 40% of those with symptomatic infections and slightly more than 5% of those with asymptomatic infections. The teeth exhibited diffuse enamel hypoplasia, significant attrition, enamel hypomaturation, and yellow coloration from the underlying dentin.

Histopathologic Features

Biopsy specimens of intraoral CMV lesions may demonstrate changes within vascular endothelial cells or salivary duct epithelial cells (Fig. 7-22). Scattered infected cells are extremely swollen, showing both intracytoplasmic and



• **Fig. 7-22 Cytomegalovirus (CMV) Infection.** Salivary ductal epithelium exhibiting distinctive "owl eye" alterations.

intranuclear inclusions and prominent nucleoli. These enlarged cells have been called "owl eye" cells. Grocott-Gomori methenamine silver and periodic acid-Schiff (PAS) stains demonstrate the cytoplasmic inclusions but not the intranuclear changes.

Diagnosis

The diagnosis of CMV infection is based upon the clinical features combined with laboratory findings. Tissue biopsy may demonstrate cells with viral inclusions suggestive of CMV infection; however, these inclusions may be scant and difficult to demonstrate on routine light microscopy. More sensitive and specific methods for confirmation of CMV infection in biopsy specimens include immunohistochemistry and *in situ* hybridization. Because specific treatments exist for CMV infection in immunocompromised patients, biopsy is recommended for chronic ulcerations refractory to conservative therapy. In addition, in such cases HSV coinfection should be excluded.

Additional CMV detection methods include serology, viral culture, and PCR. Serologic testing by enzyme-linked immunosorbent assay (ELISA) is commonly available and relatively inexpensive. A diagnosis of active CMV infection is supported by acute and convalescent serum samples showing a fourfold rise in IgG antibodies to CMV combined with the presence of either IgM antibodies to CMV or a positive CMV culture. In transplant patients and other immunocompromised individuals, plasma viral load—determined by real-time quantitative PCR—may be monitored in order to assess the need for CMV treatment or response to CMV therapy.

In CMV mononucleosis, peripheral blood typically shows a 50% or greater relative lymphocytosis, with at least 10% atypical lymphocytes. Unlike EBV mononucleosis, this condition usually is heterophile antibody-negative.

Treatment and Prognosis

Although most CMV infections resolve spontaneously, therapy often is required in the immunosuppressed patient. Ganciclovir has resolved clinical symptoms in more than 75% of treated immunocompromised patients. However, the medication must be continued to prevent a relapse if the immune dysfunction persists. In patients with oral ulcerations coinfected with CMV and HSV, IV ganciclovir will produce resolution in most instances. However, resistance to ganciclovir has been reported; other effective medications include foscarnet, cidofovir, and valganciclovir. In transplant patients, prophylactic antiviral therapy for CMV may be considered. Nevertheless, the best preventive and interventional therapy in immunocompromised patients remains improvement of immune status, such as that achieved with combination antiretroviral therapy (cART) for HIV infection (see page 253).

Immunocompetent patients with clinically evident CMV infection usually are treated symptomatically with NSAIDs. Corticosteroids or IV gamma globulins have been used in patients with hemolytic anemia or severe thrombocytopenia. Use of antiviral agents in immunocompetent patients typically is reserved for severe disease because of the risk of drug-related toxicity.

No licensed vaccine is currently available for prevention of CMV infection; however, several vaccines are under investigation and may be used in the future to protect women of reproductive age and children.

◆ ENTEROVIRUSES

Human **enteroviruses** (family Picornaviridae, genus *Enterovirus*) traditionally have been classified into echoviruses, coxsackieviruses A and B, and polioviruses, with numerical designations for individual serotypes (e.g., Coxsackie virus A1). Beginning in the 1960s, newly discovered enterovirus serotypes have been designated numerically without being placed into one of the traditional groups (e.g., enterovirus 71). Current classification, based upon molecular and biologic features, divides the human enteroviruses into four species (A through D) but maintains the traditional names for individual serotypes. More than 100 serotypes have been identified. Recently, a few enteroviruses (echoviruses 22 and 23) have been reclassified into the distinct *Parechovirus* genus. Polioviruses largely have been eradicated in developed countries by vaccination. However, the non-polio enteroviruses continue to cause disease worldwide.

Most enterovirus infections are asymptomatic or subclinical. Among symptomatic cases, the clinical presentation is variable and may range from a minor febrile illness to a severe and potentially fatal infection. More than 30 subtypes are associated with skin rashes. In addition, some of these viruses have been associated with an increased prevalence of type 1 diabetes mellitus and dilated cardiomyopathy.

The estimated annual incidence of symptomatic enterovirus infections in the United States is 10 to 15 million, with most cases affecting infants and young children. In many countries, epidemics occur every 2 to 3 years and primarily affect children 1 to 4 years old. The timing of the epidemics appears to correlate with the accumulation of a new population of susceptible young children. A male predominance has been observed among patients younger than 20 years; in contrast, a female predominance has been noted among those 20 years and older, most likely because of exposure as primary caregivers to infected children.

The present discussion focuses upon the following clinical patterns of enteroviral infection: **herpangina, hand-foot-and-mouth disease,** and **acute lymphonodular pharyngitis.** These conditions are closely related and should not be considered entirely separate. In epidemics involving the same viral strain, the clinical presentations often vary and may include both herpangina and hand-foot-and-mouth disease. Also, many authorities regard acute lymphonodular pharyngitis as a variant of herpangina rather than a distinct entity.

Herpangina usually is produced by coxsackievirus A1 to A6, A8, A10, or A22. However, it also may represent infection by coxsackievirus A7, A9, or A16; coxsackievirus B2 to B6; echovirus 9, 16, or 17; or enterovirus 71. Hand-foot-and-mouth disease usually is caused by coxsackievirus A16, but also may arise from coxsackievirus A5, A9, or A10; echovirus 11; or enterovirus 71. In particular, in the Asia-Pacific region over the past few decades, enterovirus 71 has caused several large outbreaks of hand-foot-and-mouth disease, often associated with major neurologic complications. Acute lymphonodular pharyngitis is less recognized, and coxsackievirus A10 has been found in the few reported cases.

In nontropical areas, most cases arise in the summer or early fall, with crowding and poor hygiene aiding their spread. The fecal-oral route is the major mode of transmission, and frequent hand washing is important to diminish spread during epidemics. The incubation period is 4 to 7 days. During the acute phase, the virus also can be transmitted through saliva or respiratory droplets. Infection confers immunity against reinfection by a particular strain. Over time an individual may develop immunity against numerous enterovirus types but still remain susceptible to additional strains.

Clinical Features

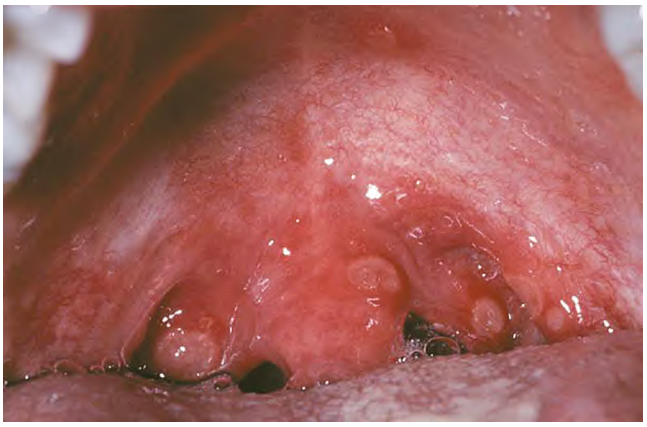
In all three clinical patterns, the severity varies by strain. Most strains produce a self-limiting disease that requires no therapy, but some strains can produce epidemics with significant complications and occasional fatalities. Potential complications include pneumonia, pulmonary edema and hemorrhage, acute flaccid paralysis, encephalitis, meningitis, and carditis. Infection with coxsackievirus B during pregnancy has been associated with fetal and neonatal death, whereas cardiac anomalies have been noted in infants who survive the initial infection.

Herpangina

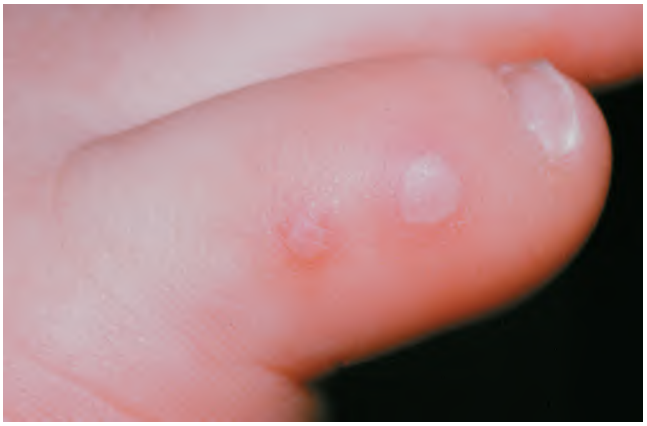
Herpangina begins with an acute onset of sore throat, dysphagia, and fever, occasionally accompanied by cough, rhinorrhea, anorexia, vomiting, diarrhea, myalgia, and headache. Most cases, however, are mild or subclinical. Typically a small number of lesions (usually two to six) develop on the soft palate or tonsillar pillars (Fig. 7-23). The lesions begin as red macules, which form fragile vesicles that rapidly ulcerate. The ulcerations average 2 to 4 mm in diameter. The systemic symptoms resolve within a few days; the ulcerations usually take 7 to 10 days to heal.

Hand-Foot-And-Mouth Disease

Hand-foot-and-mouth disease is the best-known presentation of enterovirus infection. Like herpangina, the skin rash and oral lesions typically are associated with flulike symptoms (e.g., sore throat, dysphagia, and fever), occasionally accompanied by cough, rhinorrhea, anorexia, vomiting, diarrhea, myalgia, and headache.



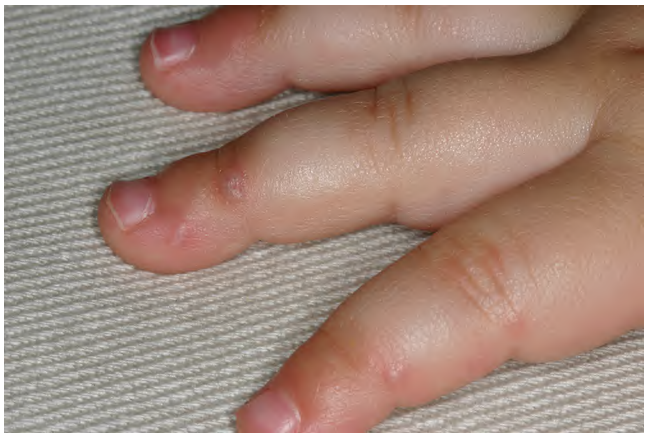
• **Fig. 7-23 Herpangina.** Numerous aphthous-like ulcerations of the soft palate.



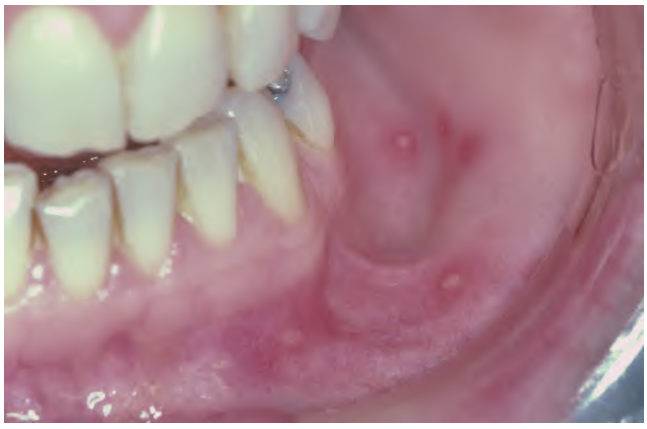
• **Fig. 7-24 Hand-foot-and-mouth Disease.** Multiple vesicles of the skin of the toe. (Courtesy of Dr. Samuel J. Jasper.)

The name fairly well describes the location of the lesions. Oral and hand lesions almost always are present. The oral lesions arise without prodromal symptoms and precede the development of the cutaneous lesions. Sore throat and mild fever usually are present also. The cutaneous lesions range from a few to dozens and primarily affect the borders of the palms and soles and the ventral surfaces and sides of the fingers and toes (Fig. 7-24). Rarely other sites, especially the buttocks, external genitals, and legs, may be involved. The cutaneous lesions begin as erythematous macules that develop central vesicles and heal without crusting (Fig. 7-25). In some cases, nail loss or ridges (Beau lines) may ensue after several weeks.

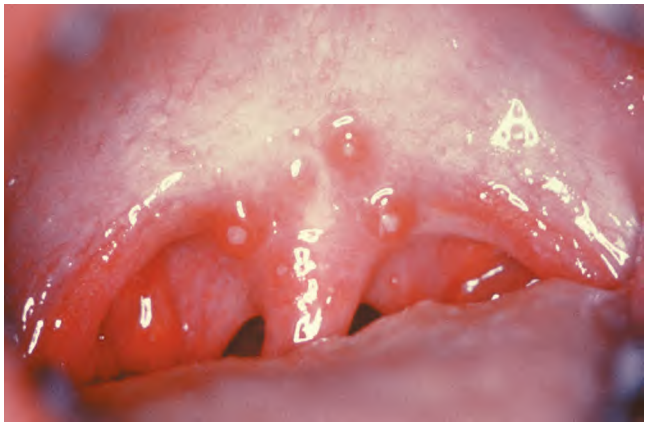
The oral lesions resemble those of herpangina but may be more numerous and more frequently involve anterior regions of the mouth. The number of lesions ranges from 1 to 30. The buccal mucosa, labial mucosa, and tongue are the most common sites, but any area of the oral mucosa may be involved (Fig. 7-26). The individual lesions typically measure 2 to 7 mm in diameter but may be larger than 1 cm. The lesions rapidly ulcerate and then typically heal within 1 week.



• **Fig. 7-25 Hand-foot-and-mouth Disease.** Numerous cutaneous vesicles on the sides of the fingers.



• **Fig. 7-26 Hand-foot-and-mouth Disease.** Multiple aphthous-like ulcerations of the mucobuccal fold.



• **Fig. 7-27 Acute Lymphonodular Pharyngitis.** Numerous dark-pink and yellow lymphoid aggregates. (Courtesy of Dr. George Blozis.)

Acute Lymphonodular Pharyngitis

Acute lymphonodular pharyngitis is characterized by sore throat, fever, and mild headache, which may last from 4 to 14 days. Low numbers (one to five) of yellow to dark-pink nodules develop on the soft palate or tonsillar pillars (Fig. 7-27). The nodules represent hyperplastic lymphoid aggregates and resolve within 10 days without vesiculation or ulceration.

Histopathologic Features

In patients with herpangina and hand-foot-and-mouth disease, the affected epithelium exhibits intracellular and intercellular edema, which lead to the formation of an intraepithelial vesicle. The vesicle enlarges and ruptures through the epithelial basal cell layer, with formation of a subepithelial vesicle. Epithelial necrosis and ulceration soon follow. Inclusion bodies and multinucleated epithelial cells are absent.

Diagnosis

Herpangina, hand-foot-and-mouth disease, and acute lymphonodular pharyngitis usually are diagnosed based upon the clinical manifestations. In patients with atypical presentations, laboratory confirmation appears prudent. Viral isolation from culture can be performed. Throat cultures tend to be positive predominantly during the early acute stage. Cultures from stool specimens are best for patients with mucosal lesions only, whereas cultures from cutaneous lesions are best for the diagnosis of hand-foot-and-mouth disease. Serologic demonstration of rising enteroviral antibody titers between the acute and convalescent stages can be used to confirm the diagnosis in questionable cases. PCR assay is increasingly available and replacing viral culture in many diagnostic laboratories.

Treatment and Prognosis

In most instances, enterovirus infections are self-limiting and without significant complications. Therapy is directed toward symptomatic relief; nonaspirin antipyretics and topical anesthetics, such as dyclonine hydrochloride, often are beneficial.

Occasionally, certain strains produce infections with a more aggressive clinical course. Body temperature above 102° F, fever for longer than 3 days, severe vomiting, and lethargy have been associated with increased risk for serious disease complications and warrant close patient monitoring.

◆ MEASLES (RUBEOLA)

Measles (rubeola) is a highly contagious infection produced by a virus in the family Paramyxoviridae and genus *Morbillivirus.* Prior to the development of an effective measles vaccine, the disease caused millions of deaths annually worldwide. In the pre-vaccine era in the United States, greater than 90% of individuals were infected by 15 years of age, with over 500,000 measles cases and about 500 measles-related deaths reported annually.

Eradication through widespread immunization is achievable yet remains a challenge. In the United States, following

the introduction of universal measles vaccination in 1963, the annual incidence of measles decreased by more than 99%. A major resurgence occurred from 1989 to 1999, mainly among unvaccinated preschool-aged children. This resurgence led to the recommendation for a second vaccine dose and intensive, widespread immunization efforts. In 2000, the CDC declared that measles had been eliminated in the United States. Nevertheless, outbreaks of measles—often linked to unvaccinated individuals and importation of the virus from abroad—continue to occur, with approximately 40 to 220 cases reported per year since 2001. Likewise, international efforts toward measles elimination by the World Health Organization, United Nations Children's Fund, and other organizations have made progress but are ongoing. Political, financial, and logistical barriers as well as public complacency and concerns regarding vaccine safety have made measles control difficult.

Clinical Features

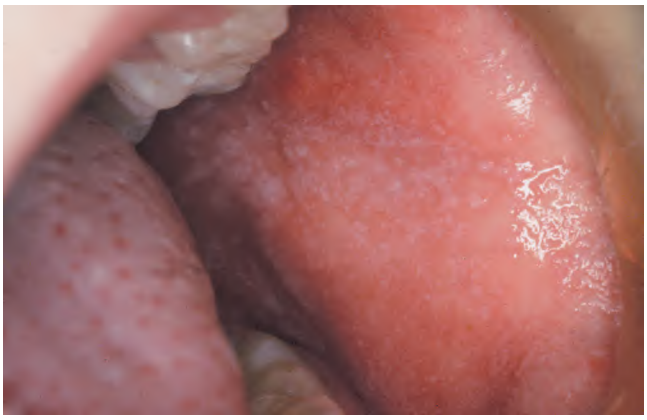
Most cases of measles arise in late winter or spring and are spread through respiratory droplets. The average incubation period is 14 days, and affected individuals are infectious from 4 days before until 4 days after appearance of the associated rash. The virus is associated with significant lymphoid hyperplasia that often involves the lymph nodes, tonsils, adenoids, and Peyer patches.

There are three stages of infection, with each stage lasting 3 days—hence the designation 9-day measles. The first 3 days are dominated by the three Cs: coryza (runny nose), cough (typically brassy and uncomfortable), and conjunctivitis (red, watery, and photophobic eyes). Fever typically accompanies these symptoms. During this initial stage, the most distinctive oral manifestation, **Koplik spots,** is seen. These lesions represent foci of epithelial necrosis and appear as numerous small, blue-white macules (or "grains of salt") surrounded by erythema (Fig. 7-28). Typical sites of involvement include the buccal and labial mucosa, and less often the soft palate.

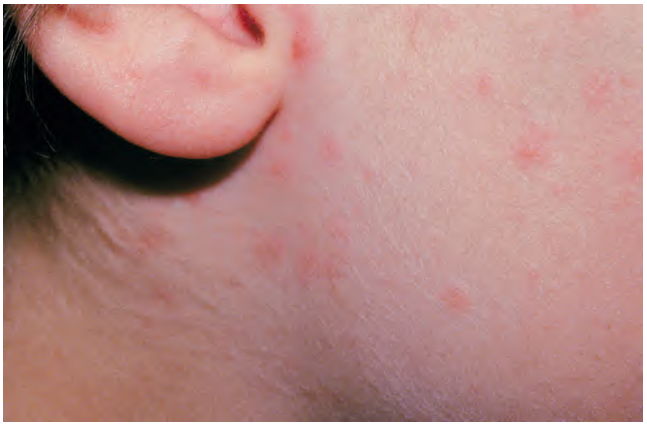
As the second stage begins, the fever continues, the Koplik spots fade, and a maculopapular and erythematous (morbilliform) rash begins. The face is involved first, with eventual downward spread to the trunk and extremities. Ultimately, a diffuse erythematous eruption is formed, which tends to blanch on pressure (Fig. 7-29). Abdominal pain secondary to lymphatic involvement is not rare.

In the third stage, the fever ends. The rash begins to fade, with downward progression and replacement by brown pigmentation. Ultimately, desquamation of the skin is noted in areas previously affected by the rash.

Complications may affect up to 40% of patients, especially those who are younger than 5 years, older than 20 years, malnourished, or immunocompromised. Common complications in young children are otitis media, pneumonia, laryngotracheobronchitis (croup), and diarrhea. Another fairly common sequela is keratoconjunctivitis, which tends to affect children with vitamin A deficiency and may cause blindness. Acute appendicitis occasionally is seen secondary to vascular obstruction created by the swelling of Peyer patches. Encephalitis develops in approximately 1 in 1000 cases, often resulting in death or permanent brain damage and intellectual disability. In about 1 in 100,000 cases, a delayed complication termed **subacute sclerosing panencephalitis (SSPE)** arises as late as 11 years after the initial infection. This degenerative CNS disorder leads to personality changes, seizures, coma, and death. Widespread vaccine use virtually has eliminated SSPE in developed nations.



• **Fig. 7-28 Rubeola.** Numerous blue-white Koplik spots of buccal mucosa. (Courtesy of Dr. Robert J. Achterberg.)



• **Fig. 7-29 Rubeola.** Erythematous maculopapular rash of the face. (Courtesy of Dr. Robert J. Achterberg.)

Measles in immunocompromised patients can be serious, with a high risk for complications and death. Most of these patients exhibit either an atypical rash or no exanthem. Pneumonitis is the primary complication.

Koplik spots are not the only oral manifestation that may be associated with measles. Candidiasis, necrotizing ulcerative gingivitis (NUG), and necrotizing stomatitis may occur if significant malnutrition also is present. Severe measles in early childhood can cause pitted enamel hypoplasia of the developing permanent teeth. Enlargement of accessory lymphoid tissues, such as the lingual and pharyngeal tonsils, also may be noted.

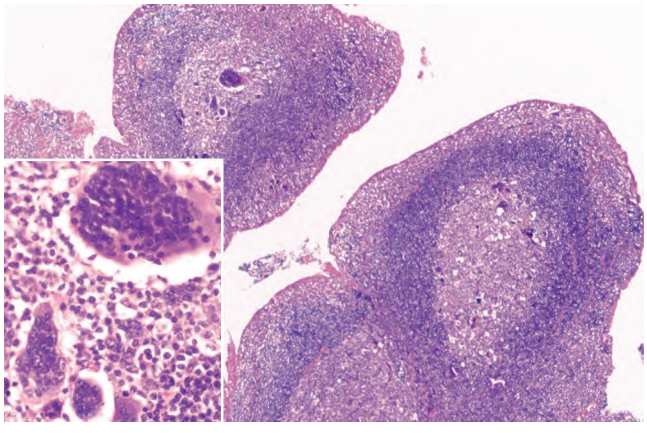
Histopathologic Features

Because of the reduced prevalence of measles and the transient nature of Koplik spots, few oral and maxillofacial pathologists have had the opportunity to view these lesions microscopically. Initially, Koplik spots represent areas of hyperparakeratotic epithelium with spongiosis, dyskeratosis, and epithelial syncytial giant cells. The number of nuclei within these giant cells ranges from 3 to more than 25. Close examination of the epithelial cells often reveals pink-staining inclusions in the nuclei or, less commonly, cytoplasm. Electron microscopy has shown that the inclusions represent microtubular aggregates characteristic of paramyxovirus infection. As the spot ages, the epithelium exhibits heavy neutrophilic exocytosis leading to microabscess formation, epithelial necrosis, and, ultimately, ulceration. Frequently, examination of the epithelium adjacent to the ulceration reveals the suggestive syncytial giant cells.

Examination of hyperplastic lymphoid tissue during the prodromal stage of measles often reveals a similar alteration. In 1931, Warthin and Finkeldey, in two separate publications, reported an unusual finding in patients who had their tonsils removed within 1 to 5 days of the clinical appearance of measles. Within the hyperplastic lymphoid tissue, there were numerous multinucleated giant lymphocytes (Fig. 7-30). These multinucleated cells subsequently have been termed **Warthin-Finkeldey giant cells** and once were thought to be specific for measles. However, similar cells have been noted in a variety of conditions, such as lymphoma, Kimura disease, AIDS-related lymphoproliferative disease, and lupus erythematosus.

Diagnosis

The diagnosis of measles in an epidemic setting usually is based on the clinical features and history. Laboratory confirmation can be of value in isolated or atypical cases. The most commonly used method is IgM antibody assay performed on a single serum sample. The antibodies usually appear within 1 to 3 days after the beginning of the exanthem and persist for 1 to 2 months. Confirmation by rising IgG titers, viral culture, and reverse transcription PCR also are possible.



• **Fig. 7-30 Rubeola.** Histopathologic section of pharyngeal tonsil demonstrating lymphoid hyperplasia with scattered multinucleated giant cells. *Inset* reveals high-power magnification of Warthin-Finkeldey giant cells.

Treatment and Prognosis

Primary prevention is essential for reducing measles-associated morbidity and mortality. The measles vaccine is a live, attenuated virus, which is included in the widely used MMR (measles, mumps, and rubella) and MMRV (measles, mumps, rubella, and varicella) vaccines. Routine childhood measles vaccination is recommended, with the first dose administered between the ages of 12 and 15 months and a second dose between the ages of 4 and 6 years. The vaccine is highly effective, with over 99% of individuals developing long-term immunity after receiving two doses. In a given population, measles eradication typically is attained with 95% vaccine coverage. Despite controversy regarding vaccine safety, adverse reactions from measles vaccination are rare and typically mild or transient. Extensive research shows no increased risk of permanent neurologic sequelae, and no scientific evidence supports an increased risk for autism or inflammatory bowel disease.

In otherwise healthy patients with measles, fluids and nonaspirin antipyretics are recommended for symptomatic relief. Children with measles also should receive vitamin A supplementation. For immunocompromised patients, ribavirin and interferon have shown promise, but controlled trials assessing their efficacy are lacking. In addition, immune globulin may be administered to prevent or modify disease in exposed immunocompromised patients.

In the United States, less than 1% of measles cases result in death, whereas in developing countries with low vaccine coverage, the case-fatality rate can be as high as 25%. The most common causes of death are pneumonia and acute encephalitis. The prognosis is especially poor for immunocompromised patients, with greater than 50% mortality for infected patients with underlying malignancy and more than 30% mortality for AIDS-associated measles.

◆ RUBELLA (GERMAN MEASLES)

Rubella is a mild illness caused by a virus in the family Togavirus and genus *Rubivirus.* The greatest importance of this infection lies not in its effects on those who contract the acute illness but in its capacity to induce birth defects in the developing fetus. The infection occurs primarily in late winter and early spring. It is contracted through respiratory droplets, with nearly 100% transmission among individuals in close living conditions. The incubation time is from 12 to 23 days, and infected patients are contagious from 1 week before to 1 week after onset of the exanthem. Infants with a congenital infection may release the virus for up to 1 year.

In the past, this infection occurred in cycles, with localized epidemics every 6 to 9 years and pandemics every 10 to 30 years. The last pandemic occurred from 1962 to 1964. In 1964 and 1965, the United States alone had more than 12.5 million cases, which resulted in more than 11,000 spontaneous or therapeutic abortions, 2,100 neonatal deaths, and 20,000 infants born with **congenital rubella syndrome (CRS).**

An effective vaccine, first released in 1969, has dramatically affected the epidemiology of the infection and broken the cycle of occurrences. In the United States, during the two decades immediately following introduction of the vaccine, the number of rubella and CRS cases reported annually decreased 99% and 97%, respectively. Like rubeola, rubella exhibited a slight resurgence from 1989 to 1990, primarily due to a lack of vaccination diligence; this resurgence prompted intensification of vaccination efforts and a new two-dose schedule. These measures resulted in an overall decline in rubella cases but a shift in epidemiology. During the early 1990s, children younger than 15 years mainly were affected; however, since the mid-1990s, most reported rubella cases have occurred in patients 15 years and older, especially among Hispanic and foreign-born individuals. Notwithstanding, since 2001, the overall annual incidence has remained low (less than 1 per 10,000,000 population). In 2004, a panel of experts declared that rubella elimination (i.e., absence of endemic transmission) had been achieved in the United States. From 2005 through 2011, only 62 cases of rubella and 4 cases of CRS were reported in the United States. However, rubella remains endemic in several parts of the world, with more than 120,000 cases reported annually worldwide.

Clinical Features

A large percentage of infections are asymptomatic; the frequency of symptoms is greater in adolescents and adults. Prodromal symptoms may be seen 1 to 5 days before the exanthem and include fever, headache, malaise, anorexia, myalgia, mild conjunctivitis, coryza, pharyngitis, cough, and lymphadenopathy. The lymphadenopathy may persist for weeks and is noted primarily in the suboccipital, postauricular, and cervical chains. The most common complication is arthritis, which increases in frequency with age and usually arises subsequent to the rash. Rare complications include encephalitis and thrombocytopenia.

The rash is often the first sign of the infection and begins on the face and neck, with spread to the entire body within 1 to 3 days. The exanthem forms discrete pink macules, then papules, and finally fades with flaky desquamation. Facial involvement often clears before the rash completes its spread into the lower body areas. Generally, the rash completely resolves by day 3—hence the designation 3-day measles.

Oral lesions, known as **Forchheimer sign,** have been reported in about 20% of cases. These lesions consist of small, discrete, dark-red papules that develop on the soft palate and may extend onto the hard palate. This enanthem arises simultaneously with the rash, becoming evident in about 6 hours after the first symptoms and not lasting longer than 12 to 14 hours. Palatal petechiae also may occur.

The risk of CRS correlates with the time of infection. The frequency of transmission from an infected mother is greater than 80% during the first 12 weeks of pregnancy, with the risk of fetal damage decreasing dramatically at 8 weeks and becoming rare after 20 weeks of gestation. The classic triad of CRS consists of deafness, heart disease, and cataracts. Deafness is the most common manifestation, affecting more than 80% of patients. This hearing loss may not become evident until 2 years of age and usually is bilateral. Less common, late-emerging complications include encephalopathy, intellectual impairment, diabetes mellitus, and thyroid disorders.

Diagnosis

The diagnosis of rubella is contingent on laboratory tests because the clinical presentation of the acquired infection is typically subclinical, mild, or nonspecific. Serologic analysis is the mainstay of diagnosis, although viral culture and PCR also are possible.

Treatment and Prognosis

Rubella is mild, and therapy usually is not required. Nonaspirin antipyretics and antipruritics may be useful in patients with significant fever or symptomatic cutaneous involvement. Passive immunity may be provided by the administration of rubella immunoglobulin. If immunoglobulin is given within a few days of exposure, it decreases the severity of the infection. This therapy typically is reserved for pregnant patients who decline abortion.

High vaccination coverage—particularly among children, women of childbearing age, and foreign-born individuals—is essential for prevention of rubella. In the United States, both the MMR (measles, mumps, and rubella) and MMRV (measles, mumps, rubella, and varicella) vaccines are licensed for rubella prevention. Routine childhood administration of either MMR or MMRV is recommended, with the first dose at 12 to 15 months of age and the second dose at 4 to 6 years of age. In addition, in the absence of evidence of rubella immunity, the following groups should receive at least one dose of MMR: adults born during or after 1957, nonpregnant women of childbearing age, and health care personnel. Evidence of immunity may include serologic testing or documentation of at least one dose of rubella-containing vaccine at 12 months of age or older; immunity also generally can be presumed in those born before 1957, as long as the individual is neither a woman who might become pregnant nor a health care worker. Contraindications for the MMR and MMRV vaccines include pregnancy, immunodeficiency, allergy to any of the vaccine components, and acute febrile illness.

Pregnant women lacking immunity should be vaccinated immediately postpartum.

MUMPS (EPIDEMIC PAROTITIS)

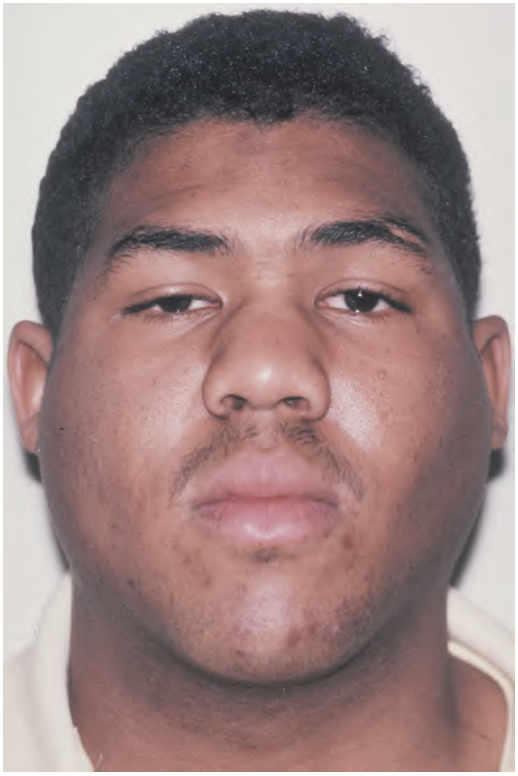
Mumps is an infection caused by a virus in the family Paramyxoviridae and genus *Rubulavirus.* This infection causes diffuse swelling of the exocrine glands; although the salivary glands are the best known sites of involvement, the pancreas, choroid plexus, and mature ovaries and testes also are affected frequently. The virus can be transmitted through respiratory droplets, saliva, and urine. The incubation period usually is 16 to 18 days, with a range of about 2 to 4 weeks. Patients are contagious from 1 day before the clinical appearance of infection to 14 days after its clinical resolution. In temperate climates, mumps most commonly occurs in winter and spring.

As with measles and rubella, the epidemiology has been affected dramatically by vaccination. Before the advent of widespread vaccination, mumps epidemics developed every 2 to 5 years; nearly everyone was exposed with 90% of infections occurring before age 15. In the United States, the mumps vaccine was licensed in 1967, although the Advisory Committee on Immunization Practices (ACIP) did not recommend universal childhood mumps vaccination until 1977. At that time, MMR (measles, mumps, and rubella) vaccine administration became the norm for children 12 to 15 months of age. Subsequently, the annual incidence of mumps decreased by 98% and reached an all-time low in 1985. In 1989, the ACIP issued a two-dose recommendation for MMR vaccination, primarily in response to a resurgence of measles. Compared with the pre-vaccine era, the two-dose vaccination schedule has reduced the prevalence of mumps by more than 99%.

Nevertheless, several mumps resurgences have occurred over the past three decades. These resurgences often have developed among adolescents and young adults, particularly in the college setting. This shift in peak age from childhood to adolescence and young adulthood is clinically significant, because certain disease complications, such as epididymo-orchitis and oophoritis, primarily affect postpubertal patients. Although outbreaks in the mid-1980s to early 1990s were attributed to single-dose vaccine failure or a lack of vaccination, several outbreaks in the 2000s have occurred despite high levels of two-dose vaccine coverage. The efficacy of the mumps component of the MMR vaccine is approximately 88% after two doses and is lower than that of the measles and rubella components. During outbreaks from 2009 to 2010, individuals in affected populations were administered a third dose of MMR vaccine under experimental protocols. Some experts believe a routine third dose of MMR vaccine may be recommended in the future.

Clinical Features

Approximately 30% of mumps infections are subclinical. In symptomatic cases, prodromal symptoms of low-grade fever, headache, malaise, anorexia, and myalgia develop first. These nonspecific findings typically are followed within 1 day by significant salivary gland changes. The parotid glands are involved most often, but the sublingual and submandibular glands also can be affected. Discomfort and swelling develop in the tissues surrounding the lower half of the external ear and extending down along the posterior inferior border of the adjacent mandible (Fig. 7-31). The enlargement and pain typically peak within 2 to 3 days. Chewing movements of the jaw or eating saliva-stimulating foods tends to increase the pain. Enlargement of the glands usually begins on one side, followed by contralateral involvement within a few days. Unilateral involvement is seen in about 25% of patients.



• **Fig. 7-31 Mumps.** Bilateral parotid enlargement. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)

The second most common finding is epididymo-orchitis, which occurs in about 25% of postpubertal males. The testicle exhibits rapid swelling, with significant pain and tenderness. The enlargement can range from a minimal swelling to a fourfold increase in size. Unilateral involvement is most common. Upon resolution of the swelling, testicular atrophy may occur; permanent sterility is rare, but subfertility develops in approximately 13% of patients with epididymo-orchitis. Less commonly, oophoritis and mastitis can be seen in postpubertal females. In addition, spontaneous abortion occurs in approximately 25% of women who contract mumps during the first trimester of pregnancy.

Less commonly, meningoencephalitis, cerebellar ataxia, hearing loss, pancreatitis, arthritis, carditis, and decreased

renal function may occur. The most common symptom associated with CNS involvement is headache, whereas involvement of the pancreas can lead to nausea and vomiting. Isolated changes, such as orchitis or meningitis, may occur in the absence of salivary gland involvement, thereby making diagnosis difficult in nonepidemic settings.

The most frequently reported oral manifestation is redness and enlargement of Wharton and Stensen salivary gland duct openings. In addition, involvement of the sublingual glands may produce bilateral enlargement of the floor of the mouth.

Diagnosis

The diagnosis of mumps in an epidemic setting usually can be made easily from the clinical presentation; however, isolated cases often require laboratory confirmation. The most frequently used diagnostic procedure is demonstration of either mumps-specific IgM or a fourfold rise of mumps-specific IgG titers between the acute and convalescent phases. In addition, a swab of secretions obtained from parotid or other affected salivary gland ducts can be used for viral culture or real-time reverse transcription PCR testing.

Treatment and Prognosis

The treatment of mumps is palliative in nature. Frequently, nonaspirin analgesics and antipyretics are administered. In an attempt to minimize orchitis, bed rest is recommended for males until the fever breaks. Avoidance of sour foods and drinks helps to decrease the salivary gland discomfort. Mumps-related mortality is exceedingly rare and primarily associated with encephalitis.

As with measles and rubella, vaccination is important for controlling disease. The mumps vaccine is a live, attenuated virus, which is incorporated into the MMR and MMRV (measles, mumps, rubella, and varicella) vaccines. Monovalent mumps vaccine is no longer available in the United States. The current recommendation is for routine childhood administration of two doses of mumps-containing vaccine, with the first dose administered between the ages of 12 and 15 months and the second dose between the ages of 4 and 6 years. In addition, two doses of MMR vaccine should be administered to adults who lack immunity and fall into any of the following categories: health care workers born in or after 1957, college students, and international travelers. One dose of MMR vaccine is recommended for all other adults who lack evidence of immunity and were born in or after 1957.

◆ HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

More articles have been written on **human immunodeficiency virus (HIV)** and its related disease states than any other infectious process. A complete bibliography easily would be longer than this chapter. Entire texts dedicated to HIV infection and **acquired immunodeficiency syndrome (AIDS)** are available for more detailed information.

HIV is a single-stranded RNA virus belonging to the family Retroviridae. There are two species: HIV-1 and HIV-2. The former exhibits a worldwide distribution and is responsible for the majority of cases, whereas the latter predominates in western Africa and is associated with a somewhat lower risk of transmission and slower disease progression.

In 1981, the CDC published the first scientific report of AIDS. This report detailed *Pneumocystis carinii* (since renamed *Pneumocystis jiroveci*) pneumonia in five previously healthy men from Los Angeles, California. A few years later, HIV was isolated and identified as the cause of AIDS. Since this initial description, more than 30 years have passed. During this time, more than 65 million individuals worldwide have become infected with HIV, and more than 30 million individuals have died of AIDS. Worldwide in 2011 alone, 2.5 million new infections occurred, 34 million people were living with HIV, and an estimated 1.7 million individuals died of AIDS. According to the most recent report by the Joint United Nations Programme on HIV/AIDS, HIV infection is most prevalent in sub-Saharan Africa—which accounts for nearly 70% of people living with HIV worldwide and more than half of global AIDS deaths—followed by the Caribbean, Eastern Europe, and Central Asia. The toll has been devastating, although through global public health efforts and treatment advances, there has been a slow decline in the number of newly infected individuals worldwide over the past decade.

In the United States, more than 619,000 people with AIDS have died since the epidemic began, and approximately 1.1 million individuals currently are living with HIV infection. The annual number of AIDS diagnoses in the United States expanded rapidly during the 1980s, peaked at around 78,000 in 1992, and subsequently sharply declined to about 40,000 in 1998. Presently, the number of AIDS cases diagnosed annually in the United States has stabilized at around 33,000. In the early years of the HIV/AIDS epidemic, the disease was nearly 100% fatal; however, since the introduction of combination antiretroviral therapy (cART) (see the Treatment and Prognosis section) in 1996, there has been significant improvement in patient survival and, thus, an increased percentage of the population living with the virus. The percentage of individuals surviving 2 years after AIDS diagnosis has increased from 44% in 1981 to 1992, to 64% in 1993 to 1995, and to 85% in 1996 to 2006.

In infected individuals, the virus can be found in most bodily fluids, including serum, blood, saliva, semen, tears, urine, breast milk, ear secretions, and vaginal secretions. In the United States, the most frequent mode of transmission is male-to-male sexual contact (accounting for nearly two-thirds of HIV infections diagnosed annually), followed by heterosexual contact and injection drug use. Perinatal

exposure and blood transfusion currently account for a small proportion of cases. Infection by artificial insemination, breast-feeding from infected mothers, and organ transplantation also has been documented rarely.

Transmission by oral fluids is somewhat controversial and has been reported only anecdotally. In rare cases, HIV transmission has occurred during breast-feeding from the oral fluids of postpartum infected infants to their previously noninfected mothers. In addition, possible transmission from oral cunnilingus or repeated passionate kissing very rarely has been described. Saliva contains a number of HIV inhibitory factors, which appear to reduce the ability of the virus to infect its target cells. However, the presence of erosions, ulcerations, and hemorrhagic inflammatory pathoses (e.g., gingivitis, periodontitis) may predispose an individual to oral transmission. In summary, the best precaution is avoidance of all body fluids of infected patients.

Initially in the United States, AIDS primarily affected whites and male homosexuals. Today, male-to-male sexual contact remains the largest single risk factor; however, the epidemiology of the HIV/AIDS epidemic has shifted over time, with a greater proportion of cases arising in blacks, Hispanics, females, and heterosexuals and a smaller proportion of cases attributed to blood transfusion, infected blood products, or perinatal transmission.

Since the initial years of the epidemic, blood-screening methods have improved dramatically and reduced the risk for HIV infection to as low as 1 in 2 million blood donations. Furthermore, because of improved viral inactivation methods and increasing use of recombinant clotting factors, HIV transmission from factor VIII and IX preparations has not occurred in the United States since 1986. Consequently, the proportion of hemophiliacs with HIV has declined from more than 50% during the early years of the epidemic to approximately 10% at present. In addition, the risk of transmission from infected mothers to newborns has decreased from approximately 25% to less than 2% because of widespread prenatal HIV testing, prophylactic use of antivirals, elective cesarean section performed before onset of labor, and avoidance of breast-feeding.

In the early years of the HIV/AIDS epidemic in the United States, non-Hispanic whites predominantly were affected, whereas currently blacks and Hispanics are the most commonly affected ethnic groups. According to the CDC, in 2010 the estimated rates of HIV infection per 100,000 population among blacks, Hispanics, and whites were 69, 28, and 9, respectively. Although blacks represented only about 14% of the United States population, they accounted for 44% of new HIV infections. Similarly, Hispanics were disproportionately affected, with this group accounting for about 16% of the population but 21% of new HIV infections. Factors contributing to these disparities may include poverty; limited access to health care and HIV education; cultural and language barriers; lack of awareness of HIV status; high rates of other sexually transmitted infections (such as, HSV-2 infection) that increase the risk of contracting HIV; and avoidance of testing and treatment for fear of discrimination. In recent years, the overall annual incidence of HIV among blacks and Hispanics has not changed significantly, although preliminary data suggests HIV incidence among black women may be declining.

Furthermore, compared to the beginning of the epidemic, a greater proportion of new HIV infections are occurring in females and heterosexuals. In 2010, approximately 25% of new HIV infections in the United States occurred in heterosexuals, and approximately two-thirds of those infected through heterosexual contact were female.

The primary target cell of HIV is the CD4+ helper T lymphocyte, although other CD4+ cells (such as, macrophages and dendritic cells) may be infected as well. The virus binds to CD4 and additional cell surface molecules in order to gain entry, upon which the viral RNA genome is reverse transcribed into complementary DNA. This complementary DNA may become incorporated into the host cell DNA. In people with HIV infection, antibodies against the virus are developed but are not protective. The virus may remain silent, cause cell death, or produce syncytial fusion of cells, which disrupts their normal function. A subsequent decrease in T-helper cell numbers occurs, with a resultant loss of immune function. The normal response to viruses, fungi, and encapsulated bacteria is diminished. In addition, infection of macrophages and microglia in the CNS may lead to neurologic disease manifestations, although the exact mechanisms of HIV-induced CNS damage are not completely understood.

Clinical Features

The clinical stages of HIV infection include an acute phase, a chronic phase (or latency period), and AIDS. During the acute phase, the patient may be asymptomatic or exhibit a self-limited **acute retroviral syndrome.** This syndrome typically develops within 1 to 6 weeks after exposure in 50% to 70% of infected patients. The symptoms resemble those of infectious mononucleosis (e.g., generalized lymphadenopathy, sore throat, fever, maculopapular rash, headache, myalgia, arthralgia, diarrhea, photophobia, and peripheral neuropathies). Oral changes may include mucosal erythema and focal ulcerations. During this initial phase, HIV infection often is not considered or investigated, and HIV antibodies are not yet detectable. Nevertheless, during this period, patients exhibit high levels of viremia and are extremely infectious.

After infection is established, an immune response is developed, viremia declines, and the patient enters a clinical latency period. Latency may last anywhere from several months to more than 15 years. Without treatment, the median duration is approximately 10 years, with much shorter periods typically seen in infants, children, or those infected via blood transfusion. Patient age, host immune responsiveness, type of exposure, viral strain, and cART may impact the duration of latency. Most patients are asymptomatic, but some patients have persistent generalized

lymphadenopathy (PGL). In some cases, before development of overt AIDS, there is a period of chronic fever, weight loss, diarrhea, oral candidiasis, herpes zoster, and/or oral hairy leukoplakia (OHL). This presentation has been termed **AIDS-related complex (ARC).**

Over time, the immune system fails to control the virus. There is a dramatic increase in viremia, and the CD4+ cell count declines, resulting in the development of AIDS. The presentation of this symptomatic phase is highly variable and often affected by a person's prior exposure to a number of chronic infections. The signs and symptoms described under ARC are often present, along with an increasing number of opportunistic infections or neoplastic processes. In many cases, pneumonia caused by the fungus *Pneumocystis jiroveci* is the presenting feature leading to AIDS diagnosis. Other infections of diagnostic significance include disseminated cytomegalovirus infection, severe herpes simplex virus infection, atypical mycobacterial infection, cryptococcal meningitis, and CNS toxoplasmosis. Persistent diarrhea is commonplace and may be bacterial or protozoal in origin. Clinically significant neurologic dysfunction is present in 30% to 50% of patients and most commonly manifests as progressive encephalopathy known as **AIDS-dementia complex**.

The most widely accepted classification of the oral manifestations of HIV disease was compiled by the EC-Clearinghouse on Problems Related to HIV Infection and the WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus. This classification divides the manifestations into three groups: 1) strongly associated, 2) less commonly associated, and 3) seen in HIV infection (Box 7-1).

The prevalence and types of oral manifestations of HIV disease have been altered dramatically by the introduction of cART. Numerous investigations of patients receiving cART have correlated an increase in CD4+ cell count and a reduction in viral load with a reduced prevalence of many oral manifestations. In particular, there have been significant reductions in the frequency of oral candidiasis, OHL, HIV-associated periodontal disease, and Kaposi sarcoma. Although the prevalence of certain lymphomas has decreased because of cART, the frequency of all HIV-related lymphomas has not demonstrated significant change. In contrast, many researchers have reported an increased prevalence of benign human papillomavirus (HPV)-induced pathoses. A similar increased frequency of HIV-associated salivary gland disease has been noted by some but disputed by others.

Importantly, the detection of oral manifestations may suggest possible HIV infection in an undiagnosed individual. In addition, the discovery of oral manifestations in a patient with known HIV infection may signal HIV disease progression and the need for initiation or adjustment of antiretroviral therapy.

The following discussion of oral manifestations concentrates primarily on the clinical presentations and special treatment considerations for HIV-infected patients. (For more detailed information regarding these conditions in the general patient population, see the discussion of each disease elsewhere in this text.) The most common oral manifestations are presented first, followed by a selection of less frequently encountered conditions.

• BOX 7-1 EC-Clearinghouse Classification of the Oral Manifestations of HIV Disease in Adults

Group 1: Strongly Associated with HIV Infection

- Candidiasis: Erythematous, pseudomembranous, and angular cheilitis
- Hairy leukoplakia
- Kaposi sarcoma (KS)
- Non-Hodgkin lymphoma (NHL)
- Periodontal diseases: Linear gingival erythema, necrotizing gingivitis, and necrotizing periodontitis

Group 2: Less Commonly Associated with HIV Infection

- Bacterial infections: *Mycobacterium avium-intracellulare* and *M. tuberculosis*
- Melanotic hyperpigmentation
- Necrotizing ulcerative stomatitis
- Salivary gland disease: Dry mouth and unilateral or bilateral swelling of major salivary glands
- Thrombocytopenia purpura
- Oral ulcerations not otherwise specified (NOS)
- Viral infections: Herpes simplex virus (HSV), human papillomavirus (HPV), and varicella-zoster virus (VZV)

Group 3: Seen in HIV Infection

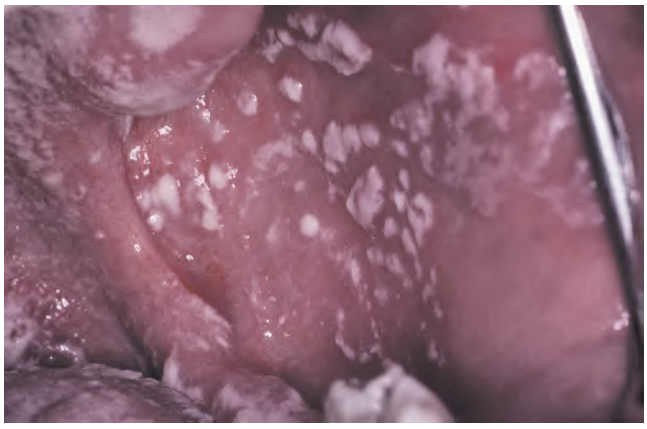
- Bacterial infections: *Actinomyces israelii, Escherichia coli,* and *Klebsiella pneumonia*
- Cat-scratch disease *(Bartonella henselae)*
- Epithelioid (bacillary) angiomatosis *(Bartonella henselae)*
- Drug reactions: Ulcerative, erythema multiforme, lichenoid, and toxic epidermolysis
- Fungal infections other than candidiasis: *Cryptococcus neoformans, Geotrichum candidum, Histoplasma capsulatum,* Mucoraceae (mucormycosis/zygomycosis), and *Aspergillus flavus*
- Neurologic disturbances: Facial palsy and trigeminal neuralgia
- Recurrent aphthous stomatitis
- Viral infections: Cytomegalovirus (CMV) and molluscum contagiosum virus (MCV)

HIV, Human immunodeficiency virus.

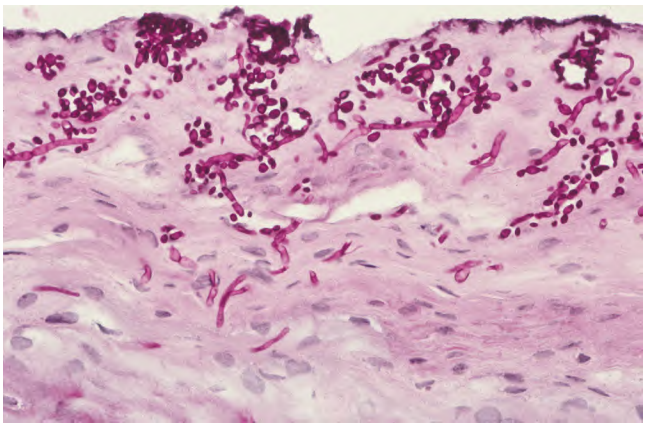
Oral and Maxillofacial Lesions Strongly Associated with HIV Infection

Candidiasis

Candidiasis is the most common intraoral manifestation of HIV infection and often is the presenting sign that leads to the initial diagnosis (Fig. 7-32). Although a number of *Candida* species have been encountered intraorally, the most common organism identified in oral candidiasis is *Candida albicans.* The presence of oral candidiasis in a patient infected with HIV is not diagnostic of AIDS but appears to be predictive for the subsequent development



• **Fig. 7-32 HIV-associated Candidiasis.** Extensive removable white plaques of the left buccal mucosa.



• **Fig. 7-33 HIV-associated Candidiasis.** Periodic acid-Schiff (PAS) stain of histopathologic section exhibiting numerous fungal organisms embedded in superficial keratin.

of full-blown AIDS in untreated patients within 2 years. Prevalence studies vary widely, but approximately one-third of HIV-infected individuals and more than 90% of patients with AIDS develop oral candidiasis at some time during their disease course. The following four clinical patterns are seen (see page 191):

1. Pseudomembranous candidiasis
2. Erythematous candidiasis
3. Hyperplastic candidiasis
4. Angular cheilitis

The first two variants constitute most cases. Although infrequently seen in immunocompetent patients, chronic multifocal oral involvement is common in HIV-infected patients. Erythematous candidiasis typically appears when the CD4+ lymphocyte count drops below 400 cells per mm^3, whereas the pseudomembranous pattern usually develops when the count drops below 200 cells per mm^3. Among patients with various types of immunocompromised status, those with HIV infection have a greater prevalence of oral candidiasis, suggesting that HIV may play a role in initiation of candidal infection. Some studies have shown that development of candidiasis correlates more closely with viral load than CD4+ cell count. Oral candidiasis can be painful and associated with a reduction in taste and smell, which may lead to decreased food intake and further wasting.

The diagnosis of candidiasis often is obvious from the clinical presentation but can be confirmed by cytologic smear or biopsy. Biopsy specimens of involved mucosa demonstrate the candidal organisms embedded in the superficial keratin, but the typical inflammatory reaction may be deficient (Fig. 7-33).

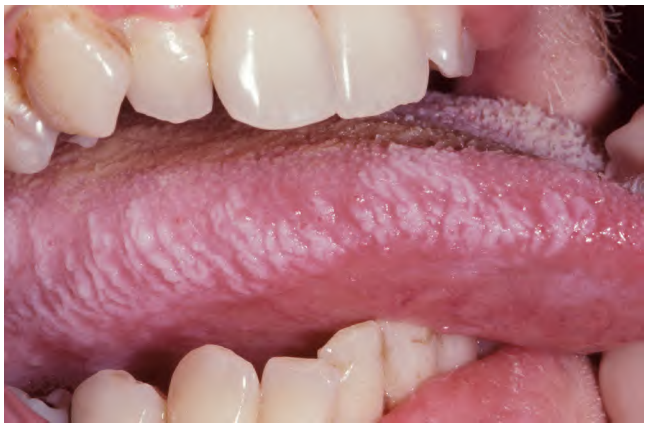
Treatment is often difficult in patients with AIDS. Among topical agents, nystatin typically is ineffective. Gentian violet is more effective than nystatin but is not used much because its application is messy; in areas with inadequate funding or limited access to newer medications, this agent may be a low-cost alternative. Clotrimazole is the treatment of choice for patients who are receiving effective antiretroviral therapy, have a CD4+ cell count exceeding 50 cells/mm^3, and have no signs of esophageal involvement. However, recurrence is more common following topical than systemic therapy.

Systemic antifungal therapy is recommended for patients not receiving effective antiretroviral therapy or those with either esophageal involvement, a CD4+ cell count below 50 cells/mm^3, or a high viral load. Fluconazole is considered by many to be the drug of choice; nevertheless, non-albicans species (such as, *C. glabrata, C. dubliniensis,* and *C. krusei*) have been isolated in HIV-infected patients, and these organisms may exhibit limited susceptibility or frank resistance to fluconazole. Itraconazole oral solution, voriconazole, and posaconazole are also effective but considered second-line agents. Clinicians should be aware that potential drug interactions exist between the antifungal azoles and antiretrovirals. For refractory cases, amphotericin B oral solution, IV amphotericin B, or IV echinocandins may be considered. Because of the potential for developing resistance, prophylactic antifungal therapy typically is reserved for patients with especially frequent and severe recurrences. Preventive regimens usually consist of either continuous or intermittent administration of fluconazole.

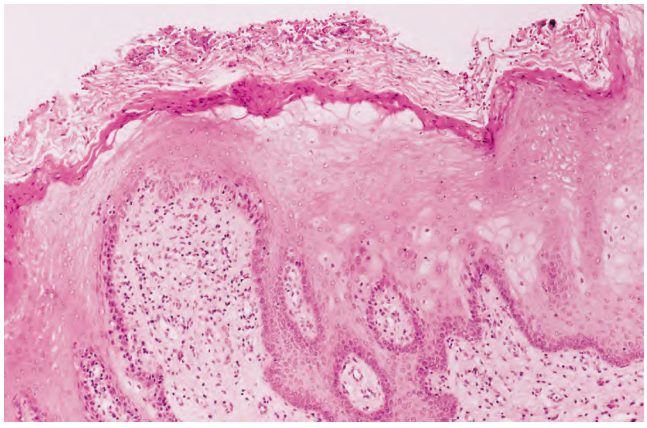
Interestingly, HIV protease inhibitors used in cART have been associated with a decrease in frequency and recurrence of oral candidiasis. These findings may be related to the ability of these agents to inhibit a candidal virulence factor, known as secreted aspartic proteinase, and exert a synergistic effect with antifungals against fungal resistance. Furthermore, in one large-scale retrospective study, investigators noted a significantly lower risk of oral candidiasis among patients receiving cART with a non-nucleoside reverse transcriptase inhibitor compared to those receiving cART without this medication type.

Oral Hairy Leukoplakia

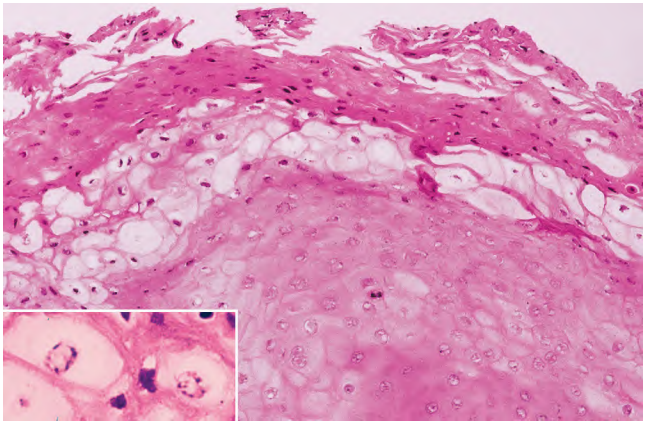
Although EBV is associated with several forms of lymphoma in HIV-infected patients, the most common EBV-related lesion in patients with AIDS is **oral hairy leukoplakia (OHL).** The presence of OHL in HIV-infected



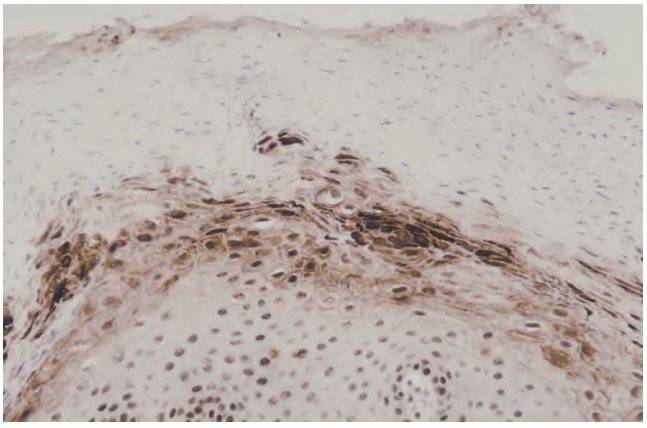
• **Fig. 7-34 HIV-associated Oral Hairy Leukoplakia (OHL).** Vertical streaks of keratin along the lateral border of the tongue.



• **Fig. 7-35 HIV-associated Oral Hairy Leukoplakia (OHL).** Oral mucosa exhibiting hyperparakeratosis with surface corrugations.



• **Fig. 7-36 HIV-associated Oral Hairy Leukoplakia (OHL).** Oral epithelium exhibiting hyperparakeratosis and layer of "balloon cells" in the upper spinous layer. *Inset* reveals high-power magnification of epithelial cells that demonstrate nuclear beading.



• **Fig. 7-37 HIV-associated Oral Hairy Leukoplakia (OHL).** Immunoperoxidase evaluation for Epstein-Barr virus (EBV) revealing positive reaction within numerous epithelial cells.

patients is a sign of severe immunosuppression and advanced disease. OHL also has been reported in transplant recipients, but its presence in the absence of a known cause of immunosuppression strongly suggests HIV infection. The lesion only very rarely has been described in immunocompetent individuals, and discovery of OHL in "normal" patients mandates a thorough physical evaluation to rule out immunocompromise.

OHL clinically presents as a white mucosal plaque that does not rub off. Most cases occur on the lateral border of the tongue and range in appearance from faint, white vertical streaks to thickened, furrowed areas of leukoplakia with a shaggy surface (Fig. 7-34). The lesions infrequently may extend to cover the entire dorsal and lateral surfaces of the tongue. Rarely, the buccal mucosa, soft palate, pharynx, or esophagus may be involved.

Histopathologically, OHL exhibits thickened parakeratin with surface corrugations or thin projections (Fig. 7-35). The epithelium is acanthotic and exhibits a bandlike zone of lightly stained cells with abundant cytoplasm ("balloon cells") in the upper spinous layer (Fig. 7-36). Close examination of the superficial epithelial cells reveals nuclear clearing and a characteristic pattern of peripheral margination of chromatin termed nuclear beading (see Fig. 7-36, *inset*), caused by extensive EBV replication that displaces the chromatin to the nuclear margin. Dysplasia is not noted. Heavy candidal infestation of the parakeratin layer may be seen, although the normal inflammatory reaction to the fungus usually is absent.

In a patient with known HIV infection, the clinical features of OHL typically are sufficient for a presumptive diagnosis. When definitive diagnosis is necessary, demonstration of EBV can be achieved by *in situ* hybridization, PCR, immunohistochemistry (Fig. 7-37), Southern blotting, or electron microscopy.

Treatment of OHL usually is not needed, although slight discomfort or aesthetic concerns may necessitate therapy. Systemic anti-herpesviral drugs produce rapid resolution, but recurrence is expected with discontinuation of therapy. Topical treatment with retinoids or podophyllum resin has resulted in temporary remissions. A few small-scale studies have demonstrated prolonged resolution after combined treatment with acyclovir cream and podophyllum resin. Surgical excision or cryotherapy also has been used by some.

A significantly reduced prevalence of OHL has been noted in patients well-controlled with cART; in resource-poor settings, the presence or absence of OHL and oral candidiasis can be used as a clinical guide to assist in judging the effectiveness of antiretroviral therapy.

Kaposi Sarcoma

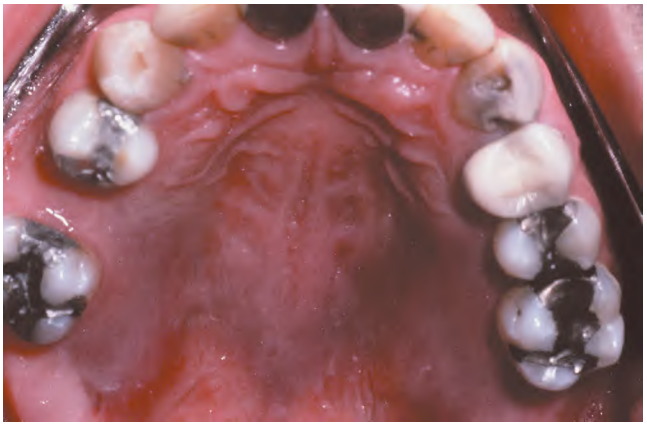
Kaposi sarcoma (KS) is a vascular endothelial neoplasm caused by human herpesvirus 8 (HHV-8, Kaposi sarcoma–associated herpesvirus [KSHV]). Since the beginning of the AIDS epidemic, most cases in the United States have arisen in association with HIV infection. At the height of the epidemic in the early 1990s, the annual incidence of KS in the United States peaked at 4.7 cases per 100,000 population. However, since the introduction of cART in 1996, the annual incidence has declined substantially and currently is estimated at less than 0.7 cases per 100,000 population. The incidence of KS among HIV-infected individuals receiving antiretroviral therapy is approximately 20% to 40% lower than that among those not receiving therapy. KS currently represents the second most common malignancy among people with AIDS in the United States.

In Western countries, KS has been reported primarily in HIV-infected, adult, male homosexuals and is thought to be related to sexual transmission of HHV-8. However, in Africa both AIDS-related and endemic types of KS frequently are seen, with no gender predilection and a significant number of children affected. Infection before sexual activity suggests alternate transmission pathways. Relatively high titers of HHV-8 have been found in saliva, and HHV-8 exhibits tropism for oral and oropharyngeal epithelial cells; these observations suggest that the oral cavity may represent an important reservoir of infectious virus and saliva may be a major transmission route.

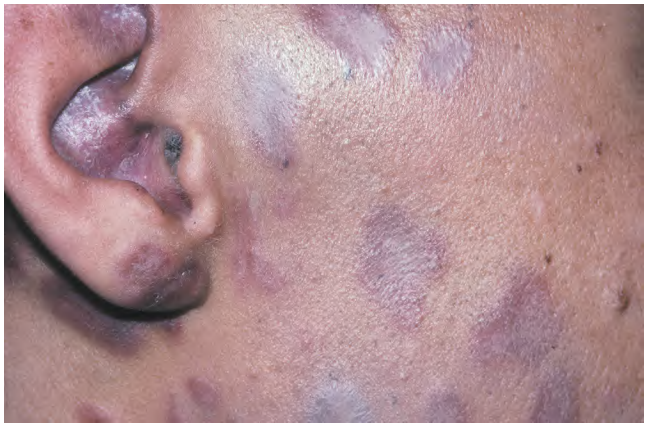
KS mainly manifests as multiple lesions on the skin or oral mucosa, although visceral and lymph node involvement also may occur. Occasionally a solitary lesion is identified first. Among AIDS-related cases, the skin lesions exhibit a predilection for the face (Fig. 7-38) and lower extremities. The oral cavity is the initial site of involvement in 22% of patients with KS, and oral lesions are found more often in AIDS-related KS than other types of KS. Approximately 70% of individuals with AIDS-related KS demonstrate oral lesions at some point. The hard palate, gingiva, and tongue are the most frequently affected oral sites (Figs. 7-39 and 7-40). When present on the palate or gingiva, the neoplasm can invade bone and cause tooth mobility. The lesions usually begin as erythematous blue or brown macules that do not blanch with pressure. Nonpigmented lesions have been reported very rarely. With time, the macules typically develop into plaques or nodules (Fig. 7-41), which may coalesce into a diffuse, exophytic mass (Fig. 7-42). Pain, bleeding, and necrosis may necessitate therapy. Uncommonly, advanced oral lesions may cause secondary lymphedema of the face and neck.

A biopsy is required for definitive diagnosis, although a presumptive clinical diagnosis sometimes is made. Other lesions can have a similar clinical appearance in HIV-infected patients, including bacillary angiomatosis (a multifocal vascular proliferation associated with the cat-scratch bacillus [see page 185]) and lymphoma.

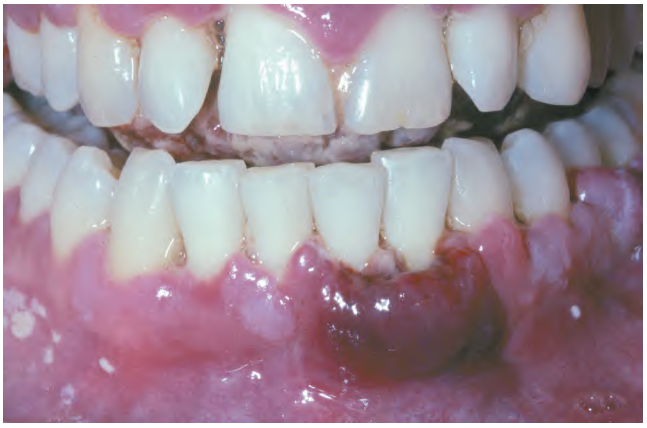
Initiation of cART may induce regression of KS lesions, and patients who develop KS despite already receiving



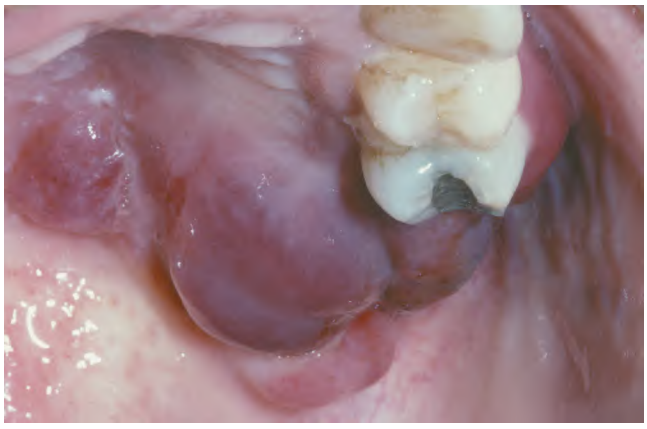
• **Fig. 7-39 HIV-associated Kaposi Sarcoma (KS).** Large zones of KS appearing as flat, brownish, and M-shaped discoloration of the hard palate.



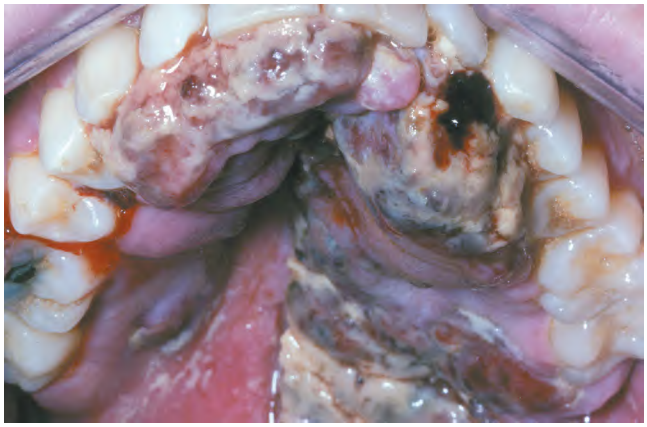
• **Fig. 7-38 HIV-associated Kaposi Sarcoma (KS).** Multiple purple macules on the right side of the face.



• **Fig. 7-40 HIV-associated Kaposi Sarcoma (KS).** Raised, dark-red enlargement of the left mandibular anterior facial gingiva.



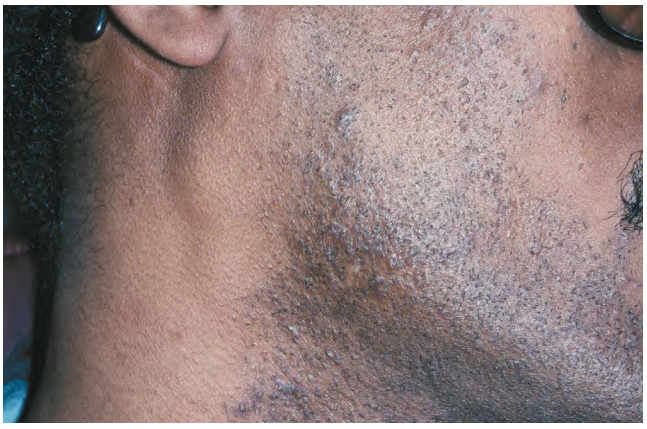
• **Fig. 7-41 HIV-associated Kaposi Sarcoma (KS).** Diffuse, red-blue nodular enlargement of the left hard palate.



• **Fig. 7-42 HIV-associated Kaposi Sarcoma (KS).** Diffuse, red-blue gingival enlargement with widespread necrosis.

cART tend to have relatively mild disease without visceral involvement. Because KS typically regresses upon return of immunocompetence, many researchers question whether KS is a true sarcoma. Locoregional therapy may be used for limited, asymptomatic mucocutaneous lesions nonresponsive to cART or for palliation of advanced mucocutaneous lesions. Treatment options include topical therapy (e.g., alitretinoin gel or imiquimod cream for skin lesions), intralesional injection of chemotherapeutic or immunomodulatory agents (e.g., vinblastine, vincristine, bleomycin, and interferon-alpha), radiation, surgical excision, cryotherapy (for skin lesions), sclerotherapy, and laser therapy. Radiation therapy generally is not advised for oral lesions because of the potential for severe mucositis. For advanced AIDS-related KS, systemic chemotherapy or immunomodulatory therapy in conjunction with cART is indicated. In addition, some authorities have suggested systemic therapy for oral lesions of AIDS-related KS even at the early macular stage, because progression to the exophytic stage in the oral cavity is associated with a poor prognosis.

Negative prognostic indicators for AIDS-related KS include tumor-associated edema; ulceration; extensive oral disease; visceral involvement; and a history of opportunistic infections, B symptoms (i.e., unexplained fever, night sweats, greater than 10% involuntary weight loss, diarrhea for more than 2 weeks), or other HIV-related illnesses. Interestingly, KS arising in lymph nodes does not necessarily represent metastasis or a poor prognosis. In the United States, the 5-year survival rate for individuals diagnosed with KS in recent years is approximately 70%. However, survival rates are much lower in regions where treatment is not widely available.



• **Fig. 7-43 HIV-associated Lymphadenopathy.** Enlarged cervical lymph nodes in a patient with persistent generalized lymphadenopathy (PGL).

Persistent Generalized Lymphadenopathy

After seroconversion, HIV disease often remains silent except for **persistent generalized lymphadenopathy (PGL).** The prevalence of this early clinical sign varies; however, in several studies it approaches 70%. PGL consists of lymphadenopathy that has been present for longer than 3 months and involves two or more extrainguinal sites. The most frequently involved sites are the posterior and anterior cervical, submandibular, occipital, and axillary nodes. Nodal enlargement fluctuates, usually is larger than 1 cm, and varies from 0.5 to 5.0 cm (Fig. 7-43).

Because lymphoma is known to occur in this population, a lymph node biopsy may be indicated for localized or bulky adenopathy, when cytopenia or an elevated erythrocyte sedimentation rate is present, or when requested for patient reassurance. Histopathologic examination reveals florid follicular hyperplasia. Although not as predictive as oral candidiasis or OHL, PGL does warn of progression to AIDS; almost one-third of affected and untreated patients will have diagnostic features of AIDS within 5 years.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) currently represents the most common malignancy among the AIDS population in the United States. Similar to KS, NHL has become significantly less common among HIV-infected individuals since the introduction of cART. Nevertheless, the risk of NHL for people with AIDS in the United States remains high, with a relative risk of 23% compared to the general

population. Most cases represent high-grade, aggressive B-cell neoplasms. HIV-associated NHL can be categorized as follows:

1. Lymphomas also occurring in immunocompetent patients (most commonly Burkitt lymphoma and diffuse large B-cell lymphoma; rarely, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue [MALT lymphoma], peripheral T-cell, and natural killer cell lymphoma)
2. Lymphomas more specifically occurring in HIV-positive patients (e.g., primary effusion lymphoma and plasmablastic lymphoma)
3. Lymphoma also occurring in other immunodeficiency states (e.g., cases resembling post-transplant associated lymphoproliferative disease [PTLD]).

Although many of these neoplasms demonstrate a relationship with EBV, studies have suggested that plasmablastic lymphoma and primary effusion lymphoma may be associated with both EBV and HHV-8.

Lymphoma in patients with AIDS usually occurs in extranodal locations. Oral lesions are seen in approximately 4% of patients with AIDS-related NHL and most frequently involve the gingiva, palate, and tongue (Fig. 7-44). Intraosseous involvement also has been documented and may resemble diffuse progressive periodontitis with loss of periodontal attachment and loosening of teeth. In these cases, widening of the periodontal ligament and loss of lamina dura may represent radiographic clues to the diagnosis.

Treatment for HIV-associated NHL usually consists of combination chemotherapy in conjunction with cART. Early in the AIDS epidemic, people with AIDS typically suffered from severe opportunistic infections at the time of lymphoma diagnosis and, thus, could not tolerate intensive chemotherapy. However, with the introduction of cART, there has been a significant reduction in comorbidity, thereby allowing for intensive lymphoma treatment. For AIDS-related lymphoma patients, an improvement in median survival from 6 months in the pre-cART era to 21 months in the cART era has been reported. Prognosis varies by specific lymphoma type. However, with the inclusion of cART, lymphoma survival for the HIV-infected population often approaches that for the general population.

HIV-Associated Periodontal Disease

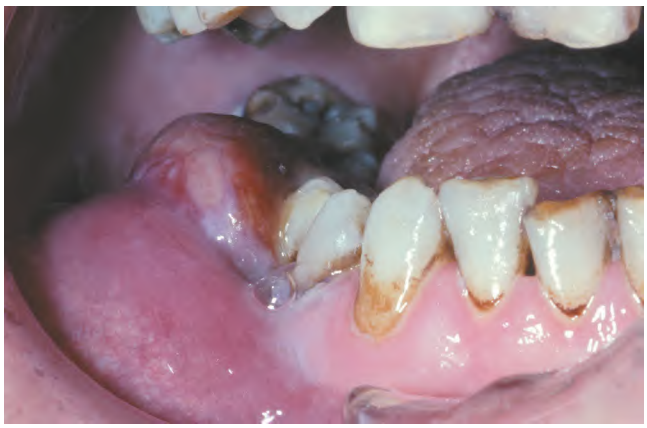
Three atypical patterns of periodontal disease are associated strongly with HIV infection:

1. Linear gingival erythema
2. Necrotizing ulcerative gingivitis (NUG)
3. Necrotizing ulcerative periodontitis (NUP)

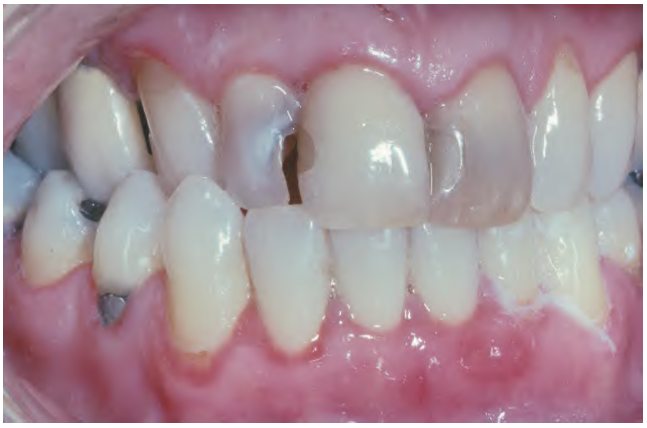
Linear gingival erythema initially was termed HIV-related gingivitis, but ultimately was noted in association with other disease processes. This unusual pattern of gingivitis appears with a distinctive linear band of erythema that involves the free gingival margin and extends 2 to 3 mm apically (Fig. 7-45). In addition, the alveolar mucosa and gingiva may demonstrate punctate or diffuse erythema in a significant percentage of cases. This diagnosis should be reserved for gingivitis that does not respond to improved plaque control and exhibits a greater degree of erythema than would be expected for the amount of plaque present. The literature related to linear gingival erythema is difficult to evaluate, because well-defined diagnostic criteria are lacking and the condition often is confused with conventional marginal gingivitis. Although some investigators believe linear gingival erythema results from an abnormal host immune response to subgingival bacteria, data suggest that this condition may represent an unusual pattern of candidiasis. Treatment may include débridement, povidone-iodine irrigation, chlorhexidine mouth rinse, and/or antifungal medication.

Necrotizing ulcerative gingivitis (NUG) (see page 143) refers to ulceration and necrosis of one or more interdental papillae with no periodontal attachment loss. Patients with NUG have interproximal gingival necrosis, bleeding, pain, and halitosis (Fig. 7-46).

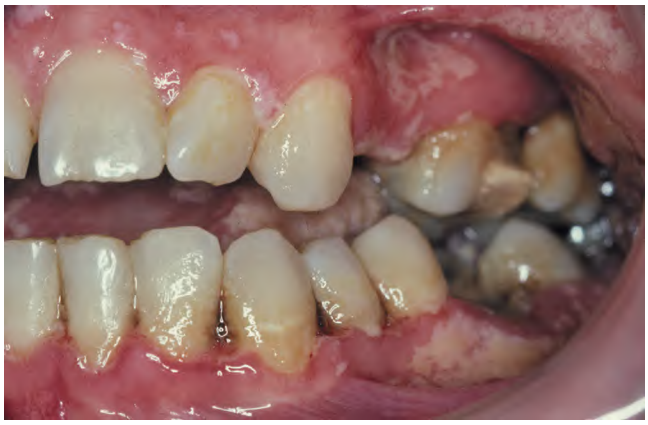
Necrotizing ulcerative periodontitis (NUP) previously was termed *HIV-associated periodontitis;* however, it is not specific for HIV infection. NUP is characterized by gingival



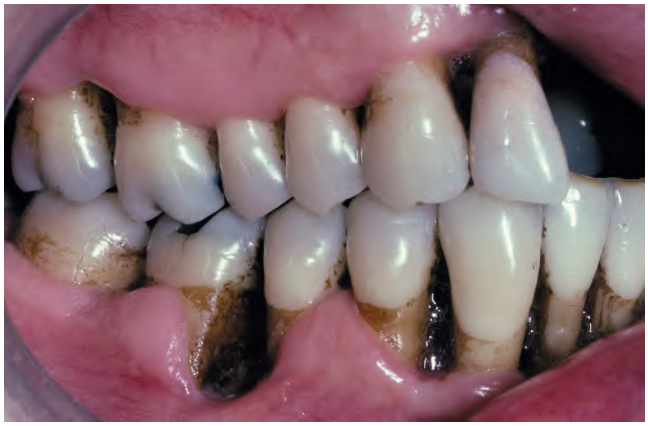
• **Fig. 7-44 HIV-associated Lymphoma.** Erythematous and ulcerated soft tissue enlargement of the posterior mandibular gingiva and mucobuccal fold on the right side.



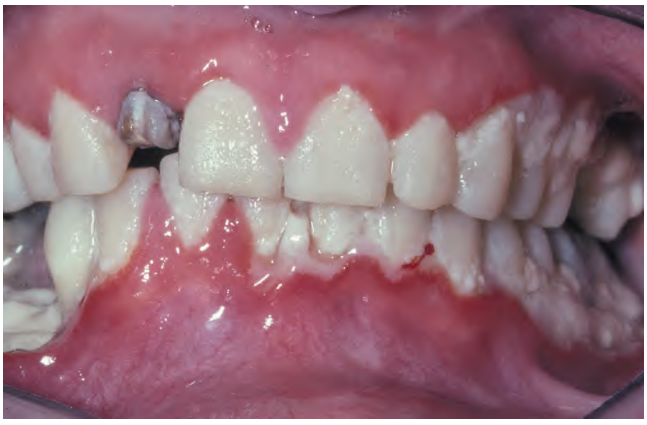
• **Fig. 7-45 HIV-associated Gingivitis.** Band of erythema involving the free gingival margin.



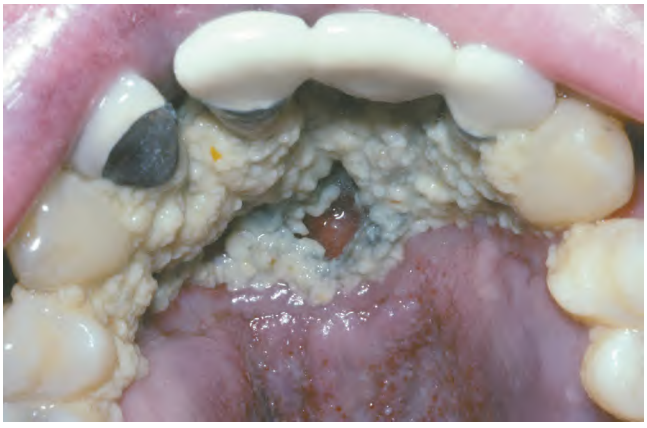
• **Fig. 7-46 HIV-associated Necrotizing Ulcerative Gingivitis (NUG).** Multiple punched-out interdental papillae of the mandibular gingiva. Note diffuse pseudomembranous candidiasis of the surrounding mucosa.



• **Fig. 7-47 HIV-associated Periodontitis.** Extensive loss of periodontal support without deep pocketing.



• **Fig. 7-48 HIV-associated Periodontitis with Necrotizing Stomatitis.** Diffuse gingival necrosis with extension onto alveolar mucosa.



• **Fig. 7-49 HIV-associated Necrotizing Stomatitis.** Massive necrosis of soft tissue and bone of the anterior maxilla.

ulceration and necrosis associated with rapidly progressing loss of periodontal attachment. Although severe cases can affect all teeth, multiple isolated defects often are seen and contrast with the diffuse pattern associated with typical chronic periodontitis. Edema, severe pain, and spontaneous hemorrhage are common. Deep pocketing usually is not seen because extensive gingival necrosis typically coincides with loss of the adjacent alveolar bone (Fig. 7-47). Attachment loss of more than 6 mm within a 6-month period is not unusual

The treatment of NUG and NUP revolves around débridement, antimicrobial therapy, pain management, immediate follow-up care, and long-term maintenance. The initial removal of necrotic tissue typically is combined with povidone-iodine irrigation. The use of systemic antibiotics usually is not necessary, but metronidazole (narrow spectrum to suppress periodontal pathogens without strongly promoting candidal overgrowth) has been administered to patients with extensive involvement and severe acute pain. All patients should use chlorhexidine mouth rinses initially and for long-term maintenance. After initial débridement, removal of additional diseased tissue should be performed within 24 hours and again every 7 to 10 days for two to three appointments, depending on the patient's response. At this point, monthly recalls are necessary until the process stabilizes; evaluations then are performed every 3 months.

In patients with gingival necrosis, the process occasionally extends away from the alveolar ridges and creates massive areas of tissue destruction termed **necrotizing stomatitis** (Fig. 7-48). This process clinically resembles noma (see page 181) and may involve predominantly soft tissue or extend into the underlying bone, resulting in extensive sequestration (Fig. 7-49). Although this process initially was thought to be an extension of NUP, necrotizing stomatitis may begin in areas of the oral mucosa other than the gingiva.

In the absence of gingival involvement, the clinical features of necrotizing stomatitis are nonspecific and mandate biopsy. In many instances, the areas of ulceration and necrosis demonstrate infection with one or more pathogens, such as HSV, CMV, and EBV.

In addition to these three forms of HIV-related periodontal disease, patients may demonstrate conventional gingivitis, chronic periodontitis, and progressive nonnecrotizing periodontitis. Studies have shown that periodontal attachment loss can be combated successfully with regular

professional scaling and root planing, plus optimization of oral hygiene. Because smoking has been associated strongly with all forms of periodontal disease, patients should be encouraged to discontinue their tobacco habit.

Less Common Oral and Maxillofacial Manifestations of HIV Infection

Mycobacterial Infection

The best known mycobacterial infection is **tuberculosis (TB),** which is caused mainly by *Mycobacterium tuberculosis* (see page 176). Less common TB-causing mycobacteria include *M. bovis, M. africanum, M. canetti,* and *M. microti.* In addition, atypical mycobacterial infection with *M. avium* and *M. intracellulare* (*M. avium-intracellulare* complex) can cause clinically evident disease, particularly in advanced stages of AIDS.

Approximately one-third of the world's population is infected with TB. In 2011 there were 8.7 million new cases of TB worldwide, of which 1.1 million (13%) arose in HIV-positive individuals. Coinfection with HIV is associated with an increased risk for TB activation and death. Among 1.4 million TB deaths reported annually, approximately 430,000 occur in association with HIV.

There is an unusual predilection for extrapulmonary involvement among HIV-infected individuals with TB. Nevertheless, oral lesions are uncommon and occur in less than 5% of all individuals with active TB. The tongue is the most frequently involved oral site, but lesions also can develop on the buccal mucosa, gingiva, floor of mouth, lips, and palate. The affected areas present as chronic ulcerations, granular leukoplakias, or exophytic proliferative masses. Jaw involvement also has been reported.

Confirming TB often is difficult in AIDS patients, because tuberculin skin tests, microscopic examination of sputum smears for acid-fast bacilli, and chest radiographs lack sensitivity in this patient population. Liquid culture or PCR may facilitate diagnosis. In resource-limited settings, screening for a history of cough, fever, and/or night sweats is useful for identification of HIV-infected patients requiring diagnostic testing for TB.

In conjunction with cART, standard TB therapy with rifampin, isoniazid, pyrazinamide, and ethambutol typically is effective for HIV-related TB. In addition, TB prevention by early antiretroviral therapy and prophylactic isoniazid is important for HIV-infected individuals; according to one meta-analysis, antiretroviral therapy reduces the risk of TB illness among HIV-infected individuals by 65%.

Hyperpigmentation

Hyperpigmentation of the skin, nails, and mucosa has been reported in HIV-infected patients. The changes are similar microscopically to focal melanosis, with increased melanin pigmentation observed in the basal cell layer of the affected epithelium. Several medications taken by AIDS patients (e.g., ketoconazole, clofazimine, pyrimethamine, zidovudine, and emtricitabine) may cause increased melanin pigmentation. Adrenocortical destruction from several AIDS-associated opportunistic infections has been reported, resulting in an Addisonian pattern of pigmentation. Finally, pigmentation with no apparent cause has arisen in HIV-infected patients, and some investigators have theorized that this may be a direct result of HIV infection.

HIV-Associated Salivary Gland Disease

HIV-associated salivary gland disease can arise anytime during HIV infection. Clinically obvious salivary gland disease is evident in approximately 5% to 10% of HIV-infected patients, with a greater prevalence among children. The etiopathogenesis is unknown, although some investigators hypothesize that autoimmune dysregulation and underlying viral opportunistic infection (e.g., with EBV or BK virus) may play a role. The main clinical sign is salivary gland enlargement, particularly affecting the parotid. Bilateral involvement is seen in about 60% of cases and often is associated with cervical lymphadenopathy. Xerostomia is a variable finding. Microscopic changes within the affected glands may include lymphocytic infiltration, hyperplasia of intraparotid lymph nodes, and, in long-standing cases, lymphoepithelial cyst formation. Interestingly, a few authors have reported an increased frequency of ranulas (see page 424) in HIV-infected patients; the significance of this finding is uncertain, although some hypothesize that ranulas may result from long-standing HIV-associated salivary gland disease.

HIV-associated salivary gland disease is considered a localized manifestation of **diffuse infiltrative lymphocytosis syndrome (DILS).** DILS is characterized by CD8+ lymphocytosis with diffuse lymphocytic infiltration of various sites, such as the major or minor salivary glands, lacrimal glands, lungs, kidneys, muscle, nerve, and liver. In addition to salivary gland enlargement and lymphadenopathy, many patients develop interstitial pneumonia. There is an association between DILS and certain human leukocyte antigen (HLA) types.

The most widely accepted treatments for DILS are oral prednisone and antiretroviral therapy, although some patients have been treated with parotidectomy or radiation therapy. Some investigators have noted regression after initiation of cART, whereas others have reported an increased prevalence with cART, possibly due to immune reconstitution syndrome (see the Treatment and Prognosis section). In patients with large lymphoepithelial cysts, aspiration or sclerotherapy with tetracycline or doxycycline may produce temporary improvement. Associated xerostomia is treated in a conventional manner (i.e., maintenance of good oral health and use of sialogogues and saliva substitutes). DILS is associated with a relatively favorable HIV disease prognosis but also an increased risk for lymphoma; therefore, some authors recommend periodic monitoring for lymphoma development by fine-needle aspiration.

Thrombocytopenia

Thrombocytopenia (see page 545) has been reported in up to 40% of patients with HIV infection. It is frequently the

first clinical manifestation of HIV infection but may occur at any time during the course of HIV disease. The underlying mechanisms may include direct infection of platelet progenitor cells, platelet destruction by anti-HIV antibodies that cross-react with platelet glycoproteins, platelet destruction by nonspecific binding of immune complexes, and defective modulation of hematopoiesis by HIV-infected T lymphocytes. In addition, thrombocytopenia may develop secondary to medications, concurrent infections, or malignancy. Cutaneous lesions are present in most cases, but oral lesions also may occur; typical findings include petechiae, ecchymosis, and spontaneous gingival hemorrhage.

Platelets have been shown to engulf HIV and play an important role in the immune response to the virus. HIV-infected patients with extended thrombocytopenia have decreased survival. cART is considered first-line treatment. For severe or refractory cases, additional treatment options may include interferon-alpha, intravenous immunoglobulin (IVIG), IV anti-Rho immunoglobulin (anti-D), platelet transfusion, corticosteroids, danazol, and splenectomy.

Herpes Simplex Virus

The prevalence of oral recurrent HSV infection among HIV-infected individuals increases significantly once the CD4+ cell count drops below 50 per mm^3. Within the setting of HIV infection, recurrent herpetic lesions may be widespread, occur in an atypical pattern, and persist for months (Fig. 7-50). Herpes labialis may extend to the facial skin and exhibit extensive lateral spread. Persistence of active HSV infection for more than 1 month in a patient infected with HIV is one accepted definition of AIDS. The clinical presentation and management of recurrent HSV infection in immunocompromised patients have been discussed previously in the section on HSV (see page 222).

Evaluation for HSV should be performed on all persistent oral ulcerations in HIV-infected individuals. Investigators have discovered HSV in 10% to 19% of such cases (with an additional 10% to 28% exhibiting coinfection by HSV and CMV).

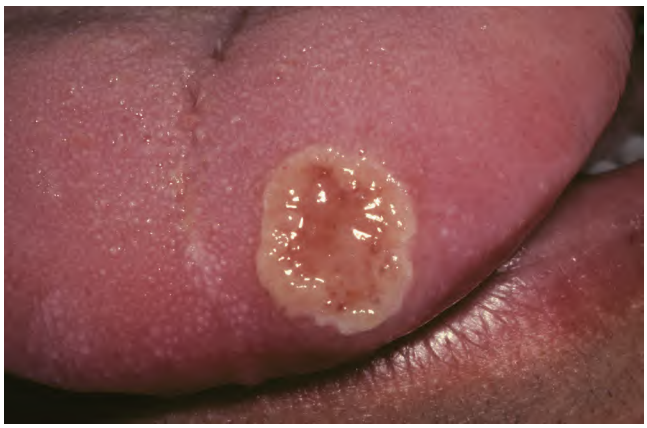


Fig. 7-50 HIV-associated Recurrent Herpetic Infection. Mucosal erosion of the anterior dorsal surface of the tongue on the left side. Note the yellowish circinate border.

Varicella-Zoster Virus

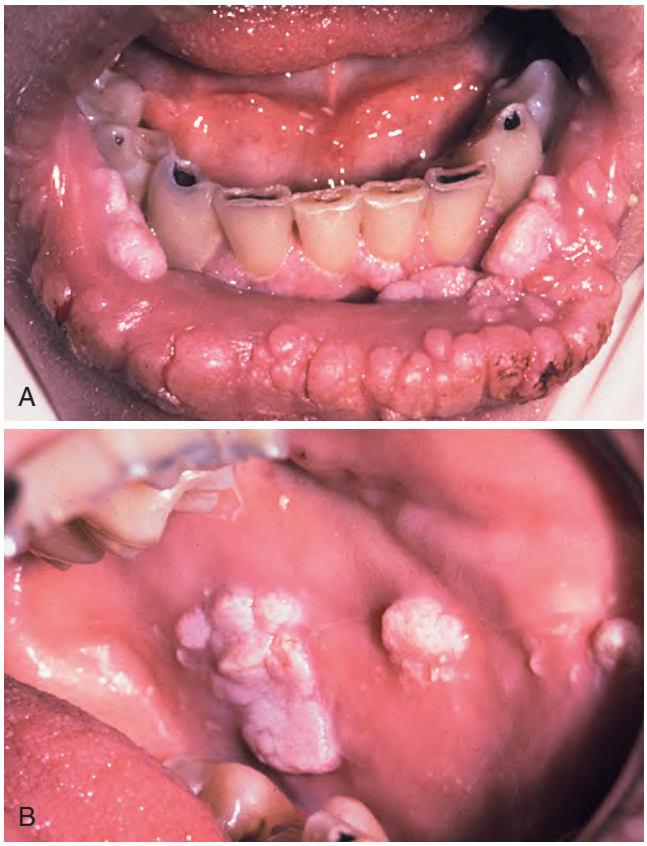
During the cART era, the prevalence of recurrent varicella-zoster virus (VZV) infection **(herpes zoster)** in HIV-infected patients has decreased significantly but still remains greater than that in the general population. Some patients paradoxically develop herpes zoster shortly after initiating cART, as a result of immune reconstitution syndrome (see the Treatment and Prognosis section). Among patients with HIV infection, herpes zoster is often severe, with increased morbidity and mortality rates. Many of these patients are younger than 40 years, in contrast to immunocompetent patients who typically develop herpes zoster later in life. In patients with well-controlled HIV disease, herpes zoster usually is confined to a single dermatome but persists longer than usual. In full-blown AIDS, dissemination to multiple dermatomes is not unusual. Severe intraoral involvement may lead to bone sequestration and loss of teeth; these sequelae may be delayed a month or more after the initial onset of herpes zoster. Associated pain typically is intense.

Although peroral antiviral medications are beneficial in immunocompetent patients, IV acyclovir is recommended for severe herpes zoster in immunocompromised individuals. Routine zoster vaccination for HIV-infected patients is not recommended currently; however, according to some experts, zoster vaccination may be considered for those with well-controlled HIV disease and CD4+ cell counts greater than 200 per mm^3.

Human Papillomavirus

Among HIV-infected individuals, most human papillomavirus (HPV) lesions arise in the anogenital region, although oral involvement also is possible. Benign oral lesions caused by HPV (commonly referred to as "oral warts") include **oral squamous papilloma** (see page 332), **verruca vulgaris** (see page 334), **condyloma acuminatum** (see page 335), and **multifocal epithelial hyperplasia** (see page 336). The prevalence of these oral HPV lesions in HIV-infected patients is approximately 1% to 4% and greater than that observed among immunocompetent individuals. Unusual HPV types (such as, HPV-7 [associated with butcher's warts], HPV-13, and HPV-32 [associated with multifocal epithelial hyperplasia]) frequently are identified in oral HPV lesions arising in HIV-infected patients.

In contrast to most other HIV-associated lesions, HPV lesions have increased in frequency since the introduction of cART. In particular, many studies have noted that the appearance of oral HPV lesions increases with the effectiveness of antiretroviral therapy. The reason for this increase is unclear. Some authors have hypothesized that immune reconstitution by cART may lead to an inflammatory response that stimulates HPV activation (i.e., immune reconstitution syndrome [see the Treatment and Prognosis section]); however, markers of local immunity, including T-cell infiltrates and cytokine expression, are notably absent in these lesions. Among HIV-infected patients, some investigators have reported a positive correlation between oral



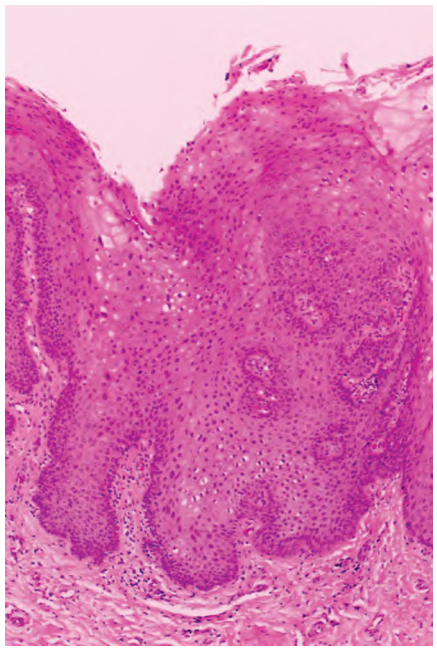
• **Fig. 7-51 HIV-associated Human Papillomavirus (HPV) Infection.** Multiple exophytic and somewhat papillary nodules of the lip, buccal mucosa, and gingiva.

HPV lesions, age, and duration of cART. Thus, some researchers have proposed that cART may extend patient survival without full restoration of HPV-specific immunity or that extended survival may allow increased cumulative risk for HPV infection acquisition over time despite restoration of immune function.

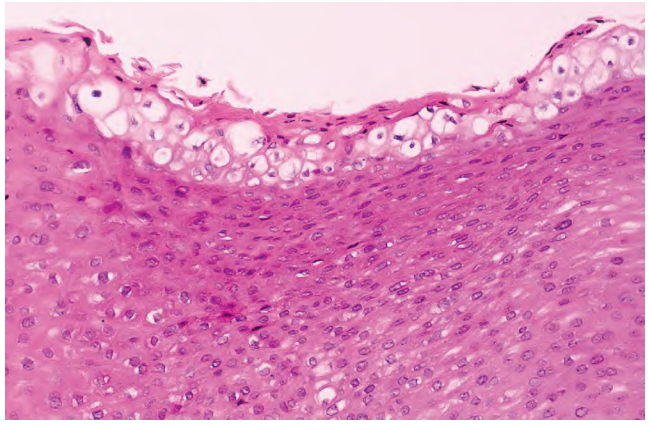
The oral lesions usually are multiple and may be located on any mucosal surface, with the labial mucosa, tongue, buccal mucosa, and gingiva most frequently involved. The lesions may exhibit a cluster of white, spikelike projections, pink cauliflower-like growths, or slightly elevated sessile papules (Fig. 7-51).

Histopathologically, the lesions may be sessile or papillary and covered by acanthotic or hyperplastic stratified squamous epithelium (Fig. 7-52). The affected epithelium often demonstrates vacuolization of numerous epithelial cells (i.e., koilocytosis) and occasionally may exhibit mild variation in nuclear size (Fig. 7-53). Immunohistochemistry or DNA *in situ* hybridization may be used to confirm the presence and type of HPV within histopathologic specimens (Fig. 7-54).

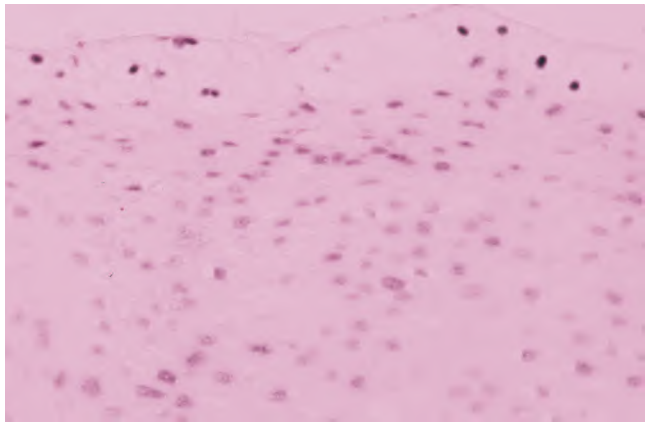
Dysplasia has been noted within HPV-related lesions in patients with AIDS and mandates close observation for development of squamous cell carcinoma. Surgical excision is the most commonly used treatment for oral HPV lesions;



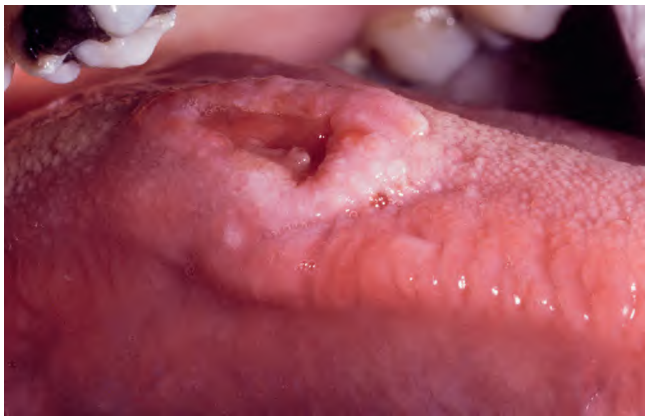
• **Fig. 7-52 HIV-associated Human Papillomavirus (HPV) Infection.** Oral mucosa exhibiting acanthosis and mild nuclear pleomorphism.



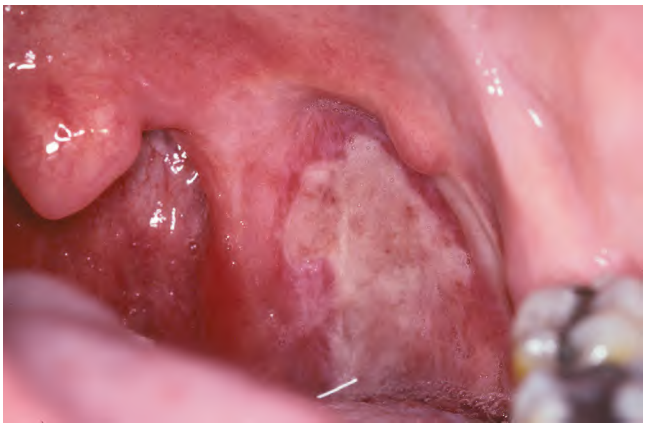
• **Fig. 7-53 HIV-associated Human Papillomavirus (HPV) Infection.** Oral mucosa exhibiting extensive koilocytosis in the superficial spinous cell layer.



• **Fig. 7-54 HIV-associated Human Papillomavirus (HPV) Infection.** DNA *in situ* hybridization of oral mucosal biopsy that reveals diffuse cellular positivity for HPV.



• **Fig. 7-55 HIV-associated Histoplasmosis.** Indurated ulceration with a rolled border on the dorsal surface of the tongue on the right side.



• **Fig. 7-56 HIV-associated Aphthous Ulceration.** Large superficial ulceration of the posterior soft palate.

additional surgical options include cryosurgery, electrocautery, and laser ablation. However, all of these surgical methods are associated with frequent recurrence, and the latter two methods may expose the surgical team and patient to a plume containing infectious HPV. Alternative treatments with anecdotal evidence of efficacy include topical cidofovir, intralesional or systemic interferon-alpha, oral cimetidine, and topical podophyllin.

Other Oral and Maxillofacial Lesions Seen in HIV Infection

Histoplasmosis

Histoplasmosis, the most common endemic respiratory fungal infection in the United States, is produced by *Histoplasma capsulatum* (see page 199). In healthy patients the infection typically is subclinical and self-limiting, but clinically evident infections often occur in immunocompromised individuals. Although a number of deep fungal infections are possible in patients with AIDS, histoplasmosis is the most common, with disseminated disease noted in approximately 5% of AIDS patients residing in areas where the fungus is endemic. Histoplasmosis also has been documented in nonendemic areas, possibly from reactivation of a previous subclinical infection.

The signs and symptoms associated with dissemination are nonspecific and include fever, weight loss, splenomegaly, and pulmonary infiltrates. Oral lesions are not uncommon and usually are caused by bloodborne organisms or spread from pulmonary involvement. On occasion, the initial diagnosis is made from the oral changes, with some patients demonstrating involvement isolated to the oral cavity. Although intrabony infection of the jaws has been reported, the most common oral presentation is a chronic, indurated mucosal ulceration with a raised border (Fig. 7-55). The oral lesions may be single or multiple and may involve any area of the mucosa.

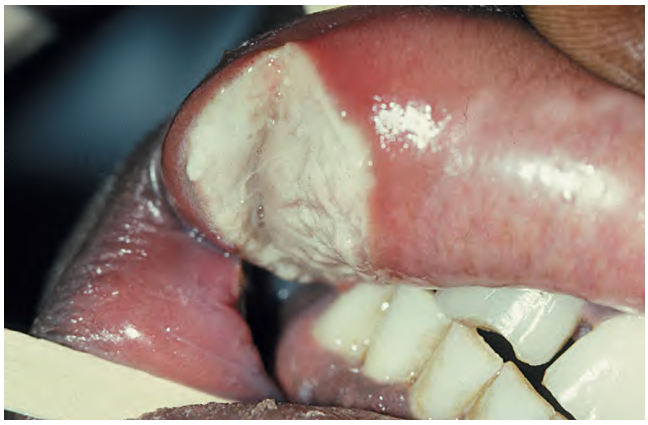
First-line agents for progressive disseminated histoplasmosis in HIV-infected patients include IV liposomal amphotericin B and oral itraconazole. Fluconazole is less effective but may be used as a second-line agent. Lifelong suppressive therapy with itraconazole may be required for patients who relapse or develop irreversible immunosuppression. Primary prophylaxis with itraconazole should be considered for HIV-infected patients who have CD4+ cell counts less than 150 per mm^3 and live in endemic areas with an especially high incidence of histoplasmosis.

Aphthous Ulcerations

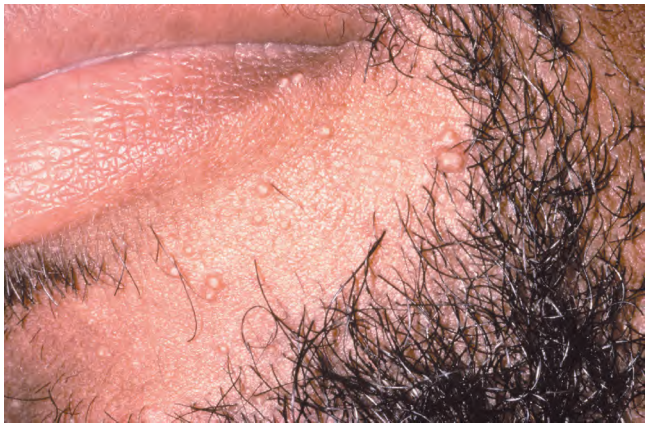
Lesions that are clinically similar to **aphthous ulcerations** (see page 303) occur with increased frequency in patients infected with HIV. All three forms (minor, major, and herpetiform) are seen; surprisingly, however, almost two-thirds of affected patients have the usually uncommon herpetiform and major variants (Fig. 7-56). As immunosuppression becomes more profound, major aphthous ulcerations demonstrate an increased prevalence.

Initiation of cART is important for inducing remission and limiting recurrences of aphthae. In addition, treatment with potent topical or intralesional corticosteroids has been successful in many patients. However, not all lesions respond, and recurrences are common. Systemic corticosteroid drugs also may prove beneficial but typically are avoided in order to prevent further immunosuppression. Secondary candidiasis may be a complication of topical or systemic corticosteroid therapy. For lesions nonresponsive to topical corticosteroids, thalidomide may be effective. However, thalidomide must be used cautiously because of its association with increased viral load and potentially serious adverse effects, including peripheral neuropathy, neutropenia, and thrombosis. In addition, there are anecdotal reports of resolution with systemic granulocyte colony–stimulating factor (G-CSF) and topical granulocyte-macrophage colony-stimulating factor (GM-CSF).

Biopsy of any chronic mucosal ulceration clinically diagnosed as an aphthous ulceration should be considered if the lesion is atypical clinically or does not respond to therapy (Fig. 7-57). In such cases, biopsy often reveals another



• **Fig. 7-57 HIV-associated Ulceration.** Atypical mucosal ulceration that mandates biopsy and may be attributable to a variety of causes.



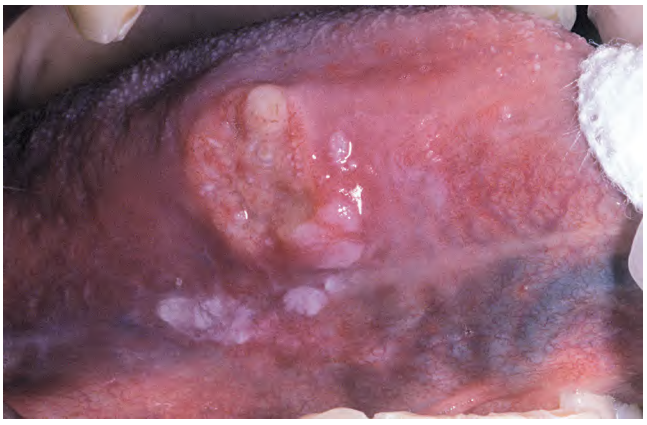
• **Fig. 7-58 HIV-associated Molluscum Contagiosum.** Numerous perioral papules.

cause, such as HSV, CMV, deep fungal infection, or neoplasia.

Molluscum Contagiosum

Molluscum contagiosum (see page 340) is an infection caused by the molluscum contagiosum virus (MCV), which is a member of the poxvirus family. The lesions classically appear on the skin and genitals as small, waxy, dome-shaped papules with central umbilication. In immunocompetent individuals, the lesions are usually localized and self-limiting. However, in patients with AIDS, the lesions may be widespread, persistent, more numerous, and larger in size. Approximately 5% to 10% of HIV-infected patients are affected, and the facial skin commonly is involved (Fig. 7-58). Rare intraoral cases have been described as erythematous, white, or pink papules on either keratinized or nonkeratinized mucosa.

The most effective treatment for molluscum contagiosum in HIV-infected patients is cART. Paradoxical worsening of lesions shortly after initiation of cART due to immune reconstitution syndrome (see the Treatment and Prognosis section) is possible but typically is transient. For lesions that persist despite cART, there is limited evidence for treatment with topical imiquimod, topical or IV cidofovir, or intralesional interferon-alpha. Because MCV may be present in perilesional skin of HIV-infected patients, conventional local therapy (e.g., curettage, cryosurgery, cautery, or topical podophyllotoxin) often is associated with recurrence.



• **Fig. 7-59 HIV-associated Squamous Cell Carcinoma.** Ulceration with raised, indurated borders on the lateral tongue.

Oral Squamous Cell Carcinoma

Relative to the general population, HIV-infected individuals have an estimated twofold increased risk of developing oral cavity and pharyngeal cancer. Studies of various HIV/AIDS cohorts have demonstrated a high prevalence of known risk factors for oral and pharyngeal cancers (e.g., tobacco use and HPV infection). Furthermore, the prevalence of these cancers has been shown to increase with the degree of immunosuppression, and oral squamous cell carcinoma tends to occur at a younger age among HIV-infected individuals than non-HIV-infected individuals. These findings suggest that in addition to conventional risk factors, HIV-related immunosuppression contributes to elevated cancer risk and accelerated cancer development.

With respect to oral squamous cell carcinoma, the clinical appearance and anatomic distribution are similar among HIV-infected persons and the general population (Fig. 7-59). Treatment also is not significantly different for HIV-infected patients and consists of surgical resection, radiation therapy, and/or chemotherapy. Clinical staging can be problematic because of HIV-related cervical lymphadenopathy. In these cases, cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) may be performed in an attempt to distinguish lymph nodes enlarged by lymphoproliferative disease from those containing metastatic carcinoma. The majority of HIV-infected patients with a diagnosis of oral squamous cell carcinoma have advanced disease and an unfavorable prognosis.

Diagnosis

Confirmation of HIV infection most commonly is obtained by antibody testing. The standard screening tool is the enzyme immunoassay (EIA); rapid HIV antibody tests also are available. Both tests may be performed on blood, oral

fluid, or urine. False-positive results are possible, and a positive or indeterminate result should be confirmed by the more specific Western blot assay. Seroconversion generally takes 3 to 12 weeks following infection; thus, repeat testing may be considered after a negative result, if there is a strong reason to suspect recent HIV infection. HIV home testing kits also are available. These kits allow the user to send a sample into a laboratory for antibody testing, although positive results still need to be confirmed by standard EIA and Western blot assay.

Less commonly used methods include HIV antigen tests (such as the p24 antigen capture assay), which are designed to detect viral antigens in blood before the development of antibodies.

In addition, reverse transcriptase polymerase chain reaction (RT-PCR) and branched-chain DNA assay can be used to detect HIV RNA in the blood of recently infected individuals. These tests also may be useful for infants born to HIV-infected mothers, because infants carry maternal antibodies for several months after birth. More commonly, such assays are used to monitor viral load for patients already diagnosed. In most developed countries, RT-PCR is used for blood supply screening as well.

AIDS is diagnosed when a patient has laboratory evidence of HIV infection combined with any of the following:

1. CD4+ T-lymphocyte count less than 200 per microliter
2. CD4+ T-lymphocyte percentage of total lymphocytes less than 14
3. Documentation of an AIDS-defining condition (Box 7-2)

Treatment and Prognosis

As mentioned previously, the introduction of cART has resulted in dramatically reduced morbidity and mortality. A wide variety of antiretroviral agents is available and continues to expand (Box 7-3). These agents are administered in combination in order to reduce the emergence of viral resistance. Although numerous combinations are possible, cART often consists of two nucleoside reverse transcriptase inhibitors combined with a non-nucleoside reverse transcriptase inhibitor, boosted protease inhibitor, or integrase inhibitor (2 NRTI + NNRTI/PI/II). With such treatment, viremia typically declines to undetectable levels, and there is clinically significant immune reconstitution. Early initiation of cART reduces the risk for AIDS, death, and disease transmission. Although cART works well for most patients, downsides of such therapy include cost, toxicity, adverse reactions, and difficulty with compliance. Some patients who receive antiretroviral therapy during advanced stages of disease develop a paradoxical worsening of their condition—termed **immune reconstitution syndrome**—despite decreasing viral load and increasing CD4+ cell counts. The underlying mechanism may be related to a hyper-inflammatory response to pathogens and pathogenic antigens present at the time of rapid immune reconstitution. Long-term cART recipients are at increased risk for premature cardiovascular disease, liver disease, kidney disease, and both HIV-related and non-HIV-related cancers. cART alone is unable to cure HIV infection, apparently because of persistence of viral reservoirs in the peripheral blood and lymphoid tissues.

Significant gains also have been achieved through public health interventions. In the United States, the CDC has recommended routine HIV screening of adults, adolescents, and pregnant women in health care settings. Routine testing is critical for life-saving early diagnosis and therapy as well as prevention of HIV transmission to others. Work is proceeding toward the development of a safe and effective vaccine, but complex issues have slowed progress.

Some health professionals have been concerned about the risk of occupational transmission of HIV. The estimated average risk for seroconversion is 0.3% following percutaneous exposure and 0.09% following mucous membrane

• BOX 7-2 AIDS-Defining Conditions

1. Bacterial infections, multiple or recurrent*
2. Candidiasis of bronchi, trachea, or lungs
3. Candidiasis, esophageal
4. Cervical cancer, invasive†
5. Coccidioidomycosis, disseminated or extrapulmonary
6. Cryptococcosis, extrapulmonary
7. Cryptosporidiosis, chronic intestinal (more than 1 month duration)
8. CMV disease (other than liver, spleen, or nodes), onset at age of more than 1 month
9. CMV-induced retinitis (with loss of vision)
10. Encephalopathy, HIV-related
11. Herpes simplex: Chronic ulcer or ulcers (more than 1 month duration) or bronchitis, pneumonitis, or esophagitis
12. Histoplasmosis, disseminated or extrapulmonary
13. Isosporiasis, chronic intestinal (more than 1 month duration)
14. Kaposi sarcoma (KS)
15. Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*
16. Lymphoma, Burkitt (or equivalent term)
17. Lymphoma, immunoblastic (or equivalent term)
18. Lymphoma, primary, of brain
19. *Mycobacterium avium* complex or *M. kansasii,* disseminated or extrapulmonary
20. *Mycobacterium tuberculosis* of any site, pulmonary,† disseminated, or extrapulmonary
21. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
22. *Pneumocystis jiroveci* pneumonia
23. Pneumonia, recurrent†
24. Progressive multifocal leukoencephalopathy
25. *Salmonella* septicemia, recurrent
26. Toxoplasmosis of brain, onset at age of more than 1 month
27. Wasting syndrome attributed to HIV

Adapted from Centers for Disease Control and Prevention: Appendix A, AIDS-Defining Conditions, *MMWR Recomm Rep* 57(RR-10):9, 2008.
AIDS, acquired immune deficiency syndrome; *CMV,* cytomegalovirus; *HIV,* human immunodeficiency virus.
*Only among children less than 13 years old.
†Only among adults and adolescents aged 13 years or older.

• BOX 7-3 Antiretroviral Therapy

1. Nucleoside reverse transcriptase inhibitors
   - Abacavir (Ziagen), didanosine (Videx), emtricitabine (Emtriva), lamivudine (Epivir), stavudine (Zerit), tenofovir (Viread), zalcitabine (Hivid), and zidovudine (Retrovir)
2. Nonnucleoside reverse transcriptase inhibitors
   - Delavirdine (Rescriptor), efavirenz (Sustiva), etravirine (Intelence), nevirapine (Viramune), and rilpivirine (Edurant)
3. Protease inhibitors
   - Atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase), and tipranavir (Aptivus)
4. Fusion inhibitors
   - Enfuvirtide (Fuzeon)
5. Integrase inhibitors
   - Raltegravir (Isentress), dolutegravir (Tivicay), and elvitegravir (experimental)
6. CCR5 inhibitors
   - Maraviroc (Selzentry) and vicriviroc (experimental)
7. Fixed-dose combination drugs
   - Abacavir + lamivudine (Epzicom), elvitegravir + cobicistat + emtricitabine + tenofovir (Stribild), emtricitabine + tenofovir + rilpivirine (Complera), lopinavir + ritonavir (Kaletra), emtricitabine + tenofovir (Truvada), emtricitabine + tenofovir + efavirenz (Atripla), zidovudine + abacavir + lamivudine (Trizivir), and zidovudine + lamivudine (Combivir)

exposure to HIV-infected blood. The risk of transmission by exposure to infected fluids or tissues other than blood has not been quantified but likely is considerably lower. In the occupational setting, postexposure prophylaxis with antiretroviral medications has been found to reduce the risk for infection by greater than 80% if initiated within hours of the event. Four weeks of therapy is recommended. Basic postexposure prophylaxis consists of a two-drug regimen, which may be expanded to a three-drug combination for more severe exposures. Because of the complexity of choosing the regimen and potential for adverse drug reactions, involvement of an infectious disease specialist or other physician experienced in antiretroviral therapy is recommended.

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8 Physical and Chemical Injuries

LINEA ALBA

Linea alba ("white line") is a common alteration of the buccal mucosa that most likely is associated with pressure, frictional irritation, or sucking trauma from the facial surfaces of the teeth. No other associated problem, such as insufficient horizontal overlap or rough restorations of the teeth, is necessary for the development of linea alba.

Clinical Features

As the name implies, the alteration consists of a white line that usually is bilateral. It may be scalloped and is located on the buccal mucosa at the level of the occlusal plane of the adjacent teeth (Fig. 8-1). The line varies in prominence and usually is restricted to dentulous areas. It often is more pronounced adjacent to the posterior teeth. In clinical surveys of oral alterations, linea alba appears to be one of the more common oral pathoses. Several studies have reported a female predominance.

Histopathologic Features

Biopsy is rarely indicated. If a biopsy is performed, hyperorthokeratosis is seen overlying otherwise normal oral mucosa. On occasion, intracellular edema of the epithelium and mild chronic inflammation of the underlying connective tissue may be noted.

Treatment and Prognosis

No treatment is required for patients with linea alba, and no difficulties are documented as a result of its development. Spontaneous regression may occur.

MORSICATIO MUCOSAE ORIS (CHRONIC MUCOSAL CHEWING)

Morsicatio mucosae oris is a classic example of medical terminology gone astray; it is the scientific term for chronic chewing of the oral mucosa. *Morsicatio* comes from the Latin word *morsus,* or *bite*. Chronic nibbling produces lesions that are located most frequently on the buccal mucosa **(morsicatio buccarum);** however, the labial mucosa **(morsicatio labiorum)** and the lateral border of the tongue **(morsicatio linguarum)** also may be involved. Similar changes have been seen as a result of suction and in glassblowers whose technique produces chronic irritation of the buccal mucosa.

A higher prevalence of classic morsicatio mucosae oris has been found in people who are under stress or who exhibit psychologic conditions. Most patients are aware of their habit, although many deny the self-inflicted injury or perform the act subconsciously. An increased prevalence has been noted in women and in patients older than 35 years.

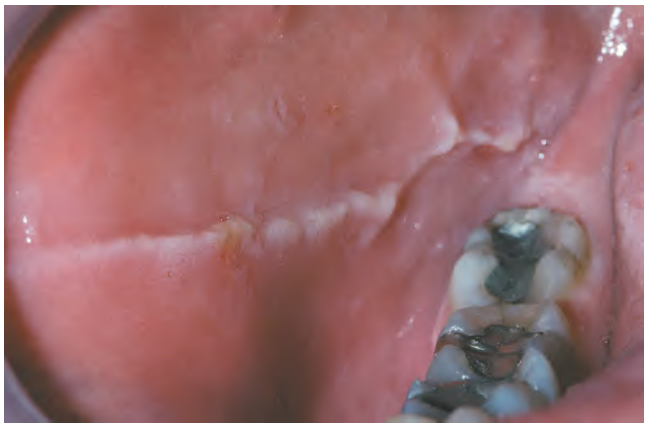
Clinical Features

Most frequently, the lesions in patients with morsicatio are found bilaterally on the anterior buccal mucosa. They also may be unilateral, combined with lesions of the lips or the tongue, or isolated to the lips or tongue. Thickened, shredded, white areas may be combined with intervening zones of erythema, erosion, or focal traumatic ulceration (Figs. 8-2 and 8-3). The areas of white mucosa demonstrate an irregular ragged surface, and the patient may describe being able to remove shreds of white material from the involved area. Although dysplastic leukoplakias tend to have more sharply demarcated borders, the periphery of morsicatio-related lesions gradually blends with the adjacent mucosa.

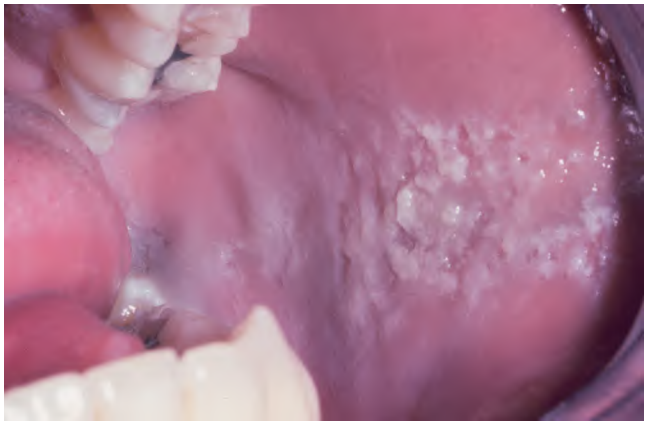
The altered mucosa typically is located in the midportion of the anterior buccal mucosa along the occlusal plane. Large lesions may extend some distance above or below the occlusal plane in patients whose habit involves pushing the cheek between the teeth with a finger.

Histopathologic Features

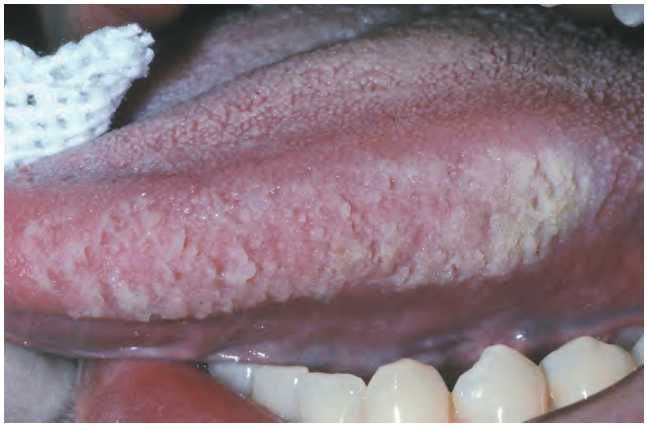
Biopsy reveals extensive hyperparakeratosis that often results in an extremely ragged surface with numerous projections of keratin. Surface bacterial colonization is typical (Fig. 8-4). On occasion, clusters of vacuolated cells are present in the superficial portion of the prickle cell layer. This histopathologic pattern is not pathognomonic of morsicatio and may bear a striking resemblance to **oral hairy leukoplakia (OHL),** a lesion that most often occurs in people who are infected with the **human immunodeficiency virus (HIV)**



• **Fig. 8-1 Linea Alba.** White line of hyperkeratosis on the right buccal mucosa at the level of the occlusal plane.

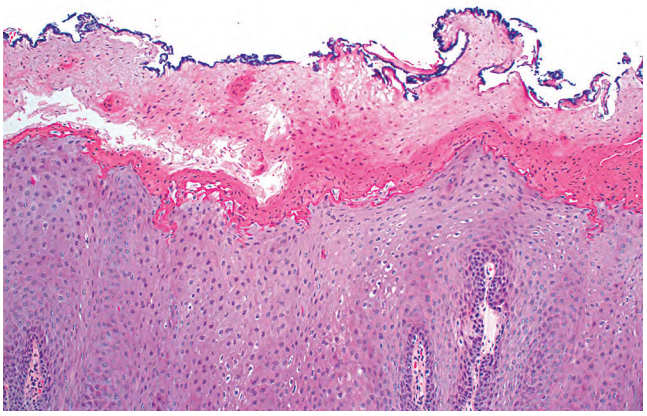


• **Fig. 8-2 Morsicatio Buccarum.** Thickened, shredded areas of white hyperkeratosis of the left buccal mucosa.



• **Fig. 8-3 Morsicatio Linguarum.** Thickened, rough areas of white hyperkeratosis of the lateral border of the tongue on the left side.

(see page 242), or to **uremic stomatitis** (see page 793). In contrast to OHL, the superficial epithelial cells will not demonstrate the characteristic nuclear beading associated with infection with Epstein-Barr virus. Lesions in patients who chronically chew betel quid (**betel chewer's mucosa;** see page 368) may resemble morsicatio microscopically. Similarities with linea alba and leukoedema also may be seen.



• **Fig. 8-4 Morsicatio Buccarum.** Oral mucosa exhibiting greatly thickened layer of parakeratin with ragged surface colonized by bacteria.

Diagnosis

In most cases, the clinical presentation of morsicatio is sufficient for a strong presumptive diagnosis, and clinicians familiar with these alterations rarely perform biopsy. Some cases of morsicatio may not be diagnostic from the clinical presentation, and biopsy may be necessary.

Treatment and Prognosis

No treatment of the oral lesions is required, and no long-term difficulties arise from the presence of the mucosal changes. For patients desiring either confirmation of the cause or preventive therapy, construction and use of acrylic shields to separate the teeth from the adjacent mucosa can provide quick resolution of the lesions.

◆ TRAUMATIC ULCERATIONS

Acute and chronic injuries of the oral mucosa are common and may be associated with surface ulcerations. The ulcerations may remain for extended periods of time but most usually heal within days. A histopathologically unique type of chronic traumatic ulceration of the oral mucosa is the **eosinophilic ulceration (traumatic granuloma**; **traumatic ulcerative granuloma with stromal eosinophilia [TUGSE]; eosinophilic granuloma of the tongue),** which exhibits a deep pseudoinvasive inflammatory reaction and is typically slow to resolve. Interestingly, many of these traumatic granulomas undergo resolution after incisional biopsy. Lesions microscopically similar to eosinophilic ulceration have been reproduced in rat tongues after repeated crushing trauma and in traumatic lesions noted in patients with familial dysautonomia, a disorder characterized by indifference to pain. In addition, similar sublingual ulcerations may occur in infants as a result of chronic mucosal trauma from adjacent anterior primary teeth, often

associated with nursing. These distinctive ulcerations of infancy have been termed **Riga-Fede disease** and should be considered a variation of the traumatic eosinophilic ulceration.

In rare subsets of TUGSE, the lesion does not appear to be associated with trauma, and sheets of large, atypical cells are seen histopathologically. In these **atypical eosinophilic ulcerations,** the nature of these atypical cells remains in dispute, although it has been suggested that they may represent reactive myofibroblasts, histiocytes**,** or T lymphocytes. Whether these atypical eosinophilic ulcerations represent a single pathosis or a variety of disorders that share stromal eosinophilia is an area for future research. Of these theories, several current investigations have shown the atypical cells to be T lymphocytes with strong immunoperoxidase reactivity for CD30. In these cases, it is thought that this subset of TUGSE may represent the oral counterpart of the **primary cutaneous CD30+ lymphoproliferative disorder,** which also exhibits sequential ulceration, necrosis, and self-regression.

In most cases of traumatic ulceration, there is an adjacent source of irritation, although this is not present invariably. The clinical presentation often suggests the cause, but many cases resemble early ulcerative squamous cell carcinoma; biopsy is performed to rule out that possibility.

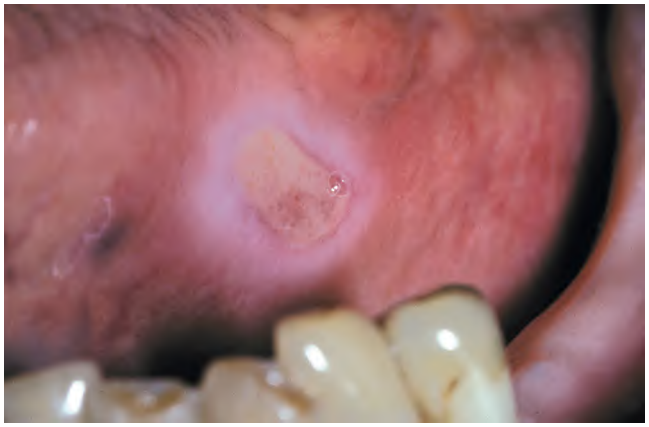
Clinical Features

As would be expected, simple chronic traumatic ulcerations occur most often on the tongue, lips, and buccal mucosa—sites that may be injured by the dentition (Fig. 8-5). Lesions of the gingiva, palate, and mucobuccal fold may occur from other sources of irritation. The individual lesions appear as areas of erythema surrounding a central removable, yellow fibrinopurulent membrane. In many instances, the lesion develops a rolled white border of hyperkeratosis immediately adjacent to the area of ulceration (Fig. 8-6).

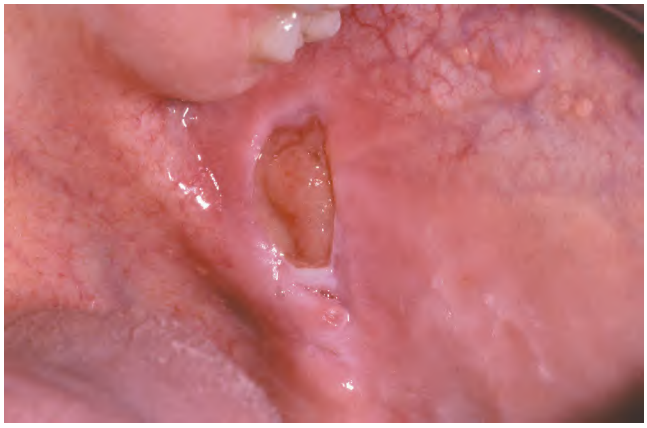
Eosinophilic ulcerations are not uncommon but frequently are not reported. The lesions occur in people of all ages, with a significant male predominance. Most have been reported on the tongue, although cases have been seen on the gingiva, buccal mucosa, floor of mouth, palate, and lip. The lesion may last from 1 week to 8 months. The ulcerations appear very similar to the simple traumatic ulcerations; however, on occasion, underlying proliferative granulation tissue can result in a raised lesion similar to a pyogenic granuloma (see page 483) (Fig. 8-7).

Riga-Fede disease typically appears between 1 week and 1 year of age. The condition often develops in association with natal teeth (see page 74). The anterior ventral surface of the tongue is the most common site of involvement, although the dorsal surface also may be affected (Fig. 8-8). Ventral lesions contact the adjacent mandibular anterior incisors; lesions on the dorsal surface are associated with the maxillary incisors. A presentation similar to Riga-Fede disease can be the initial finding in a variety of neurologic conditions related to self-mutilation, such as familial dysautonomia (Riley-Day syndrome), congenital indifference to pain, Lesch-Nyhan syndrome, Gaucher disease, cerebral palsy, or Tourette syndrome.

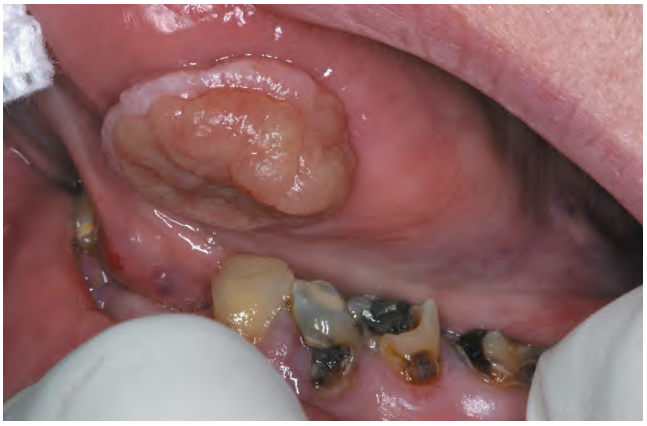
The atypical eosinophilic ulceration occurs in older adults, with most cases developing in patients older than age 40. Surface ulceration is present, and an underlying



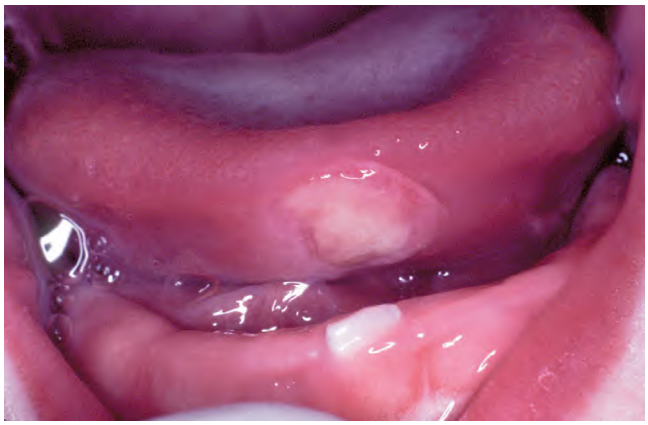
• **Fig. 8-6 Traumatic Ulceration.** Mucosal ulceration with a hyperkeratotic collar located on the ventral surface of the tongue.



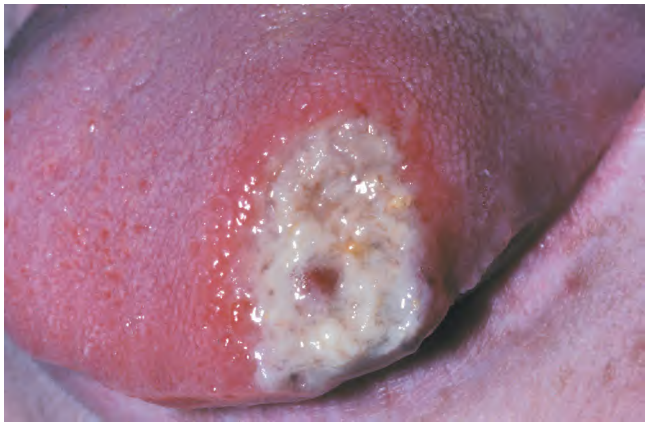
• **Fig. 8-5 Traumatic Ulceration.** Well-circumscribed ulceration of the posterior buccal mucosa on the left side.



• **Fig. 8-7 Traumatic Granuloma.** Exophytic ulcerated mass on the ventrolateral tongue associated with multiple jagged teeth.



• **Fig. 8-8 Riga-Fede Disease.** Newborn with traumatic ulceration of anterior ventral surface of the tongue. Mucosal damage occurred from contact of tongue with adjacent tooth during breastfeeding.



• **Fig. 8-9 Atypical Eosinophilic Ulceration.** Large ulceration of the anterior dorsal surface of the tongue.

tumefaction also is seen. The tongue is the most common site, although the gingiva, alveolar mucosa, mucobuccal fold, buccal mucosa, and lip may be affected (Fig. 8-9).

Histopathologic Features

Simple traumatic ulcerations are covered by a fibrinopurulent membrane that consists of fibrin intermixed with neutrophils. The membrane is of variable thickness, and the adjacent surface epithelium may be normal or may demonstrate slight hyperplasia with or without hyperkeratosis. The ulcer bed consists of granulation tissue that supports a mixed inflammatory infiltrate of lymphocytes, histiocytes, neutrophils, and, occasionally, plasma cells. In patients with eosinophilic ulcerations, the pattern is very similar; however, the inflammatory infiltrate extends into the deeper tissues and exhibits sheets of lymphocytes and histiocytes intermixed with eosinophils. In addition, the vascular connective tissue deep to the ulceration may become hyperplastic and cause surface elevation.

Atypical eosinophilic ulcerations exhibit numerous features of the traumatic eosinophilic ulceration, but the deeper tissues are replaced by a highly cellular proliferation of large lymphoreticular cells. The infiltrate is pleomorphic, and mitotic features are somewhat common. Intermixed with the large atypical cells are mature lymphocytes and numerous eosinophils. Although an associated immunohistochemical profile rarely has been reported, several investigators have shown the large cells to be T lymphocytes, the majority of which react with CD30 (Ki-1). In many instances, molecular studies for T-cell clonality by polymerase chain reaction (PCR) have been performed on the CD30+ cells and demonstrated monoclonal rearrangement. Whether this monoclonal infiltrate represents a true low-grade lymphoma or an unusual reactive lymphoproliferative process has not been determined.

Treatment and Prognosis

For traumatic ulcerations that have an obvious source of injury, the irritating cause should be removed. A topical anesthetic or protective film can be applied for temporary pain relief. If the cause is not obvious, or if a patient does not respond to therapy, then biopsy is indicated. Rapid healing after a biopsy is typical even with large eosinophilic ulcerations (Fig. 8-10). Recurrence is not expected.

The use of corticosteroids in the management of traumatic ulcerations is controversial. Some clinicians have suggested that use of such medications may delay healing. In spite of this, other investigators have reported success using corticosteroids to treat chronic traumatic ulcerations.

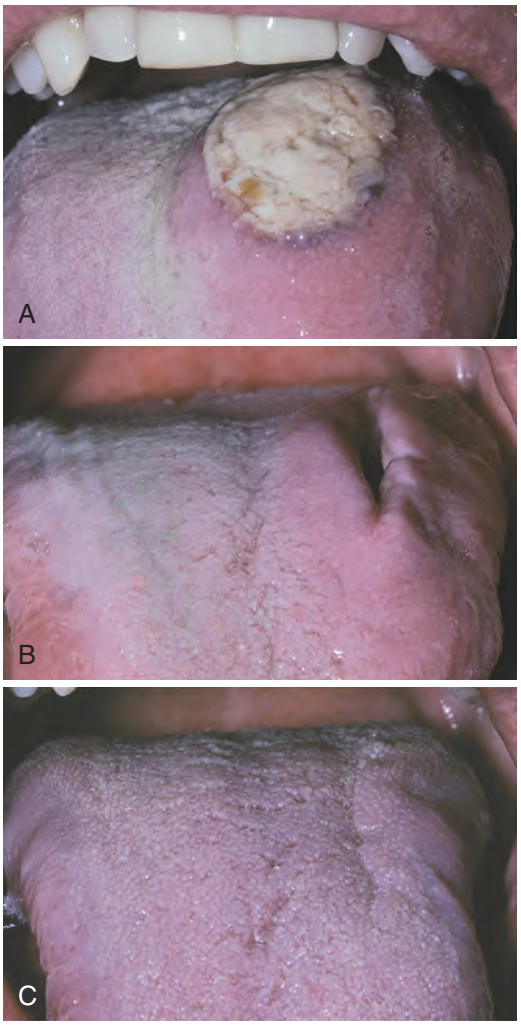
Although extraction of the anterior primary teeth is not recommended, this procedure has resolved the ulcerations in Riga-Fede disease. The teeth should be retained if they are stable. Grinding the incisal mamelons, coverage of the teeth with a light-cured composite or cellulose film, construction of a protective shield, or discontinuation of nursing have been tried with variable success.

In patients demonstrating histopathologic similarities to the cutaneous CD30+ lymphoproliferative disorder, a thorough evaluation for systemic lymphoma is mandatory, along with lifelong follow-up. Although recurrence frequently is seen, the ulcerations typically heal spontaneously, and the vast majority of patients do not demonstrate dissemination of the process. Further documentation is critical to define more fully this poorly understood process.

◆ ELECTRICAL AND THERMAL BURNS

Electrical burns to the oral cavity are fairly common, constituting approximately 5% of all burn admissions to hospitals. Two types of electrical burns can be seen: 1) **contact** and 2) **arc.**

Contact burns require a good ground and involve electrical current passing through the body from the point of contact to the ground site. The electric current can cause cardiopulmonary arrest and may be fatal. Most electrical burns affecting the oral cavity are the arc type, in which the saliva acts as a conducting medium and an electrical arc flows between the electrical source and the mouth. Extreme



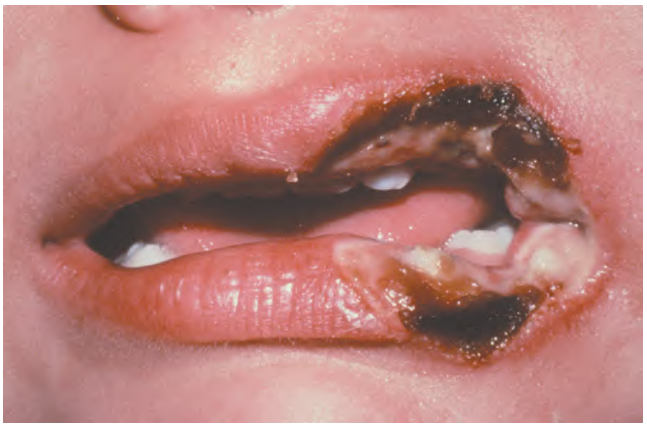
• **Fig. 8-10 Eosinophilic Ulceration. A,** Initial presentation of a large ulceration of the dorsal surface of the tongue. **B,** Significant resolution noted 2 weeks after incisional biopsy. **C,** Subsequent healing noted 4 weeks after biopsy.

heat, up to 3000° C, is possible with resultant significant tissue destruction. Most cases result from chewing on the female end of an extension cord or from biting through a live wire.

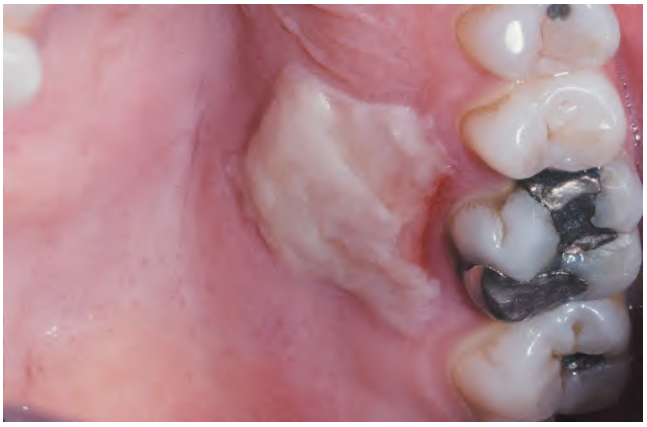
Most **thermal burns** of the oral cavity arise from ingestion of hot foods or beverages. Microwave ovens have been associated with an increased frequency of thermal burns because of their ability to cook food that is cool on the exterior but extremely hot in the interior.

Clinical Features

The hands are the most common site of electrical burns in adults. In contrast, the oral cavity is the most commonly affected location in children, with 90% of these accidents occurring before age 4. The lips are affected most frequently, and the commissure commonly is involved. Initially, the burn appears as a painless, charred, yellow area that exhibits little to no bleeding (Fig. 8-11). Significant edema often



• **Fig. 8-11 Electrical Burn.** Yellow charred area of necrosis along the left oral commissure. (Courtesy of Dr. Patricia Hagen.)



• **Fig. 8-12 Thermal Food Burn.** Area of yellow-white epithelial necrosis of the left posterior hard palate. Damage was the result of attempted ingestion of a hot pizza roll.

develops within a few hours and may persist up to 12 days. Beginning on the fourth day, the affected area becomes necrotic and begins to slough. Bleeding may develop during this period from exposure of the underlying vital vasculature, and the presence of this complication should be monitored closely. The adjacent mucobuccal fold, the tongue, or both also may be involved. On occasion, adjacent teeth may become nonvital, with or without necrosis of the surrounding alveolar bone. Malformation of developing teeth also has been documented. In patients receiving high-voltage electrical injury, resultant facial nerve paralysis is reported infrequently and typically resolves over several weeks to months. Focal enamel cavitation, which was thought to represent a high voltage exit point, also has been reported in association with an electrocution injury.

The injuries related to thermal food burns usually appear on the palate or posterior buccal mucosa (Fig. 8-12). The lesions appear as zones of erythema and ulceration that often exhibit remnants of necrotic epithelium at the periphery. If hot beverages are swallowed, swelling of the upper airway can occur and lead to dyspnea, which may develop several hours after the injury.

Treatment and Prognosis

For patients with electrical burns of the oral cavity, tetanus immunization, if not current, is required. Most clinicians prescribe a prophylactic antibiotic, usually penicillin, to prevent secondary infection in severe cases. The primary problem with oral burns is contracture of the mouth opening during healing. Without intervention, significant microstomia can develop and may produce such restricted access to the mouth that hygiene and eating become impossible in severe cases. Extensive scarring and disfigurement are typical in untreated patients.

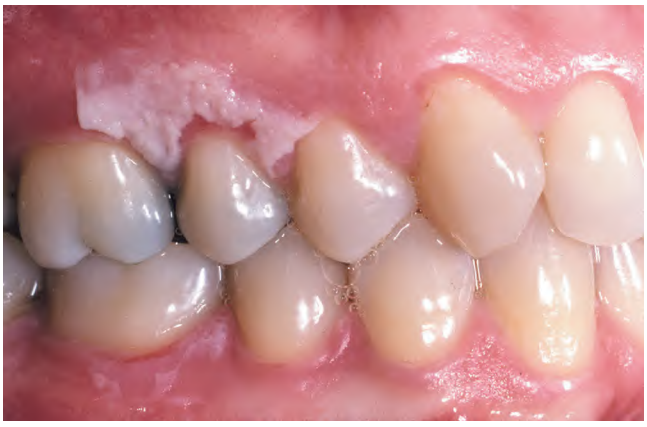
To prevent the disfigurement, a variety of microstomia prevention appliances can be used to eliminate or reduce the need for subsequent surgical reconstruction. Compliance is the most important consideration when choosing the most appropriate device. Tissue-supported appliances appear most effective for infants and young children; older, more cooperative patients usually benefit from tooth-supported devices. In most cases, splinting is maintained for 6 to 8 months to ensure proper scar maturation. Evaluation for possible surgical reconstruction is usually performed after a 1-year follow-up.

Most thermal burns are of little clinical consequence and resolve without treatment. When the upper airway is involved and associated with breathing difficulties, antibiotics and corticosteroids often are administered. In rare cases, swelling of the airway mandates intubation or tracheotomy to resolve the associated dyspnea. In these severe cases, oral intake of food often is discontinued temporarily with nutrition provided by a nasogastric tube.

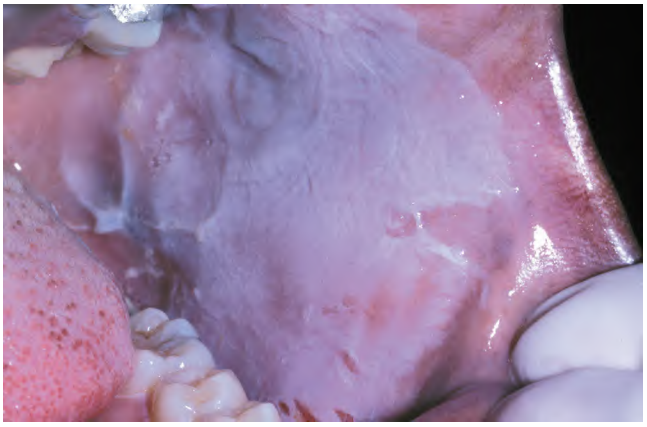
◆ CHEMICAL INJURIES OF THE ORAL MUCOSA

A large number of chemicals and drugs come into contact with the oral tissues. A percentage of these agents are caustic and can cause clinically significant damage.

Patients often can be their own worst enemies. The array of chemicals that have been placed within the mouth in an attempt to resolve oral problems is amazing. Aspirin, sodium perborate, hydrogen peroxide, gasoline, turpentine, rubbing alcohol, and battery acid are just a few of the more interesting examples. In addition, mucosal damage has been documented from many of the topical medicaments sold as treatments for toothache or mouth sores. Over-the-counter products containing isopropyl alcohol, phenol, hydrogen peroxide, or eugenol have produced adverse reactions in patients. Tooth-whitening products also contain hydrogen peroxide or one of its precursors, carbamide peroxidase, which has been shown to create mucosal necrosis (Fig. 8-13). A surprising number of medications also are potentially caustic when held in the mouth long enough. Aspirin, bisphosphonates, and two psychoactive drugs, chlorpromazine and promazine, are well-documented examples.



• **Fig. 8-13 Mucosal Burn from Tooth-whitening Strips.** Sharply demarcated zone of epithelial necrosis on the maxillary facial gingiva, which developed from the use of tooth-whitening strips. Less severe involvement also is present on the mandibular gingiva.



• **Fig. 8-14 Aspirin Burn.** Extensive area of white epithelial necrosis of the left buccal mucosa caused by aspirin placement in an attempt to alleviate dental pain.

Health care practitioners also are responsible for the use of many caustic materials. Silver nitrate, formocresol, sodium hypochlorite, paraformaldehyde, chromic acid, trichloroacetic acid, dental cavity varnishes, and acid-etch materials all can cause patient injury. Education and use of the rubber dam have reduced the frequency of such injuries.

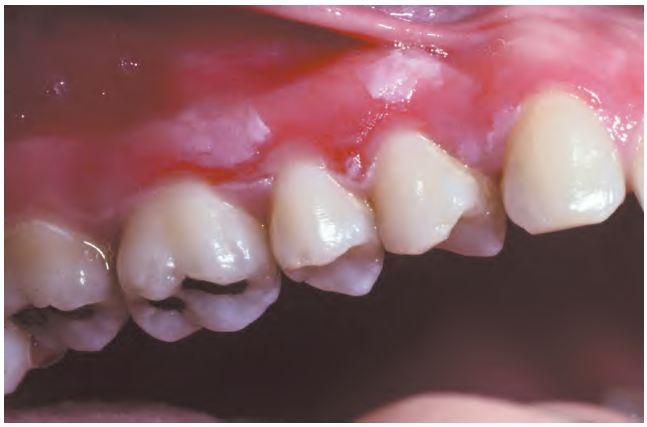
The improper use of aspirin, hydrogen peroxide, silver nitrate, phenol, and certain endodontic materials deserves further discussion because of their frequency of misuse, the severity of related damage, and the lack of adequate documentation of these materials as harmful agents.

ASPIRIN

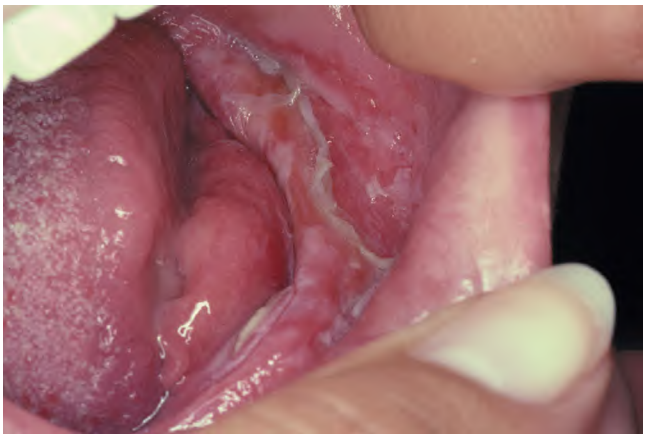
Mucosal necrosis from aspirin being held in the mouth is not rare (Fig. 8-14). Aspirin is available not only in the well-known tablets but also as powder.

HYDROGEN PEROXIDE

Hydrogen peroxide became a popular intraoral medication for prevention of periodontitis in the late 1970s. Since that



• **Fig. 8-15 Hydrogen Peroxide Burn.** Extensive epithelial necrosis of the anterior maxillary gingiva secondary to interproximal placement of hydrogen peroxide with cotton swabs.



• **Fig. 8-16 Phenol Burn.** Extensive epithelial necrosis of the mandibular alveolar mucosa on the left side. Damage resulted from placement of an over-the-counter, phenol-containing, antiseptic and anesthetic gel under a denture. (Courtesy of Dr. Dean K. White.)

time, mucosal damage has been seen more frequently as a result of this application. Concentrations at 3% or greater are associated most often with adverse reactions. Epithelial necrosis has been noted with dilutions as low as 1%, and many over-the-counter oral medications exceed this concentration (Fig. 8-15).

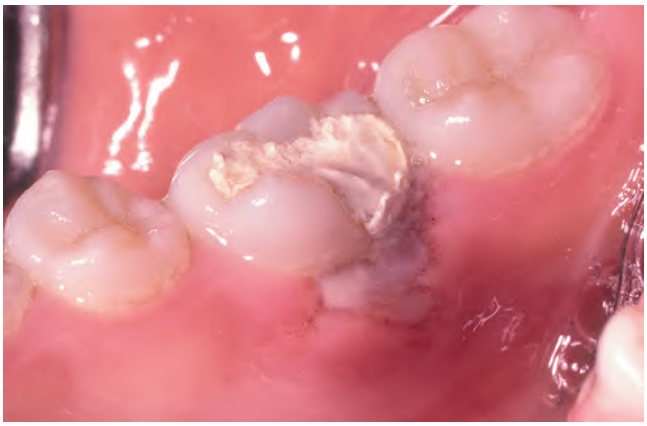
SILVER NITRATE

Silver nitrate remains a popular treatment for aphthous ulcerations, because the chemical cautery brings about rapid pain relief by destroying nerve endings. In spite of this, its use should be strongly discouraged. In all cases, the extent of mucosal damage is increased by its use. In some patients, an abnormal reaction is seen, with resultant significant damage and enhanced pain. In addition, rare reports have documented irreversible systemic argyria secondary to habitual intraoral use of topical silver nitrate after recommendation by a dentist (see page 288).

PHENOL

Occasionally, phenol has been used in dentistry as a cavity-sterilizing agent and cauterizing material. It is extremely caustic, and judicious use is required. Over-the-counter agents advertised as "canker sore" treatments may contain low concentrations of phenol, often combined with high levels of alcohol. Extensive mucosal necrosis and rarely underlying bone loss have been seen in patients who placed this material (phenol concentration 0.5%) in attempts to resolve minor mucosal sore spots (Fig. 8-16).

A prescription therapy containing 50% sulfuric acid, 4% sulfonated phenol, and 24% sulfonated phenolic agents is being marketed heavily to dentists for treatment of aphthous ulcerations. Because extensive necrosis has been seen from use of medicaments containing 0.5% phenol, this product must be closely monitored and used with great care.



• **Fig. 8-17 Formocresol Burn.** Tissue necrosis secondary to leakage of endodontic material between a rubber dam clamp and the tooth.

ENDODONTIC MATERIALS

Because of the past difficulty of obtaining profound anesthesia in some patients undergoing root canal therapy, some clinicians have used arsenical paste or paraformaldehyde formulations to devitalize the inflamed pulp. Gingival and bone necrosis have been documented as a consequence of leakage of this material from the pulp chamber into the surrounding tissues. Endodontic irrigants, such as formocresol (Fig. 8-17) or sodium hypochlorite, produce similar necrosis if the material leaks into the surrounding supporting tissues or is injected past the apex, leading some to suggest chlorhexidine as a safer irrigant. Because chlorhexidine lacks the tissue-dissolving properties of sodium hypochlorite, some clinicians have suggested alternating between chlorhexidine and sodium hypochlorite. Others have warned that contact of these two compounds results in formation of a precipitate, para-chloroaniline, which is thought to be potentially toxic and carcinogenic.

The following can reduce the chances of tissue damage during irrigation with sodium hypochlorite:

- Using a rubber dam
- Avoiding excessive pressure during application
- Keeping the syringe needle away from the apex

In some countries, clinicians have used recycled anesthetic cartridges to keep solutions of sodium hypochlorite for endodontic irrigation. A number of reports have documented massive necrosis from inadvertent injection of sodium hypochlorite into soft tissue when these cartridges were mistaken for a local anesthetic.

Clinical Features

The previously discussed caustic agents produce similar damage. With short exposure, the affected mucosa exhibits a superficial white, wrinkled appearance. As the duration of exposure increases, the necrosis proceeds, and the affected epithelium becomes separated from the underlying tissue and can be desquamated easily. Removal of the necrotic epithelium reveals red, bleeding connective tissue that subsequently will be covered by a yellowish, fibrinopurulent membrane. Mucosa bound to bone is keratinized and more resistant to damage, whereas the nonkeratinized movable mucosa is destroyed more quickly. In addition to mucosal necrosis, significant tooth erosion has been seen in patients who chronically chew aspirin or hold the medication in their teeth as it dissolves.

The use of the rubber dam can dramatically reduce iatrogenic mucosal burns. When cotton rolls are used for moisture control during dental procedures, two problems may occur. On occasion, caustic materials can leak into the cotton roll and be held in place against the mucosa for an extended period, with mucosal injury resulting from the chemical absorbed by the cotton. In addition, oral mucosa can adhere to dry cotton rolls, and rapid removal of the rolls from the mouth often can cause stripping of the epithelium in the area. The latter pattern of mucosal injury has been termed **cotton roll burn (cotton roll stomatitis)** (Fig. 8-18).

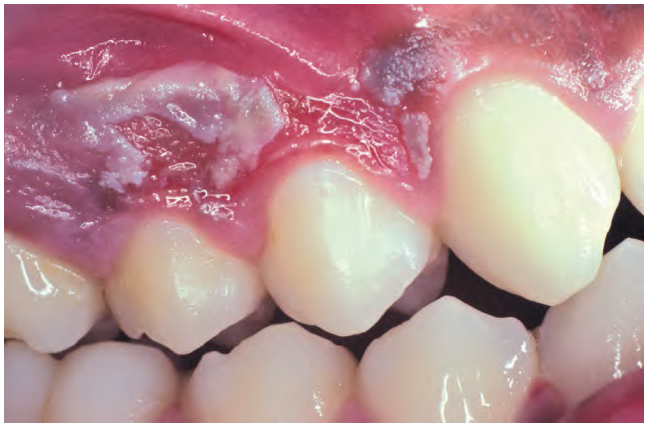


Fig. 8-18 Cotton Roll Burn. Zone of white epithelial necrosis and erythema of the maxillary alveolar mucosa.

Caustic materials injected into bone during endodontic procedures can result in significant bone necrosis, pain, and perforation into soft tissue. Necrotic surface ulceration and edema with underlying areas of soft tissue necrosis may occur adjacent to the site of perforation.

Histopathologic Features

Microscopic examination of the white slough removed from areas of mucosal chemical burns reveals coagulative necrosis of the epithelium, with only the outline of the individual epithelial cells and nuclei remaining. The necrosis begins on the surface and moves basally. The amount of epithelium affected depends on the duration of contact and the concentration of the offending agent. The underlying connective tissue contains a mixture of acute and chronic inflammatory cells.

Treatment and Prognosis

The best treatment of chemical injuries is prevention of exposure of the oral mucosa to caustic materials. When prescribing potentially caustic drugs, the clinician must instruct the patient to swallow the medication and not allow it to remain in the oral cavity for any significant length of time. Children should not use chewable aspirin immediately before bedtime, and they should rinse after use.

Superficial areas of necrosis typically resolve completely without scarring within 10 to 14 days after discontinuation of the offending agent. For temporary protection, some clinicians have recommended coverage with a protective emollient paste or a hydroxypropyl cellulose film. Topical anesthetics also may be used to provide temporary pain relief. When large areas of necrosis are present, surgical débridement and antibiotic coverage often are required to promote healing and prevent spread of the necrosis.

◆ NONINFECTIOUS ORAL COMPLICATIONS OF ANTINEOPLASTIC THERAPY

No systemic anticancer therapy currently available is able to destroy tumor cells without causing the death of at least some normal cells, and tissues with rapid turnover (e.g., oral epithelium) are especially susceptible. The mouth is a common site (and one of the most visible areas) for complications related to cancer therapy. Both radiation therapy and systemic chemotherapy may cause significant oral problems—the more potent the treatment, the greater the risk of complications.

Clinical Features

A variety of noninfectious oral complications are seen regularly as a result of both radiation and chemotherapy. Two acute changes, **mucositis** and **hemorrhage,** are

the predominant problems associated with chemotherapy, especially in cancers, such as leukemia, that involve high treatment doses.

Painful acute mucositis and dermatitis are the most frequently encountered side effects of radiation, but several chronic alterations continue to plague patients long after their courses of therapy are completed. Depending on the fields of radiation, the radiation dose, and the age of the patient, the following outcomes are possible:

- Xerostomia
- Loss of taste (hypogeusia)
- Osteoradionecrosis
- Trismus
- Chronic dermatitis
- Developmental abnormalities

Hemorrhage

Intraoral **hemorrhage** is typically secondary to thrombocytopenia, which develops from bone marrow suppression. Intestinal or hepatic damage, however, may cause lower vitamin K–dependent clotting factors, with resultant increased coagulation times. Conversely, tissue damage related to therapy may cause release of tissue thromboplastin at levels capable of producing potentially devastating disseminated intravascular coagulation (DIC). Oral petechiae and ecchymosis secondary to minor trauma are the most common presentations. Any mucosal site may be affected, but the labial mucosa, tongue, and gingiva are involved most frequently.

Mucositis

Oral mucositis has been shown to be the single most debilitating complication of high-dose chemotherapy and radiation therapy to the head and neck. In addition to significant local discomfort, the mucositis may be associated with an increased need for total parenteral nutrition, prolonged hospital stays, and most importantly, systemic bacteremia and sepsis.

Approximately 80% of patients treated with head and neck radiation develop oral mucositis, and this prevalence approaches 100% for those being treated for mouth and oropharyngeal cancers. The prevalence associated with chemotherapy is variable, depending on the regimen being used. Agents strongly associated with oral mucositis include methotrexate, 5-fluorouracil, etoposide, irinotecan, cytarabine, 6-mercaptopurine, 6-thioguanine, busulfan, melphalan, cyclophosphamide, idarubicin, doxorubicin (Adriamycin), daunorubicin, dactinomycin, bleomycin, and vinblastine. Beyond the direct effects of the antineoplastic agent, additional risk factors include young age, female sex, poor oral hygiene, oral foci of infection, poor nutrition, impaired salivary function, tobacco use, and alcohol consumption.

Cases of oral **mucositis** related to radiation or chemotherapy are similar in their clinical presentations. The manifestations of chemotherapy develop after a few days of treatment; radiation mucositis may begin to appear during the second week of therapy. Both chemotherapy and radiation-induced mucositis resolve slowly 2 to 3 weeks after cessation of treatment. Oral mucositis associated with chemotherapy typically involves the nonkeratinized surfaces (i.e., buccal mucosa, ventrolateral tongue, soft palate, and floor of the mouth), whereas radiation therapy primarily affects the mucosal surfaces within the direct portals of radiation.

The earliest manifestation is development of a whitish discoloration from a lack of sufficient desquamation of keratin. This is soon followed by loss of this layer with replacement by atrophic mucosa, which is edematous, erythematous, and friable. Subsequently, areas of ulceration develop with formation of a removable yellowish, fibrinopurulent surface membrane (Figs. 8-19 to 8-21). Pain, burning, and discomfort are significant and can be worsened by eating and oral hygiene procedures.

Dermatitis

Acute **dermatitis** of the skin in the fields of radiation is common and varies according to the intensity of the therapy. Patients with mild radiation dermatitis experience

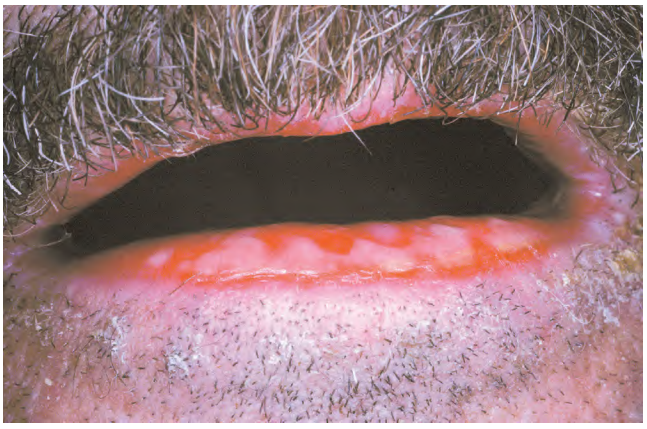


Fig. 8-19 Chemotherapy-related Epithelial Necrosis. Vermilion border of the lower lip exhibiting epithelial necrosis and ulceration in a patient receiving systemic chemotherapy.

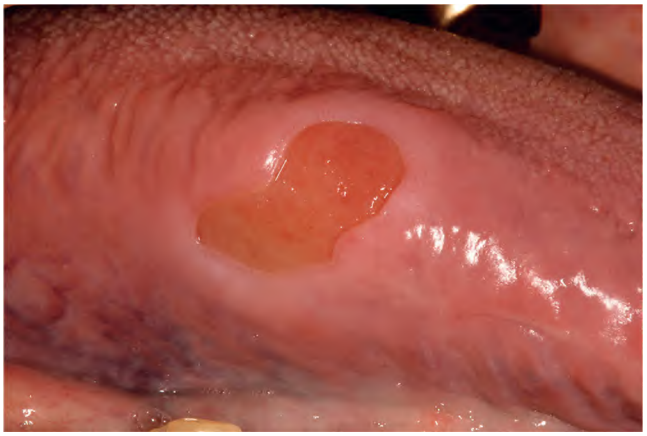
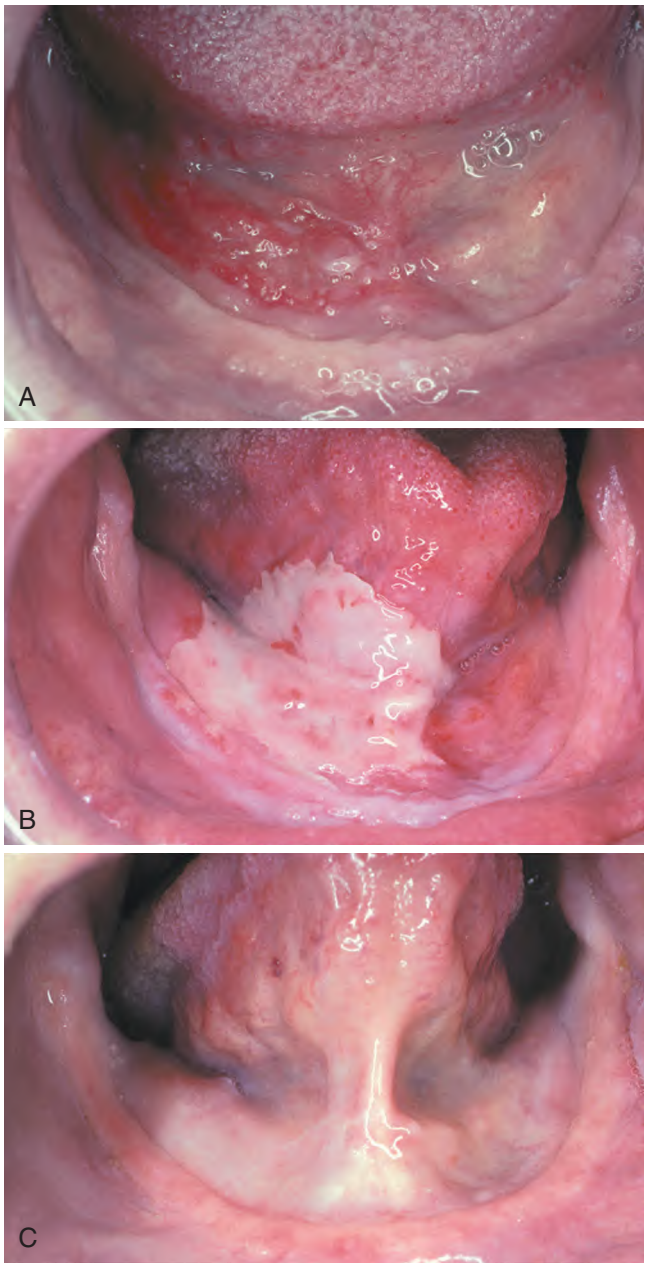
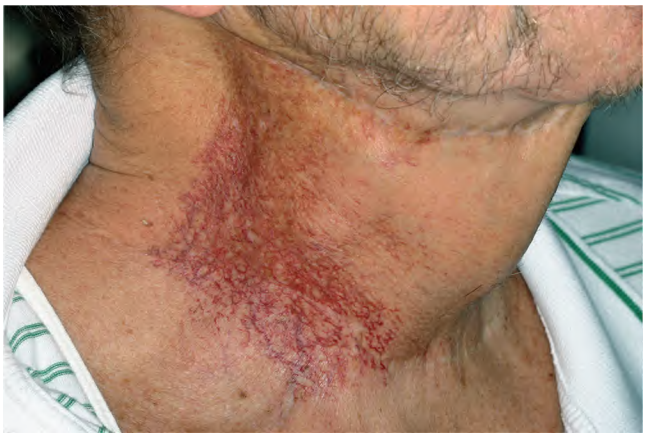


Fig. 8-20 Chemotherapy-related Ulceration. Ulceration of the right lateral border of the tongue in a patient receiving systemic chemotherapy.



• **Fig. 8-21 Radiation Mucositis. A,** Squamous cell carcinoma before radiation therapy. Granular erythroplakia of the floor of the mouth on the patient's right side. **B,** Same lesion after initiation of radiation therapy. Note the large, irregular area of epithelial necrosis and ulceration of the anterior floor of the mouth on the patient's right side. **C,** Normal oral mucosa after radiation therapy. Note resolution of the tumor and the radiation mucositis.

erythema, edema, burning, and pruritus. This condition resolves in 2 to 3 weeks after therapy and is replaced by hyperpigmentation and variable hair loss. Moderate radiation causes erythema and edema in combination with erosions and ulcerations. Within 3 months these alterations resolve, and permanent hair loss, hyperpigmentation, and scarring may ensue. Necrosis and deep ulcerations can occur in severe acute reactions. Radiation dermatitis also may become chronic and be characterized by dry, smooth, shiny, atrophic, necrotic, telangiectatic, depilated, or ulcerated areas (Fig. 8-22).



• **Fig. 8-22 Radiation Dermatitis.** Cutaneous atrophy and telangiectasia secondary to radiation therapy. (Courtesy of Dr. Terry Day.)

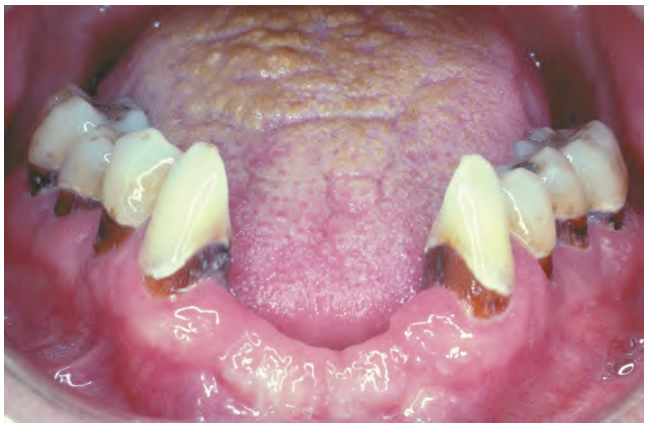
Xerostomia

Salivary glands are very sensitive to radiation, and **xerostomia** is a common complication. When a portion of the salivary glands is included in the fields of radiation, the remaining glands undergo compensatory hyperplasia in an attempt to maintain function. The changes begin within 1 week of initiation of radiation therapy, with a dramatic decrease in salivary flow noted during the first 6 weeks of treatment. Even further decreases may be noted for up to 3 years.

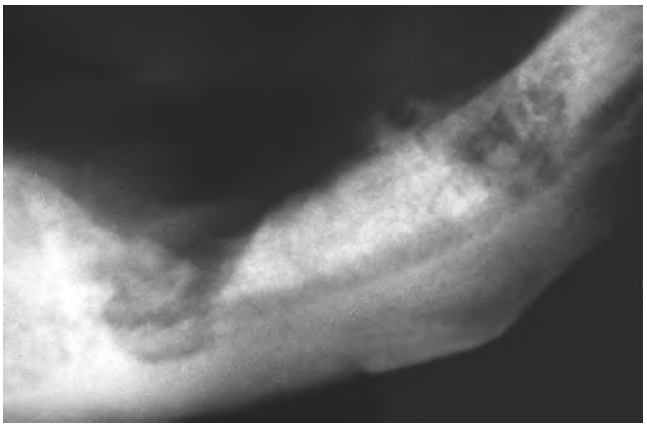
Serous glands exhibit an increased radiosensitivity when compared with the mucous glands. On significant exposure, the parotid glands are affected dramatically and irreversibly. In contrast, the mucous glands partially recover and, over several months, may achieve flow that approaches 50% of preradiation levels. In addition to the discomfort of a mouth that lacks proper lubrication, diminished flow of saliva leads to a significant decrease of the bactericidal action and self-cleansing properties of saliva.

Without intervention, patients often develop symptomatic dry mouth that affects their ability to eat comfortably, wear dentures, speak, and sleep. In addition, there often is an increase in the caries index **(xerostomia-related caries),** regardless of the patient's past caries history (Fig. 8-23). The decay is predominantly cervical in location and secondary to xerostomia (not a direct effect of the radiation).

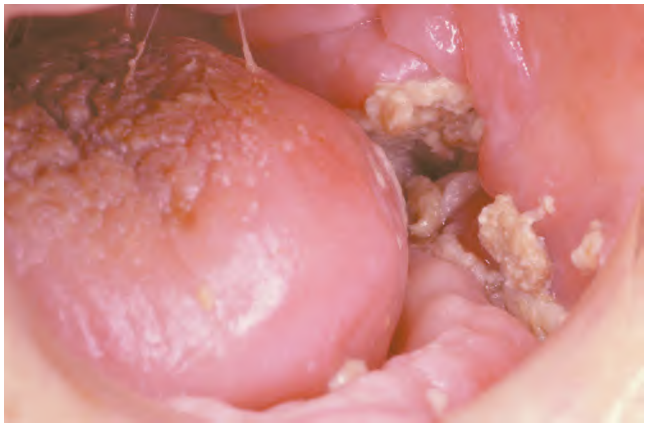
Several interventions to reduce radiation-related xerostomia have demonstrated promise. Intensity-modulated radiation therapy (IMRT) appears to be more gland-sparing than conventional radiation therapy and is emerging as the standard of care for head and neck cancer. Amifostine is a cytoprotective agent that has been shown to reduce the severity and duration of xerostomia in patients receiving radiotherapy (but not chemoradiotherapy) for head and neck cancer. On the downside, this medication has significant side effects, and there are lingering concerns related to possible tumor protective effects. Surgical transfer of a single submandibular



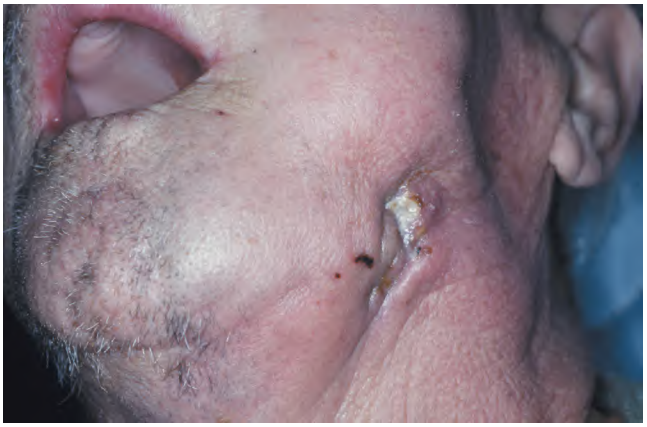
• **Fig. 8-23 Xerostomia-related Caries.** Extensive cervical caries of mandibular dentition secondary to radiation-related xerostomia.



• **Fig. 8-25 Osteoradionecrosis (ORN).** Multiple ill-defined areas of radiolucency and radiopacity of the mandibular body.



• **Fig. 8-24 Osteoradionecrosis (ORN).** Ulceration overlying left body of the mandible with exposure and sequestration of superficial alveolar bone.



• **Fig. 8-26 Osteoradionecrosis (ORN).** Same patient as depicted in Fig. 8-25. Note fistula formation of the left submandibular area resulting from ORN of the mandibular body.

salivary gland outside of the radiation field to the submental space has proven successful in selected patients.

Loss of Taste

In patients who receive significant radiation to the oral cavity, a substantial loss of all four tastes **(hypogeusia)** often develops within several weeks. Although these tastes return within 4 months for most patients, some patients are left with permanent hypogeusia; others may have persistent **dysgeusia** (altered sense of taste) (see page 809).

Osteoradionecrosis

Osteoradionecrosis (ORN) is defined as exposed nonvital irradiated bone that persists longer than 3 months in the absence of local neoplastic disease. It represents one of the most serious complications of radiation to the head and neck. In earlier studies, the prevalence approached 15%, but the risk has been reduced to less than 5% secondary to modern therapeutic advances such as IMRT and three-dimensional conformal radiation therapy (3DCRT). These newer techniques have the ability to maintain therapeutic effectiveness but decrease the total maximum radiation to the jaw bones. Most cases of ORN occur in patients who have received greater than 60 Gy, with the majority of cases occurring between 4 months and 3 years after completion of radiation therapy.

Although most instances of ORN arise secondary to local trauma (such as, tooth extraction), a minority appear spontaneous. Most spontaneous cases arise within the first few years, but patients remain at risk for trauma-induced ORN for the remainder of their lives. The mandible is involved 24 times more frequently than the maxilla (Fig. 8-24), and the process is three times more common in dentate patients. Affected areas of bone reveal ill-defined areas of radiolucency that may develop zones of relative radiopacity as the dead bone separates from the residual vital areas (Fig. 8-25). Intractable pain, cortical perforation, fistula formation, surface ulceration, and pathologic fracture may be present (Fig. 8-26).

The radiation dose is the main factor associated with bone necrosis, although the proximity of the tumor to bone, the presence of remaining dentition, and the type of treatment also exert an effect. Additional factors associated with an increased prevalence include older age, male sex, poor health or nutritional status, and continued use of tobacco or alcohol.

Prevention of bone necrosis is the best course of action. Before therapy, all unrestorable teeth and those with advanced periodontal disease should be extracted, all oral foci of infection should be eliminated, and excellent oral hygiene should be initiated and maintained. A healing time of at least 3 weeks between extensive dental procedures and the initiation of radiotherapy significantly decreases the chance of bone necrosis. Extraction of teeth or any bone trauma is strongly contraindicated during radiation therapy. Following radiation, there is a 4-month window of time during which dental extractions can be performed with a reduced prevalence of ORN. During this time, tissue repair and healing are relatively normal, but eventually progressive fibrosis and hypovascularity develop and predispose the patient to ORN.

If extractions are mandatory, several investigators believe pentoxifylline and tocopherol initiated prior to the procedure may reduce the prevalence of ORN. If necrosis develops, continuation of these medications is recommended with the addition of clodronate, a first-generation bisphosphonate thought to stimulate osteoblasts and new bone formation.

Trismus

Trismus may develop and can produce extensive difficulties concerning access for hygiene and dental treatment. Tonic muscle spasms with or without fibrosis of the muscles of mastication and the temporomandibular joint (TMJ) capsule can cause difficulties in jaw opening. When these structures are radiated heavily, jaw-opening exercises may help to decrease or prevent problems.

Developmental Abnormalities

Antineoplastic therapy during childhood can affect growth and development. The changes vary according to the age at treatment and the type and severity of therapy. Radiation can alter the facial bones and result in micrognathia, retrognathia, or malocclusion. Developing teeth are very sensitive and can exhibit a number of changes, such as root dwarfism, blunting of roots, dilaceration of roots, incomplete calcification, premature closure of pulp canals in deciduous teeth, enlarged canals in permanent teeth, microdontia, and hypodontia (see page 52).

Treatment and Prognosis

Optimal treatment planning involves the oral health practitioner before initiation of antineoplastic therapy. Elimination of all current or potential oral foci of infection is paramount, along with patient education about maintaining ultimate oral hygiene. Proper nutrition, cessation of tobacco use, and alcohol abstinence minimize oral complications. Once cancer therapy is initiated, efforts must be directed toward relieving pain, preventing dehydration, maintaining adequate nutrition, eliminating foci of infection, and ensuring continued appropriate oral hygiene.

Mucositis

Interventions can attempt to prevent mucositis or treat the damage once it occurs. Cryotherapy (placement of ice chips in the mouth 5 minutes before chemotherapy and continued for 30 minutes) has been shown to reduce significantly the prevalence and severity of oral mucositis secondary to bolus injection of chemotherapeutic drugs with a short half-life. It has been suggested that the cold may produce local vasoconstriction leading to reduced exposure of the oral mucosa to the chemotherapeutic medications. Cryotherapy has no effect on the prevalence or severity of radiation mucositis.

Intravenous recombinant human keratinocyte growth factor (palifermin) given 3 days prior to the initiation of chemotherapy has been shown in clinical studies to demonstrate a statistically significant reduction in the severity of oral mucositis. Concern remains that this epithelial growth factor may promote growth of tumor cells in patients with carcinoma, and most clinicians are limiting its use to sarcomas and hematologic malignancies.

One of the more effective mechanisms to reduce radiation-associated mucositis has been placement of midline radiation blocks or use of three-dimensional radiation treatment to limit the volume of irradiated mucosa. In addition, cotton rolls or custom splints have been used to cover metallic dental restorations to prevent localized enhanced scatter effect of the radiation. Other interventions to reduce the severity of mucositis with lesser evidence of benefit include aloe vera, allopurinol, amifostine, benzydamine, honey, intravenous glutamine, and antibiotic lozenges containing polymyxin/tobramycin/amphotericin.

Once present, the lesions are difficult to manage, and a large number of treatments (such as, anesthetic, analgesic, antimicrobial, and coating agents) have been tried with mixed reviews. Low-level laser irradiation, light-emitting diode (LED) phototherapy, and coating with sucralfate represent current interventions to reduce the severity of active mucositis. Palliative therapies include salt and soda rinse, viscous lidocaine, and "magic mouthwash" (lidocaine, diphenhydramine, and kaolin or milk of magnesia). When all treatments fail, the standard of care for the severe pain associated with oral mucositis remains intravenous morphine.

Xerostomia

Xerostomic patients should be counseled to avoid all agents that may decrease salivation, especially the use of tobacco products and alcohol. To combat xerostomia-related caries, a regimen of daily topical fluoride (1.1% neutral sodium fluoride) application should be instituted.

The problem of chronic xerostomia has been approached through the use of salivary substitutes and sialagogues. Use of liquids with a low pH or significant sugar content should be avoided as a mouth moistener. Because the mucous glands often demonstrate significant recovery after radiation, the sialagogues show promise because they stimulate the residual functional glands. Moisturizing gels and

sprays, sugar-free candies, chewing gum, and various artificial salivary substitutes are available. Gums and mints containing xylitol have an added benefit of inhibition of cariogenic bacteria. Many salivary substitutes are expensive and of short duration, with patients often alternatively choosing frequent use of water. In these cases, use of unfiltered fluoridated tap water is recommended over bottled water that may not contain sufficient fluoride. In controlled clinical studies, some of the most effective and longer-lasting products are one of the systemic sialogogues, such as pilocarpine, cevimeline, bethanechol, carbocholine, or anetholtrithione. Of these, the most widely used are pilocarpine and cevimeline. Although these drugs may be beneficial for many patients, they are contraindicated in patients with asthma, gastrointestinal ulcerations, labile hypertension, glaucoma, chronic obstructive pulmonary disease, and significant cardiovascular disease. Adverse reactions are uncommon but include excess sweating, rhinitis, headache, nausea, uropoiesis, flatulence, and circulatory disorders. Bethanechol also appears effective, is not contraindicated in patients with asthma and narrow angle glaucoma, and has been associated with fewer side effects than pilocarpine.

Loss of Taste

Although the taste buds often regenerate within 4 months after radiation therapy, the degree of long-term impairment is highly variable. In those with continuing symptoms, zinc sulfate supplements greater than the usual recommended daily doses may be beneficial.

Osteoradionecrosis

Although prevention must be stressed, cases of ORN do occur. Use of hyperbaric oxygen has numerous contraindications and possible adverse reactions. Because of the newer theories of pathogenesis for ORN, most clinicians are less inclined to use hyperbaric oxygen in extensive cases that involve large segments of the jawbone. Some clinicians have begun use of ultrasound in place of hyperbaric oxygen due to its low adverse reaction profile and its ability to stimulate tissue regeneration and angiogenesis. Therapy consists of antibiotics, débridement, irrigation, and removal of diseased bone. In extensive cases, this often involves extensive resection and immediate reconstruction. The amount of bone removed is determined by clinical judgment, with the surgery extended until brightly bleeding edges are seen.

◆ MEDICATION-RELATED OSTEONECROSIS OF THE JAW (BISPHOSPHONATE-RELATED OSTEONECROSIS; ANTIRESORPTIVE-RELATED OSTEONECROSIS)

In 2003, a pattern of gnathic osteonecrosis began to be recognized, which was difficult to treat and appeared to be associated with certain medications. This process was correlated initially to bisphosphonates, leading to the name **bisphosphonate-related osteonecrosis of the jaw (BRONJ).** In the 2011 position paper of the American Dental Association (ADA), the name was modified to **antiresorptive-related osteonecrosis of the jaw (ARONJ)** due to the discovery of an association with a monoclonal antibody designed to prevent osteoclastic maturation (denosumab). Subsequently, the 2014 position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) changed the name again to **medication-related osteonecrosis of the jaw (MRONJ)** due to the discovery that antiangiogenic therapies also may be implicated (Box 8-1). This last term is sufficiently generic and hopefully will stand the test of time.

• BOX 8-1 Medication-Related Osteonecrosis of the Jaw Case Definition

Required characteristics for diagnosis of medication-related osteonecrosis of the jaw (MRONJ):
- Current or previous treatment with antiresorptive or antiangiogenic agent
- Exposed bone in maxillofacial region for longer than 8 weeks
- No history of radiation therapy or obvious metastatic disease to the jaws

• BOX 8-2 Antiangiogenic Agents

Tyrosine kinase inhibitors:
- Sunitinib (Sutent)
- Sorafenib (NexAVAR)

Monoclonal antibody inhibiting vascular endothelial growth factor:
- Bevacizumab (Avastin)

The antiangiogenic agents are prescribed for a variety of cancers and include tyrosine kinase inhibitors and monoclonal antibodies directed against vascular endothelial growth factor (Box 8-2). The evidence supporting an association with osteonecrosis is based primarily on case reports, but a low risk does appear to exist. This risk is increased if these agents are combined with bisphosphonates. Currently, little research exists on the association between these agents and gnathic osteonecrosis.

Currently, the medications most strongly associated with gnathic osteonecrosis include the aminobisphosphonates (nitrogen-containing bisphosphonates) and denosumab (Box 8-3). These antiresorptive medications are used primarily to treat patients with osteoporosis or various cancers that involve bone (predominantly multiple myeloma, breast carcinoma, and prostate carcinoma). Less frequent uses include treatment for Paget disease, osteogenesis imperfecta, rheumatoid arthritis, and giant cell tumors of bone. The vast majority of osteonecrosis cases occur in patients receiving the medication as part of their therapy for cancer.

Once in the serum, 50% of bisphosphonates is cleared rapidly by the kidneys with the remainder going to bone.

• BOX 8-3 Antiresorptive Agents

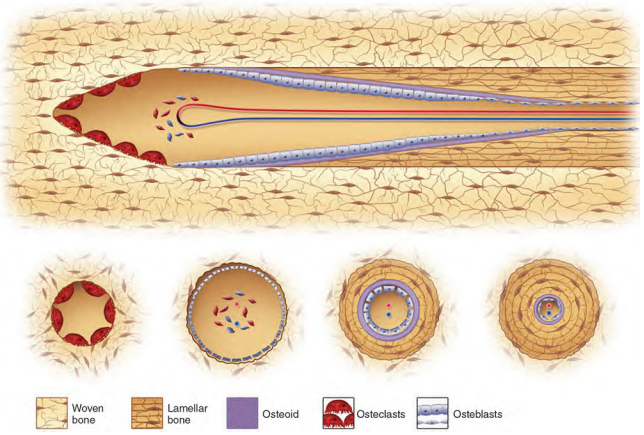
Aminobisphosphonate antineoplastics:
- Pamidronate disodium (Aredia)
  - Relative potency of 100
  - IV infusion every 4 weeks
- Ibandronate sodium (Boniva)
  - Relative potency of 10,000
  - IV infusion every 4 weeks
- Zoledronic acid (Zometa)
  - Relative potency of 100,000
  - IV infusion every 4 weeks

Denosumab antineoplastic:
- Denosumab (Xgeva)
  - Injection every 4 weeks

Aminobisphosphonates for osteoporosis:
- Risedronate sodium (Actonel)
  - Relative potency of 5,000
  - PO weekly
- Delayed release risedronate sodium (Atelvia)
  - Relative potency of 5,000
  - PO weekly
- Ibandronate sodium (Boniva)
  - Relative potency of 10,000
  - PO monthly
  - IV infusion every 3 months
- Alendronate sodium (Fosamax)
  - Relative potency of 1,000
  - PO weekly
- Zoledronic acid (Reclast)
  - Relative potency of 100,000
  - IV annually

Denosumab for osteoporosis:
- Denosumab (Prolia)
  - Injection every 6 months

IV, Intravenous; *PO,* per os (by mouth).



• Fig. 8-27 Basic Multicellular Unit (BMU). Organized synergy of osteoclasts, osteoblasts, and vasculature working together to transform immature woven bone into structural sound lamellar bone.

The medications are not distributed evenly throughout the skeleton. Osteocytes represent 85% of the cells associated with bone and do not retain the medication. In contrast, osteoclasts demonstrate an affinity eight times greater than osteocytes, but they release the drug for recycling at the end of their short 2-week life span. Osteoblasts exhibit four times the affinity of osteocytes and incorporate the medication into the bone matrix. Due to a half-life longer than 10 years, deposits of bisphosphonates have the ability to remain in place for over four decades. The effect of the medication on the bone varies with concentration. At low concentrations, the medication diminishes the ability of osteoclasts to resorb and degrade bone matrix, whereas high local concentration induces osteoclastic apoptosis. Therefore, bisphosphonates are selectively concentrated into areas of bone repair and remodeling, with potential effects over the patient's lifetime. In addition, the impact on the bone worsens as the local concentration is increased.

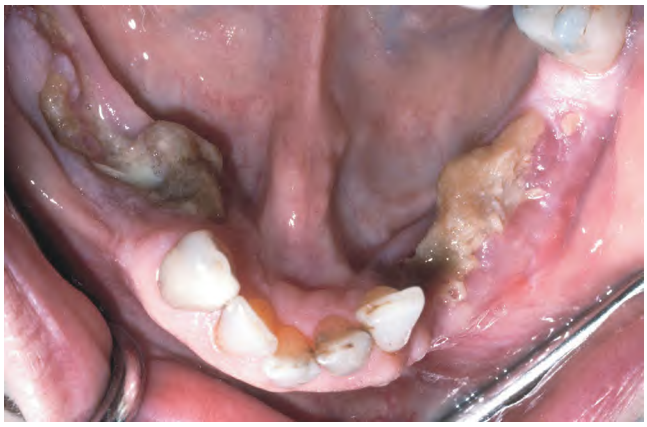
Denosumab is a monoclonal antibody that also reduces osteoclastic function, but it does this by inhibiting osteoclastic differentiation. Due to the short life span of osteoclasts, this medication quickly reduces osteoclastic activity by 85% with maximal reduction occurring within 1 month of an injection. The medication is not deposited in bone and has a half-life of 24.5 days, with complete clearance in 4 to 5 months.

Any discussion of antiresorptive agents also must include information on bone healing. When a traumatic event such as an extraction occurs, the initial clot is replaced with granulation tissue and eventually woven bone. The remodeling period of this immature bone into structurally sound lamellar bone typically is 4 months but can range from 2 to 8 months. The final remodeling is performed by an organized synergism of osteoclasts, osteoblasts, and the local vascular supply, which work together in a cell packet known as the basic multicellular unit (BMU). This is a moving structure that requires continual replacement of participating cells at exactly the correct time and place in an ever-changing position. The osteoclasts are critical cells of the BMU and are largely responsible for the signaling necessary for the participation of the other cellular components (Fig. 8-27). Functional impairment or loss of the osteoclasts by antiresorptive drugs disrupts not only resorption but also new lamellar bone deposition and angiogenesis.

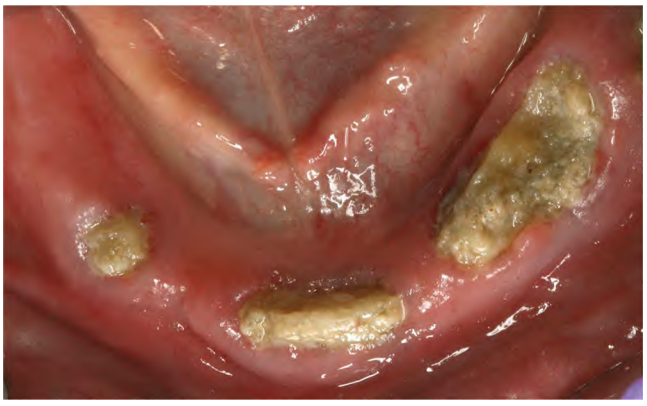
Although the vast majority of osteonecrosis cases have occurred in the jaws, problems are beginning to surface elsewhere in the skeleton. Osteonecrosis of the ear has been documented following removal of an exostosis. More significantly, numerous orthopedic surgeons have reported an increased prevalence of subtrochanteric or femoral shaft fractures associated with aminobisphosphonates, leading the US Food and Drug Administration (FDA) to add this complication to the drug information.

Clinical and Radiographic Features

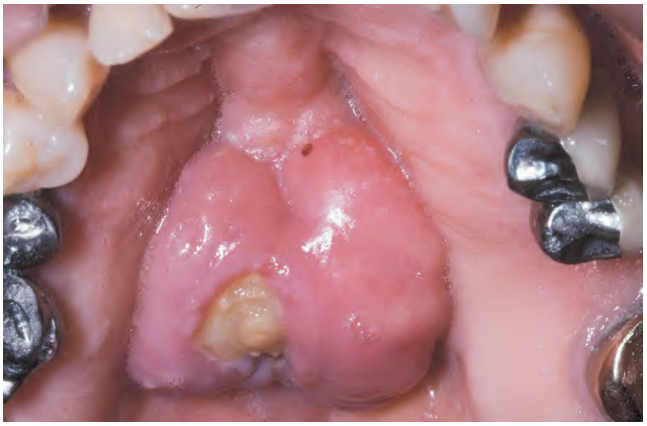
In an excellent comprehensive review of 2,408 reported cases of BRONJ, 89% were discovered in patients who were treated with the IV formulations (primarily pamidronate and



• **Fig. 8-28 Medication-related Osteonecrosis.** Bilateral necrotic exposed bone of the mandible in a patient receiving zoledronic acid for metastatic breast cancer. (Courtesy of Dr. Brent Mortenson.)



• **Fig. 8-29 Medication-related Osteonecrosis.** Multifocal areas of exposed necrotic bone of the mandible in a patient receiving zoledronic acid for cancer.



• **Fig. 8-30 Medication-related Osteonecrosis.** Lobulated palatal torus with an area of exposed necrotic bone in a patient taking alendronate for osteoporosis.

zoledronic acid) for cancer, with 43% being reported in patients with multiple myeloma. In another summary review, the prevalence of osteonecrosis associated with the IV formulations in cancer patients has been estimated to be 100 cases per 10,000 patients. Unfortunately all of the information now available is based on reported cases, and such reports frequently have inherent biases. Randomized prospective trials with appropriate controls will be necessary to obtain reliable data with respect to prevalence and management.

Osteonecrosis related to use of aminobisphosphonates for osteoporosis is most uncommon. A conservative estimate by the drug industry suggested an annual incidence of 0.7 per 100,000, but a more recent review suggested a single case occurs per 10,000 patients (100 times less frequent than that seen in cancer patients treated with antiresorptive medications). However, appropriate prospective trials for the true frequency of this complication have yet to be performed. Additional risk factors for MRONJ include advanced patient age (older than 65 years), corticosteroid use, use of chemotherapy drugs, diabetes, smoking or alcohol use, poor oral hygiene, and duration of drug use exceeding 3 years. A predictive test for those at risk for bisphosphonate osteonecrosis has not been confirmed. Some investigators have suggested use of a serum marker for bone turnover, serum C-telopeptide (CTX), but the test has demonstrated insufficient reliability and accuracy in predicting the risk of developing of MRONJ.

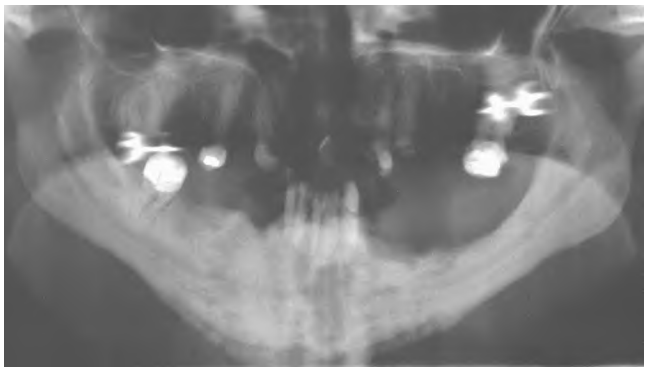
In the previously mentioned comprehensive review, the mandible was involved in 65%, the maxilla in 27%, and both jaws in 8% (Fig. 8-28). In 67% of these patients, the necrosis followed a dental extraction, with another 26% arising spontaneously, and 7% associated with a variety of triggers such as denture pressure or minor trauma of a torus (Figs. 8-29 and 8-30). In patients with exposed bone, 16% were asymptomatic, 66% were painful, and another 18% demonstrated extensive involvement in which the associated pain was not responsive to antibiotics.

Research related to denosumab-associated osteonecrosis is in its infancy when compared to BRONJ, but reviews of cancer patients randomized to zoledronic acid or denosumab have demonstrated a similar frequency of osteonecrosis with these two medications. The frequency of MRONJ appears to range from 70 to 90 cases per 10,000 cancer patients receiving denosumab.

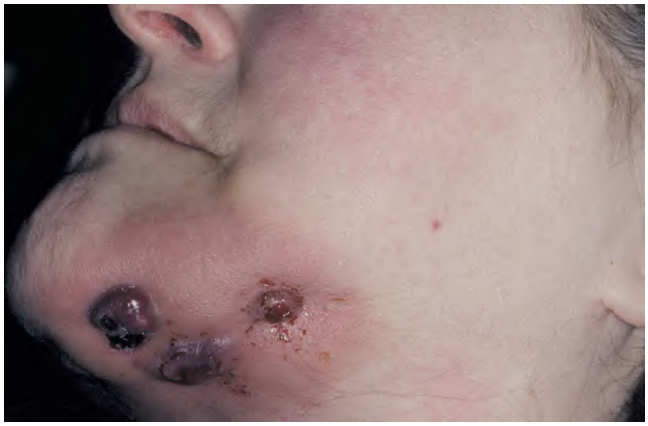
Investigators have suggested that bone at imminent risk for osteonecrosis often will demonstrate increased radiopacity before clinical evidence of frank necrosis. These changes typically occur predominantly in areas of increased bone remodeling, such as the alveolar ridges. Panoramic radiographs often will reveal a marked radiodensity of the crestal portions of each jaw, with a more normal appearance of the bone away from tooth-bearing portions. Periosteal hyperplasia also is not rare. In more severe cases, the osteonecrosis creates a moth-eaten and ill-defined radiolucency with or without central radiopaque sequestra (Fig. 8-31). In some cases the necrosis can lead to development of a cutaneous sinus or pathologic fracture (Fig. 8-32).

Histopathologic Features

Biopsy of vital bone altered by aminobisphosphonates is not common. In such cases, the specimen often reveals irregular



• **Fig. 8-31 Medication-related Osteonecrosis.** Panoramic radiograph of patient depicted in Fig. 8-28. Note sclerosis of tooth-bearing areas along with multiple radiolucencies and periosteal hyperplasia of the lower border of the mandible. (Courtesy of Dr. Brent Mortenson.)

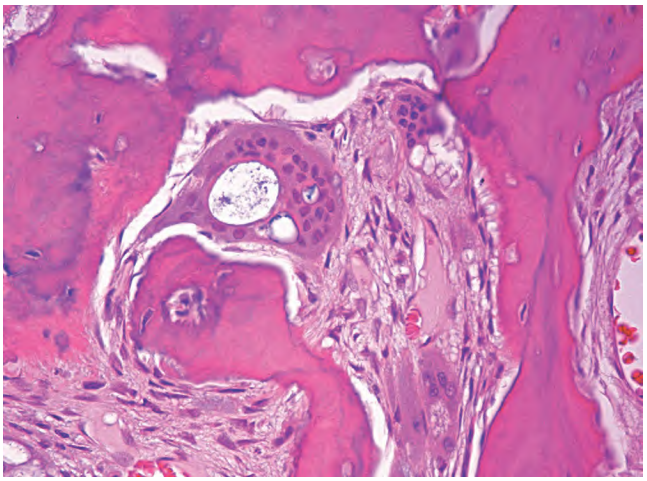


• **Fig. 8-32 Medication-related Osteonecrosis.** Patient with multiple cutaneous sinuses associated with extensive necrosis of the left side of the mandible. The patient was taking zoledronic acid for multiple myeloma. (Courtesy of Dr. Molly Rosebush.)

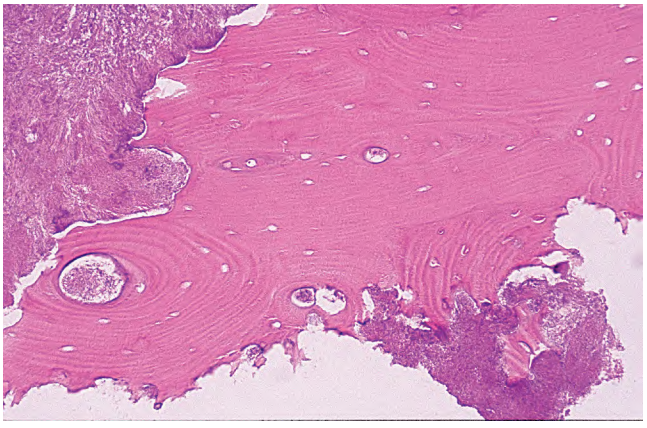
trabeculae of pagetoid bone, with adjacent enlarged and irregular osteoclasts that often demonstrate numerous intracytoplasmic vacuoles (Fig. 8-33). Specimens of active areas of MRONJ reveal trabeculae of sclerotic lamellar bone, which demonstrate loss of the osteocytes from their lacunae and frequent peripheral resorption with bacterial colonization (Fig. 8-34). Although the peripheral bacterial colonies often resemble actinomycetes, the infestation is not supportive of a diagnosis of invasive cervicofacial actinomycosis.

Treatment and Prognosis

Virtually all recommendations regarding management of patients who are taking or have been exposed to antiresorptive agents are empirical. No large, randomized, controlled studies have been done with respect to prevention or treatment of the complications of this therapy. The best therapeutic approach to MRONJ is prevention. In cancer patients evaluated before initiation of bisphosphonate therapy, the goal is to improve dental health to prevent future procedures that disrupt bone; this includes



• **Fig. 8-33 Medication-related Osseous Changes.** Pagetoid bone exhibiting enlarged, irregular osteoclasts that contain numerous intracytoplasmic vacuoles. (Courtesy of Dr. Don Cohen.)



• **Fig. 8-34 Medication-related Osteonecrosis.** Sclerotic lamellar bone exhibiting loss of the osteocytes from their lacunae and peripheral resorption with bacterial colonization.

elimination of oral foci of infection and removal of large tori or partially impacted teeth. If only noninvasive oral care is indicated, then the initiation of the medication need not be delayed. If surgical procedures need to be performed, then a month-long delay in initiation of the medication is recommended, along with prophylactic antibiotic therapy.

For cancer patients actively being treated with antiresorptive therapy, manipulation of bone should be avoided if possible. Conventional endodontics is a better option than extraction. If a nonvital tooth is not restorable, then endodontics should be performed and followed by crown amputation. Teeth with 1+ or 2+ mobility should be splinted; those with 3+ mobility can be extracted.

Despite the desire to avoid jaw surgery during IV therapy, occasional clinical situations may make surgical intervention unavoidable. Several investigators have suggested that the likelihood of osteonecrosis can be minimized by antibiotic prophylaxis starting 1 day prior and extending 3 days after any invasive dental procedure.

For patients with MRONJ, the primary goal of therapy is to minimize pain. Aggressive removal of dead bone typically results in further bone necrosis, and hyperbaric oxygen has not been significantly beneficial. Asymptomatic patients should rinse daily with chlorhexidine and be monitored closely. Any rough edges of exposed bone should be smoothed and loose sequestra can be removed carefully. If the exposed bone irritates adjacent tissues, then coverage with a soft splint may provide some relief. In symptomatic patients, systemic antibiotic therapy and chlorhexidine usually reduce discomfort. If the antibiotics fail to stop the pain, then hospitalization with IV antibiotic therapy can be considered. In recalcitrant cases, the bulk of the dead bone is reduced surgically, followed by administration of systemic antibiotics. Because of the long half-life of bisphosphonates, discontinuation of the drug offers no short-term benefit. In isolated anecdotal reports of recalcitrant cases, discontinuation of the medication for 6 to 12 months occasionally has been associated with spontaneous sequestration and resolution.

Prevention also represents the best approach for patients taking antiresorptive medications for osteoporosis. In the original ADA position paper, a 3-month drug holiday before and after osseous surgery was suggested for any patient using bisphosphonates longer than 3 years. In the 2011 update, the ADA removed this suggestion due to the fear of increasing the skeletally related risks of low bone mass during the drug-free period. In spite of this, the 2014 AAOMS update recommended use of a drug holiday for patients using bisphosphonates longer than 4 years or patients who also are utilizing systemic corticosteroids or antiangiogenic agents.

A possible alternative to minimize the risk of osteonecrosis without a drug holiday has been proposed. As previously mentioned, bisphosphonates concentrate in healing or remodeling bone. Once deposited, the medications remain for decades. As the concentration increases, the impact on the bone worsens. The best method to avoid osteonecrosis is to minimize the osseous deposition of bisphosphonates by ensuring the serum is free of the medication at the time of a surgical procedure and for the subsequent healing period. This can be accomplished by suggesting use of annual IV administration of zoledronic acid and timing all surgical procedures to occur 2 months after the annual infusion. At this time, the serum will be essentially free of bisphosphonate with an additional 10 months of healing time prior to the next infusion. Alternatively, biannual injections with denosumab could be substituted for bisphosphonate therapy with any surgical procedure planned to occur 2 months after an injection (at which time 79.9% of the medication would be degraded) with 4 months of healing time prior to the next injection. The worst approach would be to ignore totally the dates of drug administration. Surgery occurring close to the time of bisphosphonate infusion or denosumab injection would maximize the adverse effects on healing and future bone health. Due to the frequent administration pattern of the oral bisphosphonates, none of these medications can be utilized in a manner that would prevent concentration of the drug into surgical sites.

For patients with osteoporosis, all restorative, prosthodontic, conventional endodontic, and routine periodontic procedures can be implemented as needed. Although orthodontic treatment is not contraindicated, progress should be evaluated after 2 to 3 months of active therapy. At that point, therapy can proceed if the tooth movement is occurring predictably with normal forces. Invasive orthodontic techniques such as orthognathic surgery, four-tooth extraction cases, and miniscrew anchorage should be avoided, if possible.

When an osseous procedure is considered, the patient should be advised of the potential complications of antiresorptive use and the risk of MRONJ. Written informed consent and documentation of a discussion of the benefits, risks, and alternative therapies are highly advised.

Osteonecrosis associated with antiresorptive therapy for osteoporosis tends to be less extensive and more responsive to conservative therapy when compared to MRONJ in cancer patients. When the antiresorptive therapy can be discontinued, many cases of MRONJ resolve without surgical intervention. This spontaneous resolution occurs slowly over many months, but reports have documented greatly reduced healing times secondary to administration of teriparatide (recombinant human parathyroid hormone).

The clinical approach to patients treated with antiresorptive medications varies according to the formulation of the drug, the disease being treated, and the duration of drug use. All patients who take these medications should be warned of the risks and instructed to obtain and maintain ultimate oral hygiene. The oral bisphosphonates are extremely caustic; patients should be warned to minimize oral mucosal contact and ensure the medication is swallowed completely.

Overall, the benefits of antiresorptive therapy for osteoporosis and metastatic cancer appear to greatly outweigh the risk of developing MRONJ. No patient should discontinue his or her medication against medical advice. An osteoporotic hip fracture is a life-altering event, with 75% of patients never fully recovering and a mortality rate of 20% in women and 30% in men. The antiresorptive medications reduce hip fractures by approximately 50%. A similar success has been seen in cancer patients where antiresorptive medications are associated with a significant reduction in skeletal-related adverse events.

In spite of the obvious benefits of antiresorptive drugs, increased bone density does not correlate necessarily to good bone quality. The negative effects of oversuppression of bone metabolism must be considered. Reports are continuing to document spontaneous nontraumatic stress fractures with associated delayed healing in patients on long-term antiresorptive therapy for osteoporosis. Many physicians now believe that such therapy should be stopped after 5 years. Patients no longer osteoporotic could be removed from active therapy until bone density studies confirm redevelopment of significant osteoporosis. For

those with continuing osteoporosis, alternatives such as teriparatide or raloxifene could be considered.

◆ OROFACIAL COMPLICATIONS OF DRUG ABUSE

Over the last decade, numerous reports have described significant oral manifestations of drug abuse, most commonly the illegal stimulants cocaine and methamphetamine.

After marijuana, cocaine represents one of the more commonly utilized illicit drugs with 1.4 million active (past month) users in the United States during 2011. Cocaine can be ingested by snorting, injecting, or smoking as free base or crack cocaine. The drug is known by nicknames that include *blow, bump, C, candy, Charlie, coke, crack, flake, rock, snow,* and *toot.* Snorting is the main method of administration due to the associated euphoric high that lasts from 20 to 90 minutes. When snorted, cocaine is associated with a sympathetic-mediated vasoconstriction that can be associated with significant local ischemia combined with inflammation and ulceration secondary to the adulterants utilized to "cut" the cocaine.

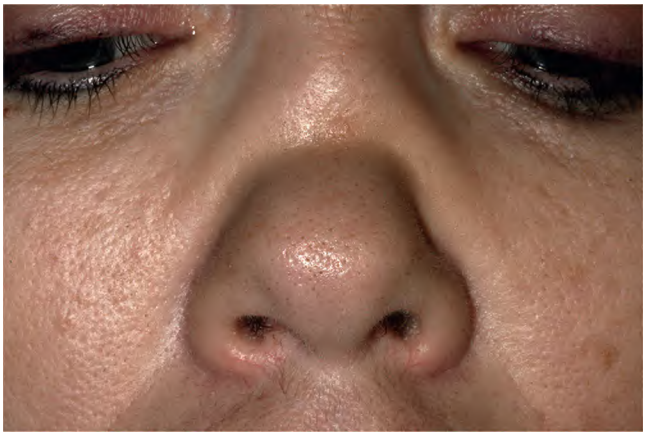
Methamphetamine is a drug with stimulant effects on the central nervous system (CNS). In 1937, the drug was approved in the United States for the treatment of narcolepsy and attention deficit hyperactivity disorder. Within a few years, many began to use the drug to increase alertness, control weight, and combat depression. Because methamphetamine users perceive increased physical ability, greater energy, and euphoria, illegal use and manufacture of the drug began to develop. Because of greater control over the main ingredient, pseudoephedrine, production of homemade methamphetamine is decreasing but often being replaced by illegal importation of the finished product. Although illicit use of methamphetamine dropped in 2011 to 439,000 active users, the drug remains a serious problem in many areas of the nation. The drug is a powdered crystal that dissolves easily in liquid and can be smoked, snorted, injected, or taken orally. The drug is known by nicknames that include *chalk*, *crank*, *crystal*, *fire*, *glass*, *go fast*, *ice*, *meth,* and *speed.*

Clinical Features

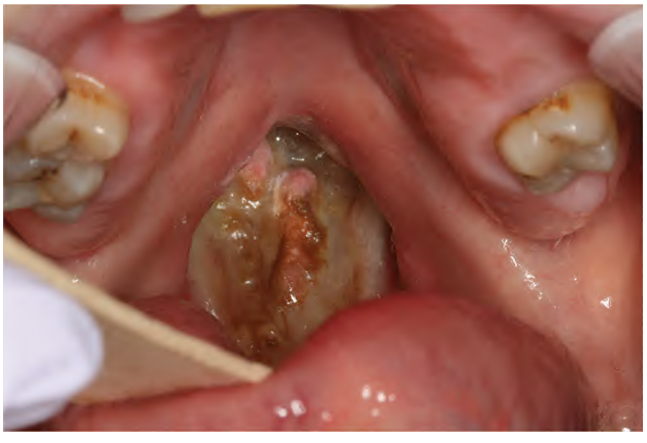
As mentioned, cocaine creates a feeling of euphoria and arousal. Other less desirable symptoms include aggressive behavior, blurred vision, dilated pupils, delirium, dizziness, light-headedness, restlessness, tinnitus, tremors, shivering, insomnia, and vomiting. Physical signs include tachycardia, tachypnea, hypertension, and hyperthermia. The sympathomimetic effects increase the oxygen demands of the myocardium, and the vasoconstrictive effects reduce oxygen delivery by the coronary arteries. This combination may trigger angina, myocardial infarction, or heart dysrhythmias.

One of the more common local complications to cocaine snorting is perforation of the nasal septum, a finding noted in approximately 5% of abusers. Loss of the nasal septum can lead to complete nasal collapse resulting in a saddle nose deformity. Less frequently, the necrosis can spread to the orbital wall, lateral nasal wall, or the hard palate and may cause palatal perforation that has been termed **cocaine-induced midline destructive lesion (CIMDL).** Associated findings include recurrent epistaxis, a nasal tone of voice (rhinolalia), regurgitation of food/drink, intranasal crusting, rhinitis, and sinusitis. The majority of the reported palatal perforations are limited to the hard palate, followed by involvement of both the hard and soft palates. Perforation isolated to the soft palate is most uncommon. Although very rare, similar nasal collapse and palatal perforations have been reported from intranasal abuse of narcotics, such as hydrocodone/acetaminophen or oxycodone/acetaminophen (Figs. 8-35 and 8-36). On occasion, mucosal burns of the lips may be seen in users of crack pipes (Fig. 8-37).

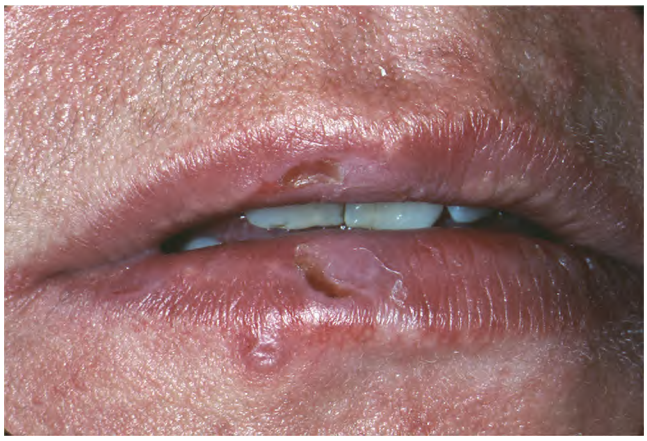
Although methamphetamine abuse may occur throughout society, most users are men between the ages of 19 and 40 years. The effects of the medication last up to 12 hours, and the typical abuser reports use that exceeds 20 days per month, creating an almost continuous effect of the drug. The short-term effects of methamphetamine include



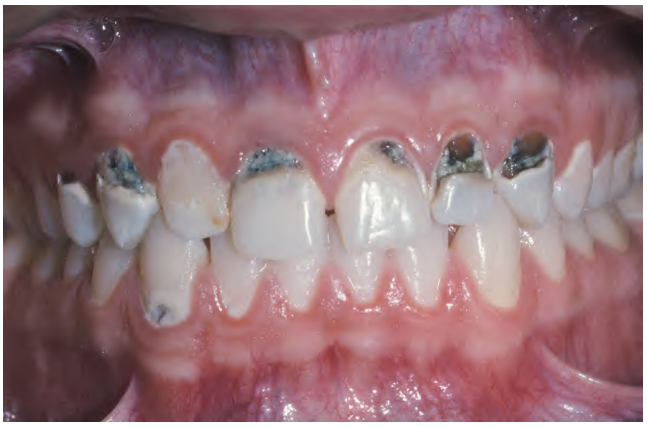
• **Fig. 8-35 Oxycodone-related Saddle Nose Deformity.** Loss of nasal septum leading to nasal collapse in abuser of oxycodone.



• **Fig. 8-36 Oxycodone-related Palatal Perforation.** Midline perforation of the palate in abuser of oxycodone.



• **Fig. 8-37 Crack Pipe Burn.** Multiple erosions of the upper and lower vermilion borders secondary to burns inflicted by use of a crack pipe.



• **Fig. 8-38 Methamphetamine-related Dental Caries.** Extensive smooth-surface decay of the anterior dentition.

insomnia, aggressiveness, agitation, hyperactivity, decreased appetite, tachycardia, tachypnea, hypertension, hyperthermia, vomiting, tremors, and xerostomia. Long-term effects additionally include strong psychologic addiction, violent behavior, anxiety, confusion, depression, paranoia, auditory hallucinations, delusions, mood changes, skin lesions, and a number of cardiovascular, CNS, hepatic, gastrointestinal, renal, and pulmonary disorders.

Many addicts develop delusions of **parasitosis** (**formication,** from the Latin word *formica,* which translates to *ant*), a neurosis that produces the sensation of snakes or insects crawling on or under the skin. This sensation causes the patient to attempt to remove the perceived parasites, usually by picking at the skin with fingernails, resulting in widespread traumatic injury. The factitial damage can alter dramatically the facial appearance in a short period of time, and these lesions have been nicknamed *speed bumps, meth sores,* or *crank bugs.*

Rampant dental caries is another common manifestation and exhibits numerous similarities with milk-bottle caries. The carious destruction initially affects the facial smooth and interproximal surfaces, but without intervention, the coronal structure of the entire dentition can be destroyed (Fig. 8-38). The carious destruction appears to be caused by poor oral hygiene combined with extreme drug-related xerostomia, which leads to heavy consumption of acidic and sugar-filled soft drinks or other refined carbohydrates.

Treatment and Prognosis

Cessation of illicit drug use is paramount in both cocaine and methamphetamine abuse. In patients with palatal perforation, complete cessation of cocaine use must be stopped 6 months prior to surgical reconstruction. If surgical reconstruction fails, a removable maxillary obturator can be constructed. Although cessation of the illicit drug use is critical, methamphetamine addicts should be encouraged during periods of xerostomia to discontinue use of highly acidic and sugar-filled soft drinks and to avoid diuretics, such as caffeine, tobacco, and alcohol. In addition, the importance of personal and oral hygiene should be stressed. Preventive measures such as topical fluorides may assist in protecting the remaining dentition.

The oral health practitioner should be alerted when an agitated, nervous adult presents with tachycardia, tachypnea, hypertension, and hyperthermia. Failure to recognize these signs can be serious. For up to 24 hours after ingestion, both cocaine and methamphetamine potentiate the effects of sympathomimetic amines. Use of local anesthetics with epinephrine or levonordefrin can lead to a hypertensive crisis, cerebrovascular accident, or myocardial infarction. Caution also should be exercised when administering sedatives, general anesthesia, nitrous oxide, or prescriptions for narcotics. A medical consultation with referral to a substance abuse center should be encouraged.

◆ ANESTHETIC NECROSIS

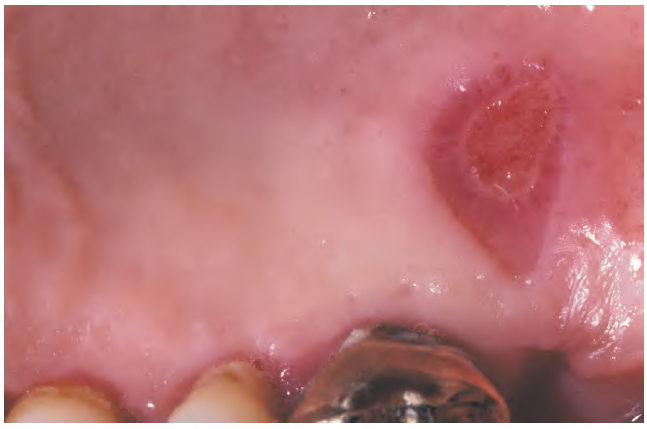
Administration of a local anesthetic agent can, on rare occasions, be followed by ulceration and necrosis at the site of injection. Researchers believe that this necrosis results from localized ischemia, although the exact cause is unknown and may vary from case to case. Faulty technique, such as subperiosteal injection or administration of excess solution in tissue firmly bound to bone, has been blamed. The epinephrine contained in many local anesthetics also has received attention as a possible cause of ischemia and secondary necrosis.

Clinical Features

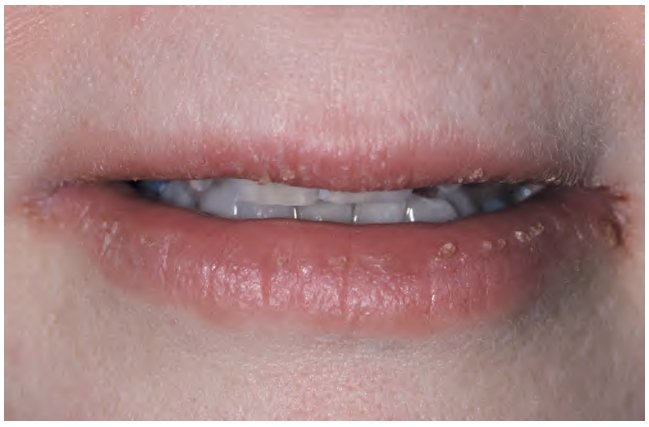
Anesthetic necrosis usually develops several days after the procedure and most commonly appears on the hard palate (Fig. 8-39). A well-circumscribed area of ulceration develops at the site of injection.

Treatment and Prognosis

Treatment of anesthetic necrosis usually is not required unless the ulceration fails to heal. Minor trauma, such as



• **Fig. 8-39 Anesthetic Necrosis.** Mucosal necrosis of the hard palate secondary to palatal injection with a local anesthetic agent containing epinephrine.



• **Fig. 8-40 Exfoliative Cheilitis.** Scaling and erythema of the vermilion border of the lower lip.

that caused by performing a cytologic smear, has been reported to induce resolution in these chronic cases. Recurrence is unusual but has been reported in some patients in association with use of epinephrine-containing anesthetics. In these cases the use of a local anesthetic without epinephrine is recommended.

◆ EXFOLIATIVE CHEILITIS

Exfoliative cheilitis is a persistent scaling and flaking of the vermilion border, usually involving both lips. The process arises from excessive production and subsequent desquamation of superficial keratin. A significant percentage of cases appear related to chronic injury secondary to habits, such as lip licking, biting, picking, or sucking. Those cases proven to arise from chronic injury are termed **factitious cheilitis.**

Many patients deny chronic self-irritation of the area. The patient may be experiencing associated personality disturbances, psychologic difficulties, or stress. In a review of 48 patients with exfoliative cheilitis, 87% exhibited psychiatric conditions and 47% also demonstrated abnormal thyroid function. Evidence suggests that there may be a link between thyroid dysfunction and some psychiatric disturbances.

In other cases, no evidence of chronic injury is evident. In these patients other causes should be ruled out (e.g., atopy, chronic candidal infection, actinic cheilitis, cheilitis glandularis, hypervitaminosis A, and photosensitivity). In a review of 165 patients with acquired immunodeficiency syndrome (AIDS), more than one-quarter had alterations that resembled exfoliative cheilitis. In this group the lip alterations appeared secondary to chronic candidal infestation. The most common presentation of bacterial or fungal infections of the lips is **angular cheilitis** (see page 194). Diffuse primary infection of the entire lip is very unusual; most diffuse cases represent a secondary candidal infection in areas of low-grade trauma of the vermilion border of the lip **(cheilocandidiasis).**

In one review of 75 patients with chronic cheilitis, a thorough evaluation revealed that more than one-third represented irritant contact dermatitis (often secondary to chronic lip licking). In 25% of the patients, the cheilitis was discovered to be an allergic contact mucositis (see page 320). Atopic eczema was thought to be the cause in 19% of cases; the remaining portion was related to a wide variety of pathoses.

In spite of a thorough investigation, there often remain a number of patients with classic exfoliative cheilitis for which no underlying cause can be found. These idiopathic cases are most troublesome and often resistant to a wide variety of interventions.

Clinical Features

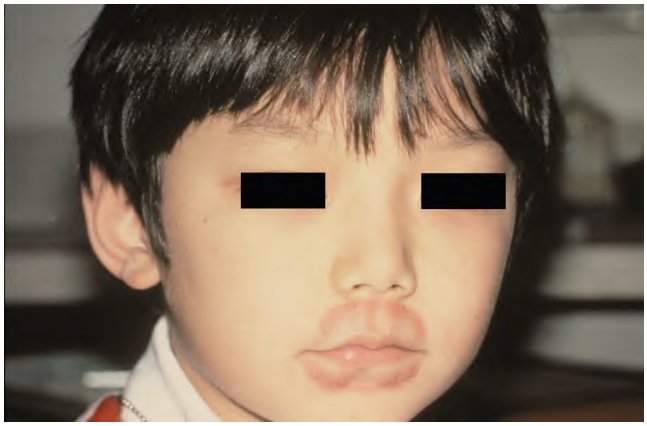
A marked female predominance is seen in cases of factitious origin, with most cases affecting those younger than 30 years of age. Mild cases feature chronic dryness, scaling, or cracking of the vermilion border of the lip (Fig. 8-40). With progression, the vermilion can become covered with a thickened, yellowish hyperkeratotic crust that can be hemorrhagic or that may exhibit extensive fissuring. The perioral skin may become involved and exhibit areas of crusted erythema (Fig. 8-41). Although this pattern may be confused with perioral dermatitis (see page 322), the most appropriate name for this process is *circumoral dermatitis.* Both lips, or just the lower lip, may be involved. On occasion, the alterations can present in a cyclical pattern in which the changes resolve but subsequently redevelop over a relatively consistent period of time.

In patients with chronic cheilitis, development of fissures on the vermilion border is not rare. In a prevalence study of more than 20,000 patients, these fissures involved either lip and were slightly more common in the upper lip. In contrast to typical exfoliative cheilitis, these fissures demonstrate a significant male predilection and a prevalence rate of approximately 0.6%. The majority arise in young adults, with rare occurrence noted in children and older adults.

Although the cause is unknown, proposed contributing factors include overexposure to sun, wind, and cold weather; mouth breathing; bacterial or fungal infections; and smoking. An increased prevalence of lip fissures has been noted in patients with Down syndrome and may be the result of the high frequency of mouth breathing or the tendency to develop orofacial candidiasis. Application of lipstick or lip balm appears to be protective. Fissure occurrence also may be related to a physiologic weakness of the tissues. Those affecting the lower lip typically occur in the midline, whereas fissures on the upper vermilion most frequently involve a lateral position. These are the sites of prenatal merging of the mandibular and maxillary processes.

Treatment and Prognosis

In those cases associated with an obvious cause, elimination of the trigger typically results in resolution of the changes. In those cases with no underlying physical, infectious, or allergic cause, psychotherapy (often combined with mild tranquilization or stress reduction) may achieve resolution.



• **Fig. 8-41 Circumoral Dermatitis.** Crusting and erythema of the skin surface adjacent to the vermilion border in a child who chronically sucked on both lips.

In cases for which no cause can be found, therapeutic interventions often are not successful.

Cases that result from candidal infections often do not resolve until the chronic trauma also is eliminated. Initial topical antifungal agents, antibiotics, or both can be administered to patients in whom chronic trauma is not obvious or is denied. If the condition does not resolve, then further investigation is warranted in an attempt to discover the true source of the lip alterations.

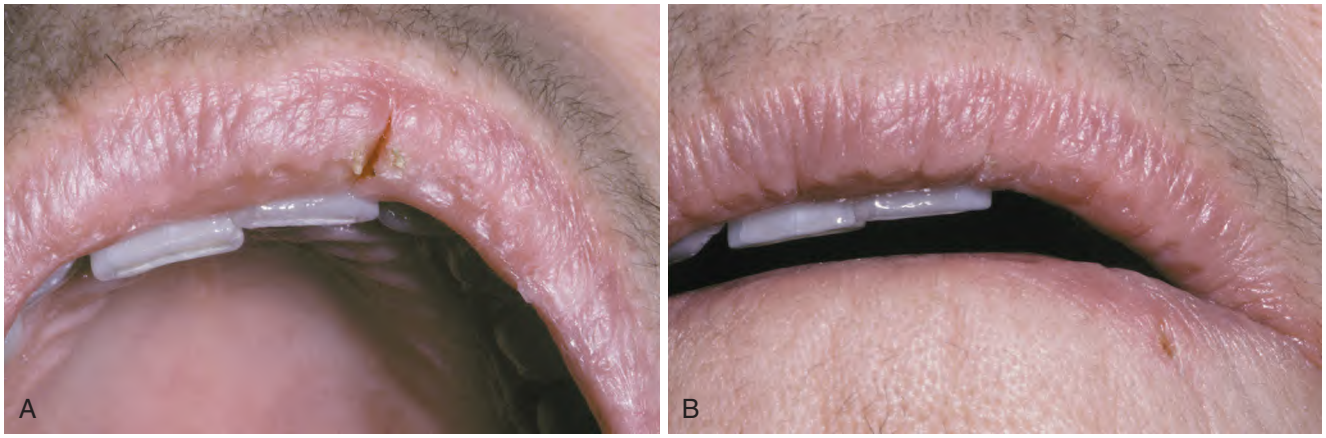
Hydrocortisone and iodoquinol (antibacterial and antimycotic) cream has been used to resolve chronic lip fissures in some patients (Fig. 8-42). Other reported therapies include various corticosteroid preparations, topical tacrolimus, sunscreens, and moisturizing preparations. In many cases, resistance to topical therapy or frequent recurrence is noted. In these cases, cryotherapy or excision with or without Z-plasty has been used successfully.

◆ SUBMUCOSAL HEMORRHAGE

Everyone has experienced a bruise from minor trauma. This occurs when a traumatic event results in hemorrhage and entrapment of blood within tissues. Different terms are used, depending on the size of the hemorrhage:

- Minute hemorrhages into skin, mucosa, or serosa are termed **petechiae.**
- If a slightly larger area is affected, the hemorrhage is termed a **purpura.**
- Any accumulation greater than 2 cm is termed an **ecchymosis.**
- If the accumulation of blood within tissue produces a mass, this is termed a **hematoma.**

Blunt trauma to the oral mucosa often results in hematoma formation. Less well known are petechiae and purpura, which can arise from repeated or prolonged increased intrathoracic pressure (Valsalva maneuver) associated with such activities as repeated coughing, vomiting, convulsions, or giving birth (Fig. 8-43). When considering a diagnosis of traumatic hemorrhage, the clinician should keep in mind that hemorrhages can result from nontraumatic causes, such



• **Fig. 8-42 Lip Fissure. A,** Chronic fissure of the vermilion border of the upper lip. **B,** Same site 2 weeks later, after use of hydrocortisone and iodoquinol cream.

as anticoagulant therapy, thrombocytopenia, disseminated intravascular coagulation (DIC), and a number of viral infections, especially infectious mononucleosis and measles.

Clinical Features

Submucosal hemorrhage appears as a nonblanching flat or elevated zone with a color that varies from red or purple to blue or blue-black (Fig. 8-44). As would be expected, traumatic lesions are located most frequently on the labial or buccal mucosa. Blunt facial trauma often is responsible, but injuries as minor as cheek biting may produce a hematoma or areas of purpura (Fig. 8-45). Mild pain may be present.

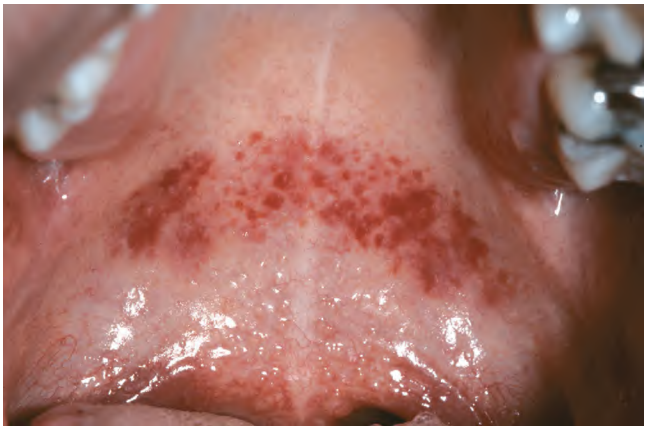
The hemorrhage associated with increased intrathoracic pressure usually is located on the skin of the face and neck and appears as widespread petechiae that clear within 24 to 72 hours. Although it has not been as well documented as the cutaneous lesions, mucosal hemorrhage can be seen in the same setting and most often appears as soft palatal petechiae or purpura.

Treatment and Prognosis

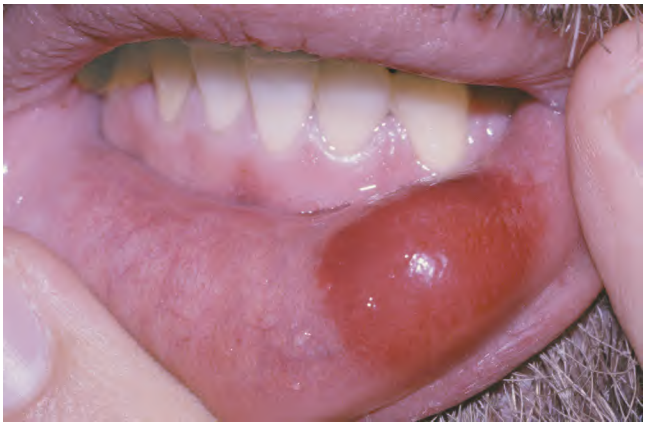
Often, no treatment is required if the hemorrhage is not associated with significant morbidity or related to systemic disease. The areas should resolve spontaneously. Large hematomas may require several weeks to resolve. If the hemorrhage occurs secondary to an underlying disorder, then treatment is directed toward control of the associated disease.

◆ ORAL TRAUMA FROM SEXUAL PRACTICES

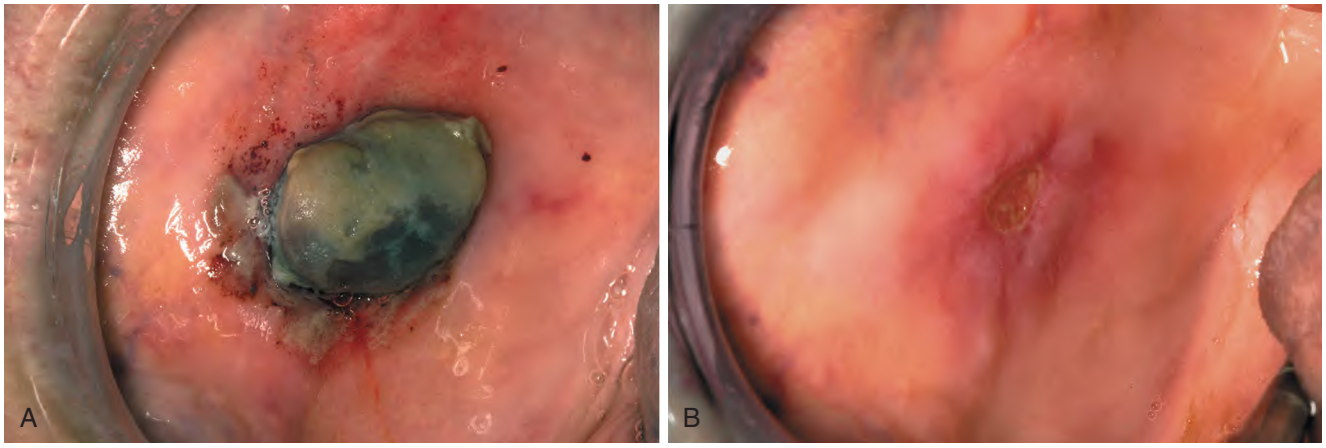
Although orogenital sexual practices are illegal in many jurisdictions, they are extremely common. Among homosexual men and women, orogenital sexual activity almost is universal. For married heterosexual couples younger than age 25, the frequency has been reported to be as high as 90%. Considering the prevalence of these practices, the frequency of associated traumatic oral lesions is surprisingly low.



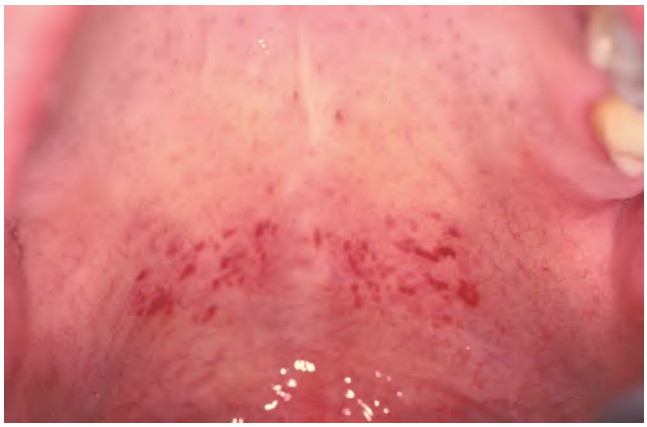
• **Fig. 8-43 Petechiae.** Submucosal hemorrhage of the soft palate caused by violent coughing.



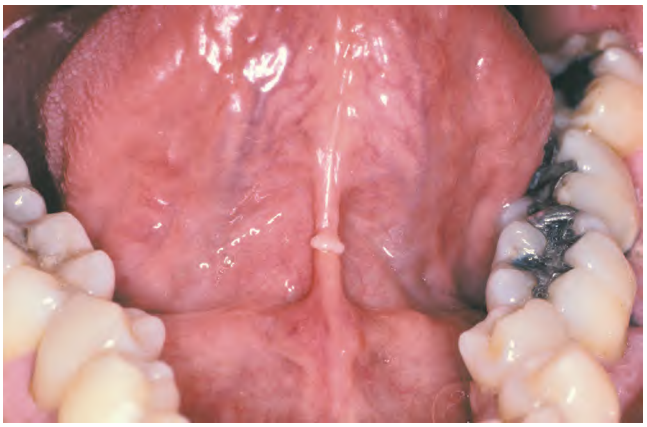
• **Fig. 8-44 Purpura.** Submucosal hemorrhage of the lower labial mucosa on the left side secondary to blunt trauma.



• **Fig. 8-45 Hematoma. A,** Dark-purple nodular mass of the buccal mucosa in a patient on Coumadin therapy. **B,** Near resolution of the lesion 8 days later after discontinuation of the medication. (Courtesy of Dr. Charles Ferguson.)



• **Fig. 8-46 Palatal Petechiae from Fellatio.** Submucosal hemorrhage of the soft palate resulting from the effects of negative pressure.



• **Fig. 8-47 Fibrous Hyperplasia from Repeated Cunnilingus.** Linear fibrous hyperplasia of the lingual frenum caused by repeated irritation from lower incisors.

Clinical Features

The most commonly reported lesion related to orogenital sex is submucosal palatal hemorrhage secondary to fellatio. The lesions appear as erythema, petechiae, purpura, or ecchymosis of the soft palate. The areas often are asymptomatic and resolve without treatment in 7 to 10 days (Fig. 8-46). Recurrences are possible with repetition of the inciting (exciting?) event. The erythrocytic extravasation is thought to result from the musculature of the soft palate elevating and tensing against an environment of negative pressure. Similar lesions have been induced from coughing, vomiting, or forceful sucking on drinking straws and glasses. Forceful thrusting against the vascular soft palate has been suggested as another possible cause.

Oral lesions also can occur from performing cunnilingus, resulting in horizontal ulcerations of the lingual frenum. As the tongue is thrust forward, the taut frenum rubs or rakes across the incisal edges of the mandibular central incisors. The ulceration created coincides with sharp tooth edges when the tongue is in its most forward position. The lesions resolve in 7 to 10 days but may recur with repeated performances. Linear fibrous hyperplasia has been discovered in the same pattern in individuals who chronically perform the act (Fig. 8-47).

Histopathologic Features

With an appropriate index of suspicion, biopsy usually is not required; however, a biopsy has been performed in some cases of palatal lesions secondary to fellatio. These suction-related lesions reveal subepithelial accumulations of red blood cells that may be extensive enough to separate the surface epithelium from underlying connective tissue. Patchy degeneration of the epithelial basal cell layer can occur. The epithelium classically demonstrates migration of erythrocytes and leukocytes from the underlying lamina propria.

Treatment and Prognosis

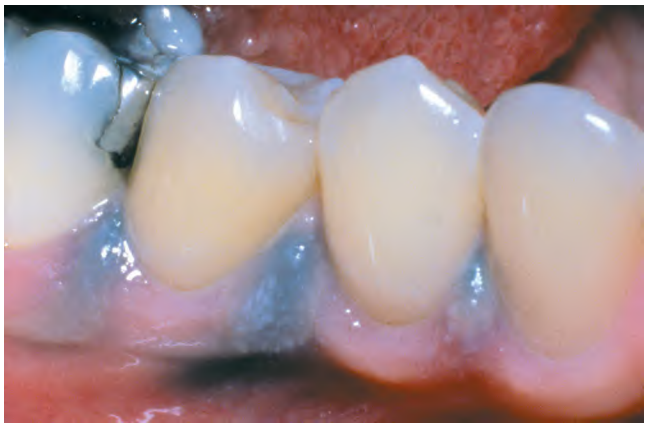
No treatment is required, and the prognosis is good. In patients who request assistance, palatal petechiae can be prevented through the use of less negative pressure and avoidance of forceful thrusting. Smoothing and polishing the rough incisal edges of the adjacent mandibular teeth can minimize the chance of lingual frenum ulceration.

◆ AMALGAM TATTOO AND OTHER LOCALIZED EXOGENOUS PIGMENTATIONS

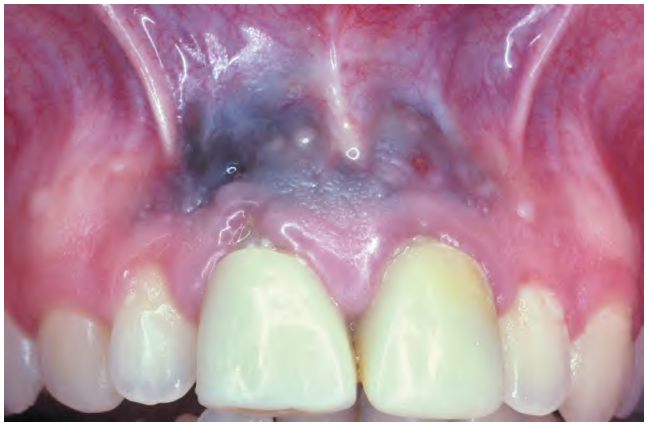
A number of pigmented materials can be implanted within the oral mucosa, resulting in clinically evident pigmentations. Implantation of dental amalgam **(amalgam tattoo)** occurs most often, with a frequency that far outdistances that for all other materials. *Localized argyrosis* has been used as another name for amalgam tattoo, but this nomenclature is inappropriate because amalgam contains not only silver but also mercury, tin, copper, zinc, and other metals.

Amalgam can be incorporated into the oral mucosa in several ways. Previous areas of mucosal abrasion can be contaminated by amalgam dust within the oral fluids. Broken amalgam pieces can fall into extraction sites. If dental floss becomes contaminated with amalgam particles of a recently placed restoration, then linear areas of pigmentation can be created in the gingival tissues as a result of hygiene procedures (Fig. 8-48). Amalgam from endodontic retrofill procedures can be left within the soft tissue at the surgical site (Fig. 8-49). Finally, fine metallic particles can be driven through the oral mucosa from the pressure of high-speed air turbines. Theoretically, the use of the rubber dam should decrease the risk; however, immediately after removal of the dam, the occlusion often is adjusted with the potential for amalgam contamination of any areas of mucosal damage.

In one interesting report, metal from silver solder on orthodontic brackets leached into adjacent gingival crevices



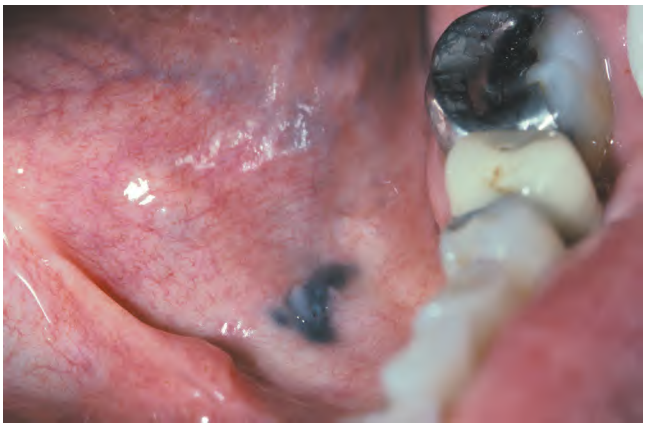
• **Fig. 8-48 Floss-related Amalgam Implantation.** Linear strips of mucosal pigmentation that align with the interdental papillae. The patient used dental floss on the mandibular first molar immediately after the placement of the amalgam restoration. Because the area was still anesthetized, the patient impaled the floss on the gingiva and then continued forward using the amalgam-impregnated floss in the bicuspid area to create additional amalgam tattoos.



• **Fig. 8-49 Endodontic-related Amalgam Implantation.** Multifocal areas of mucosal discoloration overlying the maxillary anterior incisors, which have been treated with apical retrofill procedures.

and created discolorations that were thought to be secondary to formation of insoluble precipitates from metabolic bacterial byproducts. Submucosal implantation of pencil graphite, coal and metal dust, fragments of broken carborundum disks, dental burs, and, in the past, charcoal dentifrices, have resulted in similar-appearing areas of discoloration.

Intentional tattooing, which can be found in approximately 25% of the world's population, also may be performed in the oral cavity. Although some cases are culturally related, health professionals also are responsible for a number of intentional oral and facial tattoos for the purpose of demonstrating landmarks, establishing progress of orthodontic treatment, marking sites of uncovered dental implants, judging tumor response to antineoplastic therapies, repigmenting areas of vitiligo, cosmetically disguising disfigured areas, and applying permanent cosmetic makeup. Injudicious intraoral use of these marking agents can cause



• **Fig. 8-50 Amalgam Tattoo.** Area of mucosal discoloration of the floor of the mouth on the patient's left side.

diffusion of the pigment with discoloration of the adjacent skin surface.

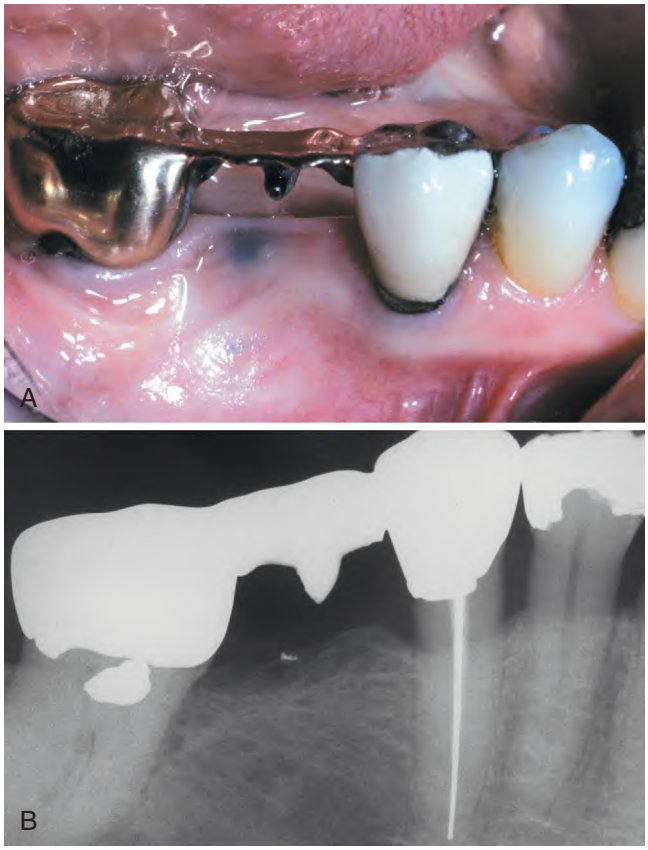
Clinical and Radiographic Features

Amalgam tattoos appear as macules or, rarely, as slightly raised lesions. They may be black, blue, or gray. The borders can be well defined, irregular, or diffuse (Fig. 8-50). Lateral spread may occur for several months after the implantation. Any mucosal surface can be involved, but the most common sites are the gingiva, alveolar mucosa, and buccal mucosa (Fig. 8-51).

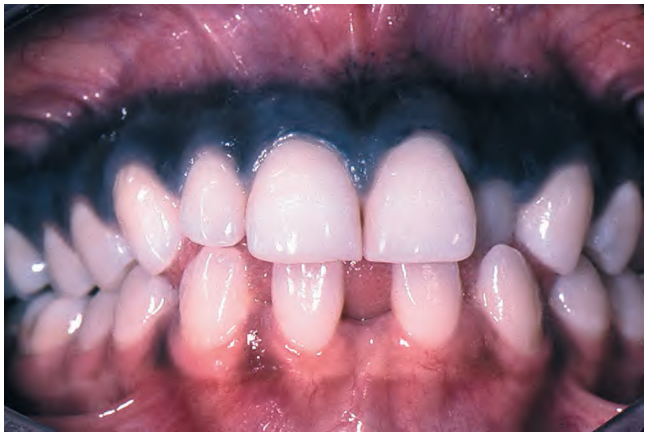
Periapical radiographs, when taken, are negative in many cases. When metallic fragments are visible radiographically, the clinical area of discoloration typically extends beyond the size of the fragment. The fragments are densely radiopaque, varying from several millimeters to pinpoint in size (see Fig. 8-51). On occasion, the pattern of the amalgam dispersal has been sufficiently unique to be used as a distinctive characteristic in the identification of unknown deceased individuals.

Cosmetic tattooing is gaining in popularity and may include injection of permanent cosmetic inks into the eyelids and vermilion border of the upper and lower lips. On occasion, patients may react to the material and experience swelling, burning, and itching at the site, followed by enlargement and induration. In such cases, biopsy often reveals a granulomatous reaction to the foreign material. One report documented rapid development of squamous cell carcinoma of the upper vermilion border arising in a patient with minimal sun exposure and recent placement of permanent red makeup tattoo.

Intentional intraoral tattoos occur most frequently on the anterior maxillary facial gingiva of individuals from a number of African countries and have been documented at institutions in the United States (Fig. 8-52). In these cases, the anterior maxillary facial gingiva is given a blue-black discoloration that tends to fade to mostly gray over time. Occasionally, tattoos are placed on the labial mucosa of



• **Fig. 8-51 Amalgam Tattoo. A,** Area of mucosal discoloration of the mandibular alveolar ridge immediately below the bridge pontic. **B,** Radiograph of the same patient showing radiopaque metallic fragment present at the site of mucosal discoloration.

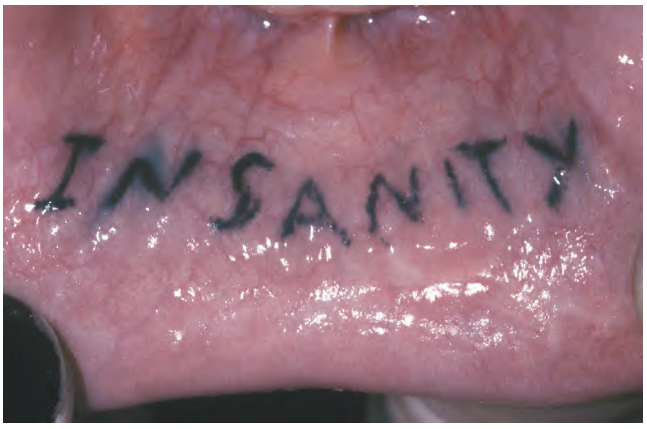


• **Fig. 8-52 Intentional Intraoral Tattoo.** Cultural tattoo of the maxillary facial gingiva in a patient from Senegal. (Courtesy of Dr. Kristin McNamara.)

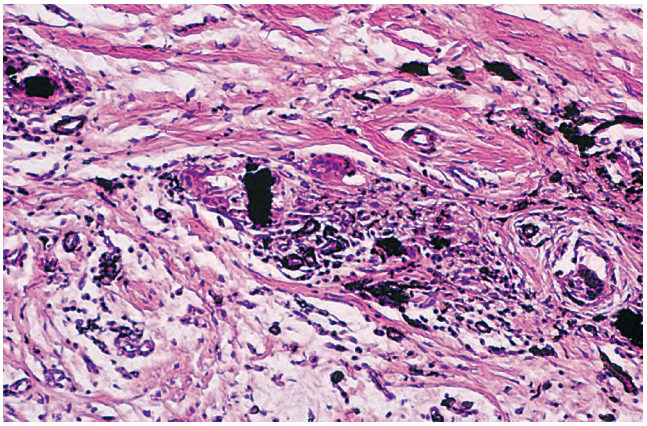
adults in the United States to convey a personal, often vulgar, message (Fig. 8-53).

Histopathologic Features

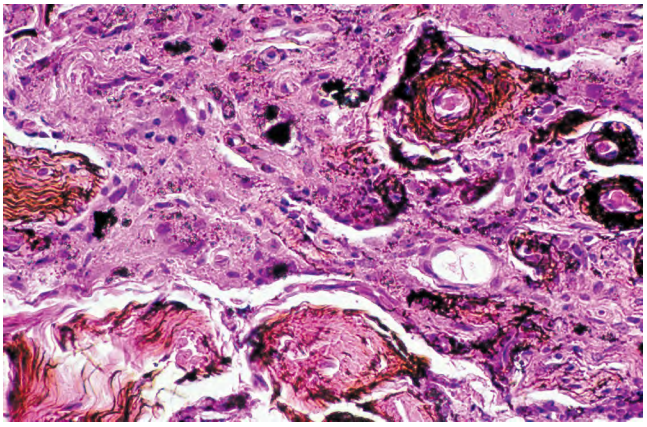
Microscopic examination of amalgam tattoos reveals pigmented fragments of the metal within the connective tissue. Scattered, large, dark, solid fragments or numerous fine,



• **Fig. 8-53 Intentional Intraoral Tattoo.** Amateur tattoo of the lower labial mucosa. (Courtesy of Dr. Edward Herschaft.)



• **Fig. 8-54 Amalgam Tattoo.** Numerous dark, solid fragments of amalgam are surrounded by a lymphohistiocytic inflammatory infiltrate.



• **Fig. 8-55 Amalgam Tattoo.** Dark amalgam stain encircling numerous vascular channels.

black, or dark-brown granules may be seen (Fig. 8-54). The silver salts of the dental amalgam preferentially stain the reticulin fibers, especially those encircling nerves and vascular channels (Fig. 8-55).

The biologic response to amalgam appears related to particle size and the elemental composition of the amalgam.

Large fragments often become surrounded by dense fibrous connective tissue with mild inflammation. Smaller particles typically are associated with a more significant inflammatory response that may be granulomatous or a mixture of lymphocytes and plasma cells. Graphite implantation appears similar microscopically to amalgam but can be differentiated by its pattern of birefringence after treatment with ammonium sulfide and by the lack of staining of the reticulin fibers. In addition, energy dispersive x-ray microanalysis can be used to identify the type of material present within areas of foreign body tattoos.

Treatment and Prognosis

To confirm the diagnosis of amalgam tattoo, the clinician can obtain radiographs of the areas of mucosal discoloration in an attempt to demonstrate the metallic fragments. The films should be capable of high detail, because many of the fragments are no larger than the point of a pin.

No treatment is required if the fragments can be detected radiographically. If no metallic fragments are found and the lesion cannot be diagnosed clinically, then biopsy may be needed to rule out the possibility of melanocytic neoplasia. On occasion, the amalgam implantation may create pigmentation in a cosmetically objectionable location such as the anterior maxillary facial gingiva. In such cases, conservative surgical excision can be performed; alternatively amalgam tattoos have been removed successfully with Q-switched ruby or alexandrite lasers. With respect to cosmetic tattoos, a variety of treatments such as corticosteroids and lasers have been used with variable results.

◆ ORAL PIERCINGS AND OTHER BODY MODIFICATIONS

Historical evidence from almost every continent shows that body piercing is an ancient practice with a strong association with religious, cultural, or superstitious beliefs. In the Western world, body piercing beyond the earlobes has become increasingly popular as a method of self-expression in recent years. In a survey of 481 college students in the United States, 51% admitted body piercing, and the prevalence still appears to be rising. Usually, the piercing is performed to place jewelry in sites such as the eyebrows, helix of the ears, nose, navel, nipples, genitals, and a number of intraoral sites.

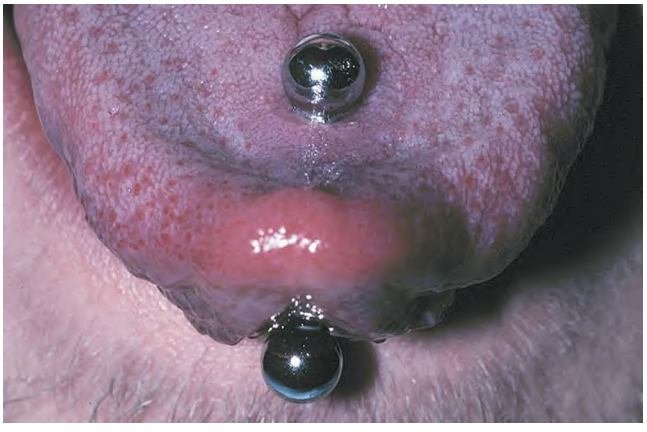
Forked tongue (split tongue, bifid tongue) is a rather recent addition to the art of body modification, with few associated publications. In this practice the anterior one-third of the tongue is split down the middle. This has been performed slowly by pulling fishing line through a pierced hole and tightening the loop over a period of 3 weeks or using a surgical instrument or laser to quickly separate the two halves. Some form of cautery is necessary to prevent the halves from reuniting. Forked tongue also has been reported as a complication of tongue piercing.

Another practice with unique orofacial manifestations is implantation of a form of **talisman** (magical charm) called **susuk (charm needles, charm pins).** This practice is common in Southeast Asia, especially Malaysia, Thailand, Singapore, Indonesia, and Brunei. The susuk is placed by a native magician or medicine man termed *bomoh* and is thought to enhance or preserve beauty, relieve pain, bring success in business, or provide protection against harm. The majority of the individuals with susuk are Muslims, although Islam strictly prohibits black magic. Therefore, many affected individuals will deny placement of susuk, even when confronted directly with hard evidence.

Clinical and Radiographic Features

Intraoral piercings are noted most frequently in adolescents and young adults, with a female predominance. The most commonly affected sites are the tongue, lips, buccal mucosa, and, rarely, the uvula. If no complications occur, healing of the piercing site takes place within 4 to 6 weeks. Currently, the jewelry most often is niobium, surgical steel, or titanium; however, a wide variety of materials such as horn, ivory, plastic, stone, wood, aluminum, brass, copper wire, platinum, silver, and gold are used. In the tongue, the most frequent adornment is a **barbell** (Dumbbell might be a better name!) consisting of a metal rod with a ball that screws onto each end (Fig. 8-56). The lip jewelry is termed a **labret** and most often consists of a ring or a rod with a flat end attached to the mucosal side and a round ball for the cutaneous surface (Fig. 8-57).

In a review of US hospital emergency departments from 2002 to 2008, an estimated 24,459 patients presented with oral piercing-related injuries. Complications during the procedure include bleeding, nerve damage, localized infection, and the risk of transmission of infectious diseases, such as hepatitis or HIV. Immediate postoperative complications include pain, swelling, hematoma formation, increased salivary flow, speech impediment, and a local allergic reaction. Serious complications such as Ludwig angina, infective endocarditis, and fatal brain abscesses have been



• **Fig. 8-56 Lingual Piercing.** Tongue pierced with a jewelry item known as a *barbell.*

documented. Chronic complications include mucosal or gingival trauma, chipped or fractured teeth, hypersalivation, aspiration or swallowing of jewelry, tissue hyperplasia around the posts, and embedded jewelry. Gingival recession (labrets, barbells) and tooth fracture (barbells) are extremely common, with the prevalence closely related to the duration of use. Habitual biting or chewing the jewelry often is associated with severe dental abrasion or movement of teeth. A fatal squamous cell carcinoma of the tongue arising at the site of a metal piercing has been reported in a 26-year-old patient.

In individuals with forked tongues, the anterior half of the tongue is split down the middle (Fig. 8-58). Risks of the procedure include inflammation, infection, profuse or prolonged hemorrhage, and permanent neurovascular damage. After healing, some individuals have developed the ability to control each half independently.

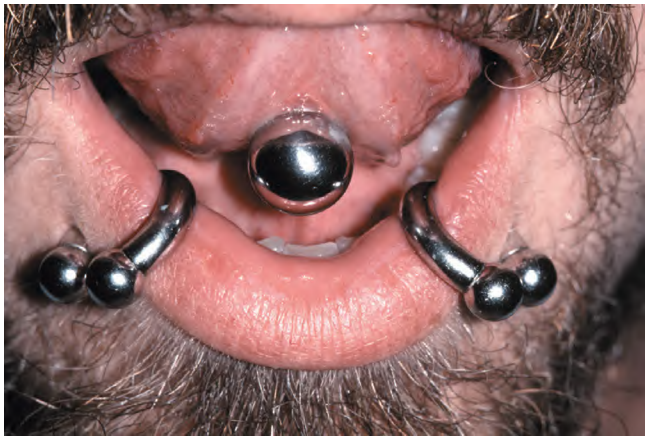
Susuk usually is shaped like a needle that is pointed on one end and blunt on the other. Most are made from silver or gold, measure 0.5 mm in diameter, and vary from 0.5 to 1.0 cm in length. Rarely, they are made from diamonds. The pins vary in number from one to many and are inserted subcutaneously, often in a symmetrical fashion. The orofacial region is the most common location (forehead, cheeks, and lips), but some choose the chest, arms, breasts, pubic region, and spinal area. In most instances, the individuals are middle-aged adults. Normally, no clinical evidence exists, either visually or by palpation, and the pins are discovered during routine radiography for unrelated medical or dental problems (Fig. 8-59).

Treatment and Prognosis

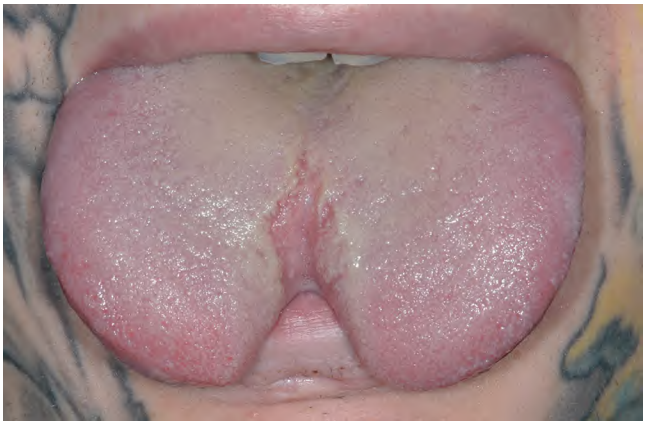
As mentioned, intraoral barbells and labrets are associated with an increasing prevalence of oral complications that relate closely with duration of use. The patient should be strongly encouraged to remove the jewelry. On removal, if the site demonstrates significant inflammation, local débridement, antibiotic therapy, and chlorhexidine mouthwash may be appropriate.

Except for slight sibilant distortions and shortening of the protrusive length of the tongue, few long-term adverse events have been noted in patients with forked tongues.

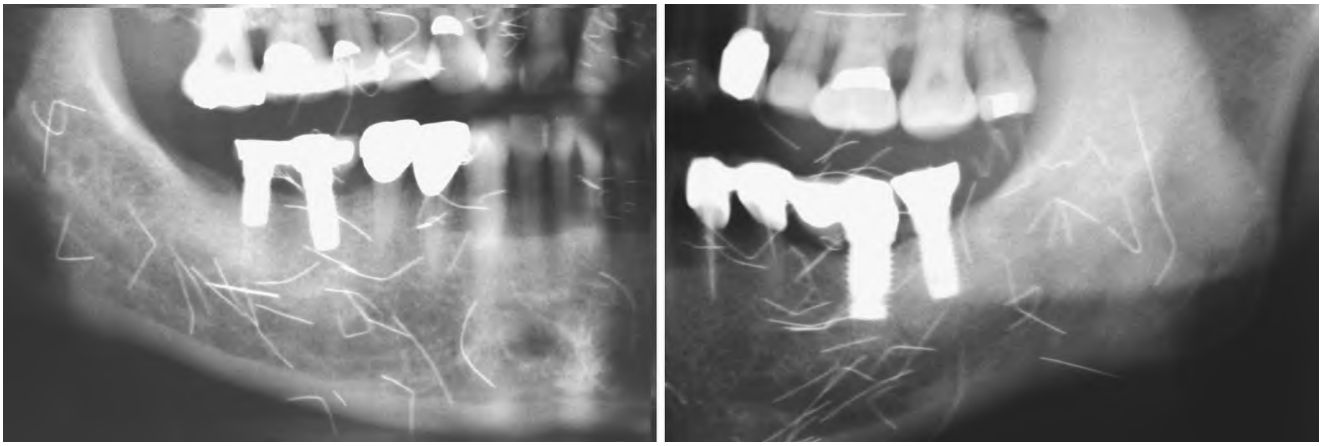
Susuk have not been associated with harmful effects, and no treatment is required. If the needles have a ferrous



• **Fig. 8-57 Labial Piercing.** Lower lip pierced bilaterally with labrets consisting of a circular rod with terminating balls. The patient also has a lingual barbell.



• **Fig. 8-58 Forked Tongue.** Anterior portion of the tongue divided into two separate lobes, each of which can be controlled independently. (Courtesy of Dr. Fleming Chisholm.)



• **Fig. 8-59 Susuk (Charm Needles).** Panoramic radiograph showing multiple radiopaque needles superimposed on the jaws. (Courtesy of Dr. Jeff Bayme.)

content, then magnetic resonance imaging (MRI) would be contraindicated. On occasion, affected individuals request removal of the susuk before they die because they believe their death will be excruciatingly painful. In spite of this, the needles should not be removed without consent.

◆ ORAL LESIONS ASSOCIATED WITH COSMETIC FILLERS

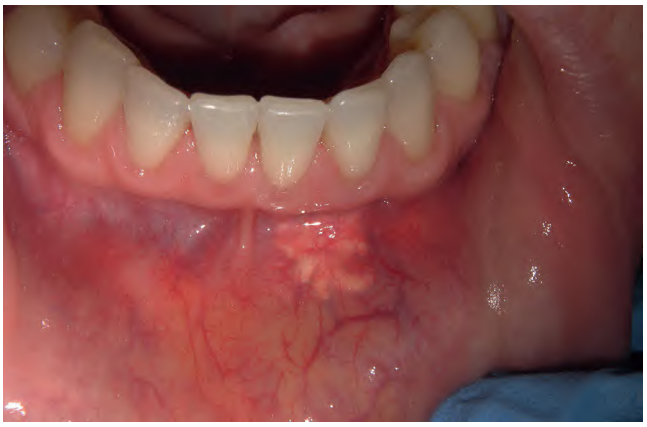
In recent years, oral health care providers have encountered a variety of oral lesions secondary to injection of cosmetic fillers. These substances are used to augment the lips, cheeks, and chin or utilized to minimize skin folds in the forehead, around the nose, and perioral surfaces. Nonpermanent fillers such as collagen, fat transfer, dextran, hyaluronic acid (Restylane, Juvederm), and poly-L-lactic acid (Sculptra) usually are biodegraded over several months to years. Permanent fillers such as liquid silicone, polyacrylamide (Aquamid), polytetrafluoroethylene (GORE-TEX, SoftForm), polymethylmethacrylate (Artecoll, ArteFill), and hydroxyapatite (Radiesse) cannot be metabolized and typically are encased by fibrous tissue, often intermixed with granulomatous inflammation. Although liquid silicone is no longer approved by the FDA due to major safety concerns, this material continues to be discovered in patients who received the filler prior to the current ban. Problems have occurred when these materials present as tumor-like masses in patients who do not make the connection to their previous cosmetic procedure or are reluctant to mention prior use of dermal filler. In order to help pathologists identify these various compounds, an online atlas of foreign materials has been established by the American Academy of Oral & Maxillofacial Pathology (AAOMP).

Clinical and Radiographic Features

Acute adverse reactions are the most common and include bruising, erythema, itching, pain, and localized infection. Severe adverse reactions occur with some materials but are rare. These reactions include local allergic response, anaphylaxis, arthralgia, myalgia, retinal artery thrombosis, facial paralysis, and renal failure. The most common presentations in the dental office are latent tumor-like nodules usually presenting in the lips, anterior buccal mucosa, and mandibular vestibule (Fig. 8-60). In patients with hydroxyapatite filler, clusters of radiopaque material have been discovered on panoramic and cone beam radiographs.

Histopathologic Features

The histopathologic features are variable but often distinctive. In many cases, the identification of the specific material by the pathologist allows the clinician to present the patient with a brand name that often convinces the reluctant individual to admit a previous cosmetic procedure.



• **Fig. 8-60 Cosmetic Filler Material.** Yellow submucosal mass of the mandibular labial vestibule. Biopsy revealed hydroxyapatite (Radiesse) with fibrosis and granulomatous inflammation. (From Daley T, Damm DD, Haden JA, et al: Oral lesions associated with injected hydroxyapatite cosmetic filler, *Oral Surg Oral Med Oral Pathol Oral Radiol* 114:107–111, 2012.)

The nonpermanent filler, hyaluronic acid, is nonimmunogenic and presents as pools of amorphous and lightly basophilic material surrounded by dense bands of collagen without a foreign body reaction. Poly-L-lactic acid and most of the permanent materials are surrounded by dense collagen and granulomatous inflammation (Fig. 8-61). In many instances, the microscopic appearance of the material is sufficient for identification.

Treatment and Prognosis

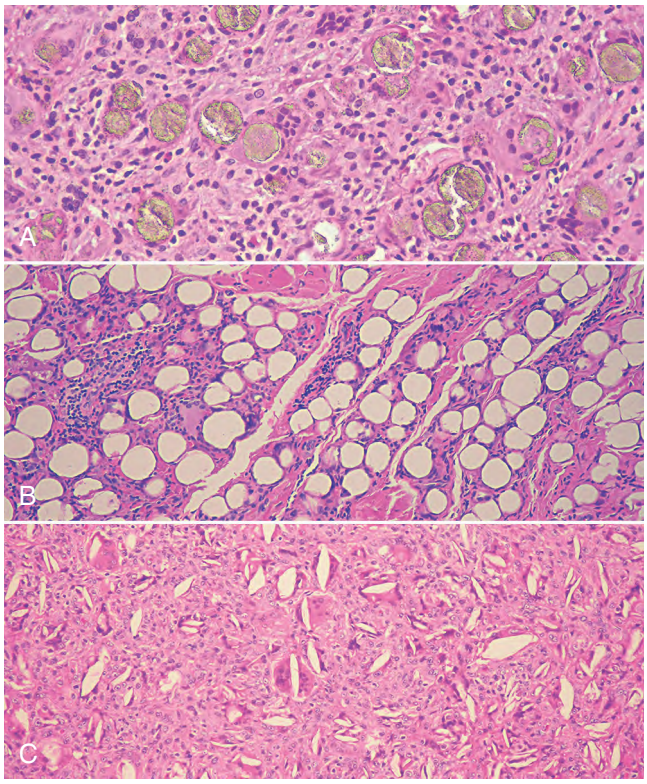
In many instances, the diagnostic biopsy is excisional and completely eradicates the problematic mass. In patients with larger lesions, surgical excision can be problematic due to numerous finger-like extensions of the material into the surrounding tissues. Intralesional or systematic corticosteroids have resulted in a satisfactory reduction in lesional size in many patients. Other therapeutic approaches include locally injected 5-fluorouracil and antibiotics, such as clindamycin or minocycline.

◆ SYSTEMIC METALLIC INTOXICATION

Ingestion or exposure to any one of several heavy metals can cause significant systemic and oral abnormalities. Exposure to heavy metals may be massive, resulting in acute reactions, or it may be minimal over a longer period, producing chronic changes. Oral alterations from ingestion of lead, mercury, silver, bismuth, arsenic, and gold are rare but may occur and warrant discussion. Oral complications from excessive zinc, iron, tin, and manganese are extremely rare.

LEAD

Little is known about the prevalence of lead poisoning **(plumbism),** but lead is one of the most widespread environmental toxins affecting children in the United States.



• **Fig. 8-61 Cosmetic Filler Material.** Cosmetic filler materials embedded in dense fibrous connective tissue with associated granulomatous inflammation. **A,** Hydroxyapatite (Radiesse) as seen in the biopsy of lesion depicted in Fig. 8-60. **B,** Different patient exhibiting polymethylmethacrylate (ArteFill). **C,** Different patient exhibiting poly-L-lactic acid (Sculptra).

Lead solder for plumbing was not banned until 1986. Homes built before then have the potential for significant water contamination, and one of the primary causes of lead intoxication in infants is formula preparation using tap water tainted by the metal.

Another significant source of lead poisoning in children is lead-based paint; children may ingest chips of the paint in older homes or be exposed to the fumes or dust during sanding and renovation. Paint with a high lead content was not restricted until 1977 and still remains in many homes. Removal of lead from gasoline began in 1972 but was not completed in the United States until 1995.

Adult exposure also occurs and often is related to industry. The potential for exposure exists during handling of lead oxide batteries, in lead-processing industries, and from the welding of lead-covered surfaces. Some food and drink containers or vegetables grown in lead-contaminated soil also may contain inappropriate levels of the metal. Lead contamination in illicit alcohol has made the distinction between symptoms of lead intoxication and chronic alcohol abuse very difficult in certain sections of the American Deep South. Lead also can be found in brass fixtures, ceramics, crystal, electrical cable, radiation shielding, folk remedies, and cosmetics. Rarely, plumbism arises from retained lead bullet fragments in gunshot victims.

MERCURY

The danger of mercury exposure is well known. Elemental mercury is poorly absorbed, and its ingestion is relatively harmless. In contrast, inhalation of mercury vapor is very hazardous, with a high rate of absorption and systemic retention. Ingestion of mercury salts (e.g., mercurous chloride) also is associated with significant adverse reactions. Exposure has occurred in association with the use of mercury in teething powders, baby powders, diapers, cathartic agents, and anthelmintic preparations. Investigators also have implicated thimerosal, an ethyl mercury antiseptic utilized in some vaccinations.

A great deal of attention has been directed toward the mercury released from dental amalgams, but no well-documented adverse health effects have been identified (except for relatively rare contact hypersensitivity to mercury, see page 324). The level of mercury that is released from amalgams has been shown not to exceed the range expected from background exposure to environmental mercury. In 2009, the FDA issued a final regulation on dental amalgam, which stated the levels of mercury released by dental amalgam fillings are not high enough to cause harm in patients. In an attempt to shed light on this controversy, the National Institutes of Health (NIH) funded two large randomized clinical trials that compared the neurologic and renal effects of dental amalgam in a 7-year study of a large cohort of children. In these pivotal investigations, no adverse effects from dental amalgam were seen. Interestingly, the control group that received only composite restorations demonstrated a 50% higher need for additional restorative treatment because of the failure of their restorations during the long-term study.

SILVER

Silver has known antibacterial properties and has been associated with a number of additional health benefits. In the past, silver compounds were used topically in nose drops and systemically for a variety of disorders including mental illness, epilepsy, nicotine addition, common colds, sinusitis, gastrointestinal ulcerations, syphilis, and gonorrhea. Because of the numerous complications, including silver intoxication, in 1999 the FDA concluded that colloidal silver or silver salts generally are not recognized as safe and effective and are misbranded. Several silver nitrate and silver sulfadiazine formulations remain available by prescription. These products should be used only under strict supervision. Well-documented examples of generalized argyria have been seen secondary to long-term treatment of aphthous ulcerations, denture sores, and minor gingival hemorrhage with topical silver nitrate.

Despite the efforts of the FDA, devices for production of homemade colloidal silver suspension and a number of colloidal silver formulations continue to be marketed over the Internet and in health food stores as essential mineral supplements for diseases such as arthritis, cancer, diabetes,

AIDS, and herpes. These unregulated silver products have no known physiologic function, and their continued use cannot be supported.

BISMUTH AND ARSENIC

In the United States, excess exposure to bismuth and arsenic currently is rare. The medical use of these metals has diminished dramatically. Most current cases arise from occupational exposure except for excessive arsenic in drinking water seen predominantly in isolated areas of India and Southeast Asia. Bismuth was used in the past for treatment of venereal diseases and various dermatoses, whereas arsenic compounds were prescribed for asthma and skin disorders, such as psoriasis. Bismuth iodoform paraffin paste continues to be used by otolaryngologists and oral surgeons as a surgical pack, with rare reports of associated toxicity. In addition, bismuth subsalicylate tablets (Pepto-Bismol) have been reported to produce localized mucosal discoloration. Chronic exposure to arsenic continues in some lesser developed areas of the world from drinking contaminated water.

GOLD

Gold has been used in medical treatment in the past and continues to be used today in selected cases of active rheumatoid arthritis and other immunologically mediated diseases. In these cases the side effects are well known, and physicians observe the patients closely. In reviews of large-scale skin testing, gold has been found to be among the top ten most frequent allergens, with positive reactions seen in about 10% of the population, including increased prevalence in patients who have gold dental restorations.

Clinical Features

Lead

Lead poisoning results in nonspecific systemic signs and symptoms, thereby making the ultimate diagnosis very difficult. The presentation is extremely variable and determined by the type of lead and the age of the patient. Patients with acute cases most often have abdominal colic, which may occur along with anemia, fatigue, irritability, and weakness. Encephalopathy and renal dysfunction also may occur. Chronic exposure causes dysfunction of the nervous system, kidneys, marrow, bone, and joints. Symptoms generally include fatigue, musculoskeletal pain, and headache. Bones and teeth represent a major reservoir in patients with chronic plumbism, with 90% of the body's deposition being within bone. In radiographs of the long bones in infants, a radiopaque lead line often is noted along the epiphyseal plates.

Oral manifestations include ulcerative stomatitis and a gingival lead line **(Burton line).** The lead line appears as a bluish line along the marginal gingiva resulting from the action of bacterial hydrogen sulfide on lead in the gingival sulcus to produce a precipitate of lead sulfide. Gray areas also may be noted on the buccal mucosa and tongue.

Mercury

Mercury poisoning also may be acute or chronic. With acute cases, abdominal pain, vomiting, diarrhea, thirst, pharyngitis, and gingivitis typically are present. With chronic cases, gastrointestinal upset and numerous neurologic symptoms occur. The neurologic symptoms are termed **erethism** and include excitability, tremors, memory loss, insomnia, shyness, weakness, and delirium. Because mercury salts formerly were used in the processing of felt, hat makers in past centuries were exposed to the metal and experienced similar symptoms, giving rise to the phrase "mad as a hatter." Oral changes include a metallic taste and ulcerative stomatitis combined with inflammation and enlargement of the salivary glands, gingiva, and tongue. The gingiva may become blue-gray to black. Mercuric sulfide can be generated by the bacterial action on the metal and can cause significant destruction of the alveolar bone with resultant exfoliation of teeth.

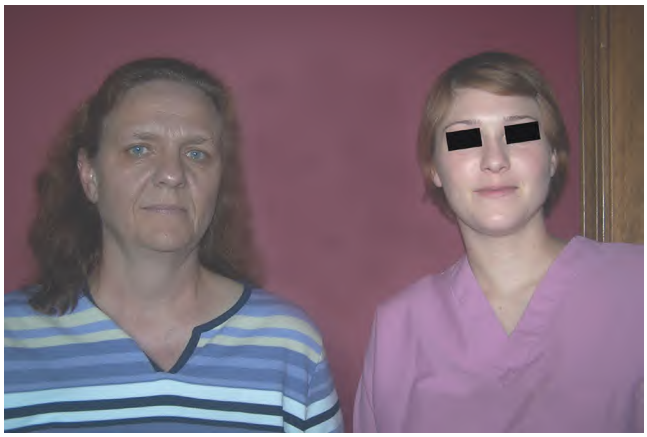
Chronic mercury exposure in infants and children is termed **acrodynia (pink disease** or **Swift-Feer disease).** An erythematous and pruritic rash is present, often with desquamation of the palms and soles. Severe sweating, increased lacrimation, photophobia, neurologic symptoms, hypertension, tachycardia, and gastrointestinal upset also may be present. On occasion, these highly irritable children have torn out patches of their hair. Oral signs include excessive salivation, ulcerative gingivitis, bruxism, and premature loss of teeth. The triad of red, painful desquamating fingers and toes, neurologic symptoms, and hypertension should warn of the possibility of mercury intoxication. Overlap with Kawasaki disease has been noted, suggesting evaluation of 24-hour urine mercury levels when considering that diagnosis.

Silver

Acute silver intoxication can produce coma, pleural edema, hemolysis, and bone marrow failure. Chronic systemic silver intoxication is known as **argyria** and may have toxic effects on the liver, spleen, kidney, intestinal tract, and respiratory system**.** Silver is disseminated throughout the body with substantial amounts accumulating as subepithelial deposits in the skin. These deposits result in a diffuse grayish discoloration that develops primarily in the sun-exposed areas (Fig. 8-62). The conjunctivae, sclerae, and nails also may be pigmented. One of the first signs of argyria occurs in the oral cavity and appears as a slate-blue silver line along the gingival margins. This discoloration is secondary to deposition of metallic silver and silver sulfide pigments. In addition, the oral mucosa often exhibits a diffuse blue-black discoloration.

Bismuth

Systemic bismuth toxicity presents with confusion, encephalopathy, hepatorenal impairment, and methemoglobinemia. Chronic bismuth exposure also can result in a diffuse blue-gray discoloration of the skin, conjunctivae, or oral



• **Fig. 8-62 Argyria.** Grayish discoloration of the face compared with a more normal facial complexion in an individual who used a silver-containing nutritional supplement. Before development of silver intoxication, this blue-eyed, red-haired individual had a very light complexion. (Courtesy of Bradford R. Williams.)

cavity. A blue-gray line along the gingival margin similar to that seen from lead intoxication is the most common intraoral presentation. Associated ptyalism, burning, stomatitis, and ulceration may be seen. Intoxication from bismuth-containing surgical packs has been associated with CNS symptoms, such as delirium. Chronic use of bismuth subsalicylate tablets can create a removable black discoloration of the otherwise normal filiform papillae (see Fig. 1-26, page 13).

Arsenic

Arsenic is a potent human carcinogen associated with cancers of the skin, lungs, kidney, urinary bladder, and possibly liver. Additional health effects from chronic excess arsenic include hypertension, diabetes mellitus, neurologic abnormalities, and disorders of the cardiovascular, pulmonary, hepatic, and renal systems. Progressive arterial occlusion can result in dry gangrene and spontaneous amputation of extremities, which has been termed "blackfoot disease." Significant cutaneous hyperkeratosis and a diffuse macular hyperpigmentation are seen frequently. The discoloration rarely may involve the oral mucosa and is due to both the presence of the metal and an increased melanin production. Additional oral manifestations are very uncommon and typically appear as excessive salivation and painful areas of necrotizing ulcerative stomatitis. In the past, extensive dorsal hyperkeratosis of the tongue was seen in patients with syphilis and may be related to arsenic therapy used before the advent of antibiotic therapy.

Gold

The most common complication of gold therapy is dermatitis, which often is preceded by a warning signal: pruritus. Although a generalized exfoliative dermatitis with resultant alopecia and loss of nails can be seen, dermatitis about the face, eyelids, and at direct sites of skin contact is the most common presentation. Because of the high frequency of allergy to gold, skin testing often is performed before administration of gold drug therapy.

The second most common adverse reaction to gold is severe oral mucositis, which most frequently involves the buccal mucosa, lateral border of the tongue, palate, and pharynx. These mucosal changes represent a systemic allergic reaction and are different from intraoral contact gold hypersensitivity (see page 317). A metallic taste often precedes development of the oral lesions and should be considered another warning signal. Therapy with gold rarely can bring about a slate-blue discoloration of sun-exposed skin **(chrysiasis).**

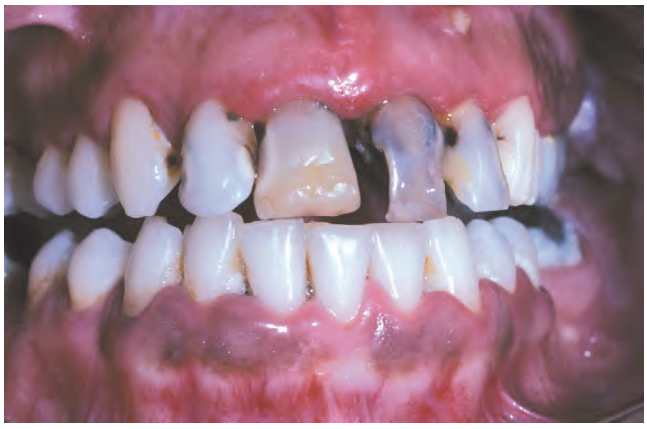
Treatment and Prognosis

The management of heavy metal intoxication involves removal from further exposure to the agent, supportive care, decontamination, and use of chelating agents. In some cases a medication may be responsible and can be discontinued; however, sometimes the source of the metal may be difficult to determine. In infants with radiographic evidence of gastrointestinal lead-containing paint chips, bowel irrigation with a polyethylene glycol electrolyte lavage solution may be warranted. In the past, two chelators, ethylenediaminetetraacetic acid (EDTA) (calcium disodium ethylenediaminetetraacetate) and BAL (2,3-dimercaptopropanol), were first-line therapy in the treatment of lead poisoning, whereas arsenic and mercury intoxication were treated with BAL. These medications may have significant side effects, and less toxic alternatives such as DMSA (2,3-dimercaptosuccinic acid) and DMPS (2,3-dimercaptopropane-1-sulfonate) now are available. No antidote exists for silver intoxication. Attempts to remove the bluish discoloration of facial argyria with dermabrasion have been unsuccessful. Sunscreen, avoiding sunlight, and cosmetics may be somewhat beneficial in minimizing the skin discoloration. Several publications have documented successful treatment of facial argyria with a low-fluence Q-switched 1064-nm Nd:YAG laser. Encephalopathy associated with use of bismuth-containing surgical packs clears on removal of the material, often combined with use of DMPS.

◆ SMOKER'S MELANOSIS

Oral pigmentations are increased significantly in heavy smokers. In one investigation of more than 31,000 whites, 21.5% of tobacco smokers exhibited areas of melanin pigmentation compared with 3% among those not using tobacco. In another study of an ethnically pigmented population, smokers had more oral surfaces exhibiting melanin pigmentation.

Melanin pigmentation in the skin exerts a well-known protective effect against ultraviolet (UV) damage. Investigations of melanocytes located away from sun-exposed areas have shown the ability of melanin to bind to noxious substances. Exposure to polycyclic amines (e.g., nicotine and benzpyrene) has been shown to stimulate melanin



• **Fig. 8-63 Smoker's Melanosis.** Light, diffuse melanin pigmentation in a white female who is a heavy smoker. Pigmentary changes are limited to the anterior facial gingiva.

production by melanocytes that also are known to bind strongly to nicotine. Research has suggested that melanin production in the oral mucosa of smokers serves as a protective response against some of the harmful substances in tobacco smoke. This concept is supported by the findings in "reverse" smokers, who smoke with the lit end of the cigarette inside the mouth and demonstrate heavy melanin pigmentation of the palate. In some reverse smokers, areas of melanocytes are lost and zones of depigmented red mucosa can develop. Cancer is found in 12% of patients with these red zones, further delineating the probable protective effects of melanocytes against toxic substances.

Clinical Features

Although any mucosal surface may be affected, smoker's melanosis most commonly affects the anterior facial gingiva (Fig. 8-63). Most people affected by this condition are cigarette users. In contrast, pipe smokers frequently exhibit pigmentations located on the commissural and buccal mucosae. Reverse smokers show alterations of the hard palate.

The areas of pigmentation significantly increase during the first year of smoking and appear correlated to the number of cigarettes smoked each day. A higher frequency is seen in females, and researchers have suggested that female sex hormones exert a synergistic effect when combined with smoking. Reports from Sweden, Germany, and Japan have shown tobacco smoking to be the most common cause for mucosal pigmentation in light-skinned adult populations.

Histopathologic Features

Biopsy specimens of affected areas in people with smoker's melanosis reveal increased melanin pigmentation of the basal cell layer of the surface epithelium, similar to a melanotic macule (see page 348). In addition, collections of incontinent melanin pigmentation are seen free within the superficial connective tissue and in scattered melanophages.

Diagnosis

The clinician can make the diagnosis by correlating the smoking history with the clinical presentation and medical history. Other causes of melanin pigmentation, such as trauma, neurofibromatosis, Peutz-Jeghers syndrome, drug-related pigmentation, endocrine disturbances, hemochromatosis, chronic pulmonary disease, and racial pigmentation should be excluded.

Treatment and Prognosis

Cessation of smoking results in gradual disappearance of the areas of related pigmentation over a 3-year period. Biopsy should be considered when the pigmentation is in unexpected locations, such as the hard palate, or when there are unusual clinical changes, such as increased melanin density or surface elevation.

◆ DRUG-RELATED DISCOLORATIONS OF THE ORAL MUCOSA

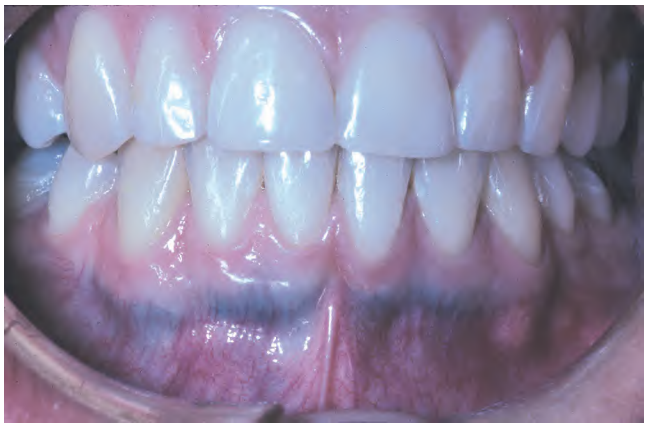
An expanding number of medications have been implicated as a cause of oral mucosal discolorations. Although many medications stimulate melanin production by melanocytes, deposition of drug metabolites is responsible for the color change in others. These pigmentary alterations have been associated with use of phenolphthalein, minocycline, tranquilizers, antimalarial medications, estrogen, chemotherapeutic agents, and some medications used in the treatment of patients with AIDS.

The antimalarial agents that are most frequently implicated are chloroquine, hydrochloroquine, quinidine, and quinacrine; chlorpromazine represents the most frequently implicated tranquilizer. Besides treating malaria, antimalarial agents are used for many other disorders, including lupus erythematosus and rheumatoid arthritis.

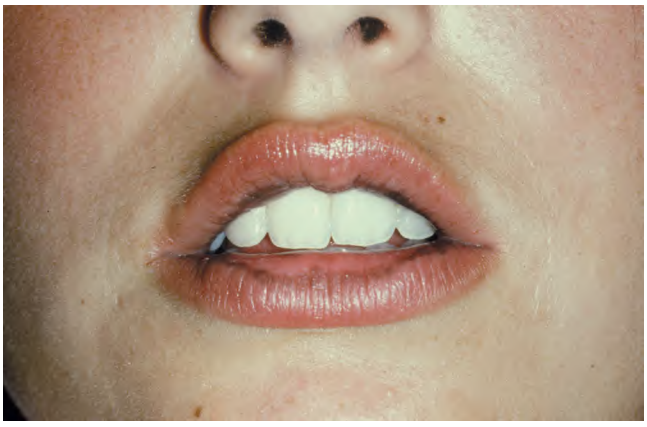
Oral mucosal pigmentation also has been associated with the use of chemotherapeutic medications, such as doxorubicin, busulfan, cyclophosphamide, 5-fluorouracil, or imatinib. Although idiopathic hyperpigmentation also may occur, AIDS patients receiving zidovudine (AZT), clofazimine, or ketoconazole have demonstrated increased melanin pigmentation.

Clinical Features

The clinical presentations of pigmentations related to drug use vary. Most agents produce a diffuse melanosis of the skin and mucosal surfaces, but others may cause a unique pattern. As in many cases of increased melanin pigmentation, females are more sensitive, most likely as a result of an interaction with sex hormones.



• **Fig. 8-64 Minocycline-related Discoloration.** Blue-gray discoloration of the facial surface of the anterior mandibular alveolus because stained alveolar bone is visible through the thin mucosa.



• **Fig. 8-65 Minocycline-associated Pigmentation.** Sharply demarcated brown pigmentation on the vermilion border of the lips, which arose in association with long-term minocycline use and is the result of increased melanin deposition.

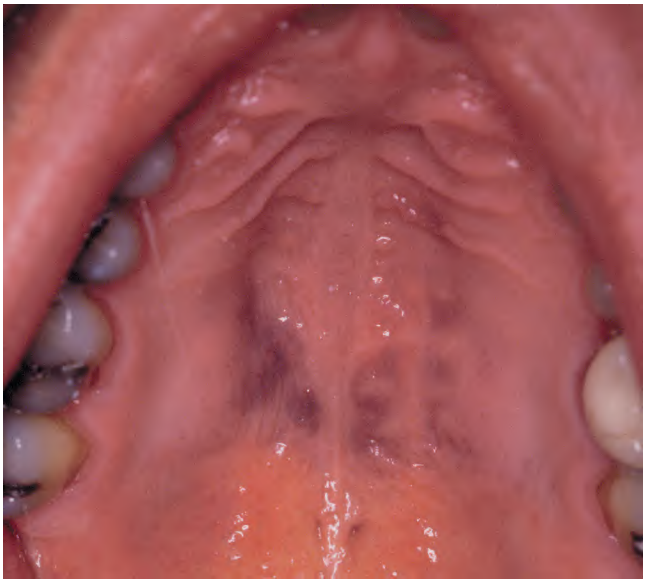
Use of phenolphthalein as a laxative has been associated with numerous small, well-circumscribed areas of hyperpigmentation on the skin. Similar areas of oral mucosal melanosis also can occur. Administration of peginterferon alfa in ethnically pigmented patients with hepatitis C has been associated with hyperpigmentation of the scattered filiform papillae on dorsal surface of the tongue.

Long-term use of minocycline, a semisynthetic derivative of tetracycline, results in discoloration of the bone and developing teeth. The affected bone is dark green but creates a blue-gray discoloration as seen through the translucent oral mucosa. The most common presentations include a linear band above the facial attached gingiva near the mucogingival junction and a broad zone of discoloration on the hard palate (Fig. 8-64). In addition, the dental pulp can become darkly stained, leading to clinically obvious darkened teeth (see page 65).

Minocycline-related pigmentation of the skin and oral mucosa unrelated to discoloration of the underlying bone also has been reported, with patients exhibiting either widespread increased melanosis or focal accumulations of iron-containing particles (Figs. 8-65 and 8-66). The cutaneous pigmentation appears to be dose-dependent and is seen in up to 15% of patients being treated for acne and as many as 70% of those treated for rheumatoid arthritis. Although the cutaneous and oral mucosal staining fades after discontinuation of the medication, the dental discoloration remains.

The classic presentation of intraoral pigmentation from use of antimalarial medications or tranquilizers is a blue-black discoloration limited to the hard palate (Fig. 8-67). In addition, the intake of antimalarial medications may occasionally lead to a more diffuse brown melanosis of the oral mucosa and skin.

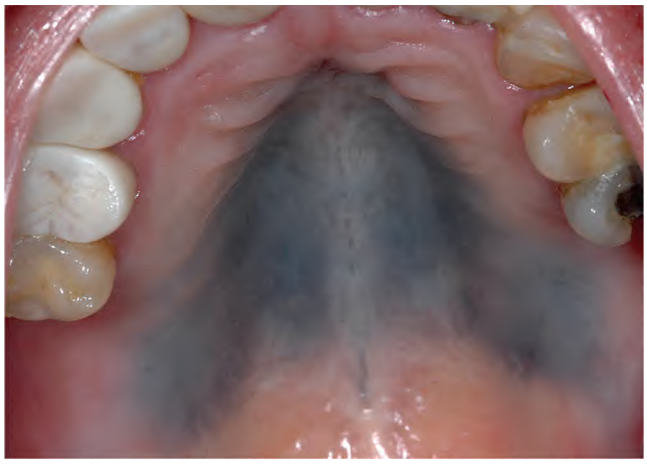
Estrogen, chemotherapeutic agents, and medications used in the treatment of AIDS patients may result in a diffuse brown melanosis of the skin and mucosal surfaces. Any mucosal surface may be involved, but the attached gingiva and buccal mucosa are most frequently affected. The pattern and appearance of the oral mucosal involvement are similar to those seen in racial pigmentation.



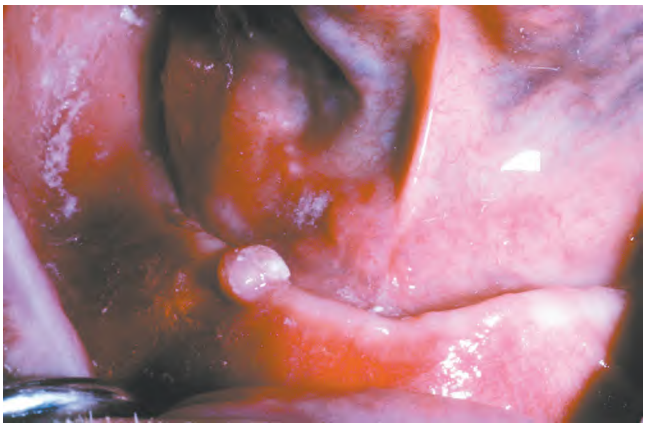
• **Fig. 8-66 Minocycline-associated Pigmentation.** Multifocal areas of palatal pigmentation secondary to deposition of drug metabolites chelated to iron in association with long-term minocycline use. (From Treister NS, Magalnick D, Woo S-B: Oral mucosal pigmentation secondary to minocycline therapy: report of two cases and a review of the literature, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97:718–725, 2004.)

Treatment and Prognosis

Although the discolorations of the oral mucosa may be aesthetically displeasing, they cause no long-term problems. In most instances, discontinuing the medication results in gradual fading of the areas of hyperpigmentation.



• **Fig. 8-67 Hydroxychloroquine Pigmentation.** Diffuse grayish pigmentation of the hard palate. (Courtesy of Dr. John Wright.)



• **Fig. 8-68 Periosteal Hyperplasia with Osseous And Chondromatous Metaplasia.** Tender, elevated nodule along the thin crest of the mandibular alveolar ridge. (Courtesy of Dr. Steven Tucker.)

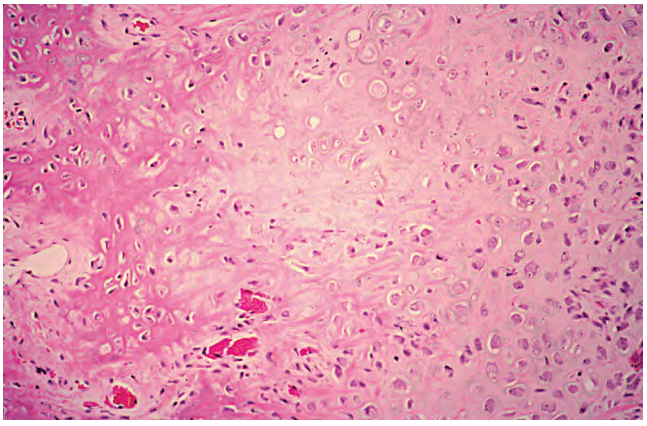
◆ REACTIVE OSSEOUS AND CHONDROMATOUS METAPLASIA (CUTRIGHT LESION)

On occasion, cartilage or bone may be discovered within soft tissue specimens removed from the oral cavity. Cartilaginous rests are known to exist in the area of the nasopalatine duct. In the past, several investigators have reported the presence of cartilage within flabby soft tissue removed from maxillary edentulous alveolar ridges of long-term denture wearers. This finding was thought to represent cartilaginous metaplasia secondary to chronic denture trauma. In retrospect, the islands of cartilage within these cases most likely represent embryologic remnants, not traumatic metaplasia. These rests also are occasionally discovered during histopathologic examination of nasopalatine duct cysts and maxillary gingivectomy specimens.

Despite the suggestion that the anterior maxillary lesions are embryologic and not traumatic, development of **osseous** and **chondromatous metaplasia** from mechanical denture irritation does occur. Although such metaplasia is probably uncommon in the anterior maxilla, its development is not rare along the crest of the posterior mandibular alveolar ridge in long-term denture wearers with atrophic ridges.

Clinical and Radiographic Features

In patients with reactive osseous and chondromatous metaplasia, an extremely tender and localized area of the alveolar ridge typically is noted that may be associated with local enlargement (Fig. 8-68). These changes almost always arise in patients with extensive atrophy of the mandibular alveolar ridge leading to a knife edge–like crest. Although most examples involve the posterior mandible, similar areas rarely may be seen overlying the maxillary alveolar ridge or associated with anterior portions of the mandible. Because of significant associated symptoms and occasional enlargement, biopsy frequently is performed.



• **Fig. 8-69 Osseous and Chondromatous Metaplasia.** High-power photomicrograph demonstrating cellular woven bone and metaplastic cartilage.

Histopathologic Features

Histopathologic examination of reactive osseous and chondromatous metaplasia typically demonstrates a mass of hypercellular periosteum that blends into areas of osseous and chondromatous tissue. The bone and cartilage frequently exhibit atypical features, such as hypercellularity, pleomorphism, nuclear hyperchromatism, and occasional binucleated or multinucleated cells (Fig. 8-69). These alterations are worrisome for sarcoma, but the appropriate diagnosis can be made when an appropriate clinicopathologic correlation is made. In contrast, the cartilaginous rest discovered incidentally in maxillary specimens is usually very bland without any atypical features that would suggest malignancy.

Treatment and Prognosis

The thin mandibular ridges may be recontoured or supplemented with graft material to improve shape and to alleviate the symptoms associated with the localized periosteal hyperplasia. Implants also may reduce the traumatic injury to the ridge and lessen the chance of recurrence. If the ridge

modification is not made, then the continued injury to the site occasionally results in recurrence of the lesion.

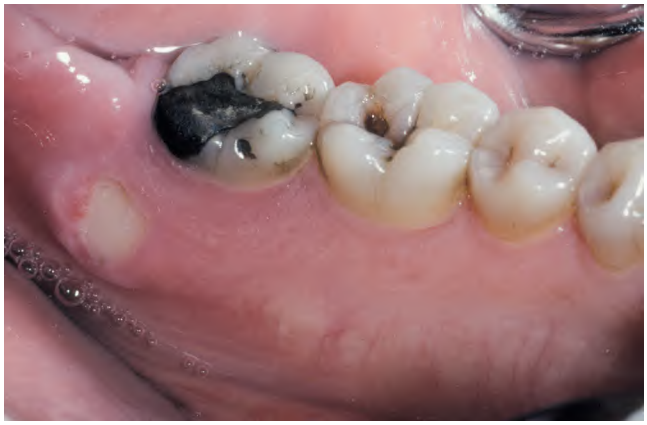
◆ ORAL ULCERATION WITH BONE SEQUESTRATION (SPONTANEOUS SEQUESTRATION; TRAUMATIC SEQUESTRATION)

Focal superficial sequestration of a fragment of cortical bone not related to systemic disease, infection, or a major traumatic event is uncommon. In such instances, the cause of the focal osteonecrosis is not known, although many believe the primary event is a traumatic or aphthous ulceration that leads to osteitis and necrosis of a small focus of adjacent cortical bone. Others have suggested the blood supply of the peripheral cortical plate may be delivered by the periosteal microvasculature, and loss of this supply leads to focal bone necrosis and sequestration. Such lesions tend to occur in anatomically unique sites in which a bony prominence is covered by a thin mucosal surface.

Clinical and Radiographic Features

In most instances, the sequestration arises without the patient's awareness of any preceding trauma. The most frequent site of sequestrum development is the lingual surface of the posterior mandible along the mylohyoid ridge (Fig. 8-70). Focal involvement of exostoses also may occur. Although any exostosis may be involved, mandibular tori are affected most frequently.

The overlying mucosa typically demonstrates a focal area of ulceration that has been present for a period of time that varies from a few days to several months. The presence and intensity of associated pain are variable. Although most cases are unilateral, bilateral involvement may occur. On occasion, an occlusal radiograph will reveal a faint radiopaque mass superimposed and partially lingual to the intact cortical plate.



• **Fig. 8-70 Spontaneous Sequestration.** Mucosal ulceration with exposed bone of the posterior lingual surface of the mandible.

The mylohyoid ridge often is prominent but typically protected from trauma by the lingual inclination of the adjacent molars. Absence of the adjacent molars or restorations that do not replace the normal inclination could predispose the area to repeated trauma; such alterations have been noted in the majority of affected patients.

Histopathologic Features

The sequestra consist of well-organized lamellar bone that exhibits loss of the osteocytes from their lacunae, along with peripheral resorption and bacterial colonization.

Treatment and Prognosis

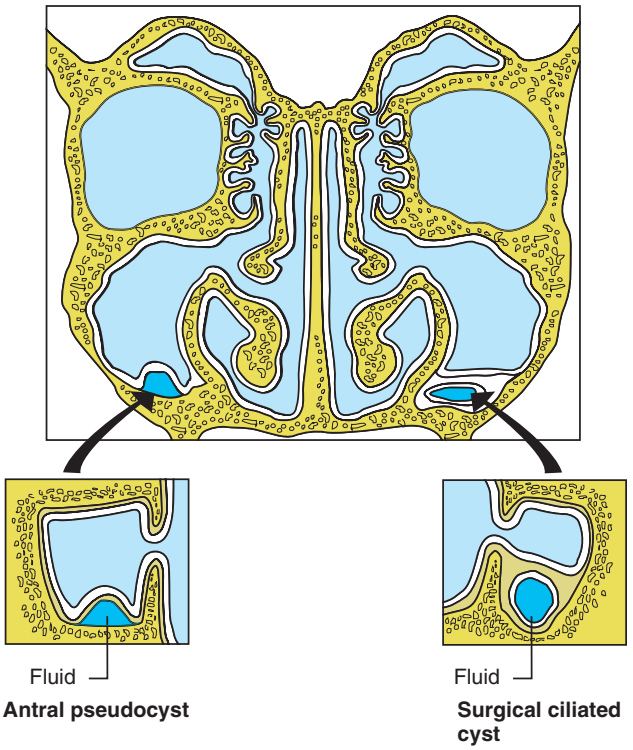
Spontaneous loss of the dead bone or surgical removal of the sequestrum results in rapid healing. Recurrence is uncommon. In some instances, the dead bone is freely movable and easily removed. In other cases, the fragment is adherent to the underlying vital bone and must be surgically excised. In an attempt to avoid surgery, some clinicians use a tetracycline rinse in addition to topical corticosteroids. Alternatively, these patients can be recalled weekly for 2 to 4 weeks, during which time the dead bone may exfoliate spontaneously without the need for invasive therapy.

◆ ANTRAL PSEUDOCYSTS

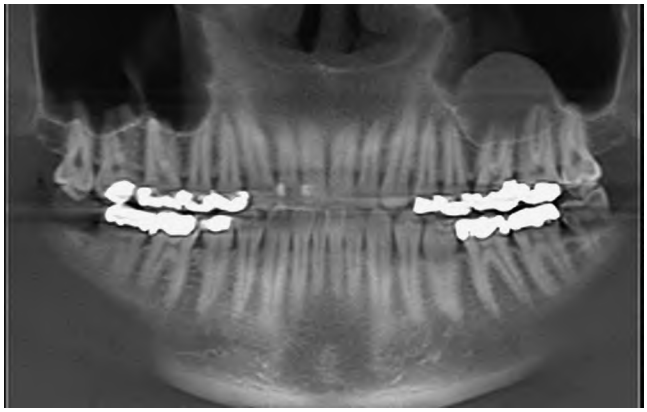
Antral pseudocysts are common findings on panoramic radiographs. The lesion appears as a dome-shaped, faintly radiopaque lesion often arising from the floor of the maxillary sinus. This condition continues to be misunderstood and is inappropriately termed **sinus mucocele** or **sinus retention cyst** by many clinicians (see next section). The antral pseudocyst develops due to an accumulation of an inflammatory exudate (serum, not mucus) beneath the maxillary sinus mucosa, causing a sessile elevation (Fig. 8-71). It must be stressed that the edematous fluid is in the stroma underneath the epithelium, not surrounded by it.

Reviews of large numbers of radiographs have reported a prevalence that ranges from 1.5% to 14% of the population. The cause of the inflammatory infiltrate has not been determined definitively, but in a radiographic review, many cases showed a possible source from an adjacent odontogenic infection. Primary irritation of the sinus lining, such as that seen from a sinus infection or allergies, also can theoretically result in the inflammatory infiltrate.

An increased prevalence of pseudocysts has been noted during the cold winter months, leading some investigators to associate these lesions with an increased frequency of upper respiratory tract infections or irritation from dry, forced-air heating. This association is difficult to confirm because these lesions often are asymptomatic, making the timing of their development difficult to pinpoint. Although allergies have been proposed as a cause, no increased prevalence has been noted during the time of peak pollen exposure.



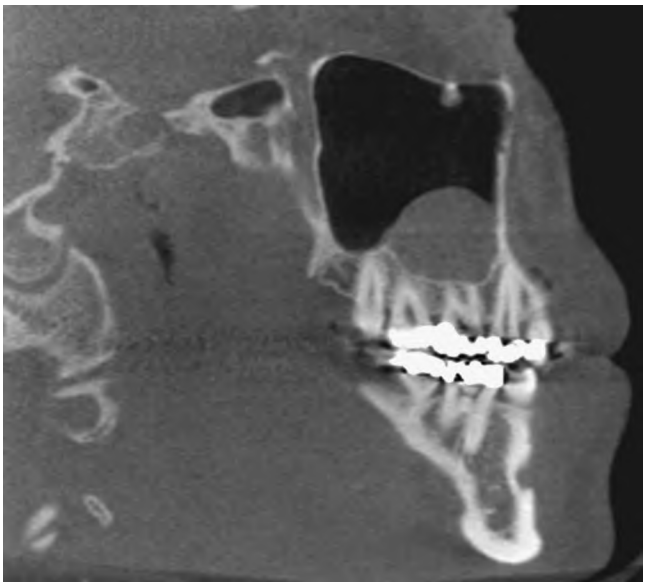
• **Fig. 8-71 Antral Pseudocyst and Surgical Ciliated Cyst.** An antral pseudocyst is an accumulation of serum beneath the sinus lining. A surgical ciliated cyst is an epithelium-lined cystic structure separate from the sinus.



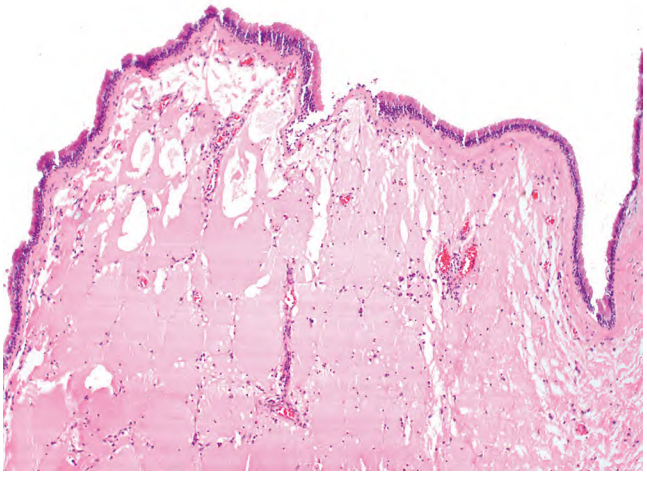
• **Fig. 8-72 Antral Pseudocyst.** Three-dimensional cone-beam radiograph showing dome-shaped radiopacity within the maxillary sinus. (Courtesy of Dr. Scott Jenkins and Dr. Nick Morrow.)

Clinical and Radiographic Features

Most pseudocysts are asymptomatic. On occasion, affected patients report symptoms, such as headache, facial sinus pain, nasal obstruction, postnasal drip, and nasal discharge. Some studies have suggested these symptoms are secondary to other sinus disease and are not relieved by removal of the pseudocyst. Radiographically, an antral pseudocyst typically presents as a uniform and spherical or dome-shaped radiodensity arising from the floor of the maxillary sinus (Figs. 8-72 and 8-73). Maxillary cysts and neoplasms can



• **Fig. 8-73 Antral Pseudocyst.** Three-dimensional cone-beam sagittal section of same patient depicted in Fig. 8-72. Note that the floor of the sinus remains intact below the lesion. (Courtesy of Dr. Scott Jenkins and Dr. Nick Morrow.)



• **Fig. 8-74 Antral Pseudocyst.** Medium-power photomicrograph demonstrating sinus lining overlying edematous connective tissue.

simulate the dome-shaped pattern of an antral pseudocyst, but close examination of a pseudocyst typically reveals the radiopaque floor of the sinus extending over the superior aspect of the lesion. Less frequently, pseudocysts also may be arise from the lateral wall, medial wall, or roof of the antrum.

Histopathologic Features

Antral pseudocysts are covered by sinus epithelium and demonstrate a subepithelial inflammatory exudate that consists of serum, occasionally intermixed with inflammatory cells (Fig. 8-74). Collections of cholesterol clefts and scattered small dystrophic calcifications may be seen.

Treatment and Prognosis

Typically, pseudocysts of the maxillary sinus are harmless, and no treatment is necessary. The adjacent teeth should be evaluated thoroughly, and any foci of infection should be eliminated. A few clinicians prefer to confirm their radiographic impression and rule out a tumor through drainage of the inflammatory exudate. Removal by means of a Caldwell-Luc operation endoscopic surgery should be performed on any radiographically diagnosed lesion that produces significant expansion or is associated definitively with symptoms.

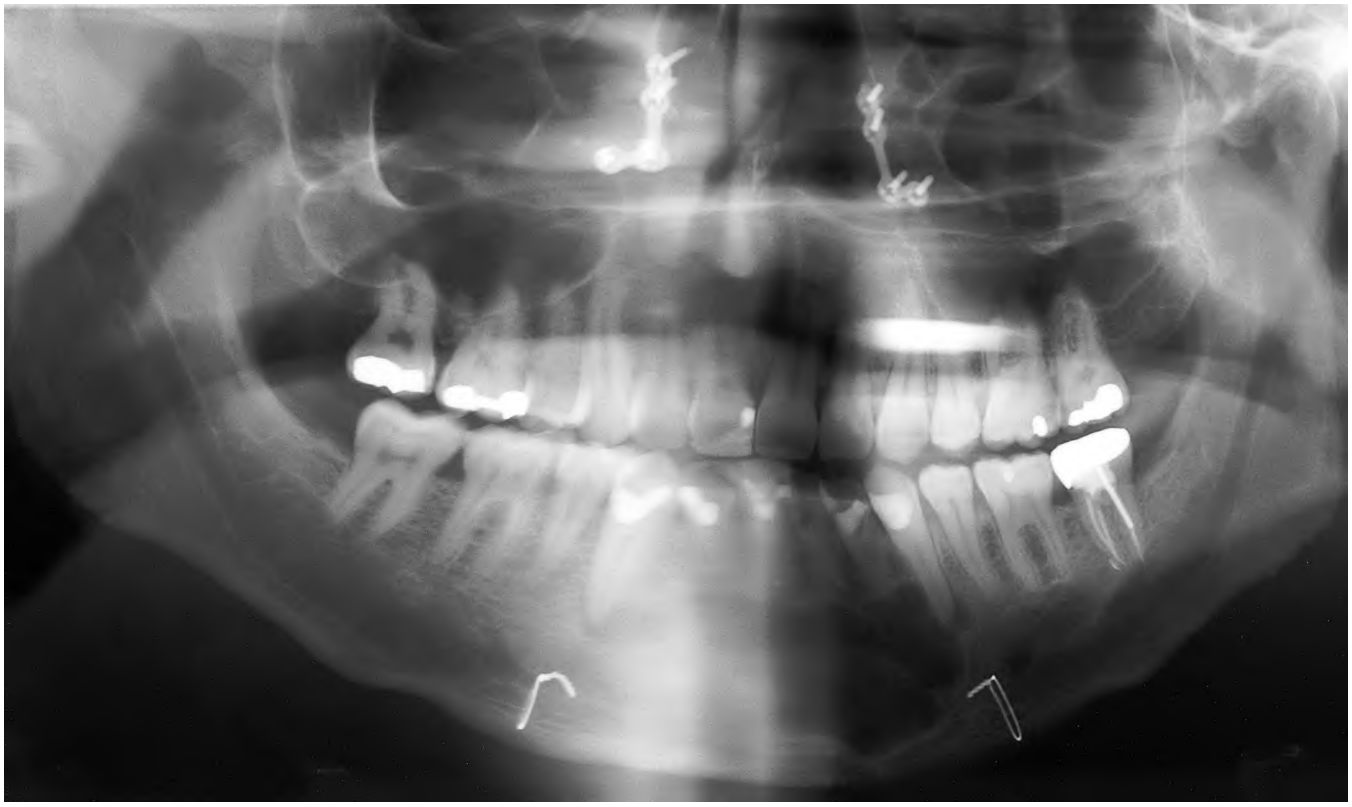
◆ TRUE CYSTS OF THE SINUSES (SINUS MUCOCELE; SURGICAL CILIATED CYST; TRAUMATIC CILIATED CYST; POSTOPERATIVE MAXILLARY CYST; RETENTION CYST)

In contrast to the antral pseudocyst, which arises from subepithelial accumulation of edema fluid, true epithelium-lined cysts also may arise from the sinonasal mucosa and glands. They occur in three situations.

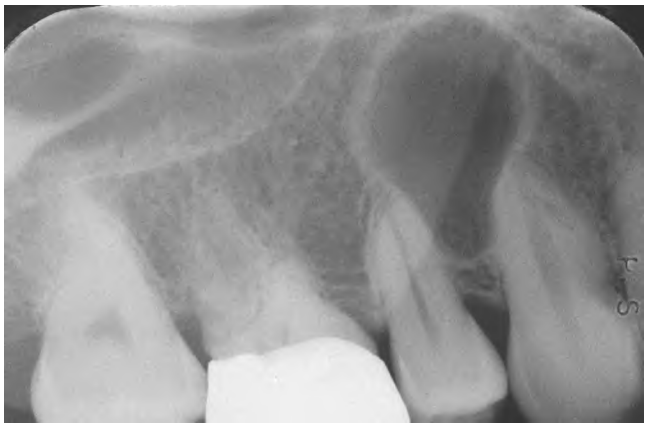
One type of cyst occurs after trauma or surgery to the sinus; this type is best known as a **surgical ciliated cyst, traumatic ciliated cyst**, or **postoperative maxillary cyst.** A portion of the sinus lining becomes separated from the main body of the sinus and forms an epithelium-lined cavity into which mucus is secreted. The cyst most frequently originates after a Caldwell-Luc operation but may arise from difficult extraction of a maxillary tooth in which the floor of the maxillary sinus is damaged. In addition, sinus or nasal epithelium rarely can be transplanted accidentally to the mandible during genioplasty or chin augmentation procedures and lead to formation of ciliated cysts in ectopic locations (Fig. 8-75).

The second type of cyst, known as a **sinus mucocele,** arises from an obstruction of the sinus ostium, thereby blocking normal drainage. This blocked sinus then acts like a separate cyst-like structure lined by epithelium and filled with mucus. Sinus mucoceles enlarge in size as the intraluminal pressure increases and can distend the walls of the sinus and erode through bone; they often clinically mimic malignancy of sinus origin. (It should be emphasized that a sinus mucocele is a distinct, separate pathologic entity that is unrelated to the common mucocele of minor salivary gland origin [see page 422]).

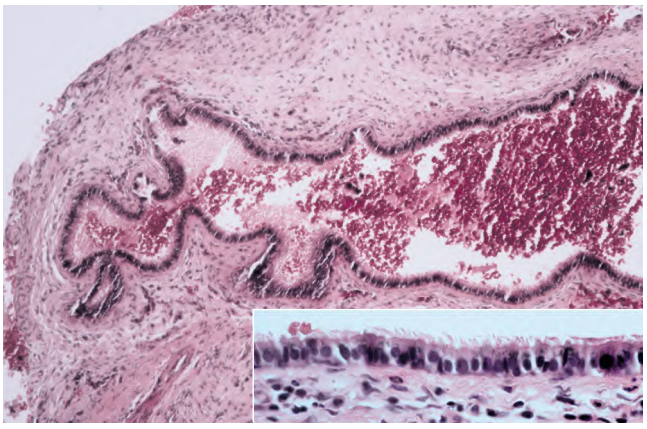
Retention cysts of the maxillary sinus are the third type of true cyst. These lesions arise from the partial blockage of a seromucous gland duct within the sinus wall, or from an invagination of the respiratory epithelium. Most retention cysts are located around the ostium or within antral polyps. The majority of retention cysts are small, not evident clinically, and discovered during histopathologic examination of antral polyps.



• **Fig. 8-75 Surgical Ciliated Cyst.** Ectopic ciliated cyst of the anterior mandible arising when respiratory epithelium was carried from LeFort 1 osteotomy site to mandible during genioplasty procedure. (Courtesy of Dr. Adam Janette.)



• **Fig. 8-76 Surgical Ciliated Cyst.** Well-defined radiolucency between vital maxillary bicuspids. (Courtesy of Dr. Patrick Coleman.)



• **Fig. 8-77 Surgical Ciliated Cyst.** True cyst lined by respiratory epithelium. Inset provides high-power view of the ciliated pseudostratified columnar epithelium that lines the cyst.

Postoperative surgical ciliated cysts appear to be uncommon in the United States and Europe but are reported more frequently in Japan due to the high prevalence of surgical therapy rather than antibiotic treatment for sinusitis prior to the 1970s. Sinus mucoceles arising from ostial obstruction are much more numerous and most frequently involve the frontal sinus, with the ethmoid and sphenoid sinuses being affected less often. Maxillary sinus mucoceles arising from blockage of the ostium are relatively rare and account for less than 10% of paranasal sinus mucoceles.

Clinical and Radiographic Features

Surgical ciliated cysts are spherical lesions that are separate from the sinus and lack the dome-shaped appearance of pseudocysts (Fig. 8-76). As these postoperative cysts enlarge, they can lead to perforation of the sinus walls. When the maxillary sinus is involved by a true sinus mucocele, the entire sinus will appear cloudy. As the lesion enlarges, the walls of the sinus may become thinned and eventually eroded. Retention cysts rarely reach a size that would produce detectable radiographic changes.

Histopathologic Features

Surgical ciliated cysts and sinus mucoceles are true cystic structures lined by ciliated pseudostratified columnar epithelium, squamous epithelium with mucous cells, or metaplastic squamous epithelium (Fig. 8-77). A sinus retention cyst shows focal dilation of a duct associated with the seromucous glands of the sinus lining. The lumen of the dilated duct is filled with thick mucus, often intermixed with chronic inflammatory cells.

Treatment and Prognosis

Because surgical ciliated cysts and sinus mucoceles are expansile and destructive lesions, the traditional therapy for these pathoses is assured surgical removal. Numerous investigators also have shown that sinus mucoceles arising from ostial obstruction often do not require surgical excision, but they respond well to endoscopic middle meatal antrostomy and marsupialization of the mucocele.

◆ CERVICOFACIAL EMPHYSEMA

Cervicofacial emphysema arises from the introduction of air into subcutaneous or fascial spaces of the face and neck. The forced air may spread through the spaces to the retropharyngeal and mediastinal areas. The first case was reported almost 100 years ago and occurred as a result of blowing into a bugle a short time after tooth extraction.

Cervicofacial emphysema of dental origin may arise in several ways:

- After the use of compressed air by the clinician
- After difficult or prolonged extractions
- As a result of increased intraoral pressure (e.g., sneezing, blowing) after an oral surgical procedure
- From no obvious cause

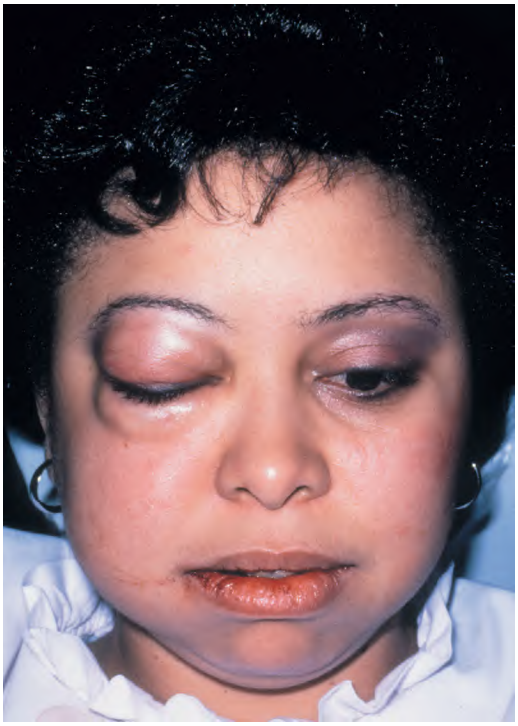
Introduction of air within tissue has been seen after a large number of dental procedures, but most instances involve either surgical extraction of teeth, endodontic procedures, osteotomies, significant trauma, or the use of air or water syringes. In addition, the prevalence has increased as a result of the use of air-driven handpieces during oral surgery or use of lasers with compressed air systems designed to remove tissue debris from the operative field. On occasion, cervicofacial emphysema has resulted from compressed air being accidentally forced into small intraoral lacerations located away from the field of operation. An analogous problem termed **pneumoparotid** can arise when air enters the parotid duct, leading to enlargement of the parotid gland caused by air insufflation. This can be accidental, self-induced, or occupational (e.g., glassblowers and wind instrument players). Stensen duct has numerous redundant mucosal folds that seal as intraoral pressure is increased; in addition, contraction of the buccinator muscle further prevents entrance of air by compressing the duct. In spite of this protection, dramatic increases in intraoral pressures can result in air filling the parotid ductal system.

Clinical and Radiographic Features

More than 90% of cases of cervicofacial emphysema develop during surgery or within the first postoperative hour. Cases with delayed onset are associated with increased postoperative pressure created by the patient. The initial change is one of soft tissue enlargement from the presence of the air in deeper tissues (Fig. 8-78). Pain usually is minimal, and crepitus is detected easily with gentle palpation. Subsequently, the enlargement increases and spreads because of secondary inflammation and edema. Variable pain, facial erythema, dysphagia, dysphonia, vision difficulties, and mild fever may occur. The facial enlargement often is confused with an angioedema, but the diagnosis can be made by identifying crepitus within the swelling. In addition, computed tomography (CT) using the Hounsfield density measuring scale can confirm the presence of soft tissue air pockets.

Significant spread into the mediastinum can result in dysphonia, dysphagia, or dyspnea. Cardiac auscultation often reveals crepitus synchronous with the heartbeat **(Hamman's crunch)** in cases with mediastinal involvement. Pneumomediastinum can be confirmed on chest radiographs by observing displacement of the mediastinal pleura.

Pneumoparotid typically appears as a unilateral enlargement of the parotid that demonstrates crepitus on gentle palpation. Milking the parotid duct produces frothy, air-filled saliva, rather than the typical clear, water-like secretion.



• **Fig. 8-78 Cervicofacial Emphysema.** Periorbital and facial enlargement caused by use of an air-driven handpiece during third molar removal.

Treatment and Prognosis

Broad-spectrum antibiotic coverage is recommended in all dental-related cases of cervicofacial emphysema. The body gradually removes the entrapped air during a 2- to 5-day period. Most cases spontaneously resolve without significant difficulty. Administration of 100% oxygen with a nonrebreather mask can shorten recovery, because the oxygen will replace the air (78% nitrogen, 21% oxygen) and is absorbed more readily. Rare cases of respiratory distress have been noted, and assisted ventilation was required.

The first goal of therapy for pneumoparotid is discovery of the inciting event. In occupation-related cases, such as those seen in trumpet players, the individual should be coached to compress the cheeks during playing. This procedure contracts the buccinator muscle and compresses the parotid duct. Acute symptoms are treated with antibiotics, massage, hydration, sialogogues, and warm compresses.

◆ MYOSPHERULOSIS

Placement of topical antibiotic in a petrolatum base into a surgical site occasionally may result in a unique foreign body reaction, known as **myospherulosis.** The resultant histopathologic pattern is most unusual and was thought initially to represent a previously undescribed endosporulating fungus.

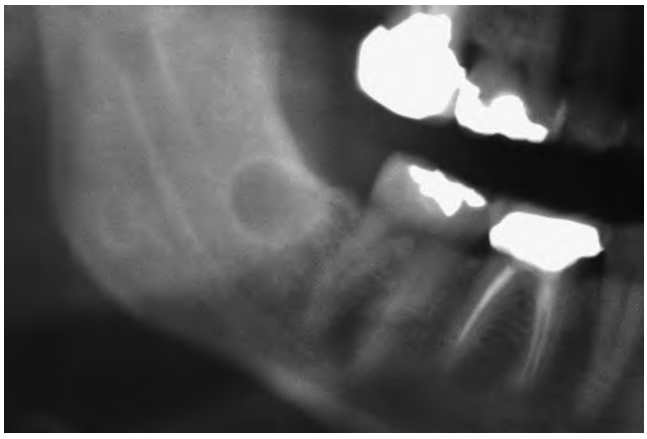
Clinical and Radiographic Features

Myospherulosis may occur at any site within soft tissue or bone where the antibiotic has been placed. Most cases in the dental literature have occurred within bone at previous extraction sites where an antibiotic had been placed in an attempt to prevent alveolar osteitis. Although maxillary and oral soft tissue examples have been documented, most cases have occurred within mandibular surgical sites. In addition, myospherulosis is reported occasionally in a paranasal sinus after a surgical procedure in which a gauze packing coated with an antibiotic ointment was used.

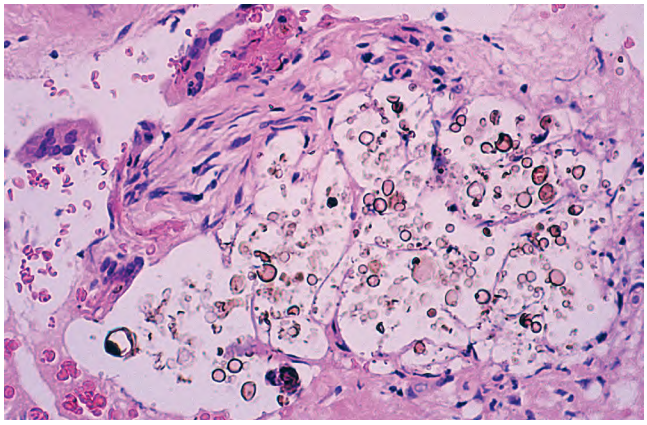
The involved area may exhibit swelling or be discovered as an asymptomatic and circumscribed radiolucency in a previous extraction site (Fig. 8-79). In some cases, pain and purulent drainage have resulted. On exploration of the lesion, a black, greasy, tarlike material is found.

Histopathologic Features

The histopathologic pattern is unique; it is the result of a tissue interaction with both the petroleum base and the antibiotic. Dense collagenous tissue is intermixed with a granulomatous inflammatory response showing macrophages and multinucleated giant cells. Within the connective tissue are multiple cystlike spaces that contain numerous brown- to black-staining spherules (Fig. 8-80). The collections of spherules sometimes are surrounded by an outer membrane known as a *parent body,* forming structures that resemble a "bag of marbles." The spherules represent red



• **Fig. 8-79 Myospherulosis.** Radiolucency has persisted after extraction of the mandibular third molar. An antibiotic ointment was placed at the time of initial surgery.



• **Fig. 8-80 Myospherulosis.** High-power photomicrograph exhibiting multiple cystlike spaces containing numerous brown-stained spherules.

blood cells that have been altered by the medication. The unusual dark coloration is due to the degradation of hemoglobin. To complicate matters, myospherulosis arising in a paranasal sinus occasionally is contaminated with respiratory fungal organisms, such as the Zygomycetes or *Aspergillus*.

Treatment and Prognosis

Myospherulosis is treated by surgical removal of the foreign material and associated tissue. Histopathologic examination of the altered tissue provides the definitive diagnosis. Recurrence is not expected. Those arising in a paranasal sinus and exhibiting fungal infestation respond well to local measures and do not require systemic antimicrobial therapy.

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9 Allergies and Immunologic Diseases

TRANSIENT LINGUAL PAPILLITIS

Transient lingual papillitis (lie bumps, tongue torches) represents a common oral pathosis that rarely has been documented. Affected patients experience clinical alterations that involve a variable number of fungiform papillae of the tongue. The pathogenesis currently is unknown, but the lesions most likely arise from a variety of influences. Suggested causes include local irritation, stress, gastrointestinal disease, hormonal fluctuation, upper respiratory tract infection, viral infection, and topical hypersensitivity to foods, drinks, or oral hygiene products.

Clinical Features

Three patterns of transient lingual papillitis have been documented. The first pattern is localized and involves one to several fungiform papillae that become enlarged and present as elevated papules that are red but may demonstrate a yellow, ulcerated cap (Fig. 9-1). The lesions appear most frequently on the anterior portion of the dorsal surface, are associated with mild to moderate pain, and resolve spontaneously within hours to several days. In a survey of 163 dental school staff members, 56% reported previous episodes of transient lingual papillitis. There was a female predominance, and the vast majority reported a single affected papilla. In one report, the occurrence of the lesions appeared to be associated with a food allergy.

In the second pattern, the involvement is more generalized and affects a large percentage of the fungiform papillae on the tip and lateral portions of the dorsal surface (Fig. 9-2). Individual papillae are very sensitive, enlarged, erythematous, and occasionally display focal surface erosion. Fever and cervical lymphadenopathy are not rare. In these cases, spread of the process among family members has been reported, suggesting a possible correlation to an unknown virus. Spontaneous resolution occurs in about 7 days with occasional recurrences reported.

The third pattern of transient lingual papillitis also demonstrates more diffuse involvement. The altered papillae are asymptomatic, appear as elevated white to yellow papules, and have been termed the *papulokeratotic variant* because of a thickened parakeratotic cap (Fig. 9-3). Although these lesions could be the result of a topical allergy, the histopathology demonstrates features similar to chronic nibbling and suggests the possibility of an unusual pattern of frictional hyperkeratosis.

Histopathologic Features

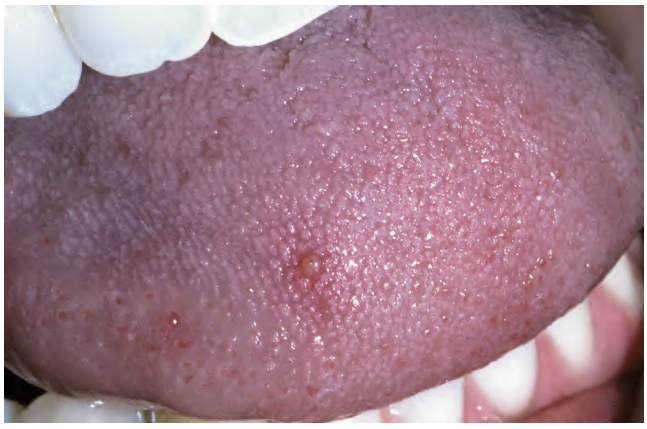
On histopathologic examination of the first two variants, affected papillae demonstrate normal surface epithelium that may reveal focal areas of exocytosis or ulceration. The underlying lamina propria exhibits a proliferation of numerous small vascular channels and a mixed inflammatory cellular infiltrate. Investigation for evidence of human papillomavirus (HPV), herpes simplex, and fungal infestation has been negative. The papulokeratotic variant demonstrates marked hyperparakeratosis in which the surface is ragged and reveals bacterial colonization. A chronic lymphocytic infiltrate is noted in the superficial lamina propria with extension into the basilar portion of the adjacent epithelium.

Treatment and Prognosis

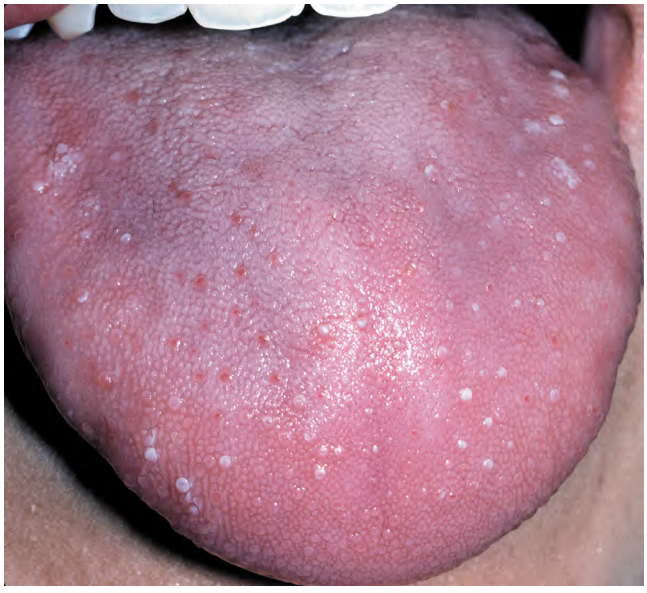
Although transient lingual papillitis resolves without therapy, topical corticosteroids, anesthetics, and coating agents have been used to reduce the pain or duration. In an attempt to eliminate the pain, occasional patients have reported removing the affected papillae with devices such as fingernail clippers. The papulokeratotic variant is asymptomatic and requires no therapy. Although frequently unsuccessful, search for a local or systemic triggering event seems prudent.

RECURRENT APHTHOUS STOMATITIS (RECURRENT APHTHOUS ULCERATIONS; CANKER SORES)

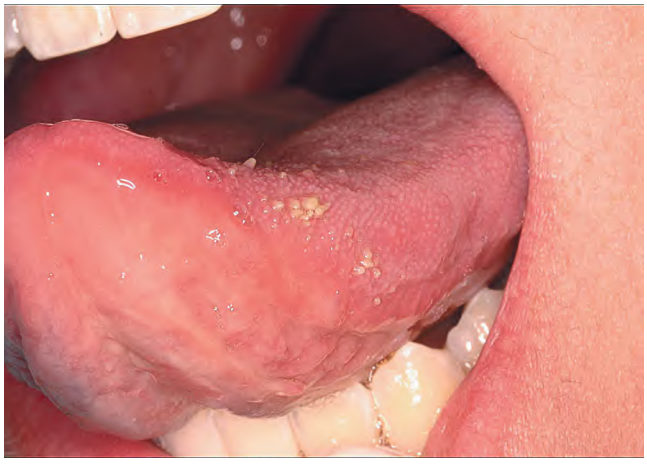
Recurrent aphthous stomatitis is one of the most common oral mucosal pathoses. The reported prevalence in the general population varies from 5% to 66%, with a mean of 20%. Different subgroups of patients appear to have different causes for the occurrence of aphthae. These factors suggest a common disease process that may be initiated by a variety of causative agents, each of which is capable of



• **Fig. 9-1 Transient Lingual Papillitis.** Tender, yellow-pink papule on the dorsum of the tongue.



• **Fig. 9-2 Transient Lingual Papillitis.** Multiple painful white papules on the lateral dorsum and tip of tongue.



• **Fig. 9-3 Transient Lingual Papillitis.** Clusters of asymptomatic, elevated, yellow papules on the dorsolateral surface of the tongue. (Courtesy of Dr. Craig Fowler.)

producing the disease in certain subgroups of patients. To state it simply, the cause appears to be "different things in different people."

Although no single triggering agent is responsible, the mucosal destruction appears to represent a T cell–mediated immunologic reaction with production of tumor necrosis factor-alpha (TNF-α). This factor is a major inflammatory cytokine and assists in the ultimate targeting of the surface epithelium for destruction by cytotoxic T cells (CD8+). Evidence of the destruction of the oral mucosa mediated by these lymphocytes is strong, but the initiating causes are elusive and most likely highly variable.

The following all have been reported to be responsible in certain subgroups of patients (and each discounted in other subgroups!):

- Allergies
- Genetic predisposition
- Hematologic abnormalities
- Hormonal influences
- Immunologic factors
- Infectious agents
- Nutritional deficiencies
- Smoking cessation
- Stress (mental and physical)
- Trauma

Investigators have theorized that aphthous ulcerations develop from an immunologic reaction to an oral antigen. This reaction may arise due the presence of a highly antigenic reagent, a decrease in the mucosal barrier that previously masked the antigen, or immunodysregulation resulting in an abnormal response to a normally present antigen. All previously described triggers can be grouped into one of these three categories. One or more of these three factors may be involved in subgroups of patients.

An antigenic stimulus appears to be the primary initiating factor in the immune-mediated cytotoxic destruction of the mucosa in many patients. The list seems endless, and every item on the list may be important in small subsets of patients. Commonly mentioned potential antigens include sodium lauryl sulfate in toothpaste, many systemic medications (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], various beta blockers, and nicorandil), microbiologic agents (e.g., L forms of streptococci, *Helicobacter pylori,* herpes simplex virus [HSV], varicella-zoster virus [VZV], adenovirus, and cytomegalovirus [CMV]), and many foods (e.g., cheese, chocolate, coffee, cow's milk, gluten, nuts, strawberries, tomatoes, dyes, flavoring agents, and preservatives).

The mucosal barrier appears to be important in the prevention of aphthous stomatitis and might explain the almost exclusive presence of aphthous stomatitis on nonkeratinized mucosa. Numerous factors that decrease the mucosal barrier increase the frequency of occurrence (e.g., trauma, nutritional deficiencies, and smoking cessation); conversely, those associated with an increased mucosal barrier have been correlated with decreased ulcerations (e.g., smoking, hormonal changes, and marked absence of aphthae on mucosa bound to bone).

• BOX 9-1 Systemic Disorders Associated with Recurrent Aphthous Stomatitis

- Behçet syndrome
- Celiac disease
- Cyclic neutropenia
- Nutritional deficiencies (iron, folate, zinc, B_1, B_2, B_6, and B_{12})
- Immunoglobulin A (IgA) deficiency
- Immunocompromised conditions, including human immunodeficiency virus (HIV) disease
- Inflammatory bowel disease
- MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
- PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis)
- Reactive arthritis
- Sweet syndrome
- Ulcus vulvae acutum

An increased prevalence of aphthous-like ulcerations has been noted in a variety of systemic disorders (Box 9-1). These ulcerations typically are identical clinically and histopathologically to those noted in otherwise healthy individuals. In many cases, resolution of the systemic disorder produces a decreased frequency and severity of the mucosal ulcerations.

Three clinical variations of aphthous stomatitis are recognized:

1. Minor
2. Major
3. Herpetiform

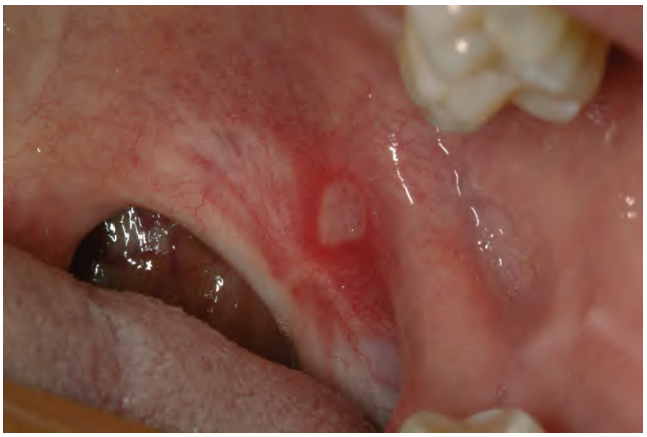
Minor aphthous ulcerations (Mikulicz aphthae) are the most common and represent the pattern present in more than 80% of those affected. **Major aphthous ulcerations** (**Sutton disease** or **periadenitis mucosa necrotica recurrens [PMNR]**) occur in approximately 10% of the patients referred for treatment. The remaining patients have **herpetiform aphthous ulcerations.** The minor and major forms most likely represent variations of the same process, although herpetiform aphthae demonstrate a unique pattern. Some investigators differentiate the herpetiform variant because of supposed evidence of a viral cause, but the proof is weak and does not justify its distinction from the other aphthous ulcerations. Some authors include Behçet syndrome as an additional variation of aphthous stomatitis, but this multisystem disorder is more complex and is considered later in this chapter.

Clinical Features

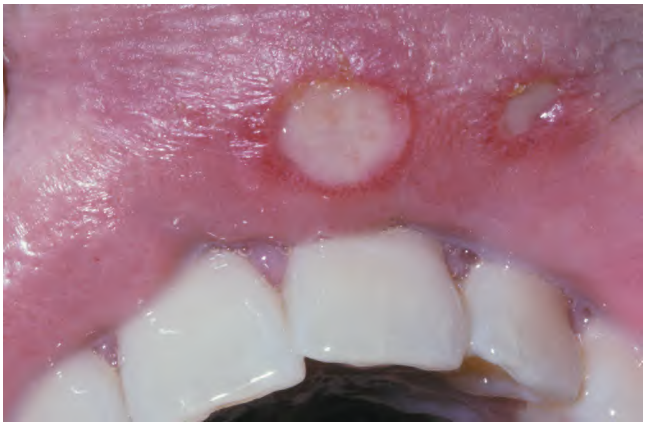
Aphthous ulcerations are noted more frequently in children and young adults, with approximately 80% of affected individuals reporting their first ulceration before the age of 30.

Minor Aphthous Ulcerations

Patients with minor aphthous ulcerations experience the fewest recurrences, and the individual lesions exhibit the shortest duration of the three variants. The ulcers arise almost exclusively on nonkeratinized mucosa and may be preceded by an erythematous macule in association with prodromal symptoms of burning, itching, or stinging. The ulceration demonstrates a yellow-white, removable fibrinopurulent membrane that is encircled by an erythematous halo (Fig. 9-4). Classically, the ulcerations measure between 3 and 10 mm in diameter, demonstrate a variable recurrence rate, and heal without scarring in 7 to 14 days (Fig. 9-5). Although scores of ulcerations may be present at once, from one to five lesions typically are present during a single episode, and the pain often is out of proportion for the size of the ulceration. The buccal and labial mucosae are affected most frequently, followed by the ventral surface of the tongue, mucobuccal fold, floor of the mouth, and soft palate (Fig. 9-6). Involvement of keratinized mucosa (e.g., hard palate, gingiva, dorsal surface of the tongue, and vermilion border) is rare and usually represents extension from adjacent nonkeratinized epithelium.



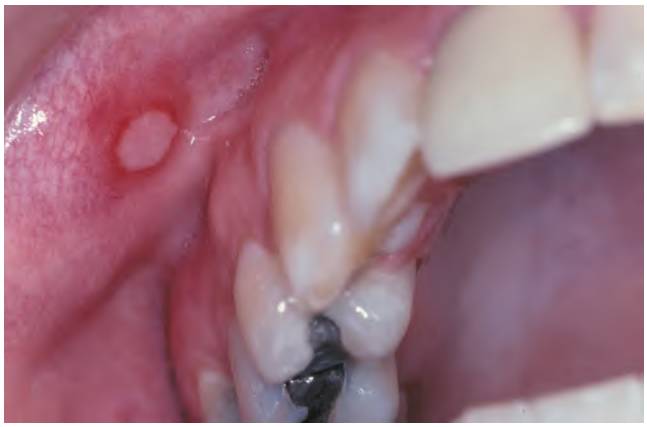
• Fig. 9-4 Minor Aphthous Ulceration. Erythematous halo encircling a yellowish ulceration of the soft palate on the left side.



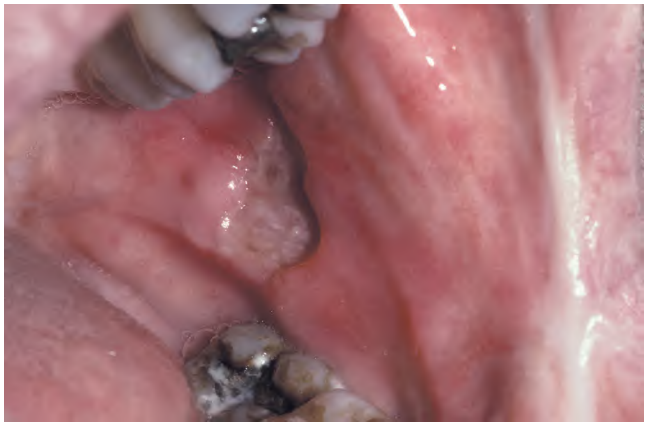
• Fig. 9-5 Minor Aphthous Ulcerations. Two ulcerations of different sizes located on the maxillary labial mucosa.

Major Aphthous Ulcerations

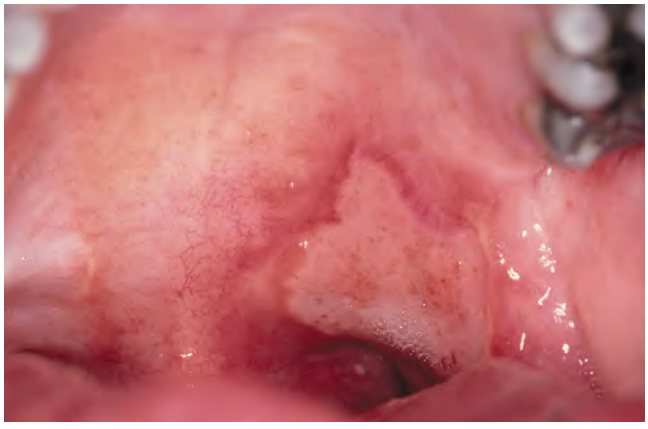
Major aphthous ulcerations are larger than minor aphthae and demonstrate the longest duration per episode. The



• **Fig. 9-6 Minor Aphthous Ulceration.** Single ulceration of the anterior buccal mucosa.

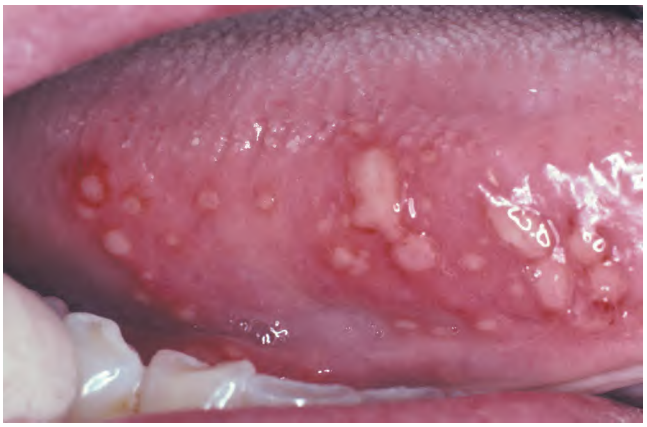


• **Fig. 9-7 Major Aphthous Ulceration.** Large, deep, and irregular ulceration of the posterior buccal mucosa. Note extensive scarring of the anterior buccal mucosa from previous ulcerations.



• **Fig. 9-8 Major Aphthous Ulceration.** Large, irregular ulceration of the soft palate.

ulcerations are deeper than the minor variant, measure from 1 to 3 cm in diameter, take from 2 to 6 weeks to heal, and may cause scarring (Fig. 9-7). The number of lesions varies from 1 to 10. Any oral surface area may be affected, but the labial mucosa, soft palate, and tonsillar fauces are involved most commonly (Fig. 9-8). The onset of major aphthae is after puberty, and recurrent episodes may continue to develop for up to 20 years or more. With time, the associated scarring can become significant, and in rare instances may lead to a restricted mouth opening.



• **Fig. 9-9 Herpetiform Aphthous Ulcerations.** Numerous pinhead ulcerations of the ventral surface of the tongue, several of which have coalesced into larger, more irregular areas of ulceration.

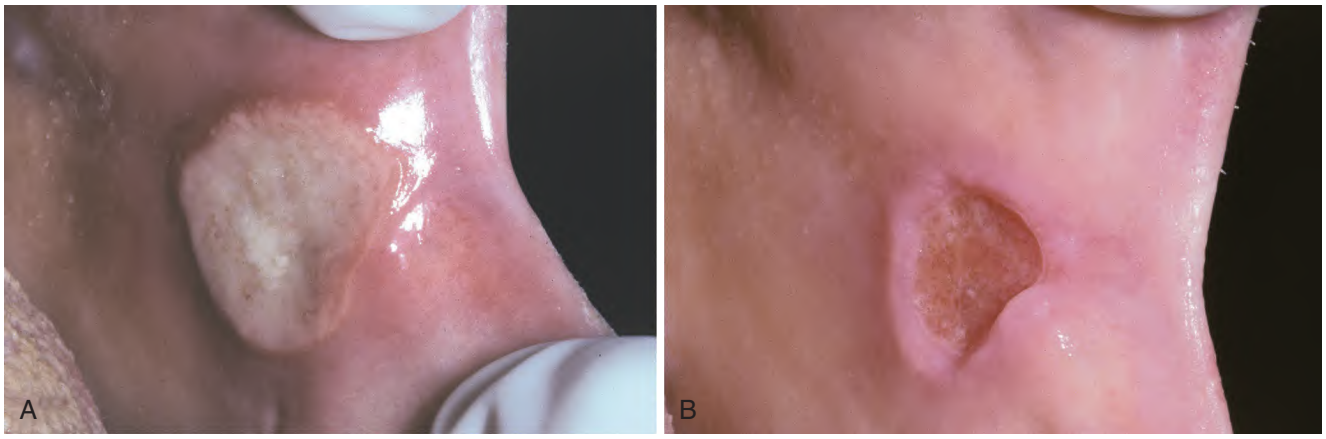
Herpetiform Aphthous Ulcerations

Herpetiform aphthous ulcerations demonstrate the greatest number of lesions and the most frequent recurrences. The individual lesions are small, averaging 1 to 3 mm in diameter, with as many as 100 ulcers present in a single recurrence. Because of their small size and large number, the lesions bear a superficial resemblance to a primary HSV infection, leading to the confusing designation, **herpetiform.** It is common for individual lesions to coalesce into larger irregular ulcerations (Fig. 9-9). The ulcerations heal within 7 to 10 days, but the recurrences tend to be closely spaced. Although the nonkeratinized, movable mucosa is affected most frequently, any oral mucosal surface may be involved. There is a female predominance, and typically the onset is in adulthood.

Further classification of all three types is valuable when planning the most appropriate diagnostic evaluation and therapy. The lesions are diagnosed as **simple aphthosis** when they appear in patients with few lesions that heal within 1 to 2 weeks and recur infrequently. In contrast, patients with **complex aphthosis** have multiple (three or more) and almost constant oral ulcerations that often develop as older lesions resolve. Severe pain and large size are common. Although associated genital or perianal lesions also may be present, there is no other evidence of an associated systemic disease.

Histopathologic Features

The histopathologic picture of aphthous stomatitis is characteristic but not pathognomonic. The early ulcerative lesions demonstrate a central zone of ulceration, which is covered by a fibrinopurulent membrane. Deep to the area of ulceration, the connective tissue exhibits an increased



• **Fig. 9-10 Major Aphthous Ulceration. A,** Large ulceration of the left anterior buccal mucosa. **B,** Same lesion after 5 days of therapy with betamethasone syrup used in a swish-and-swallow method. The patient was free of pain by the second day of therapy. The ulceration healed completely during the next week.

vascularity and a mixed inflammatory cellular infiltrate that consists of lymphocytes, histiocytes, and polymorphonuclear leukocytes. The epithelium at the margin of the lesion demonstrates spongiosis and numerous mononuclear cells in the basilar one-third. A band of lymphocytes intermixed with histiocytes is present in the superficial connective tissue and surrounding deeper blood vessels.

Diagnosis

No laboratory procedure provides definitive diagnosis. The diagnosis is made from the clinical presentation and from exclusion of other diseases that produce ulcerations that closely resemble aphthae (see Box 9-1). In patients with complex aphthous ulcerations, a systematic evaluation for an underlying trigger or associated systemic condition is prudent. In a review of 244 patients with complex aphthous ulcerations, an associated triggering condition (e.g., hematologic deficiency, gastrointestinal disease, immunodeficiency, and drug reaction) was discovered in almost 60%. Because the histopathologic features are nonspecific, a biopsy is useful only in eliminating differential possibilities and is not beneficial in arriving at the definitive diagnosis.

Treatment and Prognosis

The patient's medical history should be reviewed for signs and symptoms of any systemic disorder that may be associated with aphthous-like ulcerations. Most patients with mild aphthosis receive either no treatment, therapy with a number of over-the-counter anesthetics or protective bioadhesive products, or periodic topical medicaments that minimize the frequency and severity of the attacks.

In patients with mild disease, the mainstay of therapy is the use of topical corticosteroids, and the list of possible choices is long. Most patients with diffuse minor or herpetiform aphthae respond well to dexamethasone solution (0.5 mg/5 mL) used in a rinse-and-expectorate method. Patients with localized ulcerations can be treated successfully with 0.05% augmented betamethasone dipropionate gel or 0.05% fluocinonide gel. Adrenal suppression does not occur with appropriate use of these medications. Major aphthous ulcerations are more resistant to therapy and often warrant more potent corticosteroids (Fig. 9-10). The individual lesions may be injected with triamcinolone acetonide or covered with 0.05% clobetasol propionate gel or 0.05% halobetasol propionate ointment. Triamcinolone tablets also can be dissolved directly over the lesions. In hard-to-reach areas, such as the tonsillar pillars, beclomethasone dipropionate aerosol spray can be used. In resistant cases, systemic corticosteroids may be required to supplement the topical medications and gain control. In such instances, prednisolone oral suspension in a swish-and-swallow method is preferable to prednisone tablets. In this way, the ulcerations receive both topical and systemic therapy.

An almost endless list of alternatives to corticosteroid agents has been used to treat patients suffering from aphthous ulcerations. Caution should be exercised, however, because many of these agents have not been examined in a double-blind, placebo-controlled fashion to assess the degree of effectiveness compared with placebo. Furthermore, some of these treatments may have significant side effects or may be quite expensive. Widely accepted topical alternatives include amlexanox paste, chlorhexidine, tetracycline oral suspension, and triclosan mouthrinse. In a recent Cochran meta-analysis, no single systemic therapy was found to be effective in a wide variety of patients. Frequently mentioned systemic therapies include a number of immunomodulatory agents, such as adalimumab, colchicine, dapsone, levamisole, pentoxifylline, and thalidomide.

Although laser ablation shortens the duration and decreases associated symptoms, its use is of very limited practical benefit because patients cannot return on each recurrence. Chemical cautery with silver nitrate continues

to be suggested as an effective therapy, but it can no longer be recommended because of the numerous safer alternatives and its rare association with massive necrosis (see page 265) and systemic argyria (see page 288). A cautery that uses sulfuric acid and phenolic agents is indicated in certain situations, but must be used with caution due to the potential for significant local tissue necrosis related to its misuse.

The success of these different therapeutic approaches is variable from patient to patient. In addition, these interventions do not resolve the underlying problem and are merely an attempt to "beat back brush fires." Recurrences often continue, although breaking up the cycle may induce longer disease-free intervals between attacks. Surgical removal of aphthous ulcerations has been used but is an inappropriate therapy.

Patients with complex aphthosis require a more extensive evaluation for occult systemic disease and a search for possible triggers of the immune-mediated mucosal destruction. To go beyond the management of individual recurrences is difficult, expensive, and often frustrating. In spite of this, patients with severe disease should be offered the opportunity to investigate the underlying causes.

◆ BEHÇET SYNDROME (BEHÇET DISEASE; ADAMANTIADES SYNDROME)

The combination of chronic ocular inflammation and orogenital ulcerations was reported as early as the era of the ancient Greeks and later described in 1931 by a Greek ophthalmologist, Benedict Adamantiades. The classic triad was not delineated until 1937, when a Turkish dermatologist, Hulusi Behçet, defined the disease that bears his name. Although the disease traditionally has been thought primarily to affect the oral, genital, and ocular regions, it now is recognized to be a systemic vasculitis.

Although no clear causation has been established, **Behçet syndrome** appears to represent an abnormal immune process triggered by an infectious or environmental antigen in a genetically predisposed individual. Investigators have correlated attacks to a number of environmental agents, including bacteria (especially streptococci), viruses, pesticides, and heavy metals. Interestingly, reduction of oral bacterial load via periodontal therapy has been shown to reduce the prevalence of associated oral ulcerations in patients with Behçet syndrome.

Histocompatibility antigen B-51 (HLA-B51) has been linked closely to Behçet syndrome, and the frequency of both the disease and the haplotype is high in Turkey, Japan, and the Eastern Mediterranean countries. This distribution appears correlated to the ancient "Silk Route" that extended from China to Rome and was traveled by the Turks. Sexual reproduction between immigrants and locals along the route appears to have spread the genetic vulnerability. Interestingly, when predisposed populations migrate to nonendemic locations, the prevalence decreases, suggesting environmental factors also are involved.

Clinical Features

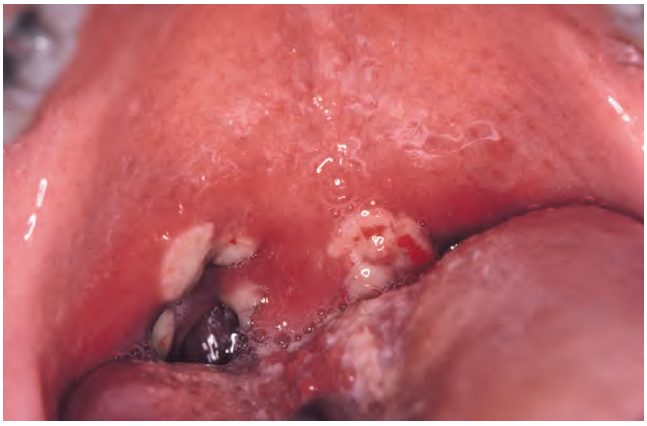
Behçet syndrome is uncommon in blacks and usually arises in the third and fourth decades with the disease rarely presenting before puberty or beyond the age of 50. Men exhibit a slightly increased prevalence and tend to have a worse clinical course.

Virtually all affected patients demonstrate oral ulcerations that often herald the onset of the disease. Other less frequently associated features in order of prevalence include genital ulcerations, cutaneous lesions, arthritis, uveitis, thrombophlebitis, gastrointestinal manifestations, and central nervous system (CNS) involvement.

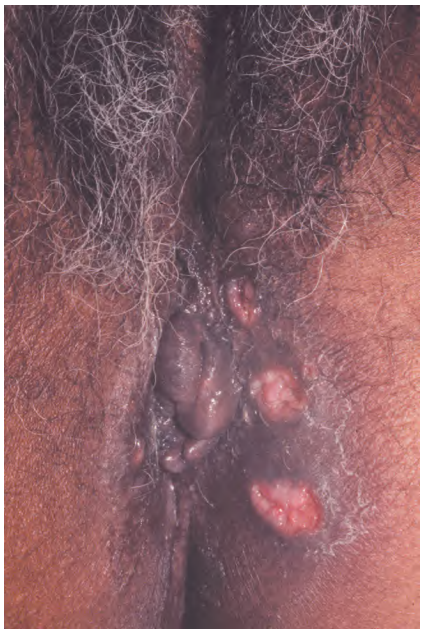
The oral lesions are similar to aphthous ulcerations occurring in otherwise healthy individuals and demonstrate the same duration and frequency. The individual lesions vary in size and are surrounded by a larger zone of diffuse erythema (Fig. 9-11). All three forms of oral aphthous stomatitis may be seen. Although the majority of affected patients have lesions that resemble minor aphthous ulcerations, some reports have documented a prevalence of major aphthae that approaches 40% in patients affected with Behçet syndrome. The herpetiform variant remains uncommon and is noted in approximately 3%.

The genital lesions occur in 75% of the patients. In males, approximately 90% of the lesions involve the scrotum, whereas those in females are most frequent on the vulva, vagina, or uterine cervix. Perineal, perianal, and groin involvement is seen in both genders (Fig. 9-12). These lesions recur less frequently than do the oral ulcerations, but they are deeper and tend to heal with scarring.

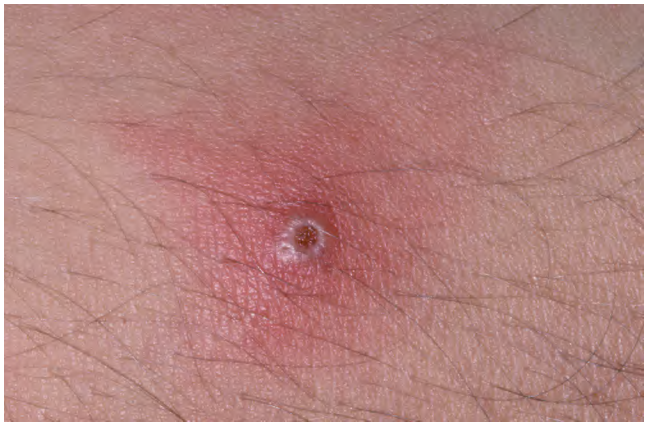
Common cutaneous lesions include erythematous papules, vesicles, pustules, pyoderma, folliculitis, acneiform eruptions, and erythema nodosum–like lesions. In addition to the typical distribution seen in adolescence, the acne-like lesions also involve unusual sites, such as the extremities. From a diagnostic standpoint, one of the most important skin manifestations is the presence of positive "pathergy." One or 2 days after the oblique insertion of a 20-gauge or



• **Fig. 9-11 Behçet Syndrome.** Diffuse erythema surrounding numerous irregular ulcerations of the soft palate.



• **Fig. 9-12 Behçet Syndrome.** Numerous irregular ulcerations of the labia majora and perineum. (From Helm TN, Camisa C, Allen C, et al: Clinical features of Behçet's disease, *Oral Surg Oral Med Oral Pathol* 72:30, 1991.)



• **Fig. 9-13 Behçet Syndrome.** Sterile pustule of the skin that developed 1 day after injection of saline. This reaction is termed *cutaneous pathergy.*

smaller needle under sterile conditions, a tuberculin-like skin reaction or sterile pustule develops (Fig. 9-13). Positive pathergy is geographically variable with a prevalence of 60% in Middle Eastern patients but seen in only approximately 3% of affected Caucasian patients.

Arthritis is one of the more common minor manifestations of the disease and is usually self-limiting and nondeforming. The knees, wrists, elbows, and ankles are affected most frequently.

Ocular involvement occurs in up to 70% of the cases and is more frequent and severe in males. The most common findings are posterior uveitis, conjunctivitis, corneal ulceration, papilledema, and arteritis. The most common secondary ocular complications are cataracts, glaucoma, and neovascularization of the iris and retina. Despite therapy, blindness occurs in 25% of patients with ocular involvement.

TABLE 9-1 International Study Group Criteria for the Diagnosis of Behçet Disease

Criteria	Description
Recurrent oral ulceration	Minor, major, or herpetiform aphthae
Plus two of the following:	
Recurrent genital ulcerations	Aphthaelike ulcerations
Eye lesions	Anterior or posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis
Skin lesions	Erythema nodosum, pseudofolliculitis or papulopustular lesions, or acneiform nodules noted in postadolescent patients not receiving corticosteroids
Positive pathergy test	Read by physician at 24 to 48 hours

Although the vascular disease may involve arteries, veins are affected more frequently and present as superficial and deep thrombophlebitis. The thrombi tend to be adherent to the diseased veins without a tendency toward embolism.

Gastrointestinal disease is variable and includes abdominal pain, anorexia, diarrhea, dyspepsia, and vomiting. CNS involvement is not common but, when present, is associated with a poor prognosis. From 10% to 25% of the patients demonstrate CNS involvement, and the alterations produced result in a number of changes that include paralysis and severe dementia.

Diagnosis

No laboratory finding is diagnostic of Behçet syndrome. In an attempt to standardize diagnoses, definitive criteria have been developed. Table 9-1 delineates the requirements proposed by the Behçet International Study Group.

Histopathologic Features

The histopathologic features are not specific for Behçet syndrome and can be seen in many disorders, including aphthous stomatitis. The pattern most frequently seen is called *leukocytoclastic vasculitis.* The ulceration is similar in appearance to that seen in aphthous stomatitis, but the small blood vessels classically demonstrate intramural invasion by neutrophils, karyorrhexis of neutrophils, extravasation of red blood cells, and fibrinoid necrosis of the vessel wall.

Treatment and Prognosis

Therapy is tailored to the disease severity and prognostic factors. Many patients are treated symptomatically, with the disease often going into remission as the patient ages. Females and older patients have a better prognosis than males or young patients. Ocular lesions and CNS involvement are associated with significant morbidity and mandate more aggressive therapy.

No single medication is universally effective with variable responses seen in different groups of patients. Systemic medications include azathioprine, colchicine, corticosteroids, cyclosporine, dapsone, interferon-α, methotrexate, pentoxifylline, sulfasalazine, thalidomide, and anti-TNF-α medications (adalimumab, etanercept, and infliximab). The oral and genital ulcerations typically respond well to potent topical or intralesional corticosteroids or topical tacrolimus.

Behçet syndrome has a highly variable course. A relapsing and remitting pattern is typical, with attacks becoming more intermittent after 5 to 7 years. In the absence of CNS disease or significant vascular complications, the prognosis generally is good.

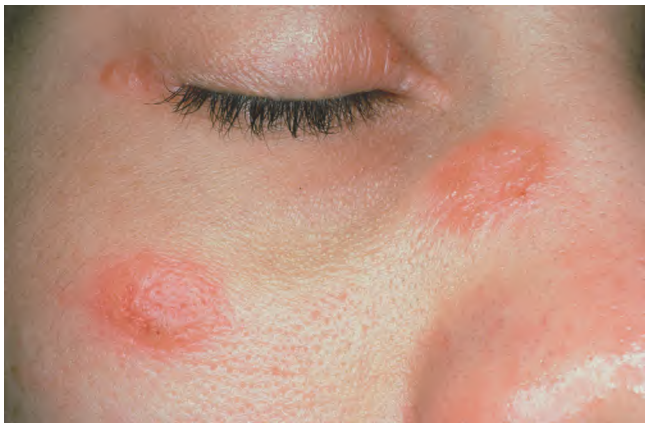
◆ SARCOIDOSIS

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. Jonathan Hutchinson initially described the disease in 1875, but Boeck coined the term *sarcoidosis* (Greek meaning "flesh-like condition") 14 years later. The evidence implicates improper degradation of antigenic material with the formation of noncaseating granulomatous inflammation. The nature of the antigen is unknown, and probably several different antigens may be responsible. Possible involved antigens include infectious agents (e.g., mycobacterium, propionibacteria, Epstein-Barr virus, human herpesvirus 8 [HHV-8]) and a number of environmental factors (e.g., wood dust, pollen, clay, mold, and silica). Several investigators have confirmed a genetic predisposition and positive associations with certain HLA types.

Clinical Features

Sarcoidosis has a worldwide distribution, tends to arise prior to age 50, and exhibits an increased prevalence in females and blacks. The disease may present acutely or demonstrate a chronic course with periods of remission and exacerbation. Acute cases often exhibit fever, fatigue, anorexia, or weight loss combined with other manifestations, such as respiratory symptoms, polyarthritis, visual problems, and skin lesions. In chronic cases, pulmonary symptoms are common and include dry cough, dyspnea, and chest discomfort. Approximately 20% of patients have no symptoms, and the disease is discovered on routine chest radiographs.

Although any organ may be affected, the lungs, lymph nodes, skin, eyes, and salivary glands are the predominant sites. Lymphoid tissue is involved in almost all cases. The mediastinal and paratracheal lymph nodes are involved commonly, and chest radiographs frequently reveal bilateral hilar lymphadenopathy. Approximately 90% of affected patients will reveal an abnormal chest radiograph sometime during the course of the disease. Cutaneous manifestations occur about 25% of the time. These often appear as chronic, violaceous, indurated lesions that are termed **lupus pernio** and frequent the nose, ears, lips, and face (Fig. 9-14). Scattered, nonspecific, tender erythematous nodules, known as **erythema nodosum,** frequently occur on the lower legs.



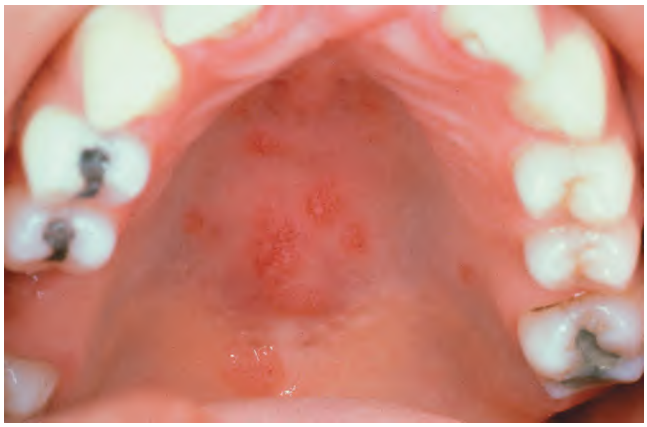
• **Fig. 9-14 Sarcoidosis.** Violaceous indurated plaques of the right malar area and bridge of nose. (Courtesy of Dr. George Blozis.)

Ocular involvement is noted in 25% of the cases and most often appears as anterior uveitis. Lesions of the conjunctiva and retina may occur. Involvement of the lacrimal glands often produces keratoconjunctivitis sicca; the salivary glands can be altered similarly, with resultant clinical enlargement and xerostomia. The salivary gland enlargement, xerostomia, and keratoconjunctivitis sicca can combine to mimic Sjögren syndrome (see page 434).

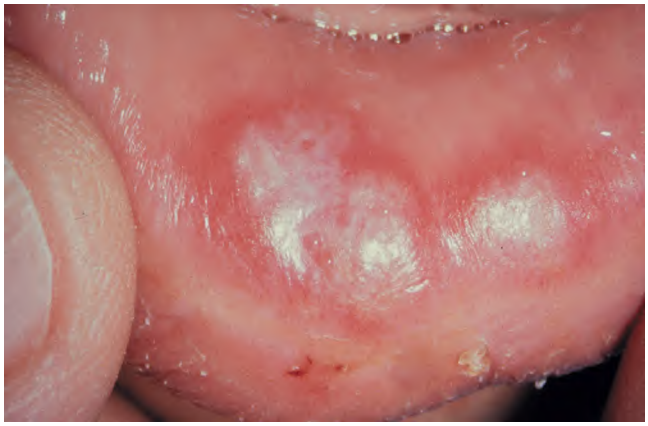
Although lymphoid, pulmonary, cutaneous, and ocular lesions are most common, virtually any organ system may be affected. Other potential sites include the endocrine system, gastrointestinal tract, heart, kidneys, liver, nervous system, and spleen. Intraosseous lesions may occur and most commonly involve the phalanges, metacarpals, and metatarsals. Less frequently, the skull, nasal bones, ribs, and vertebrae are affected.

Two distinctive clinical syndromes are associated with acute sarcoidosis. **Löfgren syndrome** consists of erythema nodosum, bilateral hilar lymphadenopathy, and arthralgia. Patients with **Heerfordt syndrome (uveoparotid fever)** have parotid enlargement, anterior uveitis of the eye, facial paralysis, and fever.

If salivary gland and lymph node involvement are excluded, clinically evident oral manifestations in sarcoidosis are uncommon. Any oral mucosal site can be affected, most often appearing as a submucosal mass, an isolated papule, an area of granularity, or ulceration. The mucosal lesions may be normal in color, brown-red, violaceous, or hyperkeratotic (Figs. 9-15 and 9-16). The most frequently affected intraoral soft tissue site is the buccal mucosa,



• **Fig. 9-15 Sarcoidosis.** Multiple erythematous macules of the hard palate. (Courtesy of Dr. George Blozis.)

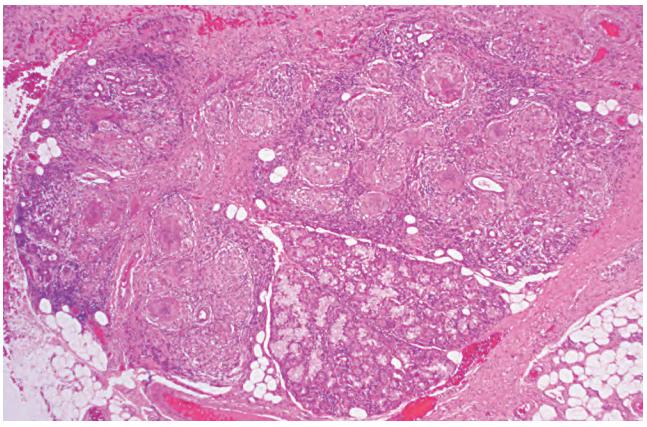


• **Fig. 9-16 Sarcoidosis.** Erythematous macules with central hyperkeratosis of the lower labial mucosa.

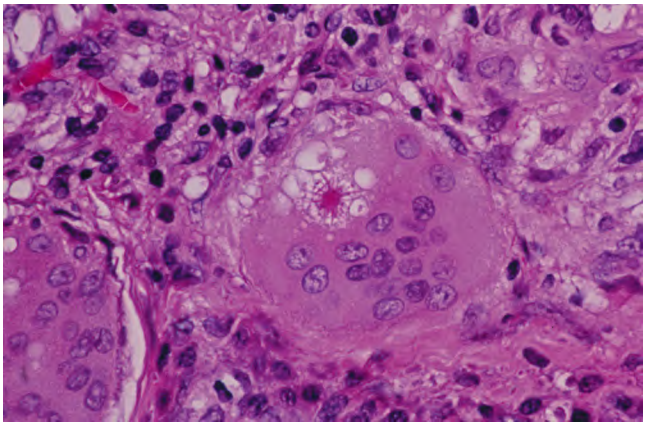
followed by the gingiva, lips, tongue, and palate. Lesions of the floor of the mouth occur but usually are secondary to salivary gland involvement. Intraosseous lesions affect either jaw and represent approximately one-fourth of all reported intraoral cases. Of these cases, most appeared as ill-defined radiolucencies that occasionally eroded the cortex but never created expansion. In the previously reported intraoral cases, the majority of patients demonstrated multisystem involvement, but the oral lesion was the initial manifestation in two-thirds of the patients.

Histopathologic Features

Microscopic examination of sarcoidosis exhibits a classic picture of granulomatous inflammation. Tightly clustered aggregates of epithelioid histiocytes are present, with a surrounding rim of lymphocytes. Intermixed with the histiocytes are scattered Langhans' or foreign body type giant cells (Fig. 9-17). The granulomas often contain laminated basophilic calcifications, known as **Schaumann bodies** (degenerated lysosomes), or stellate inclusions, known as **asteroid bodies** (entrapped fragments of collagen) (Fig. 9-18). None of these structures are specific for sarcoidosis. Special stains for fungal and bacterial organisms are negative. No



• **Fig. 9-17 Sarcoidosis.** Photomicrograph of a labial minor salivary gland demonstrating granulomatous inflammation characterized by circumscribed collections of histiocytes, lymphocytes, and multinucleated giant cells.



• **Fig. 9-18 Sarcoidosis.** Photomicrograph illustrating multinucleated giant cell with intracytoplasmic asteroid body.

polarizable, dissolvable, or pigmented foreign material can be detected.

Diagnosis

The diagnosis is established by the clinical and radiographic presentations, the histopathologic appearance, and the presence of negative findings with both special stains and cultures for organisms. Elevated serum angiotensin-converting enzyme (ACE) levels and appropriate documentation of pulmonary involvement strongly support the diagnosis. In spite of this, elevated ACE is reported in only 60% of patients with sarcoidosis and in a minority of those with oral involvement. Other laboratory abnormalities that may be seen include eosinophilia; leukopenia; anemia; thrombocytopenia; and elevation of the serum alkaline phosphatase level, erythrocyte sedimentation rate, serum calcium concentration, and urinary calcium level.

In the past, a skin test for sarcoidosis, the **Kveim test,** was performed by intradermal injection of a sterilized suspension of human sarcoid tissue. However, this procedure is no longer used because of difficulty in obtaining material

for the test, concern related to its accuracy, and the inability to guarantee the absence of contamination (e.g., prions) in this human tissue.

Minor salivary gland biopsy has been promoted as a diagnostic aid in suspected cases of sarcoidosis (see Fig. 9-17) but is less effective than a parotid biopsy. Previously, biopsy of the parotid was avoided because of the fear of salivary fistula formation and damage to the facial nerve. These concerns have been reduced through biopsy of the posterior superficial lobe of the parotid gland, and confirmation of sarcoidosis has been reported in 93% of patients from this procedure.

Treatment and Prognosis

In approximately 60% of patients with sarcoidosis, the symptoms resolve spontaneously within 2 years without treatment. Most initial diagnoses are followed by a 3- to 12-month period of observation to define the general course of the disease. Active intervention is recommended for progressive disease and patients with cardiac or neurologic involvement, hypercalcemia, disfiguring skin disease, or serious ocular lesions that do not respond to local therapy. In patients requiring treatment, corticosteroids remain first-line therapy, but resistance and relapses are common. Medications used in patients with refractory disease include methotrexate, azathioprine, chlorambucil, chloroquine, and cyclophosphamide. Several studies have shown promising results with TNF-α antagonists such as etanercept, infliximab, pentoxifylline, and thalidomide. In 10% to 20% of those affected by sarcoidosis, resolution does not occur even with treatment. Approximately 4% to 10% of patients die of pulmonary, cardiac, or CNS complications.

◆ OROFACIAL GRANULOMATOSIS

Since Wiesenfeld introduced it 1985, **orofacial granulomatosis** has become a well-accepted and unifying term encompassing a variety of clinical presentations that, on biopsy, reveal the presence of nonspecific granulomatous inflammation.

The disorder is idiopathic but appears to represent an abnormal immune reaction to a variety of inciting agents. In addition, similar lesions can be seen in association with a number of systemic diseases. Table 9-2 delineates systemic diseases that may mimic orofacial granulomatosis, and Table 9-3 lists a number of additional possible triggers.

Clinical Features

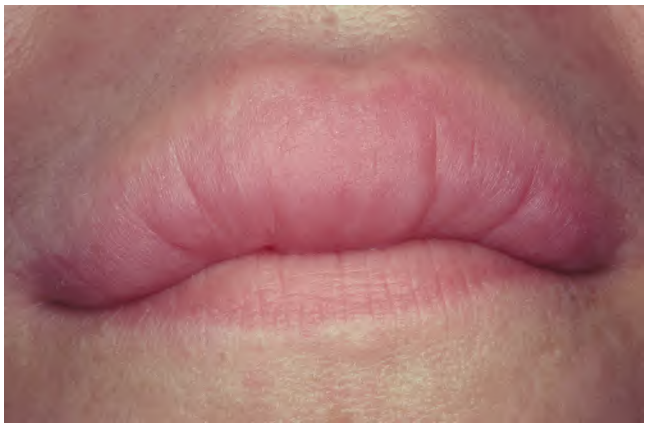
The clinical presentation of orofacial granulomatosis is highly variable. The majority of patients are adults; however,

TABLE 9-2 Systemic Evaluation of Patients with Orofacial Granulomatosis

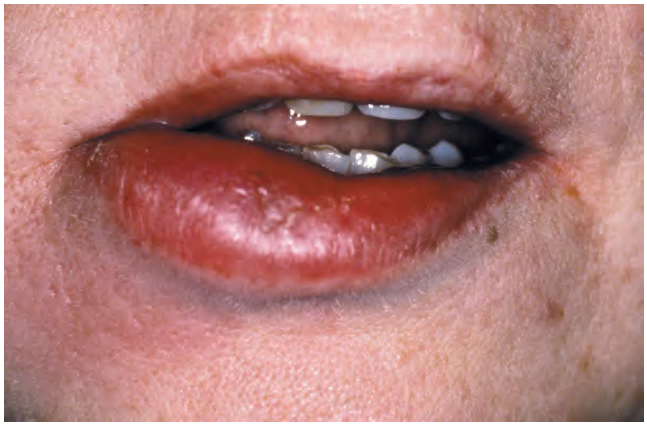
Systemic Cause	Preliminary Screening Procedure
Chronic granulomatous disease	Neutrophil nitroblue tetrazolium reduction test (perform if medical history of chronic infections is noted)
Crohn disease	Hematologic evaluation for evidence of gastrointestinal malabsorption (e.g., low albumin, calcium, folate, iron, and red blood cell count; elevated erythrocyte sedimentation rate) or leukocyte scintigraphy using ^{99m}Tc-HMPAO (hexamethyl propylene amine oxime); if initial screen is positive, then recommend esophagogastroduodenoscopy, ileocolonoscopy, and small-bowel radiographs
Sarcoidosis	Serum angiotensin–converting enzyme and chest radiograph (hilar lymphadenopathy)
Tuberculosis	Skin test and chest radiograph (negative acid-fast bacteria [AFB] stain on biopsy specimen does not rule out mycobacterial infection)

TABLE 9-3 Interventions to Rule Out Local Causes for Orofacial Granulomatosis

Local Cause	Intervention
Chronic oral infection	Eliminate all oral foci of infection.
Foreign material	The foreign debris noted in iatrogenic gingivitis is often subtle and difficult to associate definitively with the diffuse inflammatory process. If lesions are nonmigrating and isolated to gingiva, then response to local excision of a single focus should be evaluated.
Allergy	Cosmetics, foods and food additives (benzoate, carbone piperitone, carmoisine, carvone, chocolates, cinnamon, cocoa, dairy products, eggs, monosodium glutamate, peanuts, sun yellow dye, and wheat) flavorings, oral hygiene products (e.g., toothpaste and mouth rinses), and dental restorative metals have been implicated. Patch testing (i.e., contact dermatitis standard series with oral battery) or elimination diet may discover the offending antigen.



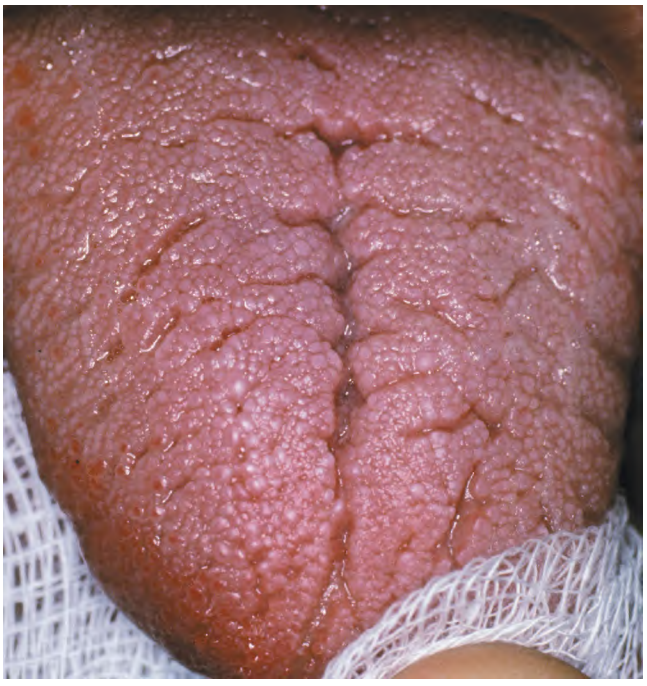
• **Fig. 9-19 Orofacial Granulomatosis (Cheilitis Granulomatosa).** Nontender, persistent enlargement of the upper lip. (From Allen CM, Camisa C: Diseases of the mouth and lips. In Sams WM, Lynch P, editors: *Principles of dermatology,* New York, 1990, Churchill Livingstone.)



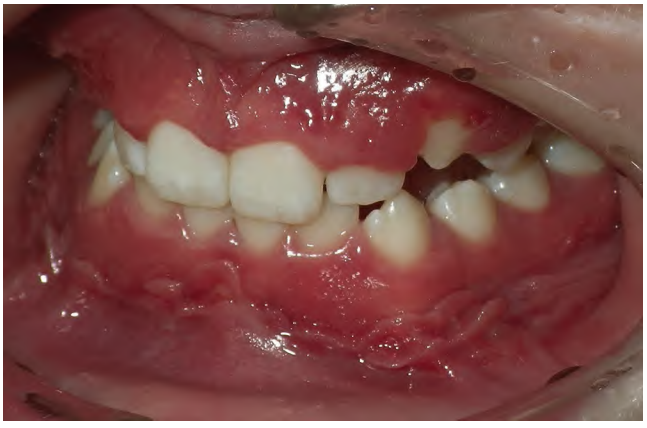
• **Fig. 9-20 Orofacial Granulomatosis (Melkersson-Rosenthal Syndrome).** Persistent enlargement of the lower lip. (Courtesy of Dr. Richard Ziegler.)

the process may occur at any age. By far, the most frequent site of involvement is the lips. The labial tissues demonstrate a nontender, persistent swelling that may involve one or both lips (Fig. 9-19). When these signs are combined with facial paralysis and a fissured tongue, the clinical presentation is called **Melkersson-Rosenthal syndrome** (Figs. 9-20 and 9-21). Involvement of the lips alone is called **cheilitis granulomatosa (of Miescher).** Neither of these two clinical presentations represents a specific disease, and it appears best to include both of these under the term *orofacial granulomatosis.*

Intraoral sites also can be affected, and the predominant lesions are edema, ulcers, and papules. The tongue may develop fissures, edema, paresthesia, erosions, or taste alteration. The gingiva can develop swelling, erythema, pain, or erosions. The buccal mucosa often exhibits a cobblestone appearance of edematous mucosa or focal areas of submucosal enlargement. Linear hyperplastic folds may occur in the sulcus, often with elongated ulcerations in the base of



• **Fig. 9-21 Orofacial Granulomatosis (Melkersson-Rosenthal Syndrome).** Same patient as depicted in Fig. 9-20. Note numerous furrows on the dorsal surface of the tongue. (Courtesy of Dr. Richard Ziegler.)



• **Fig. 9-22 Orofacial Granulomatosis.** Hyperplastic mucosa noted bilaterally in the mandibular mucobuccal fold. (Courtesy of Dr. Steven A. Anderson.)

these folds (Fig. 9-22). The palate may have papules or large areas of hyperplastic tissue. Hyposalivation rarely is reported.

Histopathologic Features

In classic cases of cheilitis granulomatosa, edema is present in the superficial lamina propria with dilation of lymphatic vessels and scattered lymphocytes seen diffusely and in clusters. Fibrosis may be present in long-term lesions. Scattered aggregates of noncaseating granulomatous inflammation, consisting of lymphocytes and epithelioid histiocytes, are present, with or without multinucleated giant cells. Typically, the granulomas appear to cluster around scattered

vessels and are not as well formed or discrete as those seen in sarcoidosis (Fig. 9-23).

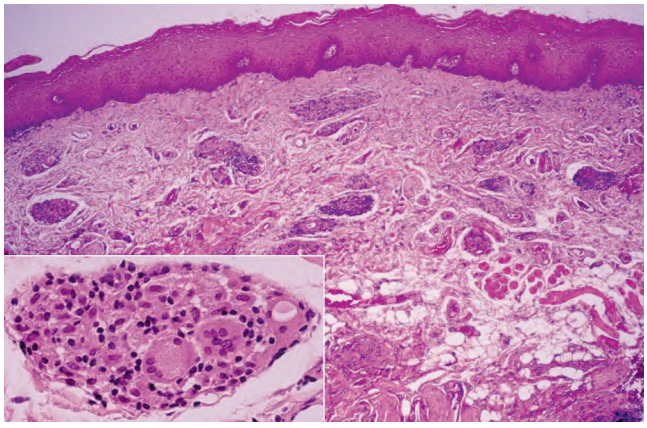
Special stains for fungal organisms and acid-fast bacteria are negative. No dissolvable, pigmented, or polarizable foreign material should be present. When the lesions are confined to the gingiva, a thorough search should be made, because many cases of granulomatous gingivitis are due to subtle collections of foreign material (see page 146).

Diagnosis

The initial diagnosis of orofacial granulomatosis is made on histopathologic demonstration of granulomatous inflammation that is associated with negative special stains for organisms and no foreign material. Because clinical and histopathologic features of orofacial granulomatosis can be produced by a variety of underlying causes, this diagnosis is the beginning, not the end, of the patient's evaluation. Prior to administering any medication or considering surgical intervention, the patient should be evaluated for the systemic diseases and local processes (see Tables 9-2 and 9-3) that may be responsible for similar oral lesions. If features diagnostic of one of these more specific disorders are discovered, then the oral lesions presumably would be related to that disease. If a specific diagnosis cannot be made, then potential foci of infection should be eliminated. If no resolution is noted after reducing local inflammatory factors, then referral of the patient for allergy testing should be considered.

Patients ultimately discovered to have Crohn disease often present at a younger age and have less lip swelling, although lesions of the buccal vestibule are more likely. Because gastrointestinal involvement has been discovered in up to 60% of patients with orofacial granulomatosis who have no intestinal symptoms, several investigators have suggested thorough gastrointestinal evaluation of all children and young adults presenting with orofacial granulomatosis.

The worldwide prevalence of allergy is estimated to be 22%, whereas the frequency noted in patients with orofacial granulomatosis is well over 50% in several studies. Although allergy testing has been useful in many patients, diet restriction has been successful irrespective of patch test results in occasional individuals. Several investigators have suggested a cinnamon- and benzoate-free diet in all patients in whom an obvious trigger cannot be found.

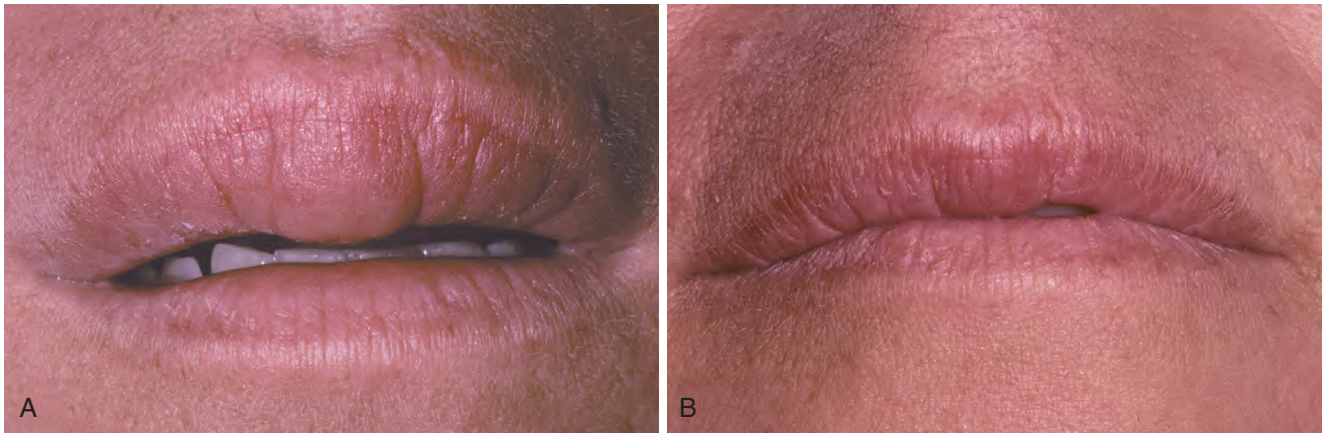


• **Fig. 9-23 Orofacial Granulomatosis.** Clusters of granulomatous inflammation around scattered vessels. The inset illustrates the histiocytes and multinucleated giant cells within the granulomas.

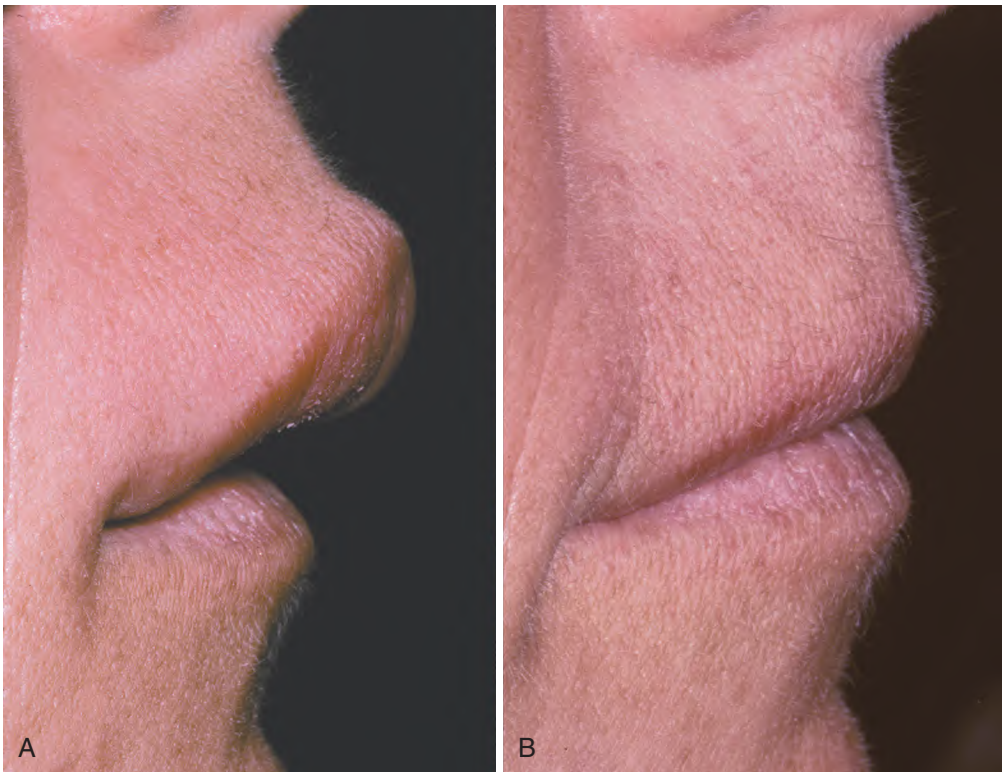
Treatment and Prognosis

The first goal of management should be discovery of the initiating cause, although this may be difficult because the trigger often is elusive.

Oral lesions have been treated with a variety of interventions, with variable results. Topical or intralesional corticosteroids, topical tacrolimus, radiotherapy, sulfasalazine, hydroxychloroquine sulfate, azathioprine, cyclosporine A, methotrexate, danazol, dapsone, TNF-α antagonists (infliximab and thalidomide), clofazimine, metronidazole, and numerous other antibiotics have been tried. Currently, most investigators administer intralesional delayed-release high-concentrate triamcinolone to control the progression of this disease (Figs. 9-24 and 9-25). In the absence of a response to other treatments, surgical recontouring has been used by



• **Fig. 9-24 Orofacial Granulomatosis. A,** Diffuse enlargement of the upper lip. **B,** Same patient after intralesional triamcinolone injections.



• **Fig. 9-25 Orofacial Granulomatosis.** Same patient depicted in Fig. 9-24. **A,** Clinical appearance before local therapy. **B,** Significant resolution after intralesional corticosteroid therapy.

some but carries a considerable risk of recurrence and rarely appears to be warranted.

The prognosis is highly variable. No therapy has proved to be the "silver bullet" in resolving the individual lesions. In some cases, lesions resolve spontaneously, with or without therapy; in others, they continue to progress in spite of a myriad of therapeutic attempts to stop the progression.

◆ WEGENER GRANULOMATOSIS

Wegener granulomatosis is a well-recognized, although uncommon, disease process of unknown cause. Initially described in the German literature in 1936 by Friedrich Wegener, the disorder includes necrotizing granulomatous lesions of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis of small arteries and veins. The pathogenesis of the disease is thought to be due to an abnormal immune reaction to an inhaled environmental antigen or infectious agent. A possible hereditary predisposition has been mentioned in some cases.

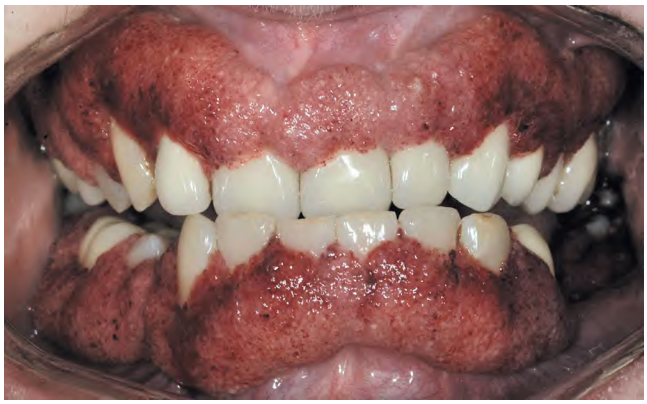
Clinical Features

Wegener granulomatosis demonstrates a wide age range from childhood to old age, with a mean of age of 41 years and no sex predilection. Although most frequently presenting in adults, approximately 15% of the cases arise prior to age 20. A prevalence of 3 out of 100,000 has been reported, and 90% of the cases arise in Caucasians. The disease can involve almost every organ system in the body. With classic Wegener granulomatosis, patients initially show involvement of the upper and lower respiratory tract; if the condition remains untreated, then renal involvement often rapidly develops **(generalized Wegener granulomatosis).**

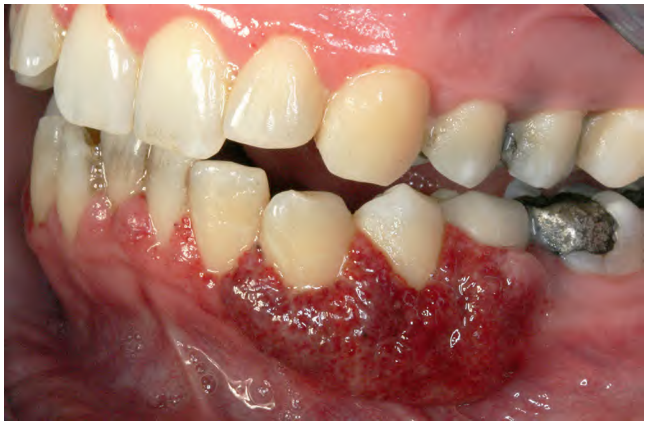
Limited Wegener granulomatosis is diagnosed when there is involvement of the respiratory system without rapid development of renal lesions. One subset of patients exhibits lesions primarily of the skin and mucosa, a condition termed **superficial Wegener granulomatosis.** In this form of the disease, systemic involvement develops slowly. These three different clinical patterns highlight the variability of the clinical aggressiveness that can occur in patients with Wegener granulomatosis.

Purulent nasal drainage, chronic sinus pain, nasal ulceration, congestion, and fever are frequent findings from upper respiratory tract involvement. Persistent otitis media, sore throat, and epistaxis also are reported. With progression, destruction of the nasal septum can result in a saddle-nose deformity. Patients with lower respiratory tract involvement may be asymptomatic, or they may have dry cough, hemoptysis, dyspnea, or chest pain. Renal involvement usually occurs late in the disease process and is the most frequent cause of death. The glomerulonephritis results in proteinuria and red blood cell casts. Occasionally, the eyes, ears, and skin also are involved.

The reported prevalence of oral lesions varies widely with oral involvement representing the initial presentation in 2% of affected patients. The most characteristic oral



• **Fig. 9-26 Wegener Granulomatosis.** Hemorrhagic and friable gingiva (strawberry gingivitis). (Courtesy of Dr. Sam McKenna.)

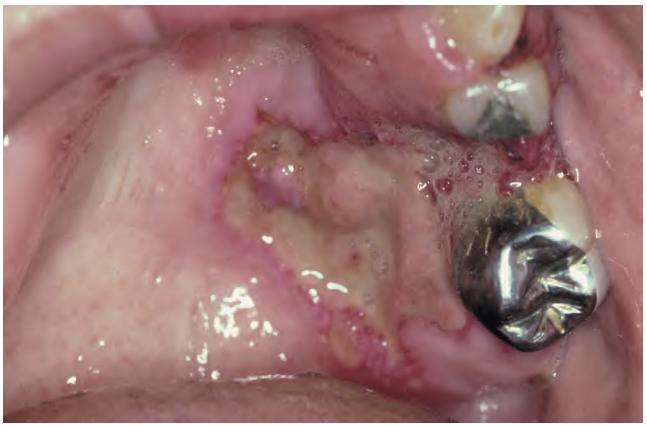


• **Fig. 9-27 Wegener Granulomatosis.** Hyperplastic and hemorrhagic mucosa of the facial mandibular gingiva on the left side. (Courtesy of Dr. James Wilson.)

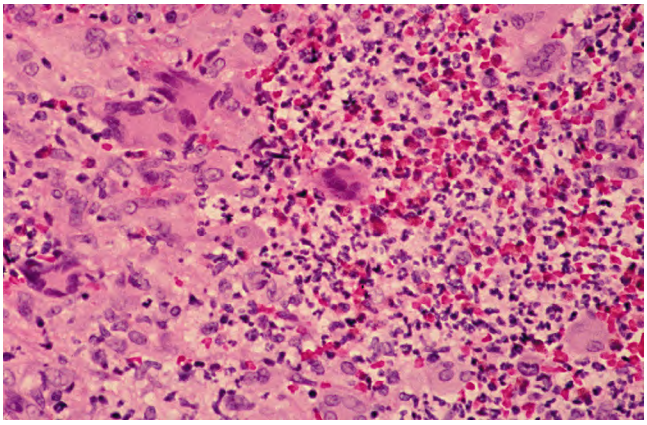
manifestation is **strawberry gingivitis.** This distinctive but uncommon pattern of gingival alteration appears to be an early manifestation of Wegener granulomatosis and has been documented before renal involvement in most cases. The affected gingiva demonstrates a florid and granular hyperplasia. The surface forms numerous short bulbous projections, which are hemorrhagic and friable; this red, bumpy surface is responsible for the strawberry-like appearance (Fig. 9-26 and 9-27). At the time of diagnosis, the involvement may be localized or generalized to multiple quadrants.

Oral ulceration also may be a manifestation of Wegener granulomatosis. These lesions are clinically nonspecific and may occur on any mucosal surface (Fig. 9-28). In contrast to the gingival changes, the oral ulcerations are diagnosed at a later stage of the disease, with more than 60% of the affected patients demonstrating renal involvement. Other less common orofacial manifestations include facial paralysis, labial mucosal nodules, sinusitis-related toothache, arthralgia of the temporomandibular joint (TMJ), jaw claudication, palatal ulceration from nasal extension, oral-antral fistulae, and poorly healing extraction sites.

Enlargement of one or more major salivary glands from primary involvement of the granulomatous process also has been reported. The glandular involvement also appears early



• **Fig. 9-28 Wegener Granulomatosis.** Deep, irregular ulceration of the hard palate on the left side. (From Allen CM, Camisa C, Salewski C, et al: Wegener's granulomatosis: report of three cases with oral lesions, *J Oral Maxillofac Surg* 49:294-298, 1991.)

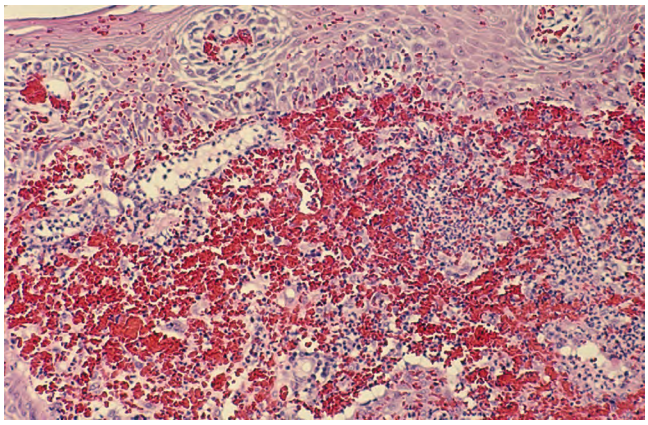


• **Fig. 9-29 Wegener Granulomatosis.** Connective tissue containing proliferation of numerous vascular channels and a heavy inflammatory infiltrate consisting of lymphocytes, neutrophils, eosinophils, and multinucleated giant cells.

in the course of the disease and may lead to early diagnosis and treatment.

Histopathologic Features

Wegener granulomatosis appears as a pattern of mixed inflammation centered around blood vessels. Involved vessels demonstrate transmural inflammation, often with areas of heavy neutrophilic infiltration, necrosis, and nuclear dust (leukocytoclastic vasculitis). The connective tissue adjacent to the vessel has an inflammatory cellular infiltrate, which contains a variable mixture of histiocytes, lymphocytes, eosinophils, and multinucleated giant cells (Fig. 9-29). Special stains for organisms are negative, and no foreign material can be found. In oral biopsy specimens, the oral epithelium may demonstrate pseudoepitheliomatous hyperplasia and subepithelial abscesses. Because of the paucity of large vessels in many oral mucosal biopsies, vasculitis may be difficult to demonstrate, and the histopathologic presentation may be one of ill-defined collections of epithelioid histiocytes intermixed with eosinophils,



• **Fig. 9-30 Wegener Granulomatosis.** Gingival biopsy specimen showing a mixed inflammatory cellular infiltrate obscured by extensive extravasation of red blood cells.

• BOX 9-2 American College of Rheumatology Criteria for Diagnosis of Wegener Granulomatosis

- Oral ulcerations or nasal discharge
- Nodules, fixed infiltrates, or cavities on chest radiograph
- Abnormal urinary sediment (red blood cell casts or more than five red blood cells/high power field)
- Granulomatous inflammation upon biopsy

lymphocytes, and multinucleated giant cells. In addition, the lesions of strawberry gingivitis typically demonstrate prominent vascularity with extensive red blood cell extravasation (Fig. 9-30).

Diagnosis

The diagnosis of Wegener granulomatosis is made from the combination of the clinical presentation and the microscopic finding of necrotizing and granulomatous vasculitis. The American College of Rheumatology proposed four diagnostic criteria with a minimum of two required for a diagnosis of Wegener granulomatosis (Box 9-2). Radiographic evaluation of the chest and sinuses is recommended to document possible involvement of these areas. The serum creatinine and urinalysis results are used to rule out significant renal alterations.

A laboratory marker for Wegener granulomatosis has been identified. Indirect immunofluorescence for serum antibodies directed against cytoplasmic components of neutrophils has been used to support a diagnosis of Wegener granulomatosis. There are two reaction patterns of these antineutrophil cytoplasm antibodies (ANCA). Antibodies against proteinase-3, a component of neutrophilic azurophilic cytoplasmic granules, are designated PR3-ANCA (previously termed c-ANCA). Likewise, antibodies against myeloperoxidase, a neutrophilic lysosomal granule, are designated MPO-ANCA (previously termed p-ANCA).

PR3-ANCA is the most useful in the diagnosis of Wegener granulomatosis and is seen in 90% to 95% of generalized Wegener granulomatosis and 60% of the early or localized cases. Immunofluorescence for PR3-ANCA should be ordered along with the specific enzyme-linked immunosorbent assay (ELISA) test for antibodies against proteinase 3 (PR3). These combined tests are associated with a sensitivity of 73% and a diagnostic specificity of 99% for Wegener granulomatosis. False positives are uncommon and may be associated with a variety of other diseases. In contrast, MPO-ANCAs are detected in several vasculitides that typically do not present in the oral cavity.

Treatment and Prognosis

The mean survival of untreated patients with disseminated classic Wegener granulomatosis is 5 months; 80% of the patients are dead at 1 year and 90% within 2 years. The prognosis is better for the limited and superficial forms of the disease, although a proportion of patients with localized disease eventually will develop classic Wegener granulomatosis.

The first line of therapy is oral prednisone and cyclophosphamide. On remission, the prednisone is gradually discontinued, with continuation of the cyclophosphamide for at least 1 year. Although high response rates are noted, serious side effects related to the therapy are not rare, especially those related to the cyclophosphamide. Trimethoprim/sulfamethoxazole has been used successfully in localized cases. When added to the standard regimen, this antibiotic combination seems to reduce associated infections and to lower the relapse rate. Low-dose methotrexate and corticosteroids also have been used in patients whose disease is not immediately life threatening or has not responded appropriately to cyclophosphamide. Alternatives for cyclophosphamide include cyclosporine, rituximab, and infliximab. For maintenance therapy, cyclophosphamide often is replaced with methotrexate or azathioprine.

Treatment has a profound effect on the progression of the disease. With appropriate therapy, prolonged remission is noted in up to 75% of affected patients; a cure often is attainable when the disease is diagnosed and appropriately treated while the involvement is localized. Because of a relapse rate up to 30%, maintenance therapy is necessary in many patients. The PR3-ANCA levels can be used to monitor the disease activity. Patients appear less likely to have relapses if their antineutrophilic antibodies disappear during treatment; in contrast, patients whose levels of antibodies persist are at greater risk for relapse.

◆ MUCOSAL REACTIONS TO SYSTEMIC DRUG ADMINISTRATION

The future of dentistry and medicine will involve a high volume of patients suffering from adverse drug reactions. By 2030, 20% of the population will be more than 65 years old. As the population ages and those affected with chronic diseases increase, patients taking multiple medications most likely will escalate. In the United States during the year

2000, more than 2.8 billion prescriptions were filled, enough to supply each inhabitant with ten prescriptions annually. Although use of two medications is associated with a 6% risk of an adverse reaction, the frequency rises to 50% with five drugs and almost 100% when eight or more medications are used simultaneously.

Two types of adverse drug reactions are seen. Type A (augmented reactions) arise from an exaggerated but otherwise expected pharmacologic action of the prescribed medication (such as, bleeding associated with warfarin). Approximately 80% of the total adverse drug reactions are Type A. Type B (bizarre reactions) are idiosyncratic reactions that are not expected, the majority of which arise from immune-mediated effects, such as hypersensitivity reactions.

Lists of medications related to several patterns of drug-related mucosal alteration are provided. Because new drug reactions are being reported on a regular basis and large numbers of new medications continue to appear, these lists should be considered incomplete and additional investigation is prudent. When presented with a patient with a possible drug reaction, all utilized medications, both prescribed and over-the-counter, that the patient is taking should be researched with a reputable online pharmaceutical reference. This should include not only the information within the drug insert but also the constantly updated results of a complete search of the health care literature.

In addition to drug-related problems, such as angioedema (see page 326), medication-related osteonecrosis (see page 271), cleft lip/palate (see page 1), erythema multiforme (see page 723), gingival hyperplasia (see page 148), methemoglobinemia, mucosal discolorations (see page 290), burning mouth disorder (see page 807), tardive dyskinesia, taste disturbances (see page 809), sialorrhea (see page 431), and xerostomia (see page 432), medications can induce a wide variety of mucosal ulcerations and erosions. A reaction of the oral mucosa to the systemic administration of a medication is called **stomatitis medicamentosa.** Several different patterns of oral mucosal disease can be seen:

- Anaphylactic stomatitis
- Intraoral fixed drug eruptions
- Lichenoid drug reactions
- Pemphigoid-like drug reactions
- Pemphigus-like drug reactions
- Lupus erythematosus–like eruptions
- Nonspecific erosive, ulcerative, or aphthous-like lesions

Anaphylactic stomatitis arises after the allergen enters the circulation and binds to immunoglobulin E (IgE)–mast cell complexes. Although systemic anaphylactic shock can result, localized alterations also occur. Fixed drug eruptions are inflammatory alterations of the mucosa or skin that recur at the same site after the administration of any allergen, often a medication. Medications reported to be associated with fixed drug eruptions are listed in Box 9-3, lichenoid drug eruptions in Box 9-4, lupus erythematosus–like drug eruptions in Box 9-5, pemphigus-like drug reactions in Box 9-6, and mucosal pemphigoid–like eruptions in Box 9-7. In addition, a long list of medications is known to be associated with nonspecific erosive, ulcerative, or aphthous-like lesions, but is not included due to its length.

• BOX 9-3 Medications Implicated in Fixed Drug Eruptions

Analgin
Barbiturates
Chlorhexidine
Co-trimoxazole
Dapsone
Gold salts
Indomethacin
Lidocaine
Penicillamine
Phenazone derivatives
Phenolphthalein
Salicylates
Sulfonamides
Tetracycline

• BOX 9-4 Medications Implicated in Lichenoid Eruptions

Allopurinol
Amiphenazole
Amphotericin
Angiotensin-converting enzyme (ACE) inhibitors
Antimalarials
Arsenicals
Barbiturates
Beta-adrenoceptor blockers
Bismuth
Carbamazepine
Carbimazole
Chloral hydrate
Chlorpropamide
Cimetidine
Clofibrate
Colchicine
Cyanamide
Dapsone
Dipyridamole
Ethionamide
Flunarizine
Furosemide
Gold salts
Griseofulvin
Interferon-alpha
Ketoconazole
Levamisole
Lincomycin
Lithium
Lorazepam
Mepacrine
Metformin
Methyldopa
Metronidazole
Niridazole
Nonsteroidal antiinflammatory drugs (NSAIDs)
Oral contraceptives
Palladium
Para-aminosalicylic acid
Penicillins
Penicillamine
Phenindione
Phenothiazines
Phenylbutazone
Phenytoin
Prazosin
Procainamide
Propylthiouracil
Protease inhibitors
Protionamide
Pyrimethamine
Pyritinol
Quinidine
Rifampicin
Spironolactone
Streptomycin
Sulfonamides
Sulfonylureas
Tetracycline
Thiazide diuretics
Tocainide
Tolbutamide
Triprolidine

Clinical Features

The patterns of mucosal alterations associated with the systemic administration of medications are varied, almost as much as the number of drugs that result in these changes. Anaphylactic stomatitis may occur alone or in conjunction with urticarial skin lesions or other signs and symptoms of anaphylaxis (e.g., hoarseness, respiratory distress, and vomiting). The affected mucosa may exhibit multiple zones of

• BOX 9-5 Medications Implicated in Lupus Erythematosus–like Eruptions

Carbamazepine
Chlorpromazine
Etanercept
Ethosuximide
Gold
Griseofulvin
Hydantoins
Hydralazine
Infliximab
Isoniazid
Lithium
Methyldopa
Penicillamine
Primidone
Procainamide
Quinidine
Reserpine
Streptomycin
Thiouracil
Trimethadione

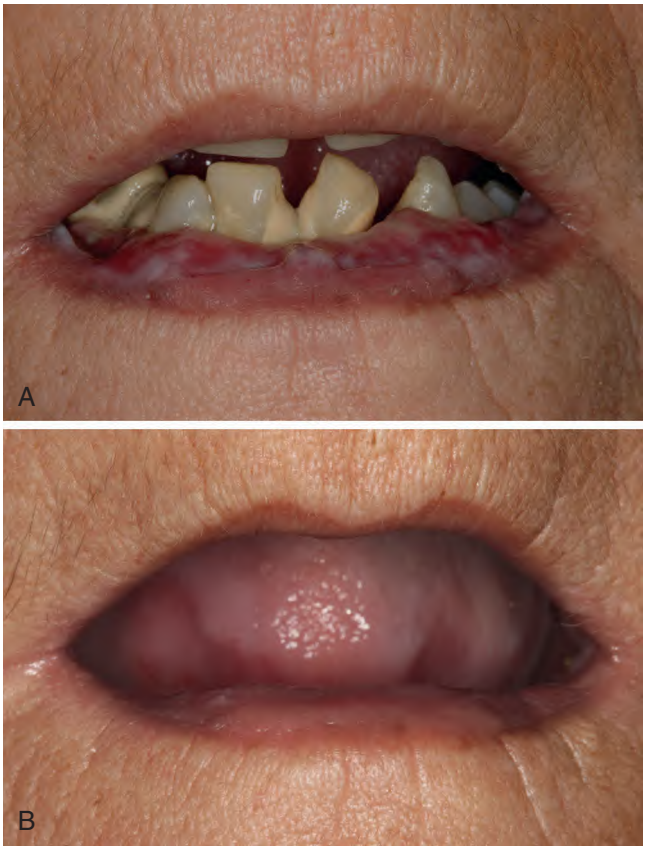
• BOX 9-6 Medications Implicated in Pemphigus-like Eruptions

Alpha-mercaptopropionyl glycine
Ampicillin
Benzylpenicillin
Captopril
Cefadroxil
Cephalexin
Diclofenac
Ethambutol
Glibenclamide
Gold
Heroin
Ibuprofen
Interleukin-2
Interferon-beta
Oxyphenbutazone
Penicillamine
Phenobarbital
Phenylbutazone
Piroxicam
Practolol
Probenecid
Procaine penicillin
Propranolol
Pyritinol chlorhydrate
Rifampin
Thioproline

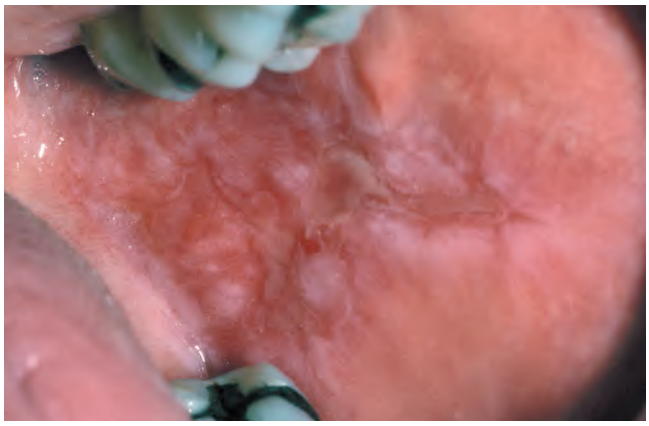
• BOX 9-7 Medications Implicated in Mucosal Pemphigoid–like Eruptions

- Amoxicillin
- Azapropazone
- Clonidine
- Furosemide
- Ibuprofen
- Isoniazid
- Mefenamic acid
- Nadolol
- Penicillamine
- Penicillin V
- Phenacetin
- Practolol
- Salicylic acid
- Sulfonamides
- Sulfasalazine

erythema or numerous aphthous-like ulcerations. Mucosal fixed drug eruptions appear as localized areas of erythema and edema, which can develop into vesiculoerosive lesions and are located most frequently on the labial mucosa. Lichenoid, lupus-like, pemphigoid-like, and pemphigus-like drug reactions resemble their namesakes clinically, histopathologically, and immunologically (Fig. 9-31). These latter chronic drug reactions may involve any mucosal surface, but the most common sites are the posterior buccal mucosa and the lateral borders of the tongue (Figs. 9-32 and 9-33). Bilateral and symmetrical lesions are fairly common.



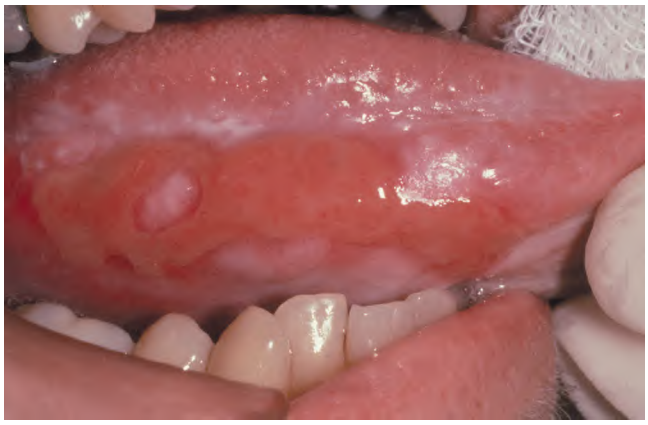
• Fig. 9-31 Allergic Mucosal Reaction to Systemic Drug Administration. A, Bilateral erosions of lower labial mucosa with intermixed striae. Biopsy revealed lichenoid pattern of mucositis but with numerous plasma cells intermixed with the lymphocytes. The erosions ultimately were proven to be associated with simvastatin. **B,** Same patient depicted in **A** after discontinuation of simvastatin.



• Fig. 9-32 Lichenoid Drug Reaction to Allopurinol. Irregular area of superficial erosion of the left buccal mucosa. Lesions were also present on the contralateral buccal mucosa and bilaterally on the lateral borders of the tongue.

Histopathologic Features

Anaphylactic stomatitis typically reveals a nonspecific pattern of subacute mucositis that contains lymphocytes intermixed with eosinophils and neutrophils. Fixed drug eruptions also reveal a mixed inflammatory cellular infiltrate



• **Fig. 9-33 Allergic Mucosal Reaction to Systemic Drug Administration.** Large irregular erosion of the right ventral surface of the tongue. The lesion arose secondary to use of oxaprozin, a nonsteroidal antiinflammatory drug (NSAID).

that consists of lymphocytes, eosinophils, and neutrophils, often combined with spongiosis and exocytosis of the epithelium. Vacuolar change of the basal cell layer and individual necrotic epithelial cells are occasionally noted. The drug reactions that simulate lichen planus, lupus erythematosus, and pemphigus resemble their namesakes. The histopathologic and immunologic features of these chronic drug reactions cannot be used reliably to separate them from their associated primary immunologic disease.

Immunofluorescence has been used in an attempt to separate drug reactions from primary vesiculoerosive disease. In most instances, this technique has proven to be unsatisfactory. In spite of these findings, a unique pattern of reaction has been seen when indirect immunofluorescence for IgG has been performed in patients with lichenoid drug reactions. In many of these patients, a distinctive annular fluorescent pattern, termed **string of pearls,** has been noted along the cell membrane of the basal cell layer of stratified squamous epithelium. The detected circulating antibody has been termed **basal cell cytoplasmic antibody.** Although further study is desirable, this technique may prove to be a useful adjunct during evaluation of oral lichenoid lesions.

Diagnosis

A detailed medical history must be obtained, and the patient should be questioned closely concerning the use of both prescription and over-the-counter medications. Once a potentially offending medication is discovered, a temporal relationship between the drug's use and the mucosal alteration must be established. The association may be acute and obvious, or the onset of the oral lesions may be delayed. If more than one medication is suspected, the most recently administrated medication often is the culprit. If the last-to-be-introduced drug does not appear responsible, serial elimination of the medications can be performed in collaboration with the patient's physician until the offending agent is discovered.

In chronic drug reactions, definitive diagnosis can be made if the mucosal alterations resolve after discontinuation of the medication and recur on reintroduction of the agent. Presumptive diagnosis usually is sufficient and justified when the mucosal alterations clear after cessation of the offending medication.

In possible lupus-like drug reactions, serum evaluation for generic antinuclear antibodies (ANAs) and antibodies against double-stranded DNA and histones often can be beneficial. Lupus-like drug reactions typically are associated with circulating generic ANAs and antibodies against histones, whereas lupus erythematosus also reveals antibodies to double-stranded DNA (a finding not typically noted in drug reactions). This pattern does not hold true in reactions associated with the TNF-α antagonists, infliximab and etanercept, which simulate systemic lupus erythematosus (SLE) very closely and are associated with antibodies to double-stranded DNA.

Treatment and Prognosis

The responsible medication should be discontinued and, if necessary, replaced with another drug that provides a similar therapeutic result. Localized acute reactions can be resolved with topical corticosteroids. When systemic manifestations are present, anaphylactic stomatitis often warrants systemic administration of adrenaline (epinephrine), corticosteroids, or antihistamines. Chronic oral lesions often resolve on cessation of the offending drug, but topical corticosteroids may sometimes be required for complete resolution.

If discontinuation of the medication is contraindicated, palliative care can be provided; however, corticosteroids often are ineffective as long as the offending medication is continued.

◆ ALLERGIC CONTACT STOMATITIS (STOMATITIS VENENATA)

The list of agents reported to cause **allergic contact stomatitis** reactions in the oral cavity is extremely diverse. Numerous foods, food additives, chewing gums, candies, dentifrices, mouthwashes, glove and rubber dam materials, topical anesthetics, restorative metals, acrylic denture materials, dental impression materials, and denture adhesive preparations have been mentioned. Two types of allergens, cinnamon (see page 322) and dental restorative materials (see page 324), demonstrate clinical and histopathologic patterns that are sufficiently unique to justify separate descriptions.

Although the oral cavity is exposed to a wide variety of antigens, the frequency of a true allergic reaction to any one antigen from this contact appears to be rare. This was verified in a prospective study of 13,325 dental patients, in which only seven acute and 15 chronic cases of adverse effects were attributed to dental materials. The oral mucosa is much less sensitive than the surface of the skin; this is most likely because of the following:

- The period of contact is often brief.
- The saliva dilutes, digests, and removes many antigens.
- The limited keratinization of oral mucosa makes hapten binding more difficult, and the high vascularity tends to remove any antigen quickly.
- The allergen may not be recognized (because of the lower density of Langerhans cells and T lymphocytes).

If the skin has been sensitized originally, the mucosa may or may not demonstrate future clinical sensitization. In contrast, if the mucosa is sensitized initially, then the skin usually demonstrates similar changes with future exposure. Long-term oral exposure may induce tolerance and reduce the prevalence of cutaneous sensitivity in some instances. For example, exposure to nickel-containing orthodontic hardware has been associated with a reduced prevalence of future cutaneous sensitivity to nickel jewelry.

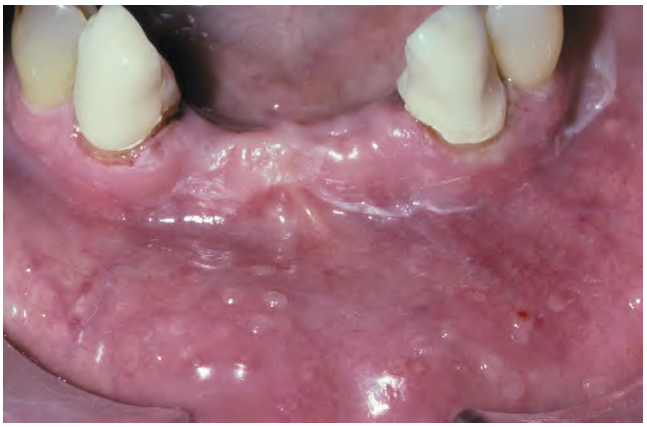
In addition to oral lesions, allergic contact reactions may produce exfoliative cheilitis (see page 278) or perioral dermatitis (see next section). As mentioned in Chapter 8, most cases of chronic cheilitis represent local irritation, usually from chronic lip licking. In spite of this, investigation has revealed that approximately 25% of affected cases are allergic contact cheilitis from a variety of antigens that include medications, lipsticks, sunscreens, toothpaste, dental floss, nail polishes, and cosmetics.

Clinical Features

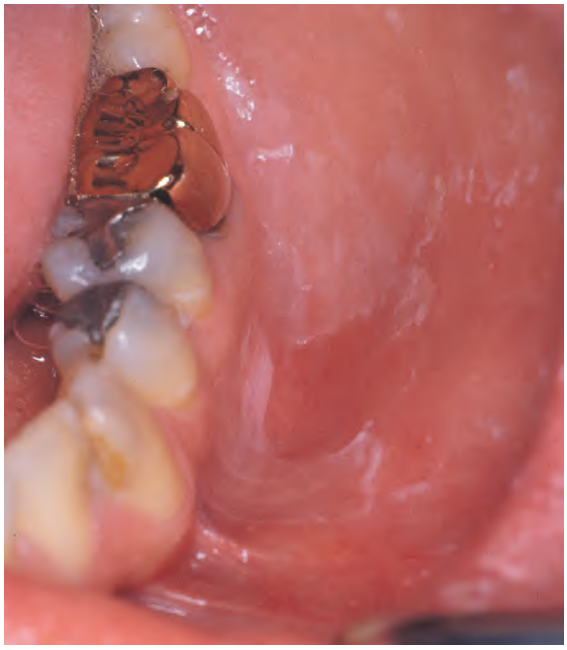
Allergic contact stomatitis can be acute or chronic. Of those cases diagnosed, there is a distinct female predominance in both forms. After eliminating focal trauma, localized signs and symptoms suggest mucositis from an isolated allergen (e.g., dental metal); in contrast, widespread mouth pain suggests an association with a more diffuse trigger, such as food, drink, flavorings, or oral hygiene materials.

In patients with acute contact stomatitis, burning is the most frequent symptom. The appearance of the affected mucosa is variable, from a mild and barely visible redness to a brilliantly erythematous lesion with or without edema. Vesicles are rarely seen and, when present, rapidly rupture to form areas of erosion (Fig. 9-34). Superficial ulcerations that resemble aphthae occasionally arise. Itching, stinging, tingling, and edema may be noted.

In chronic cases the affected mucosa is typically in contact with the causative agent and may be erythematous or white and hyperkeratotic. Periodically, erosions may develop within the affected zones. Some allergens, especially toothpastes, can cause widespread erythema, with desquamation of the superficial layers of the epithelium (Fig. 9-35). Allergic contact cheilitis demonstrates clinical features identical to those cases created through chronic irritation, and it most frequently appears as chronic dryness, scaling, fissuring, or cracking of the vermilion border of the lip. Rarely, symptoms identical to orolingual paresthesia can be present without any clinically evident signs. One distinctive pattern, plasma cell gingivitis, is discussed elsewhere (see page 145).



• Fig. 9-34 Allergic Contact Stomatitis to Aluminum Chloride. Mucosal erythema and vesicles of the lower labial mucosa caused by use of aluminum chloride on gingival retraction cord.



• Fig. 9-35 Allergic Contact Stomatitis to Toothpaste. Erythematous mucosa with superficial epithelial desquamation.

Diagnosis

Usually, the diagnosis of acute contact stomatitis is straightforward because of the temporal relationship between the use of the agent and the resultant eruption. If an acute oral or circumoral reaction is noted within 30 minutes of a dental visit, then allergy to all used dental materials, local anesthetics, and gloves should be investigated.

The diagnosis of chronic contact stomatitis is much more difficult. Most investigators require good oral health, elimination of all other possible causes, and visible oral signs, together with a positive history of allergy and a positive skin test result to the suspected allergen. If allergic contact stomatitis is strongly suspected but skin test results are negative, then direct testing of the oral mucosa can be attempted.

The antigen can be placed on the mucosa in a mixture with Orabase or in a rubber cup that is fixed to the mucosa.

Treatment and Prognosis

In mild cases of acute contact stomatitis, removal of the suspected allergen is all that is required. In more severe cases, antihistamine therapy, which is combined with topical anesthetics, usually is beneficial. Chronic reactions respond to removal of the antigenic source and application of a topical corticosteroid gel or oral suspension.

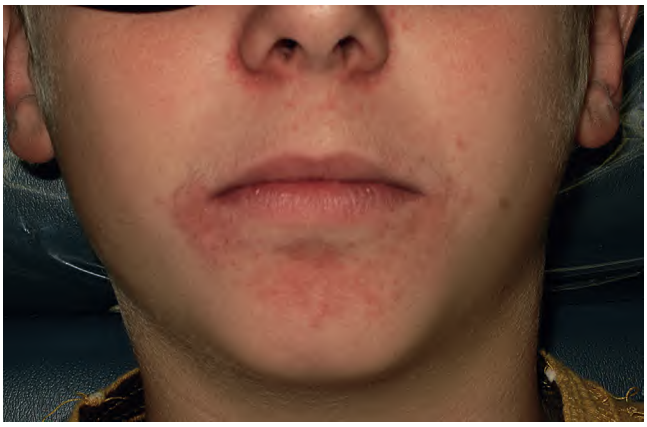
When attempting to discover the source of a diffuse allergic mucositis, use of plain baking soda or toothpaste that is free of flavoring or preservatives is recommended. The patient also should be instructed to avoid mouthwash, gum, mints, chocolate, cinnamon-containing products, carbonated drinks, and excessively salty, spicy, or acidic foods. If an association cannot be found, then cutaneous patch testing may provide helpful information.

◆ PERIORAL DERMATITIS (PERIORIFICIAL DERMATITIS)

Perioral dermatitis does not refer to every rash that occurs around the mouth but is specific for a unique inflammatory skin disease that involves the cutaneous surfaces surrounding the facial orifices. Because the disorder also often involves the paranasal and periorbital skin, **periorificial dermatitis** is the most appropriate designation. Although the process is idiopathic, the dermatitis is associated strongly with uncritical use of potent topical corticosteroids on the facial skin. Fluorinated toothpaste and overuse of heavy facial cosmetics, creams, and moisturizers also are implicated in many patients. Weaker correlations have been seen with systemic corticosteroids, corticosteroid inhalers, and nasal corticosteroids. Heavy exposure to ultraviolet light, heat, and wind appears to worsen the dermatitis. Some of these substances may initially induce an irritant or allergic contact dermatitis, whereas others are thought to produce inappropriate occlusion of the skin surface with subsequent proliferation of skin flora.

Clinical Features

Perioral dermatitis appears with persistent erythematous papules, papulovesicles, and papulopustules that involve the skin surrounding the vermilion border of the upper and lower lips. In addition, involvement of the perinasal skin is seen in approximately 40% of affected patients, and 25% have periorbital dermatitis (Fig. 9-36). Classically, there is a zone of spared skin immediately adjacent to the vermilion border. Pruritus and burning are variable. The vast majority of the cases are diagnosed in women between the ages of 20 to 45 years, lending further support to the association with cosmetic use. In spite of this, the process does occur in men and in children of either sex.



• **Fig. 9-36 Perioral Dermatitis.** Multiple erythematous papules of the skin surrounding the vermilion border of the lips. Note similar involvement around the nasal orifices (periorificial dermatitis). (Courtesy of Dr. Billy Millay.)

Histopathologic Features

Biopsy of perioral dermatitis demonstrates a variable pattern. In many cases there is a chronic lymphohistiocytic dermatitis that often exhibits spongiosis of the hair follicles. In other patients a rosacea-like pattern is noted in which there is perifollicular granulomatous inflammation. On occasion, this histopathologic pattern has been misdiagnosed as sarcoidosis.

Treatment and Prognosis

Most cases resolve with "zero therapy," which includes discontinuation of corticosteroids, cosmetics, and facial creams. Discontinuation of potent topical corticosteroid use often is followed by a period of exacerbation, which can be minimized by substitution of a less potent corticosteroid before total cessation. Oral tetracycline is considered the therapeutic gold standard for perioral dermatitis but must be avoided during childhood and pregnancy. In addition, a shortage of tetracycline in the United States has made its use problematic. No strong evidence has been presented to demonstrate that doxycycline or minocycline is equivalent or superior to tetracycline. Luckily, perioral dermatitis also responds well to topical pimecrolimus or topical erythromycin. Weaker therapeutic recommendations include topical metronidazole, clindamycin, tacrolimus, tetracycline, adapalene, or azelaic acid, plus systemic erythromycin or isotretinoin. The pathosis typically demonstrates significant improvement within several weeks and total resolution in a few months. Recurrence is uncommon.

◆ CONTACT STOMATITIS FROM ARTIFICIAL CINNAMON FLAVORING

Mucosal abnormalities secondary to the use of artificially flavored cinnamon products are fairly common, but the

range of changes was not recognized widely until the late 1980s. Cinnamon oil is used as a flavoring agent in confectionery, ice cream, soft drinks, alcoholic beverages, processed meats, gum, candy, toothpaste, breath fresheners, mouthwashes, and even dental floss. Concentrations of the flavoring are up to 100 times that in the natural spice. The reactions are documented most commonly in those products associated with prolonged or frequent contact, such as candy, chewing gum, and toothpaste. The anticalculus components of tartar-control toothpastes have a strong bitter flavor and require a significant concentration of flavoring agents including cinnamon to hide the taste, resulting in a greater chance these formulations will cause oral mucosal lesions. Although much less common, reactions to cinnamon in its natural spice form have been documented.

Clinical Features

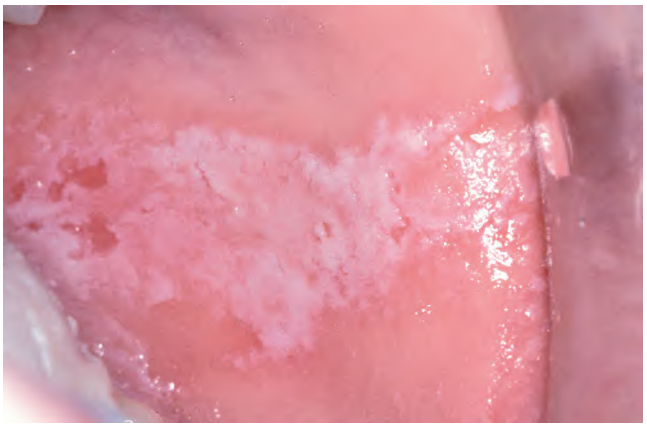
The clinical presentations of contact stomatitis vary somewhat, according to the medium of delivery. Toothpaste results in a more diffuse pattern; the signs associated with chewing gum and candy are more localized. Pain and burning are common symptoms in all cases.

The gingiva is the most frequent site affected by toothpaste, often resembling **plasma cell gingivitis** (see page 145); enlargement, edema, and erythema are common. Sloughing of the superficial oral epithelium without creation of an erosion is seen commonly. Erythematous mucositis, occasionally combined with erosion, has been reported on the buccal mucosa and tongue. Exfoliative cheilitis and circumoral dermatitis also may occur.

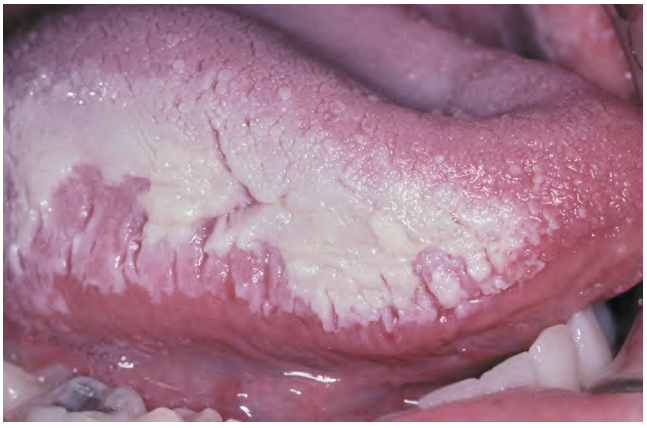
Reactions from chewing gum and candy are more localized and typically do not affect the lip vermilion or perioral skin. Most of the lesions appear on the buccal mucosa and lateral borders of the tongue. Buccal mucosal lesions often are oblong patches that are aligned along the occlusal plane (Fig. 9-37). Individual lesions have an erythematous base but often are predominantly white as a result of hyperkeratosis of the surface epithelium. Ulceration within the lesions may occur. Hyperkeratotic examples often exhibit a ragged surface and occasionally may resemble the pattern seen in morsicatio (see page 259). Lingual involvement may become extensive and spread to the dorsal surface (Fig. 9-38). Significant thickening of the surface epithelium can occur and may raise clinical concern for oral hairy leukoplakia (OHL) (see page 242) or carcinoma (Fig. 9-39).

Histopathologic Features

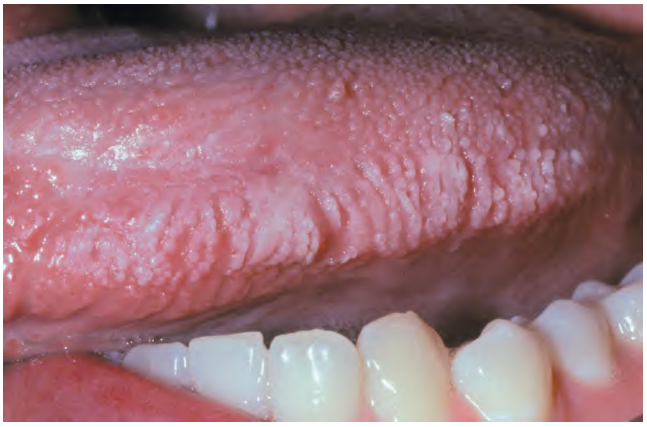
Usually, the epithelium in contact stomatitis from artificial cinnamon flavoring is acanthotic, often with elongated rete ridges and thinning of the suprapapillary plates. Hyperkeratosis and extensive neutrophilic exocytosis may be present. The superficial lamina propria demonstrates a heavy inflammatory cell infiltrate that consists predominantly of lymphocytes that may be intermixed with plasma cells, histiocytes, or eosinophils. This infiltrate often obscures the epithelium and connective tissue interface (Fig. 9-40). A characteristic feature in localized cases caused by gum, mints, or candies is the frequent presence of an obvious perivascular inflammatory infiltrate that extends well below the interface zone (Fig. 9-41).



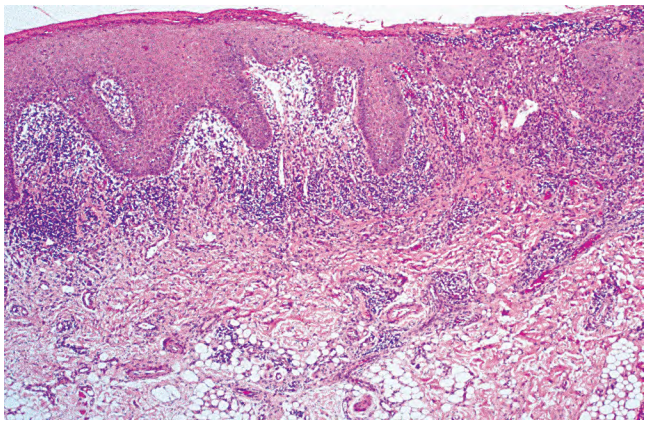
• **Fig. 9-37 Contact Stomatitis from Cinnamon Flavoring.** Oblong area of sensitive erythema with overlying shaggy hyperkeratosis.



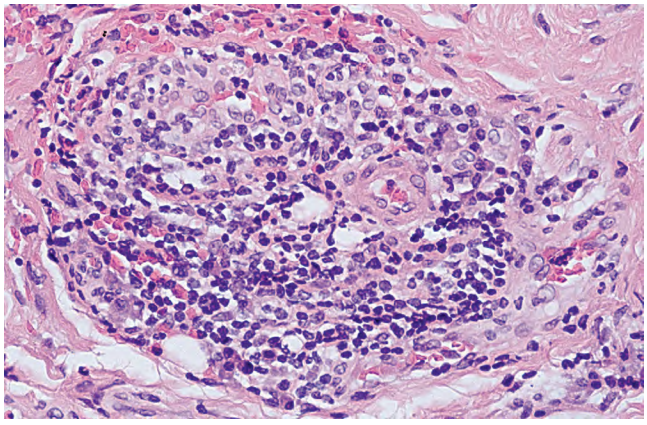
• **Fig. 9-38 Contact Stomatitis from Cinnamon Flavoring.** Sensitive and thickened hyperkeratosis of the lateral and dorsal surface of the tongue on the right side.



• **Fig. 9-39 Contact Stomatitis from Cinnamon Flavoring.** Left lateral border of the tongue demonstrating linear rows of hyperkeratosis that resemble oral hairy leukoplakia (OHL).



• **Fig. 9-40 Contact Stomatitis from Cinnamon Flavoring.** Oral mucosa demonstrating significant interface mucositis and deeper perivascular inflammation.



• **Fig. 9-41 Contact Stomatitis from Cinnamon Flavoring.** Perivascular inflammatory infiltrate consisting predominantly of lymphocytes and plasma cells.

Diagnosis

With a high index of suspicion and knowledge of the variations of the clinical pattern, the diagnosis of localized contact stomatitis often can be made from the clinical appearance and the history of cinnamon use. Often biopsies are performed for atypical or extensive cases because of the differential diagnosis, which includes several significant vesiculoerosive and neoplastic conditions. The histopathologic features are not specific, but they are sufficient to raise a high index of suspicion in an oral and maxillofacial pathologist who is familiar with the pattern. Use of cinnamon-containing toothpaste should be investigated in every patient with an atypical pattern of gingivitis. Diet-related examples often are the most difficult to diagnose and may necessitate cutaneous allergy patch testing or a diet diary to isolate the cause.

Treatment and Prognosis

Typically, the signs and symptoms disappear within 1 week after the discontinuation of the cinnamon product. If the patient resumes intake of the product, then the lesions reappear, usually within 24 hours. On occasion, resolution is more gradual and the patient may benefit from short-term use of a topical corticosteroid.

◆ LICHENOID CONTACT REACTION FROM DENTAL RESTORATIVE MATERIALS

Dental amalgam has been in active use for over 180 years and has proven to be a durable and relatively inexpensive material that remains one of the most commonly placed dental restorations. Because of an associated low-level release of mercury from these fillings (an amount significantly less than the daily contribution from food and non-dental sources), its use has been blamed for a wide variety of health concerns. Due to the controversy, a number of controlled studies were performed, showing no association between the presence of dental amalgams and systemic disease. Two oral pathoses, burning mouth syndrome and orofacial granulomatosis, also have been correlated with the presence of amalgams by some investigators, but no conclusive evidence exists to associate these disorders with the dental restorative material. The primary adverse effects that are well documented include acute and chronic hypersensitivity reactions.

Dental amalgams contain mercury, silver, tin, and copper, with some variations also including zinc, indium, palladium, or platinum. The vast majority of hypersensitivity reactions to dental restorative materials are to dental amalgam, usually associated with the mercury content. Reactions have been seen much less frequently to other dental restorations containing materials such as gold, beryllium, chromium, cobalt, or composite resins.

Although rare acute reactions to mercury may be seen following placement of amalgam, the vast majority of adverse alterations represent chronic type IV hypersensitivity reactions that are seen most commonly associated with older and corroded amalgams. It is believed the metal ions released by corrosion haptenize with oral keratinocyte surface proteins and initiate a cell-mediated autoimmune response directed at the basal cell layer of the epithelium. Some investigators have called these chronic alterations "galvanic lesions," but neither clinical nor experimental studies support the electrogalvanic hypothesis of origin.

These chronic contact reactions appear clinically and histopathologically similar to lichen planus (see page 729) but demonstrate a different mucosal distribution. When patients with true oral lichen planus are examined, the lesions migrate and exhibit no direct correlation to contact with dental materials. In addition, patients with lichen planus do not demonstrate a significantly increased positive patch testing to dental restorative materials and exhibit minimal-to-no clinical improvement on removal of their amalgams.

However, there is a subgroup of patients whose lichenoid lesions do not migrate and usually involve only the mucosa adjacent to a dental metal. On patch testing, the vast

majority of these patients react to the offending metal, and the lesions resolve rapidly after removal of adjacent amalgams. Such lesions should be diagnosed as a **lichenoid contact reaction** to a dental restorative material, not as true lichen planus.

Clinical Features

Acute reactions to dental amalgams are extremely rare and related to an immediate hypersensitivity reaction to mercury. The signs tend to arise within hours after placement of an amalgam and present with erythematous, pruritic, and urticarial lesions of the ipsilateral oral mucosa and facial skin. In severe reactions, soft tissue edema, tachycardia, and breathing difficulties also are seen.

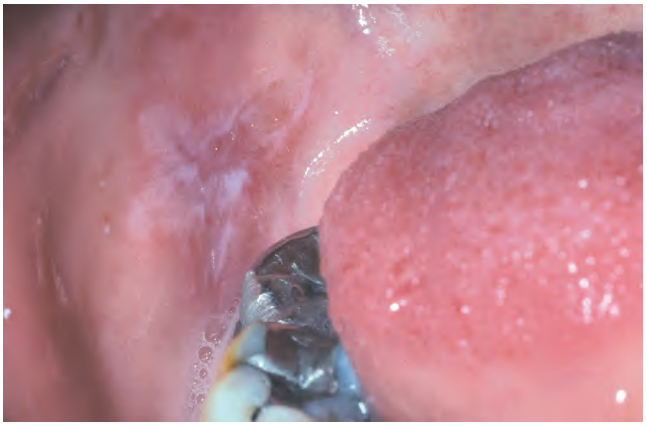
The vast majority of lichenoid contact reactions affect the posterior buccal mucosa and the ventral surface of the lateral borders of the tongue. The lesions usually are confined to the area of contact and may be white or erythematous, with or without peripheral striae (Fig. 9-42). Most patients have no symptoms, but periodic erosion may be noted. In all likelihood, many of the lesions previously reported as the so-called plaque type of lichen planus were, in reality, lichenoid contact reactions.

Diagnosis

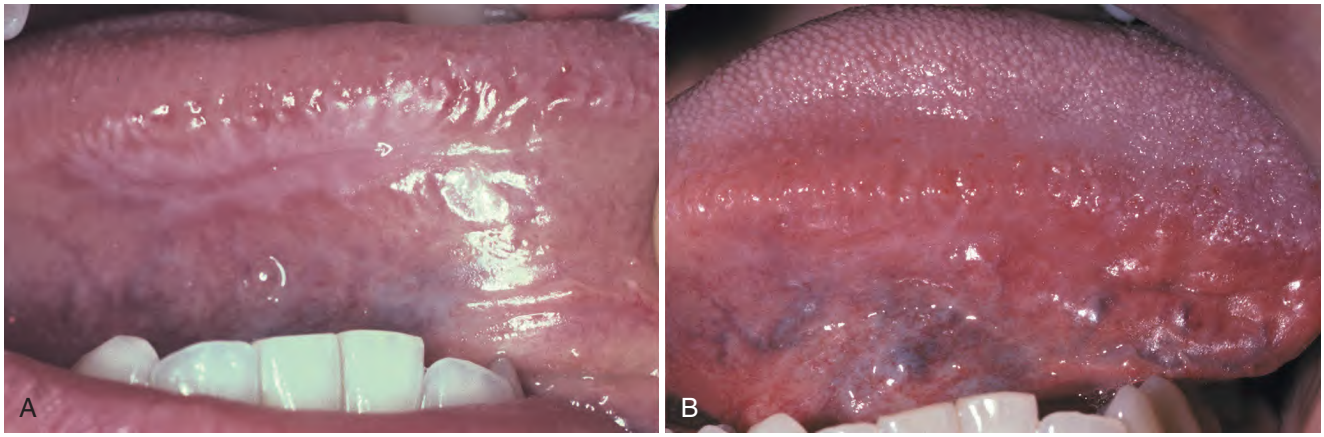
The diagnosis of a lichenoid contact reaction is made from the clinical appearance of the lesion, the lack of lesional migration, and the correlation to adjacent dental metal (Fig. 9-43). Although the histopathologic features may be indistinguishable from lichen planus, biopsy occasionally is performed to confirm the clinical impression and to rule out other pathoses such as epithelial dysplasia. Although patch testing is positive in up to 70% of patients with contact reactions and similarly reactive in less than 4% of patients with true lichen planus, the clinical presentation has proven to be a more reliable diagnostic indicator than patch testing.

Histopathologic Features

Biopsy of allergic contact stomatitis from dental materials exhibits numerous features of lichen planus. The surface epithelium may be hyperkeratotic, atrophic, or ulcerated. Areas of hydropic degeneration of the basal cell layer often are present. The superficial lamina propria contains a dense bandlike chronic inflammatory cellular infiltrate consisting predominantly of lymphocytes, but there may be scattered plasma cells. On occasion, deeper lymphoid aggregates may be noted, often in a perivascular orientation.



• Fig. 9-43 Oral Mucosal Contact Reaction to Dental Amalgam. Radiating pattern of hyperkeratotic striae on the posterior buccal mucosa that contacts a large distobuccal amalgam of the permanent mandibular second molar.



• Fig. 9-42 Oral Mucosal Contact Reaction to Dental Amalgam. A, Hyperkeratotic lesion with a peripheral radiating pattern on the lateral border of the tongue on the right side; the altered mucosa contacted the amalgams of the adjacent mandibular molar teeth. The lesion remained in the same location for 5 years and periodically became erosive and symptomatic. Smoothing and polishing of the adjacent restorations had no effect. **B,** Appearance of previously altered area of the tongue 14 days after removal of adjacent amalgams. Note total resolution of the mucosal alterations.

Treatment and Prognosis

In patients with acute hypersensitivity reactions to the mercury in an amalgam, the process usually is self-limiting and resolves spontaneously within 2 to 3 days. In spite of this, systemic symptoms, such as significant breathing difficulties, may necessitate removal of the newly placed amalgam.

For chronic lichenoid reactions, local measures, such as improved oral hygiene, smoothing, polishing, and recontouring of the amalgam restoration, should be attempted before more aggressive measures, because clinically similar lesions have been noted as a result of surface plaque accumulation. If this is unsuccessful, then the amalgam in question should be replaced. Because patients rarely may exhibit hypersensitivity to composite resins, use of inert materials (such as, glass ionomer, porcelain, or porcelain-fused-to-metal) is recommended. Like lichen planus, some investigators believe untreated lichenoid contact reactions rarely may evolve into carcinoma, although the possibility that some preneoplastic leukoplakias are mistaken for lichenoid contact reactions cannot be ruled out. Although this association is far from proven, removal of amalgams adjacent to possible lichenoid contact reactions appears prudent. Lichenoid lesions that fail to resolve following removal of the adjacent metal should be evaluated further.

◆ ANGIOEDEMA (ANGIONEUROTIC EDEMA; QUINCKE DISEASE)

Angioedema is a diffuse edematous swelling of the soft tissues that most commonly involves the subcutaneous and submucosal connective tissues but may affect the gastrointestinal or respiratory tract, occasionally with fatal results. The disorder has been referred to as **Quincke disease,** after the clinician who initially related the changes to an alteration in vascular permeability. The outdated term **angioneurotic edema** also has been used, because affected patients often complained of a choking sensation and were labeled neurotic.

The most common cause is mast cell degranulation, which leads to histamine release and the typical clinical alterations. IgE-mediated hypersensitivity reactions caused by drugs, foods, plants, dust, and inhalants produce mast cell degranulation and are fairly common. Contact allergic reactions to foods, cosmetics, topical medications, and even dental rubber dams also have been responsible. Mast cell degranulation can even result from physical stimuli, such as heat, cold, exercise, emotional stress, solar exposure, and significant vibration.

An unusual pattern of drug reaction that can produce severe forms of angioedema that are not mediated by IgE is the type associated with use of drugs called *angiotensin-converting enzyme (ACE) inhibitors.* These medications represent one of the most frequently prescribed drugs, with 35 to 40 million patients currently taking these antihypertensives. Some of the most popular are captopril, enalapril, and lisinopril. The swelling associated with these drugs does not respond well to antihistamines and was thought to be the result of excess bradykinin (ACE degrades bradykinin). In an attempt to avoid this angioedema, a second generation of medications called *angiotensin II receptor blockers* (e.g., losartan and valsartan) was developed specifically to avoid any inhibition of bradykinin degradation. These newer medications lower the frequency of angioedema but do not eliminate the adverse reaction. The prevalence of this pattern of angioedema is estimated to be 0.1% to 0.2% of those who use ACE inhibitors. In the majority of affected patients, the angioedema arises within hours of initial use of the drug. In up to 30% of the cases, the angioedema is delayed, with the longest reported interval between drug use initiation and the initial attack being 10 years. Attacks precipitated by dental procedures have been reported in long-term users of ACE inhibitors. Many clinicians overlook the association between angioedema and ACE inhibitors, with studies demonstrating continued administration of the medication in more than 50% of affected patients.

Angioedema also can result from activation of the complement pathway. This may be hereditary or acquired. Two rare autosomal dominant hereditary forms are seen. Type I, comprising 85% of the hereditary cases, is caused by a quantitative reduction in the inhibitor that prevents the transformation of C1 to C1 esterase. Without adequate levels of C1 esterase inhibitor (C1-INH), C1 esterase cleaves C4 and C2 and results in angioedema. Type II exhibits normal levels of C1-INH, but the inhibitor is dysfunctional.

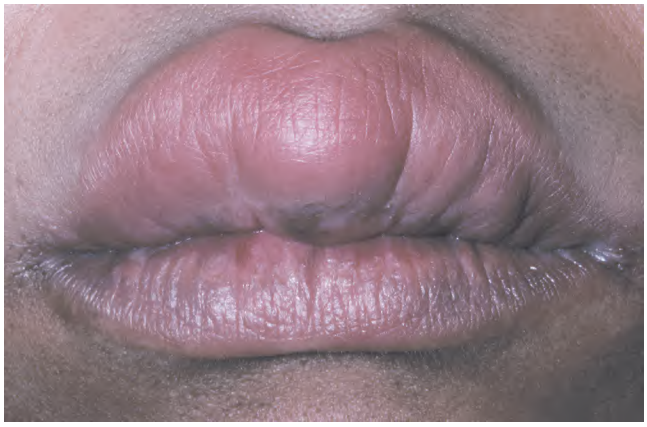
The acquired type of C1-INH deficiency is seen in association with certain types of lymphoproliferative diseases (Caldwell syndrome) or in patients who develop specific autoantibodies. In lymphoproliferative diseases, monoclonal antibodies directed against the tumor cells activate C1 and lead to consumption of C1-INH. In the autoimmune variant, the antibody attaches to the C1 receptor on the C1-INH molecule, leading to dysfunctional C1-INH and consumption of C1. In both the acquired and the hereditary forms of abnormal C1-INH activity, minor trauma, such as a dental procedure, can precipitate an attack.

Finally, angioedema has been seen in the presence of high levels of antigen-antibody complexes (e.g., lupus erythematosus and viral or bacterial infections) and in patients with grossly elevated peripheral blood eosinophil counts.

Clinical Features

Angioedema is characterized by the relatively rapid onset of soft, nontender tissue swelling, which may be solitary or multiple (Fig. 9-44). In the hereditary forms, the initial onset typically is noted in childhood or adolescence. The episodes are unpredictable and intermixed with edema-free intervals. Recurrent skin swelling and abdominal pain are the most frequent presentations. The extremities are the most common cutaneous sites of involvement, although the face, genitals, trunk, and neck also can be affected. Although

not individually frequent, edema of the larynx, pharynx, uvula, or soft palate may be noted when patients are monitored for extended periods (and may be associated with respiratory distress). A deeper voice, hoarseness, aphonia, and dyspnea are important warning signs. Recurrent snoring-induced edema of the soft palate has been reported and associated with severe dyspnea. Isolated tongue involvement is uncommon. Involvement of the skin and mucous membranes can cause enlargements that may measure up to several centimeters in diameter (Fig. 9-45). Although pain is unusual, itching is common and erythema may be present. The enlargement typically resolves over 24 to 72 hours. In contrast to the hereditary variants, allergic, acquired, and ACE inhibitor–associated angioedema demonstrate significant involvement of the head and neck, such as the face, lips, tongue, floor of mouth, pharynx, and larynx. The risk of angioedema associated with ACE inhibitors is significantly greater in blacks (three to four times that of other races), and this pattern is the type most frequently encountered by oral health practitioners.

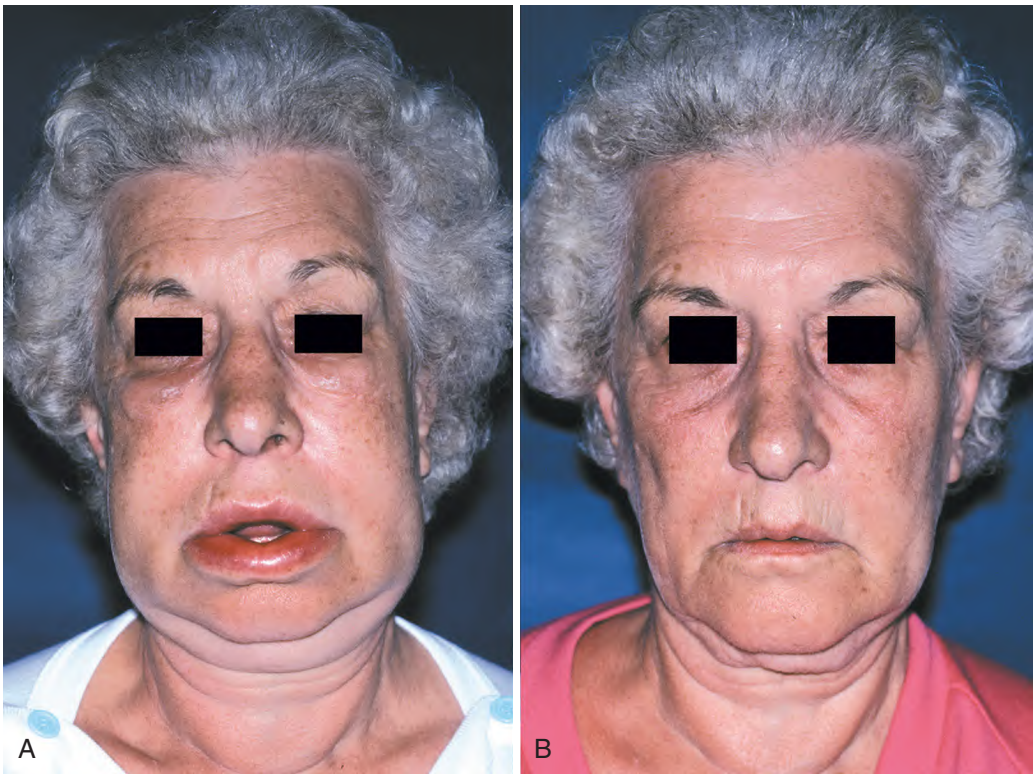


• **Fig. 9-44 Angioedema.** Diffuse upper lip swelling that arose rapidly.

Diagnosis

In cases of allergic causation, the diagnosis of angioedema often is made from the clinical presentation in conjunction with the known antigenic stimulus. When multiple antigenic exposures occur, the diagnosis of the offending agent can be difficult and involves dietary diaries and antigenic testing.

Those patients whose conditions cannot be related to antigenic exposure or medications should be evaluated for the presence of adequate functional C1-INH. In the hereditary types, both forms exhibit normal levels of C1 and decreased levels of *functional* C1-INH. Type I demonstrates a decreased quantity of C1-INH; type II exhibits normal levels of the inhibitor, but it is dysfunctional. The acquired type associated with lymphoproliferative diseases demonstrates low C1 and low C1-INH, whereas the autoimmune variant exhibits low C1 and dysfunctional C1-INH.



• **Fig. 9-45 Angioedema. A,** Soft, nontender tissue swelling of the face arose relatively rapidly after dental treatment. **B,** Facial appearance after resolution of edematous facial enlargement.

Treatment and Prognosis

The treatment of allergic angioedema usually consists of oral antihistamine therapy. If the attack is not controlled or if laryngeal involvement is present, then intramuscular epinephrine should be administered. If the epinephrine does not stop the attack, then intravenous corticosteroids and antihistamines should be given.

Cases of angioedema related to ACE inhibitors are not IgE-mediated and often do not respond to antihistamines and corticosteroids. In spite of this, some investigators believe use of corticosteroids and histamine blockers shortens the time of intubation in patients who require airway support. Although the mechanism is unclear, some patients with ACE inhibitor–associated angioedema also have responded to C1-INH concentrate. In many patients, no form of pharmaceutical intervention is effective, and the patients must be kept under close observation until the airway is no longer at risk. Patients experiencing ACE inhibitor–associated angioedema should avoid all medications in this class of drugs, and their physicians should consider alternative hypertension management strategies. Angiotensin II receptor blockers do not appear to be safe alternatives.

Those cases related to C1-INH deficiency also do not respond to antihistamine, corticosteroid, or adrenergic therapy. Intubation and tracheostomy may be required for laryngeal involvement. Fresh freeze-dried plasma has been used; however, some investigators do not recommend its use because there is a risk of transmitting infection, and it replaces not only C1-INH but also potentially harmful C1 esterase, C1, C2, and C4. C1-INH concentrate and esterase-inhibiting drugs (aprotinin or tranexamic acid) are the treatments of choice for acute attacks. Because acute attacks of hereditary angioedema are not only unpleasant but also potentially life threatening, prevention is paramount. All patients should carry medical warning cards that state the diagnosis and list elementary precautions. Prophylaxis for C1-INH deficiency is recommended in patients who have more than three attacks per year. Patients should avoid violent physical activity and trauma. Medical prophylaxis is recommended before any dental or surgical procedure. In the hereditary types, such prophylaxis typically includes a combination of: 1) an attenuated androgen, such as danazol or stanozolol (androgens induce hepatic synthesis of C1-INH); 2) tranexamic acid or aprotinin; and 3) one or more infusions of C1-INH. The autoimmune acquired type is best prevented through the use of corticosteroids.

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10 Epithelial Pathology

BENIGN EPITHELIAL LESIONS ASSOCIATED WITH HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) comprises a large group of double-stranded DNA viruses, belonging to the family *Papillomaviridae.* HPV exhibits tropism for squamous epithelium and may infect skin or mucosa. Mucosal infection may arise in the anogenital region, upper aerodigestive tract, and other sites. More than 130 HPV types have been identified, including more than 30 types known to infect the oral mucosa in particular. Although HPV is associated with a variety of benign, premalignant, and malignant epithelial lesions, most infected individuals are asymptomatic and lack clinically evident disease.

The reported prevalence of asymptomatic oral HPV infection varies considerably (range 0% to 81%, mean 11%), likely due to differences in sampling techniques, detection methods, and study cohorts. Many studies have analyzed shed epithelial cells in oral rinses, although such samples do not discriminate between oral and oropharyngeal infection. Notwithstanding, meta-analyses and systematic reviews of the literature suggest that oral HPV infection is present in approximately 5% to 12% of normal, healthy individuals. In the pediatric population, asymptomatic oral HPV infection appears to be especially prevalent among those under 1 year of age. Furthermore, a population-based study conducted as part of the National Health and Nutrition Examination Survey (NHANES) for 2009 to 2010 estimated the prevalence of oral HPV infection among individuals 14 to 69 years old in the United States to be about 7%. In this study, the age distribution exhibited a bimodal pattern, with peaks at 30 to 34 years and 60 to 64 years. Factors associated with an increased prevalence of oral HPV infection in adolescence and adulthood include male gender, an increased number of sexual partners, tobacco smoking, and human immunodeficiency virus (HIV) infection.

Proposed modes of transmission for oral HPV infection include sexual and nonsexual person-to-person contact, salivary transfer, contaminated objects, autoinoculation, breastfeeding, perinatal transmission, and, possibly, prenatal transmission. The incubation period for benign HPV disease is estimated to range from 3 weeks to 2 years.

The natural history of oral HPV infection is not well characterized; however, it appears that in most people the infection clears quickly, whereas in some individuals the infection persists. Factors associated with persistent oral infection include impaired immune function, older age, smoking, presence of hand warts, and oral sex. Among infants, persistence has been associated with parental oral HPV infection and maternal hand warts. In normal-appearing skin or mucosa, the virus may remain in a latent state within the nuclei of basal epithelial cells; in such cases, the viral DNA is present in episomal form (i.e., as an extrachromosomal circular molecule) in low copy numbers. In contrast, in benign and low-grade premalignant HPV-associated lesions, episomal HPV DNA typically is present within the various epithelial cell layers in increased copy numbers, with shedding of mature virions from the superficial cells. With division of each infected basal epithelial cell, one daughter cell remains in the basal layer to maintain a viral reservoir; the other daughter cell migrates into the suprabasal layers, interferes with cell cycle regulation, and uses the host cell machinery to synthesize proteins needed for viral replication. In the presence of high episomal numbers, viral DNA may become integrated into the host genome, leading to expression of oncoproteins and inactivation of tumor suppressor genes. Integrated HPV DNA often is found in HPV-associated malignancies and high-grade premalignant lesions, but it is not an absolute requirement for development of such lesions. Compared with HPV infection, HPV-induced malignant transformation is relatively rare. Based upon oncogenic potential, mucosal HPV types are categorized as either *low-risk* (e.g., types 6, 11, 13, 32, 40, 42, 43, 44, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, and 81) or *high-risk* (e.g., types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73).

In the United States, the Food and Drug Administration has licensed two HPV vaccines (a quadrivalent vaccine [Gardasil] targeting HPV types 6, 11, 16, and 18 and a bivalent vaccine [Cervarix] targeting HPV types 16 and 18). The Centers for Disease Control and Prevention recommend routine HPV vaccination for females and males 11 to 12 years of age. Either quadrivalent or bivalent vaccine is indicated for females for prevention of precancers and cancers of the uterine cervix, vulva, and vagina; the quadrivalent vaccine is indicated for both genders for prevention

TABLE 10-1 Human Papillomavirus Types for Select Lesions

Site Predilection	Lesion	Major HPV Types	Other Reported HPV Types
Oral/head and neck mucosa	Oral squamous papilloma	6, 11	
	Recurrent respiratory papillomatosis	6, 11	
	Fungiform sinonasal papilloma	6, 11	16, 57
	Inverted sinonasal papilloma	6, 11	16, 18, 57
	Focal epithelial hyperplasia	13, 32	1, 6, 11, 16, 18, 55
	Oropharyngeal squamous cell carcinoma	16	18, 26, 33, 35, 45, 52, 58
	Conjunctival papilloma	6, 11, 16	
Skin	Verruca vulgaris	2	1, 4, 6, 7, 11, 26, 27, 29, 41, 57, 65, 75-77
	Verruca plana	3, 10	2, 5, 26-29, 38, 41, 49, 75, 76
	Palmoplantar wart	1, 4	2, 45, 57, 60, 63, 65, 66
	Butcher's wart	2, 7	1, 3, 4, 10, 28
Anogenital region	Condyloma acuminatum	6, 11	2, 16, 18, 31, 33, 35, 39-45, 51-56, 58, 59, 66, 68, 70
	Intraepithelial neoplasia	6, 11, 16, 18, 31, 33	26, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82
	Cervical squamous cell carcinoma	16, 18	6, 11, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

HPV, Human papillomavirus.

of genital warts. Furthermore, a recent large-scale study has shown the bivalent vaccine to be more than 90% effective in preventing oral HPV 16 and 18 infections among women. A focus of ongoing investigation is the potential for these vaccines to prevent oropharyngeal cancer and other HPV-related lesions of the head and neck.

The following sections discuss benign HPV-associated lesions of the oral cavity and other head and neck sites. HPV-associated malignancies are addressed later in this chapter. Examples of HPV-related lesions and their corresponding virus types are listed in Table 10-1.

SQUAMOUS PAPILLOMA

The **squamous papilloma** is a benign, HPV-induced proliferation of stratified squamous epithelium, resulting in a papillary or verruciform mass. HPV types 6 and 11 are identified most commonly, with an extremely low virulence and infectivity rate.

The squamous papilloma occurs in one of every 250 adults and makes up approximately 3% of all oral lesions submitted for biopsy. In addition, researchers have estimated that squamous papillomas comprise 7% to 8% of all oral masses or growths in children.

Clinical Features

Most studies have reported either no significant gender predilection or a slight male predominance. Some authors have asserted that the oral squamous papilloma develops predominantly in children; however, epidemiologic studies indicate that it can arise at any age and, in fact, is diagnosed most often in persons 30 to 50 years old. Sites of predilection include the palate, tongue, and lips, but any oral surface may be affected. This lesion is the most common soft tissue mass arising from the soft palate.

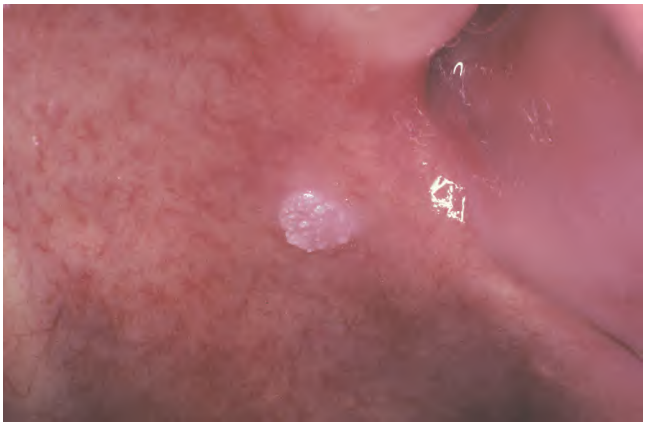
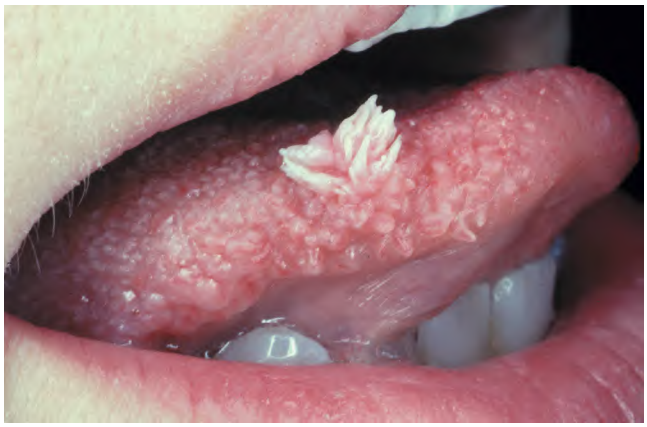
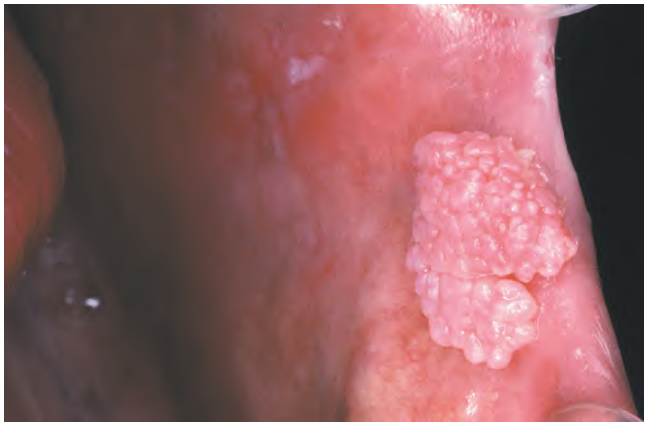


Fig. 10-1 Squamous Papilloma. An exophytic lesion of the soft palate with multiple short, white surface projections.

The squamous papilloma is a soft, painless, usually pedunculated, exophytic nodule with numerous fingerlike surface projections that impart a "cauliflower" or wartlike appearance (Fig. 10-1). Projections may be pointed or blunted (Figs. 10-2 and 10-3), and the lesion may be white, slightly red, or normal in color, depending on the amount of surface keratinization. The papilloma is usually solitary



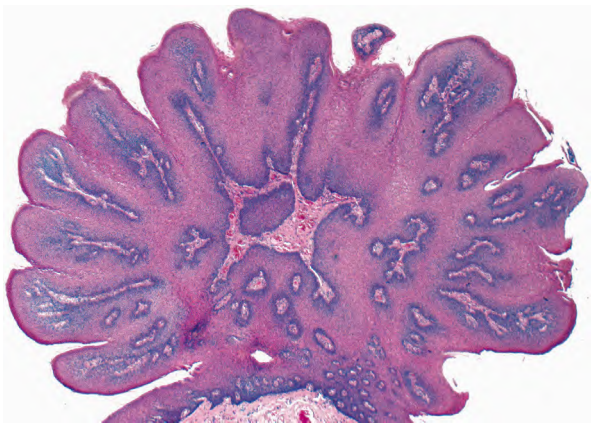
• **Fig. 10-2 Squamous Papilloma.** A pedunculated lingual mass with numerous long, pointed, and white surface projections. Note the smaller projections around the base of the lesion.



• **Fig. 10-3 Squamous Papilloma.** A pedunculated mass of the buccal commissure, exhibiting short or blunted surface projections and minimal white coloration.

and enlarges rapidly to a maximum size of about 0.5 cm, with little or no change thereafter. However, lesions as large as 3.0 cm in greatest diameter have been reported.

It is sometimes difficult to distinguish this lesion clinically from verruca vulgaris (see page 334), condyloma acuminatum (see page 335), verruciform xanthoma (see page 341), or multifocal epithelial hyperplasia (see page 336). In addition, extensive coalescing papillary lesions **(papillomatosis)** of the oral mucosa may be seen in several syndromes and skin disorders, including nevus unius lateris, acanthosis nigricans, focal dermal hypoplasia (Goltz-Gorlin) syndrome, and Down syndrome. Also attributed to HPV 6 and 11 infection, **recurrent respiratory papillomatosis (RRP)** is a rare and potentially devastating disease of the respiratory tract with a predilection for the larynx. RRP includes two distinct types: (1) **juvenile-onset** and (2) **adult-onset.** Hoarseness is the usual presenting feature, and rapidly proliferating papillomas in the juvenile-onset type may obstruct the airway. The strongest risk factor for juvenile-onset RRP is a maternal history of genital warts during pregnancy; HPV transmission via the birth canal, the placenta, or amniotic fluid has been hypothesized.



• **Fig. 10-4 Squamous Papilloma.** Low-power view showing a pedunculated squamous epithelial proliferation. There are multiple papillary projections with fibrovascular connective tissue cores.

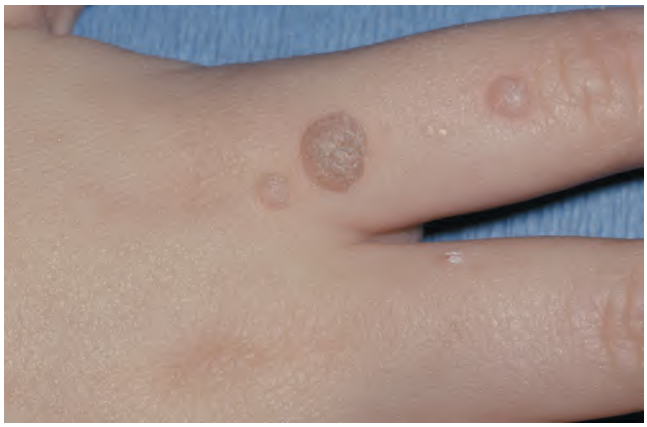
Histopathologic Features

The papilloma is characterized by a proliferation of keratinized stratified squamous epithelium arranged in fingerlike projections with fibrovascular connective tissue cores (Fig. 10-4). The connective tissue may show inflammation. The keratin layer is thickened in lesions with a white clinical appearance, and the epithelium typically exhibits a normal maturation pattern. However, some papillomas demonstrate basilar hyperplasia and mitotic activity, which can be mistaken for mild epithelial dysplasia. **Koilocytes** (virus-altered epithelial cells with crenated, pyknotic [small and dark] nuclei surrounded by clear halos) sometimes are evident high in the spinous cell layer.

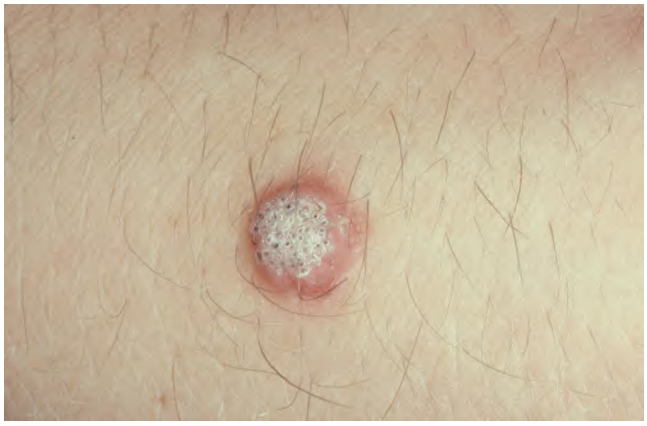
Treatment and Prognosis

Conservative surgical excision, including the base of the lesion, is adequate treatment for the oral squamous papilloma, and recurrence is unlikely. Frequently, lesions have been left untreated for years with no reported malignant transformation, continuous enlargement, or dissemination to other parts of the oral cavity.

Although spontaneous remission is possible, juvenile-onset RRP tends to be continuously proliferative, sometimes leading to death by asphyxiation. Some investigators have noted especially aggressive behavior among cases associated with HPV 11 infection. The papillomatosis is treated by repeated surgical debulking procedures to relieve airway obstruction. Use of a microdebrider may decrease the risk for postsurgical scarring and loss of vocal cord function. Adjuvant therapy with interferon-alpha and cidofovir has yielded variable results. Adult-onset RRP typically is less aggressive and more localized. Conservative surgical removal may be necessary to eliminate hoarseness from vocal cord involvement. Transformation of RRP into squamous cell carcinoma is rare and mainly occurs in patients with a history of smoking or radiation exposure.



• **Fig. 10-5 Verruca Vulgaris.** Several warts on the finger, exhibiting a rough, papillary surface.



• **Fig. 10-6 Verruca Vulgaris.** Nodular lesion of the skin exhibiting numerous short papillary projections.

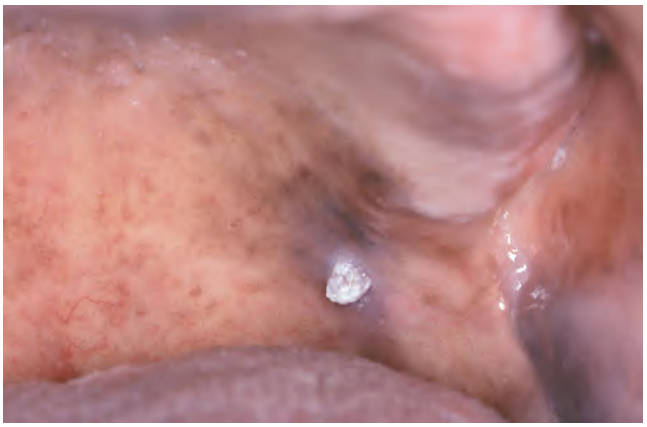
VERRUCA VULGARIS (COMMON WART)

Verruca vulgaris is a focal, benign, HPV-induced hyperplasia of stratified squamous epithelium. HPV 2 is present most often, although other HPV types may be found as well (see Table 10-1). Verruca vulgaris is contagious and can spread to other parts of a person's skin or mucosa by autoinoculation. It infrequently develops on oral mucosa but is extremely common on the skin.

Clinical Features

Verruca vulgaris most often arises in children but occasionally may develop even into middle age. The skin of the hands is the most commonly involved site (Fig. 10-5). Oral mucosal lesions usually are found on the vermilion border, labial mucosa, or anterior tongue.

Typically, the verruca appears as a painless papule or nodule with papillary projections or a rough, pebbly surface (Figs. 10-6 and 10-7). It may be pedunculated or sessile. Cutaneous lesions may be pink, yellow, or white; oral lesions are almost always white. Verruca vulgaris enlarges rapidly to its maximum size (usually <5 mm), and the size remains constant for months or years thereafter unless the lesion is irritated. Multiple or clustered lesions are common. On occasion, extreme accumulation of compact keratin may result in a hard surface projection, termed a **cutaneous horn** or **keratin horn.** Other cutaneous lesions, including seborrheic keratosis (see page 342), actinic keratosis (see page 369), and squamous cell carcinoma, also may create a cutaneous horn.



• **Fig. 10-7 Verruca Vulgaris.** Exophytic, white, papillary lesion of the lateral soft palate.

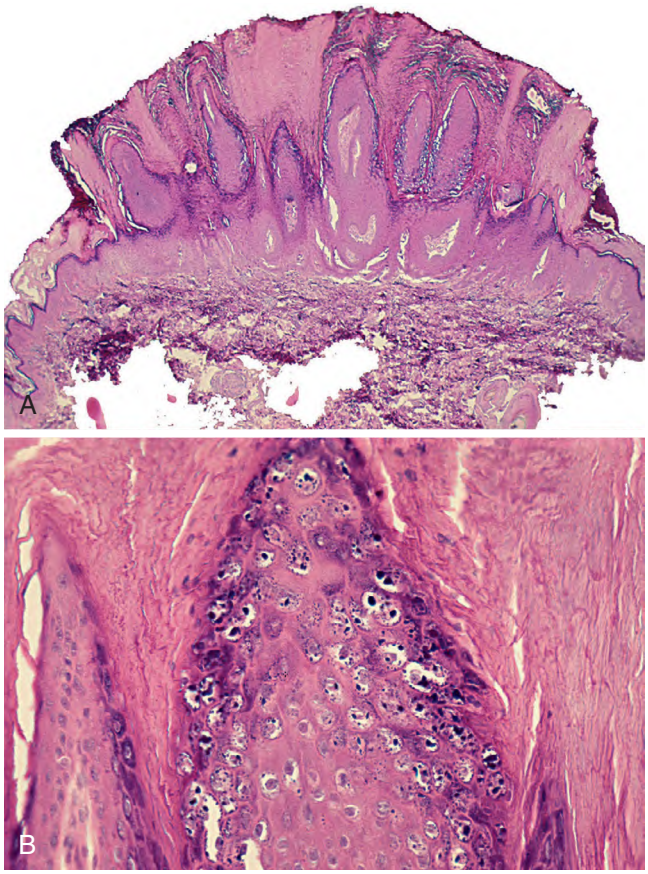
Histopathologic Features

Verruca vulgaris is characterized by a proliferation of hyperkeratotic stratified squamous epithelium arranged in finger-like, pointed projections with connective tissue cores (Fig. 10-8). Chronic inflammatory cells often infiltrate the supporting connective tissue. Elongated rete ridges tend to converge toward the center of the lesion, producing a "cupping" effect. A prominent granular cell layer (hypergranulosis) exhibits coarse, clumped keratohyaline granules. Abundant koilocytes often are seen in the superficial spinous layer. Koilocytes are HPV-altered epithelial cells with perinuclear clearing and crenated, pyknotic nuclei. Eosinophilic intranuclear viral inclusions sometimes are noted within the cells of the granular layer.

Treatment and Prognosis

Skin verrucae are treated effectively by topical salicylic acid, topical lactic acid, or liquid nitrogen cryotherapy. Surgical excision is indicated only for cases with an atypical clinical presentation in which the diagnosis is uncertain. Skin lesions that recur or are resistant to standard therapy may be treated by alternative methods, such as intralesional bleomycin, topical or intralesional 5-fluorouracil, cantharidin, topical imiquimod, intralesional immunotherapy (with *Candida* or mumps skin antigen), or photodynamic therapy.

Oral lesions usually are excised surgically, or they may be destroyed by laser, cryotherapy, or electrosurgery. Cryotherapy induces a subepithelial blister that lifts the infected epithelium from the underlying connective tissue, allowing



• **Fig. 10-8 Verruca Vulgaris. A,** Numerous papillary projections are covered by hyperkeratotic stratified squamous epithelium. Elongated rete ridges at the edge of the lesion converge toward the center. **B,** High-power view showing clear koilocytes in the upper epithelial layers.

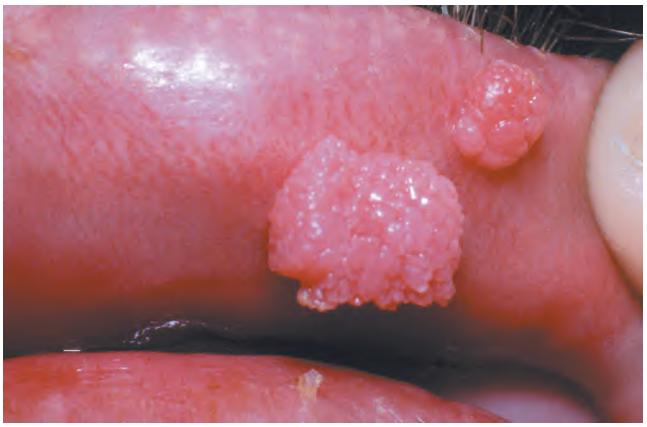
it to slough away. All destructive or surgical treatments should extend to the base of the lesion.

Recurrence is seen in a small proportion of treated cases. Without treatment, verrucae do not transform into malignancy, and two-thirds will disappear spontaneously within 2 years, especially in children.

CONDYLOMA ACUMINATUM (VENEREAL WART)

Condyloma acuminatum is a HPV-induced proliferation of stratified squamous epithelium of the anogenital region, mouth, and larynx. Approximately 90% of cases are attributed to HPV 6 and 11; however, coinfection with various other types—including the high-risk types 16 and 18—is frequent (see Table 10-1).

Condyloma represents a common sexually transmitted disease (STD), affecting about 1% of the sexually active population. Between 500,000 and 1 million new cases are diagnosed annually in the United States. However, since the introduction of HPV vaccination, significant reductions in incidence have been reported among adolescents and young adults in many regions. Condyloma may be an indicator of



• **Fig. 10-9 Condyloma Acuminatum.** Two lesions of the upper lip mucosa exhibit short, blunted projections. (Courtesy of Dr. Brian Blocher.)

sexual abuse when diagnosed in young children. In addition, studies of oral and pharyngeal HPV infection in infants have suggested that vertical transmission from mothers with genital HPV infection may occur perinatally or perhaps *in utero.* Oral and anogenital condylomata may be present concurrently. The incubation period is about 1 to 3 months, and autoinoculation of additional mucosal sites is possible.

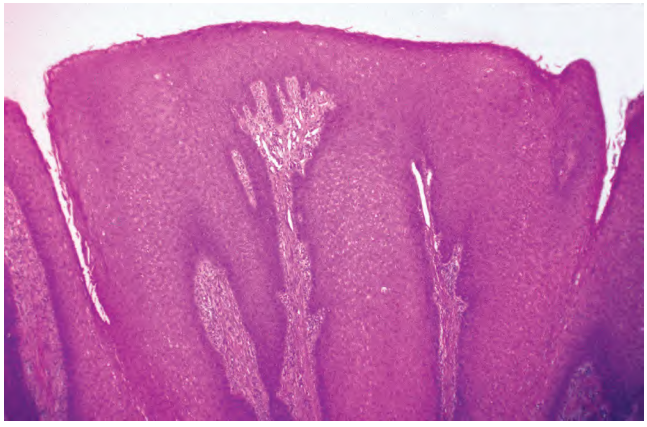
Clinical Features

Condylomata usually are diagnosed in teenagers and young adults, but people of all ages are susceptible. Oral lesions most frequently occur on the labial mucosa and lingual frenum; the soft palate often is involved as well. The typical condyloma appears as a sessile, pink, well-demarcated, nontender, exophytic mass with short, blunted surface projections (Fig. 10-9). The condyloma tends to be larger than the papilloma and characteristically is clustered with other condylomata. The average size is 1.0 to 1.5 cm, but oral lesions as large as 3 cm have been reported.

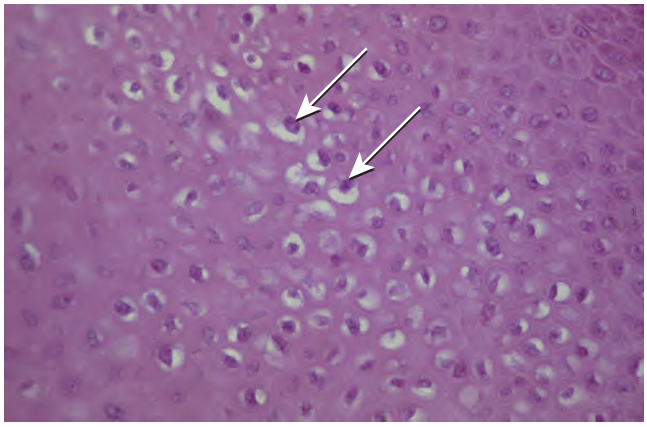
Histopathologic Features

Condyloma acuminatum appears as a benign proliferation of acanthotic stratified squamous epithelium with mildly keratotic, papillary surface projections (Fig. 10-10). Thin connective tissue cores support the papillary projections, which are more blunted and broader than those of squamous papilloma and verruca vulgaris. Keratin-filled crypts often are seen between the papillary projections. In some cases, lesions may extend from the surface mucosa to involve the underlying salivary ductal epithelium; such lesions should be distinguished from salivary ductal papillomas (see page 452).

The surface epithelium is mature and differentiated, but within the spinous cell layer, there are often **koilocytes** (HPV-altered cells with pyknotic, crinkled [or "raisin-like"] nuclei) (Fig. 10-11). Koilocytes may be less prominent in



• **Fig. 10-10 Condyloma Acuminatum.** Medium-power photomicrograph showing acanthotic stratified squamous epithelium forming a blunted projection.



• **Fig. 10-11 Condyloma Acuminatum.** High-power photomicrograph demonstrating koilocytes *(arrows)* in the spinous layer.

oral lesions compared with genital lesions, in which case distinction from squamous papilloma may be difficult. Ultrastructural examination reveals virions within the cytoplasm or nuclei of koilocytes, and the virus also can be demonstrated by immunohistochemical analysis, *in situ* hybridization (ISH), and polymerase chain reaction (PCR).

Treatment and Prognosis

Oral condylomata usually are treated by conservative surgical excision. Cryotherapy and laser ablation also may be used. However, there is some concern regarding the potential for laser therapy to produce an infectious plume that exposes the surgical team and patient to airborne HPV. Patient-applied topical agents (such as, imiquimod, podophyllotoxin, and sinecatechins) are becoming the mainstay of treatment for anogenital condylomata, although such treatments typically are not used for oral lesions. Additional treatment options for anogenital lesions include trichloroacetic acid, systemic or intralesional interferon, and topical cidofovir. Regardless of the method used, a condyloma should be removed because it is contagious and can spread by autoinoculation or to other persons

Anogenital condylomata infected with HPV 16 or 18 are associated with an increased risk for malignant transformation to squamous cell carcinoma, but such transformation has not been demonstrated in oral lesions. Interestingly, a recent population-based study of Danish patients with genital condylomata reported a long-term, increased risk for not only anogenital but also head and neck cancer. Proposed explanations for this observation include an immunologic predisposition to persistent HPV infection (resulting in increased risk for HPV-related head and neck cancer) and behavioral cofactors (e.g., tobacco and alcohol consumption, male homosexual behavior).

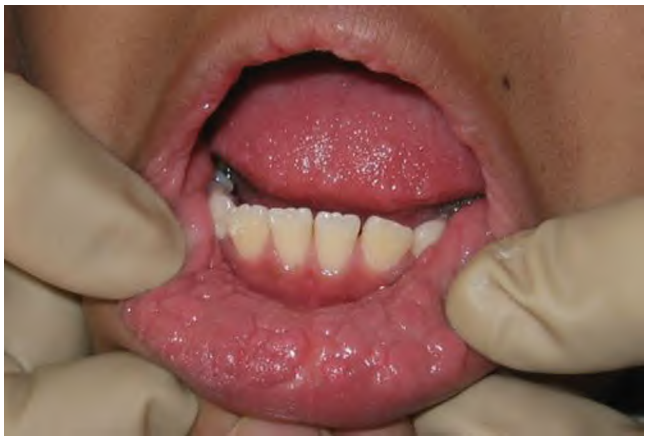
Two HPV vaccines (a quadrivalent vaccine [Gardasil] targeting HPV 6, 11, 16, and 18 and a bivalent vaccine [Cervarix] targeting HPV 16 and 18) are licensed in the United States, with routine HPV vaccination recommended for females and males 11 to 12 years of age. The quadrivalent vaccine is indicated for prevention of genital warts; in addition, both vaccines are designed to reduce HPV transmission rates and the risk of HPV-related anogenital cancers. Quadrivalent HPV vaccination would be expected to aid in preventing oral condylomata as well, although the impact of HPV vaccination on oral HPV-related disease requires study.

MULTIFOCAL EPITHELIAL HYPERPLASIA (HECK DISEASE; MULTIFOCAL PAPILLOMA VIRUS EPITHELIAL HYPERPLASIA; FOCAL EPITHELIAL HYPERPLASIA)

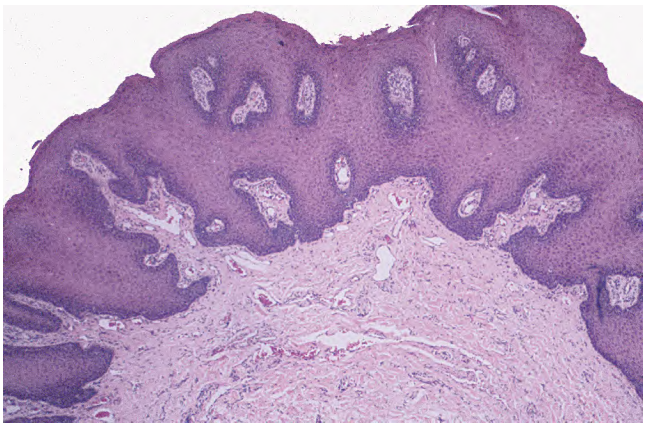
Multifocal epithelial hyperplasia is a squamous epithelial proliferation primarily attributed to HPV 13 and 32. The condition initially was described in Native Americans and Inuits but subsequently has been reported in many populations and ethnic groups. In some populations, as many as 40% of children are affected. Multifocal epithelial hyperplasia often affects multiple members of a given family; this familial tendency may be related to either genetic susceptibility or HPV transmission between family members. An association with the HLA-DR4 (DRB1*0404) allele has been described. Lower socioeconomic status, crowded living conditions, poor hygiene, malnutrition, and HIV infection appear to be additional risk factors. Although originally reported as "focal epithelial hyperplasia," the term *multifocal epithelial hyperplasia* is preferred because patients usually exhibit multiple lesions.

Clinical Features

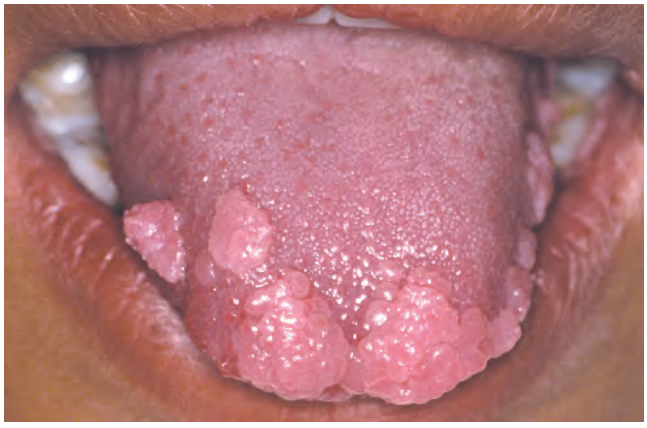
Multifocal epithelial hyperplasia predominantly arises in children and adolescents, although adults also may be affected. Studies have reported either a female predilection or no significant gender bias. The most common sites of involvement include the labial, buccal, and lingual mucosa, but gingival, palatal, oral floor, and tonsillar lesions also are possible. In addition, involvement of the conjunctiva has been described very rarely.



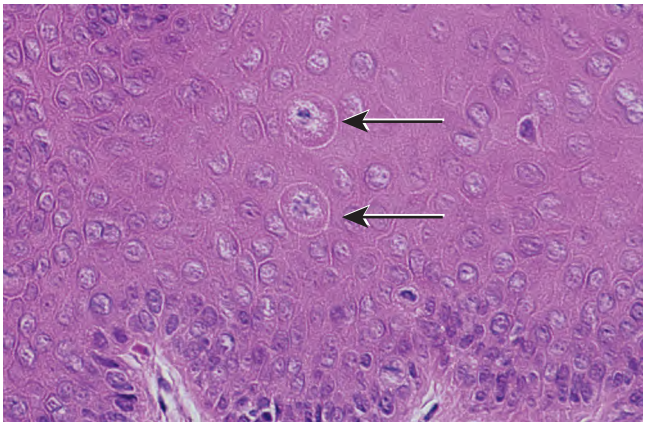
• **Fig. 10-12 Multifocal Epithelial Hyperplasia.** Multiple, flat-topped papules and nodules of normal coloration are seen on the lower lip of a child. (Courtesy of Dr. Mark Casafrancisco.)



• **Fig. 10-14 Multifocal Epithelial Hyperplasia.** Prominent acanthosis of the epithelium with broad and elongated rete ridges. The slightly papillary surface alteration noted here may or may not be present.



• **Fig. 10-13 Multifocal Epithelial Hyperplasia.** The lesions may demonstrate a papillary surface change and paleness, as demonstrated on this child's tongue. (Courtesy of Dr. Román Carlos.)



• **Fig. 10-15 Multifocal Epithelial Hyperplasia.** Mitosoid cells *(arrows)* contain altered nuclei in this otherwise mature and well-differentiated stratified squamous epithelium.

There are two major clinical variants: papulonodular and papillomatous. The more common papulonodular variant is characterized by pink, smooth-surfaced papules and nodules, with a predilection for the buccal mucosa, labial mucosa, and commissure (Fig. 10-12). The papillomatous variant appears as white to pale pink, pebbly nodules on the tongue and attached gingiva (Fig. 10-13). In both variants, the individual lesions are small (0.1 to 1.0 cm), discrete, and well-demarcated, but they may coalesce to produce a cobblestone or fissured appearance. According to some authors, the lesions tend to be smaller, fewer in number, and less exophytic among older patients compared to younger patients; this observation may reflect spontaneous regression over time.

Histopathologic Features

The hallmark of focal epithelial hyperplasia is an abrupt and sometimes considerable acanthosis of the surface epithelium (Fig. 10-14). Because the thickened mucosa extends upward, the lesional rete ridges are at the same depth as the adjacent, normal rete ridges. The rete ridges are widened, often confluent, and sometimes club-shaped. Some superficial keratinocytes show koilocytic change similar to that seen in other HPV infections. Others occasionally demonstrate an altered nucleus that resembles a mitotic figure **(mitosoid cell)** (Fig. 10-15). Viruslike particles have been noted ultrastructurally within both the cytoplasm and the nuclei of cells within the prickle cell layer, and the presence of HPV has been demonstrated by DNA *in situ* hybridization, immunohistochemistry, and polymerase chain reaction (PCR).

Treatment and Prognosis

Spontaneous regression has been reported after months or years and is inferred from the rarity of the disease in adults. Conservative surgical excision may be performed for diagnostic or aesthetic purposes or for lesions subject to recurrent trauma. Lesions also can be removed by cryotherapy, carbon dioxide (CO_2) laser, or electrocoagulation. A few

reported cases have been treated with topical interferon-beta, systemic or intralesional interferon-alpha, or topical imiquimod. Recurrence (after either treatment or spontaneous regression) is possible. There seems to be no malignant transformation potential.

SINONASAL PAPILLOMAS

Sinonasal papillomas are benign, localized proliferations of the sinonasal mucosa and include three histomorphologically distinct types:

1. Fungiform
2. Inverted
3. Cylindrical cell

Lesions exhibiting features of both the inverted and the cylindrical cell types may be termed *mixed* or *hybrid* papillomas. In addition, a keratinizing **squamous papilloma,** similar to the oral squamous papilloma (see page 332), rarely may occur in the nasal vestibule.

Collectively, **sinonasal papillomas** represent 10% to 25% of all sinonasal tumors. About half of sinonasal papillomas arise from the lateral nasal wall; the remainder predominantly involves the maxillary and ethmoid sinuses and the nasal septum. Multiple lesions may be present.

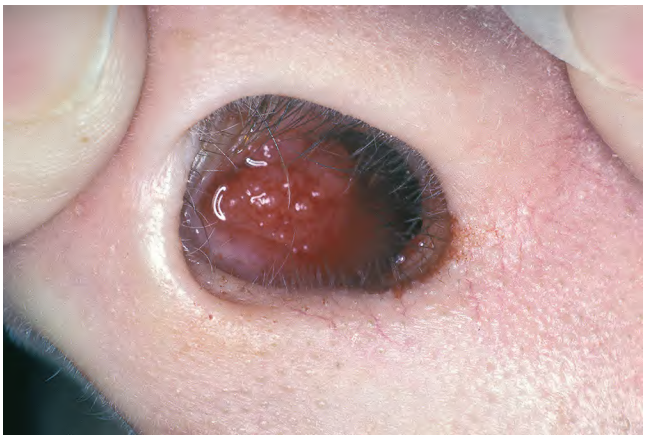
The etiopathogenesis of sinonasal papillomas remains unclear. Historically, numerous contributory factors—such as allergy, chronic sinusitis, nasal polyps, and tobacco smoke or other airborne pollutants—have been proposed but remain unsubstantiated. A variable association with HPV infection has been reported, with the strongest association noted for the fungiform type. According to a recent meta-analysis of studies using various HPV detection methods, approximately 39% of sinonasal papillomas are HPV-positive, with HPV prevalence rates for the fungiform, inverted, and cylindrical cell types of 65%, 38%, and 23%, respectively.

FUNGIFORM (SEPTAL; SQUAMOUS; EXOPHYTIC) PAPILLOMA

The **fungiform papilloma** bears some similarity to the oral squamous papilloma, although it has a somewhat more aggressive biologic behavior and more varied epithelial types. It represents 18% to 50% of all sinonasal papillomas in various investigations. The majority of cases are positive for HPV 6 or 11.

Clinical Features

The fungiform papilloma arises almost exclusively on the nasal septum and is more common in men than women (at least 2 : 1 male-to-female ratio). It occurs primarily in people 20 to 50 years of age. Typically, it causes unilateral nasal obstruction or epistaxis and appears as a pink or tan, broad-based nodule with papillary or warty surface projections (Fig. 10-16). Most lesions measure less than 2 cm in maximum diameter.



• **Fig. 10-16 Fungiform Papilloma.** Erythematous, papillary growth on the nasal septum.

Histopathologic Features

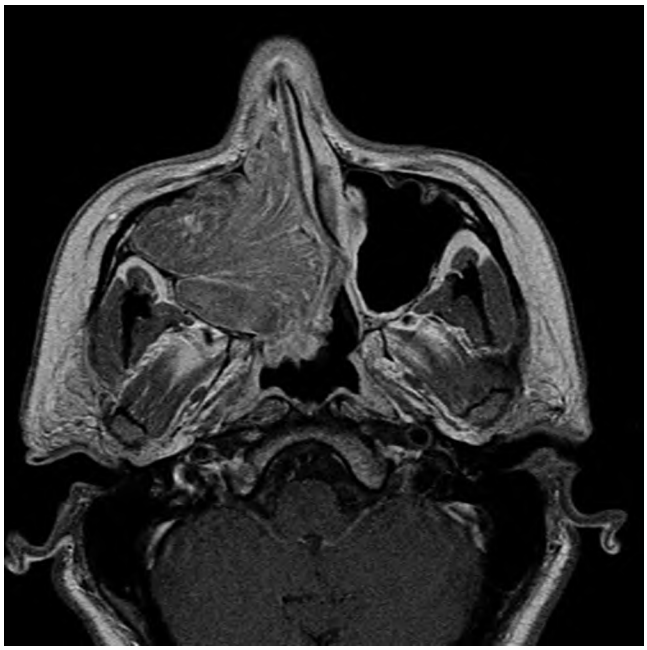
The fungiform papilloma has a microscopic appearance similar to that of the oral squamous papilloma, although the stratified squamous epithelium covering the fingerlike projections seldom is keratinized. Respiratory epithelium or "transitional" epithelium (intermediate between squamous and respiratory) may be seen in some lesions. Mucous (goblet) cells and intraepithelial microcysts containing mucus often are present. Mitoses are infrequent, and dysplasia is rare. The lamina propria consists of delicate fibrous tissue with a minimal inflammatory component, unless it is irritated.

Treatment and Prognosis

Complete surgical excision is the treatment of choice for the fungiform papilloma. Recurrence has been reported in approximately 20% to 30% of cases; however, some of these cases may reflect incomplete excision rather than true recurrence. Most authorities consider this lesion to have minimal or no potential for malignant transformation.

INVERTED PAPILLOMA (INVERTED SCHNEIDERIAN PAPILLOMA; ENDOPHYTIC PAPILLOMA)

The **inverted papilloma** is the most common sinonasal papilloma variant, comprising approximately 50% to 78% of cases. It is also the variant with the greatest potential for local destruction and malignant transformation. Molecular genetic investigations support that inverted papillomas represent true neoplasms of monoclonal origin (i.e., arising from a single progenitor cell). Systematic reviews and meta-analyses of the literature suggest that HPV is present in approximately 24% to 38% of cases, with HPV 6, 11, 16, and 18 representing the most prevalent types.



• **Fig. 10-17 Inverted Papilloma.** Magnetic resonance image (MRI) showing a tumor with a characteristic convoluted, cerebriform pattern. (Courtesy of Dr. Zoran Rumboldt.)

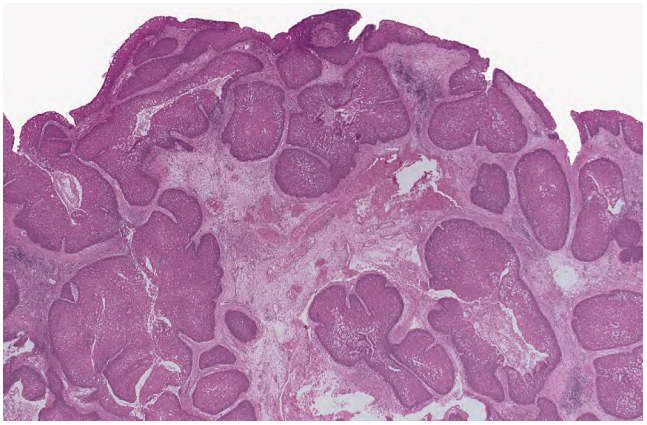
Clinical and Radiographic Features

The average age at presentation is 53 years, with a peak in the fifth and sixth decades. There is a strong male predilection (3 : 1 to 5 : 1 male-to-female ratio). Inverted papillomas arise predominantly from the lateral nasal wall or a paranasal sinus, usually the antrum. Typical signs and symptoms include unilateral nasal obstruction, epistaxis, purulent discharge, hyposmia, headache, or local deformity. The lesion appears as a soft, pink or tan, polypoid or nodular growth. Multiple lesions may be present. Bilateral involvement occurs in only about 5% of cases. The lesion has significant growth potential and, if neglected, may extend into the nasopharynx, middle ear, orbit, or cranial base.

Pressure erosion of the underlying bone often is evident radiographically. Primary sinus lesions may appear only as a soft tissue radiodensity or mucosal thickening on radiographs; sinus involvement generally represents extension from the nasal cavity. Focal hyperostosis demonstrated by computed tomography (CT) scan may indicate the site of lesion attachment, which is important for surgical planning. In addition, magnetic resonance imaging (MRI) can help to identify the extent of the lesion and often reveals a convoluted, cerebriform pattern (Fig. 10-17).

Histopathologic Features

The inverted papilloma microscopically exhibits downward proliferation of squamous epithelium into the stroma (Fig. 10-18). The basement membrane remains intact, and the epithelium appears to "push" into the underlying connective tissue. Goblet (mucous) cells and mucin-filled microcysts frequently are noted within the epithelium. Keratin production is uncommon, but thin surface keratinization may be seen. Mitoses often are noted within the basilar or parabasilar cells, and varying degrees of epithelial atypia may be seen. Papillary surface projections separated by deep clefts may be observed. The stroma consists of dense or myxomatous connective tissue with or without inflammatory cells. Destruction of underlying bone frequently is noted.



• **Fig. 10-18 Inverted Papilloma.** Low-power photomicrograph showing a squamous epithelial proliferation, with multiple "inverting" islands of epithelium extending into the underlying connective tissue.

Marked surface keratinization and moderate to severe dysplasia are worrisome histopathologic findings that warrant careful microscopic examination to rule out malignancy. Nonetheless, there are no histopathologic features that are reliably predictive of malignant transformation in inverted papillomas. A few studies suggest that increased immunohistochemical expression of p53 and p21 (cell cycle-related proteins), decreased immunohistochemical expression of CD44 (a cell adhesion molecule), and the presence of HPV 16 or 18 may be associated with an increased risk for malignant transformation. Notably, immunohistochemical expression of p16 in inverted papillomas does not appear to be a reliable surrogate marker for high-risk HPV infection.

Treatment and Prognosis

Over the past few decades, the preferred treatment has shifted from traditional open surgery (i.e., medial maxillectomy via a lateral rhinotomy or midfacial degloving approach) to transnasal endoscopic surgery. Depending upon the extent and accessibility of disease, endoscopic and external surgical approaches may be combined. With modern and aggressive surgical therapy, investigators have reported recurrence rates of 13% to 17% or less. In contrast, conservative surgical excision is associated with unacceptably high recurrence rates (nearly 75% in some studies). Recurrences usually are noted within 2 years of surgery but can happen much later. Hence, long-term follow-up is essential. Continued tobacco smoking is associated with an increased risk for recurrence.

Approximately 3% to 24% of inverted papillomas transform into malignancy (usually squamous cell carcinoma). When malignancy is present, treatment typically consists of radical surgery, with or without adjunctive radiotherapy.

CYLINDRICAL CELL PAPILLOMA (ONCOCYTIC SCHNEIDERIAN PAPILLOMA)

The **cylindrical cell papilloma** accounts for less than 7% of sinonasal papillomas. Some authorities consider this lesion to be a variant of the **inverted papilloma** because of the similarity in clinicopathologic features and a similarly low frequency of HPV.

Clinical Features

The cylindrical cell papilloma most often occurs in adults older than 50 years. Most authors report either a male predominance or no significant gender bias. There is a predilection for the lateral nasal wall, maxillary antrum, and ethmoid sinus. The most common presenting symptom is unilateral nasal obstruction, and the lesion appears as a beefy-red or brown mass with a multinodular surface.

Histopathologic Features

Microscopically, the cylindrical cell papilloma demonstrates both endophytic and exophytic growth. Surface papillary projections have a fibrovascular connective tissue core and are covered by a multilayered epithelium of tall columnar cells with small, dark nuclei and eosinophilic, occasionally granular cytoplasm. The lesional epithelial cell is similar to an oncocyte. Cilia may be seen on the surface, and there are numerous intraepithelial microcysts filled with mucin, neutrophils, or both.

Treatment and Prognosis

The treatment and recurrence potential for cylindrical cell papilloma and inverted papilloma (see previous topic) are similar. Reported malignant transformation rates for cylindrical cell papilloma range from 4% to 17%.

◆ MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is an epithelial lesion induced by the molluscum contagiosum virus (MCV), a member of the DNA poxvirus group. At least 6% of the population (more in older age groups) has antibodies to this virus, although few ever develop lesions. In adults and adolescents, MCV typically is transmitted by sexual contact, whereas in children it is transmitted mainly by nonsexual contact (e.g., wrestling, sharing clothing or towels). Warm, humid environments, such as communal baths or swimming pools, also may encourage disease spread. After an incubation period of 14 to 50 days, multiple umbilicated papules may develop on the skin or, rarely, mucous membranes. The lesions usually remain small for months or years and then spontaneously involute.

The disease exhibits a predilection for warm portions of the skin and sites of recent injury. Florid cases have been reported in immunocompromised patients, and the prevalence of MCV coinfection among the HIV-positive patient population is estimated to be 5% to 18% (see page 252). Patients with atopic dermatitis and Darier disease also are at risk for developing severe, prolonged disease.

Clinical Features

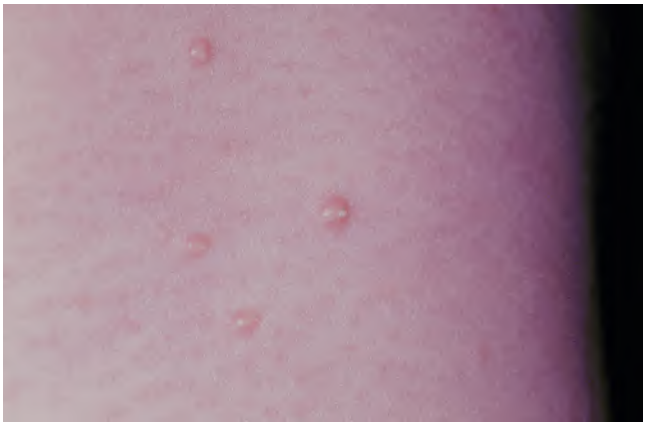
Molluscum contagiosum mainly arises in children and young adults. The lesions occur predominantly on the skin of the neck, face (particularly eyelids), trunk, and genitalia. Infrequently, oral involvement occurs, usually on the lips, buccal mucosa, palate, or gingiva.

The lesions typically appear as multiple clustered, pink or white, smooth-surfaced, sessile papules measuring 2 to 4 mm in diameter (Fig. 10-19). Many show a small central indentation or plug from which a curd-like substance containing viral particles can be expressed. Most lesions are asymptomatic, although slight tenderness or pruritus is possible. Eczematous eruptions occasionally may develop in the vicinity of molluscum contagiosum, particularly in patients with atopic dermatitis.

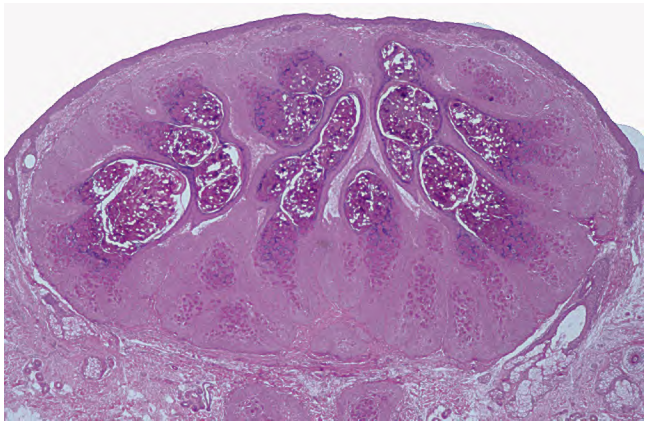
In immunocompromised patients, the lesions may be unusually large, verrucous, or markedly hyperkeratotic.

Histopathologic Features

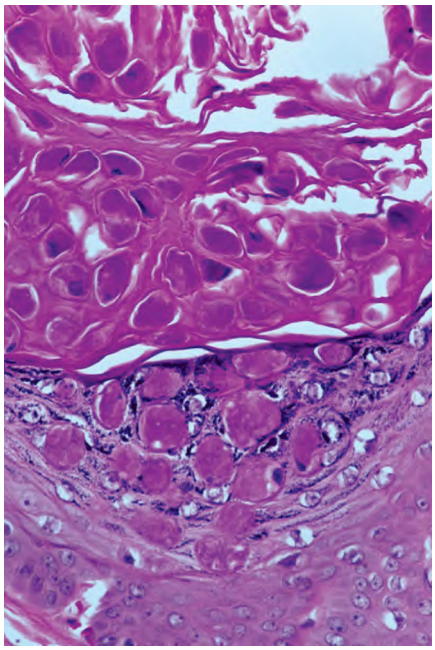
Molluscum contagiosum appears as a localized, lobular proliferation of surface stratified squamous epithelium (Fig. 10-20). The central portion of each lobule is filled with bloated keratinocytes that contain large, intranuclear, basophilic viral inclusions called **molluscum bodies** (or **Henderson-Paterson bodies**) (Fig. 10-21). These bodies begin as small, eosinophilic structures in cells just above the basal layer and enlarge as they approach the surface. A



• **Fig. 10-19 Molluscum Contagiosum.** Multiple, smooth-surfaced papules, with several demonstrating small keratin-like plugs, are seen on the neck of a child.



• **Fig. 10-20 Molluscum Contagiosum.** Well-defined epidermal proliferation demonstrating a central craterlike depression filled with virally altered keratinocytes.



• **Fig. 10-21 Molluscum Contagiosum.** Higher-power photomicrograph showing keratinocytes with large, basophilic viral inclusions (molluscum bodies) being sloughed into the central crater *(top)*.

central crater is formed at the surface as stratum corneum cells disintegrate to release their molluscum bodies.

Treatment and Prognosis

Most cases of molluscum contagiosum undergo spontaneous remission within 6 to 9 months. For immunocompetent patients, there is ongoing debate as to whether the disease should be treated or allowed to resolve on its own. Treatment may be performed to decrease the risk of disease transmission, prevent autoinoculation, provide symptomatic relief, or address cosmetic concerns.

Although there are few controlled studies of treatment efficacy, the lesions most commonly are removed by curettage or cryotherapy. Alternative treatment methods include laser therapy, electrodessication, chemical destructive agents (e.g., salicylic acid, lactic acid, silver nitrate, potassium hydroxide, podophyllotoxin, and cantharidin), topical tretinoin, and topical imiquimod. In addition, a limited number of cases have been treated by intralesional injection of *Candida* antigen (which may stimulate a local immune response and MCV clearance).

In immunosuppressed patients with recalcitrant lesions, the antiviral agent cidofovir may be effective. Moreover, in HIV-infected patients, combination antiretroviral therapy indirectly counteracts MCV infection by increasing CD4+ T cell counts and improving the immune response.

Recurrence after initial clearing has been reported in up to one-third of patients. There is no apparent malignant transformation potential.

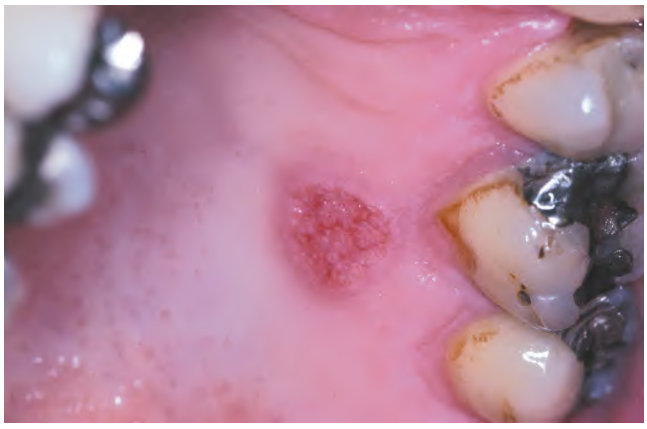
◆ VERRUCIFORM XANTHOMA

Verruciform xanthoma is a hyperplastic condition of the epithelium, with a characteristic subepithelial accumulation of lipid-laden histiocytes. It is primarily an oral disease, but skin and genital lesions also are possible. The cause is unknown. Although verruciform xanthoma is a papillary lesion, HPV has been identified in only a small number of cases, and no definitive pathogenetic role for this virus has been established. The lesion probably represents an unusual reaction or immune response to localized epithelial trauma or damage. This hypothesis is supported by cases of verruciform xanthoma that have developed in association with disturbed epithelium (e.g., lichen planus, lupus erythematosus, epidermolysis bullosa, epithelial dysplasia, squamous cell carcinoma, pemphigus vulgaris, warty dyskeratoma, graft-versus-host disease [GVHD]). The lesion is histopathologically similar to other dermal xanthomas, but it is not associated with diabetes or hyperlipidemia. Interestingly, in a few cutaneous cases, investigators have identified a somatic mutation in the gene encoding 3-beta-hydroxysteroid dehydrogenase (an enzyme essential for cholesterol biosynthesis).

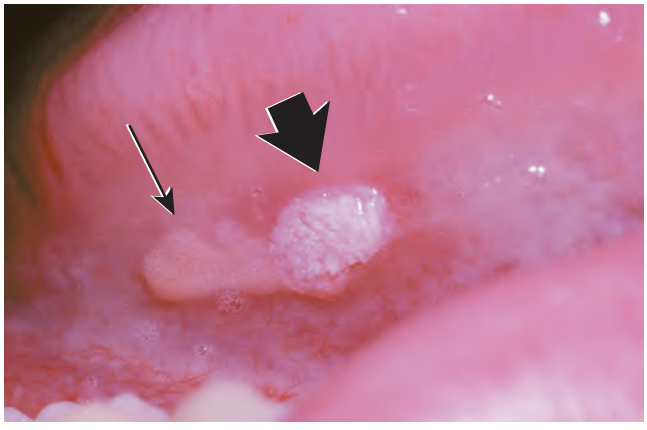
Clinical Features

Verruciform xanthoma typically is seen in whites, 40 to 70 years of age, with a slight male predilection. Approximately half of intraoral lesions occur on the gingiva and alveolar mucosa, but any oral site may be involved.

The lesion appears as a well-demarcated, soft, painless, sessile, slightly elevated mass with a white, yellow-white, or red color and a papillary or roughened (verruciform) surface (Figs. 10-22 and 10-23). Rarely, flat-topped nodules are seen without surface projections. Most lesions are smaller than 2 cm in greatest diameter; no oral lesion larger than 4 cm has been reported. Multiple lesions occasionally have been described. Clinically, verruciform xanthoma may be similar to squamous papilloma, condyloma acuminatum, or early carcinoma.



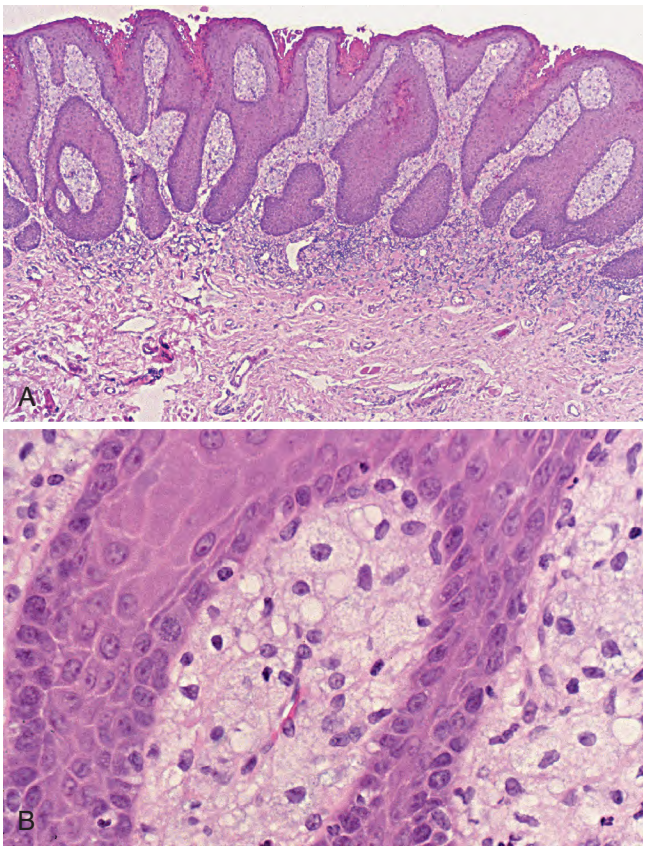
• **Fig. 10-22 Verruciform Xanthoma.** A well-demarcated, slightly elevated lesion of the hard palate that demonstrates a roughened or papillary surface.



• **Fig. 10-23 Verruciform Xanthoma.** A lesion of the ventral tongue exhibits a biphasic appearance. The anterior aspect demonstrates elongated white (well-keratinized) projections *(large arrow).* The posterior aspect demonstrates a surface of yellow, blunted projections *(small arrow).*

Histopathologic Features

Verruciform xanthoma demonstrates papillary, acanthotic surface epithelium covered by a thickened layer of parakeratin. On routine hematoxylin and eosin (H&E) staining, the keratin layer often exhibits a distinctive orange color (Fig. 10-24). Clefts or crypts between the epithelial projections are filled with parakeratin, and rete ridges are elongated to a uniform depth. The most important diagnostic feature is the accumulation of numerous large macrophages with foamy cytoplasm, which typically are confined to the connective tissue papillae. These foam cells, also known as **xanthoma cells,** contain lipid and periodic acid-Schiff (PAS)-positive, diastase-resistant granules. With immunohistochemical stains, the xanthoma cells are positive for markers consistent with monocyte-macrophage lineage, including CD68 (KP1) and cathepsin B.



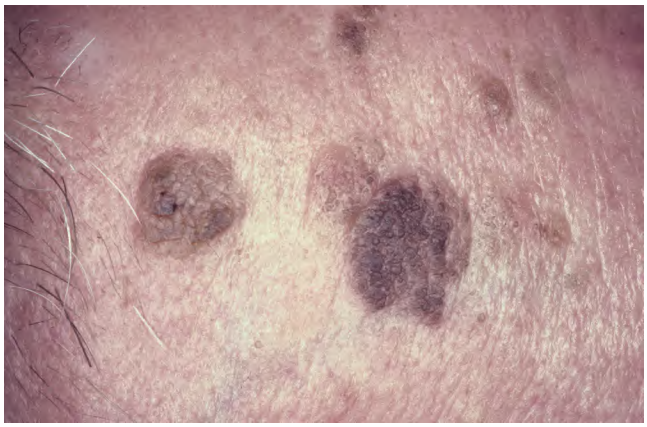
• **Fig. 10-24 Verruciform Xanthoma. A,** A slight papillary appearance is produced by hyperparakeratosis, and the rete ridges are elongated to a uniform depth. Note the parakeratin plugging between the papillary projections. **B,** The connective tissue papillae are composed almost exclusively of xanthoma cells—large macrophages with foamy cytoplasm.

Treatment and Prognosis

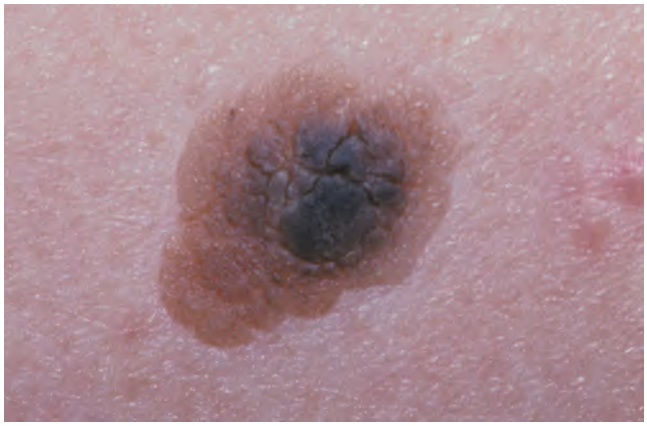
The verruciform xanthoma is treated with conservative surgical excision. Recurrence after removal is rare, and no malignant transformation has been reported. However, there are two reported cases of verruciform xanthoma arising in association with carcinoma *in situ* or squamous cell carcinoma. This observation does not necessarily imply that verruciform xanthoma is a potentially malignant lesion; however, it may indicate that hyperkeratotic or dysplastic oral lesions can undergo degenerative changes to form a verruciform xanthoma.

◆ SEBORRHEIC KERATOSIS

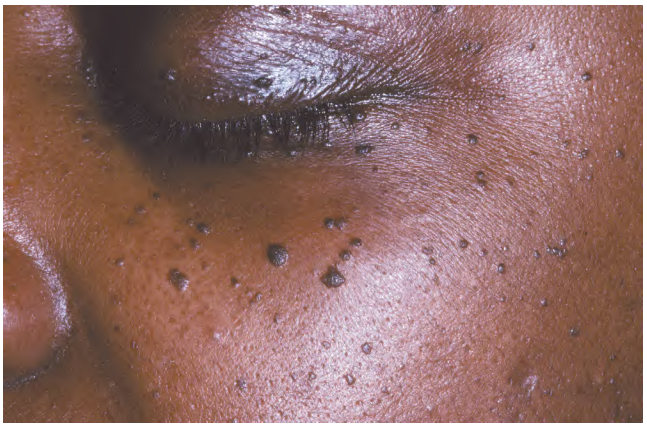
Seborrheic keratosis is an extremely common skin lesion of older people and represents an acquired, benign proliferation of epidermal basal cells. The cause is unknown, although there is a positive correlation with chronic sun exposure, sometimes with a hereditary (autosomal dominant) tendency. In addition, somatic mutations in the *fibroblast growth factor receptor 3 (FGFR3)* and *phosphatidylinositol 3-kinase, catalytic subunit alpha (PIK3CA)* genes may contribute to the pathogenesis of these lesions. In some cases,



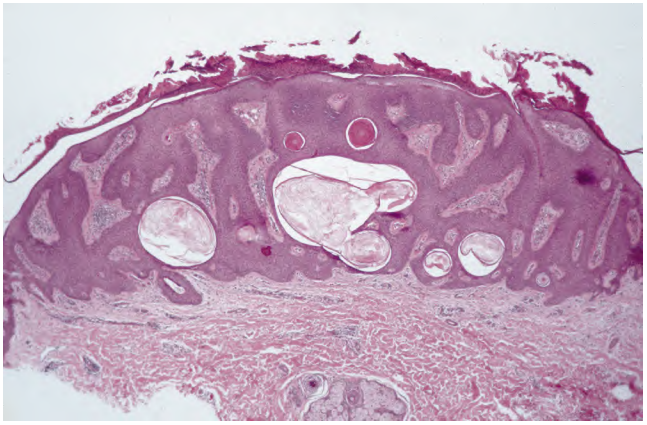
• **Fig. 10-25 Seborrheic Keratosis.** Multiple brown plaques on the face of an older man exhibit a fissured surface. They had been slowly enlarging for several years.



• **Fig. 10-26 Seborrheic Keratosis.** Crusted and pigmented epidermal plaque.



• **Fig. 10-27 Dermatosis Papulosa Nigra.** Multiple small pigmented papules of the malar area.



• **Fig. 10-28 Seborrheic Keratosis.** The acanthotic form demonstrates considerable acanthosis, surface hyperkeratosis, and numerous pseudocysts. The epidermal proliferation extends upward, above the normal epidermal surface.

HPV DNA has been detected, but this finding may be coincidental. Seborrheic keratosis does not occur in the mouth.

Clinical Features

Seborrheic keratoses begin to develop on the skin of the face, trunk, and extremities during the fourth decade of life, and they become more prevalent with each passing decade. Lesions are usually multiple, beginning as small, tan to brown macules that are clinically indistinguishable from **actinic lentigines** (see page 345). Subsequently, the lesions gradually enlarge and elevate to form sharply demarcated plaques, with finely fissured, pitted, verrucous, or smooth surfaces (Figs. 10-25 and 10-26). The plaques appear "stuck onto" the skin and are usually less than 2 cm in diameter.

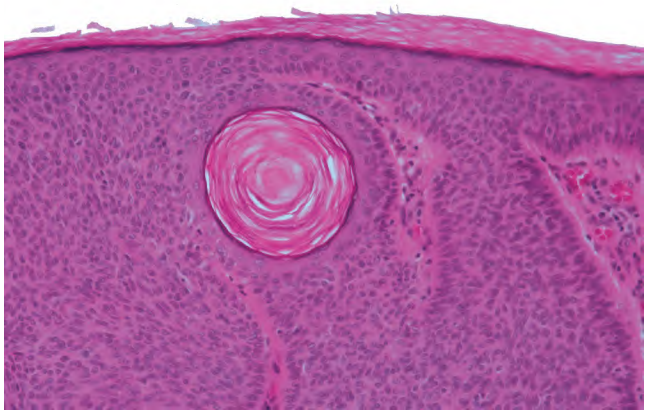
Dermatosis papulosa nigra is a form of seborrheic keratosis that occurs in approximately 30% to 77% of blacks and frequently has an autosomal dominant inheritance pattern. This condition typically appears as multiple small (1 to 4 mm), dark-brown to black papules scattered about the zygomatic and periorbital region (Fig. 10-27).

Moreover, the sudden appearance of numerous seborrheic keratoses with pruritus may be associated with internal malignancy. This rare phenomenon is called the **Leser-Trélat sign.**

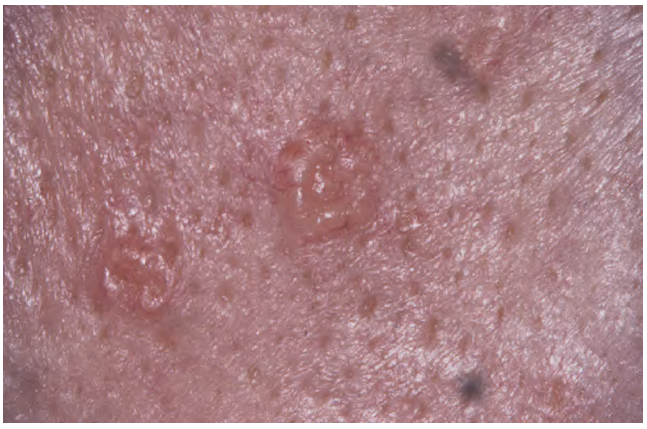
Histopathologic Features

Seborrheic keratosis consists of an exophytic proliferation of basilar epithelial cells that exhibit varying degrees of surface keratinization, acanthosis, and papillomatosis (Fig. 10-28). Characteristically, the epithelial hyperplasia extends upward, above the normal epidermal surface. The lesion usually exhibits deep, keratin-filled invaginations that appear cystic on cross-section; hence, they are called **horn cysts** or **pseudo-horn cysts** (Fig. 10-29). Melanin pigmentation often is seen within the basal layer.

Several histopathologic patterns may be seen in seborrheic keratoses. The most common is the **acanthotic** form, which exhibits little papillomatosis and marked acanthosis with minimal surface keratinization. The **hyperkeratotic** form is characterized by prominent papillomatosis and hyperkeratosis with minimal acanthosis. The **adenoid** form consists of anastomosing trabeculae of lesional cells with little hyperkeratosis or papillomatosis. The lesions of



• **Fig. 10-29 Seborrheic Keratosis.** Pseudocysts are actually keratin-filled invaginations, as seen toward the left in this high-power photomicrograph. The surrounding epithelial cells are basaloid in appearance.



• **Fig. 10-30 Sebaceous Hyperplasia.** Multiple soft papules of the midface are umbilicated and small. Sebum can often be expressed from the central depressed area.

dermatosis papulosa nigra are predominantly of the adenoid and acanthotic types.

Chronic trauma may alter these histopathologic features to produce an **irritated seborrheic keratosis** (or **inverted follicular keratosis of Helwig**). This lesion shows a mild degree of proliferation into the connective tissue and an associated chronic inflammatory cell infiltrate. Squamous metaplasia of the lesional cells results in whorled epithelial patterns called **squamous eddies.** Inflamed seborrheic keratosis may exhibit enough nuclear atypia and mitotic activity to cause confusion with squamous cell carcinoma, but enough of the basic attributes of seborrheic keratosis typically remain to allow a proper diagnosis.

Treatment and Prognosis

Except to address aesthetic concerns or secondary irritation, seborrheic keratoses seldom are removed. Cryotherapy, curettage, and shave excision are the most common methods for removal. The lesion exhibits no appreciable malignant potential. However, there are isolated reports of malignant skin lesions developing within or adjacent to seborrheic keratoses; it is unclear whether such cases are coincidental. Rarely, melanomas may resemble seborrheic keratoses clinically; thus it is important for a dermatologist or other qualified clinician to determine whether it is most appropriate to treat a lesion by cryotherapy or to excise and submit it for histopathologic confirmation.

◆ SEBACEOUS HYPERPLASIA

Sebaceous hyperplasia is a localized proliferation of sebaceous glands, with a predilection for the facial skin. The exact cause is unknown, although investigators hypothesize that hormonal and genetic factors may be important. In addition, some reported cases have developed in association with cyclosporine administration in transplant recipients or with combination antiretroviral therapy for HIV-infected patients. It is uncertain whether such cases result from immunosuppression or direct medication effects. Furthermore, sebaceous hyperplasia may arise in association with *Muir-Torre syndrome* (a rare autosomal dominant disorder characterized by visceral malignancies, sebaceous adenomas and carcinomas, and keratoacanthomas). The major significance of sebaceous hyperplasia is its clinical similarity to more serious facial tumors, such as basal cell carcinoma.

Clinical Features

Cutaneous sebaceous hyperplasia usually affects adults older than 40 years. It occurs most commonly on the skin of the face, especially the nose, cheeks, and forehead. Less commonly, lesions may involve the genital area, chest, and areola. The condition is characterized by one or more soft, nontender papules with white, yellow, or normal color (Fig. 10-30). Most lesions grow slowly and are smaller than 5 mm in greatest diameter. The lesions usually exhibit central umbilication, representing the area where the ducts of the involved sebaceous lobules terminate. The ability to express sebum (the thick, yellow-white product of the sebaceous gland) from this small, central depression aids in clinical distinction of sebaceous hyperplasia from basal cell carcinoma.

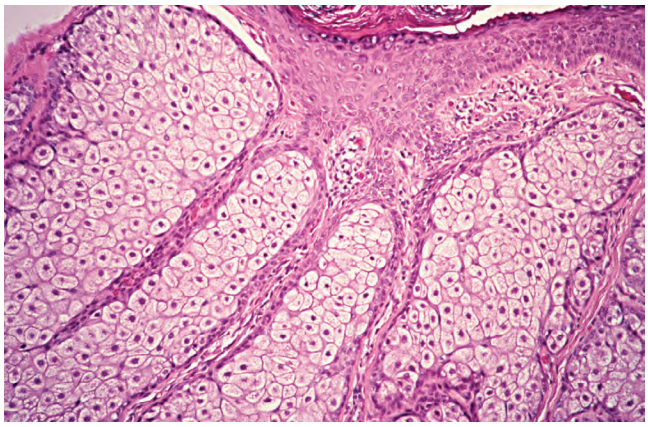
An oral counterpart, which probably has no relation to the skin lesion, appears as a white to yellow papule or nodular mass with a "cauliflower" appearance, usually involving the buccal mucosa or retromolar pad.

Histopathologic Features

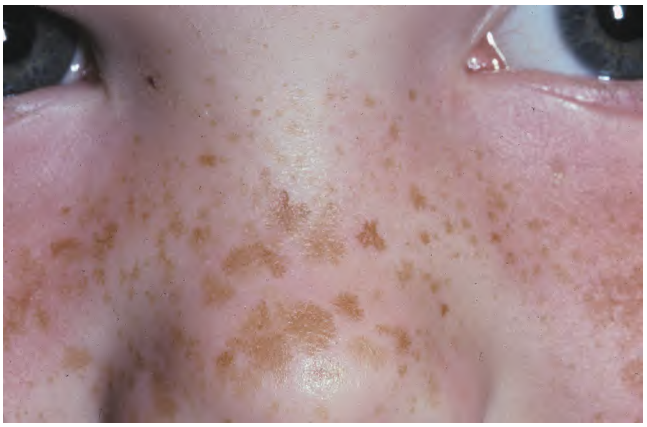
Histopathologically, sebaceous hyperplasia is characterized by a collection of enlarged but otherwise normal sebaceous gland lobules grouped around one or more centrally located sebaceous ducts (Fig. 10-31).

Treatment and Prognosis

No treatment is necessary for sebaceous hyperplasia except for cosmetic reasons or unless basal cell carcinoma cannot



• **Fig. 10-31 Sebaceous Hyperplasia.** Sebaceous glands are enlarged and more numerous than normal, but they demonstrate no other pathologic changes.



• **Fig. 10-32 Ephelides.** Multiple brown macules over the bridge of the nose.

be eliminated from the clinical differential diagnosis. Excisional biopsy is curative. Cryosurgery, electrodessication, laser therapy, photodynamic therapy, and isotretinoin are alternative treatment methods.

◆ EPHELIS (FRECKLE)

An **ephelis** is a common, small, hyperpigmented macule of the skin. The lesion results from increased melanin deposition in the epidermis, without an increase in the number of melanocytes. Ephelides may become more pronounced after sun exposure and are associated closely with a history of painful sunburns in childhood. There is a genetic predilection (autosomal dominant), and studies have demonstrated a strong relationship with certain variants of the *melanocortin 1 receptor (MC1R)* gene.

Clinical Features

Ephelides arise most often on the face, arms, and back of fair-skinned, blue-eyed, red- or blond-haired individuals. There is no gender predilection. The macules usually develop during the first decade of life, seldom arise after the teenage years, and become less prominent in adulthood.

Each lesion appears as a sharply demarcated, uniformly light brown, round or oval macule, measuring less than 3 mm in diameter (Fig. 10-32). There is great variability in the number of lesions present. Many individuals have less than 10, whereas some have hundreds. The brown color is not as dark as the lentigo simplex (see page 346), and there is never elevation above the surface of the skin, as may occur in a melanocytic nevus (see page 350).

Histopathologic Features

The ephelis exhibits abundant melanin deposition in the basal cell layer of the epidermis. Despite increased melanin, the number of melanocytes is normal or slightly reduced. In contrast to lentigo simplex, there is no elongation of rete ridges.

Treatment and Prognosis

No treatment is necessary for ephelides. Cosmetically unpleasing lesions may be treated by cryotherapy, hydroquinone, chemical peels, or laser therapy. Sunscreens can prevent the appearance of new freckles and help prevent the darkening of existing lesions.

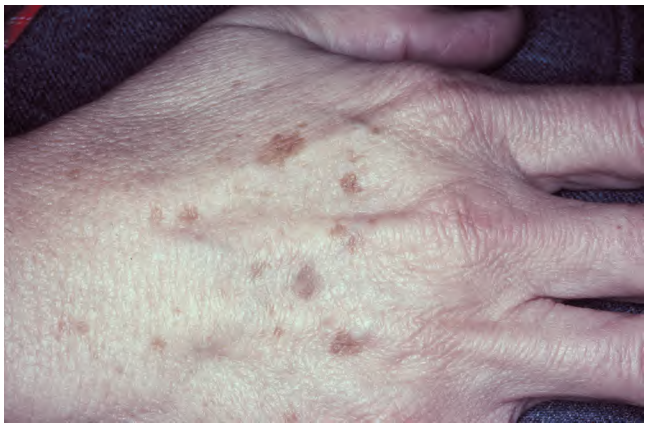
◆ ACTINIC LENTIGO (LENTIGO SOLARIS; SOLAR LENTIGO; AGE SPOT; LIVER SPOT; SENILE LENTIGO)

Actinic lentigo is a benign, brown macule that is considered a hallmark of photodamaged skin. The lesion is associated with both chronic and intermittent ultraviolet (UV) light exposure. It frequently arises on the facial skin but does not occur in the mouth. Actinic lentigo affects more than 90% of whites older than 70 years. The lesion rarely develops before age 40, although young adults with a history of severe sunburns may develop multiple large actinic lentigines on the upper back. Persons who have facial ephelides (freckles) in childhood are prone to developing actinic lentigines later in life.

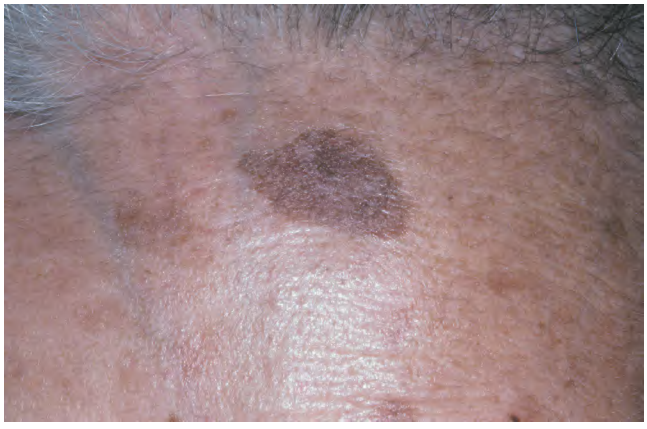
Some authorities have proposed that actinic lentigo represents a precursor to adenoid seborrheic keratosis (see page 342). Interestingly, investigators have noted that at least some cases of both actinic lentigo and seborrheic keratosis exhibit mutations in the *fibroblast growth factor receptor 3* (*FGFR3*) and *phosphatidylinositol 3-kinase catalytic subunit alpha* (*PIK3CA*) genes.

Clinical Features

Multiple lesions typically develop in older whites on sun-exposed skin, especially on the face, dorsa of the hands, forearms, shoulders, and upper back (Figs. 10-33 and



• **Fig. 10-33 Actinic Lentigines.** Multiple lesions on the sun-exposed skin of the hand of an older adult. Lesions are brown macules with irregular borders.



• **Fig. 10-34 Actinic Lentigo.** Large, flat, evenly pigmented lesion on the forehead of an older adult man.

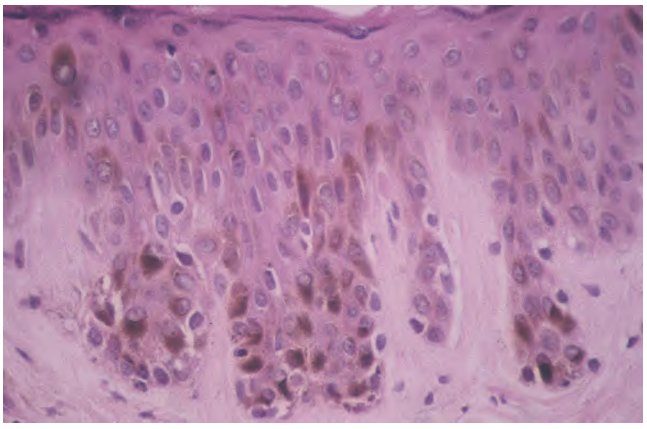
10-34). The lesions may appear more prominent and at a somewhat younger age among Asians compared to whites. The individual lesions appear as uniformly pigmented, brown to tan macules with well-demarcated but irregular borders. Most examples are smaller than 5 mm in diameter, although some lesions may measure more than 1 cm. Adjacent lesions may coalesce, and new ones continuously arise with age. Unlike ephelides, no change in color intensity is seen after UV light exposure.

Histopathologic Features

The rete ridges are elongated and club-shaped, with thinning of the epithelium above the connective tissue papillae (Fig. 10-35). The ridges sometimes coalesce with one another. Within each rete ridge, melanin-laden basilar cells are intermingled with excessive numbers of heavily pigmented melanocytes. Prominent solar elastosis typically is seen within the dermis.

Treatment and Prognosis

No treatment is required for actinic lentigo, except for aesthetic reasons. Ablative treatment methods include cryotherapy, laser therapy, intense pulsed light, and chemical peels. In addition, there is a wide range of topical therapies available, including hydroquinone, tretinoin, tazarotene, adapalene, and combined mequinol and tretinoin. Recent small studies also have shown promising results with topical undecylenoyl phenylalanine or combined L-ascorbic acid and phytic acid. Generally, sunscreens are recommended as preventive treatment and for maintenance of treatment success. Lesions rarely recur after removal, although new lesions may arise. Actinic lentigo does not undergo malignant transformation; however, the lesion represents a clinical marker of photodamage and may indicate an increased risk for developing skin cancer.



• **Fig. 10-35 Actinic Lentigo.** Rete ridges are elongated and occasionally intertwining. Pigmented melanocytes (with clear cytoplasm) are excessive and commingled with melanin-laden basilar cells.

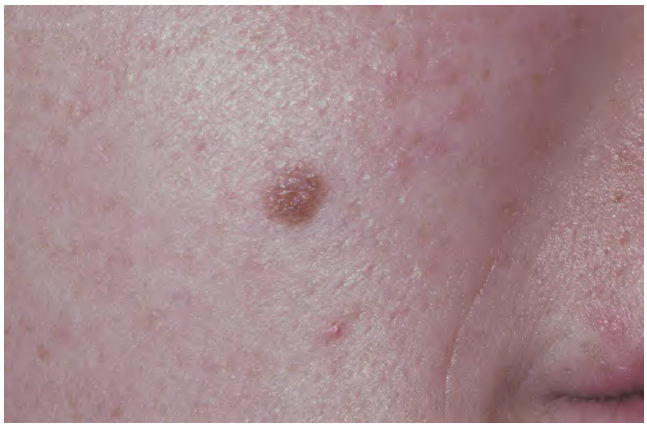
◆ LENTIGO SIMPLEX

Lentigo simplex is one of several forms of benign cutaneous melanocytic hyperplasia of unknown cause. In contrast to the ephelis (see page 345), lentigo simplex typically is found on skin that is not exposed to sunlight, appears somewhat darker in color, does not darken with sun exposure, and represents an increase in both local melanin production and the number of melanocytes. Oral lesions have been reported, but they are rare and may be examples of the oral melanotic macule (see page 348).

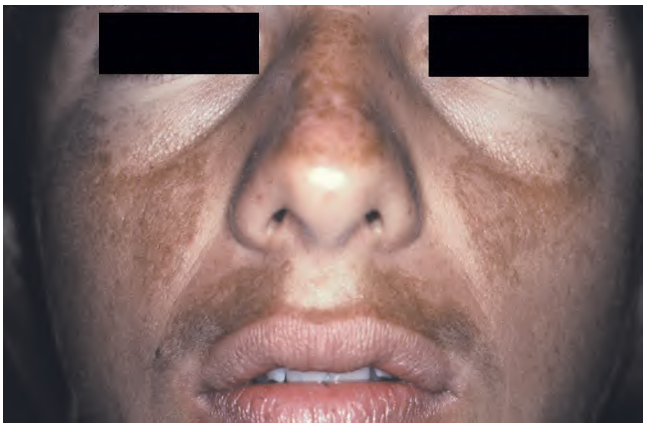
Some investigators believe that lentigo simplex represents the earliest stage of another common skin lesion, the melanocytic nevus (see page 350). However, according to one recent study, lentigo simplex lacks *BRAF* gene mutations that are commonly found in melanocytic nevi.

Clinical Features

Lentigo simplex usually is seen in children, although it may occur at any age. The typical lesion is a sharply demarcated, uniformly tan to dark-brown macule smaller than 5 mm in diameter (Fig. 10-36). It is usually solitary, although some patients may have several lesions scattered on the skin of the trunk and extremities. Lentigo simplex reaches its



• **Fig. 10-36 Lentigo Simplex.** A sharply demarcated lesion of uniform brown coloration is seen on the midface.



• **Fig. 10-37 Melasma.** Diffuse hyperpigmentation of the facial skin in a pregnant woman.

maximum size in a matter of months and may remain unchanged indefinitely thereafter.

Clinically, individual lesions of lentigo simplex are indistinguishable from the non-elevated melanocytic nevus. With multiple lesions, conditions such as lentiginosis profusa, Peutz-Jeghers syndrome (see page 701), and LEOPARD* syndrome must be considered as diagnostic possibilities.

Histopathologic Features

Lentigo simplex shows an increased number of benign melanocytes within the basal layer of the epidermis. These melanocytes often are clustered at the tips of slightly to moderately elongated rete ridges. Abundant melanin is distributed among the melanocytes and basal keratinocytes, as well as within the papillary dermis in association with melanophages **(melanin incontinence).**

Treatment and Prognosis

Lentigo simplex may fade spontaneously after many years, but most lesions remain constant over time. Treatment is not required, except for cosmetic reasons. Treatment methods include conservative surgical excision, cryotherapy, and laser therapy. No malignant transformation potential has been documented.

◆ MELASMA (MASK OF PREGNANCY; CHLOASMA)

Melasma is an acquired, symmetrical hyperpigmentation of the sun-exposed skin of the face and neck. The exact cause is unknown, but UV light exposure and hormonal influences appear to be important etiologic factors. Studies suggest that UV light stimulates production of dermal stem cell factor and alpha-melanocyte stimulating hormone, resulting in proliferation of melanocytes and increased melanin production. Melasma classically is associated with pregnancy. In addition, an association with oral contraceptives, hormone replacement therapy, thyroid disorders, phototoxic medications, antiepileptic agents, and cosmetics has been described. Several studies suggest a genetic predisposition. The condition most commonly affects medium- to dark-complexioned persons—particularly Asian and Hispanic women. In the United States, melasma affects more than 5 million individuals.

Clinical Features

Melasma typically appears in adult women as bilateral brown or grayish cutaneous macules that range from a few millimeters to more than 2 cm in diameter (Fig. 10-37). Lesions develop slowly with sun exposure and primarily involve the skin of the midface, forehead, upper lip, chin, mandibular ramus region, and (rarely) the arms. The pigmentation may remain faint or darken over time. Melasma only rarely affects men.

Histopathologic Features

Melasma is characterized by increased melanin deposition and, possibly, an increased number of melanocytes in the epidermis. The melanocytes typically are plump, full of pigment, and highly dendritic. In addition, numerous melanophages (melanin-laden macrophages) may be seen in the dermis. Some authors have noted more severe solar damage in lesional skin compared to adjacent normal-appearing skin.

Treatment and Prognosis

Melasma is difficult to treat. First-line therapy typically consists of topical triple-combination cream (Tri-Luma) containing 4% hydroquinone, 0.05% tretinoin, and 0.01%

*__L__entigines (multiple), __e__lectrocardiographic abnormalities, __o__cular hypertelorism, __p__ulmonary stenosis, __a__bnormalities of genitalia, __r__etardation of growth, and __d__eafness (sensorineural)

fluocinolone acetonide. Dual-ingredient topical agents (e.g., hydroquinone combined with glycolic acid or kojic acid) or single topical agents (e.g., hydroquinone, retinoids, and azelaic acid) are alternatives for patients who are sensitive to triple-combination therapy. Variable results have been reported with laser therapy, light therapy, or microdermabrasion. Because sun exposure is an important etiologic factor, sun avoidance, protective clothing, and the use of sunscreens containing zinc oxide or titanium dioxide are crucial for effective management. The lesions may resolve after parturition or after discontinuing oral contraceptives. There is no potential for malignant transformation.

◆ ORAL MELANOTIC MACULE (FOCAL MELANOSIS)

The **oral melanotic macule** is a flat, brown, mucosal discoloration produced by a focal increase in melanin deposition and, possibly, a concomitant increase in the number of melanocytes. The cause remains unclear. Unlike the cutaneous ephelis (freckle), the melanotic macule is not dependent on sun exposure. Some authorities have questioned the purported lack of an association with actinic irradiation for the melanotic macule located on the vermilion border and prefer to consider it a distinct entity **(labial melanotic macule).** In one study of more than 773 solitary oral melanocytic lesions submitted to an oral pathology laboratory for histopathologic examination, oral and labial melanotic macules were the most common and comprised 86% of cases; oral and labial melanotic macules were encountered much more frequently than oral melanocytic nevi, melanoacanthomas, and melanomas.

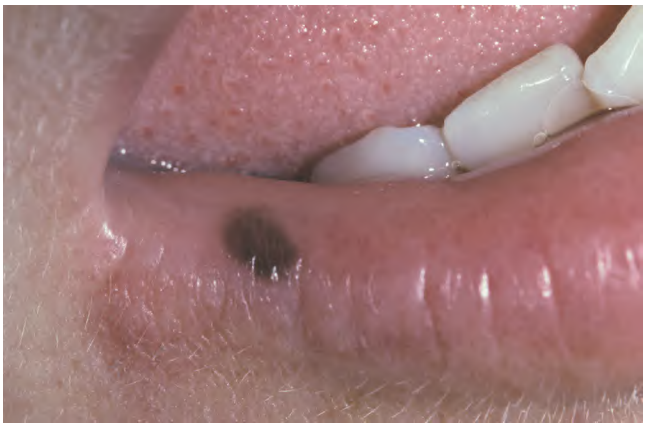
Clinical Features

The oral melanotic macule occurs over a broad age range, with an average age at diagnosis of 43 years and a 2:1 female-to-male ratio. The lower lip vermilion is the most commonly involved site (33% of cases), followed by the buccal mucosa, gingiva, and palate. Rare examples have been reported on the tongue in newborns.

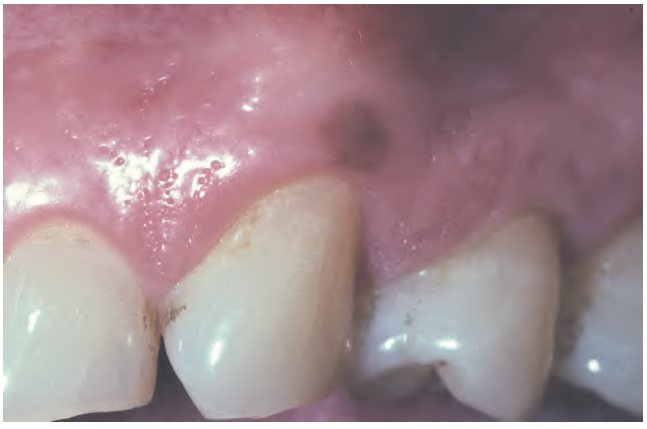
The typical lesion appears as a solitary (17% are multiple), well-demarcated, uniformly tan to dark-brown, asymptomatic, round or oval macule with a diameter of 7 mm or less (Figs. 10-38 and 10-39). Occasional lesions may be blue or black. The maximum dimension is achieved rather rapidly and remains constant thereafter.

Histopathologic Features

The oral melanotic macule is characterized by an increase in melanin (and perhaps melanocytes) in the basal and parabasal layers of an otherwise normal stratified squamous epithelium (Fig. 10-40). Melanin also may be seen free **(melanin incontinence)** or within melanophages in the subepithelial connective tissue**.** Unlike actinic lentigo (see page 345), the melanotic macule typically does not show elongated rete ridges.



• **Fig. 10-38 Oral Melanotic Macule.** A single small, uniformly pigmented brown macule on the lower lip vermilion.

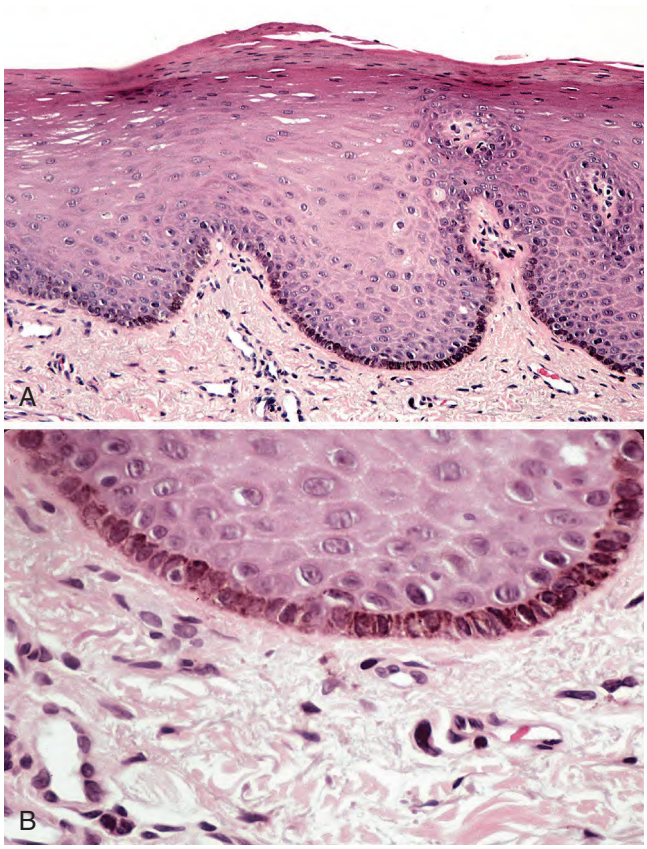


• **Fig. 10-39 Oral Melanotic Macule.** A well-demarcated brown macule of the gingival mucosa.

Treatment and Prognosis

The oral melanotic macule generally is considered a benign lesion with no malignant potential. However, a single case of apparent malignant transformation of an oral melanotic macule has been reported, and early melanoma can have a similar clinical appearance. Therefore, all oral pigmented macules of recent onset, large size, irregular pigmentation, unknown duration, or recent enlargement should be submitted for microscopic examination. In addition, because oral melanoma exhibits a predilection for the palatal and maxillary alveolar mucosa, it is advisable to submit pigmented macules in these locations for histopathologic examination. Furthermore, removal may be desirable for melanotic macules involving aesthetic areas. Excisional biopsy is the preferred treatment method. Electrocautery, laser ablation, or cryosurgery is effective, but no tissue remains for histopathologic examination after these procedures.

On occasion, flat pigmented lesions that are clinically and microscopically similar to the melanotic macule may occur in association with a systemic disease, a genetic



• **Fig. 10-40 Oral Melanotic Macule. A,** Low-power view showing increased melanin pigmentation distributed along basal epithelial layer. **B,** High-power view showing granular brown melanin pigment in the basilar cells.

disorder, or certain medications. A list of these conditions is shown in Box 10-1.

• BOX 10-1 Associations with Melanin Pigmentation of Oral Mucosa

Physiologic or Syndromic Associations

- Racial or physiologic pigmentation
- Peutz-Jeghers syndrome
- McCune-Albright syndrome
- LEOPARD syndrome (lentiginosis profusa, no intraoral melanosis)
- Laugier-Hunziker syndrome
- Cronkhite-Canada syndrome
- Bloom syndrome
- Dunnigan syndrome
- Dyskeratosis congenita
- Endocrine candidiasis syndrome
- Incontinentia pigmenti
- Oculo-cerebro-cutaneous syndrome
- Rothmund-Thomson syndrome
- Trisomy 14 mosaicism
- Unusual facies, vitiligo, spastic paraplegia syndrome
- Xeroderma pigmentosum
- Addison disease
- Neurofibromatosis type I
- Carney complex

Chronic Trauma or Irritation or Environmental Pollutant

- Chronic mucosal trauma or irritation (chronic cheek bite)
- Chronic autoimmune disease (erosive lichen planus, pemphigoid)
- Smoker's melanosis
- Yusho (chronic exposure to high levels of polychlorinated biphenyls [PCBs])

Systemic Medications

- Chloroquine and other quinine derivatives
- Phenolphthalein
- Estrogen
- AIDS-related medications

◆ ORAL MELANOACANTHOMA (MELANOACANTHOSIS)

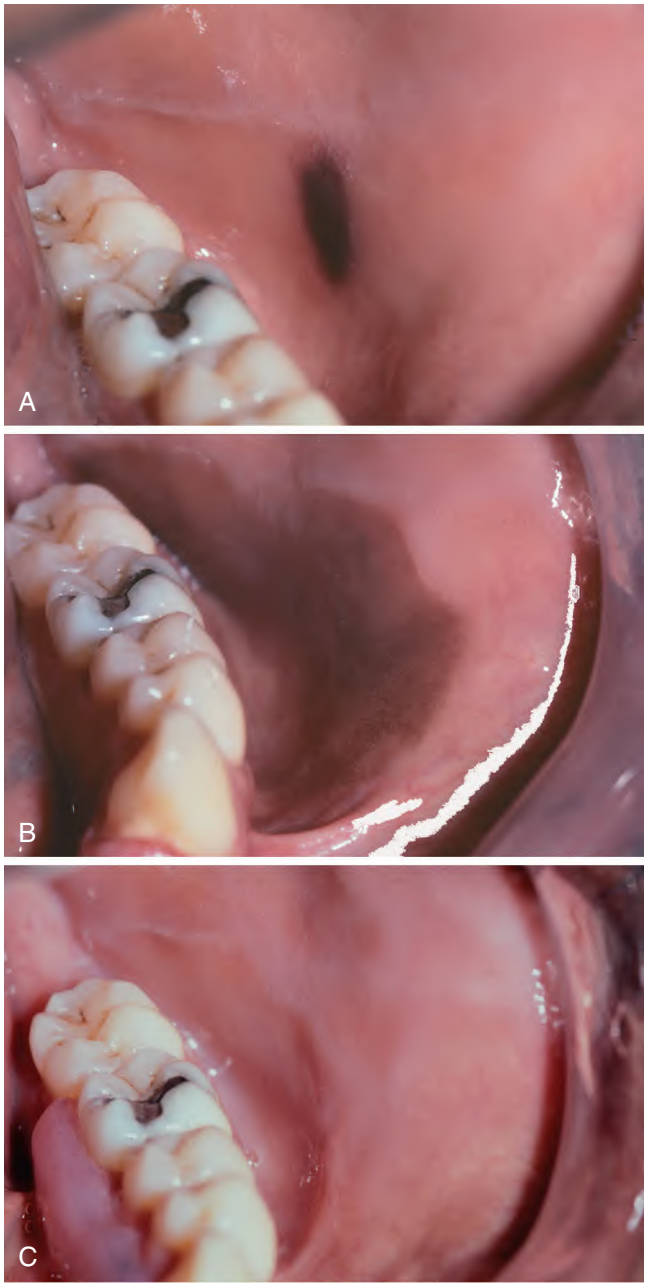
Oral melanoacanthoma is an uncommon, benign, acquired pigmentation of the oral mucosa characterized by dendritic melanocytes dispersed throughout the epithelium. The lesion appears to be a reactive process; in some cases an association with trauma has been reported. Oral melanoacanthoma appears to be unrelated to the melanoacanthoma of skin, which most authorities believe represents a variant of seborrheic keratosis.

Clinical Features

Oral melanoacanthoma is seen primarily in blacks, although some cases also have been reported in Caucasians, Hispanics, and Asians. The lesion exhibits a female predilection and most commonly arises during the third and fourth decades of life. The buccal mucosa is the most common site of occurrence. The lips, palate, gingiva, and alveolar mucosa also may be involved. Most patients exhibit solitary lesions, although bilateral or multifocal involvement is possible. Oral melanoacanthomas typically are asymptomatic; however, pain, burning, and pruritus have been reported in a few cases. The lesion appears smooth, flat or slightly raised, and dark-brown to black (Fig. 10-41). Lesions often rapidly increase in size, and they occasionally reach a diameter of several centimeters within a few weeks.

Histopathologic Features

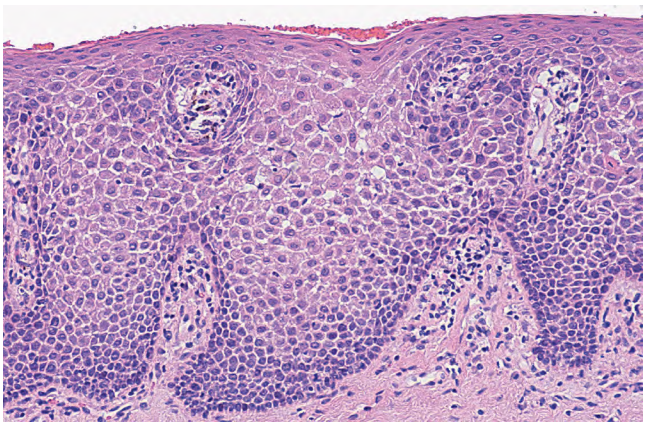
The oral melanoacanthoma is characterized by numerous benign dendritic melanocytes (cells that normally are confined to the basal layer) scattered throughout the lesional epithelium (Figs. 10-42 and 10-43). Basal layer melanocytes are also present in increased numbers. Spongiosis and mild acanthosis typically are evident. In addition, the underlying connective tissue often contains a mild to moderate chronic inflammatory cell infiltrate that may include eosinophils.



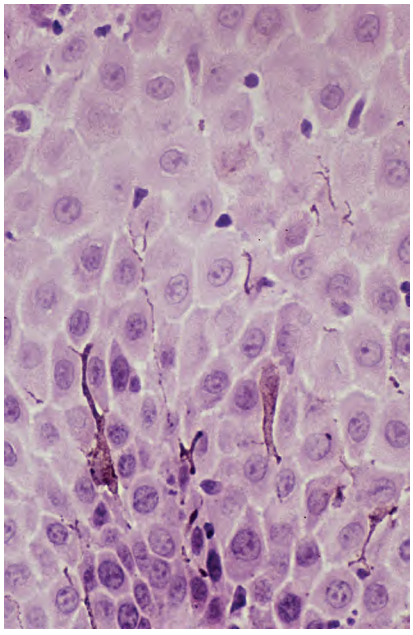
• **Fig. 10-41 Oral Melanoacanthoma. A,** Smooth, darkly pigmented macule of the buccal mucosa in a young adult. **B,** Appearance of the lesion 2 months later showing dramatic enlargement. **C,** Resolution of the lesion 3 months after incisional biopsy. (From Park SK, Neville BW: AAOMP case challenge: rapidly enlarging pigmented lesion of the buccal mucosa, *J Contemp Dent Pract* 3:69-73, 2002.)

Treatment and Prognosis

Because of the alarming growth rate of oral melanoacanthoma, incisional biopsy usually is indicated to rule out melanoma. Once the diagnosis has been established, no further treatment is necessary. In several instances, lesions have undergone spontaneous resolution after incisional biopsy. Recurrence or development of additional lesions has been reported only rarely. There is no potential for malignant transformation.



• **Fig. 10-42 Oral Melanoacanthoma.** Medium-power photomicrograph showing acanthosis of the epithelium. Spongiosis is demonstrated by intercellular spaces between the keratinocytes.



• **Fig. 10-43 Oral Melanoacanthoma.** High-power view showing numerous dendritic melanocytes extending between the spinous epithelial cells.

◆ ACQUIRED MELANOCYTIC NEVUS (NEVOCELLULAR NEVUS; MOLE)

The generic term *nevus* refers to congenital or developmental malformations of the skin (and mucosa). Nevi may arise from the surface epithelium or underlying connective tissue. The most commonly recognized nevus is the **acquired melanocytic nevus,** or common **mole**—so much so that the simple term *nevus* often is used synonymously for this pigmented lesion. However, many other developmental nevi also are recognized (Box 10-2).

The acquired melanocytic nevus represents a benign, localized proliferation of *nevus cells* derived from the neural crest. It is unclear whether these cells represent melanocytes or merely "first cousins" of melanocytes. These melanocytic

• BOX 10-2 Types of Developmental Nevi

- Epidermal nevus
- Nevus sebaceus
- Nevus flammeus (see page 508)
- Basal cell nevus (nevoid basal cell carcinoma) (see page 640)
- White sponge nevus (see page 691)

cells migrate to the epidermis during development, and lesions may appear shortly after birth.

The acquired melanocytic nevus is probably the most common of all human "tumors," with an average of 10 to 40 cutaneous nevi per white adult. Intraoral lesions are uncommon.

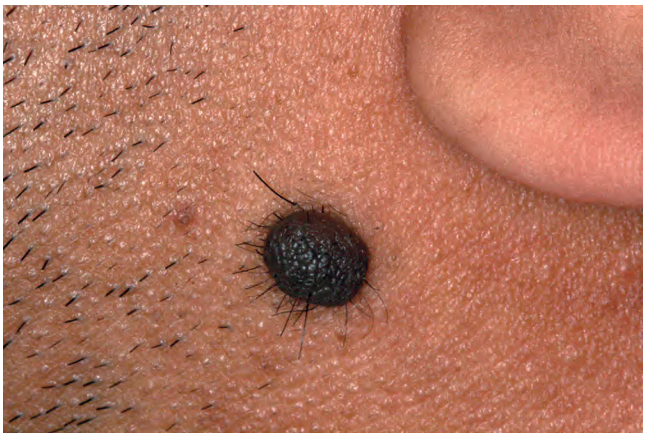
Investigators have identified *BRAF* mutations in approximately 80% of acquired melanocytic nevi; such mutations also are common in cutaneous melanomas. *BRAF* is a proto-oncogene that encodes a serine/threonine kinase involved in the mitogen-activated protein kinase (MAPK) signaling pathway, which mediates cell proliferation and differentiation. The life cycle of acquired melanocytic nevi includes four stages: initiation (development of mutations in a progenitor cell—possibly a melanocytic stem cell or differentiated melanocyte), promotion (activation and proliferation of the mutated progenitor cell), senescence (growth arrest), and involution.

Clinical Features

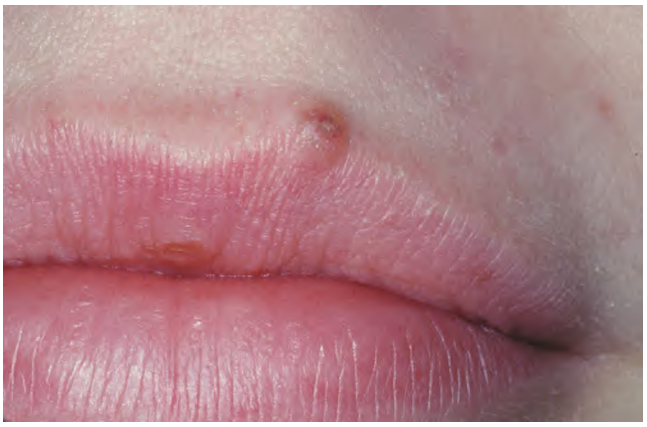
Acquired melanocytic nevi begin to develop on the skin during childhood, and most cutaneous lesions are present before 35 years of age. Women usually have a few more nevi than men, and whites tend to have more than Asians or blacks. Most lesions are distributed above the waist, and the head and neck region commonly is involved.

Acquired melanocytic nevi evolve through several developmental stages: junctional, compound, and intradermal. However, not all nevi pass through each stage. The **junctional nevus** clinically appears as a sharply demarcated, brown or black macule, typically less than 6 mm in diameter. Although this early presentation may persist into adulthood, more often the nevus cells proliferate over a period of years to produce a slightly elevated, soft papule with a relatively smooth surface **(compound nevus).** The degree of pigmentation becomes less; most lesions appear brown or tan. As time passes, the nevus gradually loses its pigmentation, the surface may become somewhat papillomatous, and hairs may be seen growing from the center **(intradermal nevus)** (Figs. 10-44 and 10-45). However, the nevus usually remains less than 6 mm in diameter. Ulceration is not a feature unless the lesion is traumatized. During the adult years, many acquired melanocytic nevi involute and disappear; therefore, fewer lesions are detected in older persons.

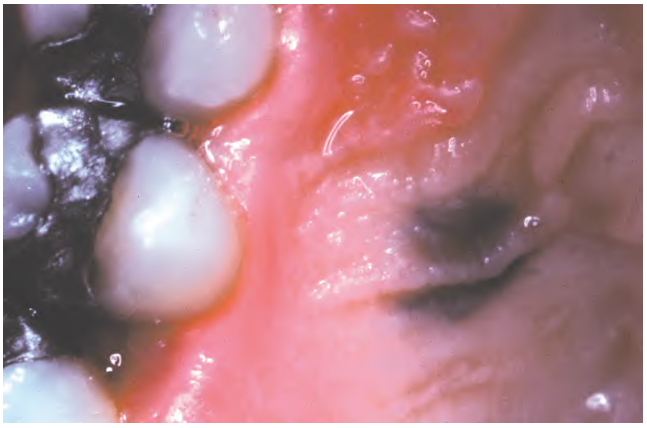
Intraoral melanocytic nevi are distinctly uncommon. Most arise on the palate, mucobuccal fold, or gingiva, although any oral mucosal site may be affected (Fig. 10-46).



• Fig. 10-44 Melanocytic (Intradermal) Nevus. A brown nodule on the facial skin with a papillomatous surface and protruding hairs.

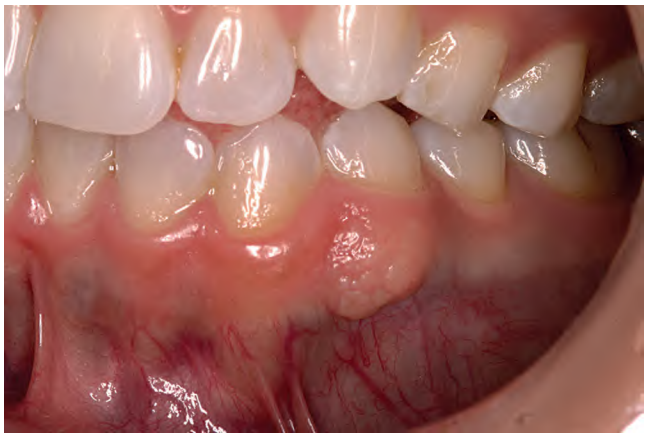


• Fig. 10-45 Melanocytic (Intradermal) Nevus. A well-demarcated, lightly pigmented, dome-shaped papule is seen at the edge of the vermilion border of the upper lip.

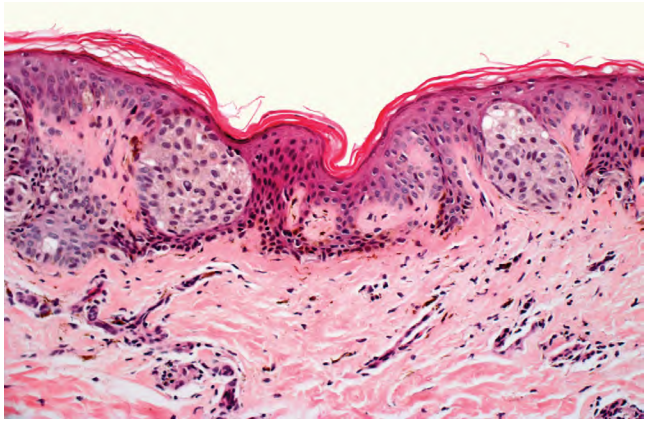


• Fig. 10-46 Intramucosal Melanocytic Nevus. Pigmented lesion of the anterior hard palate. (Courtesy of Dr. Lewis Claman.)

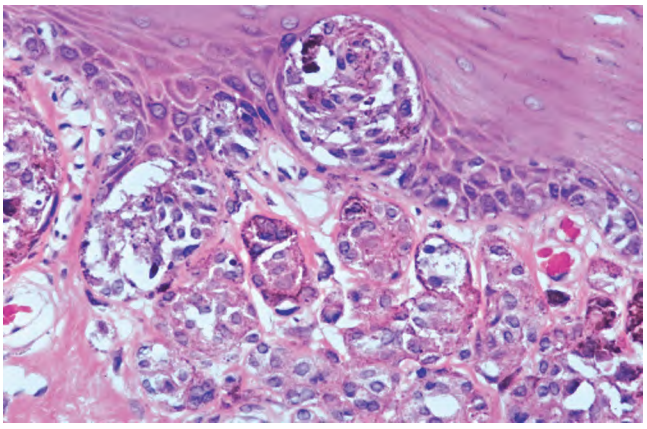
Intraoral melanocytic nevi have an evolution and appearance similar to skin nevi, although mature lesions often do not demonstrate a papillary surface. More than one in five intraoral nevi lack clinical pigmentation (Fig. 10-47). Approximately two-thirds of intraoral examples are found in females; the average age at diagnosis is 35 years.



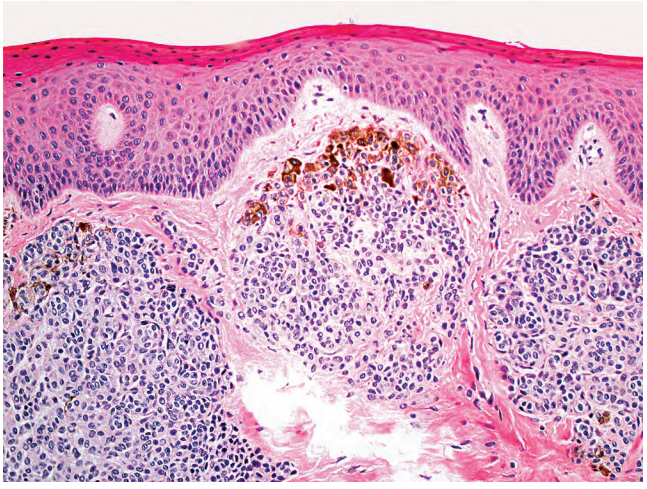
• **Fig. 10-47 Intramucosal Melanocytic Nevus.** This intramucosal nevus of the mandibular gingiva is nonpigmented. (Courtesy of Dr. James Jacobs.)



• **Fig. 10-48 Junctional Nevus.** Nests of melanocytic nevus cells along the basal layer of the epithelium.



• **Fig. 10-49 Compound Nevus.** High-power view showing nests of pigmented nevus cells within the epithelium and the superficial lamina propria.



• **Fig. 10-50 Intramucosal Nevus.** Collections of melanocytic nevus cells within the lamina propria.

Histopathologic Features

The acquired melanocytic nevus is characterized by a benign, unencapsulated proliferation of nevus cells. Zones of differentiation often are seen among the lesional cells. Superficial nevus cells tend to be organized into small, round aggregates *(thèques)* and usually appear ovoid or epithelioid, with abundant cytoplasm and frequent intracellular melanin. Deeper nevus cells may have less cytoplasm, are seldom pigmented, and appear much like lymphocytes. The deepest nevus cells appear elongated and spindle-shaped, much like Schwann cells or fibroblasts. Some authorities classify these nevus cell variations as *types A* (epithelioid), *B* (lymphocyte-like), and *C* (spindle-shaped). Nevus cells typically lack the dendritic processes that melanocytes possess.

Melanocytic nevi are classified histopathologically according to their stage of development. The **junctional nevus** represents an early stage, in which thèques of nevus cells are confined to the junction of the epithelium and connective tissue (Fig. 10-48), especially at the tips of the rete ridges. As the nevus cells proliferate, they begin to drop off into the underlying dermis or lamina propria. When nevus cells are present along the junctional area and within the connective tissue, the lesion is called a **compound nevus** (Fig. 10-49). In later stages, the nevus cells are found only within the connective tissue. In the skin, this stage is called an **intradermal nevus;** the intraoral counterpart is called an **intramucosal nevus** (Fig. 10-50). Most intraoral melanocytic nevi are classified microscopically as intramucosal nevi. However, this finding probably reflects the age (average, 35 years) at which most oral nevi undergo biopsy and diagnosis, because these lesions would have evolved earlier through junctional and compound stages.

Treatment and Prognosis

No treatment is indicated for a cutaneous melanocytic nevus unless it is cosmetically unacceptable, is chronically irritated by clothing, or changes in size or color. By midlife, cutaneous melanocytic nevi tend to regress; by age 90, very few remain. If removal is elected, then conservative surgical excision is the treatment of choice; recurrence is unlikely.

The risk of malignant transformation of an individual acquired melanocytic nevus into cutaneous melanoma is low (approximately one in 3,000 to 10,000). Nevertheless, patients with a large number (>100) of cutaneous nevi are at increased risk for developing melanoma and should be monitored closely.

Current evidence does not suggest that oral melanocytic nevi are a marker of increased risk for developing oral mucosal melanoma. However, early oral mucosal melanomas may appear clinically similar to oral melanocytic nevi or other benign pigmented lesions. Therefore, biopsy of all unexplained pigmented oral lesions generally is advised.

◆ MELANOCYTIC NEVUS VARIANTS

CONGENITAL MELANOCYTIC NEVUS

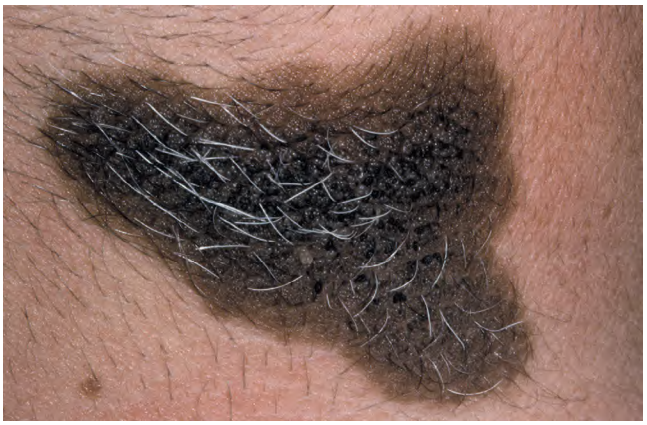
The **congenital melanocytic nevus** affects approximately 1% of newborns in the United States. The trunk and extremities are involved most commonly, although approximately 15% of lesions arise in the head and neck area. Intraoral involvement is rare. Congenital melanocytic nevi usually are classified according to projected adult size as follows: small (<1.5 cm in diameter), medium (1.5 cm to 20 cm in diameter), or large (≥20 cm in diameter). Especially large lesions may be termed "giant." Large congenital melanocytic nevi often harbor *NRAS* mutations.

Clinical Features

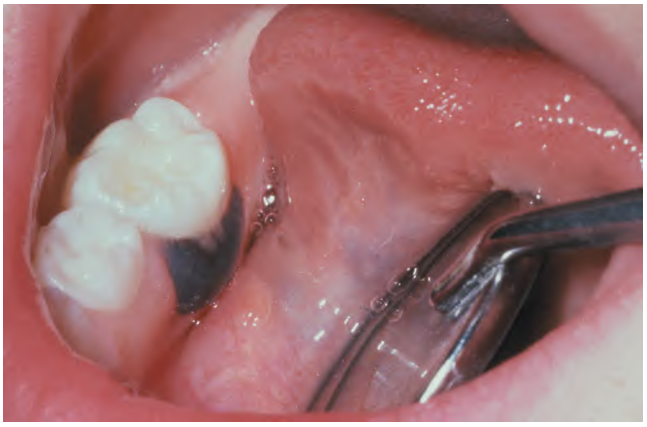
Small congenital melanocytic nevi may appear similar to acquired melanocytic nevi. However, most lesions are medium to large—appearing as light tan macules that over time develop into dark brown to black, rough-surfaced plaques or multinodular lesions (Figs. 10-51 and 10-52). A common feature is **hypertrichosis** (excess hair) within the lesion, which may become more prominent with age **(giant hairy nevus).** A very large congenital nevus sometimes may give the appearance that the patient is wearing an article of clothing and, thus, may be termed a **bathing trunk nevus** or **garment nevus**.

Histopathologic Features

The histopathologic appearance of the congenital melanocytic nevus is similar to that of the acquired melanocytic nevus, and some small congenital nevi cannot be distinguished microscopically from acquired nevi. Both congenital and acquired types are composed of nevus cells, which may have a junctional, compound, or intradermal pattern. The congenital nevus is usually of the compound or intradermal type. In contrast to the acquired melanocytic nevus, the congenital nevus often extends into deeper levels of the dermis, with "infiltration" of nevus cells between collagen bundles. In addition, congenital nevus cells often intermingle with neurovascular bundles in the reticular dermis and surround normal adnexal skin structures (e.g., hair follicles, sebaceous glands). Large congenital melanocytic nevi may extend into the subcutaneous fat.



• **Fig. 10-51 Congenital Melanocytic Nevus.** Pigmented lesion of the skin showing hypertrichosis.

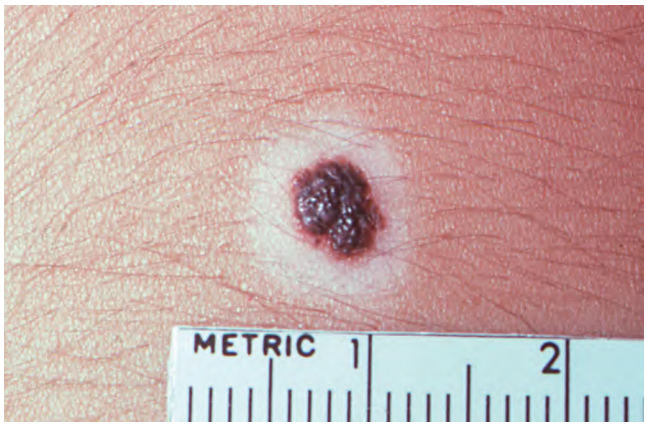


• **Fig. 10-52 Congenital Melanocytic Nevus.** Deeply pigmented lesion of the lingual mandibular gingiva in a 3-year-old child.

Treatment and Prognosis

Many congenital melanocytic nevi are excised for aesthetic purposes. Systematic reviews of the literature suggest that approximately 2% to 3% of large congenital nevi transform into malignant melanoma. However, the efficacy of excision in reducing this slightly elevated risk for melanoma is unknown and remains controversial. Also, complete excision may not be feasible for large lesions. Alternative treatment options include partial surgical removal, dermabrasion, laser therapy, cryotherapy, and chemical peels. Close clinical follow-up is recommended regardless of whether or not treatment has been rendered.

Patients with giant or multiple congenital nevi also are at risk for neurocutaneous melanosis. This rare and potentially fatal congenital syndrome is characterized by congenital nevi in conjunction with melanotic neoplasms of the central nervous system (CNS), including leptomeningeal melanosis and melanoma.



• **Fig. 10-53 Halo Nevus.** Elevated brown lesion of the skin showing surrounding depigmentation.

HALO NEVUS (SUTTON NEVUS; LEUKODERMA ACQUISITUM CENTRIFUGUM)

The **halo nevus** is a melanocytic nevus with a hypopigmented border, apparently resulting from nevus cell and melanocyte destruction by the immune system. The cause of the immune attack is unknown, but regression of the nevus usually results. Interestingly, multiple halo nevi may develop in patients who have had a recent excision of a melanoma. Infrequently, halo phenomena also may occur in association with melanomas and basal cell carcinomas.

Clinical Features

The halo nevus is typically an isolated finding that develops from a preexisting acquired melanocytic nevus. It is most common on the skin of the trunk during the second decade of life. The lesion typically appears as a pigmented papule or macule, surrounded by a hypopigmented zone measuring 2 to 3 mm or wider (Fig. 10-53).

Histopathologic Features

Histopathologically, the halo nevus differs from the routine acquired melanocytic nevus only in the presence of an intense chronic inflammatory cell infiltrate.

Treatment and Prognosis

Most halo nevi regress and do not require treatment. If treatment is elected, then conservative surgical removal is curative and recurrence is unlikely.

SPITZ NEVUS (BENIGN JUVENILE MELANOMA; SPINDLE AND EPITHELIOID CELL NEVUS)

The **Spitz nevus** is an uncommon melanocytic nevus variant that shares many histopathologic features with melanoma. It was, in fact, first described as a *juvenile melanoma.* However, this lesion's distinctly benign biologic behavior was emphasized by Spitz in 1948. Studies suggest that Spitz nevi commonly harbor *HRAS* mutations, whereas conventional melanocytic nevi and melanomas tend to exhibit *BRAF* mutations. The first oral Spitz nevus was not reported until 1990.

Clinical Features

The Spitz nevus typically develops on the skin of the extremities or the face during childhood. It usually appears as a solitary, dome-shaped, pink to reddish-brown papule smaller than 6 mm in greatest diameter. The young age at presentation and relatively small size help distinguish the Spitz nevus from melanoma.

Histopathologic Features

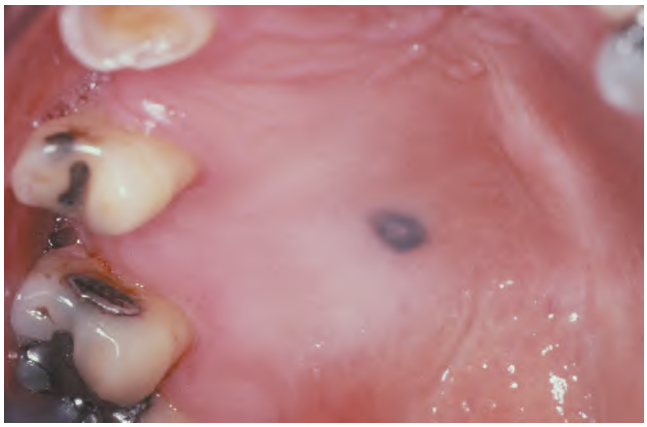
Most Spitz nevi are compound in architecture, with zonal differentiation from the superficial to deep aspects and good symmetry. Lesional cells are either spindle-shaped or plump (epithelioid), and the two types often are intermixed. The epithelioid cells may be multinucleated and appear somewhat bizarre, often lacking cohesiveness. Solitary or coalescent eosinophilic globules (Kamino bodies) may be seen within the epidermis or at the junction of the epidermis and dermis. Ectatic blood vessels (imparting the reddish color of some lesions) and normal mitotic figures may be present in the superficial aspects of the lesion. Immunohistochemistry may show the lesional cells to be positive for various melanocytic antigens, such as S-100, HMB-45, and melan-A (MART-1).

Treatment and Prognosis

Conservative surgical excision is the treatment of choice. There is little chance of recurrence after removal.

BLUE NEVUS (DERMAL MELANOCYTOMA; JADASSOHN-TIÈCHE NEVUS)

The **blue nevus** is an uncommon, benign proliferation of dermal melanocytes, usually deep within the connective tissue. Two major types are recognized: 1) the **common** blue nevus and 2) the **cellular** blue nevus. The common blue nevus is the second most frequent melanocytic nevus encountered in the mouth. The blue color of this melanin-producing lesion can be explained by the **Tyndall effect,** which relates to the interaction of light with particles in a colloidal suspension. In the case of a blue nevus, the melanin particles are deep to the surface, so that light reflected back has to pass through the overlying tissue. Colors with long wavelengths (reds and yellows) tend to be absorbed more readily by the tissue; the shorter-wavelength blue light is more likely to be reflected back to the observer's eyes. Unlike conventional acquired melanocytic nevi, blue nevi typically



• **Fig. 10-54 Blue Nevus.** A well-circumscribed, deep-blue macular lesion is seen on palatal mucosa.

exhibit mutations in the *GNAQ* gene (which encodes a G-protein alpha subunit important for signal transduction from cell-surface receptors) and only rarely harbor *BRAF* mutations.

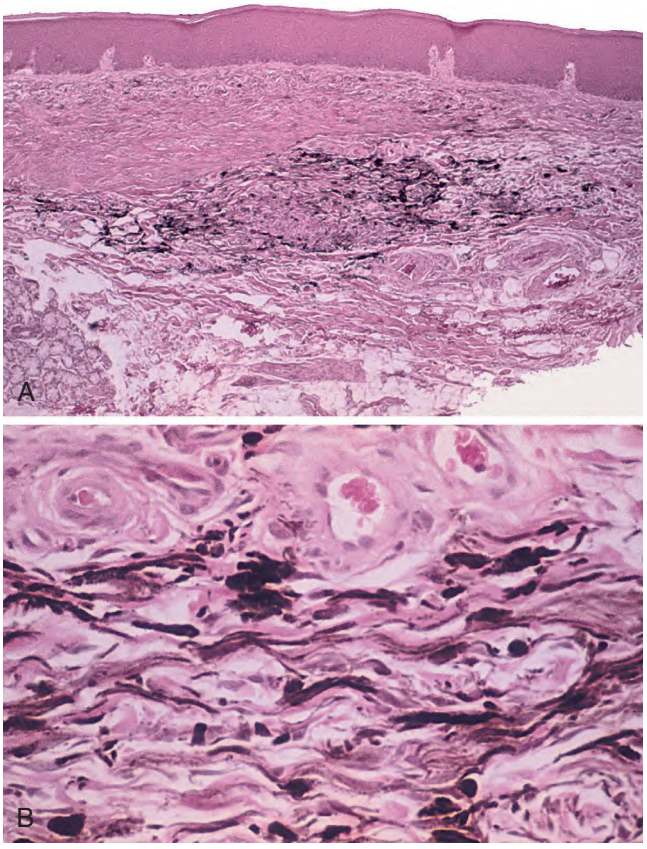
Clinical Features

The common blue nevus may affect any cutaneous or mucosal site, but it has a predilection for the dorsa of the hands and feet, the scalp, and the face. Mucosal lesions may involve the oral mucosa, conjunctiva, and, rarely, sinonasal mucosa. Oral lesions almost always are found on the palate. The lesion usually occurs in children and young adults and exhibits a female predilection. It appears as a macular or dome-shaped, blue or blue-black lesion smaller than 1 cm in diameter (Fig. 10-54).

The cellular blue nevus is much less common and usually develops during the second to fourth decades of life, but it may be congenital. More than 50% of cellular blue nevi arise in the sacrococcygeal or buttock region, although they may be seen on other cutaneous or mucosal surfaces. Clinically, this nevus appears as a slow-growing, blue-black papule or nodule that sometimes attains a size of 2 cm or more. Occasional lesions remain macular.

Histopathologic Features

Histopathologically, the common blue nevus consists of a collection of elongated, slender melanocytes with dendritic extensions and numerous melanin granules. These cells are located deep within the dermis or lamina propria (Fig. 10-55) and usually align themselves parallel to the surface epithelium. The cellular blue nevus appears as a well-circumscribed, highly cellular aggregate of plump, melanin-producing spindle cells within the dermis or submucosa. More typical pigmented dendritic spindle cells are seen at the periphery of the lesion. Occasionally, a blue nevus is found in conjunction with an overlying melanocytic nevus, in which case the term **combined nevus** is used.



• **Fig. 10-55 Blue Nevus. A,** Abundant melanin is seen within spindle-shaped melanocytes located relatively deep within the lamina propria and parallel to the surface epithelium. **B,** High-power view showing heavily pigmented spindle-shaped cells.

Treatment and Prognosis

If clinically indicated, conservative surgical excision is the treatment of choice for cutaneous blue nevi. Recurrence is minimal with this treatment. Malignant transformation to melanoma is rare but has been reported.

Because an oral blue nevus clinically can mimic an early melanoma, biopsy of intraoral pigmented lesions is usually advisable.

◆ LEUKOPLAKIA (LEUKOKERATOSIS; ERYTHROLEUKOPLAKIA)

As originally defined by the World Health Organization (WHO), oral **leukoplakia** (*leuko* = white; *plakia* = patch) represents "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease." The term is strictly a clinical one and does not imply a specific histopathologic tissue alteration.

The definition of leukoplakia is unusual in that it makes the diagnosis dependent not so much on definable appearances as on the *exclusion* of other entities that appear as oral white plaques. Such lesions as lichen planus, morsicatio buccarum (chronic cheek nibbling), frictional keratosis,

• BOX 10-3 Precancer Terminology Used in This Text

- **Precancerous lesion (precancer, premalignancy).** A benign, morphologically altered tissue that has a greater than normal risk of malignant transformation.
- **Precancerous condition.** A disease or patient habit that does not necessarily alter the clinical appearance of local tissue but is associated with a greater than normal risk of precancerous lesion or cancer development in that tissue.
- **Potentially malignant disorder.** A lesion, disease, or condition associated with a greater than normal risk of developing malignancy.
- **Malignant transformation potential.** The risk of cancer being present in a precancerous lesion or condition, either at initial diagnosis or in the future (usually expressed in percentages). The potential for mucosa without precancerous lesions or conditions is called *normal.*
- **Relative risk.** A specific epidemiologic measure of the association between exposure to a particular factor and the risk of acquiring a disease, expressed as a ratio of the incidence or prevalence of a disease among those exposed and those not exposed to the factor.

tobacco pouch keratosis, nicotine stomatitis, leukoedema, and white sponge nevus must be ruled out before a clinical diagnosis of leukoplakia can be made. As with most oral white lesions, the clinical color results from a thickened surface *keratin* layer, which appears white when wet, or a thickened *spinous* layer, which masks the normal vascularity (redness) of the underlying connective tissue.

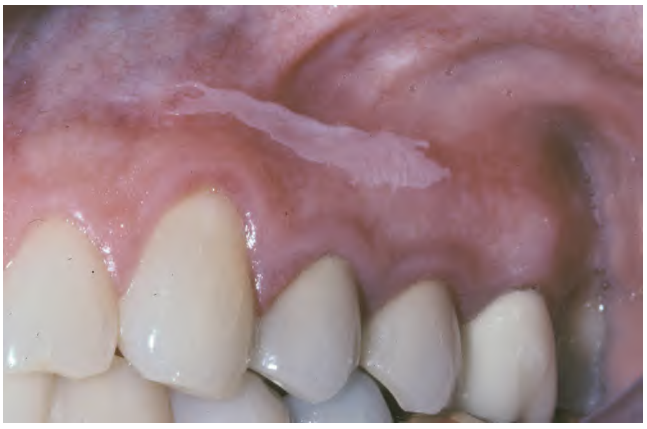
Although leukoplakia does not constitute a specific histopathologic diagnosis, it is considered a *precancerous* or *premalignant lesion* (see Box 10-3 for definitions of these and other related terms). That is, the frequency of transformation into malignancy is greater than that for normal or unaltered mucosa.

Incidence and Prevalence

Leukoplakia is by far the most common oral precancer, representing 85% of such lesions. In addition, more than one-third of oral carcinomas exhibit leukoplakia in close proximity. Based on pooled, weighted data from previously reported studies, the worldwide prevalence of leukoplakia has been estimated to fall within a range of 1.5% to 4.3%. There is a strong male predilection (70%), except in regional populations in which women use tobacco products more than men. A slight decrease in the proportion of affected males, however, has been noted over the past half century. The disease is diagnosed more frequently now than in the past, probably because of an enhanced awareness among health professionals (rather than because of a real increase in frequency).

Cause

The cause of leukoplakia remains unknown, although hypotheses abound.



• Fig. 10-56 Sanguinaria-associated Keratosis. Thin white plaque on the maxillary alveolar mucosa.

Tobacco

Among the various proposed contributory factors, tobacco smoking appears to be the most closely associated with leukoplakia. More than 80% of patients with leukoplakia are smokers, and smokers are much more likely to have leukoplakia than nonsmokers. Heavier smokers have greater numbers of lesions and larger lesions than do light smokers, especially after many years of tobacco use. In addition, leukoplakias often disappear or become smaller within the first year of smoking cessation.

Smokeless tobacco use often causes a clinically distinctive white oral plaque called **tobacco pouch keratosis** (see page 364). This lesion probably is not a true leukoplakia. In contrast, betel quid use (see page 366)—with or without smokeless tobacco—is associated with true leukoplakia; this habit is common in parts of Asia.

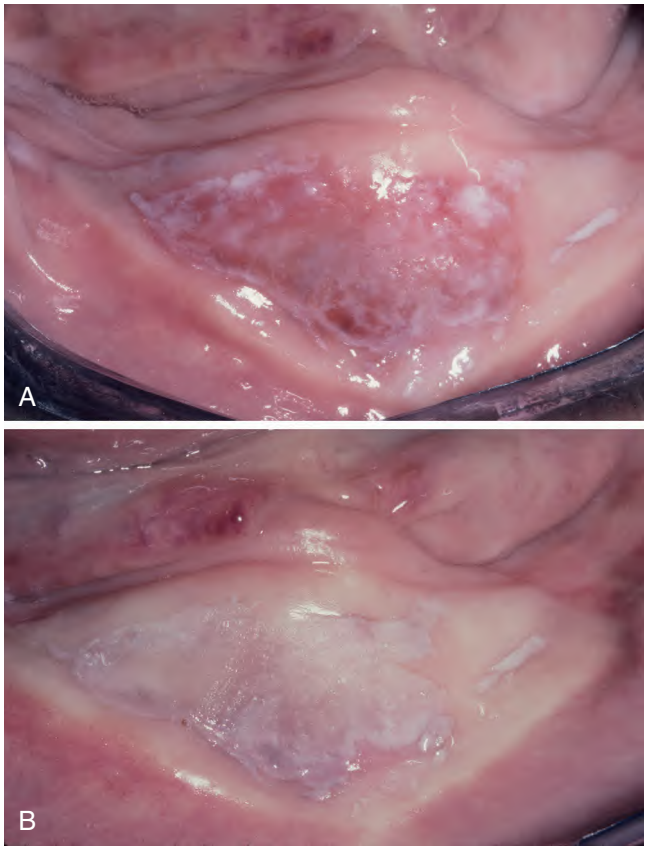
Alcohol

Alcohol exerts a strong synergistic effect with tobacco in oral cancer development. Nevertheless, there is conflicting evidence as to whether alcohol is associated independently with leukoplakia. People who excessively use mouth rinses with alcohol content greater than 25% may have grayish buccal mucosal plaques, but these lesions are not considered true leukoplakias.

Sanguinaria

Persons who use toothpaste or mouth rinses containing the herbal extract, sanguinaria, may develop a true leukoplakia called **sanguinaria-associated keratosis.** This lesion usually arises in the maxillary vestibule or on the maxillary alveolar mucosa (Fig. 10-56). More than 80% of individuals with maxillary vestibular or alveolar leukoplakia have a history of using products that contain sanguinaria, compared with 3% of the normal population.

The affected epithelium may demonstrate dysplasia identical to that seen in other leukoplakias, although the potential for cancer development is uncertain. The white plaque may persist for years even after the patient stops using the product.



• **Fig. 10-57 Candidal Leukoplakia. A,** Well-circumscribed red and white plaque on the anterior floor of mouth, which showed candidal infestation on cytology smears. **B,** After antifungal therapy, the erythematous component resolved, resulting in a homogeneous white plaque.

Ultraviolet Radiation

UV radiation is a causative factor for leukoplakia of the lower lip vermilion. Such lesions typically represent actinic cheiloses (see page 370). Immunocompromised persons, such as transplant patients, are especially prone to developing leukoplakia and squamous cell carcinoma of the lower lip vermilion.

Microorganisms

Several microorganisms have been implicated in the etiology of leukoplakia. *Treponema pallidum,* for example, produces glossitis in the late stage of syphilis, with or without the arsenic therapy in popular use before the advent of modern antibiotics. The tongue is stiff and frequently has extensive dorsal leukoplakia.

Tertiary syphilis is rare today, but oral infection by *Candida albicans* is not. *C. albicans* can colonize the keratin layer of the oral mucosa, often producing a thick, granular, red and white plaque (Fig. 10-57). The terms **candidal leukoplakia** and **candidal hyperplasia** have been used to describe such a lesion, and biopsy may show epithelial dysplasia or hyperplasia. It is unknown whether this yeast produces dysplasia or secondarily infects previously altered epithelium; however, some of these lesions disappear, shrink, or become less severely dysplastic after antifungal therapy. In some cases, tobacco smoking may cause the leukoplakia and also may predispose the patient to develop candidiasis.

The potential role of HPV in the development of oral leukoplakias remains uncertain. Investigators have detected HPV DNA about two to four times more often in oral leukoplakias than in clinically normal oral mucosa. Nevertheless, the presence of HPV DNA alone cannot exclude the possibility of coincidental (or "bystander") infection. Low viral load and frequent absence of viral integration into the host genome among many HPV-positive oral precancers and cancers bring into question the biological relevance of HPV infection in these lesions. Also problematic is the fact that HPV is found more frequently in homogeneous leukoplakias than in non-homogeneous leukoplakias, whereas non-homogeneous lesions are more likely to undergo malignant transformation (see later).

Trauma

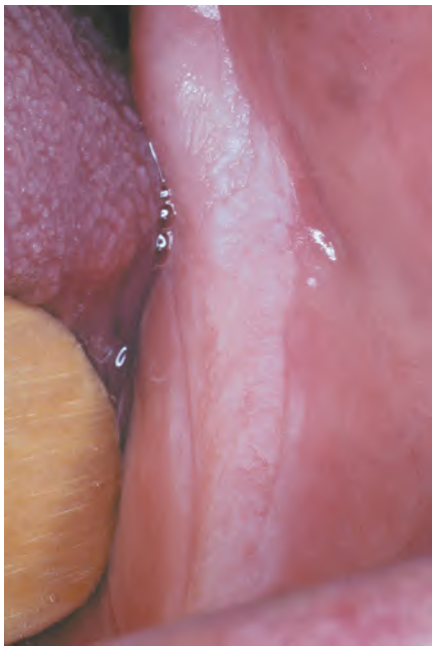
Several keratotic lesions, which until recently had been viewed as variants of leukoplakia, are now considered not to be precancers. Nicotine stomatitis is a generalized white palatal alteration that seems to be a hyperkeratotic response to the heat generated by tobacco smoking (usually a pipe), rather than a response to the carcinogens within the smoke (see page 368). Its malignant transformation potential is so low as to be about the same as that of normal palatal mucosa.

In addition, chronic mechanical irritation can produce a white lesion with a roughened keratotic surface, termed **frictional keratosis.** Although this lesion clinically appears similar to true leukoplakia, it is now thought to be no more than a normal hyperplastic response (similar to a callus on the skin). Keratoses of this type are readily reversible after elimination of the trauma, and obviously traumatic lesions—such as linea alba (see page 259), morsicatio (see page 259), and toothbrush gingival "abrasion"—have not been documented to transform into malignancy. In addition, the presence of dentures or broken and missing teeth has not been shown to increase cancer risk. Alveolar ridge keratoses (Fig. 10-58)—involving the retromolar pad or crest of an edentulous alveolar ridge—represent another form of frictional keratosis caused by masticatory function or denture trauma. Frictional keratosis should be differentiated from oral precancers.

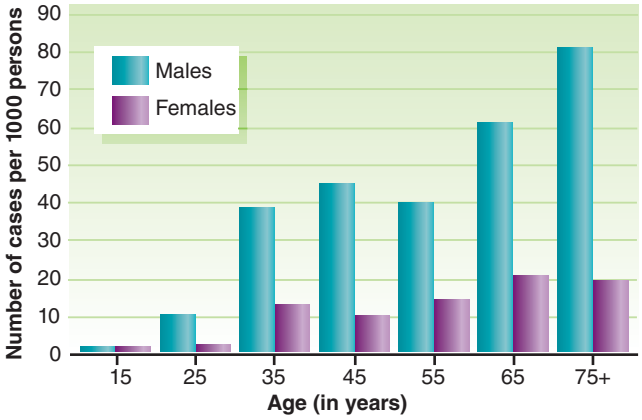
Clinical Features

Leukoplakia usually affects persons older than 40 years. Prevalence increases rapidly with age, especially for males, and as many as 8% of men older than 70 years are affected (Fig. 10-59). The average age (60 years) is similar to that for patients with oral cancer; however, in some studies, leukoplakia has been found to occur about 5 years earlier (on average) than oral squamous cell carcinoma.

Approximately 70% of oral leukoplakias are found on the lip vermilion, buccal mucosa, and gingiva. Lesions on



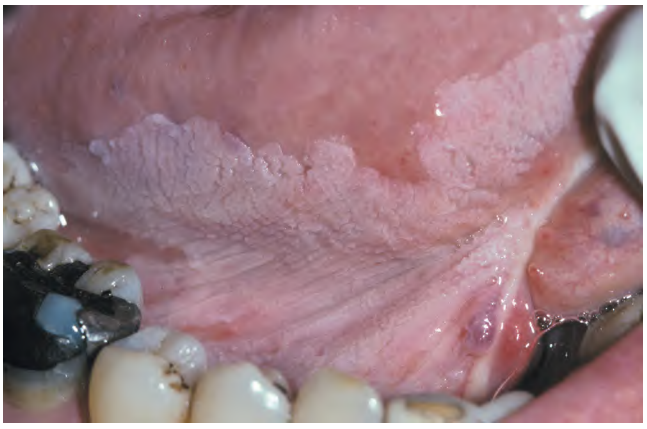
• **Fig. 10-58 Frictional Keratosis.** There is a rough, hyperkeratotic change to the posterior mandibular alveolar ridge ("alveolar ridge keratosis"), because this area is now edentulous and becomes traumatized from mastication. Such frictional keratoses should resolve when the source of irritation is eliminated and should not be mistaken for true leukoplakia.



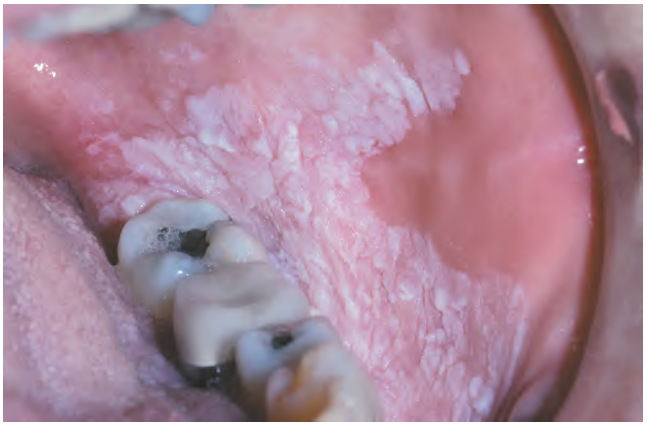
• **Fig. 10-59 Leukoplakia.** Age-specific prevalence (number of new cases per 1000 adults examined at various ages) for oral leukoplakia demonstrates increasing prevalence with increasing age, especially for men.

the tongue, lip vermilion, and oral floor, however, account for more than 90% of those that show dysplasia or carcinoma. Among betel quid users, the buccal mucosa and commissure are the major sites for leukoplakia harboring carcinoma.

Individual lesions may have a varied clinical appearance and tend to change over time. Early, mild, or **thin leukoplakia** appears as a flat to slightly elevated, gray or white plaque, which may be somewhat translucent, fissured, or wrinkled. It is usually soft with sharply demarcated borders, but occasionally it may blend gradually into normal mucosa.



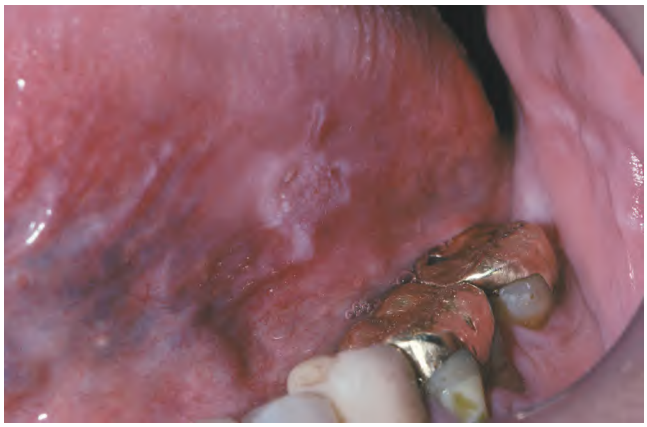
• **Fig. 10-60 Homogeneous or Thick Leukoplakia.** A diffuse, corrugated white patch on the right ventral surface of the tongue and floor of mouth.



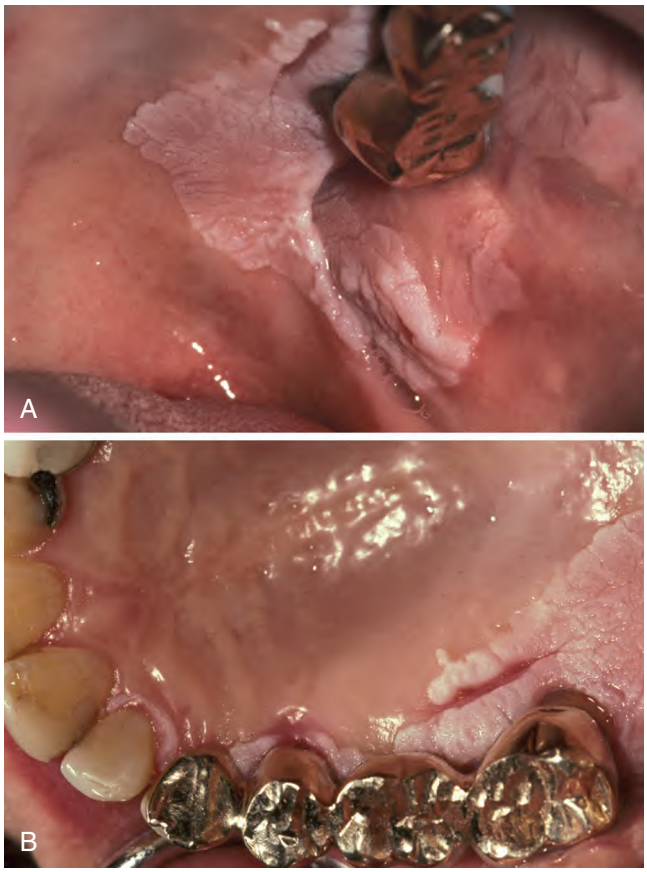
• **Fig. 10-61 Homogeneous or Thick Leukoplakia.** Extensive buccal mucosal lesion with uneven whiteness and fissures. Moderate epithelial dysplasia was noted on histopathologic evaluation, and squamous cell carcinoma later developed in this area.

Thin leukoplakia may disappear or continue unchanged and seldom shows dysplasia on biopsy. For tobacco smokers who do not reduce their habit, as many as two-thirds of such lesions enlarge and progress to a stage called **homogeneous** or **thick leukoplakia,** characterized by a thickened, leathery, distinctly white plaque with deepened fissures (Figs. 10-60 and 10-61). Most remain indefinitely at this stage. However, as many as one-third regress or disappear. Some lesions develop increased surface irregularities and are called **granular** or **nodular leukoplakia** (Figs. 10-62). Lesions with sharp or blunt, wartlike projections are called **verrucous** or **verruciform leukoplakia.**

A special high-risk form of leukoplakia, **proliferative verrucous leukoplakia (PVL),** is characterized by the development of multiple, slowly spreading, keratotic plaques with rough surface projections (Figs. 10-63 and 10-64). The relationship of PVL to cases described as *verrucous leukoplakia* is uncertain. The gingiva frequently is involved, but other sites may be affected as well. Although the lesions typically begin as simple, flat hyperkeratoses that are

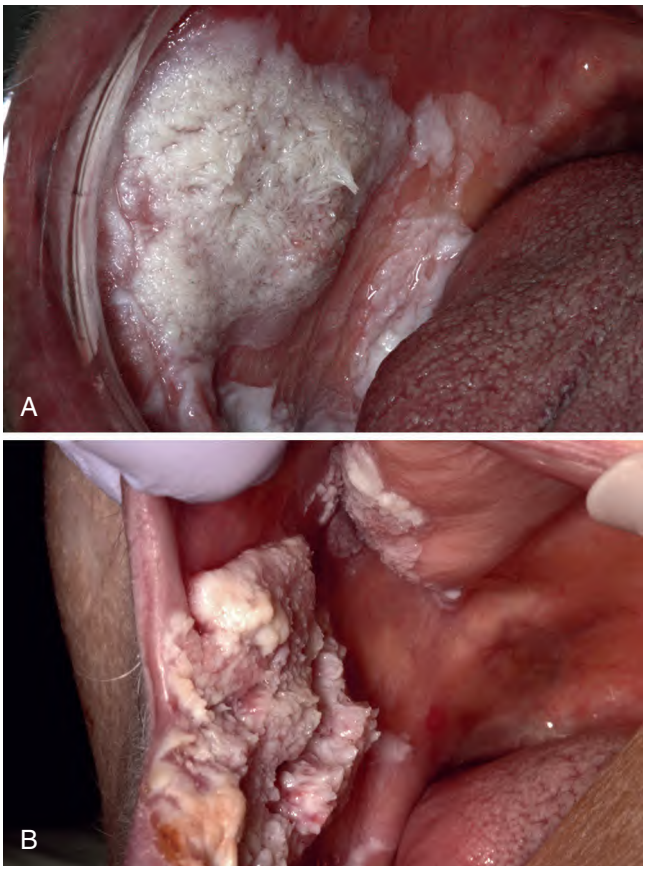


• **Fig. 10-62 Granular Leukoplakia.** Focal leukoplakic lesion with a rough, granular surface on the posterior lateral border of the tongue. Biopsy revealed early invasive squamous cell carcinoma.



• **Fig. 10-63 Proliferative Verrucous Leukoplakia (PVL). A,** Diffuse, corrugated, white lesions of the buccal and palatal mucosa. **B,** Thickened, corrugated, white lesion involving the palate, alveolar ridge, and lingual marginal gingiva.

indistinguishable from ordinary leukoplakia, PVL exhibits persistent growth, eventually becoming exophytic and verrucous. As the lesions progress, they may go through a stage indistinguishable from **verrucous carcinoma** (see page 389), but they later usually develop dysplasia and transform into full-fledged **squamous cell carcinoma** (often within 8 years of initial PVL diagnosis). These lesions rarely regress



• **Fig. 10-64 Proliferative Verrucous Leukoplakia (PVL). A,** An elderly white female developed extensive leukoplakia with rough surface projections on the buccal mucosa and mandibular alveolar ridge. **B,** After failing to comply with a recommendation for biopsy, the same patient returned 2 years later with a verrucous carcinoma.

despite therapy. PVL is unusual among the leukoplakia variants in having a strong female predilection (1:4 male-to-female ratio) and minimal association with tobacco use.

Leukoplakia may become dysplastic or even malignant, with no change in its clinical appearance. However, some lesions eventually demonstrate scattered patches of redness, called **erythroplakia** (see page 363). Such areas usually represent sites in which epithelial cells are so immature or atrophic that they can no longer produce keratin. This intermixed red-and-white lesion, called **erythroleukoplakia** or **speckled leukoplakia,** frequently exhibits advanced dysplasia on biopsy (Fig. 10-65).

Many leukoplakic lesions are a mixture of the previously mentioned phases or subtypes. Figs. 10-66 and 10-67 provide a clinical and graphic representation of such a lesion. Biopsies should be taken from areas of a lesion most likely to harbor dysplasia or carcinoma (i.e., areas with a clinical appearance similar to those toward the right in Fig. 10-67).

Over the years, several new techniques (such as vital dyes, brush cytology, chemiluminescence, and autofluorescence) have been proposed to aid in the identification or diagnosis of premalignant and malignant oral lesions. However, there

is currently insufficient evidence to support the use of such technologies in routine practice, and careful clinical evaluation with directed conventional biopsy remains the gold standard for assessment of oral leukoplakia (see Fig. 10-98).

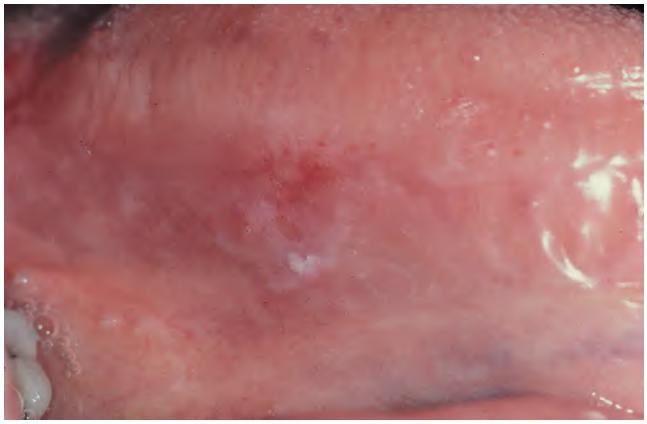
Histopathologic Features

Microscopically, leukoplakia is characterized by a thickened keratin layer of the surface epithelium **(hyperkeratosis),** with or without a thickened spinous layer **(acanthosis).** Some leukoplakias demonstrate surface hyperkeratosis but show atrophy or thinning of the underlying epithelium. Frequently, variable numbers of chronic inflammatory cells are noted within the subjacent connective tissue.

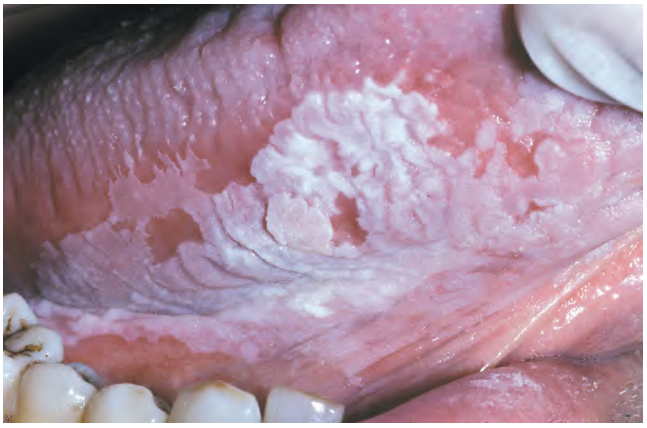
The keratin layer may consist of parakeratin **(hyperparakeratosis),** orthokeratin **(hyperorthokeratosis),** or a combination of both (Fig. 10-68). With parakeratin, there is no granular cell layer and the epithelial nuclei are retained in the keratin layer. With orthokeratin, the epithelium demonstrates a granular cell layer, and the nuclei are lost in the keratin layer.

Verrucous leukoplakia has papillary or pointed surface projections, varying keratin thickness, and broad, blunted rete ridges. It may be difficult to differentiate from early verrucous carcinoma.

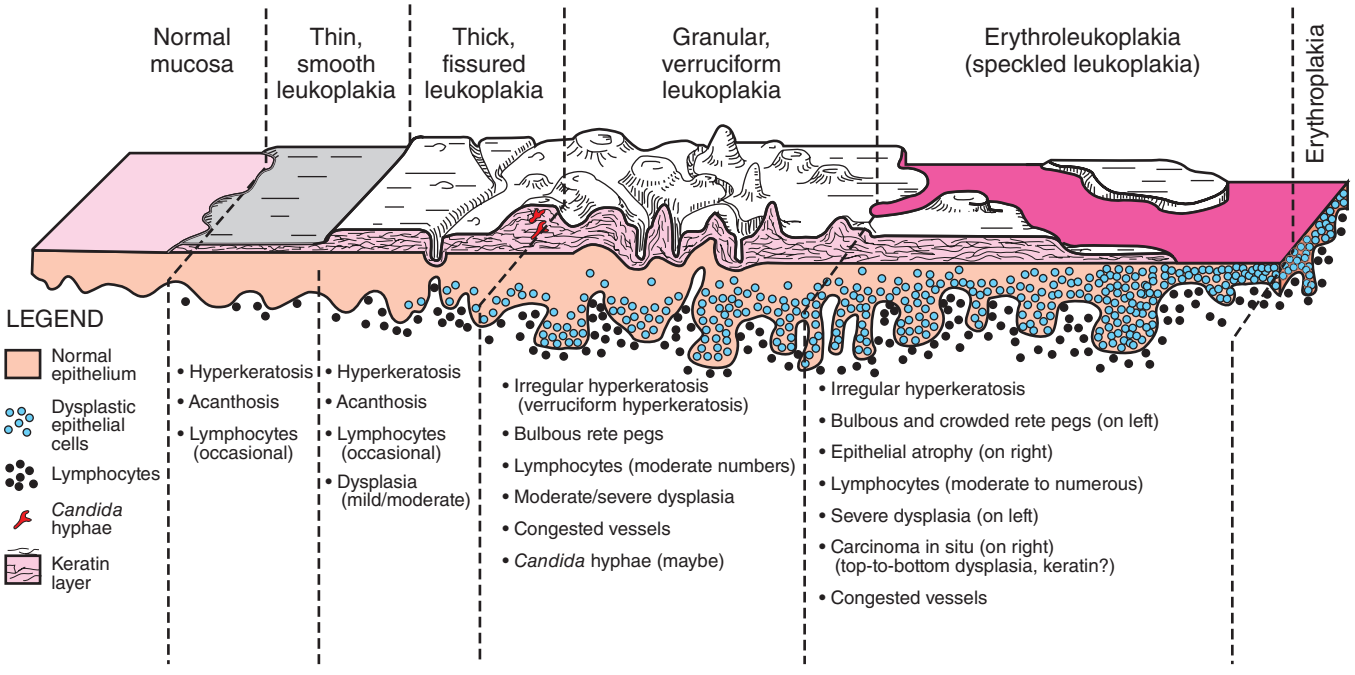
The microscopic appearance of PVL varies by lesion stage. Early PVL appears as a benign hyperkeratosis that is



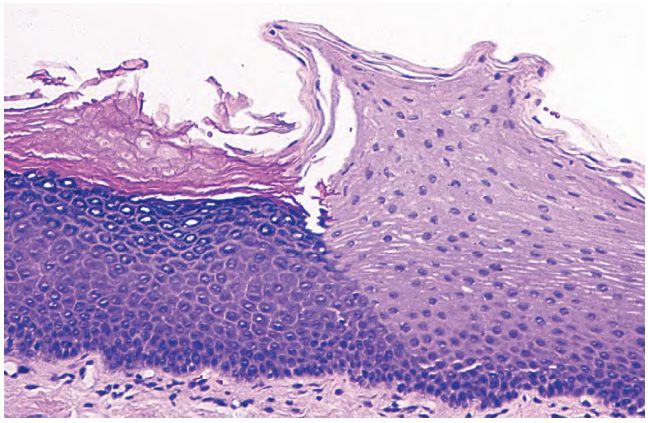
• **Fig. 10-65 Erythroleukoplakia.** Red and white lesion of the lateral border of the tongue. Biopsy revealed carcinoma *in situ.*



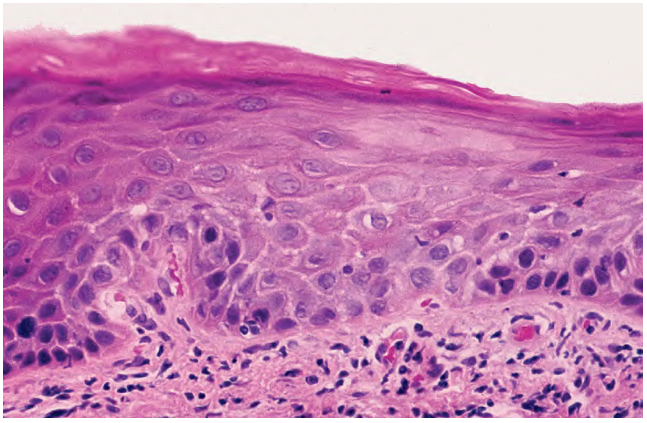
• **Fig. 10-66 Leukoplakia.** Extensive ventral and lateral tongue lesion with areas representing various possible phases or clinical appearances (compare with Fig. 10-67).



• **Fig. 10-67 Leukoplakia.** Composite representation of the various phases or clinical appearances of oral leukoplakia, with anticipated underlying histopathologic changes. Lesions have increasing malignant transformation potentials as their appearances approach those toward the right. (From Bouquot JE, Gnepp DR: Laryngeal precancer—a review of the literature, commentary and comparison with oral leukoplakia, *Head Neck* 13:488-497, 1991.)



• **Fig. 10-68 Hyperorthokeratosis.** This medium-power photomicrograph demonstrates hyperorthokeratosis with a well-defined granular cell layer on the left side. The right side shows normal parakeratinized epithelium without a granular cell layer.



• **Fig. 10-69 Mild Epithelial Dysplasia.** Hyperchromatic and slightly pleomorphic nuclei are noted in the basal and parabasal cell layers of this stratified squamous epithelium.

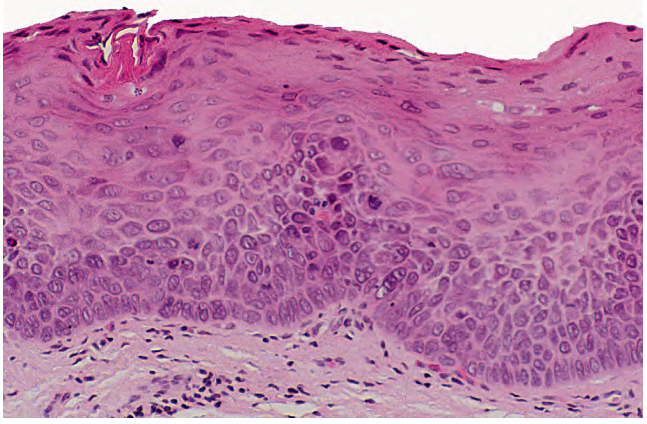
indistinguishable from conventional leukoplakia. With time, the condition progresses to a papillary, exophytic proliferation that is similar to localized lesions of verrucous leukoplakia (or what is sometimes termed **verrucous hyperplasia**). In later stages, this papillary proliferation exhibits downgrowth of well-differentiated squamous epithelium with broad, blunt rete ridges and is indistinguishable from verrucous carcinoma. In the final stages, the epithelium becomes frankly invasive and less differentiated, transforming into full-fledged squamous cell carcinoma. The diagnosis of PVL requires careful correlation of the variable clinical and microscopic findings.

Epithelial dysplasia or carcinoma is found in only about 5% to 25% of oral leukoplakias. Dysplastic changes typically begin in the basilar and parabasilar portions of the epithelium. The more dysplastic the epithelium becomes, the more the atypical epithelial changes extend to involve the entire thickness of the epithelium. The histopathologic alterations of dysplastic epithelial cells are similar to those of squamous cell carcinoma and may include the following:

- Enlarged nuclei and cells
- Large and prominent nucleoli
- Increased nuclear-to-cytoplasmic ratio
- Hyperchromatic (excessively dark-staining) nuclei
- Pleomorphic (abnormally shaped) nuclei and cells
- Dyskeratosis (premature keratinization of individual cells)
- Increased mitotic activity (excessive numbers of mitoses)
- Abnormal mitotic figures (tripolar or star-shaped mitoses or mitotic figures above the basal layer)

In addition, histomorphologic alterations of dysplastic epithelium are evident at low-power magnification, including the following:

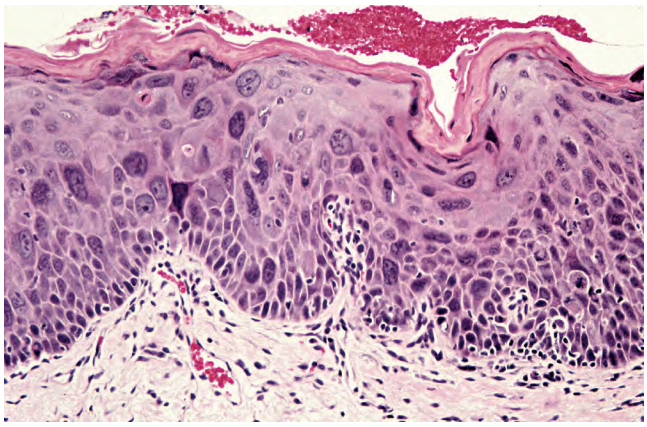
- Bulbous or teardrop-shaped rete ridges
- Loss of polarity (lack of progressive maturation toward the surface)
- Keratin or epithelial pearls (focal, round collections of concentrically layered keratinized cells)
- Loss of typical epithelial cell cohesiveness



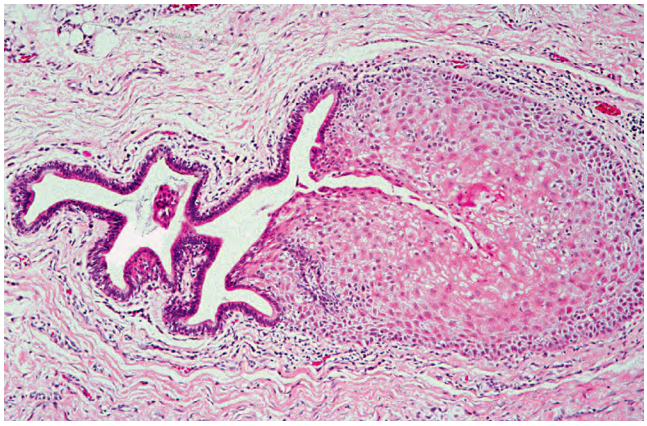
• **Fig. 10-70 Moderate Epithelial Dysplasia.** Dysplastic changes extend to the midpoint of the epithelium and are characterized by nuclear hyperchromatism, pleomorphism, and cellular crowding.

The grade of epithelial dysplasia refers to its "severity" or intensity. **Mild epithelial dysplasia** refers to alterations limited principally to the basal and parabasal layers (Fig. 10-69). **Moderate epithelial dysplasia** demonstrates involvement from the basal layer to the midportion of the spinous layer (Fig. 10-70). **Severe epithelial dysplasia** demonstrates alterations from the basal layer to a level above the midpoint of the epithelium (Fig. 10-71). Sometimes dysplasia may extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth (Fig. 10-72); such cases exhibit an increased risk for recurrence.

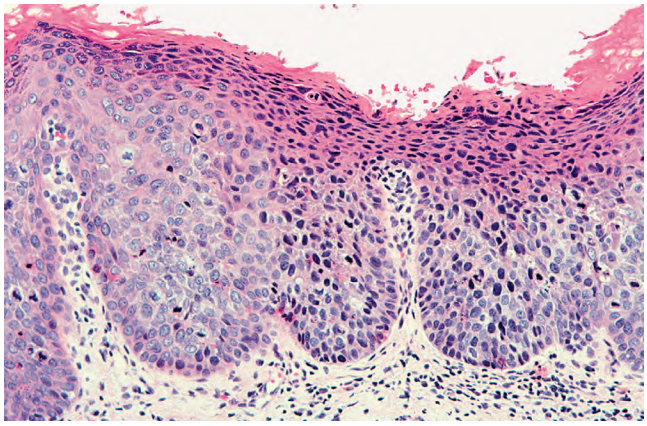
Carcinoma *in situ* is defined as dysplasia involving the entire thickness of the epithelium (i.e., extending from the basal layer to the surface or "top-to-bottom" change) (Fig. 10-73). There may or may not be a thin layer of keratin on the surface. The epithelium may be hyperplastic or atrophic. Some authorities consider carcinoma *in situ* to be a precancerous lesion, whereas others believe that it represents a genuine malignancy discovered before invasion. Regardless, an important feature of carcinoma *in situ* is absence of invasion, and without invasion, metastasis cannot occur.



• **Fig. 10-71 Severe Epithelial Dysplasia.** Epithelium exhibiting marked pleomorphism, hyperchromatism, and scattered mitotic figures. Atypical cells involve most of the epithelial thickness.



• **Fig. 10-72 Ductal Dysplasia.** Salivary gland duct exhibiting squamous metaplasia and dysplasia that originated from an overlying surface epithelial dysplasia.



• **Fig. 10-73 Carcinoma *in Situ*.** Dysplastic changes extend throughout the entire thickness of the epithelium.

In this light, keratin pearl formation is rare in carcinoma *in situ* and may indicate focal invasive squamous cell carcinoma.

Treatment and Prognosis

Because leukoplakia represents a clinical term only, a biopsy is required to obtain a histopathologic diagnosis and to guide the appropriate management. Biopsies should be taken from the clinically most "severe" areas (with features toward the right of Fig. 10-67). Multiple biopsies may be needed for large or multifocal lesions.

Leukoplakia exhibiting moderate epithelial dysplasia or worse warrants complete destruction or removal, if feasible. The management of leukoplakia exhibiting less severe change is guided by the lesion size and the response to more conservative measures, such as tobacco cessation. Some smoking-related leukoplakias with no or minimal dysplasia may disappear or diminish in size within 3 months after the patient stops smoking.

Complete removal can be accomplished with equal effectiveness by surgical excision, electrocautery, cryosurgery, or laser ablation. An advantage of surgical excision is that it allows for optimal tissue preservation for histopathologic analysis, whereas the other methods may be preferable in some cases for limiting procedure-related morbidity.

Even after removal, reported overall recurrence rates range from 10% to 35%, and development of additional leukoplakias is common. In particular, verruciform or granular leukoplakias exhibit an 83% recurrence rate and, thus, often undergo additional removal or destruction. Nevertheless, it is unclear whether surgical excision of leukoplakia significantly reduces the risk for developing malignancy. Therefore, even after removal, long-term follow-up is extremely important.

Although leukoplakia without dysplasia often is not excised, clinical evaluation every 6 months is recommended because of the possibility of disease progression. Additional biopsies are recommended if smoking continues or if the clinical changes increase in severity.

Reported malignant transformation rates for oral leukoplakia vary considerably across studies, although best estimates suggest a malignant transformation rate of less than 2% per year. Some of this variation may be due to patient selection bias, with lower rates typically reported among community-based than hospital-based studies. Additional confounding factors include variations in diagnostic definitions, clinical management, and periods of observation. Typically, the latter extend for 5 to 10 years, but several studies have observed patients for more than 20 years. Carcinomatous transformation usually occurs 2 to 4 years after leukoplakia onset, but it may occur within months or after decades.

Each clinical phase of leukoplakia has a different malignant transformation potential. Thin leukoplakia seldom becomes malignant without demonstrating a clinical change. In contrast, malignant transformation occurs in

approximately 1% to 7% of homogeneous, thick leukoplakias and 4% to 15% of granular or verruciform leukoplakias. Erythroleukoplakia carries an average transformation potential of 28%, but reported rates vary from 18% to 47%.

The transformation potential of the different phases of leukoplakia is related closely to the degree of dysplasia present. Lesions with moderate and severe dysplasia reportedly have malignant transformation potentials of 4% to 11% and 20% to 43%, respectively.

Additional factors associated with an increased risk for malignant transformation of leukoplakia include female gender, older age, nonsmoking status, lesion persistence for several years, extensive lesion size, and involvement of the ventrolateral tongue or floor of mouth. In particular, leukoplakia of the ventrolateral tongue and oral floor exhibits malignant transformation in 16% to 39% of cases and 47% of those occurring in females.

There is much interest in the identification of chromosomal, genetic, and molecular alterations that may aid in predicting the risk of malignant transformation for oral leukoplakia. Cytogenetic studies have suggested that loss of heterozygosity (LOH) of chromosome arms 3p and 9p is associated with increased risk of malignant transformation, and additional LOH at 4q, 8p, 11q, 13q, and 17p further increases this risk. Additional alterations—such as microsatellite instability (insertion or deletion of base pairs in repetitive stretches of short DNA sequences), increased telomerase activity (important for cellular longevity), and changes in expression of various molecular markers (e.g., p53, survivin, and other regulators of apoptosis; p16 and other markers of cell cycle regulation; epidermal growth factor receptor [EGFR]; matrix metalloproteinases; vascular endothelial growth factor)—have exhibited a variable association with histopathologic progression in oral premalignant lesions. Despite these interesting observations, histopathologic grading of dysplasia remains the standard method for predicting the risk of progression to malignancy.

Chemoprevention for oral leukoplakia has been attempted but remains experimental. Retinoid-based therapies (e.g., 13-cis-retinoic acid; vitamin A alone or in combination with beta-carotene) have reduced or eliminated some leukoplakic lesions in short-term studies. Toxic reactions to systemic retinoids are frequent, however, as is lesion recurrence after the conclusion of therapy. Additional potential chemopreventive agents of interest include lycopene, cyclooxgenase-2 (COX-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, green tea polyphenols, peroxisome proliferator activator (PPAR)-gamma agonists (traditionally used as oral hypoglycemics for diabetes management), and ONYX-015 (an attenuated adenovirus with selectivity for cells harboring *TP53* mutations). However, to date there is insufficient evidence to support the effectiveness of such medical therapies in preventing the progression of oral premalignant lesions to squamous cell carcinoma.

◆ ERYTHROPLAKIA (ERYTHROPLASIA; ERYTHROPLASIA OF QUEYRAT)

Similar to leukoplakia, **erythroplakia** is defined as a red patch or plaque that cannot be clinically or pathologically diagnosed as any other condition. Queyrat originally used the term *erythroplasia* to describe a precancerous red lesion on the penis. Oral erythroplakia is clinically and histopathologically similar to the genital process. Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma *in situ,* or invasive squamous cell carcinoma. The causes of erythroplakia are presumed to be the same as those associated with oral squamous cell carcinoma (see page 375).

The estimated point prevalence rate (number of persons with active lesions at a given point in time) of oral erythroplakia is 1 per 2500 adults. The reported prevalence among several large-scale epidemiologic surveys—many of which were conducted in Asia and the United States—ranges from 0.01% to 0.83%. The incidence is unknown, but the estimated annual incidence for microscopically proven oral carcinoma *in situ,* which represents the great majority of erythroplakias, is 1.2 per 100,000 population in the United States.

Erythroplakia also may occur in conjunction with leukoplakia (see page 355) and has been found concurrently with a large proportion of early invasive oral carcinomas. Although erythroplakia is less common than leukoplakia, it has a much greater potential to be severely dysplastic at the time of biopsy or to develop malignancy later.

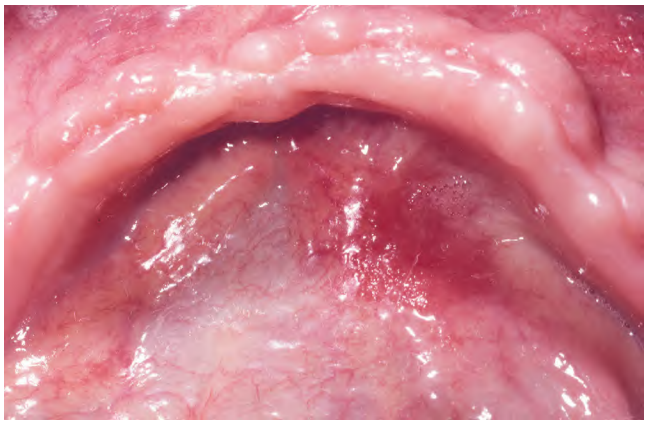
Clinical Features

Erythroplakia is predominantly a disease of middle-aged to older adults with no significant gender predilection. In the United States, a peak prevalence of 65 to 74 years has been reported. In India, the peak prevalence is in a somewhat younger age range of 45 to 54 years. The floor of mouth, tongue, and soft palate are the most common sites of involvement, and multiple lesions may be present.

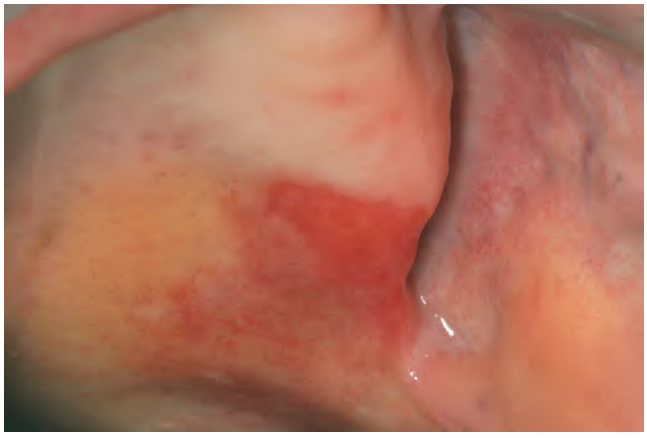
The lesion appears as a well-demarcated, erythematous patch or plaque with a soft, velvety texture (Figs. 10-74 and 10-75). It is usually asymptomatic and may be associated with an adjacent leukoplakia **(erythroleukoplakia)** (see Fig. 10-65). Biopsy typically is required to distinguish erythroplakia from other conditions with a similar clinical appearance, such as nonspecific mucositis, candidiasis, psoriasis, or vascular lesions.

Histopathologic Features

According to one large clinicopathologic investigation, 90% of erythroplakic lesions histopathologically represent severe epithelial dysplasia (see page 361), carcinoma *in situ* (see page 361), or superficially invasive squamous cell carcinoma (see page 385). The epithelium lacks keratin production and



• **Fig. 10-74 Erythroplakia.** Erythematous macule on the right floor of the mouth. Biopsy showed early invasive squamous cell carcinoma.



• **Fig. 10-75 Erythroplakia.** Well-circumscribed red patch on the posterior lateral hard and soft palate. (From Neville BW, Chi AC, Jeter M: Diagnostic challenge: a red lesion on the palate, *J Am Dent Assoc* 137:1537-1538, 2006.)

often is atrophic, thereby allowing the underlying microvasculature to show through and produce a red appearance. The underlying connective tissue frequently demonstrates chronic inflammation.

Treatment and Prognosis

Red lesions of the oral mucosa, especially those of the oral floor and ventrolateral tongue, should be viewed with suspicion, and a biopsy should be performed. If a source of irritation can be identified and removed, then biopsy may be delayed for 2 weeks to allow a clinically similar inflammatory lesion time to regress.

As with leukoplakia, the treatment of erythroplakia is guided by the histopathologic diagnosis. Moderate dysplasia or worse typically warrants complete excision or destruction (see treatment methods for leukoplakia on page 362). Excision often is preferred, because it allows for microscopic examination to rule out invasive carcinoma. Recurrence and multifocal involvement are common; hence, long-term follow-up is suggested.

◆ SMOKELESS TOBACCO USE AND SMOKELESS TOBACCO KERATOSIS (SNUFF POUCH; SNUFF DIPPER'S LESION; TOBACCO POUCH KERATOSIS; SPIT TOBACCO KERATOSIS)

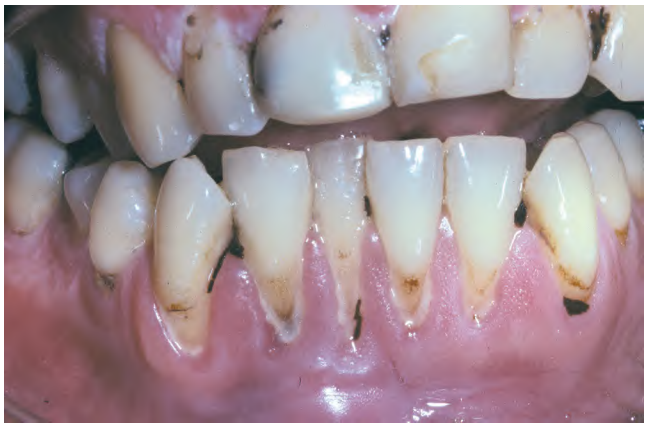
The three main types of smokeless tobacco used in the United States include chewing tobacco, dry snuff, and moist snuff. The latter is most popular, with increasing sales over the past few decades due in part to the convenience of small, inconspicuous, prepackaged pouches. Chewing tobacco often is used by men in conjunction with outdoor activities, and dry snuff is used primarily by women in the southern United States. Smokeless tobacco use also has been referred to as **spit tobacco use**—a term preferred by the US federal government in its attempt to diminish the appeal of the habit.

In the United States, according to the 2011 National Survey on Drug Use and Health, approximately 3.2% of people (or 8.2 million individuals) 12 years and older use smokeless tobacco. The highest prevalence rates are seen in some Southeastern and Midwestern states. The habit is especially common among young individuals, with approximately 13% of male high school students reporting current smokeless tobacco use. The habit typically is started at around 8 to 14 years of age, and rarely is initiated after 20 years of age. Another national survey detected smokeless tobacco lesions of all types in 1.5% (2.9% in males, 0.1% in females) of US adolescents and teenagers. As part of its *Healthy People 2020* objectives, the US Department of Health and Human Services has set a goal to reduce the national prevalence of smokeless tobacco use from 2.3% to 0.3% among adults and from 8.9% to 6.9% among adolescents.

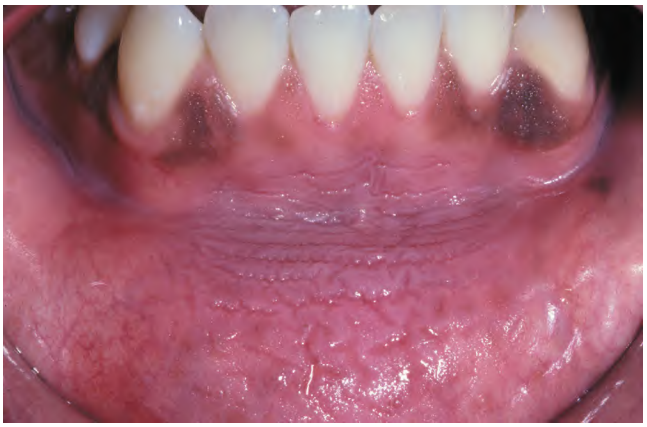
In India and other Asian countries, smokeless tobacco may be combined in a quid with betel leaves, areca nuts, and slaked lime. Oral lesions associated with betel quid use are described separately (see page 366).

Clinical Features

Several health and addiction hazards may be associated with smokeless tobacco use because of the ready absorption of nicotine and other molecules through the oral mucosa. A variety of local oral alterations also are found in chronic users. One of the most common local changes is painless gingival recession in the area of tobacco contact (Fig. 10-76), at times accompanied by destruction of the underlying facial alveolar bone. The severity of the defect correlates with the quantity and duration of smokeless tobacco use. Although the association between smokeless tobacco and gingival recession is well known, there is some variability across studies regarding the association between smokeless tobacco and periodontal bone loss. Researchers have suggested that this variability may be related to the specific type



• **Fig. 10-76 Smokeless Tobacco–related Gingival Recession.** Extensive recession of the anterior mandibular facial gingiva.



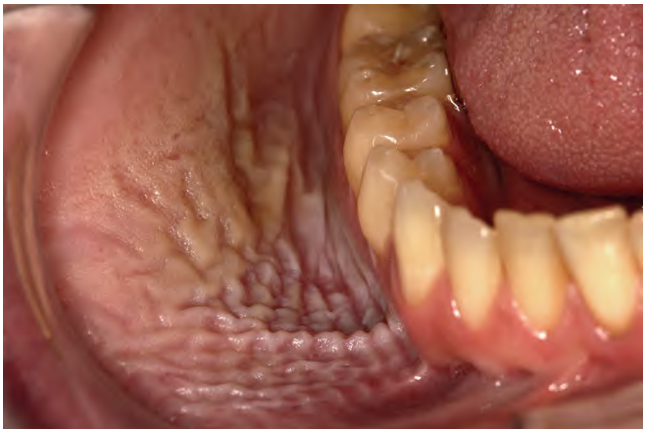
• **Fig. 10-77 Tobacco Pouch Keratosis, Mild.** A soft, fissured, gray-white lesion of the lower labial mucosa located in the area of chronic snuff placement. The gingival melanosis is racial pigmentation and not associated with the keratosis.

of smokeless tobacco used or confounding by concurrent cigarette smoking.

Dental caries also has been reported to be more prevalent in smokeless tobacco users, perhaps because of the high sugar content of some brands; other reports dispute caries susceptibility. Long-term use may lead to localized or generalized wear of occlusal and incisal surfaces, especially in those using the product in dusty environments. A brown-black extrinsic tobacco stain typically is found on the tooth surfaces adjacent to the tobacco. In addition, halitosis is a frequent finding.

Smokeless tobacco keratosis represents a characteristic white or gray plaque involving the mucosa in direct contact with snuff or chewing tobacco. In Western cultures, it affects 15% of chewing tobacco users and 60% of snuff users, if mild examples are included. Lesion development is influenced most strongly by habit duration and also by the brand of tobacco used, early onset of smokeless tobacco use, total hours of daily use, amount of tobacco consumed daily, and number of sites routinely used for tobacco placement. In Western populations, smokeless tobacco keratosis most often is noted in young adult men and men older than 65 years of age; however, in some subpopulations the prevalence is greatest among older women. Individual lesions begin to develop shortly after heavy tobacco use begins, and new lesions seldom arise in persons with a long history of use.

The altered mucosa typically is thin and almost translucent, with an indistinct border (Fig. 10-77). Sometimes mild peripheral erythema is present. Upon palpation, the lesion may feel soft and velvety. Stretching of the mucosa often reveals a distinct "pouch" **(snuff pouch, tobacco pouch)** caused by flaccidity in the area of chronic tobacco placement. The mucosa appears fissured or rippled, in a fashion resembling the sand on a beach after an ebbing tide. Similar alterations can occur when other bulky materials (e.g., hard candy, sunflower seeds, and beef jerky) are held chronically in the vestibule. Induration, ulceration, and pain are not associated with this lesion.

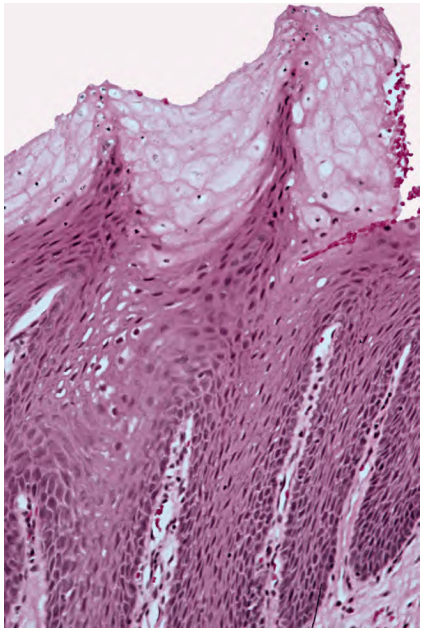


• **Fig. 10-78 Tobacco Pouch Keratosis, Severe.** A somewhat leathery, white, fissured plaque of the right mandibular vestibule, which was located in the area of chronic chewing tobacco placement.

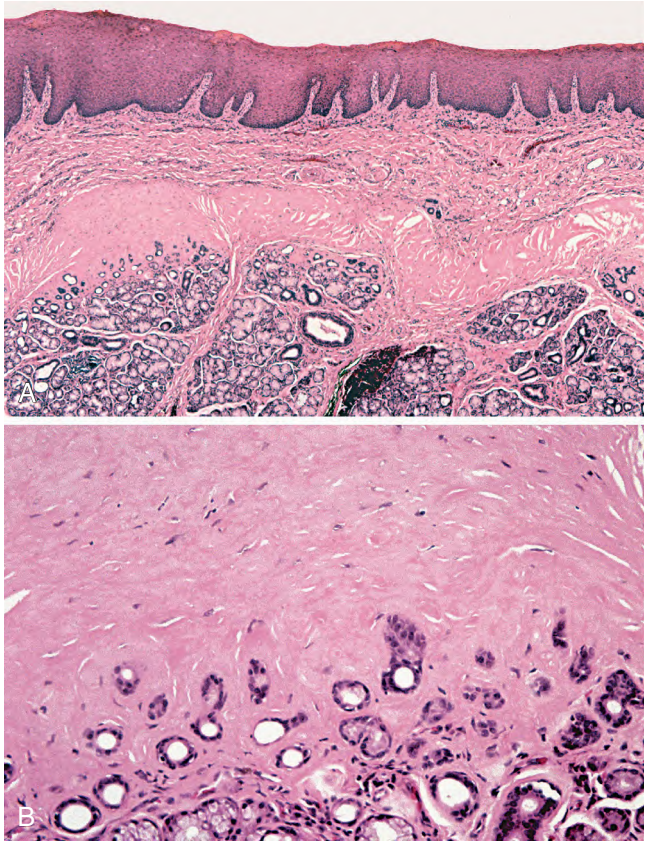
Smokeless tobacco keratosis usually takes 1 to 5 years to develop. Once it occurs, however, the keratosis typically remains unchanged indefinitely unless the daily tobacco contact time is altered. In some cases, the lesion gradually becomes thickened to the point of appearing leathery or nodular (Fig. 10-78).

Histopathologic Features

The histopathologic appearance of smokeless tobacco keratosis is not specific. The squamous epithelium is hyperkeratotic and acanthotic, with or without intracellular vacuolization or "edema" of glycogen-rich superficial cells. Parakeratin **chevrons** may be seen as pointed projections above or within superficial epithelial layers (Fig. 10-79). Increased subepithelial vascularity and vessel engorgement often are observed. In some cases, an unusual deposition of amorphous eosinophilic material is noted within the subjacent connective tissue and salivary glands (Fig. 10-80). Epithelial dysplasia is uncommon in smokeless tobacco keratosis and, when present, is typically mild. Occasionally,



• **Fig. 10-79 Tobacco Pouch Keratosis.** Epithelium exhibiting acanthosis, hyperparakeratosis, and "chevron" formation.



• **Fig. 10-80 Tobacco Pouch Keratosis. A,** Low-power view showing mild hyperkeratosis and acanthosis. Note linear deposition of amorphous, eosinophilic material in the lamina propria above the minor salivary glands. **B,** Higher-power view of the amorphous material.

however, significant dysplasia or squamous cell carcinoma may develop.

Treatment and Prognosis

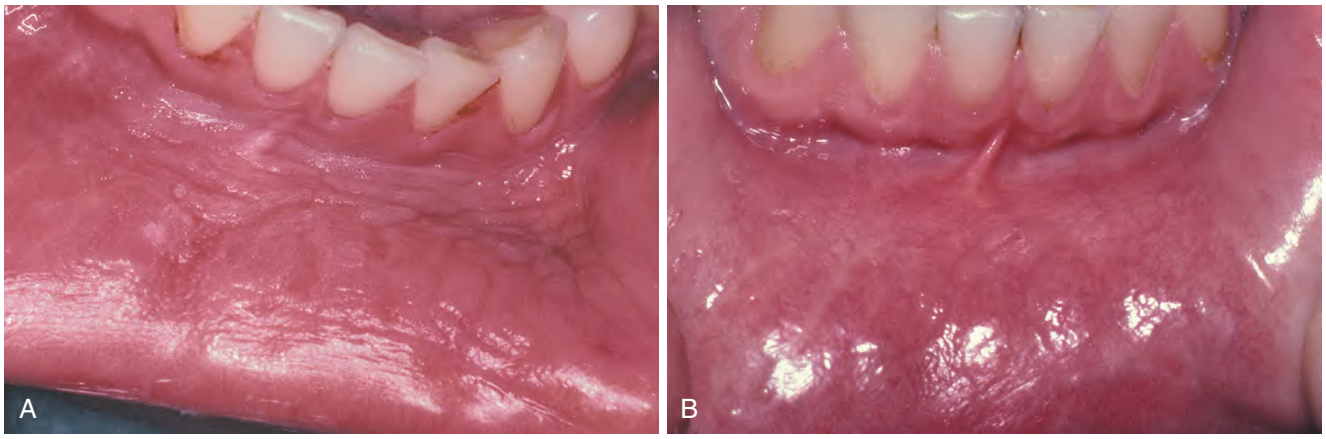
Chronic use of smokeless tobacco in the United States is considered to be carcinogenic, although the risk is less than that associated with cigarette smoking and alcohol abuse. Fortunately, the clinical appearance of smokeless tobacco keratosis is distinct enough and the malignant transformation potential is low enough that biopsy is needed for only severe or atypical lesions (i.e., those demonstrating an intense whiteness, a granular or verruciform clinical appearance, ulceration, mass formation, induration, or hemorrhage). Treatment depends on the histopathologic diagnosis. Keratoses without dysplasia or malignancy may require only continued monitoring and encouraged tobacco cessation. Alternating the tobacco-chewing sites between the left and right sides will eliminate or reduce the keratotic lesion but may result in epithelial alteration or gingival and periodontal difficulties in two sites rather than one.

Squamous cell carcinoma (see page 376) related to smokeless tobacco use typically develops after a latency period of several decades. Most such cases represent conventional squamous cell carcinoma, although an uncommon low-grade variant known as **verrucous carcinoma ("snuff dipper's" cancer)** (see page 389) also is possible. In a review of case control studies performed in the United States and Western Europe, the reported relative risk of developing oral cancer from chronic smokeless tobacco use ranged from less than 2 to 26, with lower risk associated with chewing tobacco and moist snuff and higher risk associated with dry snuff. Recent studies from Sweden, however, have failed to show an increased risk for users of Swedish moist snuff (also known as *snus*). Many of the early reports of malignant transformation described lesions among female dry snuff users in the southern United States. Only recently have epidemiologic studies tried to separate the various types of smokeless tobacco with respect to their carcinogenic potential.

Significantly, habit cessation leads to a normal mucosal appearance (usually within 2 weeks) in 98% of smokeless tobacco keratoses that are not intensely white (Fig. 10-81). A lesion that remains after 6 weeks without smokeless tobacco contact should be considered a true leukoplakia and should be biopsied and managed accordingly (see page 362).

◆ ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a high-risk, precancerous condition characterized by chronic, progressive scarring of the oral mucosa. It is seen primarily in the Indian subcontinent, Southeast Asia, Taiwan, southern China, Polynesia, and Micronesia. The condition affects more than 5 million people in India alone. Cases among Asian communities in North America, Europe, and Africa also have been reported.



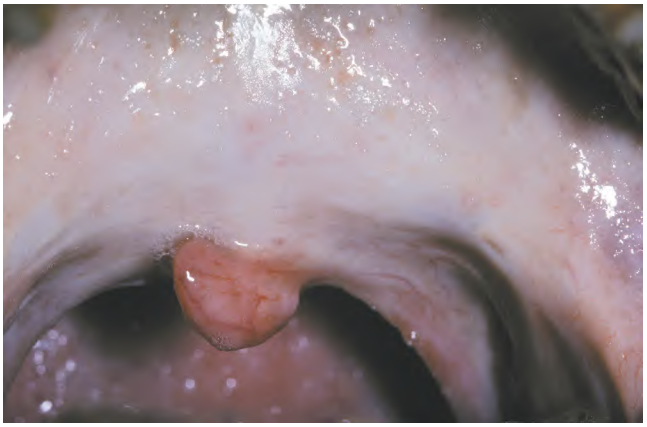
• **Fig. 10-81 Tobacco Pouch Keratosis. A,** Moderately severe lesion of the lower anterior vestibule and lip in a 15-year-old male. There is a gray-white, fissured surface. The patient had placed snuff in the area for several years. **B,** Two weeks after cessation of the tobacco habit, the mucosa returned to an almost normal appearance.

The etiology is linked to the use of betel quid *(paan)* and related products—a habit among up to 20% of the world's population. The quid consists of a betel leaf wrapped around a mixture of areca nut (from the *Areca catechu* palm tree), slaked lime, possibly tobacco, and sometimes sweeteners and spices. The slaked lime releases alkaloids from the areca nut to produce a feeling of euphoria in the user. Villagers habitually chew betel quid from an early age, frequently for 16 to 24 hours daily.

The incidence of oral submucous fibrosis has been increasing—especially among young persons—due to the growing popularity of commercially freeze-dried betel quid substitutes (such as, *pan masala, gutkha,* and *mawa*), conveniently packaged in portable sachets. These products contain a higher concentration of areca nut and may cause oral submucous fibrosis more rapidly than conventionally prepared betel quid.

The fibrosis appears to be induced by areca nut, whereas the epithelial alterations and carcinogenesis appear to result mainly from tobacco. However, several studies suggest that even betel quid without tobacco may be carcinogenic, albeit probably less so than when combined with tobacco. Nutritional deficiency increases the risk and severity of fibrosis. Furthermore, based upon human leukocyte antigen [HLA] associations and circulating immune complexes and autoantibodies, a possible underlying autoimmune mechanism with a genetic predisposition has been proposed in some cases.

The pathogenesis of oral submucous fibrosis is hypothesized to involve the disruption of collagen metabolism by components of the areca nut. Alkaloids stimulate fibroblasts to produce collagen, whereas flavonoids inhibit collagenase (an enzyme that catalyzes collagen breakdown). In addition, there are considerable amounts of copper in areca nut products. Copper upregulates lysyl oxidase, which is an enzyme involved in collagen cross-linking; this process renders collagen fibrils resistant to degradation by collagenase. Furthermore, cytokines and growth factors produced by activated inflammatory cells may promote fibrosis by inducing fibroblast proliferation, upregulating collagen synthesis, and downregulating collagenase production.

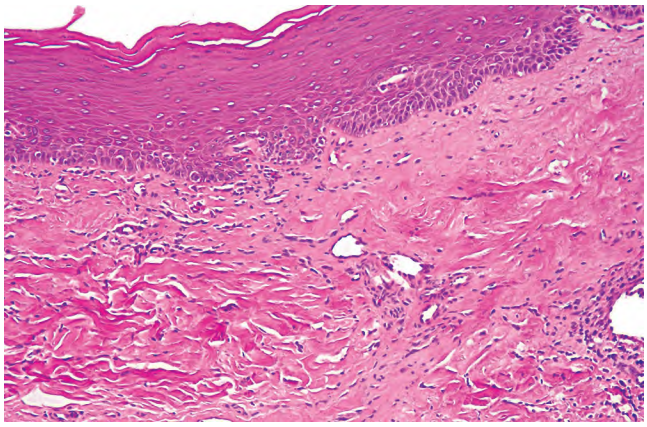


• **Fig. 10-82 Oral Submucous Fibrosis.** Pallor and fibrosis of the soft palate in a betel quid chewer. The uvula has retained its normal color.

Clinical Features

Oral submucous fibrosis often manifests in young adult betel quid users. Reported gender predilection varies by population. Typical chief complaints include an inability to open the mouth **(trismus)** and a generalized oral burning sensation **(stomatopyrosis)** with intolerance to spicy foods. An interincisal distance of less than 20 mm is considered severe; in advanced cases, the jaws may be inseparable.

Vesicles, petechiae, melanosis, xerostomia, and stomatopyrosis are usually the first signs and symptoms. The buccal mucosa, retromolar area, and soft palate are the most commonly affected sites. Subsequently, the mucosa develops a blotchy, marblelike pallor and progressive stiffness (Fig. 10-82). The tongue may become immobile, diminished in size, and devoid of papillae. Submucosal fibrous bands are palpable on the buccal mucosa, soft palate, and labial



• **Fig. 10-83 Oral Submucous Fibrosis.** Mucosal biopsy exhibiting hyperparakeratosis, basilar hyperplasia, and fibrosis in the lamina propria.

mucosa of fully developed cases. Involvement may extend to include the pharynx and upper esophagus. **Leukoplakia** of the surface mucosa often is noted as well (see page 355).

Betel quid chewers also may exhibit a brown-red discoloration of the mucosa with an irregular surface that tends to desquamate. This particular change, known as **betel chewer's mucosa,** is not believed to be precancerous. In addition, some authors have reported **betel quid lichenoid lesions,** characterized by white, parallel, wavy striae resembling oral lichen planus (see page 729). Other possible sequelae include tooth staining, attrition, and periodontal disease.

Histopathologic Features

Oral submucous fibrosis is characterized by juxtaepithelial and submucosal deposition of densely collagenized, hypovascular connective tissue with variable numbers of chronic inflammatory cells (Fig. 10-83). Epithelial changes include subepithelial vesicles in early lesions and hyperkeratosis with marked epithelial atrophy in older lesions. Epithelial dysplasia is found in 10% to 15% of cases submitted for biopsy, and carcinoma is found in at least 6% of sampled cases.

Betel chewer's mucosa appears histopathologically similar to morsicatio buccarum (see page 259), except the ragged keratinaceous surface is covered by encrusted betel quid ingredients.

Treatment and Prognosis

Unlike tobacco pouch keratosis, oral submucous fibrosis does not regress with habit cessation. Mild cases may be treated with intralesional corticosteroids to reduce symptoms and limit progression. Moderate to severe cases may require surgical splitting or excision of the fibrous bands followed by lifelong physiotherapy; however, relapse is common. There is limited evidence for various alternative treatments, such as intralesional injection of interferon-gamma; topical or intralesional proteolytics (e.g., collagenase, hyaluronidase, chymotrypsin, and human placental extract); vitamins and minerals; antioxidants (e.g., lycopene); pentoxifylline; and ayurvedic remedies (e.g., turmeric).

Frequent evaluation for development of oral squamous cell carcinoma is essential because a 17-year malignant transformation rate of 8% has been determined for betel quid users in India. Overall, persons with oral submucous fibrosis are at least 19 times more likely to develop oral cancer than persons without the disease.

◆ NICOTINE STOMATITIS (NICOTINE PALATINUS; SMOKER'S PALATE)

Once a common mucosal change of the hard palate, **nicotine stomatitis** has become less common because cigar and pipe smoking have lost popularity. Although this hyperkeratotic lesion is associated with tobacco smoking, it does not appear to have a premalignant nature, perhaps because it develops in response to heat rather than the chemicals in tobacco smoke. In particular, pipe smoking appears to generate more heat on the palate than other forms of smoking. Similar changes also can be produced by the long-term use of extremely hot beverages.

In some South American and Southeast Asian cultures, hand-rolled cigarettes and cigars are smoked with the lit end held within the mouth. This "reverse smoking" habit produces a pronounced palatal keratosis, or **reverse smoker's palate,** which has a significant potential to develop dysplasia or carcinoma.

Clinical Features

Nicotine stomatitis most commonly affects men older than 45 years. With long-term exposure to heat, the palatal mucosa becomes diffusely gray or white; numerous slightly elevated papules are noted, usually with punctate red centers (Figs. 10-84 and 10-85). Such papules represent inflamed minor salivary glands and their ductal orifices.

The palatal keratin may become so thickened that a fissured or "dried mud" appearance is imparted. The whiteness also may involve the marginal gingiva and interdental papillae, and hyperkeratosis of the buccal mucosa occasionally is seen. A heavy brown or black tobacco stain may be present on the teeth.

Histopathologic Features

Nicotine stomatitis is characterized by hyperkeratosis and acanthosis of the palatal epithelium and mild, patchy, chronic inflammation of subepithelial connective tissue and mucous glands (Fig. 10-86). Squamous metaplasia of the excretory ducts is usually seen, and an inflammatory exudate may be noted within the duct lumina. In cases with papular

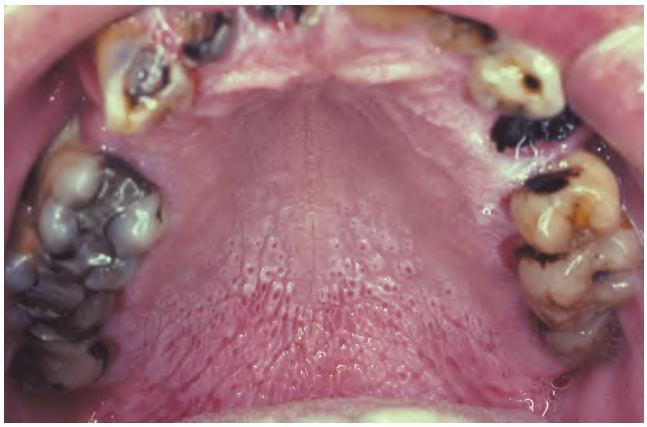


Fig. 10-84 Nicotine Stomatitis. This extensive leathery, white change of the hard palate in a pipe smoker is sprinkled throughout with numerous red papules, which represent inflamed salivary duct openings. The gingival mucosa also is keratotic.

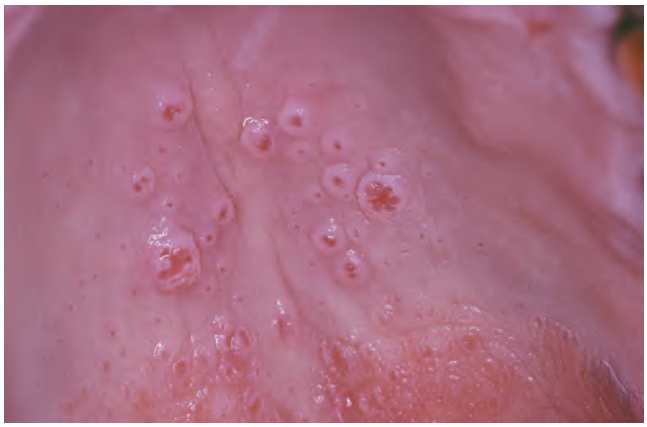


Fig. 10-85 Nicotine Stomatitis. Close-up of the inflamed ductal openings of involved salivary glands of the hard palate. Note the white keratotic ring at the lip of many of the inflamed ducts.

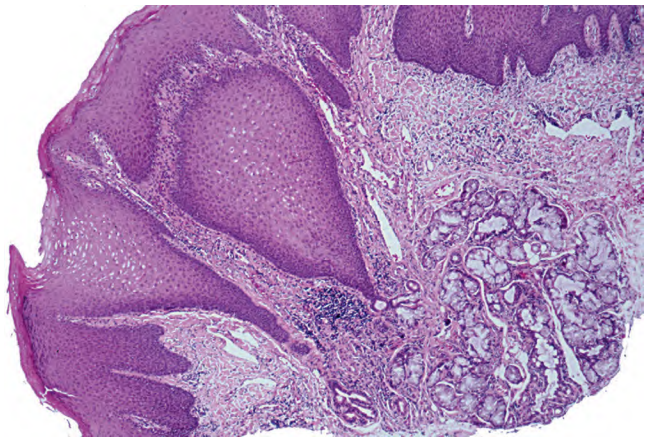


Fig. 10-86 Nicotine Stomatitis. There is hyperkeratosis and acanthosis of the palatal epithelium. Note the squamous metaplasia of the minor salivary gland ducts.

elevation, hyperplastic ductal epithelium may be seen near the orifice. The degree of epithelial hyperplasia and hyperkeratosis appears to correlate positively with the duration and the level of heat exposure. Epithelial dysplasia rarely is seen.

Treatment and Prognosis

Nicotine stomatitis is completely reversible, even when it has been present for many decades. The palate usually returns to normal within 1 to 2 weeks of smoking cessation. Although this lesion is not precancerous and does not require treatment, the patient nevertheless should be encouraged to stop smoking (and other high-risk areas should be examined closely). Any white lesion of the palatal mucosa that persists after 1 month of habit cessation should be considered a true leukoplakia and managed accordingly (see page 362).

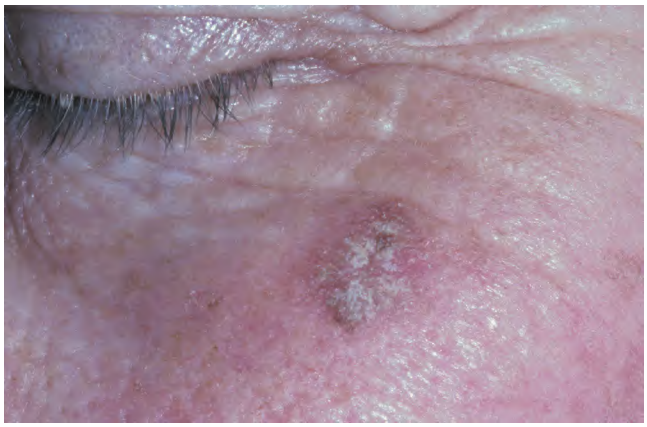
◆ ACTINIC KERATOSIS (SOLAR KERATOSIS)

Actinic keratosis is a common, cutaneous premalignant lesion that is caused by chronic, high-level exposure to UV radiation. A similar phenomenon, **actinic cheilosis,** is associated with sun damage to the lower lip vermilion (see page 370). UV light exposure can produce mutations in various genes, such as the tumor suppressor gene *TP53.* Additional risk factors for actinic keratosis include fair skin, old age, immunosuppression, arsenic exposure, and certain genetic abnormalities (e.g., albinism, Rothmund-Thompson syndrome, Cockayne syndrome, xeroderma pigmentosum [see page 696], and Bloom syndrome). Furthermore, recent studies suggest that HPV infection may be a cofactor in some cases, especially those arising in immunosuppressed individuals.

Actinic keratosis affects more than 50% of white adults with significant lifetime sun exposure. In the United States, reported prevalence rates range from 14% to 27% for men and 6% to 10% for women. According to the National Ambulatory Medical Care Survey, more than 47 million physician office visits were conducted in the United States over a 10-year period for the diagnosis of actinic keratosis. Another study reported that actinic keratosis accounts for more than 5 million physician office visits per year in the United States.

Clinical Features

Actinic keratosis seldom occurs in persons younger than 40 years. Common sites of involvement include the face, neck, dorsum of the hands, forearms, and balding scalp. The lesions most often occur in clusters (apparently due to UV-induced *field cancerization* [see page 389]), although solitary lesions also are possible. The lesions appear as irregular, scaly plaques, which range in color from normal to white, gray, or brown, and may be superimposed on an



• **Fig. 10-87 Actinic Keratosis.** A plaque of the skin of the face with a rough, sandpaper-like surface.

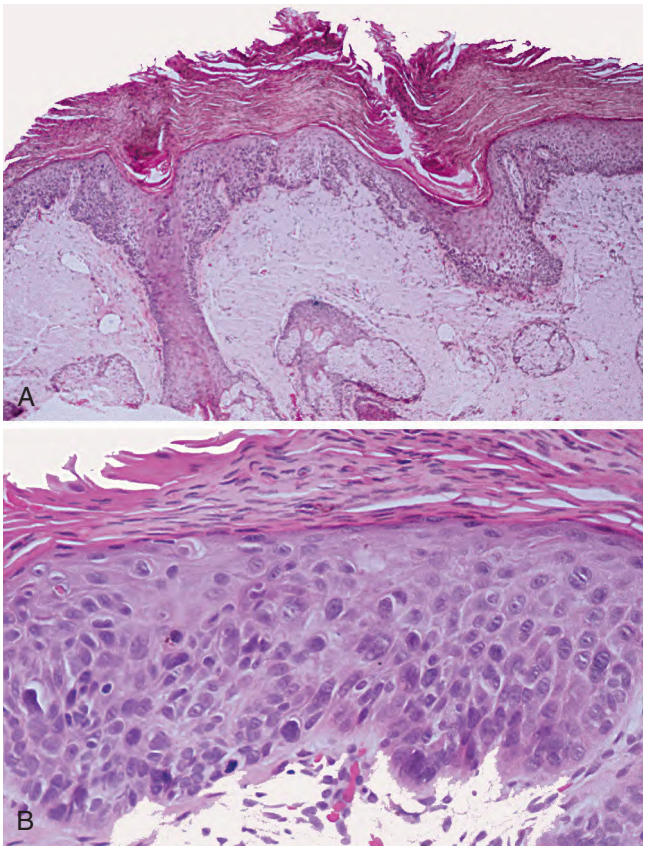
erythematous background (Fig. 10-87). The keratotic scale peels off with varying degrees of difficulty. Palpation reveals a rough, "sandpaper-like" texture, and some lesions can be felt more easily than they can be seen. Each lesion typically is smaller than 7 mm in diameter, but some lesions may reach a size of 2 cm or more. Most lesions are minimally elevated above the skin surface, although occasional lesions produce so much keratin that a central "horn" may be evident. Other skin lesions, such as verruca vulgaris or seborrheic keratosis, also may produce **keratin** or **cutaneous horns.**

Histopathologic Features

Histopathologically, actinic keratosis is characterized by hyperparakeratosis and acanthosis (Fig. 10-88). The epithelium often exhibits teardrop-shaped rete ridges, and by definition, some degree of epithelial dysplasia is present. When full-thickness dysplasia is noted, this is termed **bowenoid actinic keratosis.** Suprabasilar acantholysis may be seen, as well as melanosis and a lichenoid inflammatory infiltrate. The dermis exhibits a pale, basophilic band of sun-damaged collagen and elastic fibers **(solar elastosis).** In this band of sun-damaged connective tissue, there is a fourfold increase in the amount of elastic fibers, and band thickness increases with further exposure to actinic rays. Variable numbers of chronic inflammatory cells are typically present.

Treatment and Prognosis

Preventive measures include avoiding sun exposure, wearing protective clothing, and using sunscreen. Because of its precancerous nature, actinic keratosis should be treated. For solitary lesions, the most common treatment is cryotherapy; additional treatment options include curettage, electrodesiccation, and surgical excision. In contrast, multifocal lesions or sun-damaged skin fields at risk for lesion development may be treated with topical agents (e.g., 5-fluorouracil, imiquimod, diclofenac, tretinoin, and ingenol mebutate), chemical peels, laser therapy, or photodynamic therapy.



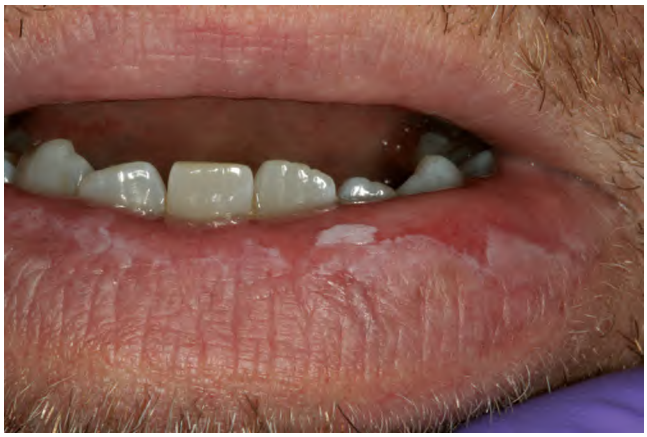
• **Fig. 10-88 Actinic Keratosis. A,** An extremely excessive amount of parakeratin is noted on the epidermal surface. **B,** High-power view showing hyperchromatism and pleomorphism of the epidermal cells.

Alternatively, cryotherapy may be combined with broader application of topical agents. Recurrence is rare, but additional lesions frequently arise in adjacent sun-damaged skin. Long-term follow-up, therefore, is recommended.

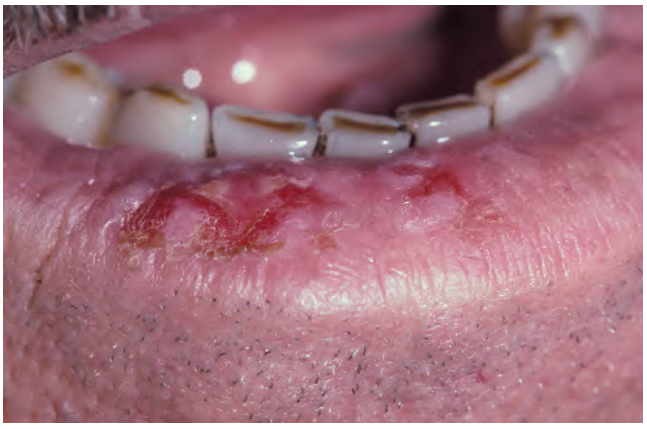
The estimated malignant transformation rate for an individual lesion varies considerably (0.025% to 16% per year) but generally is considered low. However, the risk increases significantly for a patient with a large number of lesions over an extended period. The average person initially presents to a dermatologist with six to eight actinic keratoses; a person with this many lesions is estimated to have a 6% to 10% risk of progression to squamous cell carcinoma over a 10-year period. Longitudinal studies suggest that malignancy most often develops within 2 years, and spontaneous regression may occur in up to 26% of cases within 12 months of reduced sun exposure.

◆ ACTINIC CHEILOSIS (ACTINIC CHEILITIS; SOLAR CHEILOSIS)

Actinic cheilosis is a common premalignant alteration of the lower lip vermilion that results from chronic UV light exposure. Its etiopathogenesis is similar to that of **actinic keratosis** of the skin (see previous topic). The incidence of



• **Fig. 10-89 Actinic Cheilosis.** Diffuse, irregular white plaque at the wet line of the lower lip vermilion.



• **Fig. 10-90 Actinic Cheilosis.** Crusted and ulcerated lesions of the lower lip vermilion.

actinic cheilosis increases with proximity to the equator, and there is a predilection among middle-aged to elderly, fair-complexioned men. Outdoor occupations are associated with this condition, leading to popular terms, such as *farmer's lip* and *sailor's lip.* In addition, there is increased susceptibility among patients with certain genetic disorders (e.g., xeroderma pigmentosum, albinism, and porphyria cutanea tarda). Furthermore, cofactors—such as immunosuppression and tobacco smoking—may increase the likelihood of progression to squamous cell carcinoma.

Clinical Features

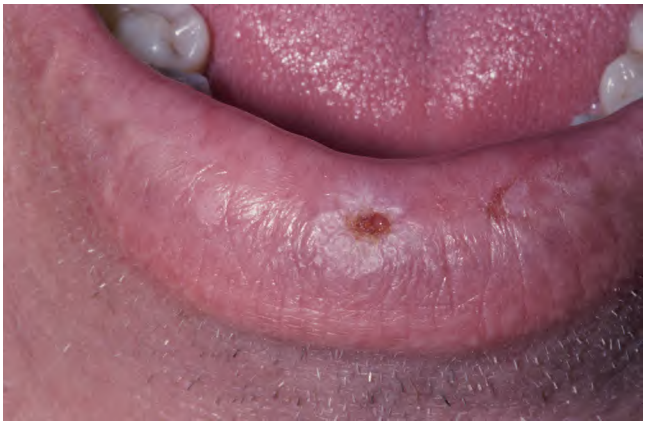
Actinic cheilosis seldom occurs in persons younger than 45 years. There is a strong male predilection (reported male-to-female ratio as high as 10:1), which may reflect more outdoor occupational activity and less frequent use of lip protective agents among men compared to women.

The lesion develops so slowly that patients often are unaware of a change. Early clinical findings include atrophy (characterized by smooth, blotchy, pale areas), dryness, and fissures of the lower lip vermilion, with blurring of the margin between the vermilion and the adjacent skin. As the lesion progresses, rough, scaly areas develop on the drier portions of the vermilion. These areas may thicken to form leukoplakic lesions, especially when they extend near the wet line of the lip (Fig. 10-89). The patient may peel off the scale with some difficulty, only to see it reform within a few days.

Eventually, chronic ulceration may develop (Fig. 10-90). Such ulcerations may last for months and suggest progression to squamous cell carcinoma (Fig. 10-91).

Histopathologic Features

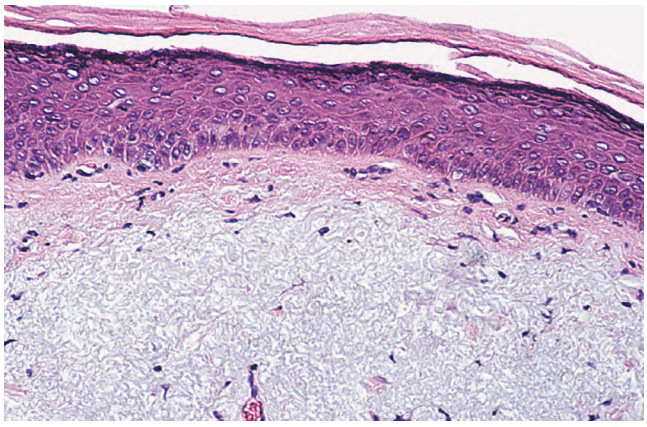
The surface epithelium exhibits varying degrees of dysplasia. There is usually hyperkeratosis, and the epithelium may be either atrophic or acanthotic. The underlying connective tissue invariably demonstrates a band of amorphous, acellular, basophilic change known as **solar elastosis**, an UV light–induced alteration of collagen and elastic fibers (Fig. 10-92). A chronic inflammatory cell infiltrate and dilated blood vessels may be present as well.



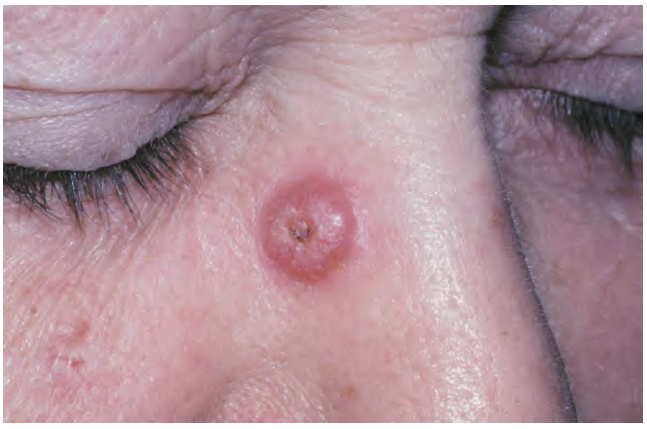
• **Fig. 10-91 Squamous Cell Carcinoma Arising in Actinic Cheilosis.** Patient with actinic cheilosis of the lower lip, who developed a small, chronic ulceration. Biopsy revealed early invasive squamous cell carcinoma.

Treatment and Prognosis

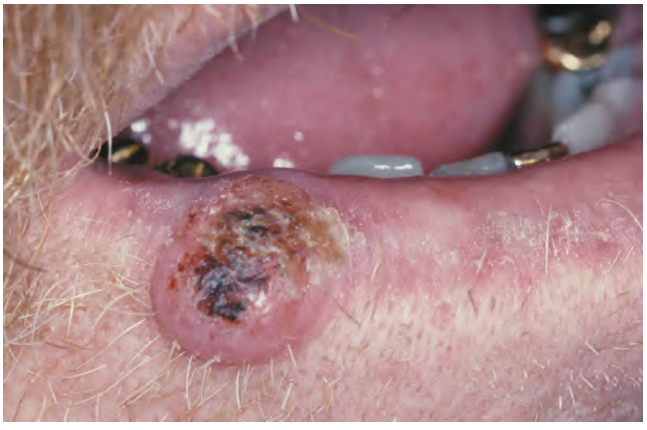
Many of the changes associated with actinic cheilosis are probably irreversible, but patients should be encouraged to reduce sun exposure, wear a wide-brimmed hat, and use sunscreen to prevent further damage. Areas of induration, thickening, ulceration, or leukoplakia should be submitted for biopsy to rule out carcinoma. In clinically severe cases without obvious malignant transformation, a lip shave procedure **(vermilionectomy)** may be performed. The vermilion mucosa is removed, and either a portion of the intraoral labial mucosa is pulled forward or the wound is allowed to heal by secondary intention. The advantage of this technique is that it provides tissue for histopathologic examination should areas of superficially invasive squamous cell carcinoma be present. Alternative treatments include CO_2 or erbium:YAG (Er:YAG) laser ablation, electrodesiccation,



• **Fig. 10-92 Actinic Cheilosis.** Hyperorthokeratosis and epithelial atrophy. Note the striking underlying solar elastosis.



• **Fig. 10-93 Keratoacanthoma.** A nontender, well-demarcated nodule of the skin of the nose in an older woman. The nodule demonstrates a central keratin plug.



• **Fig. 10-94 Keratoacanthoma.** This lesion, which is located at the outer edge of the vermilion border of the lip, demonstrates a prominent core or plug of keratin.

cryotherapy, 5-fluorouracil, topical imiquimod, and photodynamic therapy. Long-term follow-up is recommended. Of course, if a squamous cell carcinoma is identified, then the involved lip is treated accordingly.

Actinic cheilosis more than doubles an individual's risk for developing squamous cell carcinoma of the lip. Also, the risk of malignant transformation is approximately 2.5 times greater for actinic cheilosis compared to actinic keratosis. However, it typically takes several decades for actinic cheilosis to transform into squamous cell carcinoma, and the resulting carcinoma usually is histopathologically well differentiated. Metastasis, if it occurs, is generally a late event.

◆ KERATOACANTHOMA ("SELF-HEALING" CARCINOMA; PSEUDOCARCINOMA; KERATOCARCINOMA; SQUAMOUS CELL CARCINOMA, KERATOACANTHOMA TYPE)

Keratoacanthoma is a self-limiting, epithelial proliferation with a strong clinical and histopathologic similarity to well-differentiated **squamous cell carcinoma.** Indeed, many dermatopathologists consider it to represent an extremely well-differentiated squamous cell carcinoma. Cutaneous lesions presumably arise from the infundibulum of hair follicles. Intraoral lesions have been reported, but they are rare; in fact, some authorities do not accept keratoacanthoma as an intraoral disease.

The exact cause is unknown. An association with sun damage is suggested by the fact that most solitary lesions are found on sun-exposed skin in older adults. Additional potential contributing factors include tar exposure, HPV, immunosuppression, certain drugs (such as, *BRAF* inhibitors and tyrosine kinase inhibitors), tattooing, and burns or other trauma. Keratoacanthoma-like lesions have been produced in animals by the cutaneous application of carcinogens.

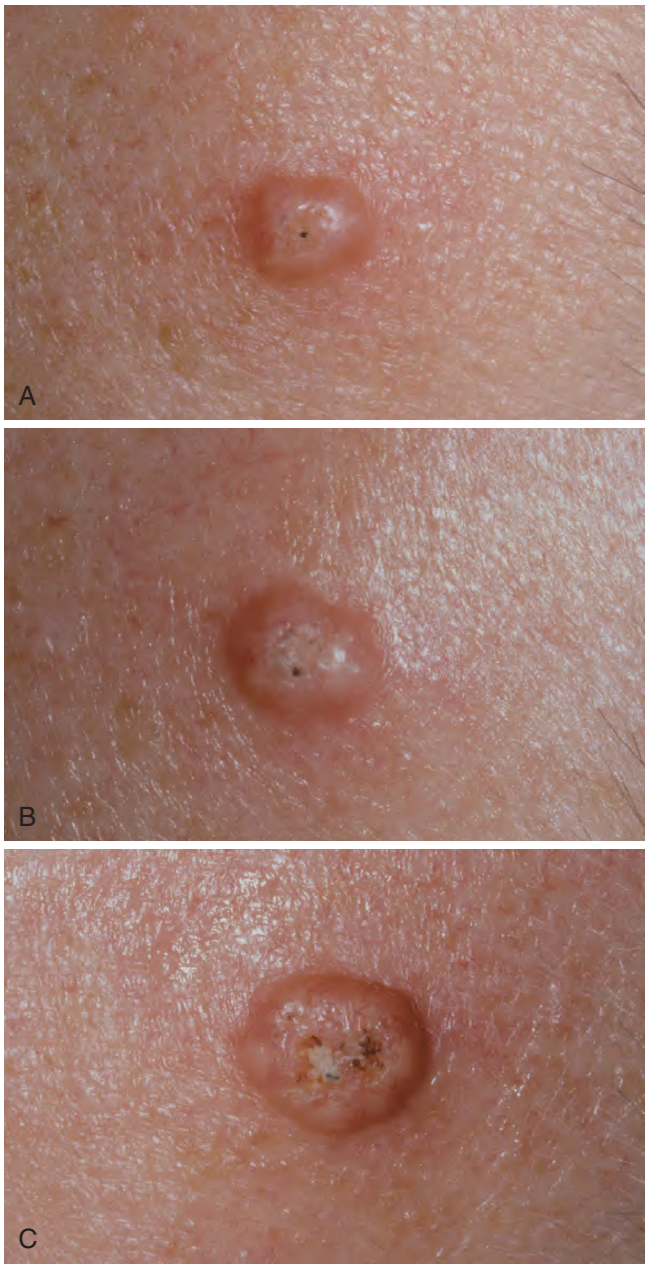
There appears to be a hereditary predisposition for multiple lesions, and the lesions occur with increased frequency in certain heritable conditions attributed to defects in DNA repair, including **Muir-Torre syndrome** (sebaceous neoplasms, keratoacanthomas, and gastrointestinal carcinomas) and **xeroderma pigmentosum** (see page 696).

Comparative genomic hybridization has shown that keratoacanthomas and squamous cell carcinomas typically exhibit distinct genetic profiles, which suggest different underlying pathogenetic mechanisms.

Clinical Features

Keratoacanthoma shows a male predilection and rarely occurs before 45 years of age. Almost 95% of solitary lesions involve sun-exposed skin, and 8% of all cases involve the outer edge of the vermilion border of the lips, with equal frequency on the upper and lower lips.

Keratoacanthoma appears as a firm, well-demarcated, sessile, dome-shaped nodule with a central plug of keratin (Figs. 10-93 and 10-94), although lesions reported as intraoral keratoacanthoma usually have lacked a central plug. The outer portion of the nodule typically has a normal texture and color but may be erythematous. The central



• **Fig. 10-95 Keratoacanthoma. A,** Appearance on initial presentation. Note small, central keratin-filled invagination. **B,** Same lesion 1 week later showing slight enlargement. **C,** Same lesion showing further growth 3 weeks after initial presentation. All three photographs were taken at the same magnification. (Courtesy of Dr. John Lovas.)

keratin plug is yellowish, brown, or black and has an irregular, crusted, often verruciform surface. Most lesions are asymptomatic, although pruritus and mild tenderness are possible.

The evolution of keratoacanthoma can be divided into three phases: 1) growth phase, 2) stationary phase, and 3) involution phase. During the growth phase, rapid enlargement is typical, with the lesion usually attaining a diameter of 1 to 2 cm within 6 weeks (Fig. 10-95). This critical feature helps to distinguish it from the more slowly enlarging squamous cell carcinoma. The lesion stabilizes during the stationary phase, which usually is of similar duration as the growth phase. Most lesions regress spontaneously within 6 to 12 months of onset, frequently leaving behind a depressed scar. The regression of keratoacanthomas is a curious phenomenon, which some investigators have theorized is related to a cytotoxic immune response to the tumor or mechanisms similar to those controlling normal cycling of hair follicles. Some authors also have described a subset of lesions (termed *abortive keratoacanthoma*) that involute after only 4 to 6 weeks.

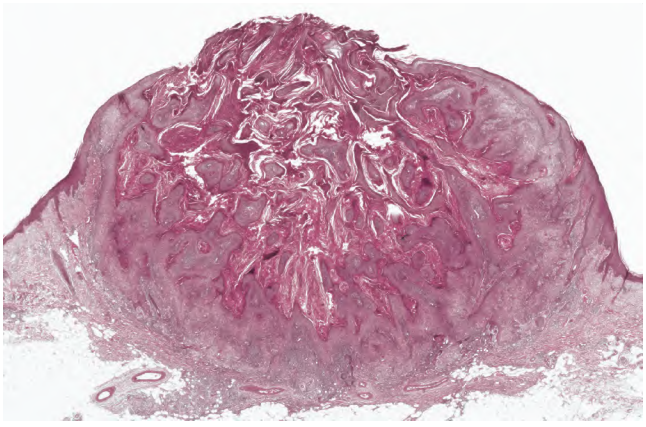
Several other variants exist, including *giant keratoacanthoma* (greater than 2 to 3 cm in diameter), *keratoacanthoma centrifugum marginatum* (characterized by continuous peripheral growth and central scarring), *subungual keratoacanthoma* (involving the nail bed), and *mucosal keratoacanthoma* (involving the oral, nasal, genital, ocular, or other regions). These variants often do not regress.

In addition, early onset of multiple keratoacanthomas has been described in association with two rare, heritable conditions: **Ferguson-Smith syndrome** and **Witten-Zak syndrome**. The former is characterized by nodular lesions and primarily affects patients of Scottish descent; the latter typically exhibits a mixture of variably sized lesions. In contrast, **Grzybowski syndrome** manifests later in life as hundreds or thousands of small papules of the skin and upper digestive tract and may be associated with internal malignancy.

Histopathologic Features

Because the overall architectural pattern is crucial for the diagnosis of keratoacanthoma, excisional or large incisional biopsy with inclusion of adjacent, clinically normal epithelium is necessary for proper histopathologic interpretation. The tumor cells appear mature, although considerable dyskeratosis (abnormal keratin production) typically is seen in the form of deeply located individually keratinizing cells and keratin pearls similar to those found in well-differentiated squamous cell carcinoma.

The surface epithelium at the edge of the tumor appears normal; at the lip of the central crater, however, a characteristic acute angle (or "buttress") is formed between the overlying epithelium and the lesion. The crater is filled with keratin, and the epithelium at the base of the crater proliferates downward (Fig. 10-96), often with a pronounced chronic inflammatory cell response. Downward proliferation typically does not extend below the sweat glands in skin lesions or into underlying muscle in vermilion lesions. Late-stage lesions show considerably more keratinization in the deeper aspects of the tumor than do early lesions. Perineural and vascular invasion have been reported rarely; although worrisome, such features do not necessarily indicate a worse prognosis. Migration of eosinophils or neutrophils into the epithelium with resultant microabscess formation is a frequent finding. Regressing lesions tend to flatten, hollow out, and exhibit an underlying band of fibrosis.



• **Fig. 10-96 Keratoacanthoma.** Low-power microscopic view showing extensive epidermal proliferation with a central keratin plug.

Numerous immunohistochemical studies comparing keratoacanthoma and squamous cell carcinoma have been reported, but no reliable marker for discernment between these two lesions has been identified

Treatment and Prognosis

Because of the difficulty in clinically and histopathologically distinguishing between keratoacanthoma and squamous cell carcinoma, many authorities advocate excision without waiting for spontaneous regression. Also, early treatment may prevent significant scarring. Approximately 4% to 8% of lesions recur after excision. Although conventional surgical excision is preferred, alternative therapies include cryosurgery (reserved for small early lesions), electrodessication and curettage, Mohs micrographic surgery (especially for lesions of the central face), laser therapy, intralesional injection of chemotherapeutic agents (such as, 5-fluorouracil, bleomycin, methotrexate, or interferon alpha), and topical agents (such as, imiquimod or 5-fluorouracil). Systemic retinoids may be used alone or in combination with local treatment for patients with multiple or especially large lesions.

Aggressive behavior and transformation into carcinoma have been reported in a small proportion of keratoacanthomas—particularly those occurring in the setting of immunosuppression. However, the close histopathologic similarities between this lesion and squamous cell carcinoma sometimes make it difficult to rule out the possibility of microscopic misinterpretation.

◆ SQUAMOUS CELL CARCINOMA

In the United States, approximately one of every two men and one of every three women will develop a malignancy (other than nonmelanoma skin cancer) at some point. It is estimated that in the United States in 2013, more than 1.6 million new cancer cases will be diagnosed, in addition to around 3.5 million nonmelanoma skin cancers. Although the relative 5-year cancer survival rate is approximately 68%, cancer still causes more than 580,000 deaths each year in the United States and accounts for more than 20% of all deaths. From 1930 to 1991, the annual cancer death rate (excluding nonmelanoma skin cancer) increased and reached a peak of 215 per 100,000 population. This trend reflected an increase in the incidence of lung cancer as well as a decrease in mortality at an early age from other common disorders, such as cardiovascular disease and infection. Since 1991, however, the annual cancer death rate has declined to about 173 per 100,000 population. In part, this decline is related to a decrease in tobacco use and lung cancer deaths; in addition, improvements in detection and treatment have resulted in declines in breast, colorectal, and prostate cancer deaths.

Squamous cell carcinoma accounts for more than 90% of oral malignancies**.** Statistics for oral cancer can be difficult to review, because cancer registries and investigators often report oral and pharyngeal cancers in aggregate. Also, a distinction between intraoral and lip vermilion cancers is not always made. With that said, in the United States oral cancer accounts for less than 2% of all cancers (excluding nonmelanoma skin cancers and *in situ* carcinomas for all sites but urinary bladder). It represents the eleventh most common cancer in males and the sixteenth most common in females. Around 27,000 new cases of oral cancer are diagnosed annually, and approximately 5,500 individuals die of this disease each year.

The risk for oral and pharyngeal cancer increases with age, especially among males. In the United States, according to the Surveillance, Epidemiology, and End Results (SEER) Program, the age-adjusted incidence rate for oral and pharyngeal cancer from 2005 to 2009 was 60 per 100,000 for males aged 65 years and older, compared to 10 per 100,000 for males younger than 65 years. Among those 65 years and older, the incidence was somewhat higher for white males (62 per 100,000) than black males (52 per 100,000), whereas similar incidence rates were seen for black and white males under 65 years. Notably, there was a marked disparity in age-adjusted mortality rates between black and white males (5.7 versus 3.6 per 100,000, respectively) with oral and pharyngeal cancer. This disparity traditionally has been explained by socioeconomic factors and differences in access to quality health care. However, recent studies suggest that patient outcomes actually are similar between races for oral and other non-oropharyngeal head and neck cancers; instead much of this disparity may be due to racial differences in oropharyngeal cancers. Specifically, white patients are more likely to have HPV-positive oropharyngeal tumors compared to black patients, and these HPV-positive tumors are associated with a better response to treatment and prolonged survival. It is unknown why racial differences exist in the prevalence of HPV-positive oropharyngeal carcinomas, although some investigators have hypothesized that differences in behavior, oral HPV acquisition rates, and/or viral clearance may play a role.

In the United States, females overall have a much lower incidence of oral and pharyngeal cancer than males, with a male-to-female ratio of approximately 2.5:1. However,

among young adults and pediatric patients, recently reported incidence rates for oral and pharyngeal cancers in females have been similar or even slightly higher than that in males. Interestingly, over the past several decades, a significant increase in the incidence of oral tongue cancer has been noted among young individuals, especially white women aged 18 to 44 years. The underlying cause for this trend is uncertain. Such cases often are not associated with the traditional risk factors of tobacco and alcohol use, and the oral tongue—unlike the base of tongue—is an infrequent site for HPV-positive carcinomas.

Carcinoma of the lip vermilion is somewhat different from intraoral carcinoma. It has a pathophysiology more akin to squamous cell carcinoma of sun-exposed skin. According to recent SEER data, the overall age-adjusted annual incidence rate for lip cancer in the United States is 0.7 per 100,000 population. However, the incidence increases with age, with annual rates among those 75 years and older of approximately 7 per 100,000 for males and 3 per 100,000 for females. White males are affected most commonly, although there has been a considerable decrease in the incidence of lip cancer in this group over the last several decades; this trend may be related to a decline in the number of white males engaged in outdoor occupations. Among women and nonwhite men, lip carcinoma is very infrequent. The low incidence among women may be related to little outdoor occupational activity and prevalent use of lip protective agents. In nonwhites, racial pigmentation may provide protection against sun exposure.

The worldwide incidence of oral cancer is approximately 263,000 cases per year, with an especially high incidence reported in the Indian subcontinent, Taiwan, Hungary, France, Brazil, and parts of southern Africa. Exceptionally wide variations in oral cancer incidence and mortality across regions likely results from differences in population habits, life expectancies, preventive education, and accuracy of disease reporting. Despite the difficulties involved in interpreting such data, these findings have been helpful in identifying potential causative factors.

Etiology of Oral Cancer

The cause of oral squamous cell carcinoma is multifactorial. No single causative agent or factor (carcinogen) has been clearly defined or accepted, but both extrinsic and intrinsic factors may be involved. It is likely that more than a single factor is needed to produce such a malignancy (cocarcinogenesis). *Extrinsic* factors include tobacco smoke, alcohol, and (for vermilion cancers only) sunlight. *Intrinsic* factors include systemic or generalized states, such as malnutrition or iron-deficiency anemia. Heredity does not appear to play a major causative role, although a few heritable conditions (e.g., dyskeratosis congenita [see page 695], Fanconi anemia) have been associated with an increased risk for oral squamous cell carcinoma. Many oral squamous cell carcinomas have been documented to be associated with or preceded by a precancerous lesion, especially **leukoplakia** (Table 10-2).

TABLE 10-2 Precancerous Lesions of the Oral, Pharyngeal, and Laryngeal Mucosa (Clinical Terms Only)

Disease Name	Malignant Transformation Potential
Proliferative verrucous leukoplakia (PVL)*	★★★★★★
Nicotine palatinus in reverse smokers†	★★★★★
Erythroplakia	★★★★★
Oral submucous fibrosis	★★★★★
Erythroleukoplakia	★★★★
Granular leukoplakia	★★★★
Laryngeal keratosis	★★★
Actinic cheilosis	★★★
Smooth, thick leukoplakia	★★
Smooth, red tongue of Plummer-Vinson syndrome	★★
Smokeless tobacco keratosis	★
Lichen planus (erosive forms)‡	★?
Smooth, thin leukoplakia	+/–

From Speight PM, Farthing PM, Bouquot JE: The pathology of oral cancer and precancer, *Curr Diag Pathol* 3:165-176, 1997.
*PVL: High-risk, high-recurrence form of oral leukoplakia affecting multiple sites.
†Reverse smoking: Smoking with the lit end of the cigarette in one's mouth.
‡Precancer character is controversial.

Tobacco Smoking

Tobacco smoking reached its greatest popularity in the United States during the 1940s, when at least 65% of white men smoked and other population subgroups were beginning to smoke in large numbers. Today less than 20% of US adults, men and women alike, smoke cigarettes. Although an overall decrease in smoking prevalence has been observed over the past decade, intensive efforts will be required to meet the US Department of Health and Human Services' Healthy People objective to reduce smoking prevalence by the year 2020 to 12% or less.

Tobacco smoke contains more than 70 carcinogens, including nitrosamines, arsenic, benzo[a]pyrene, and benzene. In addition, smoking produces free radicals and oxidants that promote the destruction and counteract the protective effects of endogenous antioxidants (such as, glutathione-S-transferase, glutathione reductase, and superoxide dismutase).

Much indirect clinical evidence implicates tobacco smoking in the development of oral squamous cell carcinoma. The proportion of smokers (80%) among patients with oral carcinoma is about four times greater than that

among the general population. For patients who quit smoking, the risk for developing oral cancer declines over time; approximately 10 years after cessation, the incidence of oral cancer approaches that of individuals who have never smoked. The risk for a second primary carcinoma of the upper aerodigestive tract is two to six times greater for treated patients with oral cancer who continue to smoke than for those who quit after diagnosis.

According to a meta-analysis of observational studies on tobacco smoking and cancer in various regions of the world, the pooled risk for oral cancer is approximately three times greater among smokers than nonsmokers. Moreover, the relative risk (smoker's risk for oral cancer compared with that of a nonsmoker) is dose-dependent. It is at least five for persons who smoke 40 cigarettes daily, but increases to as much as 17 for persons who smoke 80 or more cigarettes daily. The risk also increases the longer a person smokes. Furthermore, studies suggest that cigar or pipe smoking is associated with a similar or greater risk for oral cancer compared to cigarette smoking.

In India it is common to smoke bidi (small, hand-rolled cigarettes consisting of flaked tobacco rolled in a temburni or tendu leaf), and bidi smoking is associated with an approximately threefold greater risk of oral cancer compared to cigarette smoking. The highest risk of all probably is found in certain Indian and South American cultures in which the practice of reverse smoking is popular, especially among women. In reverse smoking, the burning end of a handmade cigar or cigarette is held inside the mouth. Where reverse smoking is practiced, as many as 50% of all oral malignancies are found on the hard palate, a site usually spared by this disease.

Smokeless Tobacco

Smokeless tobacco use in Western cultures may increase a chronic user's risk for oral carcinoma by a factor ranging from less than two to as high as 26. This variation in reported relative risk may be influenced by the type of smokeless tobacco used, with some studies suggesting a lower risk associated with moist snuff and chewing tobacco and a higher risk associated with dry snuff. This apparent increased risk is supported by clinicopathologic investigations that have found an abnormal male-to-female ratio for oral carcinoma (>1.0:1.5) in geographic areas where the habit is more popular among women than among men. These geographic areas are typically in the southeastern United States, where women use dry snuff. In addition, approximately 50% of all oral cancers in smokeless tobacco users occur at the site where the tobacco is habitually placed.

Betel Quid (Paan)

Betel quid (or *paan*) is a combination of natural substances (i.e., areca palm nuts, betel leaf, slaked lime, and perhaps tobacco leaf) chewed for their psychostimulating effects. The carcinogenicity of betel quid traditionally has been attributed to tobacco, although areca nut alone also appears to be carcinogenic. In addition, commercially freeze-dried betel quid substitutes (e.g., *pan masala* and *gutkha*) packaged in convenient sachets have become increasingly popular. Among betel quid users in Asia, the lifetime risk of developing oral cancer is a remarkable 8%. This habit also is associated with development of precancers, such as leukoplakia. As many as 600 million persons worldwide chew these quids on a regular basis.

Alcohol

It is well established that alcohol in combination with tobacco is a significant risk factor for oral cancer development, with a reported relative risk of 15 or more among heavy users of both substances. Furthermore, even after controlling for tobacco use, epidemiologic studies have reported a twofold to fourteenfold increased risk for oral cancer among heavy drinkers (often defined as individuals who consume more than four alcoholic beverages or 60 g of alcohol per day). The risk generally appears to be dose-dependent and time-dependent, although a few studies have suggested that light or moderate drinking may exhibit a protective effect, especially among females. Nevertheless, the lowest annual oral cancer incidence rate in the United States is found in Utah, where 75% of the population follows Mormon doctrines that forbid tobacco and alcohol use.

Indirect evidence for alcohol's role in oral cancer development includes the fact that approximately one-third of male patients with oral cancer are heavy alcohol users, whereas less than 10% of the general population can be classified as such. Likewise, cirrhosis of the liver is found in at least 20% of male patients with oral cancer.

The exact role of alcohol in oral carcinogenesis is not well understood, although several mechanisms have been proposed. Ethanol in alcoholic beverages is metabolized into acetaldehyde, which is a known carcinogen. In addition, carcinogenic impurities—such as, polycyclic aromatic hydrocarbons and nitrosamines—may be present in some alcoholic beverages. Moreover, alcohol may help solubilize other carcinogenic compounds and may increase the permeability of oral epithelium to these compounds. Nutritional deficiencies associated with heavy alcohol consumption also may be a contributory factor.

There is much debate in the literature regarding the potential for alcohol-containing mouthwashes to increase the risk for oral cancer. High-quality epidemiologic studies are limited, and inconsistent findings across studies have failed to establish a definite link.

Occupational Exposures and Environmental Pollutants

Some studies have reported an increased oral cancer risk for workers in the wood products industry chronically exposed to certain chemicals, such as phenoxyacetic acids. Such workers also are at increased risk for nasal and nasopharyngeal carcinoma. In addition, there is limited and inconsistent evidence for elevated oral cancer risk among metal workers, electrical workers, plumbers, machinists, painters,

and other individuals with occupational exposure to solvents or metal dust.

In regions of Taiwan with a particularly high incidence of oral cancer, investigators have reported elevated levels of heavy metal pollutants (e.g., nickel, chromium, and arsenic) in farm soil and increased blood concentrations of some of these metals in affected patients.

Radiation

The effects of UV radiation on the lips are discussed elsewhere (actinic cheilosis, see page 370). Interestingly, a recent large-scale retrospective study has suggested that certain antihypertensive medications (e.g., hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine) may act as photosensitizers and may potentiate the development of UV-induced lip cancer. However, further studies are needed to confirm these findings and to establish direct causality.

In addition, it is well known that **x-irradiation** decreases immune reactivity and produces chromosomal abnormalities. Indeed, radiotherapy to the head and neck area increases the risk for later development of a new primary oral malignancy, either a carcinoma or sarcoma. This effect is dose-dependent, but even low-dose radiotherapy for benign entities may increase the local risk somewhat. Although there has been controversy regarding whether dental radiography may pose an increased risk for developing various tumors, dental imaging has not been associated with oral carcinoma.

Vitamin/Mineral Deficiencies and Dietary Factors

Iron deficiency, especially the severe, chronic form known as the **Plummer-Vinson** or **Paterson-Kelly syndrome** (see page 772), is associated with an elevated risk for squamous cell carcinoma of the esophagus, oropharynx, and posterior mouth. Malignancies develop at an earlier age than in patients without iron deficiency anemia. Iron deficiency may cause impaired cell-mediated immunity. In addition, because the epithelium of the upper digestive tract has a relatively high turnover rate, rapid loss of iron-dependent enzymes may lead to degenerative changes, including mucosal atrophy and **esophageal webs** (intertwining fibrous bands of scar tissue), with heightened susceptibility to malignant transformation.

Vitamin-A deficiency produces excessive keratinization of the skin and mucous membranes, and researchers have suggested that this vitamin may help to prevent oral precancer and cancer. Some believe that blood levels of retinol and the amount of dietary betacarotene ingested are inversely proportional to the risk of oral squamous cell carcinoma and leukoplakia. Long-term therapy with retinoic acids and betacarotene also has been associated with regression of at least some leukoplakic lesions and a concomitant reduction in the severity of dysplasia within such lesions.

Several epidemiologic studies suggest that high intake of fruits and vegetables decreases the risk for numerous cancer types, including oral cancer. This finding may be related to the protective effects of not only vitamin A but also various other substances (e.g., vitamins C and E, folate, flavonoids, fiber, lycopene, and phytosterols) present within plant foods. However, tobacco and alcohol may represent confounding factors, because heavy tobacco and alcohol users often consume small amounts of fruits and vegetables. Also, some studies suggest that animal fats and processed or salted meat may increase the risk for oral cancer.

A few studies have reported an increased risk for oral cancer in association with drinking hot maté (an herbal tea mainly consumed in parts of South and Central America). Furthermore, there has been interest in the potential protective effects of green tea, coffee, and their associated polyphenols. However, further studies are needed to confirm and explain the carcinogenic or protective properties of such beverages.

Bacteria

The potential for microflora of the oral cavity to contribute to carcinogenesis represents a growing area of scientific investigation. Studies suggest that oral bacteria may interact with tobacco and alcohol. Ethanol is metabolized into the carcinogen acetaldehyde by not only hepatocytes and oral epithelial cells but also bacteria. In particular, high levels of acetaldehyde production have been associated with certain *Streptococcus* species, *Neisseria* species, and other bacteria; overgrowth of such bacteria has been described in smokers and heavy drinkers. In addition to bacteria, *Candida* may contribute to acetaldehyde production.

Furthermore, some investigators hypothesize that periodontal disease-causing bacteria may induce production of proinflammatory cytokines. These cytokines may enhance cell proliferation and inhibit apoptosis, thereby producing a microenvironment favorable for carcinogenesis. However, epidemiological studies of associations between poor oral hygiene, poor dental status, and oral cancer have yielded variable results. Some of this variation may be due to difficulty in controlling for confounding factors, such as tobacco use, alcohol consumption, nutrition, and socioeconomic status.

Although rarely seen today, tertiary syphilis has been associated with a fourfold increased risk for development of dorsal tongue carcinoma. This risk may be due to the carcinogenic properties of the arsenical agents and other heavy metals that were used to treat syphilis before the advent of modern antibiotic therapy.

Candida

Hyperplastic candidiasis (see page 195) frequently is cited as an oral precancerous condition. Because this lesion appears as a white plaque that cannot be rubbed off, it also has been called *candidal leukoplakia.* Unfortunately, it is difficult both clinically and histopathologically to distinguish between a true hyperplastic candidiasis and a preexisting leukoplakia with superimposed candidiasis. Experimentally, some strains of *Candida albicans* have produced hyperkeratotic lesions of the dorsal rat tongue without any other contributing factors. Other studies have

demonstrated that certain strains may produce nitrosamines (carcinogens that can activate certain proto-oncogenes) or may convert ethanol into the carcinogen acetaldehyde. However, the evidence for the promotion of oral carcinogenesis by *Candida* is largely circumstantial.

Oncogenic Viruses

Oncogenic (tumor producing) viruses may play a major role in a wide variety of cancers. Viral integration into the host's genetic material may result in abnormal cell growth and proliferation. The oncogenic viruses may immortalize the host cell, thereby facilitating malignant transformation. In the past, adenoviruses, Epstein-Barr virus (EBV), herpes simplex virus (HSV), human papillomavirus (HPV), and retroviruses (e.g., human immunodefiency virus [HIV]) all have been suggested to play a role in the development of oral carcinoma. However, HPV and HIV are the only ones still implicated. HPV is discussed here; oral squamous cell carcinoma in the setting of HIV infection is discussed in the following section on immunosuppression and also on page 252.

HPV actually is best known for its role in the development of cancers of the anogenital region (especially the uterine cervix but also the anus, vulva, vagina, and penis). In addition, over the past decade, a strong link between HPV and oropharyngeal carcinoma has been established. In contrast, only a small subset of oral carcinomas has been attributed to HPV infection.

The high-risk HPV types (see page 331) are most closely associated with dysplasia and squamous cell carcinoma. In particular, detection of HPV 16 in exfoliated oral epithelial cells is associated with a nearly fourfold increased risk for oral cancer and a more than fourteenfold increased risk for oropharyngeal cancer. Investigators have proposed that persistent oral infection with HPV 16 and other high-risk HPV types increases the risk for eventual development of oropharyngeal cancer. HPV 16 has been identified in more than 90% of HPV-positive oropharyngeal squamous cell carcinomas. Similarly, in HPV-positive oral squamous cell carcinomas, HPV 16 appears to be the most common type, although some authors have reported a greater diversity of high-risk HPV types in oral carcinomas compared to oropharyngeal carcinomas.

In the United States, based upon data from the SEER Program, investigators have estimated that from 1988 to 2004 the incidence of HPV-positive oropharyngeal cancers increased by 225% (from 0.8 to 2.6 per 100,000 population) and the incidence of HPV-negative oropharyngeal cancers decreased by 50%. If this trend were to continue, by the year 2020, the annual number of HPV-positive oropharyngeal cancers would be expected to surpass the annual number of cervical cancers. This epidemiologic shift has been hypothesized to result from an increase in oral sexual behavior and a decline in tobacco use. Significant increases in HPV-positive oropharyngeal cancer incidence also have been reported in Sweden, Australia, Canada, and other countries. In North America since the year 2000, the proportion of oropharyngeal cancers attributable to HPV infection has been estimated to be approximately 70%.

On the other hand, the proportion of oral carcinomas caused by HPV infection appears to be small. Various reviews of the literature have estimated the prevalence of HPV DNA in oral squamous cell carcinomas as determined by PCR to range from 20% to 40%; nonetheless, the presence of HPV DNA is not indicative of transcriptionally active HPV infection and cannot discriminate between biologically relevant versus bystander infection. Instead, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for detection of high-risk HPV *E6* and *E7* oncogene expression is considered the gold standard for evidence of HPV infection as a likely cause of tumor development. The primary mechanisms by which HPV is believed to contribute to carcinogenesis are linked to the products of these viral oncogenes: 1) E6 protein promotes degradation of the tumor suppressor protein p53 and 2) E7 protein leads to inactivation of the tumor suppressor protein pRb. Using qRT-PCR, one multi-center retrospective study reported that only 6% of oral squamous cell carcinomas analyzed could be attributed to HPV infection.

The characteristic risk profile for patients with HPV-positive head and neck squamous cell carcinoma differs from that for patients with HPV-negative disease. In both patient groups, there is a male predilection, although the average age is approximately 10 years younger among the HPV-positive group. Unlike HPV-negative lesions, HPV-positive lesions tend to affect individuals of higher socioeconomic status. The proportion of HPV-positive cases affecting blacks is much smaller than that affecting whites (4% versus 34%, respectively). Compared to HPV-negative cases, HPV-positive cases are more strongly associated with certain parameters of sexual behavior (e.g., increased number of lifetime sexual or oral sexual partners, early age at sexual debut). In addition, HPV-positive lesions are less likely to occur in patients with an extensive history of tobacco and alcohol history. Nevertheless, patients with HPV-positive tumors often have some history of tobacco and alcohol use, and there are conflicting reports regarding potential interactions between HPV, tobacco, and alcohol in promoting head and neck cancer development. Furthermore, studies assessing a possible association between marijuana use and HPV-positive head and neck carcinomas have yielded variable results.

Immunosuppression

Immunosuppression may play a role in the development of at least some malignancies of the upper aerodigestive tract. Without effective immunologic surveillance and attack, it is thought that malignant cells cannot be recognized and destroyed at an early stage. Persons with HIV infection and those who are undergoing immunosuppressive therapy for malignancy or organ transplantation are at increased risk for oral squamous cell carcinoma and other head and neck malignancies, especially when tobacco smoking and alcohol abuse are present.

Oncogenes and Tumor Suppressor Genes

The molecular basis of carcinogenesis involves an accumulation of mutations or epigenetic changes in two broad classes of genes: **proto-oncogenes** and **tumor suppressor genes**. Proto-oncogenes may be transformed into activated oncogenes by environmental agents (e.g., viruses, irradiation, and chemical carcinogens) or inherited changes. Activated oncogenes promote uncontrolled cell division and are involved in the initiation and progression of a wide variety of malignancies. Tumor suppressor genes, on the other hand, inhibit cell division and indirectly allow tumor production when they become inactivated or mutated. Most authorities propose that an accumulation of several genetic aberrations is necessary before the affected cell expresses a malignant phenotype.

Genetic aberrations commonly identified in oral squamous cell carcinomas include abnormalities of the *ras, myc,* and epidermal growth factor receptor (EGFR; also known as *c-erbB1*) oncogenes, and the *TP53, pRb, p16,* and *E-cadherin* tumor suppressor genes. Head and neck squamous cell carcinomas associated with tobacco and alcohol use often exhibit mutated *TP53*, pRb overexpression, and decreased p16 expression. In contrast, HPV-associated cases typically express wild-type *TP53*, low levels of pRb, and increased levels of p16.

Clinical and Radiographic Features

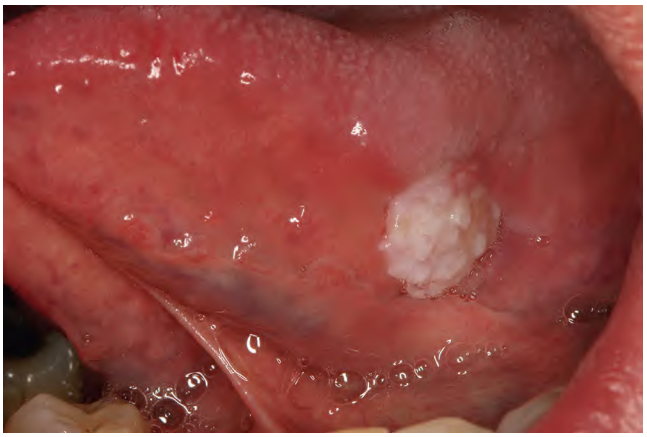
Persons with oral squamous cell carcinoma are most often older men who have been aware of an alteration for 4 to 8 months before seeking professional help (8 to 24 months among lower socioeconomic groups). There is minimal pain during the early growth phase, which may explain the delay in seeking professional care. If the health care professional does not have a high index of suspicion, then additional weeks or months may elapse before a biopsy is performed.

Oral squamous cell carcinoma has a varied clinical presentation, including the following:

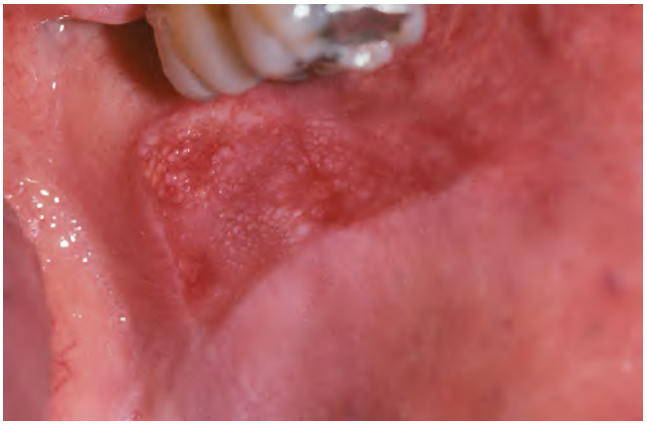
- Exophytic (mass-forming; fungating, papillary, and verruciform)
- Endophytic (invasive, burrowing, and ulcerated)
- Leukoplakic (white patch) (Fig. 10-97)
- Erythroplakic (red patch)
- Erythroleukoplakic (combined red-and-white patch) (Fig. 10-98)

The *leukoplakic* and *erythroplakic* examples are probably early cases that have not yet produced a mass or ulceration, and the clinical features are identical to those described for premalignant leukoplakia and erythroplakia (see pages 355 and 363).

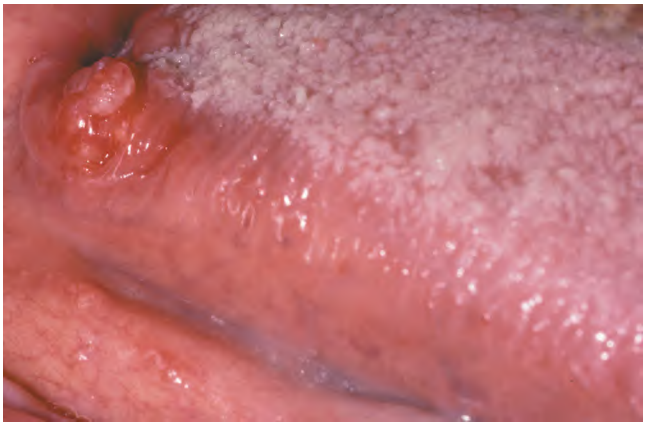
An *exophytic* lesion typically has a surface that is irregular, fungating, papillary, or verruciform, and its color may vary from normal to white or red, depending on the amount of keratin and vascularity (Figs. 10-99 and 10-100). The surface is often ulcerated, and the tumor feels hard **(indurated)** on palpation (Fig. 10-101).



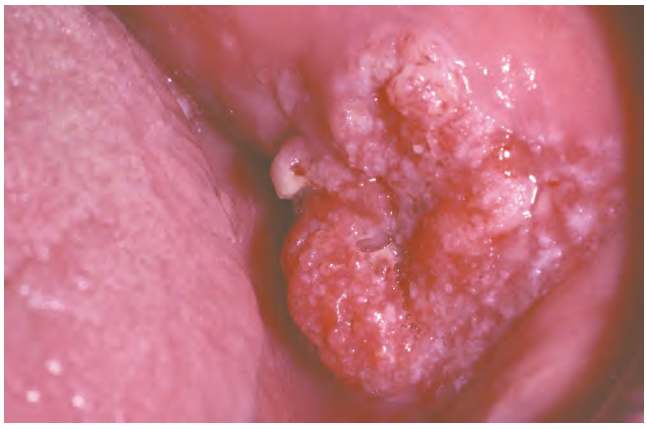
• **Fig. 10-97 Squamous Cell Carcinoma.** Leukoplakic lesion with a granular surface on the left ventrolateral tongue. (Courtesy of Dr. Larry Cunningham.)



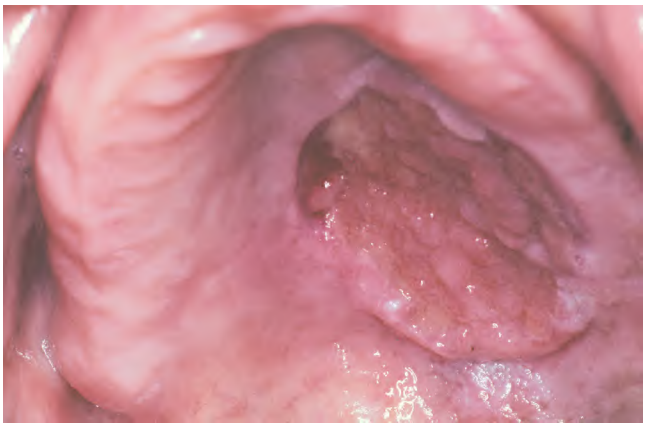
• **Fig. 10-98 Squamous Cell Carcinoma.** Speckled erythroplakia of the left posterior buccal mucosa. Brush sampling had been reported to be negative for epithelial abnormality, but incisional biopsy revealed invasive squamous cell carcinoma. (From Chi AC, Ravenel MC: AAOMP case challenge: a "speckled" lesion, *J Contemp Dent Pract* 6:168-172, 2005.)



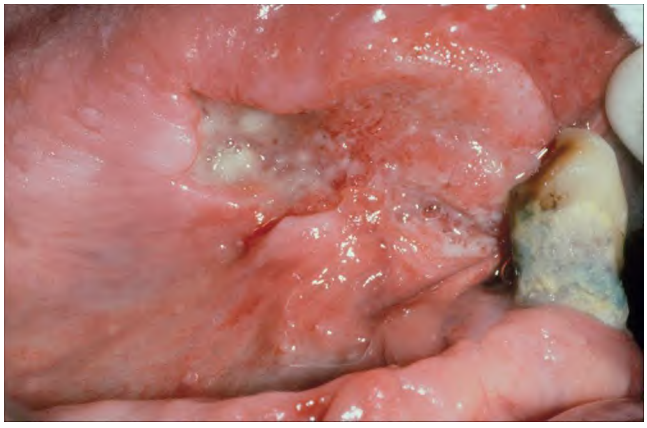
• **Fig. 10-99 Squamous Cell Carcinoma.** An exophytic lesion of the posterior lateral tongue demonstrates surface nodularity and minimal surface keratin production. It is painless and indurated.



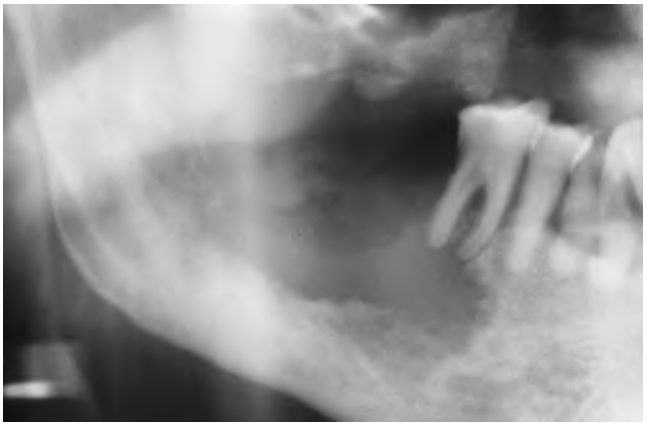
• **Fig. 10-100 Squamous Cell Carcinoma.** An exophytic buccal lesion shows a roughened and irregular surface with areas of erythema admixed with small areas of white keratosis. Surface ulceration is evident.



• **Fig. 10-102 Squamous Cell Carcinoma.** An ulcerated or endophytic lesion of the hard palate demonstrates rolled borders and a necrotic ulcer bed. This cancer was painless, although it had partially destroyed underlying palatal bone.



• **Fig. 10-101 Squamous Cell Carcinoma.** Chronic ulcerated lesion on the right ventral surface of the tongue. The rolled anterior margin felt indurated on palpation.



• **Fig. 10-103 Squamous Cell Carcinoma.** Bone involvement is characterized by an irregular, "moth-eaten" radiolucency with ragged margins—an appearance similar to that of osteomyelitis.

The *endophytic* growth pattern has a central, depressed, irregularly shaped ulcer with a surrounding "rolled" border of pink, red, or white mucosa (Fig. 10-102). The rolled border results from invasion of the tumor downward and laterally under adjacent epithelium. Traumatic granulomas, deep fungal infections, tuberculosis, tertiary syphilis, and oral lesions of Wegener granulomatosis or Crohn's disease may exhibit a similar clinical appearance.

Destruction of underlying bone, when present, may be painful or completely painless; it appears on radiographs as a "moth-eaten" radiolucency with ill-defined or ragged margins (an appearance similar to osteomyelitis) (Fig. 10-103). Perineural invasion may cause paresthesia.

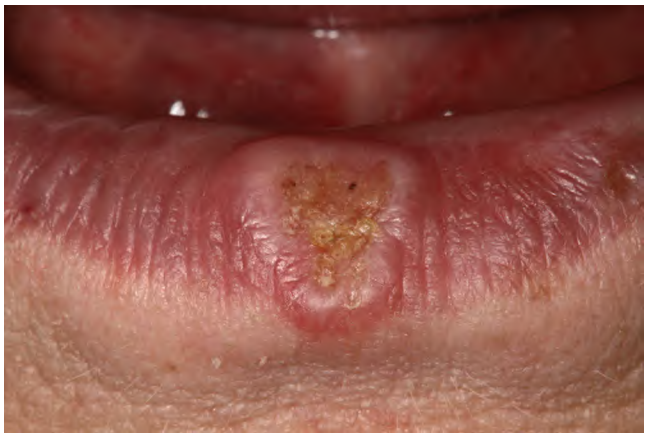
Lip Vermilion Carcinoma

Carcinoma of the lip vermilion typically is found in light-skinned persons with chronic exposure to UV radiation from sunlight. Seventy percent of affected individuals have outdoor occupations. It usually is associated with **actinic cheilosis** (see page 370) and may arise at the site where the patient holds a cigarette, cigar, or pipe. Almost 90% of lesions are located on the lower lip.

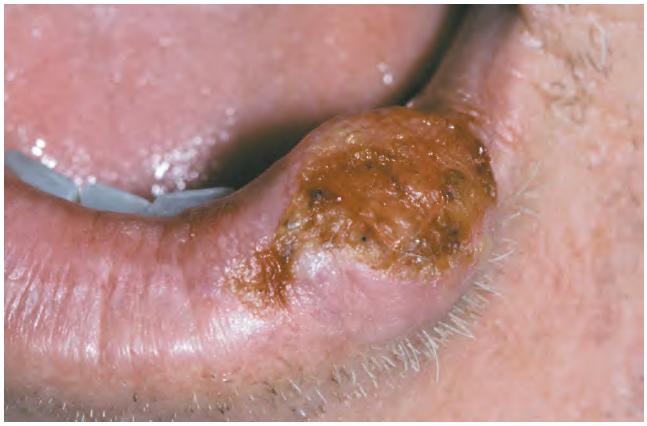
The typical vermilion carcinoma is a crusted, oozing, nontender, indurated ulceration that is usually less than 1 cm in greatest diameter when discovered (Figs. 10-104 and 10-105). The tumor usually grows slowly, and most patients are aware of a "problem" in the area for 12 to 16 months before diagnosis. Metastasis is a late event; at diagnosis, fewer than 10% of patients have lymph node metastasis, usually in the submental region. Perineural invasion may result in extension of the tumor into the mandible through the mental foramen. Although this tumor typically is diagnosed and treated at an early stage, patient neglect can result in considerable destruction of normal tissue (Fig. 10-106).

Intraoral Carcinoma

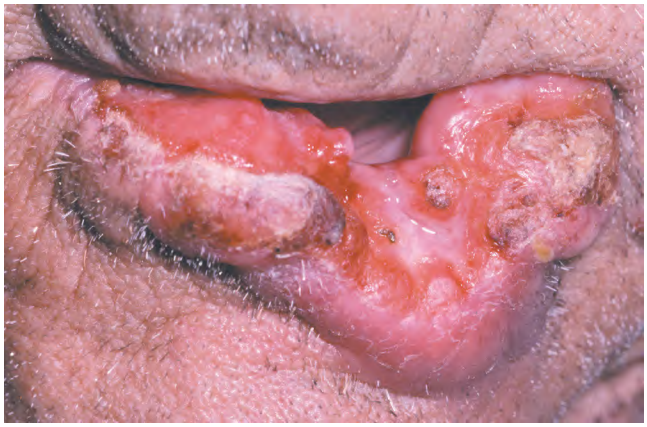
In the United States, the most common sites for intraoral carcinoma are the tongue (usually the posterior lateral and ventral surfaces) and floor of mouth. Other sites of



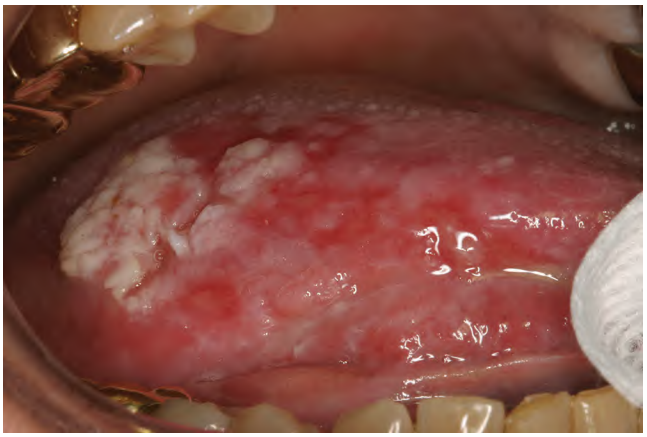
• **Fig. 10-104 Squamous Cell Carcinoma.** Crusted, ulcerated nodule of the lower lip vermilion. Risk factors in this patient included chronic sun exposure as well as immunosuppression due to bone marrow transplantation.



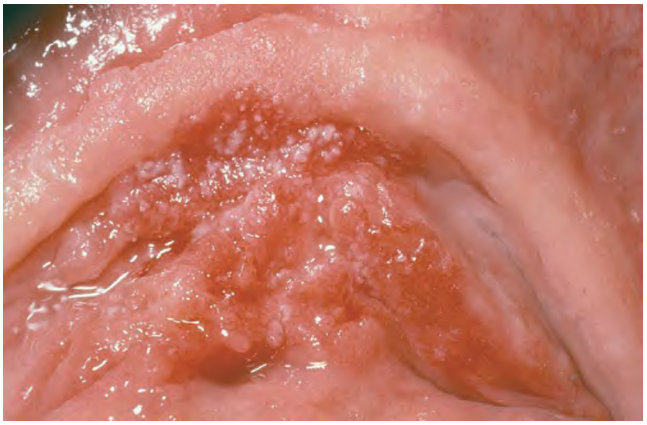
• **Fig. 10-105 Squamous Cell Carcinoma.** Ulcerated mass of the lower lip vermilion.



• **Fig. 10-106 Squamous Cell Carcinoma.** Patient neglect can result in extensive involvement, even in a readily visible site such as the lip vermilion. This ulcerating lesion of the lower lip had been present for more than 1 year before diagnosis.



• **Fig. 10-107 Squamous Cell Carcinoma.** Diffuse, red and white lesion of the posterior lateral border of the tongue.



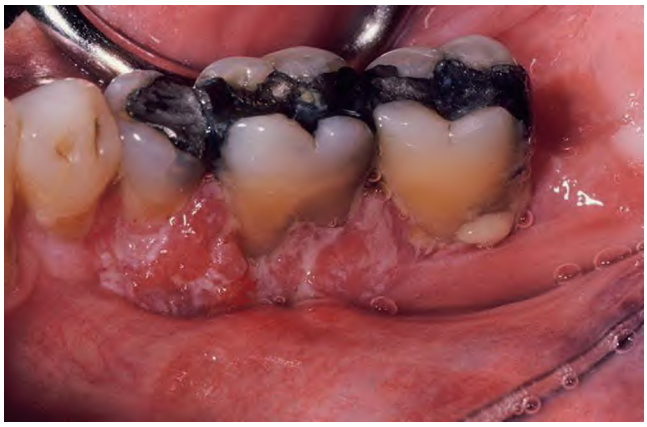
• **Fig. 10-108 Squamous Cell Carcinoma.** Granular red and white lesion in the anterior floor of mouth.

involvement (in descending order of frequency) are the gingiva, buccal mucosa, labial mucosa, and hard palate.

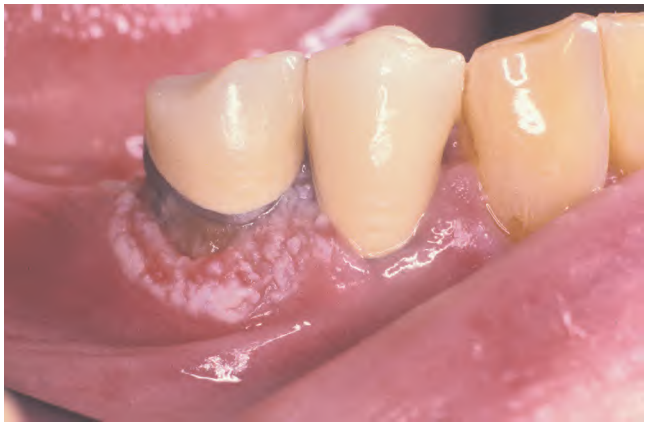
Carcinoma of the tongue accounts for more than 50% of intraoral cancers in the United States (Figs. 10-107). Two-thirds of lingual carcinomas appear as painless, indurated masses or ulcers of the posterior lateral border; 20% occur on anterior lateral or ventral surfaces, and only 4% occur on the dorsum. For unknown reasons, the oral tongue represents an increasingly common site of involvement in young patients.

Of all intraoral carcinomas, floor of mouth lesions are the most likely to arise from a preexisting leukoplakia or erythroplakia (Fig. 10-108). The floor of mouth also represents the oral cancer site most often associated with the development of a second primary malignancy, either elsewhere in the aerodigestive tract or in a distant organ. Floor of mouth carcinomas most often arise in the midline region near the frenum.

Gingival and alveolar carcinomas are usually painless and most frequently arise from keratinized, posterior mandibular mucosa (Fig. 10-109). Interestingly, among intraoral carcinomas, gingival lesions are least associated with tobacco smoking and have the greatest predilection for females.



• **Fig. 10-109 Squamous Cell Carcinoma.** Red and white granular lesion of the posterior lingual mandibular gingiva.

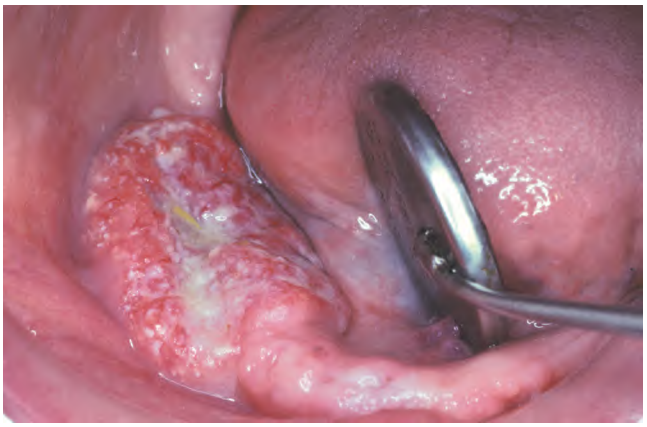


• **Fig. 10-110 Squamous Cell Carcinoma.** An innocuous, pebbled surface change of the gingiva was interpreted as inflammatory until multifocal white keratoses developed.

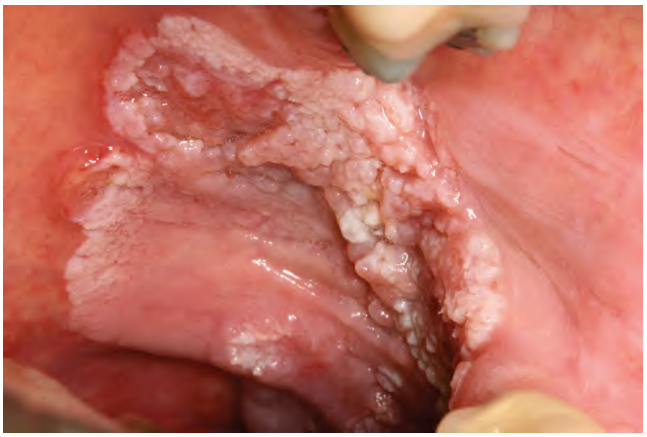
Gingival and alveolar carcinomas have a special propensity to mimic common, benign inflammatory and reactive lesions, such as the pyogenic granuloma, gingivitis (Fig. 10-110), and periodontal disease. Gingival tumors often destroy the underlying bone and cause tooth mobility. The lesion may go unrecognized until after tooth extraction, when it proliferates out of the socket to mimic the hyperplastic granulation tissue of an epulis granulomatosa (see page 484). Cancers that develop in an edentulous area may "wrap around" a denture flange and superficially resemble inflammatory fibrous hyperplasia (epulis fissuratum) (Fig. 10-111). Tumors of the maxillary alveolar ridge may extend onto the hard palate. Recent studies suggest that carcinomas involving the maxillary mucosa may be more aggressive than previously thought, with nearly 30% of cases harboring occult cervical lymph node metastasis.

Similarly, recent evidence suggests that carcinomas of the buccal mucosa may be more aggressive than previously suspected, with reported locoregional recurrence rates ranging from 30% to 80%. The buccal mucosa is an especially common site for oral carcinoma in regions of the world where betel quid use is prevalent.

Carcinomas of the retromolar trigone may spread to numerous adjacent structures, including the oropharynx,



• **Fig. 10-111 Squamous Cell Carcinoma.** An exophytic lesion with an irregular and pebbled surface. There is a linear indentation along the facial aspect resulting from pressure from the patient's lower denture. The underlying alveolar bone was destroyed.



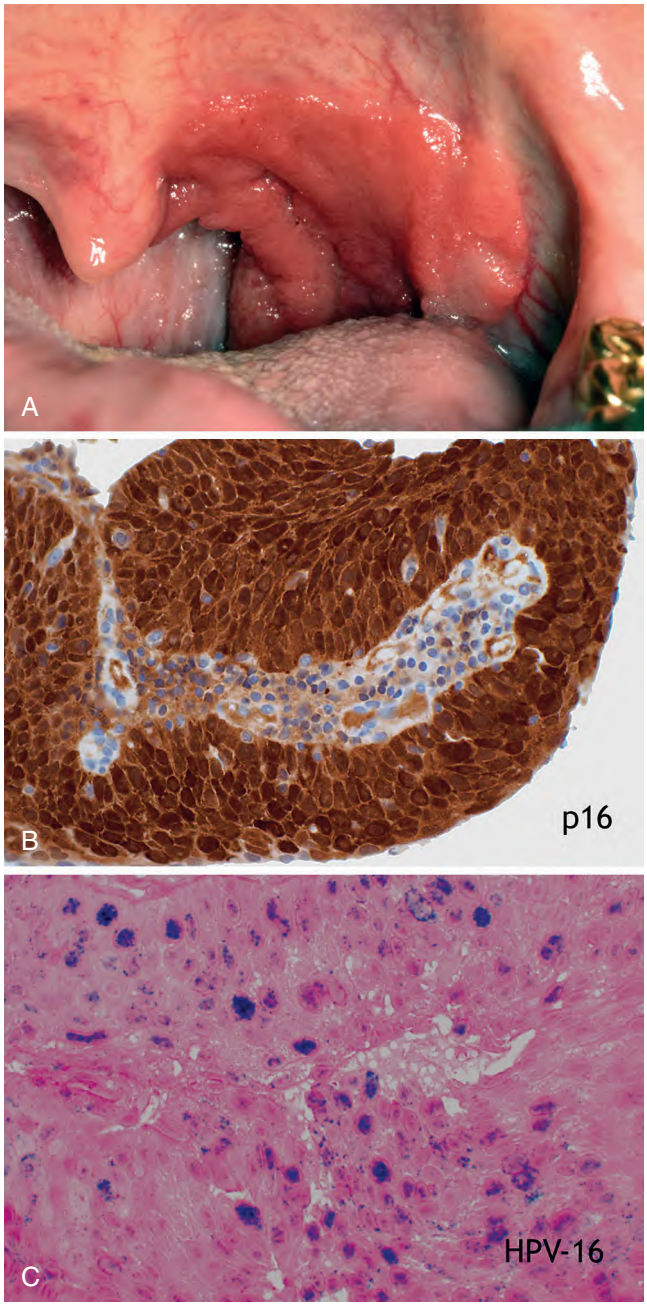
• **Fig. 10-112 Squamous Cell Carcinoma.** Carcinoma of the retromolar trigone with extension into the oropharynx (including the soft palate and anterior faucial pillar). Associated leukoplakia also extends anteriorly along the buccal mucosa.

buccal mucosa, alveolar ridge, and pterygomandibular raphe (Fig. 10-112). Invasion of the pterygomandibular raphe may lead to involvement of the skull base, masticator space, and floor of mouth.

Oropharyngeal Carcinoma

Subsites for oropharyngeal carcinoma include the soft palate, base of tongue, tonsillar region (i.e., tonsil, tonsillar fossa, and pillars), and posterior pharyngeal wall. Among these subsites, the tonsillar region accounts for the majority (approximately 70% to 80%) of cases. Indeed, the tonsillar region is a favored site for HPV-associated carcinomas, and the majority of oropharyngeal carcinomas in the United States currently are attributed to HPV infection (Fig. 10-113).

Oropharyngeal carcinomas exhibit the same basic clinical appearance as more anterior carcinomas; however, in this posterior location, lesions often go unrecognized for long periods. By the time of diagnosis, tumor size is typically greater than that of oral carcinomas, and the proportion of cases with cervical and distant metastasis is higher. Common presenting symptoms for oropharyngeal carcinoma include

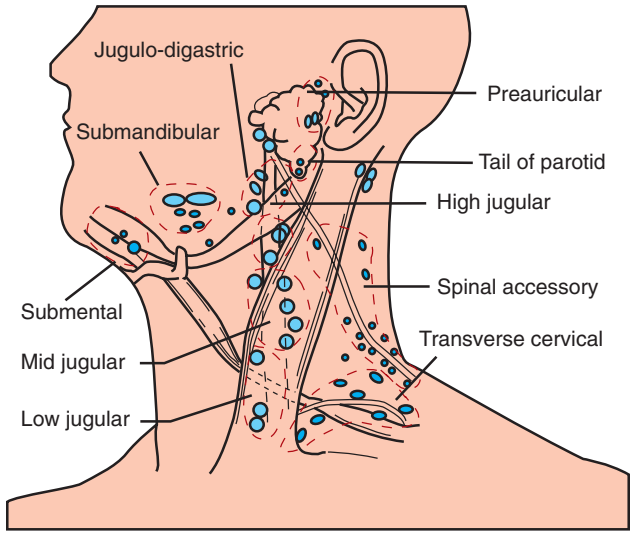


• **Fig. 10-113 Squamous Cell Carcinoma, Oropharyngeal. A,** Large, erythroplakic lesion involving the left soft palate and tonsillar region. **B,** Immunohistochemical staining showed the tumor to be positive for p16, which is a surrogate marker for transcriptionally active, high-risk human papilloma virus (HPV) infection among oropharyngeal squamous cell carcinomas. **C,** *In situ* hybridization (ISH) demonstrated the presence of intranuclear HPV 16 DNA.

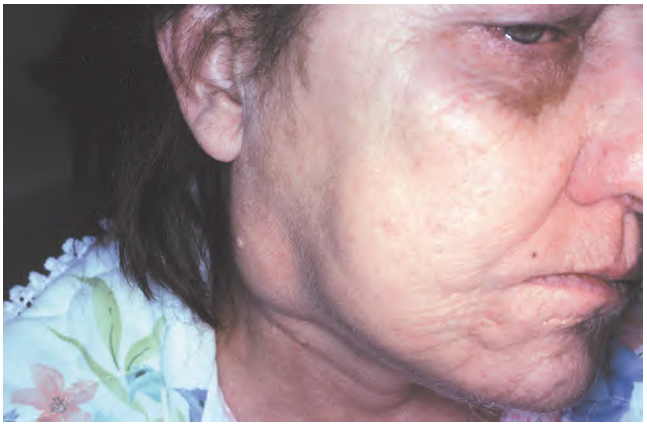
persistent sore throat, difficulty in swallowing **(dysphagia),** and pain on swallowing **(odynophagia).** The pain may be dull or sharp and frequently is referred to the ear.

Metastasis

Metastasis of oral squamous cell carcinoma occurs largely via the lymphatics to the ipsilateral cervical lymph nodes (Fig. 10-114). A cervical lymph node that contains metastatic carcinoma is usually firm to stony hard, nontender,



• **Fig. 10-114 Squamous Cell Carcinoma, Metastatic Spread.** Diagram demonstrating potential sites for metastatic spread of oral carcinoma to regional lymph nodes.



• **Fig. 10-115 Squamous Cell Carcinoma.** Metastatic deposits within cervical lymph nodes present as firm, painless enlargements as seen in this patient with metastasis to a superior jugular node from a posterior lateral tongue carcinoma.

and enlarged (Fig. 10-115). If the malignant cells have perforated the capsule of the node and invaded into surrounding tissues, then the node will feel "fixed," or not easily movable. **Extracapsular spread** (extension of metastatic deposits outside of the lymph node capsule) is a microscopic feature associated with poor prognosis, including increased risk for locoregional recurrence, distant metastasis, and shortened survival.

Occasionally, contralateral or bilateral metastatic deposits are seen, and at least 2% of patients have distant ("below the clavicles") metastasis at diagnosis; in some studies this figure is as high as 22%. The most common sites of distant metastasis are the lungs, liver, and bones, but any part of the body may be affected.

Carcinoma of the lower lip and oral floor tends to travel to the submental nodes; tumors from the posterior portions of the mouth typically travel to the superior jugular and

digastric nodes. Metastatic deposits from oropharyngeal carcinoma usually are found in the jugulodigastric or retropharyngeal nodes.

Metastasis is not an early event for carcinomas of the oral cavity proper. However, because of delay in diagnosis, approximately 21% of patients have cervical metastases at diagnosis (60% in reports from tertiary care medical centers). In contrast, oropharyngeal tumors are prone to early metastasis, with more than 50% of affected persons exhibiting cervical lymph node metastasis and 10% exhibiting distant metastasis at diagnosis.

Staging

Tumor size and the extent of metastatic spread are the best prognostic indicators for oral squamous cell carcinoma. Quantifying these clinical parameters is called **staging.** Table 10-3 summarizes the tumor-node-metastasis (TNM)

TABLE 10-3 Tumor-node-metastasis (TNM) Staging System for Oral and Oropharyngeal Carcinoma

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face) (Oropharynx) Tumor invades the larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible (*Note:* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.)
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery
Regional Lymph Node Involvement (N)*	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node more than 3 cm but not greater than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a node more than 6 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

**Note:* Metastases at level VII are considered regional lymph node metastases.
From Lip and Oral Cavity. In Edge SB, Byrd DR, Compton CC, et al, editors, *AJCC Cancer Staging Manual,* ed 7, New York, 2010, Springer, pp 29-40; Pharynx. In Edge SB, Byrd DR, Compton CC, et al, editors, *AJCC Cancer Staging Manual,* ed 7, New York, 2010, Springer, pp 41-56.

TABLE 10-4 Tumor-node-metastasis (TNM) Clinical Staging Categories for Oral and Oropharyngeal Squamous Cell Carcinoma with Corresponding Survival Rates

Stage	TNM Classification	5-Year Relative Survival Rate		
		Oral Cavity*	Lip†	Oropharynx†
Stage 0	Tis N0 M0			
Stage I	T1 N0 M0	72%	96%	**56%‡‡**
Stage II	T2 N0 M0	58%	83%	**58%‡‡**
Stage III	T3 N0 M0 T3 N0 M0 T1 N1 M0 T2 N1 M0 T3 N1 M0	45%	57%	**55%‡‡**
Stage IV		32%	48%	**43%‡‡**
IVA	T4a N0 M0 T4a N1 M0 T1 N2 M0 T2 N2 M0 T3 N2 M0 T4a N2 M0			
IVB	Any T N3 M0 T4b Any N M0			
IVC	Any T Any N M1			

*From Lip and Oral Cavity. In Edge SB, Byrd DR, Compton CC, et al, editors, *AJCC Cancer Staging Manual,* ed 7, New York, 2010, Springer, pp 29-40.
†Based on SEER data for patients treated from 1988 to 2001. Source: American Cancer Society. Oral cavity and oropharyngeal cancer. http://www.cancer.org/cancer/oralcavityandoropharyngealcancer/detailedguide/oral-cavity-and-oropharyngeal-pdf. Accessed August 29, 2013.
‡‡Due to the increasing incidence in HPV-related oropharyngeal carcinoma, recent studies have shown a significant improvement in survival over that reflected in the SEER data from 1998-2001. Some centers have reported an overall 5-year survival rate of 54%-89% for HPV(+) oropharyngeal carcinoma, whereas the 5-year survival rate for HPV(–) tumors ranges from 33%-65%.

system for staging oral and oropharyngeal carcinoma. This staging protocol depends on three basic clinical features:
1. T—Size of the primary tumor, in centimeters
2. N—Regional lymph node involvement
3. M—Distant metastasis

These three parameters are tallied together to determine the stage (Table 10-4). In general, the higher the stage, the worse the prognosis. In other words, a stage IV lesion is associated with a much worse prognosis than a stage I lesion. However, for oropharyngeal carcinoma, survival rates are similar for patients with stage I, II, and III disease (see Table 10-4); instead, HPV status appears to be the most important prognostic factor for patients with oropharyngeal carcinoma (see later).

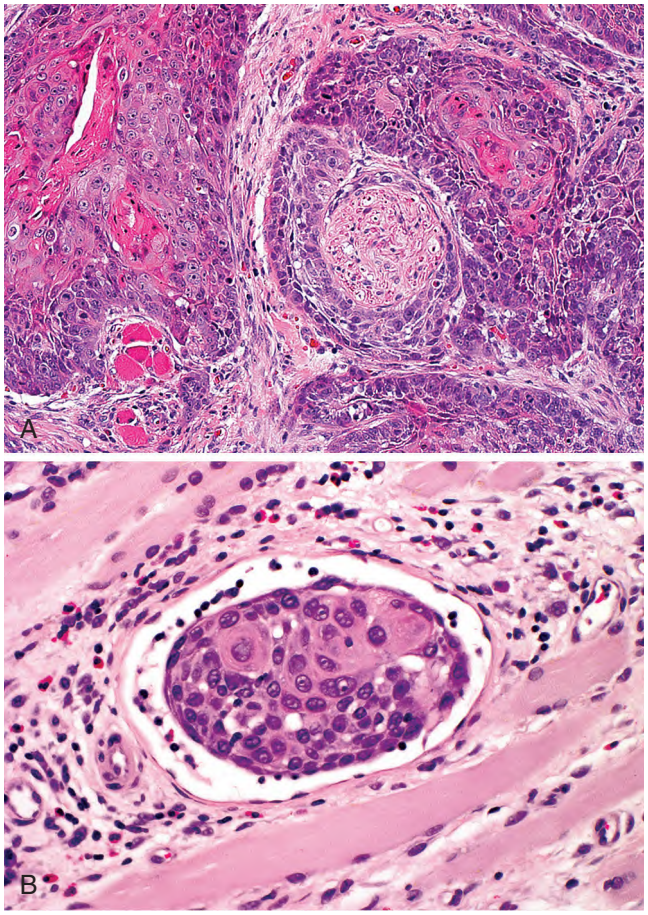
Histopathologic Features

Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasive islands and cords of malignant squamous epithelial cells. At the earliest moment of invasion, the adjectives *superficially invasive* or *microinvasive* often are used. The features of epithelial dysplasia are discussed in more detail in the section on leukoplakia (see page 360).

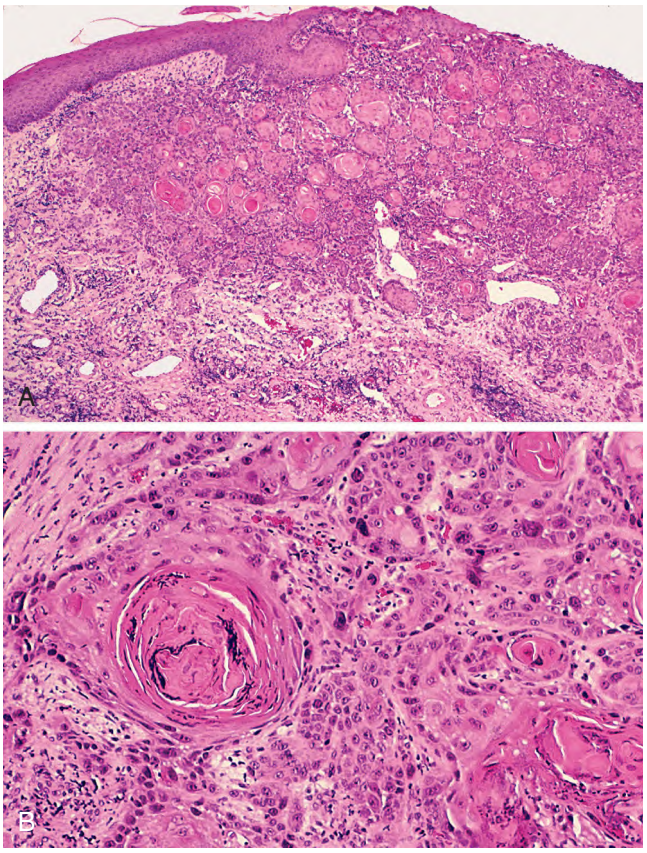
Invasion is represented by irregular extension of lesional epithelium through the basement membrane and into subepithelial connective tissue. Individual squamous cells and sheets or islands of cells proliferate within the connective tissue, without attachment to the surface epithelium. The invading tumor destroys normal tissue and may extend deeply into underlying adipose tissue, muscle, or bone. Lesional cells may breach the perineurium that encases nerve bundles **(perineural invasion)** or may invade the lumina of veins or lymphatics **(vascular invasion)** (Fig. 10-116). There is often a strong inflammatory or immune cell response to invading epithelium, and necrosis may be present. The tumor may induce dense fibrosis **(desmoplasia** or **scirrhous change)** and the formation of new blood vessels **(angiogenesis).**

The lesional cells generally show abundant eosinophilic cytoplasm with large, often darkly staining **(hyperchromatic)** nuclei and an increased nuclear-to-cytoplasmic ratio. Varying degrees of cellular and nuclear pleomorphism are seen. The normal product of squamous epithelium is keratin, and **keratin pearls** (a round focus of concentrically layered, keratinized cells) may be produced within lesional epithelium. Individual cells also may undergo keratinization.

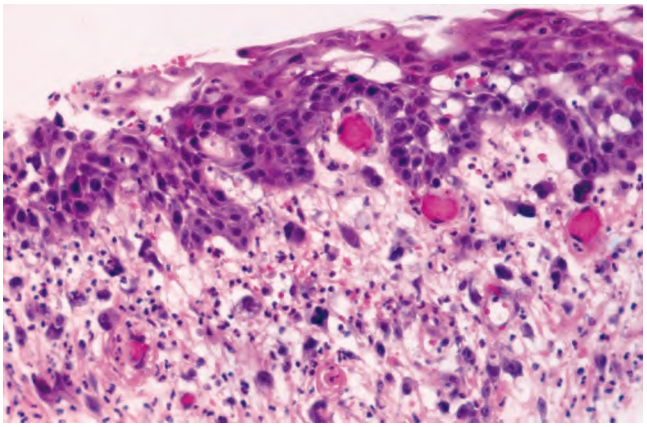
Histopathologic **grading** of squamous cell carcinoma is based upon the degree of resemblance to normal squamous epithelium and the amount of keratin production**.** Lesions are graded on a three-point (grades I to III) or a four-point (grades I to IV) scale. The less differentiated tumors receive the higher numerals. The histopathologic grade of a tumor is related somewhat to its biologic behavior. In other words, a



• **Fig. 10-116 Squamous Cell Carcinoma. A,** Perineural invasion. Tumor has breached the perineurium encasing this nerve fiber. **B,** Angioinvasion. Tumor is present within the lumen of this vessel.



• **Fig. 10-117 Well-differentiated Squamous Cell Carcinoma. A,** Low-power photomicrograph showing islands of malignant squamous epithelium invading into the lamina propria. **B,** High-power view showing dysplastic epithelial cells with keratin pearl formation.

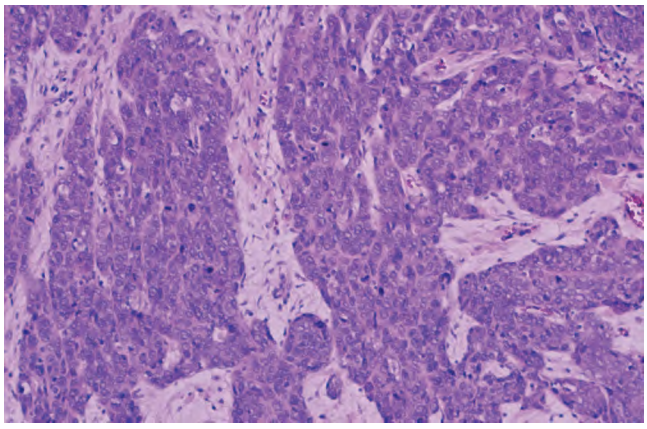


• **Fig. 10-118 Poorly Differentiated Squamous Cell Carcinoma.** The numerous pleomorphic cells within the lamina propria represent anaplastic carcinoma.

tumor that is mature enough to closely resemble its tissue of origin often grows at a slightly slower pace and metastasizes later in its course. Such a tumor is called *low-grade, grade I,* or *well-differentiated* (Fig. 10-117). In contrast, a tumor with marked pleomorphism and little or no keratin production may be so immature that it becomes difficult to identify the tissue of origin. In such cases, immunohistochemical studies (e.g., for cytokeratins or p63) may be needed to support an epithelial origin. Such tumors often enlarge rapidly, metastasize early, and are termed *high-grade, grade III/IV, poorly differentiated,* or *anaplastic* (Fig. 10-118). A tumor with a microscopic appearance somewhere between these two extremes is called *moderately differentiated* (Fig. 10-119).

Grading is a somewhat subjective process, depending on the area of the tumor sampled and the individual pathologist's criteria for evaluation. Moreover, clinical staging correlates much better with the prognosis than microscopic grading. Over the past several decades, investigators have proposed various multi-parameter histopathologic assessment systems in an attempt to provide more objective criteria that correlate with prognosis. Variables such as pattern of invasion, tumor thickness, degree of keratinization, nuclear pleomorphism, lymphocytic response, and mitotic rate have been included in such grading systems. However, widespread agreement regarding the use of such methods is lacking.

For oropharyngeal squamous cell carcinoma, detection of transcriptionally active HPV infection is especially important in determining prognosis. HPV-positive oropharyngeal squamous cell carcinomas often are poorly differentiated and nonkeratinizing with basaloid cytologic features; in addition, the majority of cases are diagnosed at an



• **Fig. 10-119 Moderately Differentiated Squamous Cell Carcinoma.** Although no keratinization is seen in this medium-power view, these malignant cells are still easily recognizable as being of squamous epithelial origin.

advanced clinical stage. Despite these features, HPV-positive oropharyngeal squamous cell carcinomas typically exhibit better treatment outcomes compared to HPV-negative cases. The gold standard for determining whether a carcinoma likely was caused by HPV is high-risk HPV E6 and E7 oncogene expression analysis by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). However, this method is best suited for fresh frozen tissue and is technically demanding. In comparison, detection of p16 by immunohistochemistry is more widely available, is readily performed on formalin-fixed paraffin-embedded tissue, and is considered a highly sensitive (albeit not highly specific) surrogate for transcriptionally active, high-risk HPV infection in oropharyngeal carcinomas (see Fig. 10-113, *B*). (The molecular basis for this finding is that overexpression of p16 results from inactivation of the tumor suppressor pRB [retinoblastoma protein] by the HPV oncoprotein E7.) Also, in the case of a cervical lymph node with metastatic carcinoma of unknown origin, some studies suggest that p16 immunoreactivity may be useful in directing the search for the primary tumor to the oropharynx. Furthermore, investigators have found that *in situ* hybridization (ISH) for HPV 16 exhibits strong agreement with p16 immunohistochemistry, although it may fail to detect the minority of oropharyngeal tumors caused by other HPV types (see Fig. 10-113, *C*). In particular, the recent development of RNA ISH probes complementary to E6 and E7 mRNA allows for detection of transcriptionally active HPV in routinely processed tissue. Also, there is currently much interest in evaluating liquid-phase hybridization assays for detection of HPV in cytologic preparations from head and neck squamous cell carcinomas. Importantly, widely accepted testing algorithms, validated commercially available assays, and standardized reporting criteria for determination of HPV status in oropharyngeal and other head and neck tumors still need to be established.

In contrast to oropharyngeal squamous cell carcinomas, p16 immunohistochemistry performed on oral squamous cell carcinomas exhibits low positive predictive value for transcriptionally active HPV infection and is not useful for prognostication. Furthermore, there is only limited data regarding qRT-PCR analysis of high-risk HPV E6 and E7 expression in oral squamous cell carcinoma, with no significant correlation with prognosis demonstrated thus far.

Treatment and Prognosis

Clinical staging guides the treatment of squamous cell carcinoma. Most lip vermilion carcinomas are detected at an early stage and treated by surgical excision (typically a wedge resection) with excellent results. In contrast, advanced cases may be treated by definitive radiation therapy or combined chemoradiation therapy. At diagnosis, less than 10% of all lip vermilion carcinomas have metastasized; therefore, neck dissection seldom is indicated. However, a notable exception is squamous cell carcinoma of the upper lip vermilion, which exhibits a high risk for regional lymph node metastasis (apparently related to the extensive lymphatic network in this location). Fortunately, squamous cell carcinoma only rarely occurs in the upper lip.

For intraoral squamous cell carcinoma, early-stage lesions usually are treated with surgery; definitive radiation therapy may be an alternative for patients unable to tolerate surgery. Moderately advanced tumors typically are treated with surgery followed by either radiation therapy or concurrent chemoradiation therapy. Very advanced disease or cases in which surgery would result in unacceptable functional outcomes may be treated with radiation therapy and/or chemotherapy.

In addition to advanced stage, indications for postoperative *(adjuvant)* radiation or chemoradiation therapy in the treatment of intraoral carcinoma may include close or positive resection margins, high-grade histopathologic features, extracapsular spread, and perineural or angiolymphatic invasion. *Intensity-modulated radiation therapy (IMRT)* often is used to target the treatment area while minimizing damage to neighboring tissue. *Brachytherapy* (placement of tiny, radioactive seeds) may be used for select applications (e.g., definitive treatment of small intraoral tumors or as an adjunct with IMRT to deliver an additional radiation dose).

In patients with intraoral carcinoma, cervical lymph node involvement is evident at presentation in approximately 30% of cases and occult (or subclinical) in about 10% to 40% of cases. However, the risk for regional metastasis varies considerably by subsite. In the past, **radical neck dissection** (*en bloc* removal of the lymphatics of the lateral triangle of the neck along with associated nonlymphatic structures, including the internal jugular vein, submandibular gland, sternocleidomastoid muscle, and spinal accessory nerve) was standard treatment for clinically evident or suspected cervical lymph node metastasis. However, over the past several decades, **modified radical neck dissection** (similar to radical neck dissection but with preservation of nonlymphatic structures) and **selective neck dissection** (removal of only select cervical lymph node groups) have gained favor; these techniques are associated with decreased

morbidity and, depending upon the extent of disease, often allow for disease control comparable to that of classical radical neck dissection. Histopathologic findings (e.g., number of positive nodes and presence of extracapsular spread) in a selective neck dissection may aid in determining the need for postoperative radiation or chemoradiation therapy.

The *depth of invasion* or *tumor thickness* may help predict occult cervical lymph node metastasis despite early T-stage and may be used to determine the need for *elective* selective neck dissection. Although some investigators have used these terms interchangeably, depth of invasion represents the distance from the basement membrane to the deepest portion of the tumor, whereas tumor thickness is the distance from the tumor surface to the deepest portion of the tumor. Many studies suggest a significantly increased risk for nodal metastasis with a depth of invasion or tumor thickness greater than about 3 to 5 mm; however, suggested cutoffs vary considerably by tumor subsite and study methodology. In addition, **sentinel-node biopsy** (biopsy of the first lymph node in the lymphatic basin to receive drainage from the tumor) has shown promise in identifying patients with occult neck metastasis, but this technique remains investigational for patients with oral cancer.

Chemotherapeutic agents commonly used for treating intraoral carcinoma include platinum-containing compounds (e.g., cisplatin and carboplatin), 5-fluorouracil, and taxanes (e.g., paclitaxel and docetaxel). *Induction* or *neoadjuvant* chemotherapy may be administered initially to shrink a tumor prior to additional therapy and has been advocated by some investigators to decrease the risk for distant metastasis; however, studies suggest this approach may yield either no or minimal improvement in locoregional disease control and patient survival. In contrast, for patients with locally advanced (stage III, IVa, or IVb) disease, current evidence supports *postoperative* concurrent chemoradiation therapy (especially incorporating cisplatin) for optimal locoregional control and disease-free survival. For intraoral carcinomas with distant metastasis (stage IVc), single- or multi-agent chemotherapy may be administered.

In addition, there are several promising targeted therapies, including monoclonal antibodies (e.g., cetuximab and panitumumab) or small molecule tyrosine kinase inhibitors (e.g., erlotinib) directed against epidermal growth factor receptor (EGFR); anti-vascular endothelial growth factor (VEGF) antibodies; and mammalian target of rapamycin (mTOR) inhibitors. In particular, cetuximab has been approved by the United States Food and Drug Administration for treatment of head and neck squamous cell carcinoma and typically is combined with radiation and/or chemotherapy. Molecular-based targeted therapies are anticipated to become increasingly important treatment strategies in the future.

For oropharyngeal squamous cell carcinoma, early-stage disease may be treated by either definitive radiation therapy or surgery; however, most cases are diagnosed at an advanced stage and require multimodal therapy involving various combinations of surgery, radiation therapy, or chemotherapy. Oncologists traditionally have preferred radiation or concurrent chemoradiation therapy over surgery in this anatomic location; however, recent advances in surgical techniques have led some to reconsider this view.

TABLE 10-5 Overall 5-year Relative Survival Estimates for Oral and Pharyngeal Cancers*

Cancer Site	Estimated 5-Year Relative Survival Rate
Oral cavity and pharynx (combined)	65%
Lip	88%
Tongue	65%
Floor of mouth	54%
Oropharynx	65%†

*Based upon Surveillance Epidemiology and End Results (SEER) 9 data for patients diagnosed in 2006. Source: Surveillance Research Program, National Cancer Institute. Fast Stats: An interactive tool for access to SEER cancer statistics, http://seer.cancer.gov/faststats. Accessed April 9, 2015.
†Survival of oropharyngeal carcinoma is related to HPV status of the tumor. Some centers have reported overall 5-year survival rates of 54%-89% for HPV(+) oropharyngeal carcinomas and 33%-65% for HPV(–) tumors.

Based upon available data for patients recently diagnosed in the United States, the estimated 5-year relative survival rate for oral and pharyngeal cancers combined is approximately 64%. Although some patients die of their disease as many as 10 years after initial treatment, the great majority of deaths occur within the first 5 years. The prognosis varies considerably by tumor stage and subsite (Tables 10-4 and 10-5). Because most lip vermilion carcinomas are diagnosed at an early stage, the overall 5-year relative survival rate is excellent (approximately 95%). In contrast, intraoral and oropharyngeal carcinomas often are diagnosed at later stages, with significantly lower 5-year relative survival rates (e.g., 51% for floor of mouth lesions and 65% for oropharyngeal lesions).

For both intraoral and lip vermilion carcinomas, tumor stage is the best prognostic indicator. However, for oropharyngeal carcinoma, HPV tumor status (i.e., presence or absence of transcriptionally active HPV [see page 378]) is considered the most important prognostic factor, followed by tobacco exposure and tumor stage. Compared to patients with HPV-negative tumors, those with HPV-positive tumors typically exhibit a better response to chemotherapy and/or radiation therapy, with an approximately 60% reduction in risk of death and 30% greater 5-year absolute survival rate. Improved survival may reflect the unique biology of HPV-positive carcinomas as well as the low rate of comorbidity among the relatively young age group typically affected. Possible biologic reasons for favorable prognosis include an intact p53-mediated apoptotic response to radiation and a lack of field cancerization (see next section). Investigations of targeted therapies and less intensive treatment regimens for HPV-positive oropharyngeal tumors are ongoing.

Various molecular markers associated with oral squamous cell carcinoma, such as *TP53* mutations, have shown

equivocal results as prognostic indicators. Several investigators have reported that overexpression of survivin (a member of the inhibitor of apoptosis protein family) is associated with poor prognosis, but the clinical utility of this finding requires further study. Moreover, unlike oropharyngeal carcinoma (see later), there is no clear correlation between HPV tumor status and prognosis for oral squamous cell carcinomas.

In the United States, deaths from oral and pharyngeal cancers have been decreasing over the past several decades. The age-adjusted death rate for oral and pharyngeal cancers combined decreased from 4.3 per 100,000 population in 1975 to 2.5 per 100,000 population in 2010. From 2000 to 2010, the mortality rate decreased by approximately 1.3% annually. In particular, for oropharyngeal cancers, 5-year relative survival rates have improved—from approximately 51% to 59% for those diagnosed from 1995 through 2001 to approximately 65% for those diagnosed from 2002 through 2005. (This trend is reflected in the difference between oropharyngeal survival rates shown in Tables 10-4 and 10-5). Areas of investigational interest for continuing declines in oral and pharyngeal cancer mortality include improvements in prevention, early diagnosis, and treatment.

Multiple Carcinomas

Patients with one carcinoma of the mouth or throat are at increased risk for additional concurrent (synchronous) or, more commonly, later (metachronous) primary surface epithelial malignancies of the upper aerodigestive tract, stomach, lungs, and other sites. This risk has been estimated to be as low as 6% and as high as 44%; the highest figures are associated with male patients who continue to smoke and abuse alcohol after therapy. Overall, 9% to 25% of patients with oral carcinoma develop additional mouth or throat malignancies.

This tendency for the development of multiple mucosal cancers is hypothesized to result from *field cancerization*—a process whereby exposure to carcinogens, such as tobacco and alcohol, creates a diffuse field of altered epithelial cells with increased potential for malignant transformation. Molecular analyses of various markers, including loss of heterozygosity (LOH), microsatellite alterations, *TP53* tumor suppressor gene mutations, and X-chromosome inactivation, have identified genetic alterations shared between tumor tissue and adjacent clinically normal-appearing tissue in one-third to one-half of cases examined. In addition, investigators have shown that a significant proportion of second primary tumors develop from the same preneoplastic precursor lesion or "field," with the remaining cases representing tumors that develop independently. Furthermore, researchers have proposed that patches of clonal cells can progress to develop additional mutations and give rise to subclones in a process known as *clonal divergence,* which would account for the genetic heterogeneity typically seen among these tumors. Interestingly, field cancerization does not appear to be associated with malignancies attributed to HPV infection.

VERRUCOUS CARCINOMA (SNUFF DIPPER'S CANCER; ACKERMAN'S TUMOR)

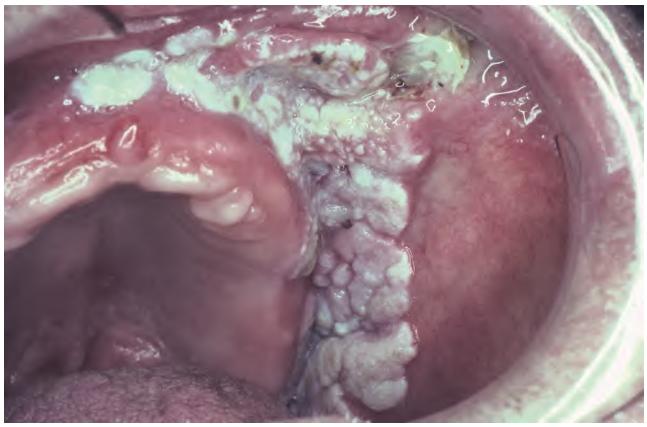
Verrucous carcinoma is a low-grade variant of oral squamous cell carcinoma. In 1948, Ackerman described this lesion in detail, although the term *verrucous carcinoma* had been used in 1944 in a series of cases reported by Burford, Ackerman, and Robinson. Ackerman postulated that some of these lesions might be associated with smokeless tobacco use, because 11 of his 31 patients were "tobacco chewers." However, there was no mention of the type of smokeless tobacco used and no mention of whether any of these patients also had smoked tobacco. In addition to the oral mucosa, verrucous carcinoma has been identified at several extraoral sites, including laryngeal, vulvovaginal, penile, anorectal, sinonasal, and esophageal mucosa, as well as the skin of the breast, axilla, ear canal, and soles of the feet. Extraoral cases are unrelated to tobacco use. Several investigators have identified DNA from HPV types 6, 11, 16, and 18 in a minority of oral verrucous carcinomas, although the possibility that these cases represent coincidental HPV infection cannot be excluded.

Verrucous carcinoma represents less than 1% to 16% of all oral squamous cell carcinomas, depending on the local popularity of smokeless tobacco use. The only epidemiologic assessment of this tumor in a Western culture reported an average annual incidence rate of one to three oral lesions per 1 million population each year. Among 411,534 cases of head and neck carcinoma recorded in the National Cancer Database from 1985 to 1996, only 0.6% of cases were diagnosed as verrucous carcinoma.

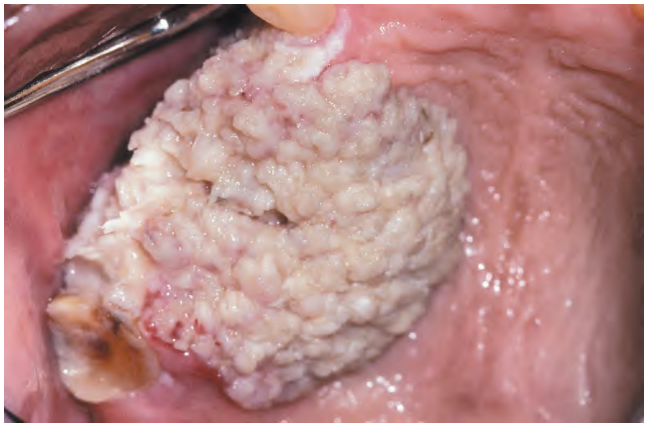
Some oral verrucous carcinomas arise in people who chronically use chewing tobacco or snuff. Cases also occur in those who combine habits (i.e., smokeless tobacco, smoking, and alcohol), exclusively smoke tobacco, or have no identifiable risk factors. However, exact figures are difficult to assess because patients often deny their habits. Nevertheless, among smokeless tobacco users, conventional squamous cell carcinoma is much more likely to develop than this low-grade variant.

Clinical Features

Verrucous carcinoma is found predominantly in men older than 55 years (average age: 65 to 70 years). In areas where women frequently use dry snuff, however, older females may predominate. The most common sites of oral mucosal involvement include the mandibular vestibule, buccal mucosa, gingiva, tongue, and hard palate. The involved area often corresponds to the site of chronic tobacco placement. In cultural groups who keep the tobacco in the maxillary vestibule or under the tongue, these locations are involved most commonly.



• **Fig. 10-120 Verrucous Carcinoma.** Extensive papillary, white lesion of the maxillary vestibule.



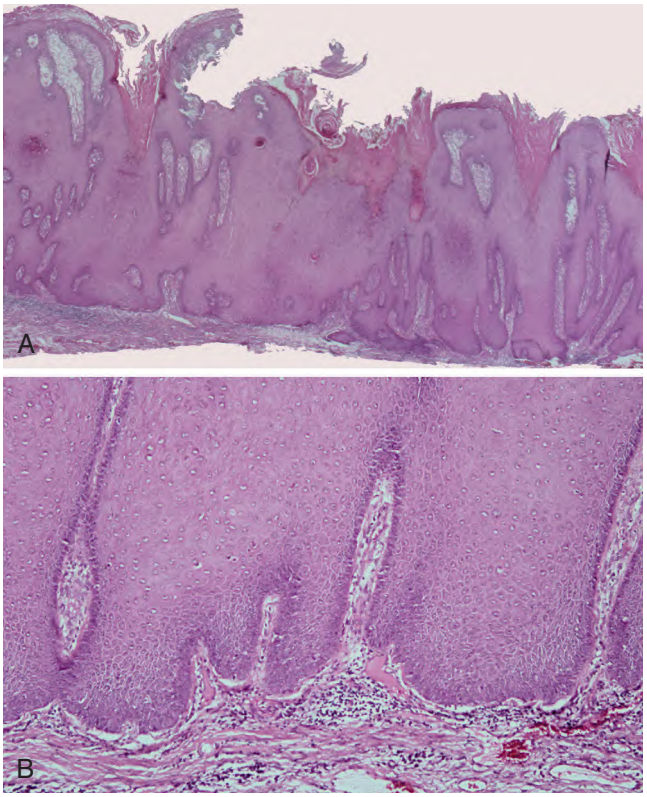
• **Fig. 10-121 Verrucous Carcinoma.** Large, exophytic, papillary mass of the maxillary alveolar ridge.

Oral verrucous carcinoma is usually extensive by the time of diagnosis, and it is not unusual for a tumor to be present for 2 to 3 years before definitive diagnosis. The lesion appears as a diffuse, well-demarcated, painless, thick plaque with papillary or verruciform surface projections (Figs. 10-120 and 10-121). Lesions are typically white but also may appear erythematous or pink. The color depends on the amount of keratin produced and the degree of host inflammatory response to the tumor. When left untreated, the lesions may destroy underlying structures, such as bone, cartilage, muscle, and salivary glands. Enlarged cervical lymph nodes in patients with verrucous carcinoma usually represent inflammatory reactive changes rather than nodal metastasis.

Leukoplakia or **tobacco pouch keratosis** may be seen on adjacent mucosal surfaces, and verrucous carcinoma is a lesion that may develop from the high-risk precancer, proliferative verrucous leukoplakia (PVL) (see page 358). PVL and verrucous carcinoma may have been reported in the past by the name **oral florid papillomatosis.**

Histopathologic Features

Verrucous carcinoma has a deceptively benign microscopic appearance; it is characterized by wide and elongated rete ridges that appear to "push" into the underlying connective tissue (Fig. 10-122). Lesions usually show abundant keratin (usually parakeratin) production and a papillary or verruciform surface. Parakeratin typically fills the depressions **(parakeratin clefts)** between the surface projections. These projections may be long and pointed or short and blunted. The lesional epithelial cells generally show no significant cytologic atypia. There is frequently an intense inflammatory cell infiltrate in the subjacent connective tissue.



• **Fig. 10-122 Verrucous Carcinoma. A,** Low-power photomicrograph showing marked epithelial hyperplasia with a rough, papillary surface and keratin plugging. **B,** High-power view showing bulbous rete ridges without significant dysplasia.

The histopathologic diagnosis of verrucous carcinoma requires an adequate incisional biopsy. Because the individual cells are not very dysplastic, the pathologist must evaluate the overall histomorphologic configuration of the lesion to make the diagnosis. Adequate sampling also is important because conventional squamous cell carcinoma develops concurrently within up to 20% of verrucous carcinomas.

Treatment and Prognosis

The treatment of choice is surgical excision. The surgery generally need not be as extensive as that required for conventional squamous cell carcinoma of a similar size. If cervical lymph node enlargement is clinically evident, then a selective neck dissection may be performed, although most such cases turn out to represent reactive lymphadenopathy rather than metastasis. Approximately 90% of patients are disease free 5 years after surgery, but some patients will require at least one additional surgical procedure during

that time. The treatment failures usually occur in patients with the most extensive involvement or in those unable to tolerate extensive surgery because of unrelated systemic diseases. An additional cause of treatment failure is the initial inability to identify focal, concurrent conventional squamous cell carcinoma; such cases should be treated as conventional squamous cell carcinomas.

Radiotherapy is an alternative primary treatment modality but provides poorer local control and, thus, is considered less effective than surgery. In addition, radiotherapy has been unpopular because of published reports of poorly differentiated or anaplastic carcinoma developing within the lesion after treatment. However, more recent analysis suggests that this threat is overexaggerated. In a limited number of cases, tumor regression after chemotherapy, radiochemotherapy, or photodynamic therapy has been reported, although these treatment alternatives require further study.

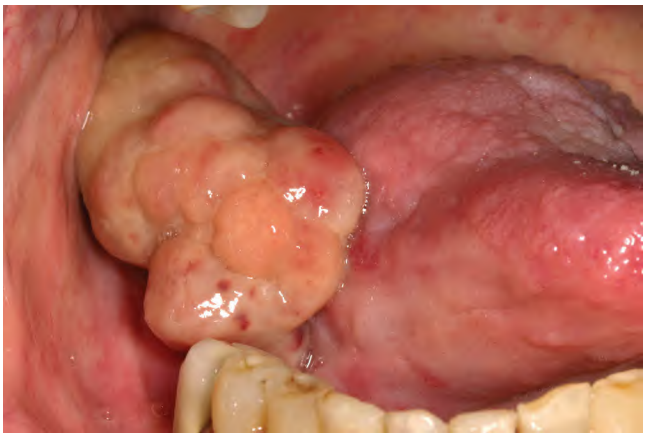
◆ SPINDLE CELL CARCINOMA (SARCOMATOID SQUAMOUS CELL CARCINOMA; POLYPOID SQUAMOUS CELL CARCINOMA; CARCINOSARCOMA; PSEUDOSARCOMA)

Spindle cell carcinoma is a rare variant of squamous cell carcinoma characterized by dysplastic surface epithelium in conjunction with an invasive spindle cell element. With routine light microscopy, it may be indistinguishable from connective tissue sarcomas or other spindle cell malignancies. Spindle cell carcinoma of the upper aerodigestive tract is closely associated with tobacco and alcohol use. Some cases develop after radiotherapy for a more differentiated squamous cell carcinoma, a phenomenon known as **dedifferentiation.** Transcriptionally active HPV appears to be exceptionally rare in this variant.

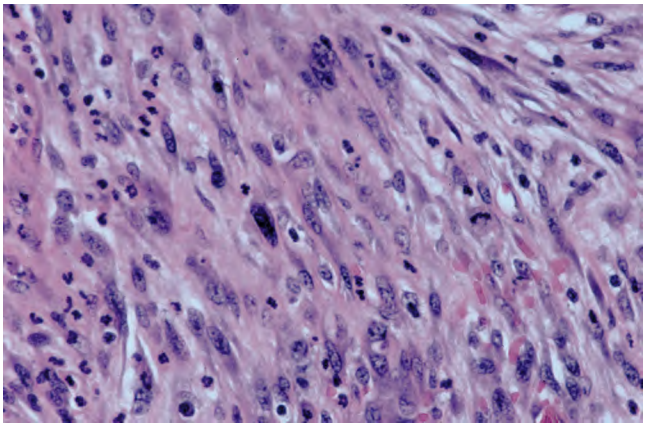
In the past, this biphasic lesion was thought to be a "collision" tumor between a carcinoma and sarcoma, but most authorities now consider the spindle cells to represent anaplastic carcinoma cells. Electron microscopy and immunohistochemical analysis support the concept that these lesional cells are of epithelial origin, with the ability to produce mesenchymal intermediate filaments. Based on immunohistochemical studies, some investigators have hypothesized that a dysfunctional cadherin-catenin complex important for intercellular adhesion causes the tumor cells to shift from a squamous to a spindled type, with increased infiltrative behavior.

Clinical Features

Spindle cell carcinoma may arise anywhere within the upper aerodigestive tract, with a predilection for the larynx and oral cavity. In the mouth, the alveolar mucosa, tongue, buccal mucosa, and lower lip are common sites, but other areas may be involved. Males are affected more often than females. According to the largest reported series restricted to oral cases, the mean age at diagnosis is 57 years (range: 29 to 93 years).



• **Fig. 10-123 Spindle Cell Carcinoma.** Large polypoid mass arising from the right lateral tongue.



• **Fig. 10-124 Spindle Cell Carcinoma.** Streaming fascicles of pleomorphic spindle cells that represent anaplastic epithelial cells.

In contrast to other oral cancers, spindle cell carcinoma typically appears as a pedunculated, polypoid mass, but occasionally it may appear as a sessile, nodular or fungating mass (Fig. 10-123). The surface often is ulcerated. Pain and paresthesia are prominent features. The tumor grows rapidly, tends to metastasize early, and typically is diagnosed at a late stage. Lower lip lesions seem to have a special propensity to travel along nerves through the mental foramen and into the mandibular canal.

Histopathologic Features

Spindle cell carcinoma is composed predominantly of fascicles of anaplastic, spindle-shaped cells (Fig. 10-124). Some spindle cells may appear as obvious epithelial elements, but others strongly resemble atypical mesenchymal cells. On rare occasions, bone, cartilage, or muscle differentiation may be seen. Numerous mitotic figures often are present. The overall picture is similar to that of an anaplastic fibrosarcoma (see page 516), except for the often-inconspicuous squamous element.

The squamous component usually consists of dysplasia or carcinoma *in situ* of the overlying surface epithelium but may appear as islands of atypical squamous epithelium among the spindle cells. Direct transition between the two cell types may be seen. Because of frequent surface ulceration, a neoplastic surface component may be difficult to discern. Metastatic lesions may show only spindle cells, only squamous cells, or a combination of spindle and squamous cells.

Serial sections may be needed to find areas of unequivocal squamous cell carcinoma, and immunohistochemical techniques can be particularly useful in distinguishing this tumor from mesenchymal spindle cell malignancies. Most mesenchymal tumors express vimentin but not epithelial markers. In contrast, approximately 65% to 80% of spindle cell carcinomas react with antibodies directed against at least one epithelial marker, such as cytokeratin, epithelial membrane antigen (EMA), or p63. Nearly all cases express vimentin; immunoreactivity for other mesenchymal markers is possible but highly variable.

Treatment and Prognosis

The treatment of choice for oral spindle cell carcinoma is radical surgery, with neck dissection when clinically positive nodes are present. Most authors agree that radiotherapy and chemotherapy are ineffective. However, adjuvant radiation therapy may be of benefit when surgical margins are positive for tumor. The 5-year disease-free survival rate is approximately 30% for oral lesions, with most deaths occurring within 1 year of diagnosis. The prognosis for oral spindle cell carcinoma is somewhat worse than that for spindle cell carcinoma arising in other anatomic sites, but it is similar to the prognosis for high-grade, conventional oral squamous cell carcinoma. Surprisingly, tumor size seems to have little effect on the prognosis. Negative prognostic factors include endophytic (rather than polypoid) growth and an origin from a previously irradiated carcinoma.

◆ ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma is a rare squamous cell carcinoma variant that is characterized histopathologically by a combination of adenocarcinoma and squamous cell carcinoma. The adenoid (glandular) pattern, which includes mucus production, has been demonstrated clearly in metastatic deposits. Some authorities consider this carcinoma to be merely a high-grade **mucoepidermoid carcinoma** (see page 454). In some cases, tobacco and alcohol use have been implicated as causative factors. In addition, transcriptionally active HPV has been identified in a few cases involving the oropharynx and nasal cavity.

Clinical Features

Adenosquamous carcinoma may involve the tongue, oral floor, and other mucosal surfaces, usually in older adults. There is a male predilection. The tumor typically presents as a nodular, broad-based, variably painful mass with or without surface ulceration. The majority of patients have cervical lymph node metastasis at diagnosis.

Histopathologic Features

Adenosquamous carcinoma appears as an admixture of a surface squamous cell carcinoma and an underlying adenocarcinoma. The glandular component tends to be most prominent in deeper portions of the tumor. Mucicarmine staining demonstrates intracytoplasmic mucin in most cases, making differentiation from mucoepidermoid carcinoma difficult but helping to distinguish adenosquamous carcinoma from forms of squamous cell carcinoma that exhibit a pseudoglandular pattern of degeneration. Both squamous and glandular components immunoreact with antibodies directed against high molecular–weight cytokeratins (KL1).

Treatment and Prognosis

Adenosquamous carcinoma typically is treated with radical surgical excision, at times supplemented with radiation or chemoradiation therapy. The prognosis is poor; for upper aerodigestive tract lesions, the overall 5-year survival rate is approximately 13%, with about 42% of patients dying of disease within 2 years of diagnosis. Among previously reported head and neck cases, local recurrence has developed in approximately 32%; cervical lymph node metastasis in approximately 46%; and distant metastasis in approximately 29%, with the lung being the most common site of dissemination.

◆ BASALOID SQUAMOUS CARCINOMA (BASALOID SQUAMOUS CELL CARCINOMA)

Basaloid squamous carcinoma is a recently described squamous cell carcinoma variant that arises primarily in the upper aerodigestive tract, with a predilection for the larynx, hypopharynx, and tongue base. More than 100 oral cases also have been reported. Heavy tobacco and alcohol use appear to represent major risk factors. In addition, recent studies suggest that HPV may play an important role in the etiopathogenesis of a distinct subset of oropharyngeal basaloid squamous cell carcinomas—particularly those arising in the palatine and lingual tonsils.

Clinical Features

Basaloid squamous carcinoma tends to occur in persons 40 to 85 years of age and arises more commonly in males than females. The lesion clinically appears as a fungating mass or ulcer and may be painful or interfere with swallowing **(dysphagia).** Approximately two-thirds of cases are diagnosed at an advanced clinical stage.

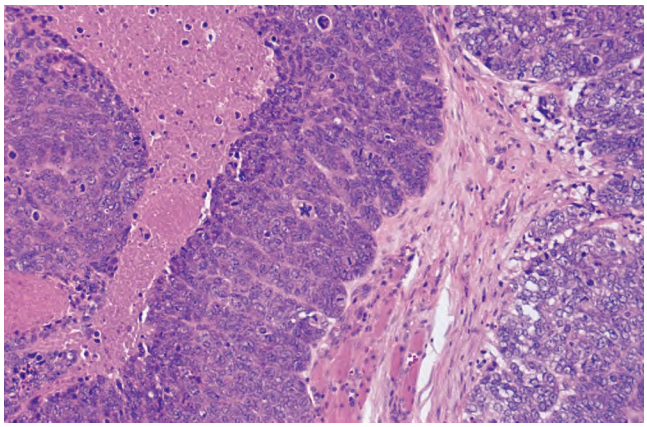


Fig. 10-125 Basaloid Squamous Carcinoma. Sheets of basaloid squamous epithelium exhibiting a high mitotic index and tumor necrosis.

Histopathologic Features

As its name connotes, basaloid squamous carcinoma has two microscopic components. The first is a superficial, well-differentiated or moderately differentiated squamous cell carcinoma, often with surface ulceration, multifocal origin, and areas of carcinoma *in situ.* The second, deeper component is an invasive basaloid epithelium arranged in islands, cords, and glandlike lobules. This deeper tumor often shows palisading of peripheral cells, central necrosis, and occasional squamous differentiation (Fig. 10-125). This component appears similar to basal cell carcinoma, adenoid cystic carcinoma, basal cell adenocarcinoma, or neuroendocrine carcinoma. The interface between the two components is typically sharp and distinct, but gradual transition from squamous to basaloid cells may be seen occasionally. The tumor islands often are surrounded by mucoid stroma (basal lamina material). Microcystic spaces filled with PAS-positive basal lamina material may be interspersed among the tumor islands as well.

Treatment and Prognosis

Treatment typically consists of surgery, often followed by radiation or chemoradiation therapy. Basaloid squamous carcinoma generally is considered a highly aggressive malignancy, with a mean survival of only 23 months. However, several authors have suggested that basaloid squamous cell carcinoma may have a similar outcome compared with conventional squamous cell carcinoma when cases are matched by clinical stage and anatomic location. Therefore, the poor prognosis for basaloid squamous cell carcinoma simply might reflect a tendency for these patients to be diagnosed with late-stage disease. Furthermore, recent evidence suggests that HPV status has a major impact on the prognosis of oropharyngeal basaloid squamous cell carcinomas, with significantly improved survival among HPV-positive cases compared to HPV-negative cases. Therefore, conflicting reports in the literature regarding prognosis may reflect differences in subsite distribution and HPV tumor status among study cohorts.

CARCINOMA OF THE MAXILLARY SINUS

Carcinoma of the maxillary sinus or antrum is an uncommon malignancy of largely unknown cause. It does not appear to be related to sinusitis or nasal polyps. Unlike squamous cell carcinomas in other head and neck sites, squamous cell carcinomas of the paranasal sinuses have been associated only weakly with tobacco use. A strong causal relationship to occupational wood and leather dust exposure has been established for the rarely occurring sinonasal intestinal type of adenocarcinoma. In addition, emerging evidence suggests that HPV may be an etiologic factor in some cases, with one large series detecting transcriptionally active high-risk HPV in approximately 20% of sinonasal carcinomas examined.

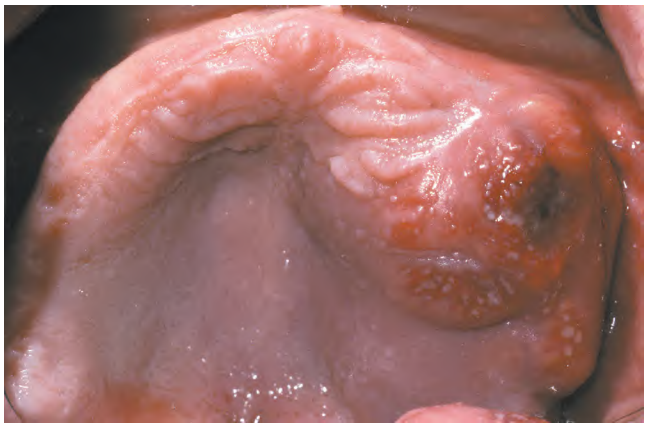
Maxillary sinus carcinomas comprise only 3% of all head and neck carcinomas; however, among paranasal sinus carcinomas, the maxillary sinus is the most common site (accounting for 80% of lesions). Most lesions remain asymptomatic or mimic sinusitis for long periods while the tumor grows to fill the sinus. Therefore, the diagnosis may not be made until the lesion has perforated through the surrounding bone.

The majority of maxillary sinus carcinomas represent squamous cell carcinomas. However, additional carcinomas that may arise in this location include sinonasal adenocarcinoma, **sinonasal undifferentiated carcinoma (SNUC)** (see next section), neuroendocrine (small cell undifferentiated) carcinoma, and salivary gland-type adenocarcinoma.

Clinical and Radiographic Features

Carcinoma of the maxillary sinus mainly affects older adults, with a slight male predilection. More than 80% of cases are advanced (stage III or IV) at the time of diagnosis. Patients generally complain of chronic unilateral nasal stuffiness or notice an ulceration or mass of the hard palate or alveolar bone (Fig. 10-126). When the second division of the trigeminal nerve is involved, intense pain or paresthesia of the midface or maxilla may occur, perhaps simulating a toothache. Adjacent teeth may become loose, and dental radiographs often reveal a "moth-eaten" destruction of the lamina dura and surrounding bone. A panoramic radiograph shows a cloudy sinus with destruction of its bony wall; however, the extent of the tumor is best visualized by CT or MRI.

If the tumor perforates the lateral wall of the sinus, unilateral facial swelling and pain are usually present. With medial extension, nasal obstruction and hemorrhage are common. Superior extension results in displacement or protrusion of the eyeball. Approximately 9% to 14% of patients



• **Fig. 10-126 Carcinoma of the Maxillary Sinus.** The tumor has produced a bulge of the posterior maxillary alveolar ridge and is beginning to ulcerate through the surface mucosa.

have cervical or submandibular lymph node metastasis at the time of diagnosis. Distant metastasis is uncommon until late in the progression of disease.

Histopathologic Features

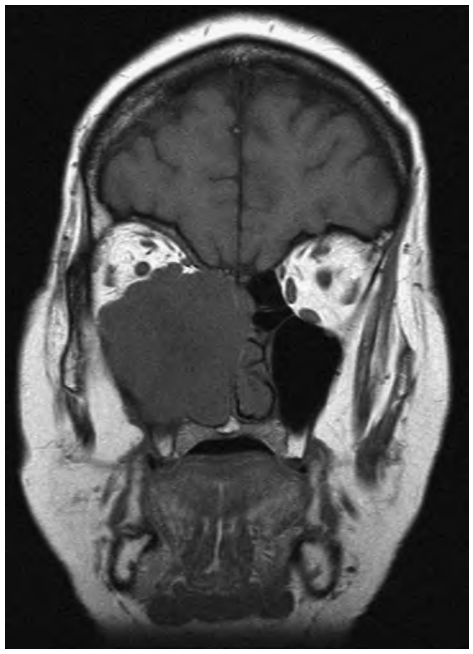
Although the antrum is lined by respiratory epithelium, the great majority of maxillary sinus carcinomas are **squamous cell carcinomas,** usually moderately or poorly differentiated.

Treatment and Prognosis

Carcinoma confined within the maxillary sinus usually is treated by hemimaxillectomy. Resectable tumors that have perforated through the surrounding bone are treated by surgery combined with radiotherapy and/or chemotherapy. Despite radical treatment, the prognosis generally is poor, with a 5-year survival rate of approximately 40%. Regional lymph node metastasis or involvement of the pterygopalatine fossa reduces the survival rate to less than 8%. Death usually occurs from local destruction and the inability to control the primary disease. Recent analysis suggests that HPV-positive sinonasal carcinomas may exhibit improved clinical outcomes compared to HPV-negative cases; however, additional studies are needed to confirm this finding.

◆ SINONASAL UNDIFFERENTIATED CARCINOMA

Sinonasal undifferentiated carcinoma (SNUC) is a rare, highly aggressive, and clinicopathologically distinctive neoplasm of the nasal cavity and paranasal sinuses. The tumor initially was described in 1986, and since then more than 200 cases have been reported. In the earlier literature, these tumors probably were classified as anaplastic carcinomas or high-grade olfactory neuroblastomas.



• **Fig. 10-127 Sinonasal Undifferentiated Carcinoma (SNUC).** T1-weighted magnetic resonance image (MRI) showing a large destructive mass filling the right maxillary sinus with extension into the orbital region and nasal cavity. (Courtesy of Dr. Zoran Rumboldt.)

The histogenesis and pathogenesis are poorly understood. Some investigators have theorized that the cell of origin may be related to the Schneiderian membrane or olfactory epithelium. There is only a weak association with tobacco smoking or Epstein-Barr virus (EBV). In some instances, patients have developed SNUC secondary to radiation therapy for nasopharyngeal carcinoma or retinoblastoma.

Clinical and Radiographic Features

SNUC occurs over a broad age range (third through ninth decades), with a median age at presentation in the sixth decade. The male-to-female ratio is approximately 2:1 to 3:1.

The tumor is well known for rapid development of locally extensive disease. It typically appears as a large mass that can involve multiple regions of the sinonasal tract, including the nasal cavity, maxillary sinus, and ethmoid sinuses. In addition, extension into contiguous sites—such as, the nasopharynx, orbit, and cranial cavity—is common. Inferior penetration into the oral cavity is possible as well. There is often rapid development of multiple sinonasal symptoms, including nasal obstruction or discharge, epistaxis, swelling, and pain. Orbital involvement may lead to proptosis, periorbital swelling, diplopia, and vision loss. Cranial nerve palsies are common as well.

Tumor extent is best assessed by CT or MRI, which typically reveals a large, expansile sinonasal mass with bony destruction and invasion of adjacent structures (Fig. 10-127).

Histopathologic Features

SNUC is characterized by trabeculae, ribbons, sheets, and nests of polygonal cells with minimal cytoplasm and pleomorphic, hyperchromatic to vesicular nuclei. No squamous or glandular differentiation should be observed. Mitotic figures are numerous. Tumor necrosis, apoptosis, and lymphovascular invasion usually are prominent. The surface epithelium overlying the tumor may exhibit dysplasia or carcinoma *in situ.* Immunohistochemical staining for cytokeratin or epithelial membrane antigen (EMA) typically is positive. Careful histopathologic examination and a broad immunohistochemical panel typically are needed to rule out other entities, such as poorly differentiated squamous cell carcinoma, olfactory neuroblastoma, undifferentiated nasopharyngeal carcinoma, neuroendocrine carcinoma, melanoma, lymphoma, and nuclear protein in testis (NUT) midline carcinoma. (The latter is a recently described, highly lethal malignancy defined by balanced translocations involving the *NUT* gene on chromosome 15q14.)

Treatment and Prognosis

Most patients present with locally advanced disease. In such cases, the standard approach is aggressive multimodal therapy, including surgical resection followed by adjuvant radiation and/or chemotherapy. Unresectable disease is treated by definitive chemoradiation therapy. When resectability is questionable, some authorities advocate induction chemotherapy in order to shrink the tumor prior to additional treatment and, possibly, to decrease the risk for distant metastasis. However, this approach is somewhat controversial and is associated with significant toxicity. The prognosis is generally poor, although several centers have reported improved outcomes with modern treatment approaches. Overall 5-year survival rates in the recent literature range from 20% to 74%. Local recurrence is common and is the major cause of morbidity and mortality. Metastasis is possible, usually to cervical lymph nodes, bone, liver, or brain.

◆ NASOPHARYNGEAL CARCINOMA

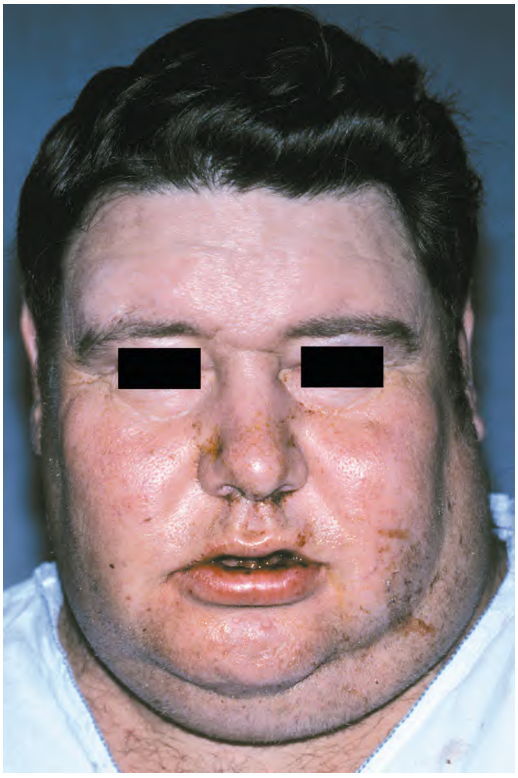
Nasopharyngeal carcinoma represents a group of malignancies that arise from the lining epithelium of the lymphoid tissue–rich nasopharynx; similar tumors are found in the palatine tonsil and base of tongue. These three anatomic sites are collectively called **Waldeyer tonsillar tissue** or **Waldeyer ring.**

Nasopharyngeal carcinoma is rare in most areas of the world. The average annual incidence rate in the United States is less than 1 per 100,000 persons. In southern Chinese men, however, the rate is a startling 20 to 55 per 100,000. Among southern Chinese men who migrate to the United States, the rate is intermediate, which suggests an environmental causative agent. Intermediate rates also are observed among many indigenous people of Southeast Asia (including Thais, Vietnamese, Malays, and Filipinos), Inuits of Alaska and Greenland, and Arabs of North Africa.

Infection with Epstein-Barr virus (EBV), diets deficient in vitamin C, and consumption of salt fish containing carcinogenic N-nitrosamines have been implicated as contributory factors. Tobacco also has been implicated as a risk factor; however, the risk for carcinoma development for a given level of tobacco exposure is lower in the nasopharynx than in other parts of the upper aerodigestive tract. In addition, recent studies have detected high-risk HPV in a small subset of nasopharyngeal carcinomas with a predilection for white individuals.

Clinical Features

Nasopharyngeal carcinoma occurs in all age groups but most commonly affects those who are 40 to 60 years old. It also occurs three times more commonly in men than in women. The primary lesion, which usually arises from the lateral nasopharyngeal wall, often is small and difficult to detect, even by endoscopy. The first sign of disease for 50% to 60% of patients is an enlarged, firm to hard, cervical lymph node, which represents metastatic tumor (Fig. 10-128). Symptoms related to the ear are described by slightly less than half of patients. If the tumor obstructs the eustachian tube, then unilateral serous otitis media, otalgia, or hearing loss may be the presenting complaint.



• **Fig. 10-128 Nasopharyngeal Carcinoma.** This patient initially appeared with metastatic carcinoma in the left lateral neck. Further evaluation revealed a primary tumor of the nasopharynx. (Courtesy of Dr. D. E. Kenady.)

Epistaxis, nasal obstruction, and pharyngeal pain may be present. The tumor may invade through the foramen lacerum into the brain, producing CNS symptoms, or it may involve cranial nerves in the area, causing specific symptoms related to those nerves. Involvement of the pterygoid muscles can produce facial pain with limited jaw movement, thereby mimicking a temporomandibular joint disorder. Significantly, 5% to 10% of patients also have distant metastasis at the time of diagnosis.

Histopathologic Features

The surgeon often has difficulty finding the primary lesion, and multiple systematic biopsy samples of the nasopharyngeal mucosa may be necessary for tumor identification and diagnosis. Nasopharyngeal carcinoma mainly includes the following histopathologic types:

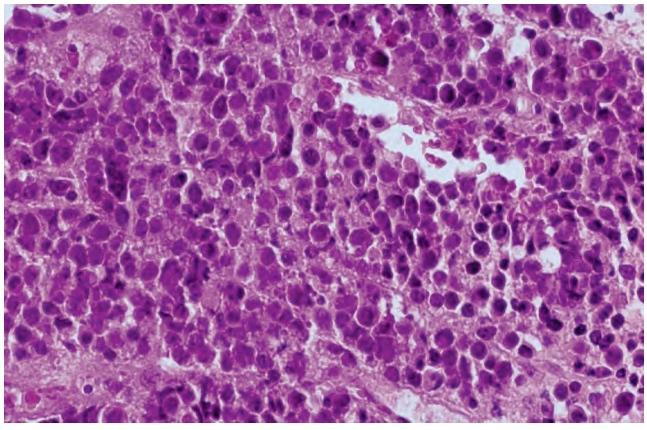
1. Keratinizing squamous cell carcinoma (squamous cell carcinoma)
2. Differentiated nonkeratinizing carcinoma (nonkeratinizing squamous cell carcinoma)
3. Undifferentiated nonkeratinizing carcinoma (poorly differentiated carcinoma, anaplastic carcinoma, and lymphoepithelioma)

When more than one histopathologic type is present, the tumor is classified according to the predominant type.

The histopathologic features of **keratinizing squamous cell carcinoma** are identical to those of squamous cell carcinoma of other head and neck regions (see page 385). Keratinization must be evident at the light microscopic level.

The lesional cells of **differentiated nonkeratinizing carcinoma** are relatively mature and somewhat squamous in nature, but they produce no keratin. Broad interconnecting bands of oval or round cells are organized in plexiform and papillary patterns.

Undifferentiated nonkeratinizing carcinoma consists of sheets of undifferentiated cells with indistinct margins, very little cytoplasm, and large, vesicular nuclei (Fig. 10-129). These tumor cells are often intermixed with the lymphoid cells normally found at this anatomic site. The term **lymphoepithelioma** has been used to describe this lesion because it was once thought to be a malignancy that originated from both epithelial and lymphoid tissues. This terminology should be discouraged, however, because the lymphoid tissue is not part of the neoplastic process. Such undifferentiated tumors may be difficult to distinguish from lymphoma by routine light microscopic examination, and immunohistochemical studies often are used to demonstrate cytokeratins within the carcinoma cells. Occasional cases show neuroendocrine differentiation.



• **Fig. 10-129 Nasopharyngeal Carcinoma.** Poorly differentiated tumor exhibiting sheets of rounded tumor cells.

The undifferentiated lesions tend to occur in younger individuals and account for virtually all nasopharyngeal carcinomas in people younger than 40 years. Among southern Chinese patients, the vast majority (95%) of cases are classified as undifferentiated nonkeratinizing carcinomas, whereas in nonendemic areas, 25% to 50% of cases are keratinizing squamous cell carcinomas.

The differentiated and undifferentiated nonkeratinizing types are very closely associated with EBV, which is best demonstrated by *in situ* hybridization for EBV-encoded early RNA (EBER). In contrast, EBV status is highly variable in the keratinizing type, with EBV most often detected among cases in endemic areas. Among the small subset of HPV-positive cases, the nonkeratinizing types predominate.

Treatment and Prognosis

Because of the inaccessibility of the nasopharynx and the keen radiosensitivity of nasopharyngeal carcinoma, radiotherapy is the mainstay of treatment. Early-stage disease typically is managed by radiotherapy alone. However, most patients present with advanced locoregional disease, for which current evidence supports concurrent platinum-based chemotherapy and radiation therapy. Targeted therapies (e.g., inhibitors of epidermal growth factor receptor [EGFR] and angiogenesis) and immunotherapy directed against EBV antigens are currently under investigation.

In the United States, the relative 5-year survival rates for patients with stage I, II, III, and IV disease are 72%, 64%, 62%, and 38%, respectively. For all stages combined, the relative 5-year survival rate is 59%. When treated with radiation therapy, the differentiated and undifferentiated nonkeratinizing types exhibit a higher local control rate but a greater risk for distant metastasis compared with the keratinizing type. In the United States, higher survival rates have been observed among Chinese-American patients compared with other ethnic groups. This trend traditionally has been attributed to the prevalence of the more radiosensitive undifferentiated nonkeratinizing type among Chinese-American patients; however, for unknown reasons, Chinese ethnicity is a favorable prognostic factor even independent of histopathologic type. Additional favorable prognostic factors include age under 40 years, female gender, and low titers of circulating EBV DNA (determined pre-treatment and post-treatment by real-time PCR). The prognostic significance of HPV-positivity currently is unclear. Persons treated for nasopharyngeal carcinoma are also at increased

risk for developing a second primary malignancy of the head and neck mucosa.

◆ BASAL CELL CARCINOMA (BASAL CELL EPITHELIOMA; RODENT ULCER)

Basal cell carcinoma represents the most common skin cancer, as well as the most common of all cancers. It is a locally invasive, slowly spreading, epithelial malignancy that arises from the basal cell layer of the skin and its appendages. About 80% are found on the skin of the head and neck.

The incidence is difficult to determine because basal cell carcinoma typically is not reported to cancer registries. However, researchers estimate that 2.8 million basal cell carcinomas were treated in the United States in 2006. Moreover, according to one study, as of 2007 there were about 13 million non-Hispanic whites in the United States with a personal history of at least one nonmelanoma skin cancer, with the majority (80%) of these cases representing basal cell carcinomas. The worldwide incidence of basal cell carcinoma varies considerably by region, with the highest rates (>2000 per 100,000 person-years) reported in parts of Australia. The risk generally increases with age, proximity to the equator, and lighter skin pigmentation. Furthermore, the incidence in North America and Europe has increased sharply over the past several decades; in part, this trend may be due to aging populations, although some investigators have reported a disproportionate increase among young adults (particularly women) as well.

This cancer mainly results from cumulative (including chronic and intermittent) UV radiation exposure. Frequent sunburns and tendency for freckling in childhood are associated with an increased risk. Additional risk factors include outdoor occupational activity, psoralen and ultraviolet A (PUVA) treatment (often used for psoriasis), tanning device use, ionizing radiation exposure, immunosuppression, and arsenic ingestion. Allelic variations in genes related to DNA repair or pigmentation (e.g., the *melanocortin 1 receptor [MC1R]* gene) also may confer increased susceptibility. Furthermore, several genodermatoses are associated with basal cell carcinoma, including the nevoid basal cell carcinoma syndrome (see page 640), xeroderma pigmentosum (see page 696), albinism, Rasmussen syndrome, Rombo syndrome, Bazex-Christol-Dupré syndrome, and the Dowling-Meara subtype of epidermolysis bullosa simplex (see page 708).

Molecular genetic studies have shown that dysregulation of the hedgehog signaling pathway is a critical early event in the development of basal cell carcinoma. Inactivating mutations in the *patched (PTCH)* gene on chromosome 9q22 have been identified in both sporadic cases and patients with the nevoid basal cell carcinoma syndrome. Mutations in other genes participating in this pathway (e.g., *smoothened [SMO]*) occasionally may be found in sporadic cases as well. These mutations lead to constitutive activation of hedgehog signaling and enhanced cellular proliferation. In addition, *TP53* mutations are found in more than 50% of sporadic basal cell carcinomas and may represent a later event in tumor development.

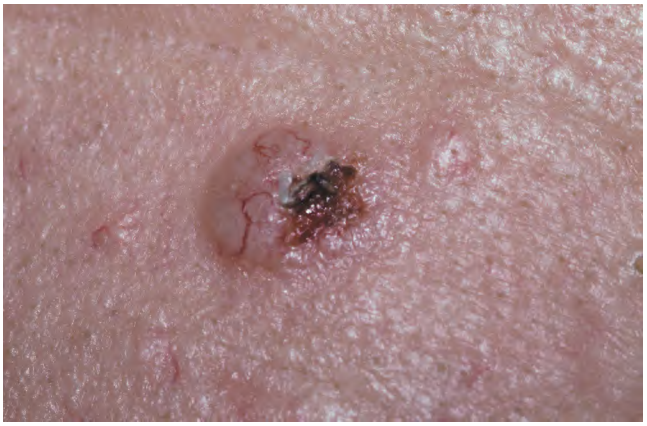
Well-documented reports of oral basal cell carcinoma are rare. Many of the cases described in the literature actually represent misdiagnosed salivary or odontogenic neoplasms.

Clinical Features

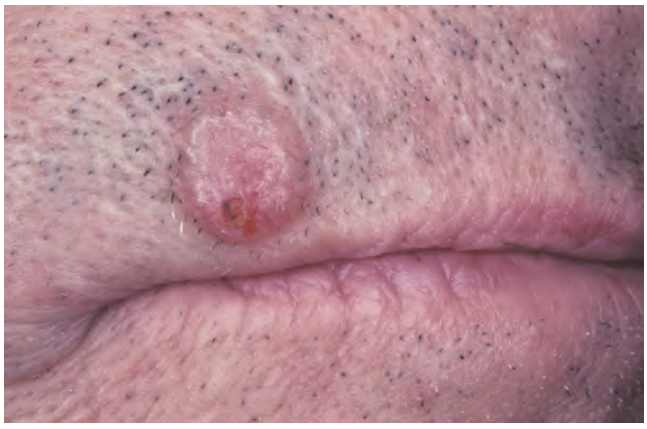
Basal cell carcinoma most often affects white adults, especially those with fair complexions. Although most patients are older than 40 years at diagnosis, some lesions are detected as early as the second decade of life, particularly in patients with red or blonde hair and blue or green eyes. Males are affected about twice as often as females; however, among young patients, there is a female predilection (possibly due to tanning bed use). Approximately 80% of lesions occur on the head and neck, with the remainder involving the trunk and limbs.

The most common clinicopathologic variant, **nodular (noduloulcerative) basal cell carcinoma,** begins as a firm, painless papule that slowly enlarges and develops a central depression or umbilication. Telangiectatic blood vessels usually are evident within the rolled border surrounding the central depression (Figs. 10-130 and 10-131). When the lesion is pressed, a characteristic pearly opalescent quality is discerned. Expanding ulceration often develops in the central depression, and the patient may report intermittent bleeding followed by healing. Untreated lesions continue to enlarge slowly, with ulceration and destruction of underlying structures—hence the term **rodent ulcer** (Fig. 10-132)**.** Destruction of underlying bone or cartilage may occur, but metastasis is extremely rare.

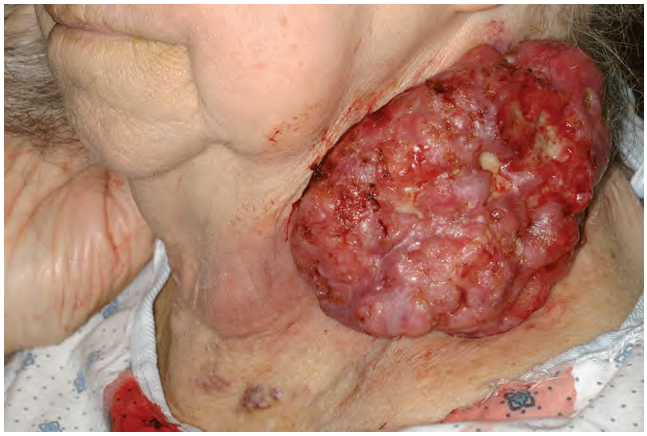
Several other variants have been described. **Pigmented basal cell carcinoma** represents a noduloulcerative tumor colonized by benign melanocytes (Fig. 10-133). The melanin production imparts a tan, brown, black, or even bluish color, and usually the pigment is not distributed uniformly, as it would be in a melanocytic nevus (see page 350).



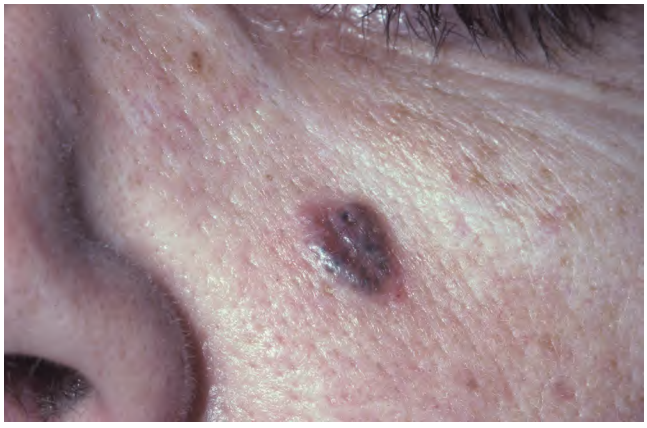
• **Fig. 10-130 Basal Cell Carcinoma.** Early noduloulcerative basal cell carcinoma of the forehead showing raised, rolled borders and focal ulceration. Fine, telangiectatic blood vessels can be seen on the surface.



• **Fig. 10-131 Basal Cell Carcinoma.** Noduloulcerative lesion of the upper lip demonstrating telangiectasia and small ulceration.

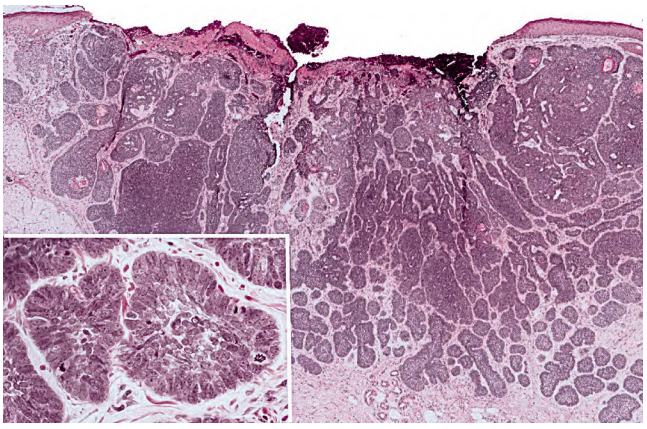


• **Fig. 10-132 Basal Cell Carcinoma.** This tumor was neglected for many years and became exceptionally large. (Courtesy of Dr. Terry Day.)



• **Fig. 10-133 Basal Cell Carcinoma.** Pigmented basal cell carcinoma of the cheek.

Sclerosing (morpheaform) basal cell carcinoma is an insidious lesion that often mimics scar tissue. The overlying skin appears pale and atrophic, and the lesion is firm to palpation with poorly demarcated borders. A slight elevation may be noted at the tumor edges. Often a great deal of invasion has occurred before the patient becomes aware of a problem.



• **Fig. 10-134 Basal Cell Carcinoma.** Low-power photomicrograph showing ulceration of the epidermal surface associated with an invading tumor of hyperchromatic epithelial cells. *Inset* demonstrates islands of basophilic epithelium with peripheral palisading.

Superficial basal cell carcinoma occurs primarily on the skin of the trunk. Often, lesions are multiple and appear as well-demarcated, erythematous, scaly patches that may be mistaken clinically for psoriasis or eczema. A fine, elevated, "threadlike" border is seen at the margins.

Some investigators believe that basal cell carcinomas associated with the **nevoid basal cell carcinoma syndrome** (see page 640) should be placed in a separate category. These lesions develop in both sun-exposed and protected areas of the skin and may number in the hundreds on a single patient. The tumors associated with this syndrome usually do not produce significant tissue destruction.

Histopathologic Features

Basal cell carcinoma displays considerable histopathologic diversity and includes the following microscopic patterns: noduloulcerative (nodulocystic), pigmented, keratotic, adenoid, superficial, infiltrative, sclerosing (morpheaform), and micronodular. The noduloulcerative, pigmented, and syndrome-related basal cell carcinomas are comprised of uniform, ovoid, dark-staining basaloid cells with medium-sized nuclei and little cytoplasm (Fig. 10-134). The cells are arranged in well-demarcated islands and strands, which appear to arise from the basal cell layer of the overlying epidermis and invade the underlying connective tissue. Epithelial islands typically demonstrate palisading of the peripheral cells; frequently, artifactual retraction is seen between the epithelial islands and the connective tissue. Although most of these neoplasms show no differentiation, some exhibit areas of keratin production, sebaceous differentiation, or interlacing strands of lesional cells that resemble duct formation ("adenoid"). Necrosis of epithelial islands may produce a cystic appearance. Actinic damage in the form of **solar elastosis** almost always is seen in adjacent stroma.

Pigmented basal cell carcinoma demonstrates dendritic melanocytes within tumor islands, and melanophages may

be seen in the surrounding stroma. Both the infiltrative and sclerosing types exhibit infiltrating thin strands of basaloid tumor cells; the latter type also shows a densely collagenous background. Superficial basal cell carcinoma includes lobules of tumor cells that drop from the epidermis in a multifocal pattern. Micronodular basal cell carcinoma exhibits small, round tumor nests less than 0.15 mm in diameter (or about the size of a hair follicle bulb). Occasionally, basal cell carcinoma is admixed with an independent primary squamous cell carcinoma of the skin. The resulting "collision" tumor is called **basosquamous carcinoma.** Some authorities consider basosquamous carcinoma to be a simple basal cell carcinoma with abundant squamous metaplasia.

Some studies suggest that immunohistochemical expression of Ber-EP4 (a cell surface glycoprotein preferentially expressed in cutaneous basal cell carcinoma) may help to distinguish extremely rare cases of intraoral basal cell carcinoma from peripheral ameloblastoma.

Treatment and Prognosis

The following features are associated with increased risk for recurrence among cutaneous basal cell carcinomas of the head and neck:

- Lesions of 6 mm or more in the so-called "mask area" of the face (i.e., skin of the central face/nose, ocular region, temples, auricular region, and perioral/mandibular region)
- Lesions more than 1 cm in head and neck sites outside the "mask area"
- Ill-defined clinical borders
- Micronodular, infiltrative, and sclerosing types
- Perineural invasion
- Recurrent lesions
- Lesions arising in immunosuppressed individuals or in a prior site of radiotherapy

Lesions with low risk for recurrence typically are treated by routine surgical excision or electrodesiccation and curettage, with 3- to 5-mm margins of clinically normal-appearing skin beyond the visible lesion. These methods result in a cure rate of 95% to 98%. Head and neck lesions with a high risk for recurrence often are treated by **Mohs micrographic surgery.** This technique uses intraoperative, frozen-section evaluation of specially mapped and marked surgical specimens to ensure complete tumor removal. Radiotherapy may be an option for patients unable to tolerate surgery.

Alternative treatments—such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or vigorous cryotherapy—may be effective for low-risk, superficial basal cell carcinomas. However, such alternatives are associated with suboptimal cure rates and, thus, typically are reserved for cases in which surgery and radiation are contraindicated or impractical. Recently, the United States Food and Drug Administration approved vismodegib (a small-molecule inhibitor of the hedgehog signaling pathway) for the treatment of recurrent, advanced basal cell carcinomas or lesions in patients unable to tolerate surgery or radiation. Several other targeted agents are under development.

Recurrence of a properly treated basal cell carcinoma is uncommon, and metastasis is exceptionally rare. In patients with uncontrollable disease, death usually results from local invasion into vital structures. However, with early detection and the advent of Mohs surgery, such an outcome is unusual today.

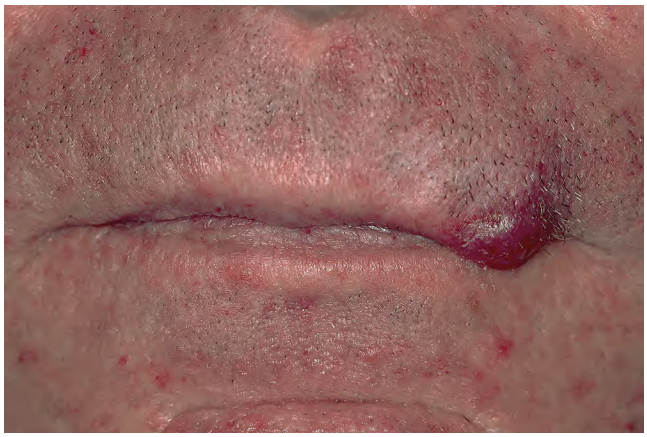
Patients with a history of basal cell carcinoma must be evaluated periodically. There is an estimated 44% chance of a second basal cell carcinoma and 6% chance of a cutaneous squamous cell carcinoma developing within 3 years of treatment of the initial tumor.

◆ MERKEL CELL CARCINOMA (MERKEL CELL TUMOR; NEUROENDOCRINE CARCINOMA OF SKIN; SMALL CELL CARCINOMA OF SKIN; TRABECULAR CARCINOMA OF SKIN)

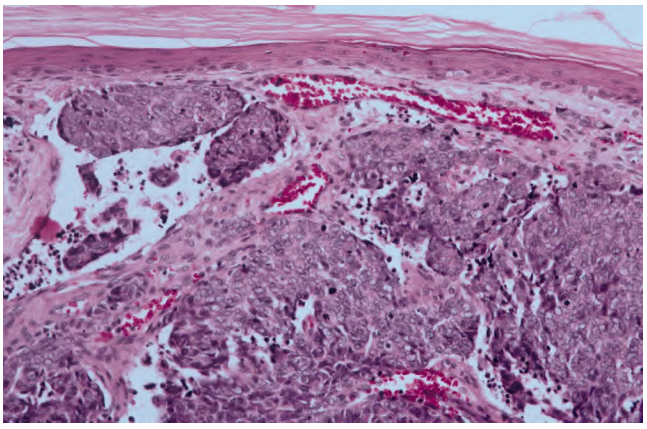
Merkel cell carcinoma is a rare, aggressive malignancy with neuroendocrine features. It most often occurs on the skin of the head and neck region. As with other skin malignancies, UV light exposure and old age are major risk factors. In addition, there is an increased frequency among immunocompromised individuals, including transplant recipients, patients receiving immunosuppressive therapy for autoimmune diseases, patients with other underlying malignancies (especially chronic lymphocytic leukemia), and patients with HIV infection. Recently, investigators have detected DNA from the novel Merkel cell polyomavirus (MCPyV) in up to 80% of cases.

Based upon the identification of cytoplasmic neurosecretory granules by electron microscopy and neuroendocrine markers by immunohistochemistry, this neoplasm traditionally was thought to arise from Merkel cells (mechanoreceptor cells found primarily in skin, but also found at other sites, including keratinized oral mucosa). However, because of the presence of nonendocrine epithelial and sarcomatous elements in some cases, many authorities currently favor an origin from pluripotent epidermal or dermal stem cells. These hypotheses may be reconciled by the recent discovery that Merkel cells are derived from epidermal stem cells.

Intraoral and lip vermilion cases have been reported rarely. However, some oral neuroendocrine malignancies previously reported as Merkel cell carcinomas actually may be more akin to high-grade small cell neuroendocrine carcinomas of the upper aerodigestive tract mucosa. The latter tumor type is closely associated with tobacco and alcohol abuse, is not associated with UV light exposure or MCPyV, exhibits microscopic features similar to small cell carcinoma of the lung, and may behave even more aggressively than Merkel cell carcinoma.



• **Fig. 10-135 Merkel Cell Carcinoma.** Red nodule on the vermilion border of the upper lip. (From Chang JYF, Stewart JM, Cheng YSL, et al: Upper lip nodule, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 105:549-553, 2008.)



• **Fig. 10-136 Merkel Cell Carcinoma.** A sheet of undifferentiated basophilic cells is seen beneath the epidermal surface.

Clinical Features

More than 70% of Merkel cell carcinomas arise in individuals 70 years or older. The tumor mainly affects whites (95% of cases) and exhibits a male predominance. It occurs primarily on sun-exposed areas of fair-skinned individuals, with a predilection for the skin of the face, upper limbs, and shoulders. The lip vermilion is also susceptible (Fig. 10-135). Extracutaneous lesions are rare and most often affect the salivary glands, although involvement of the oral, nasal, pharyngeal, laryngeal, esophageal, and genital mucosa also are possible. The tumor usually appears as an asymptomatic, rapidly enlarging, smooth, dome-shaped nodule with prominent surface vessels **(telangiectasias).** Some authors have used the acronym **AEIOU** (**A**symptomatic, **E**xpanding rapidly, **I**mmunosuppression, **O**ld age, **U**ltraviolet-exposed fair skin) to summarize the salient clinical findings. The lesion typically is red, violaceous, or pink and ranges in size from 0.5 to 5.0 cm. An often innocuous clinical appearance may cause delay in diagnosis. Approximately 27% of cases demonstrate regional lymph node metastasis at diagnosis. In about 14% of cases, there is nodal disease of unknown primary origin, presumably due to regression of the primary tumor.

Histopathologic Features

Merkel cell carcinoma consists of sheets and anastomosing strands of small to moderately sized, round, basophilic cells, which infiltrate the dermis and subcutaneous fat (Fig. 10-136). Epidermal involvement is present in only a small proportion of cases. Pseudoglandular, trabecular, cribriform ("Swiss cheese"), and sheetlike patterns may be seen. The tumor cells typically exhibit overlapping nuclei, finely granular chromatin, scant cytoplasm, indistinct cell borders, and brisk mitotic activity. MCPyV-positive lesions tend to have uniformly round nuclei, whereas MCPyV-negative cases often exhibit irregular nuclei. Intracytoplasmic argyrophilic granules may be demonstrated by the Grimelius stain, and immunohistochemical staining for cytokeratin 20 (CK20) usually shows a "perinuclear dot" pattern. Immunopositivity for neuroendocrine markers (e.g., chromogranin A, synaptophysin, neuron-specific enolase, and CD56) and neurofilament also may be helpful in establishing the diagnosis. In approximately 70% to 80% of cases, MCPyV DNA is detectable by polymerase chain reaction (PCR). Lack of immunoreactivity for thyroid transcription factor 1 (TTF-1) may help to exclude metastatic small cell carcinoma of the lung, which may have similar histomorphologic features. The microscopic differential diagnosis also may include amelanotic melanoma, metastatic esthesioneuroblastoma, lymphoma, and other "round-cell" malignancies. Immunohistochemical studies and thorough physical examination may aid in excluding these other entities. Furthermore, Merkel cell carcinomas may occur in combination with other neoplasms, especially actinic keratosis and invasive or *in situ* squamous cell carcinoma.

Treatment and Prognosis

Surgery (i.e., wide local excision or Mohs micrographic surgery) is the mainstay of treatment and often is combined with adjuvant radiotherapy. Lymph node dissection is performed when clinically palpable nodes are found. Sentinel lymph node biopsy typically is used to determine whether regional lymph node dissection and/or radiation are indicated in patients with clinically negative nodes. Chemotherapy is reserved for cases with distant metastasis. Immune reconstitution by combination antiretroviral therapy is important for controlling Merkel cell carcinoma in patients with HIV infection. Also, in some cases, tumor regression has been reported after cessation of immunosuppressive therapy.

Recurrence develops in 55% of cases, most commonly within the draining lymph nodes. The relative 10-year survival rates for patients with localized, regional, and distant disease are 71%, 48%, and 20%, respectively. The overall 10-year survival rate is approximately 57%. Female sex,

upper limb involvement, and age under 70 years are positive predictors of survival. Primary mucosal lesions exhibit a worse prognosis than the more common, primary cutaneous lesions. Similarly, lip lesions may have a worse prognosis than those arising in more frequently involved head and neck sites. There is some controversy regarding whether tumor positivity for MCPyV represents a favorable prognostic factor.

Approximately 25% of patients with Merkel cell carcinoma develop additional malignancies (e.g., squamous cell carcinomas of the skin, hematologic malignancies, or adenocarcinomas of the breast or ovary). Thus these patients should be monitored closely.

◆ MELANOMA (MALIGNANT MELANOMA; MELANOCARCINOMA)

Melanoma is a malignant neoplasm of melanocytic origin; it may arise *de novo* or from a preexisting benign melanocytic lesion. Most cases occur on the skin, although mucosal lesions also are possible. UV radiation exposure from sunlight is a major etiologic factor, with increased incidence of melanoma among white populations as they approach the equator. Acute sun damage may be of greater causative importance than chronic exposure. Oral mucosal lesions, of course, are not related to sun exposure.

Risk factors for melanoma include a fair complexion, light-colored hair and eyes, a tendency to sunburn or freckle easily, a history of painful or blistering sunburns in childhood, an indoor occupation with outdoor recreational habits, a personal or family history of melanoma, a personal history of dysplastic or congenital nevus, and a personal history of excessive (>100) common nevi. Potential associations with tanning device use, immunosuppressive therapy for organ transplantation, and various childhood malignancies also have been proposed. Furthermore, among some melanoma-prone kindreds, investigators have identified mutations (e.g., in the *cyclin-dependent kinase inhibitor 2A* [*CDKN2A*] and *cyclin-dependent kinase 4* [*CDK4*] genes) that confer a high risk for melanoma development. Moreover, recent genomic studies have identified numerous genetic loci associated with a slightly- to moderately-increased risk for melanoma (e.g., allelic variants in the key pigmentation gene, *melanocortin 1 receptor* [*MC1R*]).

Melanoma represents the third most common skin cancer. It accounts for less than 5% of total skin cancer cases but 75% of skin cancer deaths. In the United States for the year 2013, the American Cancer Society estimates that 76,690 new cases of cutaneous melanoma will be diagnosed and 9,480 people will die of the disease. According to the most recent estimate by the SEER Program, 1 in 50 persons in the United States will be diagnosed with cutaneous melanoma during his or her lifetime. For 2009, the age-adjusted annual incidence rates for skin melanoma were approximately 29 per 100,000 men and 18 per 100,000 women. Over the past several decades, dramatic increases in the incidence of melanoma have been reported worldwide. Some investigators contend that this trend reflects increased numbers of skin biopsies and improved diagnosis of early-stage disease. However, others have demonstrated increased frequency of both early- and late-stage disease and, thus, propose that there is a true increase in disease rate. Despite increasing incidence, the mortality rate for cutaneous melanoma has remained relatively constant since the late 1980s, apparently because a large proportion of cases are diagnosed at an early stage.

According to the *National Cancer Database Report on Cutaneous and Noncutaneous Melanoma,* 91.2% of all melanomas arise on the skin, whereas ocular, mucosal, and unknown primaries account for 5.2%, 1.3%, and 2.2% of cases, respectively. Almost 25% of cutaneous melanomas arise in the head and neck area, 40% on the extremities, and the rest on the trunk. More than half of mucosal melanomas occur in the head and neck (including the oral and sinonasal regions), with the remainder primarily involving the urogenital and anorectal mucosa. Importantly, mucosal melanoma is much more aggressive than its cutaneous counterpart.

Oral mucosal melanoma is rare in the United States, where it occurs in only 1.2 per 10 million population annually and comprises much less than 1% of all melanomas. An analysis of various worldwide cancer registries has shown similarly low incidence rates, with primary oral melanoma accounting for only 0.26% of all oral cavity cancers. Several reports suggest that mucosal melanoma is more frequent in certain countries, such as Japan and Uganda; however, other investigators have suggested that the true incidence of mucosal melanoma is not greater in these countries but only appears so because of the comparatively low incidence of cutaneous melanoma in these racial groups.

In recent years, there have been many discoveries regarding recurrent genetic alterations in melanomas, including those involving the Ras/Raf/MEK/mitogen-activating protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways. In particular, approximately 50% of melanomas possess mutations in the gene encoding *BRAF,* a protein kinase involved in the Ras/Raf/MEK/MAPK pathway. Among mucosal melanomas, frequent alterations have been identified in the *KIT* gene, which encodes a receptor tyrosine kinase that interacts with Ras.

Clinical Features

Cutaneous melanomas most commonly develop in white adults. Although the lesion occurs over a broad age range, most cases arise in individuals 45 through 84 years old, with a median age at diagnosis of 61 years. There is a female predilection among patients younger than 40 years (possibly related to tanning bed use); in contrast, a male predilection is seen among older patients. The most frequent primary site in men is the back, whereas in women the lower extremities are affected most commonly. Because many clinical

• BOX 10-4 The "ABCDE" Clinical Features of Melanoma

- **A**symmetry (because of its uncontrolled growth pattern)
- **B**order irregularity (often with notching)
- **C**olor variegation (which varies from shades of brown to black, white, red, and blue, depending on the amount and depth of melanin pigmentation)
- **D**iameter greater than 6 mm (which is the diameter of a pencil eraser)
- **E**volving (lesions that have changed with respect to size, shape, color, surface, or symptoms over time)

similarities exist between cutaneous melanoma and its benign counterpart, the melanocytic nevus, an "ABCDE" clinical evaluation system has been developed to help distinguish between these two entities (Box 10-4).

The following major clinicopathologic types of melanoma are described below:

1. Superficial spreading melanoma
2. Nodular melanoma
3. Lentigo maligna melanoma
4. Acral lentiginous melanoma

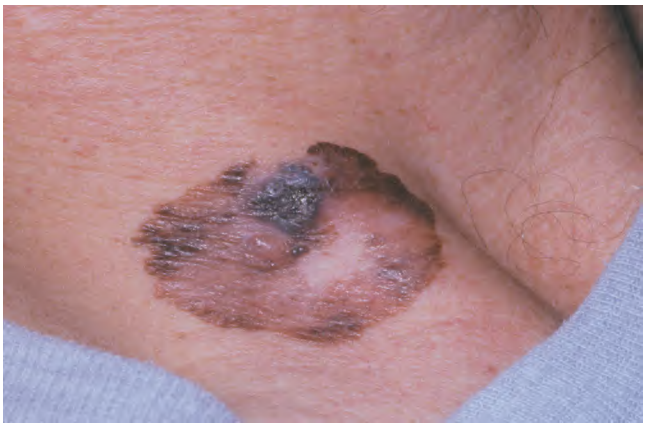
Melanomas tend to exhibit two directional patterns of growth: 1) the **radial growth phase** and 2) the **vertical growth phase.** In the early stages, the radial growth phase tends to predominate in lentigo maligna melanoma, superficial spreading melanoma, and acral lentiginous melanoma. In these lesions, the malignant melanocytes have a propensity to spread horizontally through the basal layer of the epidermis. Eventually, however, the malignant cells begin to invade the underlying connective tissue, thus initiating the vertical growth phase. In nodular melanoma, the radial growth phase is very short or nonexistent, and the vertical growth phase predominates.

Superficial Spreading Melanoma

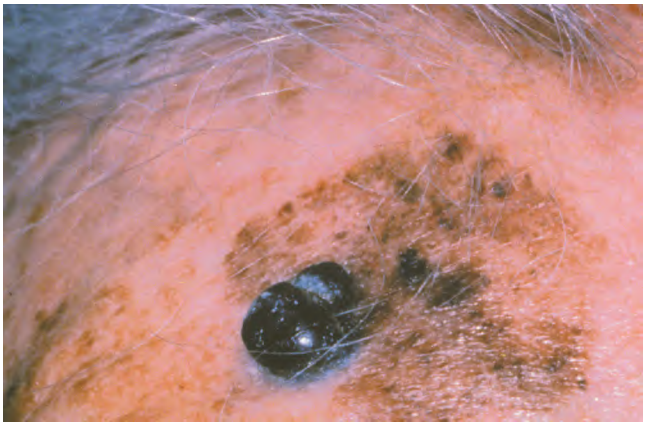
Superficial spreading melanoma is the most common form of melanoma, representing 70% of cutaneous lesions (Fig. 10-137). The most common sites of origin are the interscapular area of males and the back of the legs of females. The lesion appears as a macule or plaque with a variety of potential colors (i.e., tan, brown, gray, black, blue, white, and pink). Typically, the lesion is smaller than 3 cm in greatest diameter at diagnosis, but it may be several times that size. Clinically, invasion is indicated by the appearance of surface nodules or induration, and usually occurs within 1 year of discovery of the precursor macule. Satellites may develop around the primary lesion.

Nodular Melanoma

Nodular melanoma represents 15% of cutaneous melanomas, and one-third of such lesions develop in the head and neck. Nodular melanoma is thought to begin almost immediately in the vertical growth phase; therefore, it typically appears as a nodular elevation that rapidly invades the connective tissue. Nodular melanoma is usually deeply pigmented, although sometimes the melanoma cells are so poorly differentiated that they no longer can produce melanin, resulting in a nonpigmented **amelanotic melanoma.**



• Fig. 10-137 Superficial Spreading Melanoma. This lesion on the neck demonstrates the ABCDE warning signs of melanoma: **A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter larger than a pencil eraser, and **E**volving larger size. (Courtesy of Dr. Mark Bowden.)

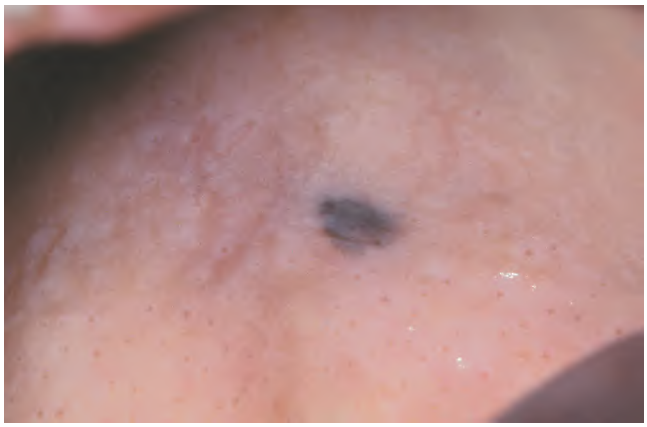


• Fig. 10-138 Lentigo Maligna Melanoma. A slowly evolving pigmented lesion of the facial skin in an older adult man.

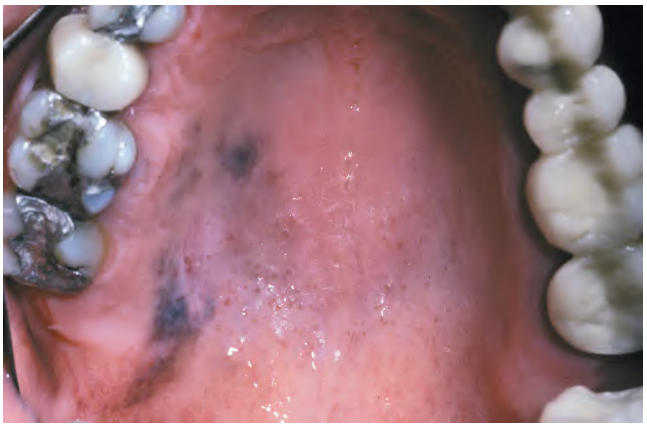
Lentigo Maligna Melanoma

Lentigo maligna melanoma, which accounts for 5% to 10% of cutaneous melanomas, develops from a precursor lesion called **lentigo maligna (Hutchinson freckle).** Lentigo maligna occurs almost exclusively on the sun-exposed skin of fair-complexioned older adults, particularly in the midfacial region, and represents a **melanoma *in situ*** in a purely radial growth phase.

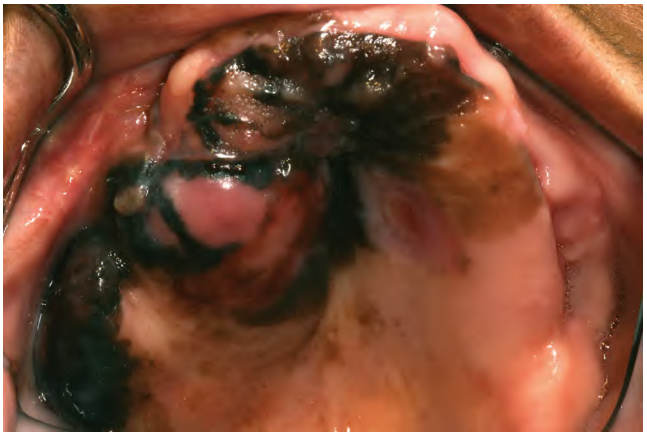
The lesion appears as a large, slowly expanding macule with irregular borders and a variety of colors, including tan, brown, black, and even white (Fig. 10-138). Patients usually indicate that the lesion has been present and has slowly expanded laterally for years. The average duration of the radial growth phase is 15 years. The appearance of nodularity within a lentigo maligna signals the onset of the invasive or vertical growth phase and the transition to lentigo maligna melanoma.



• **Fig. 10-139 Oral Melanoma.** This discrete area of pigmentation, measuring approximately 5 mm in diameter, was discovered on the posterior hard palate of a middle-aged woman during a routine oral examination. Biopsy revealed melanoma *in situ*.



• **Fig. 10-140 Oral Melanoma.** Diffuse, splotchy area of pigmentation of the lateral hard palate. (Courtesy of Dr. Len Morrow.)



• **Fig. 10-141 Oral Melanoma.** Extensive, pigmented mass of the palate and maxillary alveolar ridge. An exophytic component is evident.

Acral Lentiginous Melanoma (Mucosal Lentiginous Melanoma)

Acral lentiginous melanoma is the most common form of melanoma in blacks, and it is also the most common form of **oral melanoma.** It typically develops on the palms of the hands, soles of the feet, subungual area, and mucous membranes. It begins as a dark, irregularly marginated macule, which later develops a nodular invasive growth phase. Some authorities have separated this lesion into two entities: 1) **acral lentiginous melanoma** and 2) **mucosal lentiginous melanoma.**

Oral melanoma is often nodular at the time of diagnosis, but early lesions may be flat. There is a male predilection, and affected persons are usually in their fifth through seventh decades of life. Approximately 70% to 80% of oral melanomas are found on the hard palate or maxillary alveolus. At least one in three patients with oral melanoma has a history of a pigmented macule in the tumor region for some time before melanoma diagnosis. The lesion typically begins as a brown to black macule with irregular borders (Figs. 10-139 and 10-140). However, some lesions contain little pigment and exhibit either a normal mucosal tint or a vascular appearance. The macule extends laterally, and a lobulated, exophytic mass develops once vertical growth is initiated (Fig. 10-141). Ulceration may develop early, but many lesions are not ulcerated at the time of diagnosis. Pain is uncommon except in ulcerated lesions, and most lesions remain relatively soft to palpation. Adjacent bone may show radiographic evidence of irregular or "moth-eaten" destruction. Cervical lymph node metastasis often is evident at initial presentation. In addition, melanoma occasionally affects the parotid gland, usually as a metastatic deposit from a scalp, conjunctival, or paranasal tumor.

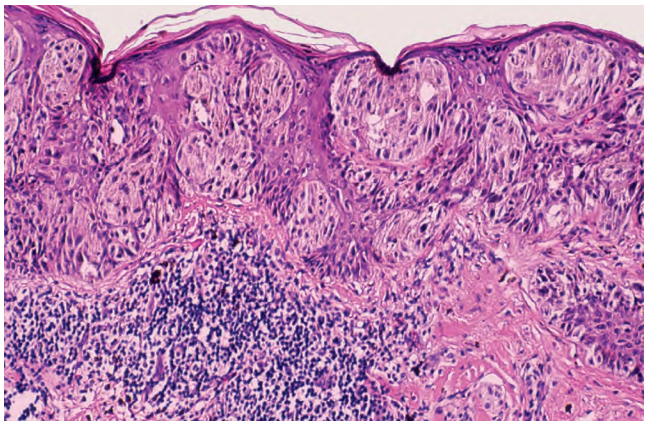
Histopathologic Features

With cutaneous and oral melanomas, atypical melanocytes initially are seen at the epithelial and connective tissue junction. From here, they have the potential to proliferate throughout the epithelium, laterally along the basal cell layer, and downward into the connective tissue. In early stages, atypical melanocytes are seen either scattered singly among the basal epithelial cells or as nests within the basal cell layer. The atypical melanocytes are enlarged, with varying degrees of nuclear pleomorphism and hyperchromatism.

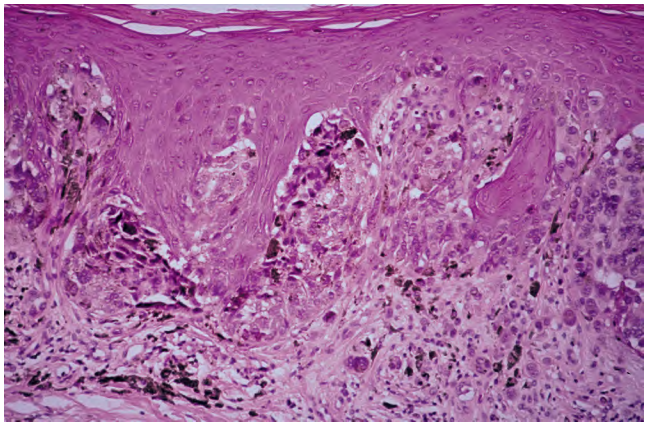
In superficial spreading melanoma, there is often *pagetoid spread* (i.e., single tumor cells infiltrating into the upper layers of the surface epithelium) (Fig. 10-142). This microscopic pattern resembles an intraepithelial adenocarcinoma known as *Paget's disease of skin*.

The spread of the lesional cells along the basal layer of the surface epithelium constitutes the radial growth phase. Appreciable lateral spread prior to invasion of the underlying connective tissue is characteristic of superficial spreading melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. In acral lentiginous melanoma, many of the melanocytes have prominent dendritic processes (Fig. 10-143).

The vertical growth phase is characterized by malignant melanocytes invading the connective tissue. In nodular



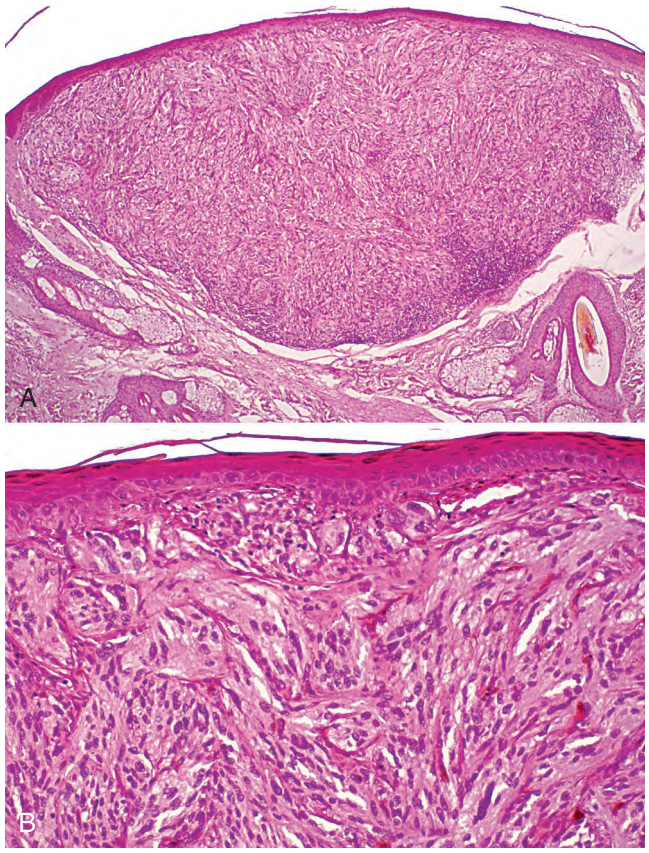
• **Fig. 10-142 Superficial Spreading Melanoma.** The radial growth phase is characterized by the spread of atypical melanocytes along the basilar portion of the epidermis. Also note the presence of individual melanocytes invading the higher levels of the epithelium.



• **Fig. 10-143 Acral Lentiginous Melanoma.** This palatal melanoma demonstrates numerous atypical melanocytes in the basilar portion of the epithelium with invasion into the superficial lamina propria. This represents the biopsy specimen from Fig. 10-140.

melanoma, this vertical growth phase occurs early in the disease course. No radial growth can be observed in the overlying epithelium beyond the edge of the invasive tumor (Fig. 10-144). The tumor usually appears as pleomorphic, spindle-shaped or epithelioid cells arranged in loosely aggregated cords or sheets. Oral lesions show invasion of lymphatic and blood vessels more often than skin lesions. Several mucosal melanomas have been reported to contain unequivocal bone and cartilage, a feature that may cause diagnostic confusion with pleomorphic adenoma, sarcomatoid carcinoma, osteosarcoma, and mesenchymal chondrosarcoma.

Approximately 10% of oral melanomas are amelanotic. A lack of melanin production may cause diagnostic confusion with various other undifferentiated tumors at the light microscopic level. Immunohistochemical studies showing reactivity for S-100 protein, HMB-45, MART-1 (Melan-A), and microphthalmia-associated transcription factor (Mitf) may aid in diagnosis.



• **Fig. 10-144 Nodular Melanoma. A,** Low-power photomicrograph showing a nodular mass of malignant melanocytes invading into the dermis. Note the lack of radial growth in the adjacent overlying epidermis. **B,** Higher-power photomicrograph showing atypical spindle-shaped melanocytes.

Treatment and Prognosis

Depth of invasion is an important prognostic factor for cutaneous melanoma. The Clark system assigns a "level" corresponding to the deepest region that has been invaded by tumor cells (Table 10-6). The more recent Breslow classification, however, correlates more accurately with prognosis and is based on measurement of the distance from the top of the granular cell layer to the deepest identifiable point of tumor invasion.

Clinical staging for cutaneous melanoma is performed using a TNM classification system that takes into account Breslow tumor thickness, ulceration, regional metastasis, and distant metastasis (Table 10-7). In addition, mitotic activity is considered in subclassifiying T1 (or "thin") melanomas, and the serum level of lactate dehydrogenase (LDH) considered in subclassifying cases with distant metastasis.

Surgical excision is the mainstay of treatment. Current evidence indicates that a 1-cm margin is adequate for cutaneous tumors with a thickness of 1 mm or less. For more deeply invasive tumors, wide surgical excision with at least 2-cm margins typically is recommended. However, in aesthetically sensitive areas, 1-cm margins may be acceptable for lesions thinner than 2 mm.

TABLE 10-6 Clark's Classification for Cutaneous Melanoma

Clark's Definition of Level of Tumor Invasion	Clark's Classification
Cells confined to epithelium	Level I
Cells penetrating papillary dermis	Level II
Cells filling papillary dermis	Level III
Cells extending into reticular dermis	Level IV
Cells invading subcutaneous fat	Level V

Lymph node dissection usually is performed on patients with clinically evident regional metastasis in the absence of distant metastasis. Elective lymph node dissection for patients with intermediate thickness (1 to 4 mm) lesions in the absence of clinically palpable nodes is somewhat controversial. The rationale for this procedure is that these patients have a high probability of occult regional nodal disease and low probability of distant metastasis. However, the reported survival benefit of this strategy is variable, and significant morbidity can be associated with lymph node dissection. To address this problem, sentinel-node biopsy (biopsy of the first lymph node in the lymphatic basin to receive drainage from the tumor) often is used as an

TABLE 10-7 Tumor-node-metastasis (TNM) Classification System and Stage Groupings for Cutaneous Melanoma

T Classification	*Thickness (mm)*	Ulceration Status/Mitoses
TX	NA (Primary tumor cannot be assessed [e.g., curettaged or severely regressed melanoma])	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	
T1	Melanomas 1.0 mm or less in thickness	a: w/o ulceration and mitosis $<1/mm^2$ b: With ulceration or mitoses $\geq 1/mm^2$
T2	Melanomas 1.01–2.0 mm	a: w/o ulceration b: With ulceration
T3	Melanomas 2.01–4.0 mm	a: w/o ulceration b: With ulceration
T4	Melanomas more than 4.0 mm	a: w/o ulceration b: With ulceration
N Classification	***No. of Metastatic Nodes***	**Nodal Metastatic Mass**
NX	Patients in whom the regional lymph nodes cannot be assessed (e.g., previously removed for another reason)	
N0	No regional metastases detected	
N1	1 node	a: Micrometastasis* b: Macrometastasis†
N2	2–3 nodes	a: Micrometastasis* b: Macrometastasis† c: In transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	
M Classification	**Site**	**Serum Lactate Dehydrogenase**
M0	No detectable evidence of distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastasis	Normal
M1b	Lung metastasis	Normal

Continued

TABLE 10-7 Tumor-node-metastasis (TNM) Classification System and Stage Groupings for Cutaneous Melanoma—cont'd

M Classification	Site	Serum Lactate Dehydrogenase
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Clinical Staging	TNM Classification	5-Year Survival Rate
Stage 0	Tis N0 M0	
Stage IA	T1a N0 M0	97%
Stage IB	T1b N0 M0	94%
	T2a N0 M0	91%
Stage IIA	T2b N0 M0	82%
	T3a N0 M0	79%
Stage IIB	T3b N0 M0	68%
	T4a N0 M0	71%
Stage IIC	T4b N0 M0	53%
Stage III	Any T ≥ N1 M0	40% to 78%
Stage IV	Any T Any N M1	about 15% to 20%

NA, not applicable
From Melanoma of the skin. In Edge SB, Byrd DR, Compton CC, et al, editors, *AJCC cancer staging manual,* ed 7, New York, 2010, Springer, pp 325–344.
*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).
†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
In transit metastases defined arbitrarily as clinically evident cutaneous and/or subcutaneous metastases identified at a distance greater than 2 cm from the primary melanoma in the region between the primary and the first echelon of regional lymph nodes.
Satellite metastases defined arbitrarily as grossly visible cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma.

alternative to elective lymph node dissection to identify patients with occult nodal metastases who would benefit from total lymphadenectomy.

Most patients with early-stage lesions are cured by surgery alone. However, adjuvant radiation therapy or immunotherapy (often with interferon-alpha) may be considered for certain subsets of patients at high risk for recurrence. For patients with distant metastasis, various agents (e.g., high-dose interleukin-2 [IL-2], dacarbazine, imatinib, and paclitaxel) have been tried with limited success. Notably, in 2011 the United States Food and Drug Administration approved two novel treatments for metastatic melanoma: vemurafenib (a *BRAF* inhibitor) and ipilimumab (a monoclonal antibody that promotes T-cell antitumoral activity by blocking cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]). These recent developments in genotype-directed and immunotherapy have led to prolonged survival for patients with advanced disease and likely will form the foundation for the next generation of therapies for metastatic melanoma.

The 5-year survival rates for patients with cutaneous melanomas that are thin and confined to the skin exceed 90%, whereas patients with regional or distant metastasis exhibit 5-year survival rates of approximately 40% to 78% and 15 to 20%, respectively (see Table 10-7). Primarily as a result of public education efforts, the clinical features of cutaneous melanoma are so widely known that the majority of lesions are discovered and treated at an early stage.

Other factors may influence outcome besides the depth of invasion. For reasons that are unclear, cutaneous melanomas on the trunk, head, and neck carry a worse prognosis than those on the extremities. In particular, among head and neck lesions, those arising on the scalp and neck are associated with decreased survival rates. In contrast, positive prognostic factors include age younger than 50 years and female gender. Follow-up after treatment is important not only to monitor for metastatic disease but also because, in 3% to 5% of these patients, a second primary melanoma eventually will develop.

For mucosal melanomas of the head and neck, TNM classification takes into account the anatomic extent of the primary tumor (i.e., confined to mucosa or invading adjacent structures), regional lymph node metastasis, and distant metastasis (Table 10-8). Because head and neck mucosal lesions typically exhibit aggressive behavior, they are classified at a minimum as stage III. For patients with stage III or IVb disease, radical surgery is indicated and often is combined with adjunctive radiation therapy. Patients with

TABLE 10-8 Tumor-node-metastasis (TNM) Classification System and Stage Groupings for Mucosal Melanoma of the Head and Neck

Primary Tumor (T)	
T3	Mucosal disease
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, and XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Anatomic Stage/Prognostic Groups	
Stage III	T3 N0 M0
Stage IVA	T4a N0 M0 T3-4a N1 M0
Stage IVB	T4b any N M0
Stage IVC	Any T Any N M1

From Mucosal melanoma of the head and neck. In Edge SB, Byrd DR, Compton CC, et al, editors: *AJCC cancer staging manual*, ed 7, New York, 2010, Springer, pp 97–100.

stage IVb or IVc disease should strongly consider clinical trial participation. Because *KIT* mutations often are present in mucosal melanomas, clinical trials evaluating tyrosine kinase inhibitors (such as, imatinib) are of particular interest.

The prognosis for oral melanoma is extremely poor. Most authors report 5-year survival rates in the range of only 10% to 25%. Death usually results from distant metastasis rather than lack of local control. The poor prognosis for oral melanoma appears to be related to difficulty in achieving wide resection and a tendency for early metastasis. Younger patients exhibit better survival than older ones, and patients with amelanotic lesions appear to have a particularly poor prognosis. There is generally a marked deterioration in prognosis among patients with oral mucosal melanomas exceeding a depth of 0.5 mm, although depth of invasion and presence of ulceration are not so closely correlated with prognosis of mucosal melanomas compared to cutaneous melanomas.

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11 Salivary Gland Pathology

SALIVARY GLAND APLASIA

Salivary gland aplasia is a rare developmental anomaly that can affect one or more of the major salivary glands. The condition may occur alone, although agenesis of the glands is often a component of one of several syndromes, including mandibulofacial dysostosis (Treacher Collins syndrome; see page 41), hemifacial microsomia, and lacrimo-auriculo-dento-digital (LADD) syndrome.

Clinical and Radiographic Features

Salivary gland aplasia has been reported more frequently in males than females by a 2:1 ratio. Some individuals are affected by agenesis of all four of the largest glands (both parotids and submandibular glands), but others may be missing only one to three of the four glands. In spite of the absence of the glands, the face still has a normal appearance because the sites are filled in by fat or connective tissue. Intraorally, the orifices of the missing glands are absent. Some patients also may exhibit absence of the lacrimal glands or lacrimal puncta.

As would be anticipated, the most significant symptom associated with salivary gland aplasia is severe xerostomia with its attendant problems (see page 432). The tongue may appear leathery, and the patient is at greater risk for developing dental caries and erosion (Fig. 11-1). However, some degree of moisture still may be present because of the continued activity of the minor salivary glands. Absence of the major glands can be confirmed by technetium-99m pertechnetate scintiscan, computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography.

LADD syndrome is an autosomal dominant disorder that is caused by mutations in the fibroblast growth factor 10 *(FGF10)* gene. It is characterized by aplasia or hypoplasia of the lacrimal and salivary glands, cup-shaped ears, hearing loss, and dental and digital anomalies. Dental features may include hypodontia, microdontia, and mild enamel hypoplasia.

Treatment and Prognosis

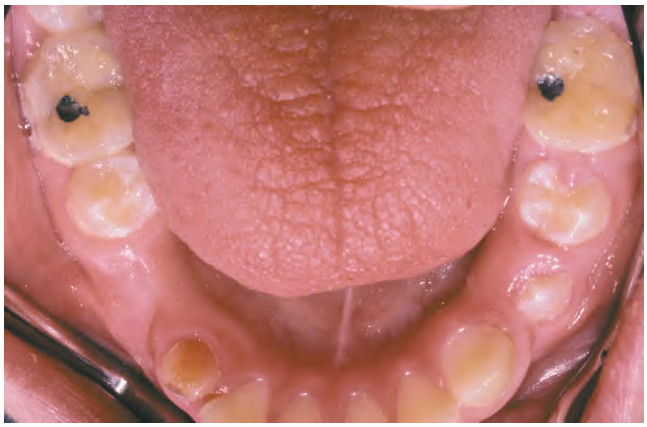
Patient management is directed toward compensating for the saliva deficiency, and saliva substitutes are often necessary. If any residual functional salivary gland tissue is present, then sialagogue medications (such as, pilocarpine or cevimeline) may be used to increase saliva production. Salivary flow also may be stimulated via the use of sugarless gum or sour candy. Regular preventive dental care is important to avoid xerostomia-related caries and enamel breakdown.

MUCOCELE (MUCUS EXTRAVASATION PHENOMENON; MUCUS ESCAPE REACTION)

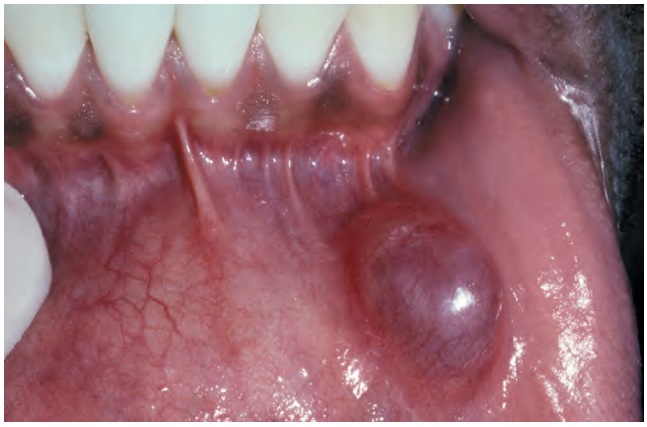
The **mucocele** is a common lesion of the oral mucosa that results from rupture of a salivary gland duct and spillage of mucin into the surrounding soft tissues. This spillage is often the result of local trauma, although there is no known history of trauma in many cases. Unlike the salivary duct cyst (see page 425), the mucocele is not a true cyst because it lacks an epithelial lining. Some authors, however, have included true salivary duct cysts in their reported series of mucoceles, sometimes under the classification of *retention mucocele* or *mucus retention cyst*. Because these two entities exhibit distinctly different clinical and histopathologic features, they are discussed as separate topics in this chapter.

Clinical Features

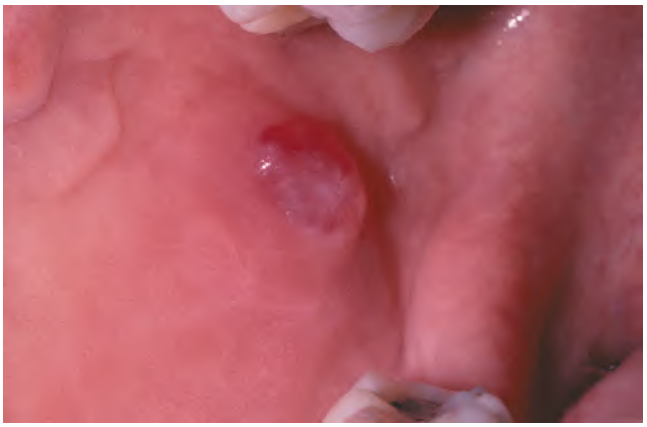
Mucoceles typically appear as dome-shaped mucosal swellings that can range from 1 or 2 mm to several centimeters in size (Figs. 11-2 to 11-4). They are most common in children and young adults, perhaps because younger people are more likely to experience trauma that induces mucin spillage. However, mucoceles have been reported in patients of all ages, including infants and older adults. The spilled mucin below the mucosal surface often imparts a bluish translucent hue to the swelling, although deeper mucoceles may be normal in color. The lesion characteristically is fluctuant, but some mucoceles feel firmer to palpation. The reported duration of the lesion can vary from a few days to several years; most patients report that the lesion has been present for several weeks. Many patients relate a history of a recurrent swelling that periodically may rupture and release its fluid contents.



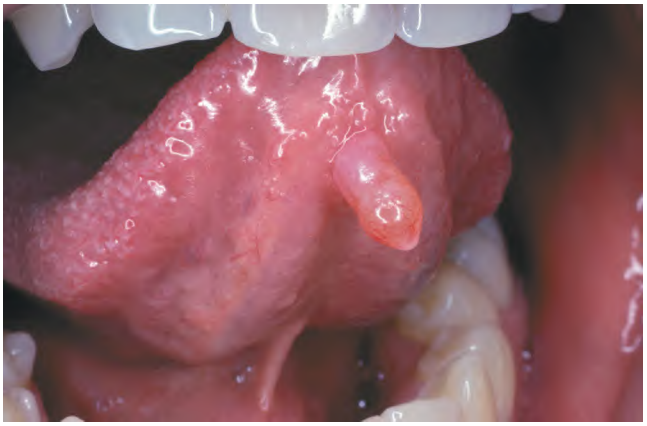
• **Fig. 11-1 Salivary Gland Aplasia.** Dry, leathery tongue and diffuse enamel erosion in a child with aplasia of the major salivary glands.



• **Fig. 11-2 Mucocele.** Blue-pigmented nodule on the lower lip.



• **Fig. 11-3 Mucocele.** Nodule on the posterior buccal mucosa.



• **Fig. 11-4 Mucocele.** Exophytic lesion on the anterior ventral tongue.

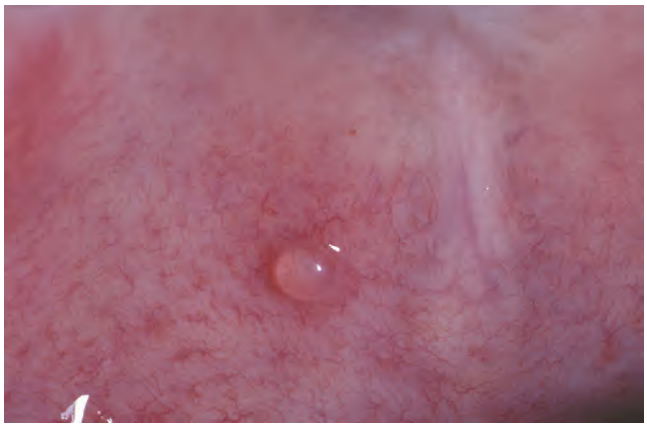
The lower lip is by far the most common site for the mucocele; a recent large study of 1715 cases found that 81.9% occurred at this one site (Table 11-1). Lower lip mucoceles usually are found lateral to the midline. Less common sites include the floor of mouth (ranulas: 5.8%), anterior ventral tongue (from the glands of Blandin-Nuhn: 5.0%), buccal mucosa (4.8%), palate (1.3%), and retromolar pad (0.5%). Mucoceles rarely develop on the upper lip. In the large series summarized in Table 11-1, not a single example was identified from the upper lip. This is in contrast to salivary gland tumors, which are not unusual in the upper lip but are distinctly uncommon in the lower lip.

As noted, the soft palate and retromolar area are uncommon sites for mucoceles. However, one interesting variant, the **superficial mucocele,** does develop in these areas and along the posterior buccal mucosa. Superficial mucoceles present as single or multiple tense vesicles that measure 1 to 4 mm in diameter (Fig. 11-5). The lesions often burst, leaving shallow, painful ulcers that heal within a few days. Repeated episodes at the same location are not unusual. Some patients relate the development of the lesions to mealtimes. Superficial mucoceles also have been reported to

TABLE 11-1 Location of Mucoceles

Location	Number of Cases	Percentage of All Cases
Lower lip	1405	81.9
Floor of mouth	99	5.8
Ventral tongue	86	5.0
Buccal mucosa	82	4.8
Palate	23	1.3
Retromolar	9	0.5
Unknown	11	0.6
Upper lip	0	0.0
Total	**1715**	**100**

Data from Chi AC, Lambert PR 3rd, Richardson MS, et al: Oral mucoceles: a clinicopathologic review of 1,824 cases, including unusual variants, *J Oral Maxillofac Surg* 69:1086–1093, 2011.



• **Fig. 11-5 Superficial Mucocele.** Vesicle-like lesion on the soft palate.

occur in association with lichenoid disorders, such as lichen planus, lichenoid drug eruptions, and chronic graft-versus-host disease (GVHD). The vesicular appearance is created by the superficial nature of the mucin spillage, which causes a separation of the epithelium from the connective tissue. The pathologist must be aware of this lesion and should not mistake it microscopically for a vesiculobullous disorder, especially mucous membrane pemphigoid.

Histopathologic Features

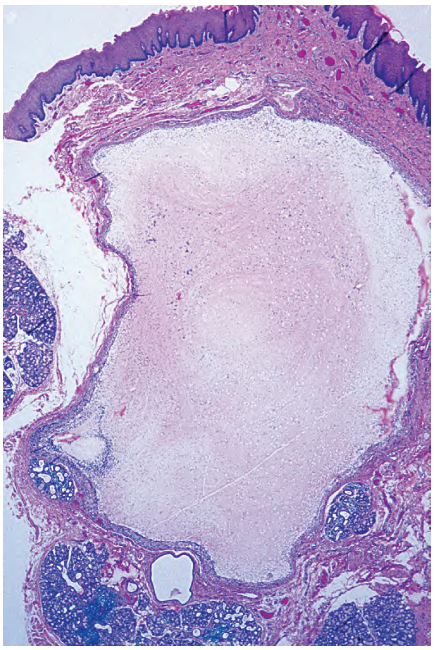
On microscopic examination, the mucocele shows an area of spilled mucin surrounded by a granulation tissue response (Figs. 11-6 and 11-7). The inflammation usually includes numerous foamy histiocytes (macrophages). In some cases, a ruptured salivary duct may be identified feeding into the area. The adjacent minor salivary glands often contain a chronic inflammatory cell infiltrate and dilated ducts.

Treatment and Prognosis

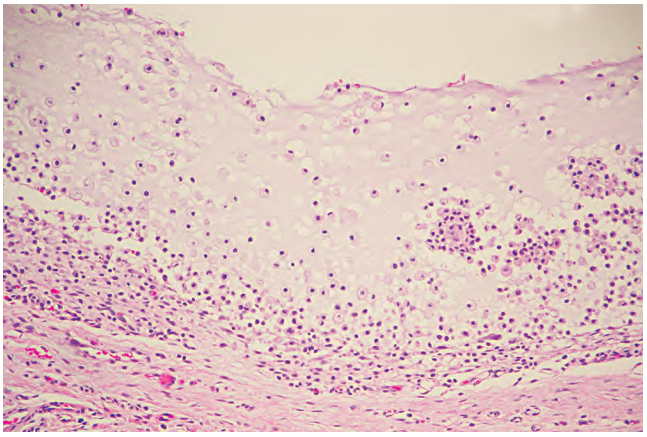
Some mucoceles are short-lived lesions that rupture and heal by themselves. Many lesions, however, are chronic in nature, and local surgical excision is necessary. To minimize the risk of recurrence, the surgeon should remove any adjacent minor salivary glands that may be feeding into the lesion when the area is excised. The excised tissue should be submitted for microscopic examination to confirm the diagnosis and rule out the possibility of a salivary gland tumor. The prognosis is excellent, although occasional mucoceles will recur, necessitating reexcision, especially if the feeding glands are not removed.

◆ RANULA

Ranula is a term used for mucoceles that occur in the floor of the mouth, arising from the sublingual gland. The name is derived from the Latin word *rana,* which means "frog," because the swelling may resemble a frog's translucent underbelly. The term *ranula* also has been used to describe



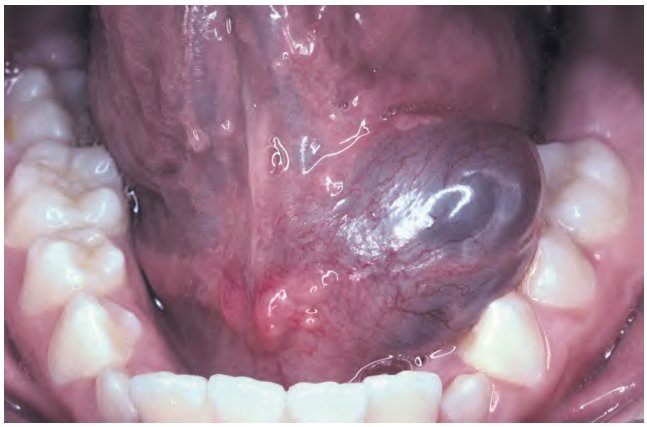
• **Fig. 11-6 Mucocele.** Mucin-filled cystlike cavity beneath the mucosal surface. Minor salivary glands are present below and lateral to the spilled mucin.



• **Fig. 11-7 Mucocele.** High-power view showing spilled mucin that is associated with granulation tissue containing foamy histiocytes.

other similar swellings in the floor of the mouth, including true salivary duct cysts, dermoid cysts, and cystic hygromas. However, the term is best used for mucus escape reactions (mucoceles).

The sublingual gland has a complex anatomy. The lesser sublingual gland actually consists of 15 to 30 smaller glands, each secreting through a short duct of Rivinus to the sublingual plica. Some individuals also have a greater sublingual gland with an excretory duct (Bartholin duct) that either joins with Wharton duct or opens next to it at the sublingual caruncle. Unlike the submandibular gland, the sublingual gland produces a continuous flow of mucus even in the absence of neural stimulation, which accounts for its



• **Fig. 11-8 Ranula.** Blue-pigmented swelling in the left floor of the mouth.

ability to produce a ranula after rupture of one of its multiple ducts.

Clinical Features

The ranula usually appears as a blue, dome-shaped, fluctuant swelling in the floor of the mouth (Fig. 11-8), but deeper lesions may be normal in color. Ranulas are seen most frequently in children and young adults. They tend to be larger than mucoceles in other oral locations, often developing into large masses that fill the floor of the mouth and elevate the tongue. The ranula usually is located lateral to the midline, a feature that may help to distinguish it from a midline dermoid cyst (see page 30). Like other mucoceles, ranulas may rupture and release their mucin contents, only to re-form.

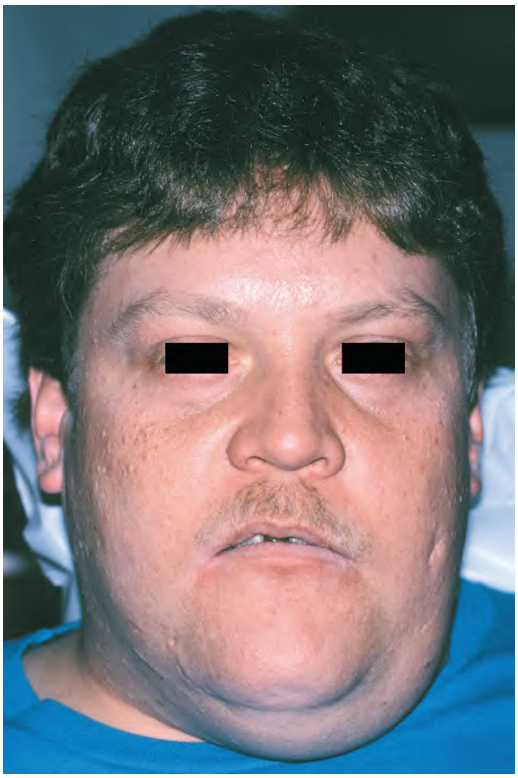
An unusual clinical variant, the **plunging** or **cervical ranula,** occurs when the spilled mucin dissects through the mylohyoid muscle and produces swelling within the neck (Fig. 11-9). A concomitant swelling in the floor of the mouth may or may not be present. If no lesion is produced in the mouth, then the clinical diagnosis of ranula may not be suspected. Imaging studies can be helpful in supporting a diagnosis of plunging ranula and in determining the origin of the lesion. CT and MRI images of plunging ranulas from the sublingual gland often exhibit a slight extension of the lesion into the sublingual space, known as a "tail sign."

Histopathologic Features

The microscopic appearance of a ranula is similar to that of a mucocele in other locations. The spilled mucin elicits a granulation tissue response that typically contains foamy histiocytes.

Treatment and Prognosis

Treatment of the ranula consists of removal of the feeding sublingual gland and/or marsupialization. Marsupialization



• **Fig. 11-9 Plunging Ranula.** Soft swelling in the neck.

(exteriorization) entails removal of the roof of the intraoral lesion, which often can be successful for small, superficial ranulas. However, marsupialization is often unsuccessful for larger ranulas, and most authors emphasize that removal of the offending gland is the most important consideration in preventing a recurrence of the lesion. If the gland is removed, then meticulous dissection of the lining of the lesion may not be necessary for the lesion to resolve, even for the plunging ranula. If the specific portion of the sublingual gland giving rise to the lesion can be identified, then partial excision of the gland may be successful.

◆ SALIVARY DUCT CYST (MUCUS RETENTION CYST; MUCUS DUCT CYST; SIALOCYST)

The **salivary duct cyst** is an epithelium-lined cavity that arises from salivary gland tissue. Unlike the more common mucocele (see page 422), it is a true developmental cyst that is lined by epithelium that is separate from the adjacent normal salivary ducts. The cause of such cysts is uncertain.

Cystlike dilatation of salivary ducts also may develop secondary to ductal obstruction (e.g., mucus plug), which creates increased intraluminal pressure. Although some authors refer to such lesions as *mucus retention cysts,* such lesions probably represent salivary ductal ectasia rather than a true cyst.

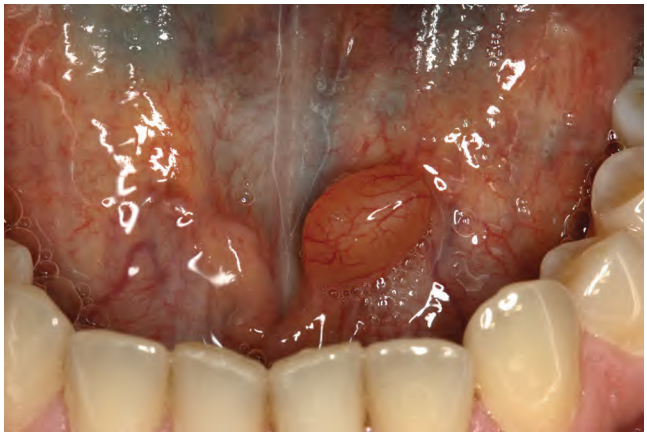
Clinical Features

Salivary duct cysts usually occur in adults and can arise within either the major or minor glands. Cysts of the major glands are most common within the parotid gland, presenting as slowly growing, asymptomatic swellings. Intraoral cysts can occur at any minor gland site, but most frequently they develop in the floor of the mouth, buccal mucosa, and lips (Fig. 11-10). They often look like mucoceles and are characterized by a soft, fluctuant swelling that may appear bluish, depending on the depth of the cyst below the surface. Some cysts may feel relatively firm to palpation. Cysts in the floor of the mouth often arise adjacent to the submandibular duct and sometimes have an amber color.

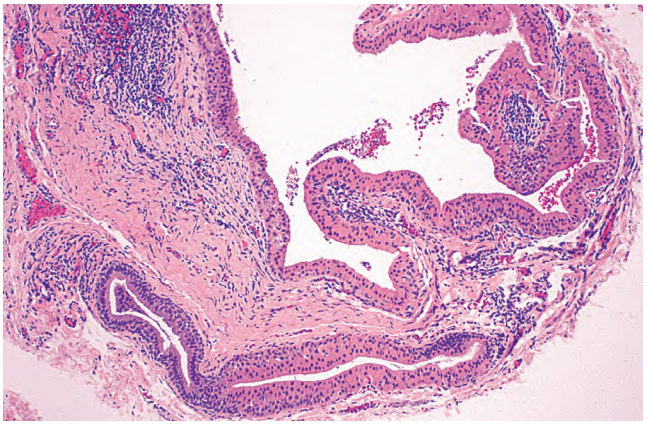
On rare occasions, patients have been observed to develop prominent ectasia of the excretory ducts of many of the minor salivary glands throughout the mouth. Such lesions have been termed "mucus retention cysts," although they probably represent multifocal ductal dilatation. The individual lesions often present as painful nodules that demonstrate dilated ductal orifices on the mucosal surface. Mucus or pus may be expressed from these dilated ducts.

Histopathologic Features

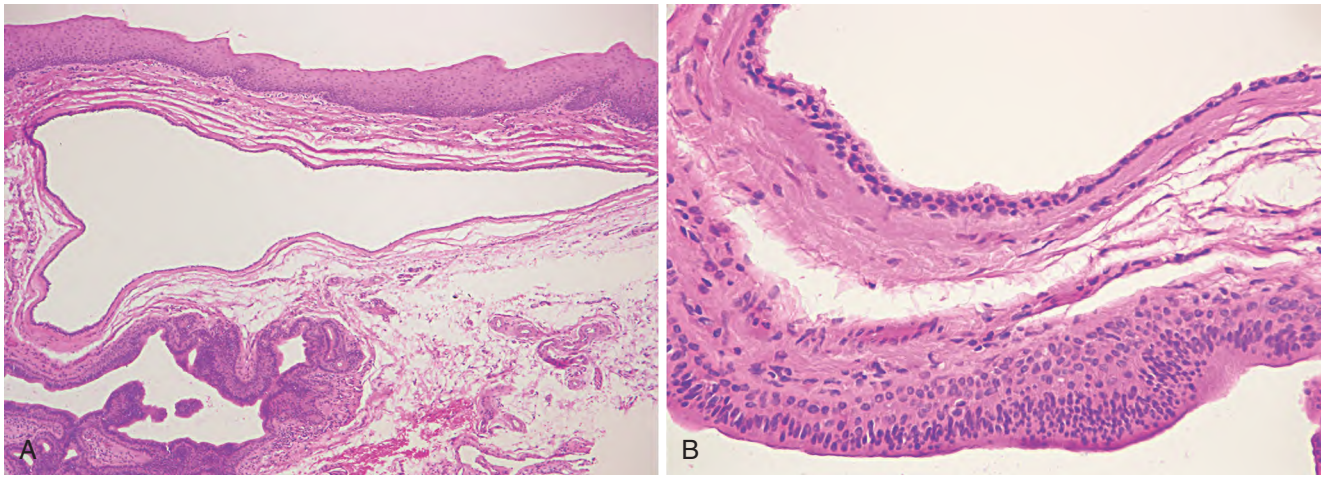
The lining of the salivary duct cyst is variable and may consist of cuboidal, columnar, or atrophic squamous epithelium surrounding thin or mucoid secretions in the lumen (Fig. 11-11). In contrast, ductal ectasia secondary to salivary obstruction is characterized by oncocytic metaplasia of the epithelial lining. This epithelium often demonstrates papillary folds into the cystic lumen, somewhat reminiscent of a small Warthin tumor (see page 449) but without the prominent lymphoid stroma (Fig. 11-12). If this proliferation is extensive enough, then these lesions sometimes are diagnosed as **papillary cystadenoma,** although it seems likely that most are not true neoplasms. The individual



• **Fig. 11-10 Salivary Duct Cyst.** Nodular swelling overlying Wharton duct.



• **Fig. 11-12 Oncocytic Salivary Ductal Ectasia.** This dilated duct is lined by columnar eosinophilic oncocytes that exhibit papillary folds into the ductal lumen. Such lesions may develop secondary to ductal obstruction.



• **Fig. 11-11 Salivary Duct Cyst. A,** Low-power photomicrograph showing a cyst below the mucosal surface. **B,** High-power view of cystic cavity *(top)* lined by thin cuboidal epithelium. Adjacent to the cyst is an excretory salivary gland duct lined by columnar epithelium *(bottom).*

lesions of patients with multiple "mucus retention cysts" also show prominent oncocytic metaplasia of the epithelial lining.

Treatment and Prognosis

Isolated salivary duct cysts are treated by conservative surgical excision. For cysts in the major glands, partial or total removal of the gland may be necessary. The lesion should not recur.

For rare patients who develop multifocal salivary ductal ectasia ("mucus retention cysts"), local excision may be performed for the more problematic swellings; however, surgical management does not appear feasible or advisable for all of the lesions, which may number as many as 100. In one reported case, systemic erythromycin and chlorhexidine mouth rinses were helpful in relieving pain and reducing drainage of pus. Sialagogue medications also may be helpful in stimulating salivary flow, thereby preventing the accumulation of inspissated mucus within the dilated excretory ducts.

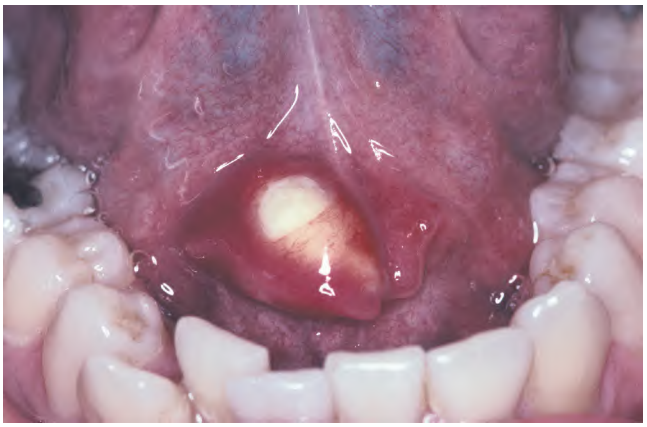
◆ SIALOLITHIASIS (SALIVARY CALCULI; SALIVARY STONES)

Sialoliths are calcified structures that develop within the salivary ductal system. Researchers believe that they arise from deposition of calcium salts around a nidus of debris within the duct lumen. This debris may include inspissated mucus, bacteria, ductal epithelial cells, or foreign bodies. The cause of sialoliths is unclear, but their formation can be promoted by chronic sialadenitis and partial obstruction. Their development typically is not related to any systemic derangement in calcium and phosphorus metabolism.

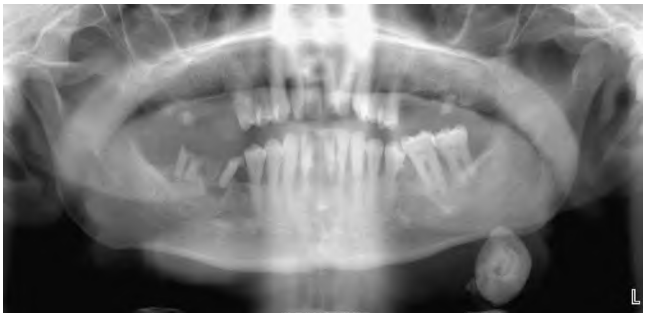
Clinical and Radiographic Features

Sialoliths most often develop within the ductal system of the submandibular gland, which accounts for about 80% of cases; the formation of stones within the parotid gland system is distinctly less frequent. The long, tortuous, upward path of the submandibular (Wharton) duct and the thicker, mucoid secretions of this gland may be responsible for its greater tendency to form salivary calculi. Sialoliths also can form within the minor salivary glands, most often within the glands of the upper lip or buccal mucosa. Salivary stones can occur at almost any age, but they are most common in young and middle-aged adults.

Major gland sialoliths most frequently cause episodic pain or swelling of the affected gland, especially at mealtime. The severity of the symptoms varies, depending on the degree of obstruction and the amount of resultant backpressure produced within the gland. If the stone is located toward the terminal portion of the duct, then a hard mass may be palpated beneath the mucosa (Fig. 11-13).



• **Fig. 11-13 Sialolithiasis.** Hard mass at the orifice of Wharton duct.



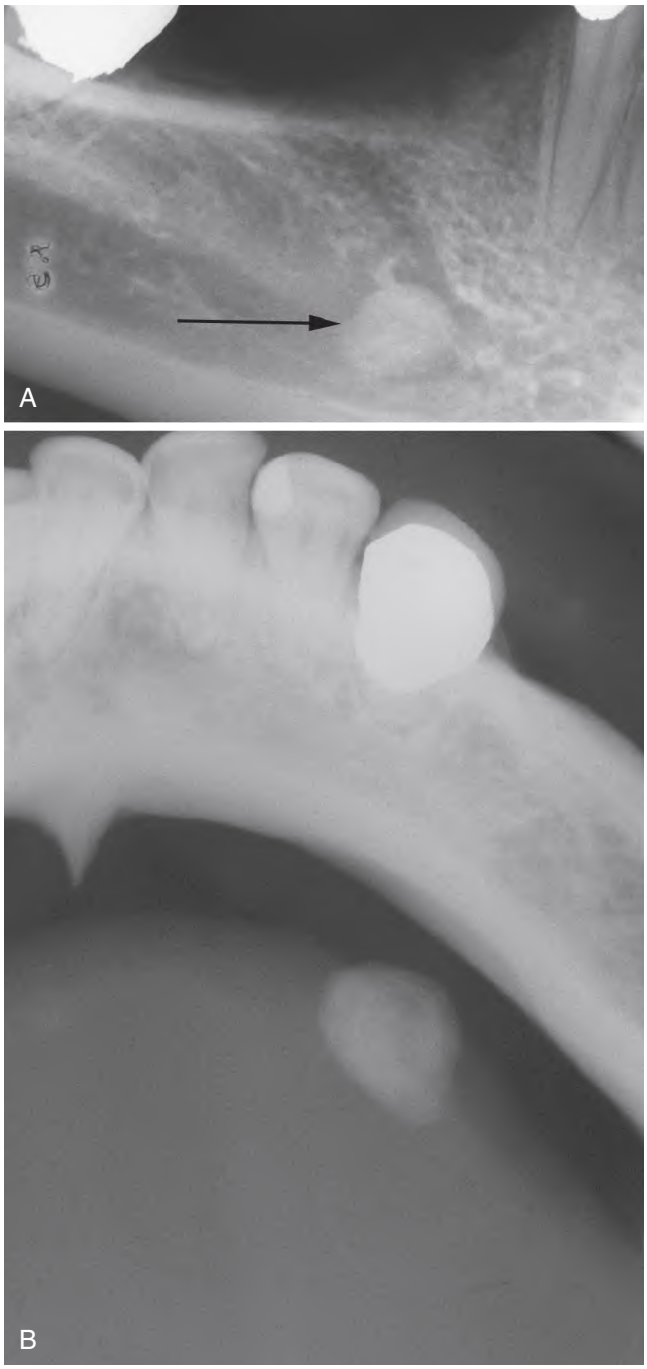
• **Fig. 11-14 Sialolithiasis.** Radiopaque mass located at the left angle of the mandible. (Courtesy of Dr. Roger Bryant.)

Sialoliths typically appear as radiopaque masses on radiographic examination. However, not all stones are visible on standard radiographs (perhaps because of the degree of calcification of some lesions). They may be discovered anywhere along the length of the duct or within the gland itself (Fig. 11-14). Stones in the terminal portion of the submandibular duct are best demonstrated with an occlusal radiograph. On panoramic or periapical radiographs, the calcification may appear superimposed on the mandible and care must be exercised not to confuse it with an intrabony lesion (Fig. 11-15). Multiple parotid stones radiographically can mimic calcified parotid lymph nodes, such as might occur in tuberculosis. Sialography, ultrasound, and CT scanning may be helpful additional imaging studies for sialoliths. Diagnostic sialendoscopy also can be a valuable tool in the evaluation and diagnosis of ductal obstructions. In this technique, a miniaturized endoscope is inserted into the duct orifice, allowing visualization of the ductal system for any stones, strictures, or adhesions.

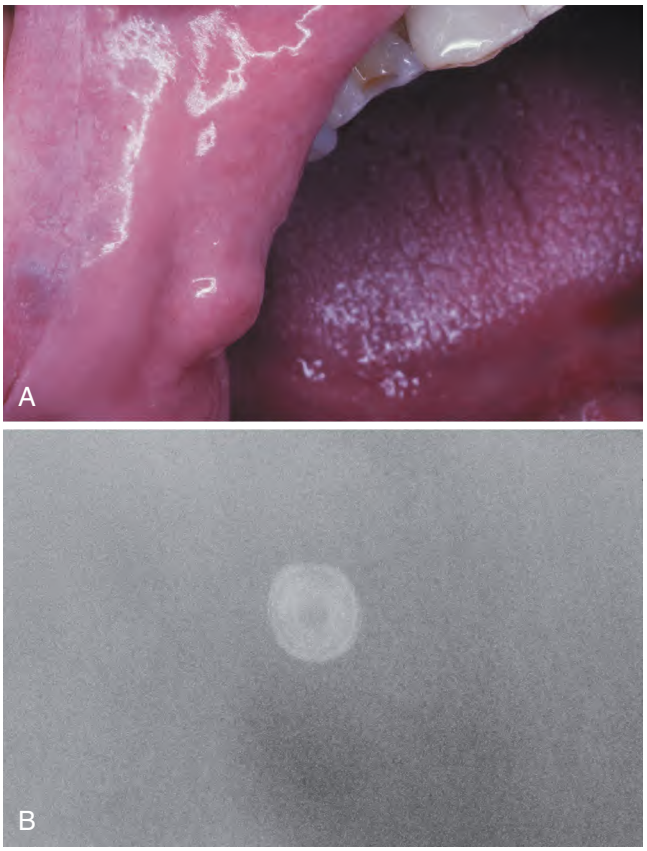
Minor gland sialoliths often are asymptomatic but may produce local swelling or tenderness of the affected gland (Fig. 11-16). A small radiopacity often can be demonstrated with a soft tissue radiograph.

Histopathologic Features

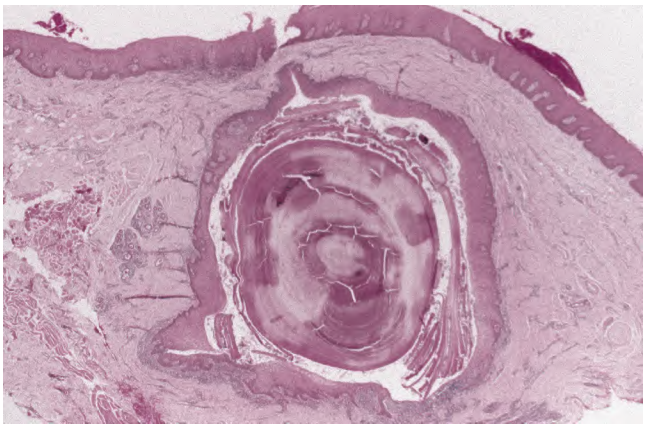
On gross examination, sialoliths appear as hard masses that are round, oval, or cylindrical. They are typically yellow,



• **Fig. 11-15 Sialolithiasis. A,** Periapical film showing discrete radiopacity *(arrow)* superimposed on the body of the mandible. Care must be taken not to confuse such lesions with intrabony pathosis. **B,** Occlusal radiograph of same patient demonstrating radiopaque stone in Wharton duct.



• **Fig. 11-16 Sialolithiasis. A,** Minor salivary gland sialolith presenting as a hard nodule in the upper lip. **B,** A soft tissue radiograph of the same lesion revealed a laminated calcified mass.



• **Fig. 11-17 Sialolithiasis.** Intraductal calcified mass showing concentric laminations. The duct exhibits squamous metaplasia.

although they may be a white or yellow-brown color. Submandibular stones tend to be larger than those of the parotid or minor glands. Sialoliths are usually solitary, although occasionally two or more stones may be discovered at surgery.

Microscopically, the calcified mass exhibits concentric laminations that may surround a nidus of amorphous debris (Fig. 11-17). If the associated duct also is removed, then it often demonstrates squamous, oncocytic, or mucous cell metaplasia. Periductal inflammation is also evident. The ductal obstruction frequently is associated with an acute or chronic sialadenitis of the feeding gland.

Treatment and Prognosis

Small sialoliths of the major glands sometimes can be treated conservatively by gentle massage of the gland in an

effort to milk the stone toward the duct orifice. Sialagogues (drugs that stimulate salivary flow), moist heat, and increased fluid intake also may promote passage of the stone. Larger sialoliths usually need to be removed surgically. If significant inflammatory damage has occurred within the feeding gland, then the gland may need to be removed. Minor gland sialoliths are best treated by surgical removal, including the associated gland.

Extracorporeal shock wave lithotripsy and interventional sialendoscopy with basket retrieval are newer techniques that can be effective in the removal of sialoliths from the major glands. These minimally invasive techniques have low morbidity and may preclude the necessity of gland removal.

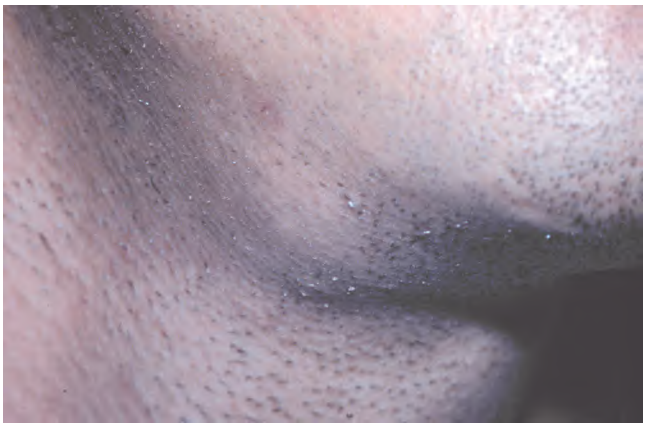
SIALADENITIS

Inflammation of the salivary glands **(sialadenitis)** can arise from various infectious and noninfectious causes. The most common viral infection is mumps (see page 238), although a number of other viruses also can involve the salivary glands, including Coxsackie A, ECHO, choriomeningitis, parainfluenza, human immunodeficiency virus (HIV), and cytomegalovirus (CMV) (in neonates). Most bacterial infections arise as a result of ductal obstruction or decreased salivary flow, allowing retrograde spread of bacteria throughout the ductal system. Blockage of the duct can be caused by sialolithiasis (see page 427), congenital strictures, or compression by an adjacent tumor. Decreased flow can result from dehydration, debilitation, or medications that inhibit secretions.

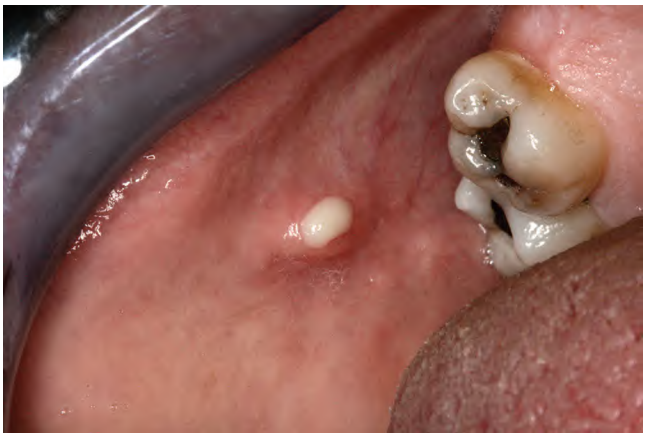
One of the more common causes of sialadenitis is recent surgery (especially abdominal surgery), after which an acute parotitis *(surgical mumps)* may arise because the patient has been kept without food or fluids (NPO) and has received atropine during the surgical procedure. Other medications that produce xerostomia as a side effect also can predispose patients to such an infection. Most community-acquired cases of acute bacterial sialadenitis are caused by *Staphylococcus aureus* or streptococcal species. Hospital-acquired infections are also most frequently associated with *S. aureus,* but they also may be caused by a variety of other species, including *Eikenella corrodens, Escherichia coli, Fusobacterium, Haemophilus influenzae, Klebsiella, Prevotella, Proteus, and Pseudomonas*. Noninfectious causes of salivary inflammation include Sjögren syndrome (see page 434), sarcoidosis (see page 310), radiation therapy (see page 266), and various allergens.

Clinical and Radiographic Features

Acute bacterial sialadenitis is most common in the parotid gland and is bilateral in 10% to 25% of cases. The affected gland is swollen and painful, and the overlying skin may be warm and erythematous (Fig. 11-18). An associated low-grade fever and trismus may be present. A purulent discharge often is observed from the duct orifice when the gland is massaged (Fig. 11-19).



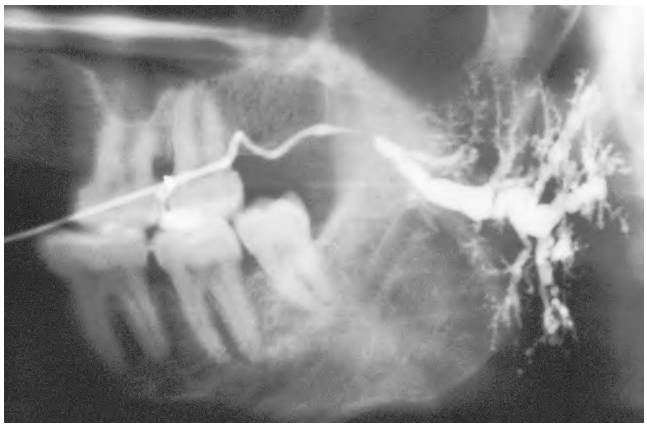
• **Fig. 11-18 Sialadenitis.** Tender swelling of the submandibular gland.



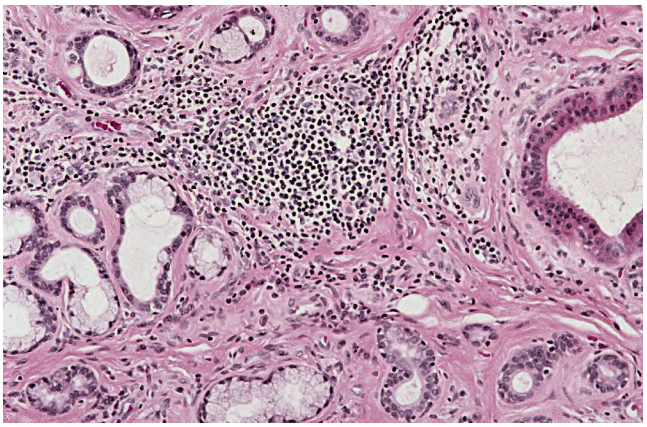
• **Fig. 11-19 Sialadenitis.** A purulent exudate can be seen arising from Stensen duct when the parotid gland is massaged.

Recurrent or persistent ductal obstruction (most commonly caused by sialoliths) can lead to a chronic sialadenitis. Periodic swelling and pain occur within the affected gland, usually developing at mealtime when salivary flow is stimulated. Sialography often demonstrates sialectasia (ductal dilatation) proximal to the area of obstruction (Fig. 11-20). In chronic parotitis, Stensen duct may show a characteristic sialographic pattern known as "sausaging," which reflects a combination of dilatation plus ductal strictures from scar formation. Chronic sialadenitis also can occur in the minor glands, possibly as a result of blockage of ductal flow or local trauma.

Juvenile recurrent parotitis is the most common inflammatory salivary disorder of children in the United States and the second most common such disorder worldwide (following mumps). It is characterized by recurring episodes of unilateral or bilateral, non-suppurative parotid swelling, usually beginning between the ages of 3 and 6 years. The exact cause is unknown, although congenital duct malformations, genetic factors, immunologic disorders, and dental malocclusion have been suggested as possible contributing factors. Although multiple recurrences often develop, the condition usually resolves around the time of puberty.



• **Fig. 11-20 Chronic Sialadenitis.** Parotid sialogram demonstrating ductal dilatation proximal to an area of obstruction. (Courtesy of Dr. George Blozis.)



• **Fig. 11-21 Chronic Sclerosing Sialadenitis.** Chronic inflammatory infiltrate with associated acinar atrophy, ductal dilatation, and fibrosis.

Subacute necrotizing sialadenitis is a form of salivary inflammation that occurs most commonly in teenagers and young adults. The lesion usually involves the minor salivary glands of the hard or soft palate, presenting as a painful nodule that is covered by intact, erythematous mucosa. Unlike necrotizing sialometaplasia (see page 439), the lesion does not ulcerate or slough necrotic tissue. An infectious or allergic cause has been hypothesized.

Histopathologic Features

In patients with acute sialadenitis, accumulation of neutrophils is observed within the ductal system and acini. Chronic sialadenitis is characterized by scattered or patchy infiltration of the salivary parenchyma by lymphocytes and plasma cells. Atrophy of the acini is common, as is ductal dilatation. If associated fibrosis is present, then the term **chronic sclerosing sialadenitis** is used (Fig. 11-21).

Subacute necrotizing sialadenitis is characterized by a heavy mixed inflammatory infiltrate consisting of neutrophils, lymphocytes, histiocytes, and eosinophils. There is loss of most of the acinar cells, and many of the remaining ones exhibit necrosis. The ducts tend to be atrophic and do not show hyperplasia or squamous metaplasia.

Treatment and Prognosis

Patients with sialadenitis should have a screening panoramic radiograph to investigate for the presence of a sialolith. Additional imaging studies, such as CT or MRI scans, may also be warranted. If purulence is noted at the duct orifice, then bacterial culture and sensitivity studies should be performed.

The treatment of acute sialadenitis includes appropriate antibiotic therapy and rehydration of the patient to stimulate salivary flow. Surgical drainage may be needed if there is abscess formation. Although this regimen is usually sufficient, a 20% to 50% mortality rate has been reported in debilitated patients because of the spread of the infection and sepsis.

The management of chronic sialadenitis depends on the severity of the condition and ranges from conservative therapy to surgical intervention. Initial management often includes antibiotics, analgesics, short-term corticosteroids, sialagogues, and glandular massage. Early cases that develop secondary to ductal blockage may respond to removal of the sialolith or other obstruction. However, if sialectasia is present, then the dilated ducts can lead to stasis of secretions and predispose the gland to further sialolith formation. Sialoendoscopy and ductal irrigation often are employed to dilate ductal strictures and to eliminate sialoliths and mucus plugs. If necessary, a period of ductal stenting can also be performed. If conservative methods cannot control chronic sialadenitis, then surgical removal of the affected gland may be necessary.

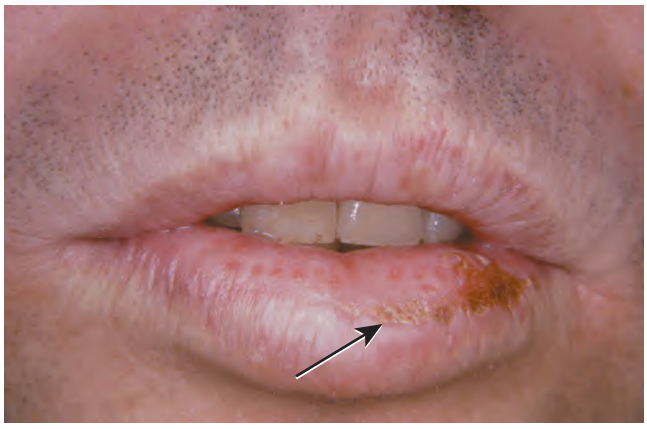
Sialoendoscopy with saline irrigation also has proven to be a useful technique for patients with juvenile recurrent parotitis, often greatly reducing the number of recurring episodes until the disorder resolves at puberty. Subacute necrotizing sialadenitis is a self-limiting condition that usually resolves within 2 weeks of diagnosis without treatment.

◆ CHEILITIS GLANDULARIS

Cheilitis glandularis is a rare inflammatory condition of the minor salivary glands. The cause is uncertain, although several etiologic factors have been suggested, including actinic damage, tobacco, poor hygiene, and heredity.

Clinical Features

Cheilitis glandularis characteristically occurs on the lower lip vermilion, although cases also have been reported to involve the upper lip and palate. Affected individuals experience swelling and eversion of the lower lip as a result of hypertrophy and inflammation of the glands (Fig. 11-22).



• **Fig. 11-22 Cheilitis Glandularis.** Prominent lower lip with inflamed openings of the minor salivary gland ducts. An early squamous cell carcinoma has developed on the patient's left side just lateral to the midline *(arrow).* (Courtesy of Dr. George Blozis.)

The openings of the minor salivary ducts are inflamed and dilated, and pressure on the glands may produce mucopurulent secretions from the ductal openings. The condition most often has been reported in middle-aged and older men, although cases also have been described in women and children. However, some of the childhood cases may represent other entities, such as exfoliative cheilitis (see page 278). Examples also have been described in albino patients, presumably secondary to sun sensitivity.

Historically, cheilitis glandularis has been classified into three types, based on the severity of the disease:

1. Simple
2. Superficial suppurative (Baelz disease)
3. Deep suppurative (cheilitis glandularis apostematosa)

The latter two types represent progressive stages of the disease with bacterial involvement; they are characterized by increasing inflammation, suppuration, ulceration, and swelling of the lip.

Histopathologic Features

The microscopic findings of cheilitis glandularis may include chronic sialadenitis, ductal dilatation with mucin accumulation, and oncocytic ductal metaplasia. Concomitant dysplastic changes may be observed in the overlying surface epithelium in some cases.

Treatment and Prognosis

The treatment of choice for most cases of persistent cheilitis glandularis associated with actinic damage is vermilionectomy (lip shave), which usually produces a satisfactory cosmetic result. It has been noted that some cases have been associated with the development of squamous cell carcinoma of the overlying epithelium of the lip. Because actinic damage has been implicated in many cases of cheilitis glandularis, it is likely that this same solar radiation is responsible for the malignant degeneration.

◆ SIALORRHEA

Sialorrhea, or excessive salivation, is an uncommon condition that has various causes. Minor sialorrhea may result from local irritations, such as aphthous ulcers or ill-fitting dentures. Patients with new dentures often experience excess saliva production until they become accustomed to the prosthesis. Episodic hypersecretion of saliva, or "water brash," may occur as a protective buffering system to neutralize stomach acid in individuals with gastroesophageal reflux disease. Sialorrhea is a well-known clinical feature of rabies and heavy-metal poisoning (see page 286). It also may occur as a consequence of certain medications, such as antipsychotic agents, especially clozapine, and cholinergic agonists used to treat dementia of the Alzheimer type and myasthenia gravis.

Drooling can be a problem for patients who are intellectually disabled, who have undergone surgical resection of the mandible, or who have various neurologic disorders such as cerebral palsy, Parkinson disease, amyotrophic lateral sclerosis (ALS), or stroke. In these instances, the drooling is probably not caused by overproduction of saliva but by poor neuromuscular control.

In addition, there is a second group of patients who report complaints of drooling; however, no obvious clinical evidence of excessive saliva production is observed, and they do not have any of the recognized causes for sialorrhea. Personality analysis has suggested that the complaint of drooling in such otherwise healthy patients does not have an organic basis but may be associated with high levels of neuroticism and a tendency to dissimulate.

Clinical Features

Excess saliva production typically produces drooling and choking, which may cause social embarrassment. In children with intellectual disability or cerebral palsy, uncontrolled salivary flow may lead to macerated sores around the mouth, chin, and neck that can become secondarily infected. The constant soiling of clothes and bed linens can be a significant problem for the parents and caretakers of these patients.

An interesting type of supersalivation of unknown cause has been termed **idiopathic paroxysmal sialorrhea.** Individuals with this condition experience short episodes of excessive salivation lasting from 2 to 5 minutes. These episodes are associated with a prodrome of nausea or epigastric pain.

Treatment and Prognosis

Some causes of sialorrhea are transitory or mild, and no treatment is needed. For individuals with increased salivation associated with gastroesophageal reflux disease, medical management of their reflux problem may be beneficial.

For persistent severe drooling, therapeutic intervention may be indicated. Speech therapy can be used to improve

neuromuscular control, but patient cooperation is necessary. Anticholinergic medications can decrease saliva production but may produce unacceptable side effects. Transdermal scopolamine has been tried with some success, but it should not be used in children younger than age 10. Intraglandular injection of botulinum toxin has been shown to be successful in reducing salivary secretions, with duration of action that varies from 6 weeks to 6 months.

Several surgical techniques have been used successfully to control severe drooling in individuals with poor neuromuscular control:

- Relocation of the submandibular ducts (sometimes along with excision of the sublingual glands)
- Relocation of the parotid ducts
- Submandibular gland excision plus parotid duct ligation
- Ligation of the parotid and submandibular ducts
- Bilateral tympanic neurectomy with sectioning of the chorda tympani

In ductal relocation, the ducts are repositioned posteriorly to the tonsillar fossa, thereby redirecting salivary flow and minimizing drooling. The use of bilateral tympanic neurectomy and sectioning of the chorda tympani destroys parasympathetic innervation to the glands, reducing salivary secretions and possibly inducing xerostomia. However, this procedure, which results in a loss of taste to the anterior two-thirds of the tongue, is rarely performed today.

◆ XEROSTOMIA

Xerostomia refers to a subjective sensation of a dry mouth; it is frequently, but not always, associated with salivary gland hypofunction. A number of factors may play a role in the cause of xerostomia, and these are listed in Box 11-1. Xerostomia is a common problem that has been reported in 25% of older adults. In the past, complaints of dry mouth in older patients often were ascribed to the predictable result of aging. However, it is now generally thought that any reductions in salivary function associated with age are modest and probably are not associated with any significant reduction in salivary function. Instead, xerostomia in older adults is more likely to be the result of other factors, especially medications. More than 500 drugs have been reported to produce xerostomia as a side effect, including 63% of the 200 most frequently prescribed medicines in the United States. A list of the most common and significant drugs associated with xerostomia is provided in Table 11-2. Not only are specific drugs known to produce dry mouth, but the prevalence of xerostomia also increases in relation to the total number of drugs that a person takes, regardless of whether the individual medications are xerogenic or not.

Clinical Features

Examination of the patient typically demonstrates a reduction in salivary secretions, and the residual saliva appears either foamy or thick and "ropey." The mucosa appears dry,

• BOX 11-1 Causes of Xerostomia

Developmental Origin

Salivary gland aplasia

Water/Metabolite Loss

Impaired fluid intake
Hemorrhage
Vomiting/diarrhea

Iatrogenic Origin

Medications
Radiation therapy to the head and neck
Chemotherapy

Systemic Diseases

Sjögren syndrome
Diabetes mellitus
Diabetes insipidus
Sarcoidosis
Amyloidosis
Human immunodeficiency virus (HIV) infection
Hepatitis C infection
Graft-versus-host disease (GVHD)
Psychogenic disorders

Local Factors

Decreased mastication
Smoking
Mouth breathing

TABLE 11-2 Medications That May Produce Xerostomia

Class of Drug	Example
Antihistamine agents	Diphenhydramine Chlorpheniramine
Decongestant agents	Pseudoephedrine Loratadine
Antidepressant agents	Amitriptyline Citalopram Fluoxetine Paroxetine Sertraline Bupropion
Antipsychotic agents	Phenothiazine derivatives Haloperidol
Sedatives and anxiolytic agents	Diazepam Lorazepam Alprazolam
Antihypertensive agents	Reserpine Methyldopa Chlorothiazide Furosemide Metoprolol Calcium channel blockers
Anticholinergic agents	Atropine Scopolamine

and the clinician may notice that the examining gloves stick to the mucosal surfaces. The dorsal tongue often is fissured with atrophy of the filiform papillae (see Fig. 11-1). The patient may complain of difficulty with mastication and swallowing, and they may even indicate that food adheres to the oral membranes during eating. The clinical findings, however, do not always correspond to the patient's symptoms. Some patients who complain of dry mouth may appear to have adequate salivary flow and oral moistness. Conversely, some patients who clinically appear to have a dry mouth have no complaints. The degree of saliva production can be assessed by measuring both resting and stimulated salivary flow.

There is an increased prevalence of oral candidiasis in patients with xerostomia because of the reduction in the cleansing and antimicrobial activity normally provided by saliva. In addition, these patients are more prone to dental decay, especially cervical and root caries. This problem has been associated more often with radiation therapy, and it is sometimes called *radiation-induced caries* but more appropriately should be called *xerostomia-related caries* (see page 268).

Treatment and Prognosis

The treatment of xerostomia is difficult and often unsatisfactory. Artificial salivas are available and may help make the patient more comfortable, as may continuous sips of water throughout the day. In addition, sugarless candy can be used in an effort to stimulate salivary flow. One of the better patient-accepted management approaches includes the use of oral hygiene products that contain lactoperoxidase, lysozyme, and lactoferrin (e.g., Biotene toothpaste and mouth rinse, and Oralbalance gel). If the dryness is secondary to the patient's medication, then discontinuation or dose modification in consultation with the patient's physician may be considered; a substitute drug can also be tried.

Systemic pilocarpine is a parasympathomimetic agonist that can be used as a sialagogue. At doses of 5 to 10 mg, three to four times daily, it can be an effective promoter of salivary secretion. Excess sweating is a common side effect, but more serious problems, such as increased heart rate and blood pressure, are uncommon. Cevimeline hydrochloride, a cholinergic agonist with affinity for muscarinic M_3 receptors, also has been proven to be an effective sialagogue. Both pilocarpine and cevimeline are contraindicated in patients with narrow-angle glaucoma.

Because of the increased potential for dental caries in patients with xerostomia, frequent dental visits are recommended. Office and daily home fluoride applications can be used to help prevent decay, and chlorhexidine mouth rinses minimize plaque buildup.

◆ IgG4-RELATED DISEASE

In the late 1800s, Johann von Mikulicz-Radecki described a patient with an unusual bilateral painless swelling of the lacrimal glands and all of the salivary glands, which was caused by an intense chronic inflammatory infiltrate. This clinical presentation became known as **Mikulicz disease.** Similar cases of parotid and lacrimal enlargement caused by other diseases (e.g., tuberculosis, sarcoidosis, and lymphoma) were considered to be different from Mikulicz disease and were termed **Mikulicz syndrome.** However, these two terms have become so confusing and ambiguous that they should no longer be used.

Although the true nature of his original patient's condition is uncertain, some examples of so-called Mikulicz disease likely have been benign lymphoepithelial lesions associated with Sjögren syndrome (see page 434). However, it is thought that other examples would be classified today as **IgG4-related disease,** a newly described fibroinflammatory disorder.

IgG4-related disease was first recognized as a sclerosing inflammatory process of the pancreas under the designation "autoimmune pancreatitis." This condition later was linked to elevated serum levels of IgG4, as well as the presence of IgG4-positive plasma cells within pancreatic tissues. The systemic nature of IgG4-related disease was established when it was recognized that a variety of inflammatory lesions in other organs, including the salivary and lacrimal glands, represent the same disease process. Serum concentrations of polyclonal IgG4 can measure up to 25 times greater than normal levels, although 20% to 40% of patients will have IgG4 levels within normal limits. Allergic disorders such as asthma, allergic rhinitis, and atopic dermatitis are common.

Clinical Features

IgG4-related disease typically occurs in middle-aged and older adults, with a mean age of approximately 60 years. Men are affected equally or slightly more often than women, although reports from Japan have shown a female predilection. Following the pancreas, the head and neck region is the second most common site affected by this condition. IgG4-related sialadenitis occurs most frequently in the submandibular gland and only rarely involves the parotid gland and minor salivary glands. Patients present with unilateral or bilateral submandibular gland swelling ranging from 1.5 cm to 5 cm in diameter, which often mimics a neoplastic process.

Because IgG4-related disease can affect almost any tissue or organ within the body, the severity and course of the disorder depend on the specific site of involvement. Pancreatitis can lead to obstructive jaundice, weight loss, and abdominal discomfort. Sclerosing cholangitis can result in hepatic failure. Other complications include abdominal aortitis with aneurysm formation, inflammatory pseudotumors of the kidney, thyroid inflammation (Riedel thyroiditis), and lymphadenopathy.

Histopathologic Features

Microscopic examination reveals chronic sclerosing sialadenitis, which is characterized by a heavy lymphoplasmacytic

infiltrate, hyperplastic lymphoid follicles, and acinar atrophy. Prominent interlobular fibrosis results in a storiform pattern when the gland is viewed at low power. Another common finding is obliterative phlebitis, which can be highlighted with an elastic stain. This overall pattern has sometimes been termed a **Küttner tumor.**

Treatment and Prognosis

IgG4-related disease often requires immediate, aggressive treatment with systemic corticosteroids to prevent significant organ damage and failure. Glucocorticoid-sparing agents, such as azathioprine, mycophenolate mofetil, and methotrexate, also can be used. Most patients show a rapid response to immunosuppressive therapy and have a favorable prognosis. For patients with recurrent disease, B-cell depletion with rituximab can be effective.

◆ SJÖGREN SYNDROME

Sjögren syndrome is a chronic, systemic autoimmune disorder that principally involves the salivary and lacrimal glands, resulting in xerostomia (dry mouth) and xerophthalmia (dry eyes). The effects on the eye often are called **keratoconjunctivitis sicca** (*sicca* means "dry"), and the clinical presentation of both xerostomia and xerophthalmia is also sometimes called the *sicca syndrome.* Traditionally, two forms of the disease are recognized:

1. *Primary* Sjögren syndrome (sicca syndrome alone; no other autoimmune disorder is present)
2. *Secondary* Sjögren syndrome (the patient manifests sicca syndrome in addition to another associated autoimmune disease)

However, some authors have suggested that the distinction between primary and secondary Sjögren syndrome may now be obsolete.

The cause of Sjögren syndrome is unknown. Although it is not a hereditary disease *per se,* there is evidence of a genetic influence. Examples of Sjögren syndrome have been reported in twins or in two or more members of the same family. Relatives of affected patients have an increased frequency of other autoimmune diseases. In addition, certain histocompatibility antigens (HLAs) are found with greater frequency in patients with Sjögren syndrome. HLA-DRw52 is associated with both forms of the disease; HLA-B8 and HLA-DR3 are seen with increased frequency in the primary form of the disease. Researchers have suggested that viruses, such as Epstein-Barr virus (EBV) or human T-cell lymphotropic virus, may play a pathogenetic role in Sjögren syndrome, but evidence for this is still speculative.

Clinical and Radiographic Features

Sjögren syndrome is not a rare condition. Although the exact prevalence depends on the clinical criteria used, current estimates place the population prevalence at 0.5%, with a 9:1 female-to-male ratio. It is seen predominantly in middle-aged adults, but rare examples have been described in children. The classification criteria suggested by the American-European Consensus Group are shown in Box 11-2. More recently, the American College of Rheumatology has proposed new classification criteria based on three objective features, as presented in Box 11-3.

When the condition is associated with another connective tissue disease, it is called *secondary Sjögren syndrome*. It can be associated with almost any other autoimmune disease, but the most common associated disorder is rheumatoid arthritis. About 15% of patients with rheumatoid arthritis have Sjögren syndrome. In addition, secondary Sjögren syndrome may develop in 30% of patients with systemic lupus erythematosus (SLE).

The principal oral symptom is xerostomia, which is caused by decreased salivary secretions; however, the severity of this dryness can vary widely from patient to patient. The saliva may appear frothy, with a lack of the usual pooling saliva in the floor of the mouth. Affected patients may complain of difficulty in swallowing, altered taste, or difficulty in wearing dentures. The tongue often becomes fissured and exhibits atrophy of the papillae (Fig. 11-23). The oral mucosa may be red and tender, usually as a result of secondary candidiasis. Related denture sore mouth and angular cheilitis are common. The lack of salivary cleansing action predisposes the patient to dental decay, especially cervical caries.

From one-third to one-half of patients have diffuse, firm enlargement of the major salivary glands during the course of their disease (Fig. 11-24). This swelling is usually bilateral, may be nonpainful or slightly tender, and may be intermittent or persistent in nature. The greater the severity of the disease, the greater the likelihood of this salivary enlargement. In addition, the reduced salivary flow places these individuals at increased risk for retrograde bacterial sialadenitis.

Although it is not diagnostic, sialographic examination often reveals punctate sialectasia and lack of normal arborization of the ductal system, typically demonstrating a "fruit-laden, branchless tree" pattern (Fig. 11-25). Scintigraphy with radioactive technetium-99m pertechnetate characteristically shows decreased uptake and delayed emptying of the isotope.

The term **keratoconjunctivitis sicca** describes not only the reduced tear production by the lacrimal glands but also the pathologic effect on the epithelial cells of the ocular surface. As in xerostomia, the severity of xerophthalmia can vary widely from one patient to the next. The lacrimal inflammation causes a decrease of the aqueous layer of the tear film; however, mucin production is normal and may result in a mucoid discharge. Patients often complain of a scratchy, gritty sensation or the perceived presence of a foreign body in the eye. Defects of the ocular surface epithelium develop, which may result in blurred vision and, sometimes, an aching pain. The ocular manifestations are least severe in the morning on wakening and become more pronounced as the day progresses.

• BOX 11-2 Revised International Classification Criteria for Sjögren Syndrome

I. Ocular symptoms: A positive response to at least one of the following questions:
   A. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   B. Do you have a recurrent sensation of sand or gravel in the eyes?
   C. Do you use tear substitutes more than three times a day?

II. Oral symptoms: A positive response to at least one of the following questions:
   A. Have you had a daily feeling of dry mouth for more than 3 months?
   B. Have you had recurrently or persistently swollen salivary glands as an adult?
   C. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs: Objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
   A. Schirmer I test, performed without anesthesia (≤5 mm in 5 minutes)
   B. Rose bengal score or other ocular dye score (≤4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
   A. Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)
   B. Parotid sialography showing the presence of diffuse sialectasia (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts
   C. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer

VI. Autoantibodies: Presence in the serum of the following autoantibodies:
   A. Antibodies to Ro(SS-A) or La(SS-B) antigens, or both

Rules for Classification

Primary Sjögren Syndrome

In patients without any potentially associated disease, primary Sjögren syndrome is defined as follows:

I. Presence of any four of the six items is indicative of primary Sjögren syndrome, as long as either item IV (histopathology) or VI (serology) is positive
II. Presence of any three of the four objective criteria items (items III, IV, V, and VI)

Secondary Sjögren Syndrome

In patients with a potentially associated disease (e.g., another well-defined connective tissue disease), presence of item I or item II plus any two from among items III, IV, and V is considered indicative of secondary Sjögren syndrome.

Exclusion Criteria

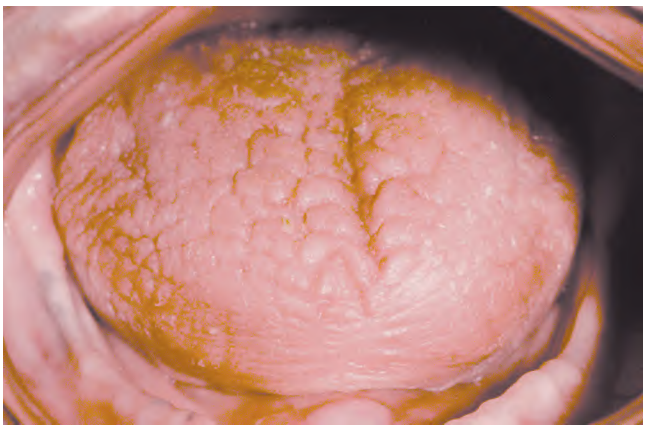
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency syndrome (AIDS)
Preexisting lymphoma
Sarcoidosis
Graft-versus-host disease (GVHD)
Use of anticholinergic drugs

• BOX 11-3 American College of Rheumatology Proposed Classification Criteria for Sjögren Syndrome*

Patients must have at least two of the following three objective features:

1. Positive autoantibodies to Ro(SS-A) and/or La(SS-B) antigens, *or* positive rheumatoid factor (RF) *and* antinuclear antibody (ANA) titer ≥1:320
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2
3. Keratoconjunctivitis sicca with ocular staining score ≥3 (assuming the patient is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)

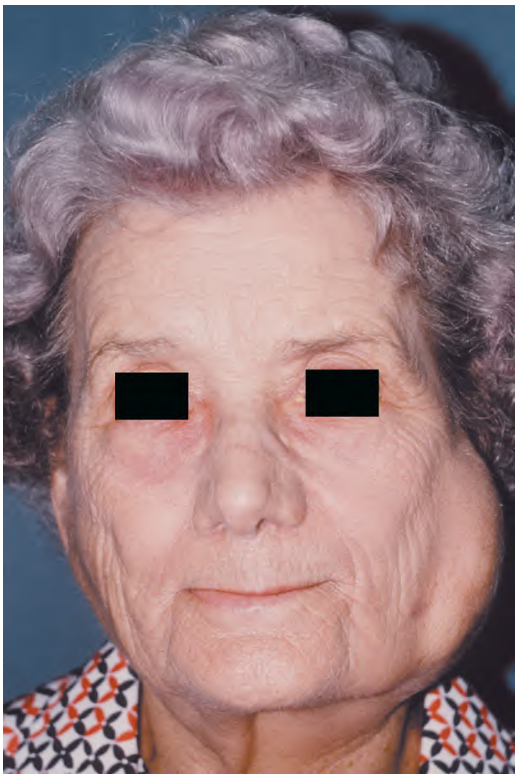
*Exclusion criteria are similar to the Revised International Classification Criteria in Box 11-2.



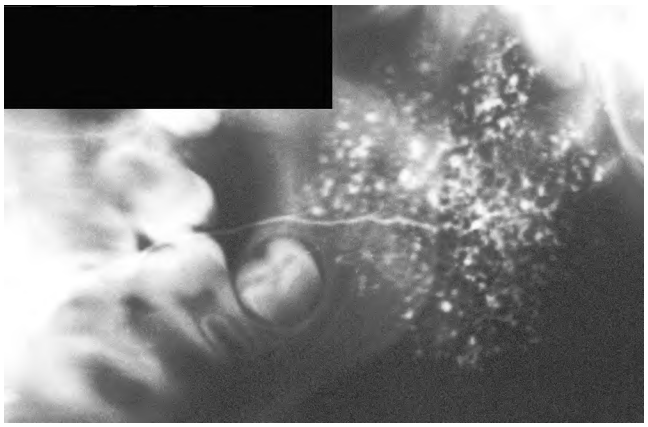
• **Fig. 11-23 Sjögren Syndrome.** Dry and fissured tongue. (Courtesy of Dr. David Schaffner.)

A simple means to confirm the decreased tear secretion is the Schirmer test. A standardized strip of sterile filter paper is placed over the margin of the lower eyelid, so that the tabbed end rests just inside the lower lid. By measuring the length of wetting of the filter paper, tear production can be assessed. Values less than 5 mm (after a 5-minute period) are considered abnormal. In addition, the possibility of damage to the corneal and conjunctival surfaces can be assessed by slit lamp examination after rose bengal and lissamine green staining.

Sjögren syndrome is a systemic disease, and the inflammatory process also can affect various other body tissues. The skin is often dry, as are the nasal and vaginal mucosae.



• **Fig. 11-24 Sjögren Syndrome.** Benign lymphoepithelial lesion of the parotid gland. (Courtesy of Dr. David Schaffner.)

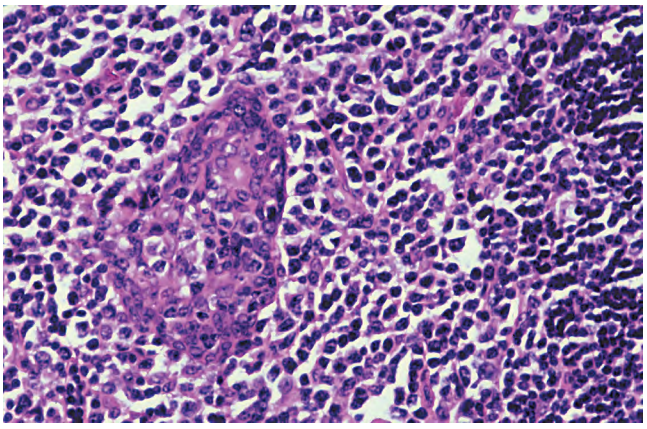


• **Fig. 11-25 Sjögren Syndrome.** Parotid sialogram demonstrating atrophy and punctate sialectasia ("fruit-laden, branchless tree"). (Courtesy of Dr. George Blozis.)

Fatigue is fairly common, and depression sometimes can occur. Other possible associated problems include lymphadenopathy, primary biliary cirrhosis, Raynaud phenomenon, interstitial nephritis, interstitial lung fibrosis, vasculitis, and peripheral neuropathies.

Laboratory Values

In patients with Sjögren syndrome, the erythrocyte sedimentation rate is high and serum immunoglobulin (Ig) levels, especially IgG, typically are elevated. A variety of autoantibodies can be produced, and although none of these is specifically diagnostic, their presence can be another helpful clue to the diagnosis. A positive rheumatoid factor (RF) is found in approximately 60% of cases, regardless of whether the patient has rheumatoid arthritis. Antinuclear antibodies (ANAs) are also present in 75% to 85% of patients. Two particular nuclear autoantibodies—anti-SS-A (anti-Ro) and anti-SS-B (anti-La)—may be found, especially in patients with primary Sjögren syndrome. Anti-SS-A antibodies have been detected in approximately 50% to 76% of patients, whereas anti-SS-B antibodies have been discovered in 30% to 60% of these individuals. Occasionally, salivary duct autoantibodies also can be demonstrated, usually in secondary Sjögren syndrome. However, because these are infrequent in primary cases, they are believed to occur as a secondary phenomenon (rather than playing a primary role in pathogenesis).

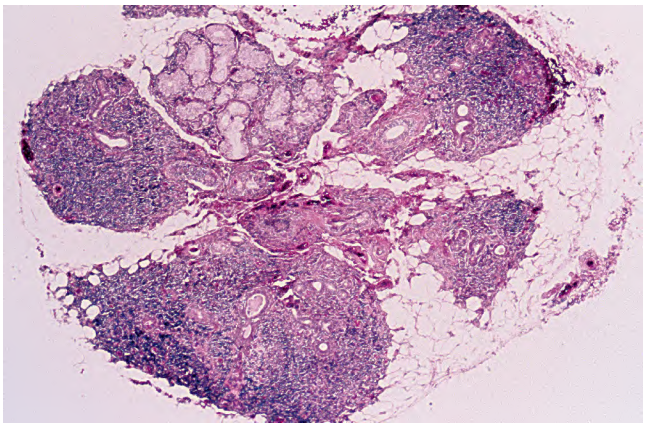


• **Fig. 11-26 Benign Lymphoepithelial Lesion in Sjögren Syndrome.** Lymphocytic infiltrate of the parotid gland with an associated epimyoepithelial island.

Histopathologic Features

The basic microscopic finding in Sjögren syndrome is a lymphocytic infiltration of the salivary glands, which leads to destruction of the acinar units. More advanced lesions result in a pattern known as a **benign lymphoepithelial lesion (myoepithelial sialadenitis).** Although the acini are destroyed, the ductal epithelium persists. The ductal cells and surrounding myoepithelial cells become hyperplastic, forming highly characteristic groups of cells, known as *epimyoepithelial islands,* throughout the lymphoid proliferation (Fig. 11-26). Germinal centers may or may not be seen. Lymphocytic infiltration of the minor glands also occurs, although epimyoepithelial islands are rarely seen in this location.

Biopsy of the minor salivary glands of the lower lip sometimes is used as a diagnostic test for Sjögren syndrome. A 1.5- to 2.0-cm incision is made on clinically normal lower labial mucosa, parallel to the vermilion border and lateral to the midline, allowing the harvest of five or more accessory glands. These glands then can be examined histopathologically for the presence of focal chronic inflammatory aggregates composed of 50 or more lymphocytes and plasma cells. The aggregates should be adjacent to normal-appearing



• **Fig. 11-27 Sjögren Syndrome.** Labial gland biopsy showing multiple lymphocytic foci.

acini and should be found consistently in most of the glands in the specimen. The following formula has been suggested:

$$\text{Focus score} = \frac{\text{Number of inflammatory aggregates} \times 4}{\text{Number of mm}^2 \text{ of salivary gland parenchyma}}$$

The focus score calculates the number of inflammatory aggregates per 4-mm^2 area of salivary gland tissue. A focus score ≥ 1 (i.e., one or more foci of 50 or more cells per 4-mm^2 area of glandular tissue) is considered supportive of the diagnosis of Sjögren syndrome (Fig. 11-27). The greater the number of foci (up to 12 or confluent foci) is, the greater is the correlation with this diagnosis. The focal nature of this chronic inflammation among otherwise normal acini is a highly suggestive pattern; in contrast, the finding of scattered inflammation with ductal dilatation and fibrosis (chronic sclerosing sialadenitis) does not support the diagnosis of Sjögren syndrome.

Although labial salivary gland biopsy has become a widely used test in the diagnosis of Sjögren syndrome, it is not 100% reliable. Some patients diagnosed with Sjögren syndrome will show no significant labial gland inflammation; conversely, examination of labial glands removed incidentally from non-Sjögren patients sometimes will show focal lymphocytic infiltrates. Sjögren syndrome patients who smoke have been shown to have a significantly lower frequency of abnormal lymphocytic foci scores in their labial gland specimens. It also is important that a pathologist experienced in the analysis of these specimens examines the labial gland biopsies. One study showed that slightly more than half of labial gland specimens required a revised diagnosis after being reviewed by a second pathologist.

Other authors have advocated incisional biopsy of the parotid gland through a posterior auricular approach instead of a labial salivary gland biopsy. One study has shown this technique to be more sensitive in demonstrating inflammatory changes that support the diagnosis of Sjögren syndrome; however, other authors think that this technique confers no increased benefit over labial gland biopsy. Parotid biopsy may enable the clinician to evaluate an enlarged gland for the development of lymphoma and rule out the possibility of sialadenosis or sarcoidosis.

Treatment and Prognosis

The treatment of the patient with Sjögren syndrome is mostly supportive. The dry eyes are best managed by periodic use of artificial tears. In addition, attempts can be made to conserve the tear film through the use of sealed glasses to prevent evaporation. Sealing the lacrimal punctum at the inner margin of the eyelids also can be helpful by blocking the normal drainage of any lacrimal secretions into the nose.

Artificial salivas are available for the treatment of xerostomia; sugarless candy or gum can help to keep the mouth moist. Symptoms often can be relieved by the use of oral hygiene products that contain lactoperoxidase, lysozyme, and lactoferrin (e.g., Biotene toothpaste and mouth rinse, and Oralbalance gel). Sialagogue medications, such as pilocarpine and cevimeline, can be useful to stimulate salivary flow if enough functional salivary tissue still remains. Medications known to diminish secretions should be avoided, if at all possible. Because of the increased risk of dental caries, daily fluoride applications may be indicated in dentulous patients. Antifungal therapy often is needed to treat secondary candidiasis.

Patients with Sjögren syndrome have a lifetime risk for lymphoma of 5% to 15%, which is estimated to be about 20 times greater than the general population. These tumors may arise initially within the salivary glands or within lymph nodes. With the advent of modern molecular pathology techniques to detect B-cell monoclonality (e.g., *in situ* hybridization, polymerase chain reaction [PCR]), many salivary gland infiltrates formerly thought to represent benign lymphoepithelial lesions are now being diagnosed as lymphomas. These tumors are predominantly low-grade non-Hodgkin B-cell lymphomas of the mucosa-associated lymphoid tissue (i.e., **MALT lymphomas, extranodal marginal zone B-cell lymphomas**), although occasionally, high-grade lymphomas can develop that demonstrate more aggressive behavior. Prognostic risk factors for lymphoma development include persistent parotid gland enlargement, lymphadenopathy, splenomegaly, neutropenia, low C4 complement levels, cryoglobulinemia, and palpable purpura. The detection of immunoglobulin gene rearrangements in labial salivary gland biopsies may prove to be a useful marker for predicting the development of lymphoma.

◆ SIALADENOSIS (SIALOSIS)

Sialadenosis is an unusual noninflammatory disorder characterized by salivary gland enlargement, particularly involving the parotid glands. The condition frequently is associated with an underlying systemic problem, which may be endocrine, nutritional, or neurogenic in origin (Box 11-4). The best known of these conditions include diabetes mellitus, general malnutrition, alcoholism, and bulimia.

• BOX 11-4 Conditions Associated with Sialadenosis

Endocrine Disorders

- Diabetes mellitus
- Diabetes insipidus
- Acromegaly
- Hypothyroidism
- Pregnancy

Nutritional Conditions

- General malnutrition
- Alcoholism
- Cirrhosis
- Anorexia nervosa
- Bulimia

Neurogenic Medications

- Antihypertensive drugs
- Psychotropic drugs
- Sympathomimetic drugs used for treating asthma

These conditions are believed to result in dysregulation of the autonomic innervation of the salivary acini, causing an aberrant intracellular secretory cycle. This leads to excessive accumulation of secretory granules, with marked enlargement of the acinar cells. In addition, reduced innervation of myoepithelial cells may lead to atrophy of the supporting myofilaments around the acinar cells.

Clinical and Radiographic Features

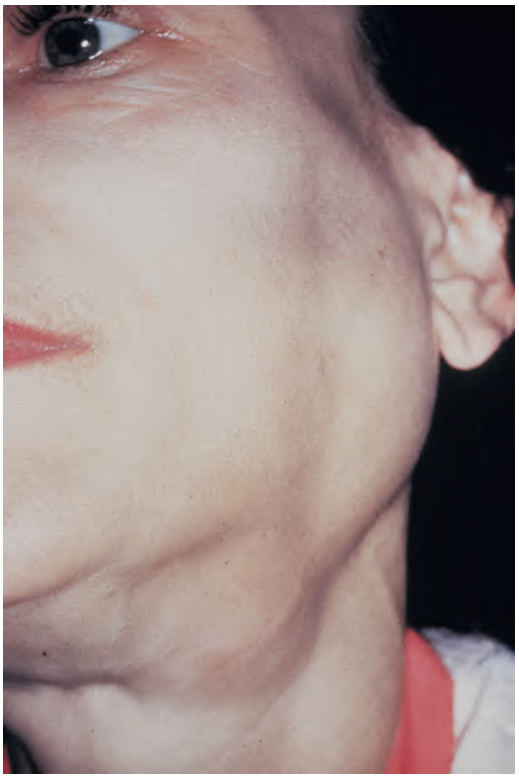
Sialadenosis usually appears as a slowly evolving swelling of the parotid glands, which may or may not be painful (Fig. 11-28). The condition is usually bilateral, but it also can be unilateral. In some patients, the submandibular glands may be affected, but involvement of minor salivary glands is distinctly rare. Decreased salivary secretion may occur. Sialography demonstrates a "leafless tree" pattern, which is thought to be caused by compression of the finer ducts by hypertrophic acinar cells.

Histopathologic Features

Microscopic examination reveals hypertrophy of the acinar cells, sometimes two to three times greater than normal size. The nuclei are displaced to the cell base, and the cytoplasm is engorged with zymogen granules. In cases associated with long-standing diabetes or alcoholism, there may be acinar atrophy and fatty infiltration. Significant inflammation is not observed.

Treatment and Prognosis

The clinical management of sialadenosis is often unsatisfactory because it is closely related to the control of the underlying cause. Mild examples may cause few problems. If the swelling becomes a cosmetic concern, then partial parotidectomy can be performed. Pilocarpine has been reported to be beneficial in reducing salivary gland enlargement in bulimic patients.



• Fig. 11-28 Sialadenosis. Enlargement of the parotid and submandibular glands secondary to alcoholism. (Courtesy of Dr. George Blozis.)

◆ ADENOMATOID HYPERPLASIA OF THE MINOR SALIVARY GLANDS

Clinical Features

Adenomatoid hyperplasia is a rare lesion of the minor salivary glands characterized by localized swelling that mimics a neoplasm. This pseudotumor most often occurs on the hard or soft palate, although it also has been reported in other oral minor salivary gland sites. The pathogenesis of adenomatoid hyperplasia is uncertain, but it has been speculated that local trauma may play a role. It is most common in the fourth to sixth decades of life. Most examples present as sessile, painless masses that may be soft or firm to palpation. They usually are normal in color, although a few lesions are red or bluish.

Histopathologic Features

Microscopic examination demonstrates lobular aggregates of relatively normal-appearing mucous acini that are greater in number than normally would be found in the area. These glands also sometimes appear to be increased in size. In

some instances, the glands are situated close to the mucosal surface. Chronic inflammation occasionally is seen, but it usually is mild and localized.

Treatment and Prognosis

Because the clinical presentation of adenomatoid hyperplasia mimics a tumor, biopsy is necessary to establish the diagnosis. Once the diagnosis has been established, no further treatment is indicated and the lesion should not recur.

The pathologist should be wary of making a diagnosis of adenomatoid hyperplasia without good clinical correlation. On occasion, attempted biopsy of a true salivary gland tumor may harvest only adjacent normal salivary tissue, which might be misinterpreted as adenomatoid hyperplasia. Good communication between the clinician and pathologist is important.

◆ NECROTIZING SIALOMETAPLASIA

Necrotizing sialometaplasia is an uncommon, locally destructive inflammatory condition of the salivary glands. Although the cause is uncertain, most authors believe it is the result of ischemia of the salivary tissue that leads to local infarction. The importance of this lesion rests in the fact that it mimics a malignant process, both clinically and microscopically.

A number of potential predisposing factors have been suggested, including the following:

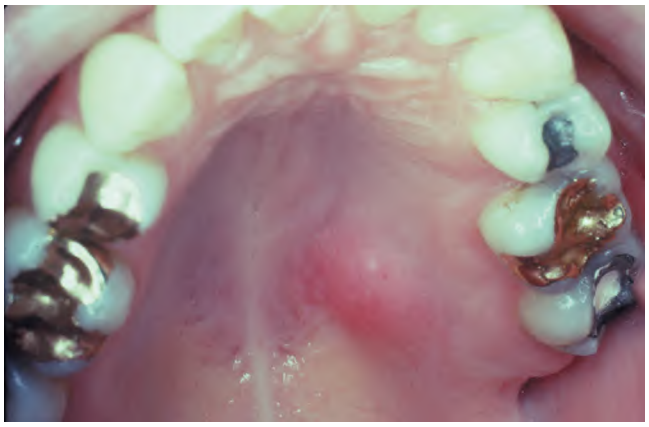
- Traumatic injuries
- Dental injections
- Ill-fitting dentures
- Upper respiratory infections
- Adjacent tumors
- Previous surgery
- Eating disorders with binge-purging

Researchers have suggested that these factors may play a role in compromising the blood supply to the involved glands, resulting in ischemic necrosis. However, many cases occur without any known predisposing factors.

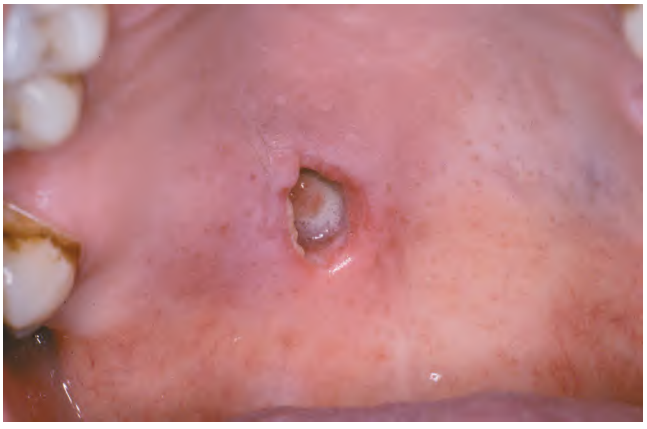
Clinical Features

Necrotizing sialometaplasia most frequently develops in the palatal salivary glands; more than 75% of all cases occur on the posterior palate. The hard palate is affected more often than the soft palate. About two-thirds of palatal cases are unilateral, with the rest being bilateral or midline in location. Necrotizing sialometaplasia also has been reported in other minor salivary gland sites and, occasionally, in the parotid gland. The submandibular and sublingual glands are rarely affected. Although it can occur at almost any age, necrotizing sialometaplasia is most common in adults; the mean age of onset is 46 years. Males are affected nearly twice as often as females.

The condition appears initially as a nonulcerated swelling, often associated with pain or paresthesia (Fig. 11-29).



• **Fig. 11-29 Necrotizing Sialometaplasia.** Early lesion demonstrating swelling of the posterior lateral hard palate. (From Allen CM, Camisa C: Diseases of the mouth and lips. In Sams WM, Lynch P, editors: *Principles of dermatology,* New York, 1990, Churchill Livingstone.)

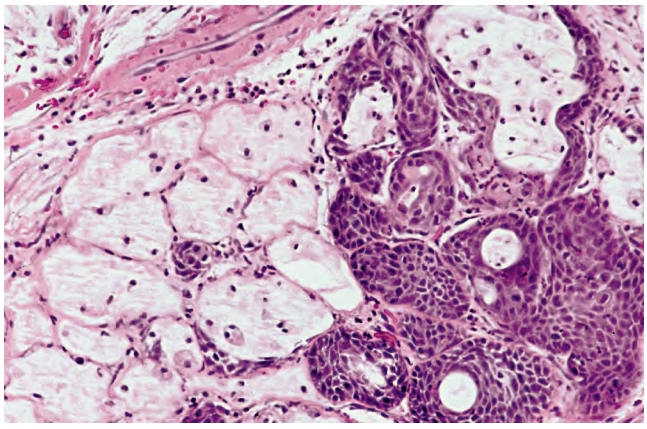


• **Fig. 11-30 Necrotizing Sialometaplasia.** Later-stage lesion showing craterlike defect of the posterior palate.

Within 2 to 3 weeks, necrotic tissue sloughs out, leaving a craterlike ulcer that can range from less than 1 cm to more than 5 cm in diameter (Fig. 11-30). The patient may report that "a part of my palate fell out." At this point, the pain often subsides. In rare instances, there can be destruction of the underlying palatal bone.

Histopathologic Features

The microscopic appearance of necrotizing sialometaplasia is characterized by acinar necrosis in early lesions, followed by associated squamous metaplasia of the salivary ducts (Fig. 11-31). Although the mucous acinar cells are necrotic, the overall lobular architecture of the involved glands is still preserved—a helpful histopathologic clue. There may be liberation of mucin, with an associated inflammatory response. The squamous metaplasia of the salivary ducts can be striking and produce a pattern that is easily misdiagnosed as squamous cell carcinoma or mucoepidermoid carcinoma. The frequent association of pseudoepitheliomatous hyperplasia of the overlying epithelium may further compound



• **Fig. 11-31 Necrotizing Sialometaplasia.** Necrotic mucous acini *(left)* and adjacent ductal squamous metaplasia *(right)*.

this mistaken impression. In most cases, however, the squamous proliferation has a bland cytologic appearance. In examples that are difficult to distinguish from carcinoma, low immunoreactivity for p53 protein and Ki-67 may help to support a diagnosis of necrotizing sialometaplasia.

Treatment and Prognosis

Because of the worrisome clinical presentation of necrotizing sialometaplasia, biopsy usually is indicated to rule out the possibility of malignant disease. Once the diagnosis has been established, no specific treatment is indicated or necessary. The lesion typically resolves on its own accord, with an average healing time of 5 to 6 weeks.

SALIVARY GLAND TUMORS

◆ GENERAL CONSIDERATIONS

Tumors of the salivary glands constitute an important area in the field of oral and maxillofacial pathology. Although such tumors are uncommon, they are by no means rare. The annual incidence of salivary gland tumors around the world ranges from about 1.0 to 6.5 cases per 100,000 people. Although soft tissue neoplasms (e.g., hemangioma), lymphoma, and metastatic tumors can occur within the salivary glands, the discussion in this chapter is limited to primary epithelial neoplasms.

An often-bewildering array of salivary tumors has been identified and categorized. In addition, the classification scheme is a dynamic one that changes as clinicians learn more about these lesions. As an example, since the last edition of this text, mammary analogue secretory carcinoma has been newly recognized as an important low-grade salivary malignancy that may occur in both major and minor glands. Box 11-5 includes most of the currently recognized tumors. Some of the tumors on this list are not specifically discussed because their rarity places them outside the scope of this text.

• BOX 11-5 Classification of Salivary Gland Tumors

Benign

- Pleomorphic adenoma (mixed tumor)
- Myoepithelioma
- Basal cell adenoma
- Canalicular adenoma
- Warthin tumor (papillary cystadenoma lymphomatosum)
- Oncocytoma
- Sebaceous adenoma
- Sebaceous lymphadenoma
- Ductal papillomas
  - Sialadenoma papilliferum
  - Intraductal papilloma
  - Inverted ductal papilloma
- Papillary cystadenoma

Malignant

- Malignant mixed tumors
  - Carcinoma ex pleomorphic adenoma
  - Carcinosarcoma
  - Metastasizing mixed tumor
- Mucoepidermoid carcinoma
- Acinic cell adenocarcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Basal cell adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Mammary analogue secretory carcinoma
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Cystadenocarcinoma
- Sebaceous adenocarcinoma
- Sebaceous lymphadenocarcinoma
- Clear cell adenocarcinoma
- Oncocytic carcinoma
- Squamous cell carcinoma
- Malignant lymphoepithelial lesion (lymphoepithelial carcinoma)
- Small cell carcinoma
- Sialoblastoma
- Adenocarcinoma, not otherwise specified (NOS)

A number of investigators have published their findings on salivary gland neoplasia, but a comparison of these studies is often difficult. Some studies have been limited to only the major glands or have not included all the minor salivary gland sites. In addition, the ever-evolving classification system makes an evaluation of some older studies difficult, especially when researchers attempt to compare them with more recent analyses. Notwithstanding these difficulties, it is still helpful to compare these studies because they provide a good overview of salivary neoplasia in general. An evaluation of various studies shows fairly consistent trends (with minor variations) with regard to salivary gland tumors.

Tables 11-3 and 11-4 summarize five large series of primary epithelial salivary gland tumors, analyzed by sites of occurrence and frequency of malignancy, respectively. Some variations between studies may represent differences in diagnostic criteria, geographic differences, or referral bias

TABLE 11-3 Sites of Occurrence of Primary Epithelial Salivary Gland Tumors

Author (Year)	Number of Cases	Parotid	Submandibular	Sublingual	Minor
Eveson and Cawson (1985)	2,410	73%	11%	0.3%	14%
Seifert et al. (1986)	2,579	80%	10%	1.0%	9%
Spiro (1986)	2,807	70%	8%	(included with minor gland tumors)	22%
Ellis et al. (1991)	13,749	64%	10%	0.3%	23%
Tian et al. (2010)	6,982	61%	10%	1.0%	28%

TABLE 11-4 Frequency of Malignancy for Salivary Tumors at Different Sites

Author (Year)	Number of Cases	Parotid	Submandibular	Sublingual	Minor
Eveson and Cawson (1985)	2,410	15%	37%	86%	46%
Seifert et al. (1986)	2,579	20%	45%	90%	45%
Spiro (1986)	2,807	25%	43%	(included with minor gland tumors)	82%
Ellis et al. (1991)	13,749	32%	41%	70%	49%
Tian et al. (2010)	6,982	18%	26%	95%	62%

in the cases seen. (Some centers may tend to see more malignant tumors on referral from other sources.)

The most common site for salivary gland tumors is the parotid gland, accounting for 61% to 80% of all cases. Fortunately, a relatively low percentage of parotid tumors are malignant, ranging from 15% to 32%. Overall, it can be stated that two-thirds to three-quarters of all salivary tumors occur in the parotid gland, and two-thirds to three-quarters of these parotid tumors are benign.

Table 11-5 summarizes four large series of parotid neoplasms. The pleomorphic adenoma is overwhelmingly the most common tumor (50% to 77% of all cases in the parotid gland). Warthin tumors are also fairly common; they account for 5% to 22% of cases. A variety of malignant tumors occur, with the mucoepidermoid carcinoma appearing to be the most frequent overall. Although previous studies suggested that the United Kingdom may have a lower frequency of this tumor, a more recent series showed prevalence numbers equivalent to other countries.

From 8% to 11% of all salivary tumors occur in the submandibular gland, but the frequency of malignancy in this gland is much greater than that of the parotid gland, ranging from 26% to 45%. However, as shown in Table 11-6, the pleomorphic adenoma is still the most common tumor and makes up 53% to 72% of all neoplasms. Unlike its occurrence in the parotid gland, the Warthin tumor is unusual in the submandibular gland, making up no more than 1% to 2% of all tumors. Adenoid cystic carcinoma is the most common malignancy, ranging from 11% to 17% of all cases.

Tumors of the sublingual gland are rare, comprising no more than 1% of all salivary neoplasms. However, 70% to 95% of sublingual tumors are malignant.

Tumors of the various smaller minor salivary glands make up 9% to 28% of all tumors, which makes this group the second most common site for salivary neoplasia. Table 11-7 summarizes the findings of five large surveys of minor gland tumors. Unfortunately, relatively high proportions (38% to 49%) of these have been malignant in most studies. Excluding rare sublingual tumors, it can be stated that the smaller the gland is, the greater is the likelihood of malignancy for a salivary gland tumor.

As observed in the major glands, the pleomorphic adenoma is the most common minor gland tumor and accounts for about 40% of all cases. Mucoepidermoid carcinoma is the most frequent malignancy of minor gland origin, comprising 13% to 23% of all tumors. Adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma are also recognized as relatively common malignant tumors arising from the minor salivary glands.

The palate is the most frequent site for minor salivary gland tumors, with 42% to 54% of all cases found there (Table 11-8). Most of these occur on the posterior lateral hard or soft palate, which have the greatest concentration of glands. Table 11-9 shows the relative prevalence of various tumors on the palate. The lips are the second most common

TABLE 11-5 Parotid Tumors

	Tian et al. (China, 2010)	Ellis et al. (United States, 1991)	Eveson & Cawson (Great Britain, 1985)	Eneroth (Sweden, 1971)
Total number of cases	4264	8222	1756	2158
Benign Tumors				
Pleomorphic adenoma	49.9%	53.0%	63.3%	76.8%
Warthin tumor	22.4%	7.7%	14.0%	4.7%
Oncocytoma	0.5%	1.9%	0.9%	1.0%
Basal cell adenoma	5.8%	1.4%	—	—
Other benign tumors	3.4%	3.7%	7.1% *	—
Total	82.1%	67.7%	85.3%	82.5%
Malignant Tumors				
Mucoepidermoid carcinoma	4.3%	9.6%	1.5%	4.1%
Acinic cell carcinoma	3.2%	8.6%	2.5%	3.1%
Adenoid cystic carcinoma	1.8%	2.0%	2.0%	2.3%
Malignant mixed tumor	2.3%	2.5%	3.2%	1.5%
Squamous cell carcinoma	0.7%	2.1%	1.1%	0.3%
Other malignant tumors	5.6%	7.5%	4.4%	6.3%
Total	17.9%	32.3%	14.7%	17.5%

*Includes all "other monomorphic adenomas."

TABLE 11-6 Submandibular Tumors

	Tian et al. (China, 2010)	Ellis et al. (United States, 1991)	Eveson & Cawson (Great Britain, 1985)	Eneroth (Sweden, 1971)
Total number of cases	663	1235	257	170
Benign Tumors				
Pleomorphic adenoma	72.2%	53.3%	59.5%	60.0%
Warthin tumor	0.6%	1.3%	0.8%	2.4%
Oncocytoma	0.2%	1.5%	0.4%	0.6%
Basal cell adenoma	0.3%	1.0%	—	—
Other benign tumors	0.6%	1.7%	1.9% *	—
Total	73.9%	58.8%	62.6%	62.9%
Malignant Tumors				
Mucoepidermoid carcinoma	4.2%	9.1%	1.6%	3.5%
Acinic cell carcinoma	1.1%	2.7%	0.4%	0.6%
Adenoid cystic carcinoma	11.2%	11.7%	16.8%	15.3%
Malignant mixed tumor	4.1%	3.5%	7.8%	1.8%
Squamous cell carcinoma	1.1%	3.4%	1.9%	7.1%
Other malignant tumors	4.5%	10.8%	8.9%	8.8%
Total	26.1%	41.2%	37.4%	37.1%

*Includes all "other monomorphic adenomas."

TABLE 11-7 Minor Salivary Gland Tumors

	Jones et al. (United Kingdom, 2008)	Buchner et al. (United States, 2007)	Pires et al. (United States, 2007)	Ellis et al. (United States, 1991)	Waldron et al. (United States, 1988)
Total number of cases	455	380	546	3355	426
Benign Tumors					
Pleomorphic adenoma	40.4%	39.2%	33.2%	38.1%	40.8%
"Monomorphic" adenoma (canalicular and basal cell adenoma)	15.2%	7.6%	9.2%	4.5%	10.8%
Other benign tumors	6.6%	12.1%	13.5%	8.8%	5.9%
Total	62.2%	58.9%	55.9%	51.3%	57.5%
Malignant Tumors					
Mucoepidermoid carcinoma	13.0%	21.8%	22.9%	21.5%	15.3%
Acinic cell carcinoma*	1.3%	1.6%	3.8%	3.5%	3.5%
Adenoid cystic carcinoma	11.4%	6.3%	6.4%	7.7%	9.4%
Malignant mixed tumor	2.4%	0.5%	0.4%	1.7%	1.4%
Polymorphous low-grade adenocarcinoma	6.2%	7.1%	5.1%	2.2%	11.0%
Other malignant tumors	3.5%	3.7%	5.5%	12.1%	1.9%
Total	37.8%	41.1%	44.1%	48.7%	42.5%

*Incidence numbers for acinic cell carcinoma are probably high because they predate recognition of mammary analogue secretory carcinoma, which has similar features.

TABLE 11-8 Location of Minor Salivary Gland Tumors

Author (Year)	Number of Cases	Palate	Lips	Buccal	Retromolar	Floor of Mouth	Tongue	Other
Waldron et al. (1988)	426	42%	22%	15%	5%	5%	1%	9%
Ellis et al. (1991)	3355	44%	21%	12%	2%	3%	5%	12%
Buchner et al. (2007)	380	54%	22%	14%	5%	3%	1%	0%
Jones et al. (2008)	455	51%	24%	12%	2%	2%	2%	8%

location for minor gland tumors (21% to 24% of cases), followed by the buccal mucosa (12% to 15% of cases). Labial tumors are significantly more common in the upper lip, which accounts for 74% to 87% of all lip tumors (Table 11-10). Although mucoceles are commonly found on the lower lip, this is a surprisingly rare site for salivary gland tumors.

Significant differences in the percentage of malignancies and the relative frequency of various tumors can be noted for different minor salivary gland sites. As shown in Table 11-11, 41% to 47% of palatal tumors and 30% to 50% of buccal mucosa tumors are malignant, similar to the overall prevalence of malignancy in all minor salivary gland sites combined. In the upper lip, however, only 9% to 25% of tumors are malignant because of the high prevalence of the canalicular adenoma, which has a special affinity for this location. In contrast, although lower lip tumors are uncommon, 43% to 86% are malignant (mostly mucoepidermoid carcinomas). Up to 95% of retromolar tumors are malignant, also because of a predominance of mucoepidermoid carcinomas. Unfortunately, most tumors in the floor of the mouth and tongue are also malignant.

TABLE 11-9 Palatal Salivary Gland Tumors

	Buchner et al. (United States, 2007)	Pires et al. (United States, 2007)	Ellis et al. (United States, 1991)	Waldron et al. (United States, 1988)	Eveson & Cawson (Great Britain, 1985)
Total number of cases	206	181	1478	181	183
Benign Tumors					
Pleomorphic adenoma	46.6%	39.8%	48.2%	51.9%	47.0%
Other benign tumors	10.2%	13.2%	5.0%	6.0%	6.0%
Total	56.8%	53.0%	53.2%	58.0%	53.0%
Malignant Tumors					
Mucoepidermoid carcinoma	18.9%	23.8%	20.7%	9.9%	9.3%
Acinic cell carcinoma*	0.0%	2.2%	1.4%	1.7%	1.1%
Adenoid cystic carcinoma	8.7%	7.7%	8.3%	10.5%	15.3%
Malignant mixed tumor	0.5%	0.0%	2.4%	2.2%	8.2%
Polymorphous low-grade adenocarcinoma	10.2%	6.1%	3.0%	16.0%	—
Other malignant tumors	4.9%	7.2%	11.0%	1.7%	13.1%
Total	43.2%	47.0%	46.8%	42.0%	47.0%

*Incidence numbers for acinic cell carcinoma are probably high because they predate recognition of mammary analogue secretory carcinoma, which has similar features.

TABLE 11-10 Location of Labial Salivary Gland Tumors

Author (Year)	Number of Cases	Upper Lip	Lower Lip
Waldron et al. (1988)	93	85%	15%
Neville et al. (1988)	103	84%	16%
Ellis et al. (1991)	536	77%	23%
Pires et al. (2007)	144	74%	26%
Buchner et al. (2007)	82	78%	22%
Jones et al. (2008)	107	87%	13%

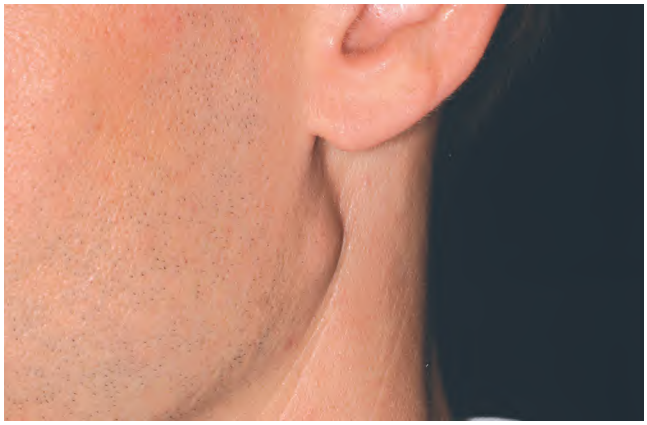
◆ PLEOMORPHIC ADENOMA (BENIGN MIXED TUMOR)

The **pleomorphic adenoma,** or **benign mixed tumor,** is easily the most common salivary neoplasm. It accounts for 50% to 77% of parotid tumors, 53% to 72% of submandibular tumors, and 33% to 41% of minor gland tumors.

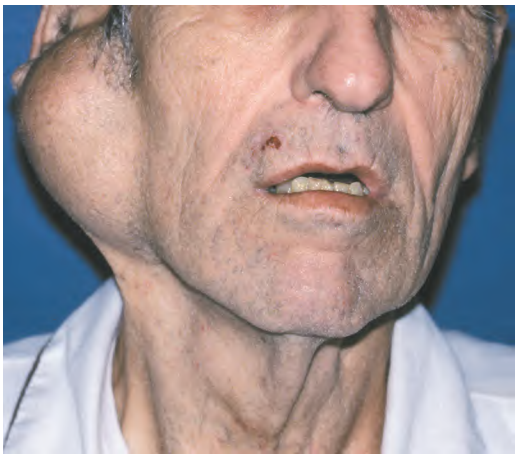
Pleomorphic adenomas are derived from a mixture of ductal and myoepithelial elements. A remarkable microscopic diversity can exist from one tumor to the next, as well as in different areas of the same tumor. The terms *pleomorphic adenoma* and *mixed tumor* both represent attempts to describe this tumor's unusual histopathologic features, but neither term is entirely accurate. Although the basic tumor pattern is highly variable, rarely are the individual cells actually pleomorphic. (However, focal minor atypia is acceptable.) Likewise, although the tumor often has a prominent mesenchyme-appearing "stromal" component, it is not truly a mixed neoplasm that is derived from more than one germ layer. Cytogenetic analysis has shown

TABLE 11-11 Intraoral Minor Salivary Gland Tumors: Percentage Malignant by Site

Author (Year)	Palate	Upper Lip	Lower Lip	Buccal	Retromolar	Floor of Mouth	Tongue
Eveson & Cawson (1985)	47%	25%	50%	50%	60%	—	92%
Waldron et al. (1988)	42%	14%	86%	46%	91%	80%	75%
Ellis et al. (1991)	47%	22%	60%	50%	90%	88%	86%
Buchner et al. (2007)	43%	9%	56%	37%	95%	69%	60%
Jones et al. (2008)	41%	15%	43%	30%	88%	75%	71%



• **Fig. 11-32 Pleomorphic Adenoma.** Small, firm nodule located below the left ear in the parotid gland. (Courtesy of Dr. Mike Hansen.)

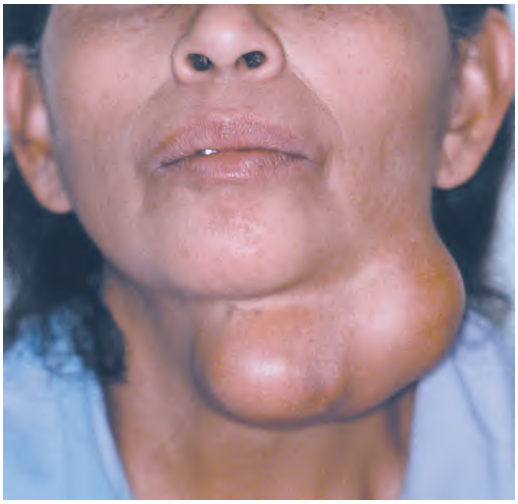


• **Fig. 11-33 Pleomorphic adenoma.** Slowly growing tumor of the parotid gland.

translocations in approximately 70% of pleomorphic adenomas, primarily involving *pleomorphic adenoma gene 1 (PLAG1)* located at chromosome region 8q12.

Clinical and Radiographic Features

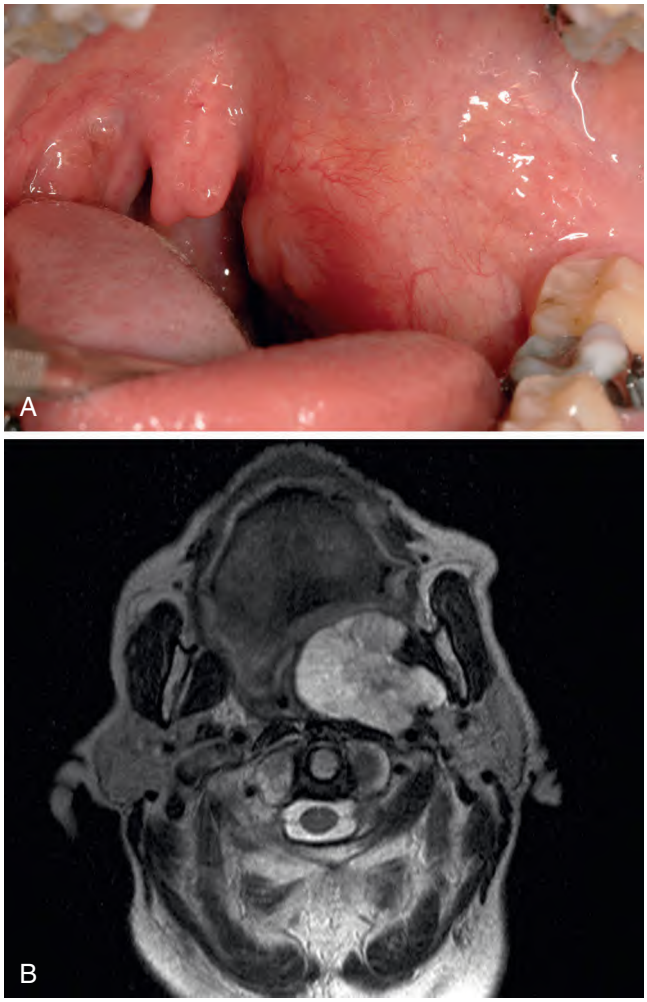
Regardless of the site of origin, the pleomorphic adenoma typically appears as a painless, slowly growing, firm mass



• **Fig. 11-34 Pleomorphic Adenoma.** Tumor of the submandibular gland. (Courtesy of Dr. Román Carlos.)

(Figs. 11-32 to 11-34). The patient may be aware of the lesion for many months or years before seeking a diagnosis. The tumor can occur at any age but is most common in young and middle-aged adults between the ages of 30 and 60. Pleomorphic adenoma is also the most common primary salivary gland tumor to develop during childhood. There is a slight female predilection.

Most pleomorphic adenomas of the parotid gland occur in the superficial lobe and present as a swelling overlying the mandibular ramus in front of the ear. Facial nerve palsy and pain are rare. Initially, the tumor is movable but becomes less mobile as it grows larger. If neglected, then the lesion can grow to grotesque proportions. About 10% of parotid mixed tumors develop within the deep lobe of the gland beneath the facial nerve (Fig. 11-35). Sometimes these lesions grow in a medial direction between the ascending ramus and stylomandibular ligament, resulting in a dumbbell-shaped tumor that appears as a mass of the lateral pharyngeal wall or soft palate. On rare occasions, bilateral pleomorphic adenomas of the parotid glands have been reported, developing in either a synchronous or metachronous fashion.

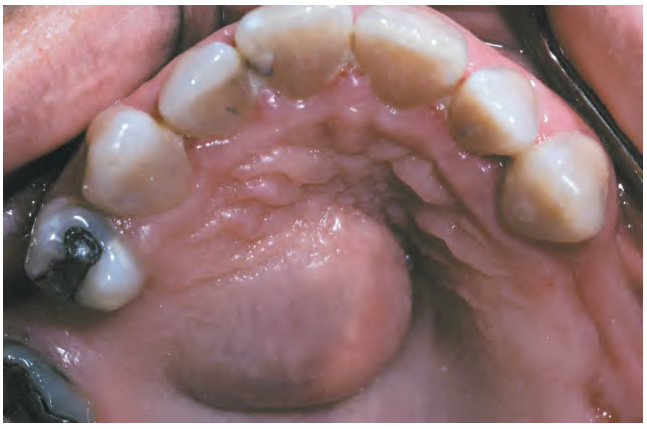


• **Fig. 11-35 Pleomorphic Adenoma. A**, Large tumor from the deep lobe of the parotid gland, which has resulted in a firm mass of the lateral soft palate. **B**, Contrast-enhanced axial magnetic resonance image (MRI) of a tumor of the deep lobe of the parotid gland. (Courtesy of Dr. Terry Day.)

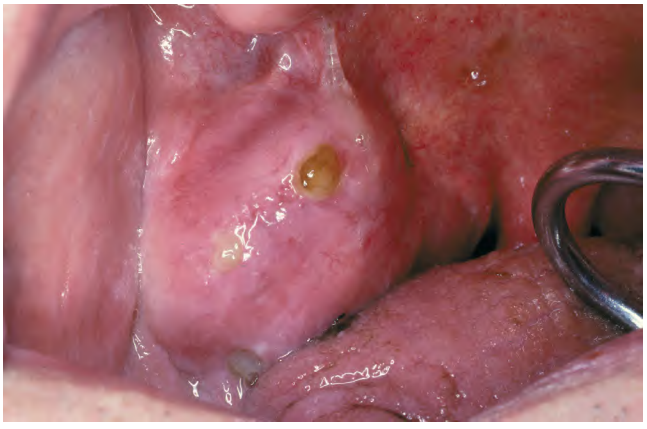
The palate is the most common site for minor gland mixed tumors, accounting for approximately 50% to 65% of intraoral examples. This is followed by the upper lip (19% to 27%) and buccal mucosa (13% to 17%). Palatal tumors almost always are found on the posterior lateral aspect of the palate, presenting as smooth-surfaced, dome-shaped masses (Figs. 11-36 and 11-37). If the tumor is traumatized, then secondary ulceration may occur. Because of the tightly bound nature of the hard palate mucosa, tumors in this location are not movable, although those in the lip or buccal mucosa frequently are mobile.

Histopathologic Features

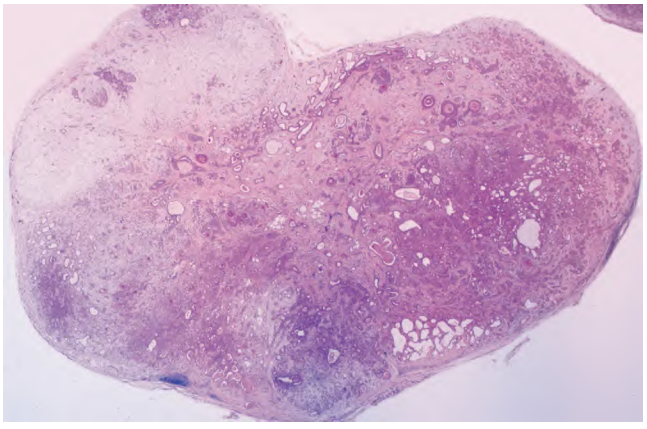
The pleomorphic adenoma is typically a well-circumscribed, encapsulated tumor (Fig. 11-38). However, the capsule may be incomplete or show infiltration by tumor cells. This lack of complete encapsulation is more common for minor gland tumors, especially along the superficial aspect of palatal tumors beneath the epithelial surface.



• **Fig. 11-36 Pleomorphic Adenoma.** Firm mass of the hard palate lateral to the midline.



• **Fig. 11-37 Pleomorphic Adenoma.** Tumor of the pterygomandibular area.



• **Fig. 11-38 Pleomorphic Adenoma.** Low-power view showing a well-circumscribed, encapsulated tumor mass. Even at this power, the variable microscopic pattern of the tumor is evident.

The tumor is composed of a mixture of glandular epithelium and myoepithelial cells within a mesenchyme-like background. The ratio of the epithelial elements and the mesenchyme-like component is highly variable among different tumors. Some tumors may consist almost entirely of background "stroma." Others are highly cellular with little background alteration.

The epithelium often forms ducts and cystic structures or may occur as islands or sheets of cells. Keratinizing squamous cells and mucus-producing cells also can be seen. Myoepithelial cells often make up a large percentage of the tumor cells and have a variable morphology, sometimes appearing angular or spindled. Some myoepithelial cells are rounded and demonstrate an eccentric nucleus and eosinophilic hyalinized cytoplasm, thus resembling plasma cells (Fig. 11-39). These characteristic plasmacytoid myoepithelial cells are more prominent in tumors arising in the minor glands.

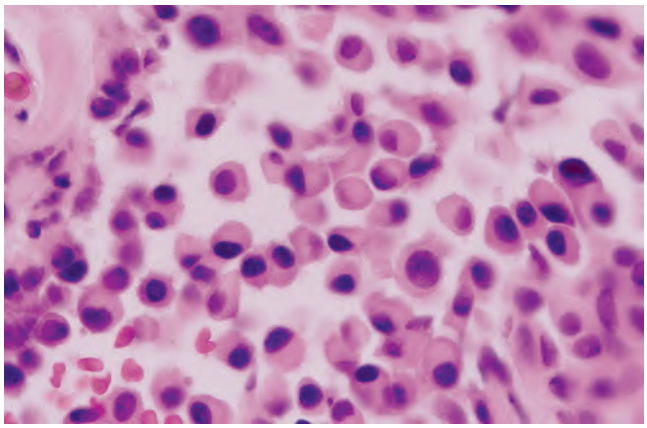
The highly characteristic "stromal" changes are believed to be produced by the myoepithelial cells. Extensive accumulation of mucoid material may occur between the tumor cells, resulting in a myxomatous background (Fig. 11-40). Vacuolar degeneration of cells in these areas can produce a chondroid appearance (Fig. 11-41). In many tumors, the stroma exhibits areas of an eosinophilic, hyalinized change (Fig. 11-42). At times, fat or osteoid also is seen.

Occasionally, salivary tumors are seen that are composed almost entirely of myoepithelial cells with no ductal elements. Such tumors often are called **myoepitheliomas,** although they probably represent one end of the spectrum of mixed tumors.

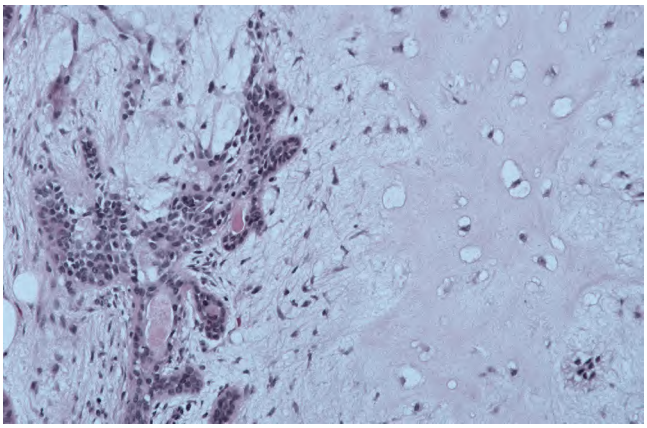
Treatment and Prognosis

Pleomorphic adenomas are best treated by surgical excision. For lesions in the superficial lobe of the parotid gland, superficial parotidectomy with identification and preservation of the facial nerve is recommended. Local enucleation should be avoided because the entire tumor may not be removed or the capsule may be violated, resulting in seeding of the tumor bed. For tumors of the deep lobe of the parotid, total parotidectomy is usually necessary, also with preservation of the facial nerve, if possible. Submandibular tumors are best treated by total removal of the gland with the tumor. Tumors of the hard palate usually are excised down to periosteum, including the overlying mucosa. In other oral sites the lesion often enucleates easily through the incision site.

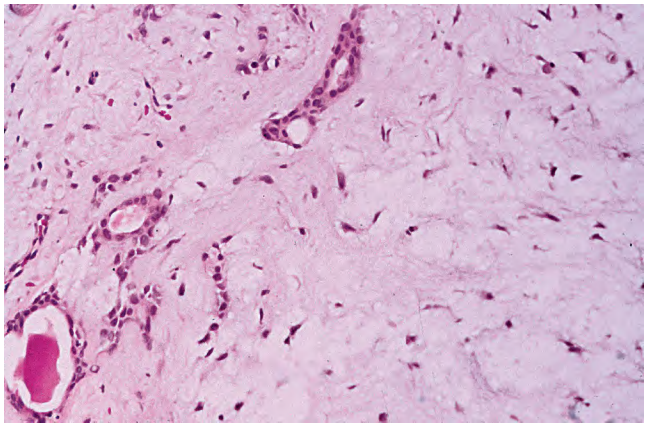
With adequate surgery the prognosis is excellent, with a cure rate of more than 95%. The risk of recurrence appears to be lower for tumors of the minor glands. Conservative



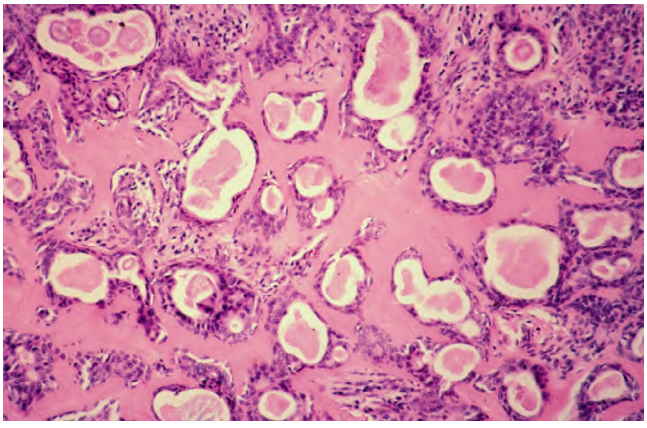
• **Fig. 11-39 Pleomorphic Adenoma.** Plasmacytoid myoepithelial cells.



• **Fig. 11-41 Pleomorphic Adenoma.** Chondroid material *(right)* with adjacent ductal epithelium and myoepithelial cells.



• **Fig. 11-40 Pleomorphic Adenoma.** Ductal structures *(left)* with associated myxomatous background *(right)*.



• **Fig. 11-42 Pleomorphic Adenoma.** Many of the ducts and myoepithelial cells are surrounded by a hyalinized, eosinophilic background alteration.

enucleation of parotid tumors often results in recurrence, with management of these cases made difficult as a result of multifocal seeding of the primary tumor bed. In such cases, multiple recurrences are not unusual and may necessitate adjuvant radiation therapy. Tumors with a predominantly myxoid appearance are more susceptible to recur than those with other microscopic patterns.

Malignant degeneration is a potential complication, resulting in a **carcinoma ex pleomorphic adenoma** (see page 460). The risk of malignant transformation is probably small, but it may occur in as many as 3% to 4% of all cases. This risk increases with the duration of the tumor.

◆ ONCOCYTOMA (OXYPHILIC ADENOMA)

The **oncocytoma** is a benign salivary gland tumor composed of large epithelial cells known as **oncocytes.** The prefix *onco-* is derived from the Greek word *onkoustai,* which means *to swell.* The swollen granular cytoplasm of oncocytes is due to excessive accumulation of mitochondria. Focal oncocytic metaplasia of salivary ductal and acinar cells is a common finding that is related to patient age; oncocytes are uncommon in persons younger than 50, but they can be found in almost all individuals by age 70. In addition to salivary glands, oncocytes have been identified in a number of other organs, especially the thyroid, parathyroid, and kidney. The oncocytoma is a rare neoplasm, representing approximately 1% of all salivary tumors.

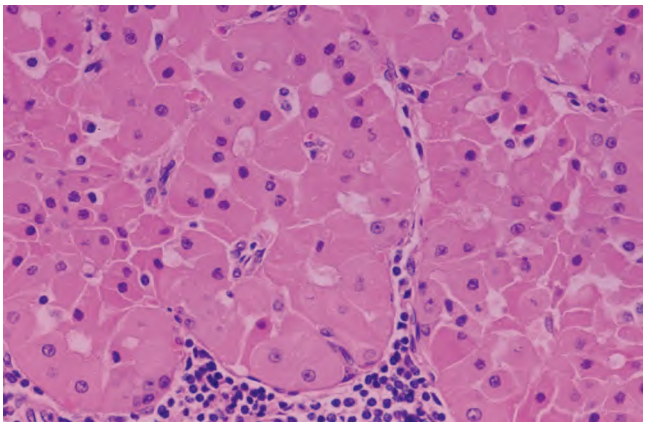
Clinical Features

The oncocytoma is predominantly a tumor of older adults, with peak prevalence in the sixth to eighth decades of life. No significant sex predilection has been observed. Oncocytomas occur primarily in the major salivary glands, especially the parotid gland, which accounts for about 85% to 90% of all cases. Oncocytomas of the minor salivary glands are exceedingly rare.

The tumor appears as a firm, slowly growing, painless mass that rarely exceeds 4 cm in diameter. Parotid oncocytomas usually are found in the superficial lobe and are clinically indistinguishable from other benign tumors. On occasion, bilateral tumors can occur, although these may represent examples of **oncocytosis (multinodular oncocytic hyperplasia)** (see next topic).

Histopathologic Features

The oncocytoma is usually a well-circumscribed tumor that is composed of sheets of large polyhedral cells (oncocytes), with abundant granular, eosinophilic cytoplasm (Fig. 11-43). Sometimes these cells form an alveolar or glandular pattern. The cells have centrally located nuclei that can vary from small and hyperchromatic to large and vesicular. Little stroma is present, usually in the form of thin fibrovascular septa. An associated lymphocytic infiltrate may be noted.



• **Fig. 11-43 Oncocytoma.** Sheet of large, eosinophilic oncocytes.

The granularity of the cells corresponds to an overabundance of mitochondria, which can be demonstrated by electron microscopy. These granules also can be identified on light microscopic examination with a phosphotungstic acid hematoxylin (PTAH) stain. The cells also contain glycogen, as evidenced by their positive staining with the periodic acid-Schiff (PAS) technique but by negative PAS staining after digestion with diastase.

Oncocytomas may contain variable numbers of cells with a clear cytoplasm. In rare instances, these clear cells may compose most of the lesion and create difficulty in distinguishing the tumor from low-grade salivary clear cell adenocarcinoma or metastatic renal cell carcinoma.

Treatment and Prognosis

Oncocytomas are best treated by surgical excision. In the parotid gland, this usually entails partial parotidectomy (lobectomy) to avoid violation of the tumor capsule. The facial nerve should be preserved whenever possible. For tumors in the submandibular gland, treatment consists of total removal of the gland. Oncocytomas of the oral minor salivary glands should be removed with a small margin of normal surrounding tissue.

The prognosis after removal is good, with a low rate of recurrence. However, oncocytomas of the sinonasal glands can be locally aggressive and have been considered to be low-grade malignancies. Rare examples of histopathologically malignant oncocytomas **(oncocytic carcinoma)** also have been reported. These carcinomas have a relatively poor prognosis.

◆ ONCOCYTOSIS (MULTINODULAR ONCOCYTIC HYPERPLASIA)

Oncocytic metaplasia is the transformation of ductal and acinar cells to oncocytes. Such cells are uncommon before the age of 50; however, as people get older, occasional oncocytes are common findings in the salivary glands. Focal

oncocytic metaplasia also may be a feature of other salivary gland tumors. **Oncocytosis** refers to both the proliferation and the accumulation of oncocytes within salivary gland tissue. It may mimic a tumor, both clinically and microscopically, but it also is considered to be a metaplastic process rather than a neoplastic one.

Clinical Features

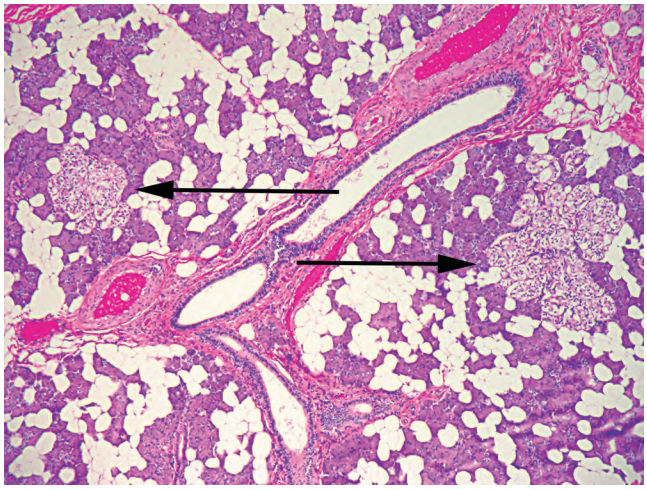
Oncocytosis is found primarily in the parotid gland; however, in rare instances, it may involve the submandibular or minor salivary glands. It can be an incidental finding in otherwise normal salivary gland tissue, but it may be extensive enough to produce clinical swelling. Usually the proliferation is multifocal and nodular, but sometimes the entire gland can be replaced by oncocytes **(diffuse hyperplastic oncocytosis).** As with other oncocytic proliferations, oncocytosis occurs most frequently in older adults.

Histopathologic Features

Microscopic examination usually reveals focal nodular collections of oncocytes within the salivary gland tissue. These enlarged cells are polyhedral and demonstrate abundant granular, eosinophilic cytoplasm as a result of the proliferation of mitochondria. On occasion, these cells may have a clear cytoplasm from the accumulation of glycogen (Fig. 11-44). The multifocal nature of the proliferation may be confused with that of a metastatic tumor, especially when the oncocytes are clear in appearance.

Treatment and Prognosis

Oncocytosis is a benign condition and often is discovered only as an incidental finding. No further treatment is necessary, and the prognosis is excellent.



• **Fig. 11-44 Oncocytosis.** Multifocal collections of clear oncocytes *(arrows)* in the parotid gland.

◆ WARTHIN TUMOR (PAPILLARY CYSTADENOMA LYMPHOMATOSUM)

Warthin tumor is a benign neoplasm that occurs almost exclusively in the parotid gland. Although it is much less common than the pleomorphic adenoma, it represents the second most common benign parotid tumor, accounting for 5% to 22% of all parotid neoplasms. The name **adenolymphoma** also has been used for this tumor, but this term should be avoided because it overemphasizes the lymphoid component and may give the mistaken impression that the lesion is a type of lymphoma. Analyses of the epithelial and lymphoid components of the Warthin tumor usually have shown both to be polyclonal; this suggests that this lesion may not represent a neoplasm but would be better classified as a tumorlike process. However, a small percentage of Warthin tumors have been shown to demonstrate a chromosomal translocation and fusion gene transcript similar to that seen in mucoepidermoid carcinoma. This finding may indicate that subsets of these tumors are true neoplasms, although such examples also could represent evidence of an early mucoepidermoid carcinoma developing within a Warthin tumor.

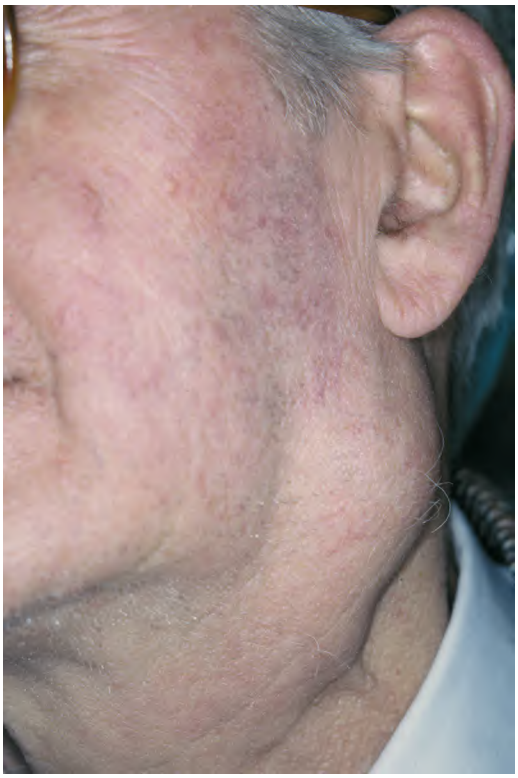
The pathogenesis of Warthin tumor is uncertain. The traditional hypothesis suggests that it arises from heterotopic salivary gland tissue found within parotid lymph nodes. However, researchers have also suggested that these tumors may develop from a proliferation of salivary gland ductal epithelium that is associated with secondary formation of lymphoid tissue. A number of studies have demonstrated a strong association between the development of this tumor and smoking. Smokers have an eightfold greater risk for Warthin tumor than do nonsmokers.

Clinical Features

The Warthin tumor usually appears as a slowly growing, painless, nodular mass of the parotid gland (Fig. 11-45). It may be firm or fluctuant to palpation. The tumor most frequently occurs in the tail of the parotid near the angle of the mandible, and it may be noted for many months before the patient seeks a diagnosis. One unique feature is the tendency of Warthin tumor to occur bilaterally, which has been noted in 5% to 17% of reported cases. Most of these bilateral tumors do not occur simultaneously but are metachronous (occurring at different times).

In rare instances, the Warthin tumor has been reported within the submandibular gland or minor salivary glands. However, because the lymphoid component is often less pronounced in these extraparotid sites, the pathologist should exercise caution to avoid overdiagnosis of a lesion better classified as a papillary cystadenoma or a salivary duct cyst with oncocytic ductal metaplasia.

Warthin tumor most often occurs in older adults, with peak prevalence in the sixth and seventh decades of life. The observed frequency of this tumor is much lower in blacks



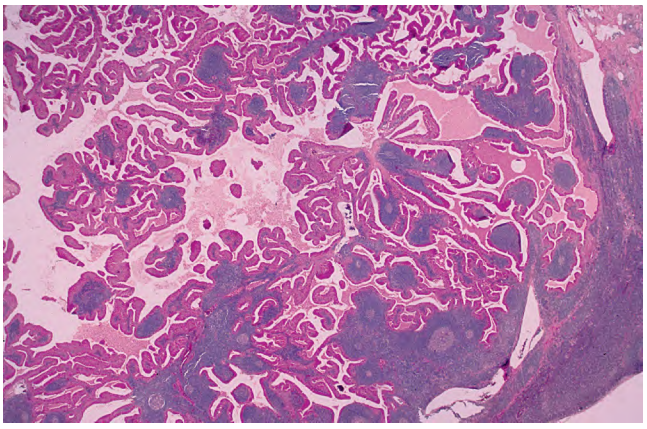
• **Fig. 11-45 Warthin Tumor.** Mass in the tail of the parotid gland. (Courtesy of Dr. George Blozis.)

than in whites. Most studies show a decided male predilection, with some early studies demonstrating a male-to-female ratio up to 10 : 1. However, more recent investigations show a more balanced sex ratio. Because Warthin tumors have been associated with cigarette smoking, this changing sex ratio may be a reflection of a more equal prevalence of smoking in women over the past few decades. This association with smoking also may help explain the frequent bilaterality of the tumor, because any tumorigenic effects of smoking would be manifested in both parotids.

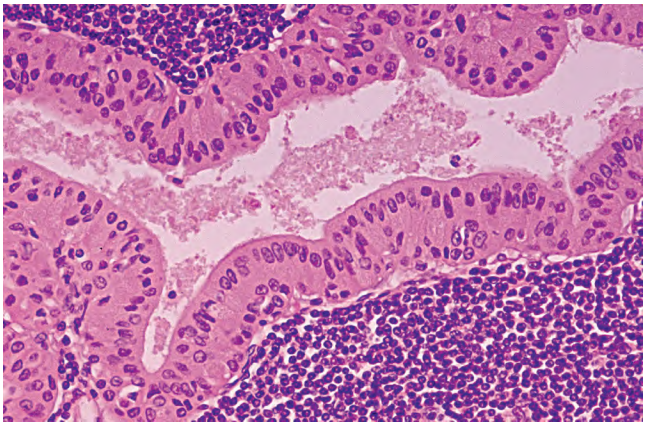
Histopathologic Features

The Warthin tumor has one of the most distinctive histopathologic patterns of any tumor in the body. Although the term **papillary cystadenoma lymphomatosum** is cumbersome, it accurately describes the salient microscopic features.

The tumor is composed of a mixture of ductal epithelium and a lymphoid stroma (Figs. 11-46 and 11-47). The epithelium is oncocytic in nature, forming uniform rows of cells surrounding cystic spaces. The cells have abundant, finely granular eosinophilic cytoplasm and are arranged in two layers. The inner luminal layer consists of tall columnar cells with centrally placed, palisaded, and slightly hyperchromatic nuclei. Beneath this is a second layer of cuboidal or polygonal cells with more vesicular nuclei. The lining epithelium demonstrates multiple papillary infoldings that protrude into the cystic spaces. Focal areas of squamous



• **Fig. 11-46 Warthin Tumor.** Low-power view showing a papillary cystic tumor with a lymphoid stroma.



• **Fig. 11-47 Warthin Tumor.** High-power view of epithelial lining showing double row of oncocytes with adjacent lymphoid stroma.

metaplasia or mucous cell prosoplasia may be seen. The epithelium is supported by a lymphoid stroma that frequently shows germinal center formation.

Treatment and Prognosis

Surgical removal is the treatment of choice for most patients with Warthin tumor. The procedure usually is easily accomplished because of the superficial location of the tumor. Some surgeons prefer local resection with minimal surrounding tissue; others opt for superficial parotidectomy to avoid violating the tumor capsule and because a tentative diagnosis may not be known preoperatively. If a confident diagnosis of Warthin tumor can be made by fine-needle aspiration cytology of a non-suspicious parotid growth, some clinicians will elect to manage the patient conservatively with regular follow-up visits rather than surgery.

A 2% to 6% recurrence rate has been reported following surgery. Many authors, however, believe that the tumor is frequently multicentric in nature; therefore, it is difficult to determine whether these are true recurrences or secondary tumor sites. Malignant Warthin tumors **(carcinoma ex papillary cystadenoma lymphomatosum)** have been reported but are exceedingly rare.

MONOMORPHIC ADENOMA

The term **monomorphic adenoma** originally was used to describe a group of benign salivary gland tumors demonstrating a more uniform histopathologic pattern than the common pleomorphic adenoma. In some classification schemes, a variety of tumors were included under the broad heading of monomorphic adenoma, including Warthin tumor, oncocytoma, basal cell adenoma, and canalicular adenoma. Other authors have used this term more specifically as a synonym just for the basal cell adenoma or canalicular adenoma. Because of its ambiguous nature, the term *monomorphic adenoma* probably should be avoided, and each of the tumors mentioned should be referred to by its more specific name.

CANALICULAR ADENOMA

The **canalicular adenoma** is an uncommon tumor that occurs almost exclusively in the minor salivary glands. Because of its uniform microscopic pattern, the canalicular adenoma also has been called a *monomorphic adenoma.* However, because this term also has been applied to other tumors, its use probably should be discontinued. Likewise, the term **basal cell adenoma** sometimes has been used synonymously for this tumor but should be avoided because it refers to a separate tumor with different clinical features (see next topic).

Clinical Features

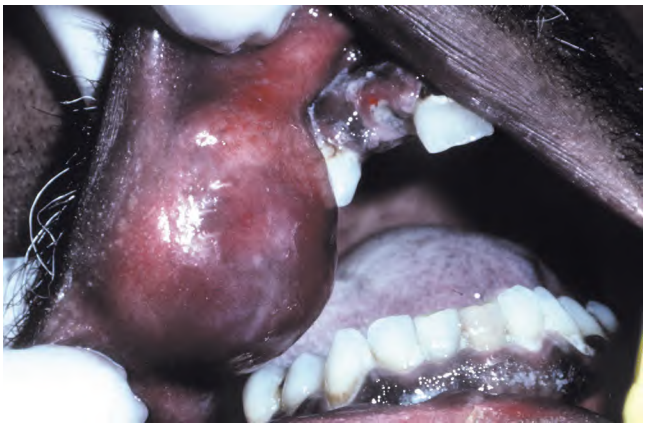
The canalicular adenoma shows a striking predilection for the upper lip, with nearly 75% occurring in this location. It represents the first or second most common tumor (along with pleomorphic adenoma) of the upper lip. The buccal mucosa is the second most common site. Occurrence in other minor salivary glands is uncommon, and canalicular adenomas of the parotid gland are rare.

The tumor nearly always occurs in older adults, with peak prevalence in the seventh decade of life. There is a definite female predominance, ranging from 1.2 to 1.8 females for each male.

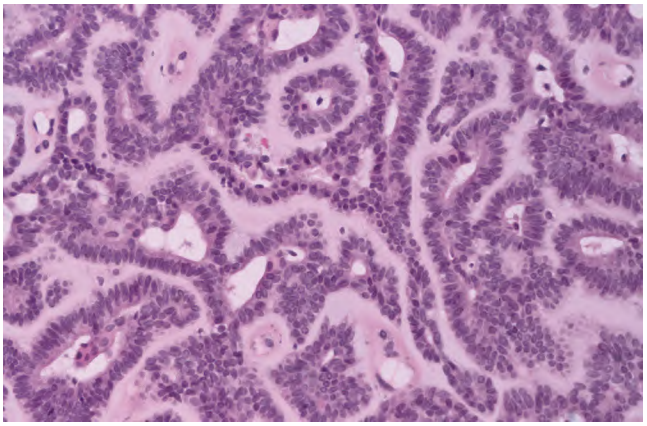
The canalicular adenoma appears as a slowly growing, painless mass that usually ranges from several millimeters to 2 cm (Fig. 11-48). It may be firm or somewhat fluctuant to palpation. The overlying mucosa may be normal in color or bluish and can be mistaken for a mucocele. However, mucoceles of the upper lip are rare. In some instances, the lesion has been noted to be multifocal, with multiple separate tumors discovered in the upper lip or buccal mucosa.

Histopathologic Features

The microscopic pattern of canalicular adenoma is monomorphic in nature. This pattern is characterized by single-layered cords of columnar or cuboidal epithelial cells with deeply basophilic nuclei (Fig. 11-49). In some areas, adjacent parallel rows of cells may be seen, resulting in a bilayered appearance of the tumor cords. These cells enclose ductal structures, sometimes in the form of long canals. Larger cystic spaces often are created, and the epithelium may demonstrate papillary projections into the cystic lumina. The tumor cells are supported by a loose connective tissue stroma with prominent vascularity. Unlike the appearance in pleomorphic adenomas, stromal alterations, such as chondroid metaplasia, do not occur. A thin, fibrous capsule often surrounds the tumor, although satellite islands are observed in the surrounding salivary gland tissue in approximately 22% to 24% of cases, which explains the tendency for multifocal tumors.



• **Fig. 11-48 Canalicular Adenoma.** Mass in the upper lip. (Courtesy of Dr. John Fantasia.)



• **Fig. 11-49 Canalicular Adenoma.** Uniform columnar cells forming canal-like ductal structures.

Treatment and Prognosis

The canalicular adenoma is best treated by local surgical excision. Recurrence is uncommon and actually may represent cases that are multifocal in nature.

BASAL CELL ADENOMA

The **basal cell adenoma** is a benign salivary tumor that derives its name from the basaloid appearance of the tumor

cells. It is an uncommon neoplasm that represents only 1% to 4% of all salivary tumors. Because of its uniform histopathologic appearance, it often has been classified as one of the monomorphic adenomas. However, as mentioned previously, this term probably should be avoided because of its imprecise and frequently confusing definition. In addition, ultrastructural and immunohistochemical studies have shown that basal cell adenomas are not necessarily composed of only one cell type but sometimes of a combination of salivary ductal epithelium and myoepithelial cells. The basal cell adenoma shows some histopathologic similarity to the canalicular adenoma; in the past, these two terms have been used synonymously. However, histopathologic and clinical differences warrant that they be considered as distinct entities.

Clinical Features

Unlike the canalicular adenoma, the basal cell adenoma is primarily a tumor of the parotid gland, with around 75% of all cases occurring there. However, the minor glands represent the second most common site, specifically the glands of the upper lip and buccal mucosa. The tumor can occur at any age but is most common in middle-aged and older adults, with peak prevalence in the seventh decade of life. The tumor appears to be more common in women, with some studies showing as high as a 2:1 female-to-male ratio.

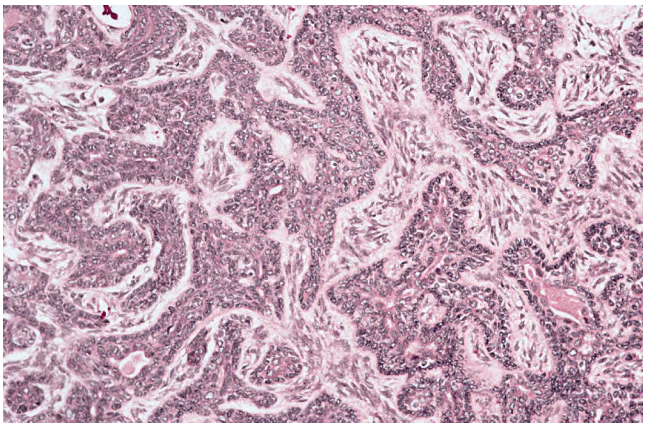
Clinically, the basal cell adenoma appears as a slowly growing, freely movable mass similar to a pleomorphic adenoma. Most tumors are less than 3 cm in diameter. Parotid tumors usually are located within the superficial lobe of the gland.

One subtype, the **membranous basal cell adenoma,** deserves separate mention. This form of the tumor appears to be hereditary, often occurring in combination with skin appendage tumors, such as **dermal cylindromas** and **trichoepitheliomas.** Multiple bilateral tumors may develop within the parotids. Because these tumors often bear a histopathologic resemblance to the skin tumors, they also have been called **dermal analogue tumors.**

Histopathologic Features

The basal cell adenoma is usually encapsulated or well circumscribed. The most common subtype is the solid variant, which consists of multiple islands and cords of epithelial cells that are supported by a small amount of fibrous stroma. The peripheral cells of these islands are palisaded and cuboidal to columnar in shape, similar to the microscopic appearance of basal cell carcinoma. These peripheral cells are frequently hyperchromatic; the central cells of the islands tend to have paler staining nuclei. The central cells occasionally form eddies or keratin pearls.

The trabecular subtype demonstrates narrow cordlike epithelial strands (Fig. 11-50). The tubular subtype is characterized by the formation of small, round, ductlike structures. Some basal cell adenomas demonstrate zones with a cribriform pattern that can mimic adenoid cystic carcinoma. Frequently, a mixture of histopathologic subtypes is seen.



• **Fig. 11-50 Basal Cell Adenoma.** Parotid tumor showing cords of basaloid cells arranged in a trabecular pattern.

The membranous basal cell adenoma exhibits multiple large lobular islands of tumor that are molded together in a jigsaw puzzle fashion. These islands are surrounded by a thick layer of hyaline material, which represents reduplicated basement membrane. Similar hyaline droplets also are often found among the epithelial cells. The microscopic appearance is similar to that of a dermal cylindroma, one of the skin tumors with which it is often associated.

Treatment and Prognosis

The treatment of basal cell adenoma is similar to that of pleomorphic adenoma and consists of complete surgical removal. Recurrence is rare for most histopathologic subtypes. However, the membranous subtype has a 25% to 37% recurrence rate, possibly related to its multifocal nature.

The malignant counterpart of the basal cell adenoma is the **basal cell adenocarcinoma.** Most basal cell adenocarcinomas arise *de novo,* but some examples develop from malignant degeneration of a preexisting basal cell adenoma. Fortunately, these tumors have a relatively good prognosis; although local recurrence is common, the tumor rarely metastasizes or results in death.

◆ DUCTAL PAPILLOMAS (SIALADENOMA PAPILLIFERUM; INTRADUCTAL PAPILLOMA; INVERTED DUCTAL PAPILLOMA)

A number of salivary gland tumors can be characterized microscopically by a papillomatous pattern, the most common being Warthin tumor (papillary cystadenoma lymphomatosum). The **sialadenoma papilliferum, intraductal papilloma,** and **inverted ductal papilloma** are

three rare salivary tumors that also show unique papillomatous features.

It also should be mentioned that, on occasion, the common squamous papilloma (see page 332) of the oral mucosa will arise at the site where a minor salivary gland duct merges with the surface epithelium. Because of this location, such squamous papillomas may contain scattered mucous cells within the exophytic papillary growth, and these lesions have sometimes been called *ductal papillomas.* However, it should be emphasized that these lesions are surface papillomas and not primary salivary gland tumors.

Clinical Features

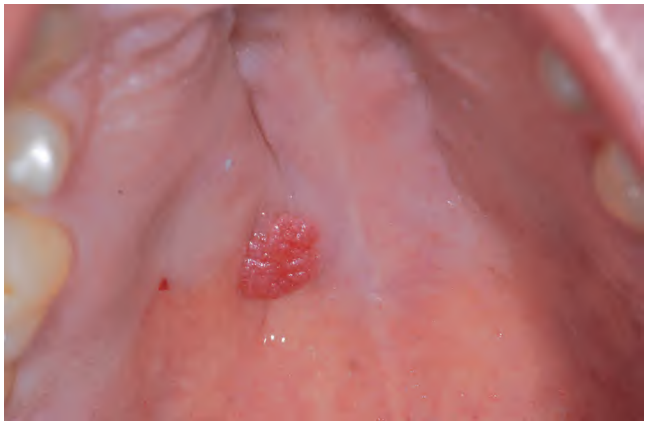
The sialadenoma papilliferum most commonly arises from the minor salivary glands, especially on the palate, although it also has been reported in the parotid gland. It usually is seen in older adults and has a 1.5 : 1.0 male-to-female ratio. The tumor appears as an exophytic, papillary surface growth that is clinically similar to the common squamous papilloma (Fig. 11-51).

The intraductal papilloma is an ill-defined lesion that often has been confused with other salivary gland lesions, such as the papillary cystadenoma. It usually occurs in adults and is most common in the minor salivary glands, where it appears as a submucosal swelling.

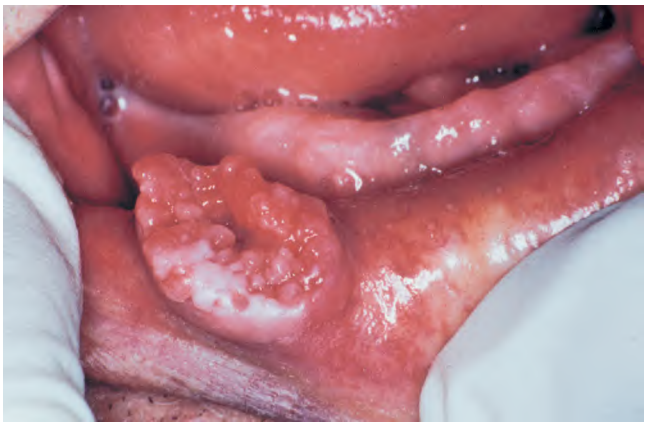
The inverted ductal papilloma is a rare tumor that has been described only in the minor salivary glands of adults. The lower lip and mandibular vestibule are the most common locations. The lesion usually appears as an asymptomatic nodule, which sometimes may show a pit or indentation in the overlying surface mucosa (Fig. 11-52).

Histopathologic Features

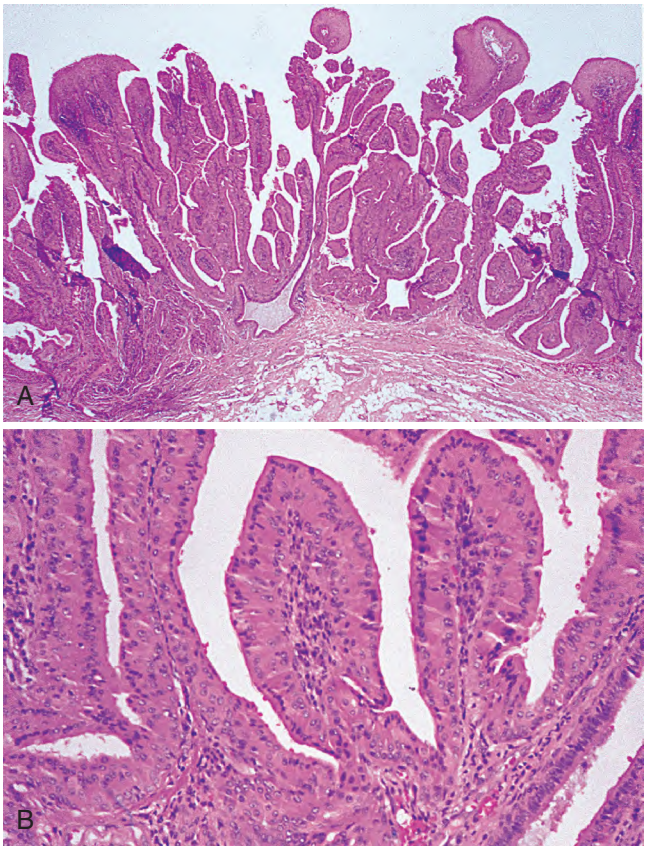
At low-power magnification, the sialadenoma papilliferum is somewhat similar to the squamous papilloma, exhibiting multiple exophytic papillary projections that are covered by stratified squamous epithelium. This epithelium is contiguous with a proliferation of papillomatous ductal epithelium found below the surface and extending downward into the deeper connective tissues (Fig. 11-53). Multiple ductal lumina are formed, which characteristically are lined by a double-rowed layer of cells consisting of a luminal layer of tall columnar cells and a basilar layer of smaller cuboidal cells. These ductal cells often have an oncocytic appearance. An inflammatory infiltrate of plasma cells, lymphocytes,



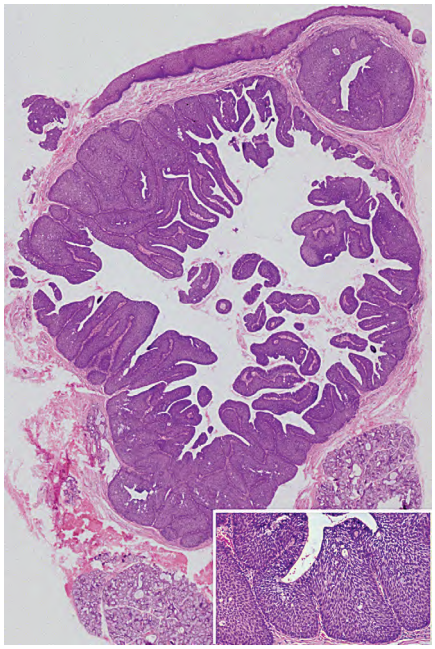
• **Fig. 11-51 Sialadenoma Papilliferum.** Exophytic papillary mass on the palate. (Courtesy of Dr. Peter Lyu.)



• **Fig. 11-52 Inverted Ductal Papilloma.** Exophytic mass with central papillary projections on the lower labial mucosa. (Courtesy of Dr. Amy Bogardus.)



• **Fig. 11-53 Sialadenoma Papilliferum. A,** Low-power view showing a papillary surface tumor with associated ductal structures in the superficial lamina propria. **B,** High-power view of cystic areas lined by papillary, oncocytic epithelium.



• **Fig. 11-54 Inverted Ductal Papilloma.** Papillary intraductal proliferation located beneath the mucosal surface. Higher-power view shows both squamous cells and mucous cells *(inset).* (Courtesy of Dr. Dean K. White.)

and neutrophils is characteristically present. Because of their microscopic similarity, this tumor has been considered to be an analogue of the cutaneous syringocystadenoma papilliferum.

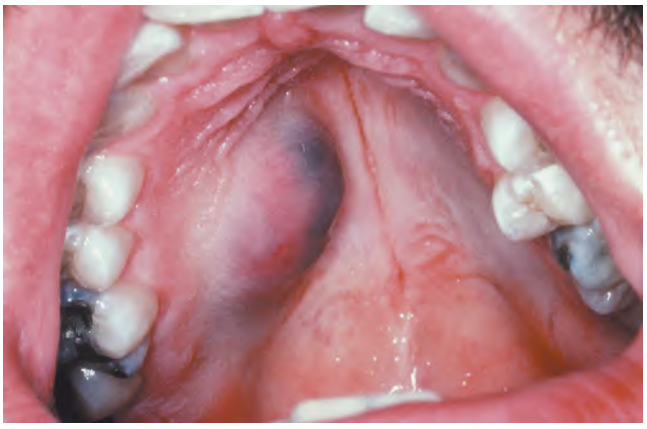
The intraductal papilloma exhibits a dilated, unicystic structure that is located below the mucosal surface. It is lined by a single or double row of cuboidal or columnar epithelium, which has multiple arborizing papillary projections into the cystic lumen. In contrast, the inverted ductal papilloma is composed primarily of a proliferation of squamoid epithelium with multiple thick, bulbous papillary projections that fill the ductal lumen (Fig. 11-54). This epithelium may be contiguous with the overlying mucosal epithelium, communicating with the surface through a small pore-like opening. Although the tumor is primarily squamous in nature, the luminal lining cells of the papillary projections are often cuboidal or columnar in shape, with scattered mucus-producing cells. *In situ* hybridization analysis has shown positivity for human papillomavirus (HPV) types 6 and 11 in both the surface and inverted epithelium of some inverted ductal papillomas.

Treatment and Prognosis

All three forms of ductal papilloma are best treated by conservative surgical excision. Recurrence is rare.

◆ MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma is the most common salivary gland malignancy. Because of its highly variable biologic



• **Fig. 11-55 Mucoepidermoid Carcinoma.** Blue-pigmented mass of the posterior lateral hard palate. (Courtesy of Dr. James F. Drummond.)

potential, it was originally called **mucoepidermoid tumor.** The term recognized one subset that acted in a malignant fashion and a second group that appeared to behave in a benign fashion with favorable prognosis. However, researchers later recognized that even low-grade tumors occasionally will exhibit malignant behavior; therefore, the term *mucoepidermoid carcinoma* is the preferred designation.

The pathogenesis of this tumor is uncertain, although radiation exposure may be one risk factor. Published series have reported that 38% to 82% of mucoepidermoid carcinomas will show a t(11;19) reciprocal translocation, which results in the production of the CRTC1-MAML2 fusion oncogene. This translocation is identified more frequently in low- and intermediate-grade tumors.

Clinical Features

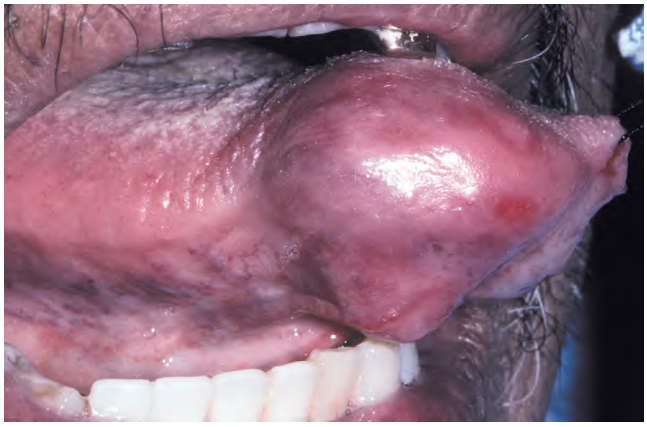
Most large series show mucoepidermoid carcinoma to be the most common malignant salivary gland neoplasm, comprising 4% to 10% of all major gland tumors and 13% to 23% of minor gland tumors. The tumor occurs fairly evenly over a wide age range, extending from the second to seventh decades of life. Rarely is it seen in the first decade of life. However, mucoepidermoid carcinoma is the most common malignant salivary gland tumor in children.

The mucoepidermoid carcinoma is most common in the parotid gland and usually appears as an asymptomatic swelling. Most patients are aware of the lesion for 1 year or less, although some report a mass of many years' duration. Pain or facial nerve palsy may develop, usually in association with high-grade tumors. The minor glands constitute the second most common site, especially the palate (Fig. 11-55). Minor gland tumors also typically appear as asymptomatic swellings, which are sometimes fluctuant and have a blue or red color that can be mistaken clinically for a mucocele. Although the lower lip, floor of mouth, tongue, and retromolar pad areas are uncommon locations for salivary gland neoplasia, the mucoepidermoid carcinoma is the most common salivary tumor in each of these

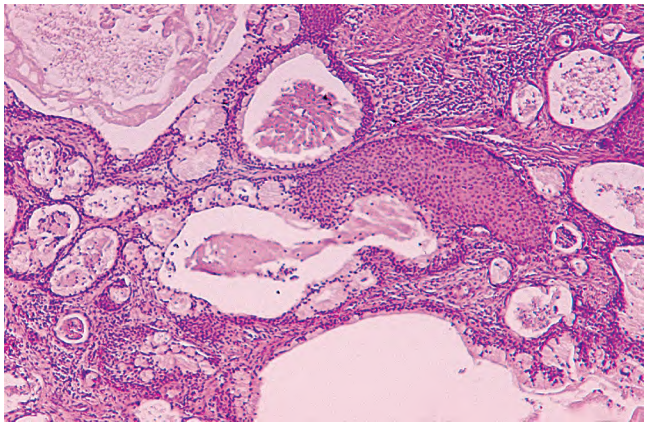
sites (Fig. 11-56). Intraosseous tumors also may develop in the jaws (see page 457).

Histopathologic Features

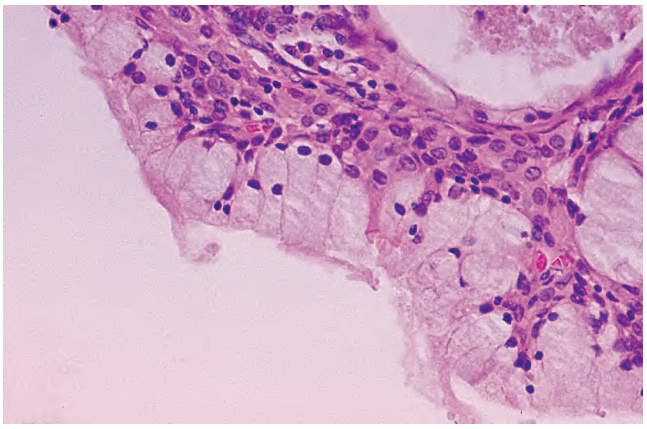
As its name implies, the *mucoepidermoid carcinoma* is composed of a mixture of mucus-producing cells and squamous (epidermoid) cells (Figs. 11-57 to 11-59). The mucous cells vary in shape but contain abundant foamy cytoplasm that stains positively with mucin stains. The epidermoid cells are characterized by squamoid features, often demonstrating a polygonal shape, intercellular bridges, and, rarely, keratinization. In addition, a third type of cell—the intermediate cell—is typically present and is believed to be a progenitor of both the mucous and the epidermoid cells. Intermediate cells vary in appearance from small, basaloid ("maternal") cells to slightly larger ovoid cells with scant, pale eosinophilic cytoplasm. Some tumors also show variable numbers of clear cells, which sometimes can predominate the microscopic picture (Fig. 11-60). An associated lymphoid infiltrate is not unusual and may be so prominent in some cases that the lesion can be mistaken for a metastatic tumor within a lymph node. Other variants of mucoepidermoid carcinoma can demonstrate numerous oncocytes or prominent sclerosis of the tumor stroma.



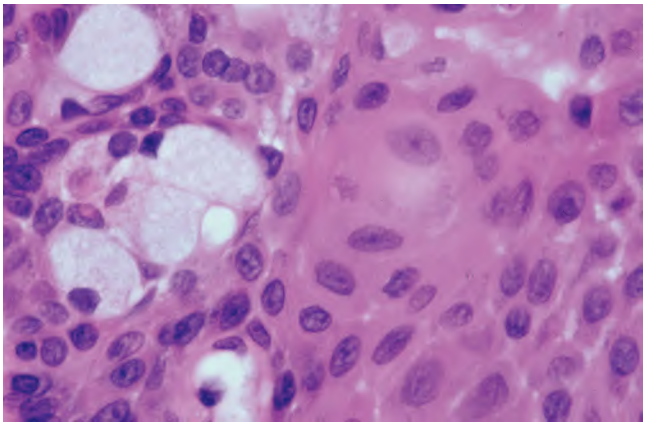
• **Fig. 11-56 Mucoepidermoid Carcinoma.** Mass of the tongue.



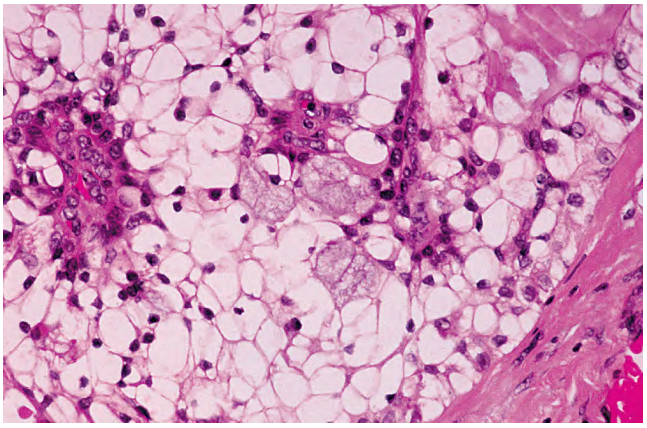
• **Fig. 11-57 Mucoepidermoid Carcinoma.** Low-power view of a moderately well-differentiated tumor showing ductal and cystic spaces surrounded by mucous and squamous cells.



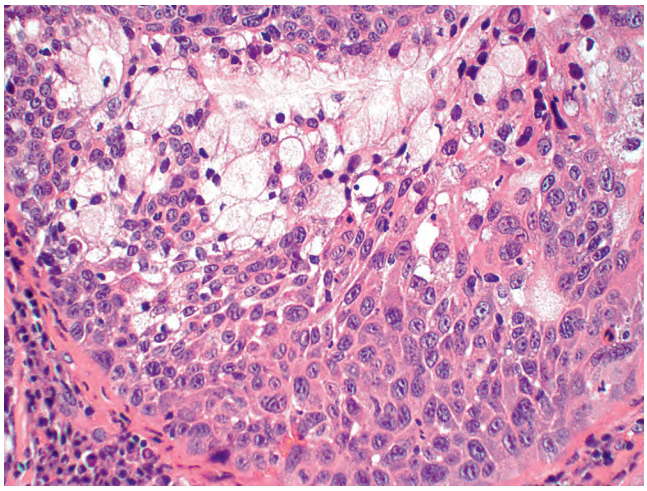
• **Fig. 11-58 Mucoepidermoid Carcinoma.** This low-grade tumor shows numerous large mucous cells surrounding a cystic space.



• **Fig. 11-59 Mucoepidermoid Carcinoma.** High-power view showing a sheet of squamous cells with focal mucus-producing cells *(left)*.



• **Fig. 11-60 Mucoepidermoid Carcinoma.** Clear cell mucoepidermoid carcinoma.



• **Fig. 11-61 Mucoepidermoid Carcinoma.** High-power view showing a sheet of pleomorphic squamous epithelial cells intermixed with mucous and intermediate cells.

Traditionally, mucoepidermoid carcinomas have been categorized into one of three histopathologic grades based on the following:

1. Amount of cyst formation
2. Degree of cytologic atypia
3. Relative numbers of mucous, epidermoid, and intermediate cells

Low-grade tumors show prominent cyst formation, minimal cellular atypia, and a relatively high proportion of mucous cells. **High-grade** tumors consist of solid islands of squamous and intermediate cells, which can demonstrate considerable pleomorphism and mitotic activity (Fig. 11-61). Mucus-producing cells may be infrequent, and the tumor sometimes can be difficult to distinguish from squamous cell carcinoma.

Intermediate-grade tumors show features that fall between those of the low-grade and high-grade neoplasms. Cyst formation occurs but is less prominent than that observed in low-grade tumors. All three major cell types are present, but the intermediate cells usually predominate. Cellular atypia may or may not be observed.

However, some authors have found that the relative proportion of the three different cell types does not necessarily correlate with prognosis. To overcome this, two expert groups have proposed evaluation schemes based on significant microscopic parameters, to which relative point values have been assigned to determine the grade of the tumor (Table 11-12).

TABLE 11-12 Mucoepidermoid Carcinoma: Comparison of Two Grading Systems

Parameter	Point Value
Auclair et al. (1992)	
Intracystic component < 20%	2
Neural invasion present	2
Necrosis present	3
Four or more mitoses per 10 high-power fields	3
Anaplasia present	4
Grade	**Total Point Score**
Low	0-4
Intermediate	5-6
High	7-14
Brandwein et al. (2001)	
Intracystic component < 25%	2
Tumor front invades in small nests and islands	2
Pronounced nuclear atypia	2
Lymphatic or vascular invasion	3
Bony invasion	3
Greater than four mitoses per 10 high-power fields	3
Perineural spread	3
Necrosis	3
Grade	**Total Point Score**
I	0
II	2-3
III	4 or more

From Auclair PL, Goode RK, Ellis GL: Mucoepidermoid carcinoma of intraoral salivary glands: evaluation and application of grading criteria in 143 cases, *Cancer* 69:2021–2030, 1992; Brandwein MS, Ivanov K, Wallace DI, et al: Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading, *Am J Surg Pathol* 25:835–845, 2001.

Treatment and Prognosis

The treatment of mucoepidermoid carcinoma is predicated by the location, histopathologic grade, and clinical stage of the tumor. Early-stage tumors of the parotid often can be treated by subtotal parotidectomy with preservation of the facial nerve. Advanced tumors may necessitate total removal of the parotid gland, with sacrifice of the facial nerve. Submandibular gland tumors are treated by total removal of the gland. Mucoepidermoid carcinomas of the minor glands usually are treated by assured surgical excision. For low-grade neoplasms, only a modest margin of surrounding normal tissue may need to be removed, but high-grade or large tumors warrant wider resection, similar to that required for squamous cell carcinomas. If there is underlying bone destruction, then the involved bone must be excised.

Neck dissection is indicated for patients with clinical evidence of metastatic disease and also may be considered for patients with larger or high-grade tumors. Postoperative radiation therapy also may be used for more aggressive tumors.

The prognosis depends on the grade and stage of the tumor. Patients with low-grade tumors generally have a good prognosis. For most primary sites, local recurrences or regional metastases are uncommon, and around 90% to 98% of patients are cured. The prognosis for those with intermediate-grade tumors is slightly worse than that for low-grade tumors. The outlook for patients with high-grade tumors is more guarded, with only 30% to 54% of patients surviving. Tumors that exhibit the t(11;19) translocation and CRTC1-MAML2 fusion gene transcript have a better prognosis than tumors without this translocation.

For unknown reasons, submandibular gland tumors are associated with a poorer outlook than those in the parotid gland. Mucoepidermoid carcinomas of the oral minor salivary glands generally have a good prognosis, probably because they are mostly low- to intermediate-grade tumors. However, tumors of the tongue and floor of the mouth are less predictable and may exhibit more aggressive behavior.

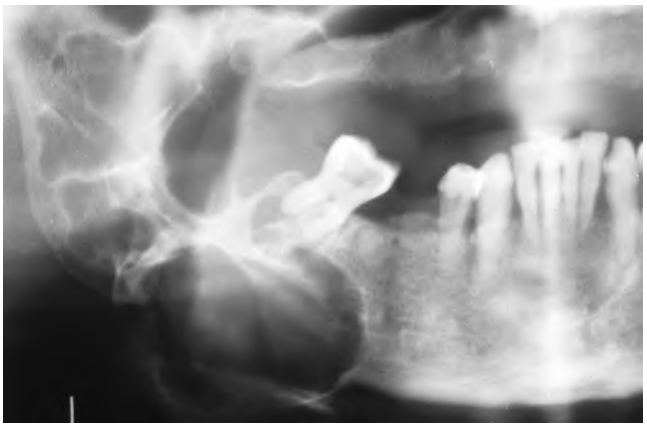
◆ INTRAOSSEOUS MUCOEPIDERMOID CARCINOMA (CENTRAL MUCOEPIDERMOID CARCINOMA)

On rare occasions, salivary gland tumors arise centrally within the jaws. The most common and best-recognized intrabony salivary tumor is the **intraosseous mucoepidermoid carcinoma.** However, other salivary tumors have been reported to develop within the jaws, including adenoid cystic carcinoma, benign and malignant mixed tumors, adenocarcinoma, acinic cell adenocarcinoma, epithelial-myoepithelial carcinoma, and monomorphic adenoma.

Several hypotheses have been proposed to explain the pathogenesis of intraosseous salivary tumors. One theory suggests that they may arise from ectopic salivary gland tissue that was developmentally entrapped within the jaws. However, the discovery of ectopic salivary tissue is uncommon in biopsy specimens from the jaws; therefore, this seems an unlikely source for most intrabony salivary tumors. Some maxillary tumors may arise from glands of the sinus lining, but this is often difficult to prove or disprove. The most likely source for most intraosseous tumors is odontogenic epithelium. Mucus-producing cells are common in odontogenic cyst linings, especially dentigerous cysts (see page 632). In addition, many intraosseous mucoepidermoid carcinomas develop in association with impacted teeth or odontogenic cysts.

Clinical and Radiographic Features

Intraosseous mucoepidermoid carcinomas are most common in middle-aged adults and demonstrate a slight female predilection. They are more common in the mandible than in the maxilla and are most often seen in the molar-ramus area. The most frequent presenting symptom is cortical swelling, although some lesions may be discovered as incidental findings on radiographs. Pain, trismus, and paresthesia are reported less frequently.



• **Fig. 11-62 Intraosseous Mucoepidermoid Carcinoma.** Multilocular lesion of the posterior mandible. (Courtesy of Dr. Joseph F. Finelli.)

Radiographs usually reveal either a unilocular or multilocular radiolucency with well-defined borders (Fig. 11-62). However, some examples are characterized by a more irregular and ill-defined area of bone destruction. Some cases are associated with an unerupted tooth and, therefore, clinically may suggest an odontogenic cyst or tumor.

Histopathologic Features

The microscopic appearance of intraosseous mucoepidermoid carcinoma is similar to that of its soft tissue counterpart. Most tumors are low-grade lesions, although high-grade mucoepidermoid carcinomas also have been reported within the jaws.

Treatment and Prognosis

The primary treatment modality for patients with intraosseous mucoepidermoid carcinoma is surgery; adjunctive radiation therapy also sometimes is used. Radical surgical resection offers a better chance for cure than do more conservative procedures, such as enucleation or curettage. The local recurrence rate with conservative treatment is 40%, in contrast to 13% for more radical treatment. Metastasis has been reported in about 12% of cases. The overall prognosis is fairly good; around 10% of patients die, usually as a result of local recurrence of the tumor.

◆ ACINIC CELL CARCINOMA

The **acinic cell carcinoma** is a salivary gland malignancy with cells that show serous acinar differentiation. Because

many of these tumors act in a nonaggressive fashion and are associated with a good prognosis, this neoplasm formerly was called **acinic cell tumor,** a nonspecific designation that did not indicate whether the lesion was benign or malignant. However, because some of these tumors do metastasize or recur and cause death, it is generally agreed today that acinic cell carcinoma should be considered a low-grade malignancy.

Many cases previously reported as acinic cell carcinoma, but which are poor in zymogen granules, would be reclassified today as examples of a newly delineated salivary neoplasm—mammary analogue secretory carcinoma (see next topic). This is especially true for purported acinic cell carcinomas in non-parotid sites. Therefore, evaluation of the literature and data on acinic cell carcinoma prior to 2010 is made more difficult.

Clinical Features

Around 85% to 90% of all acinic cell carcinomas occur in the parotid gland, a logical finding because this is the largest gland and one that is composed entirely of serous elements (Fig. 11-63). Most surveys have shown that this neoplasm makes up 2% to 3% of all parotid tumors, although one study showed it represented 8.6% of all parotid tumors (see Table 11-4). It is much less common in the submandibular gland, which is the site for only 2.7% to 5% of these tumors. About 9% of all acinic cell carcinomas reportedly develop in the oral minor salivary glands, with the buccal mucosa, lips, and palate being the most common sites. Overall, around 1.3% to 3.8% of all minor salivary gland tumors have been reported to be acinic cell carcinomas, although it is likely that many of these cases would be reclassified today as mammary analogue secretory carcinoma.

The tumor occurs over a broad age range, with a relatively even peak prevalence stretching from the second to the seventh decades of life; the mean age is in the middle 40s to early 50s. The tumor usually appears as a slowly growing mass, and the lesion often is present for many months or years before a diagnosis is made. The tumor may be otherwise asymptomatic, although associated pain or tenderness sometimes is reported. Facial nerve paralysis is an infrequent but ominous sign for parotid tumors.

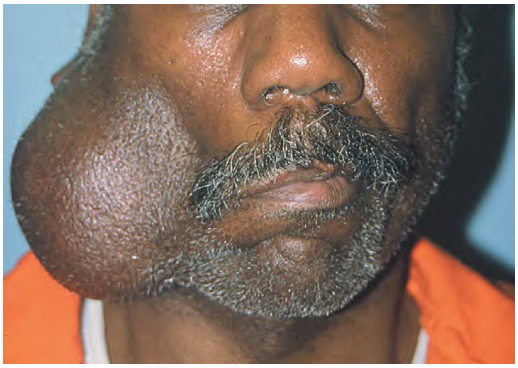
Histopathologic Features

Acinic cell carcinomas are highly variable in their microscopic appearance. The tumor often is well circumscribed and sometimes may even appear encapsulated; however, some tumors exhibit an infiltrative growth pattern. The most characteristic cell is one with features of the serous acinar cell, with abundant granular basophilic cytoplasm and a round, darkly stained eccentric nucleus. These cells are fairly uniform in appearance, and mitotic activity is uncommon. Other cells may resemble intercalated duct cells, and some tumors also have cells with a clear, vacuolated cytoplasm. On rare occasions, the tumor may demonstrate high-grade features, including pleomorphism, increased mitotic activity, and necrosis.

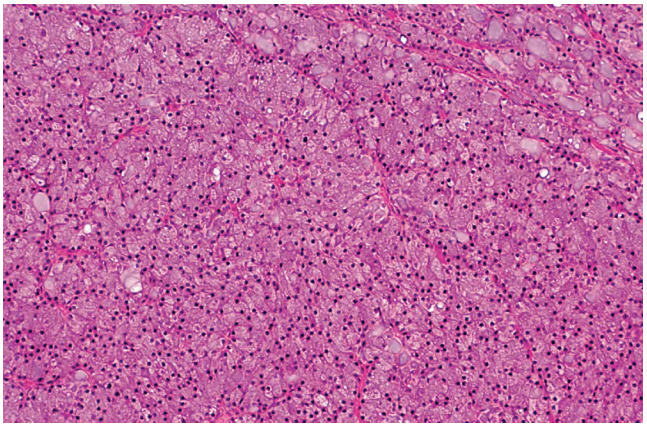
Several growth patterns have been described. The **solid** variety consists of numerous well-differentiated acinar cells arranged in a pattern that resembles normal parotid gland tissue (Figs. 11-64 and 11-65). In the **microcystic** variety, multiple small cystic spaces are created that may contain some mucinous or eosinophilic material. In the **papillary-cystic** variety, larger cystic areas are formed that are lined by epithelium having papillary projections into the cystic spaces. The **follicular** variety has an appearance similar to that of thyroid tissue. A lymphoid infiltrate, sometimes with germinal center formation, is not unusual.

Treatment and Prognosis

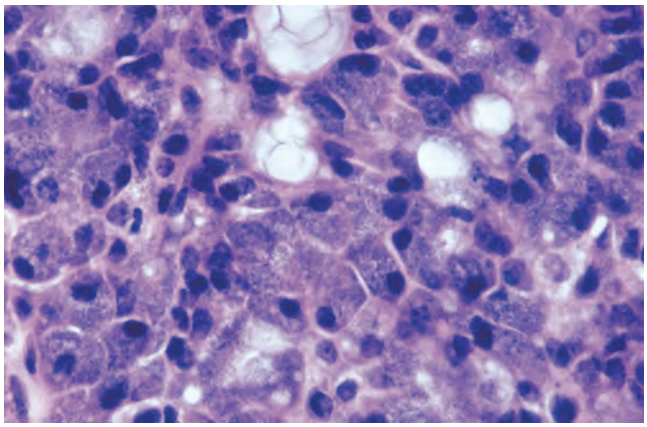
Acinic cell carcinomas confined to the superficial lobe of the parotid gland are best treated by lobectomy; for those in the deep lobe, total parotidectomy is usually necessary. The facial nerve may need to be sacrificed if it is involved by tumor. Submandibular tumors are managed by total removal of the gland, and minor gland tumors are treated with assured surgical excision. Lymph node dissection is not



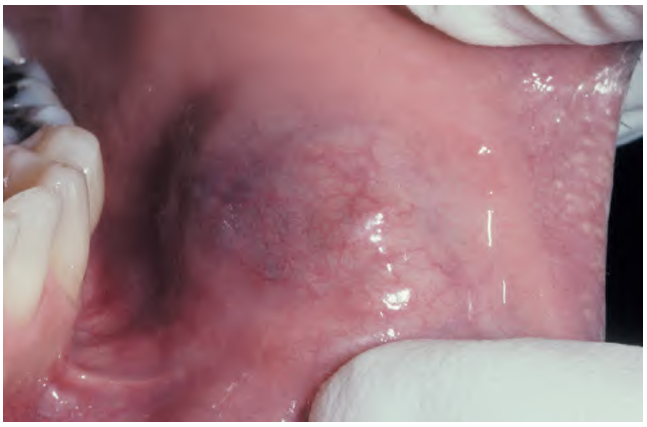
• **Fig. 11-63 Acinic Cell Carcinoma.** Large, firm mass of the right parotid gland.



• **Fig. 11-64 Acinic Cell Carcinoma.** Parotid tumor demonstrating sheet of granular, basophilic serous acinar cells.



• **Fig. 11-65 Acinic Cell Carcinoma.** High-power view of serous cells with basophilic, granular cytoplasm.



• **Fig. 11-66 Mammary Analogue Secretory Carcinoma.** Bluish swelling of the anterior buccal mucosa, which could be mistaken clinically for a mucocele. (This tumor originally was diagnosed as acinic cell carcinoma before mammary analogue secretory carcinoma was recognized as a distinct entity. This same image was used to illustrate an acinic cell carcinoma in the previous edition of this text!)

indicated unless there is clinical evidence of metastatic disease. Adjunctive radiation therapy may be considered for uncontrolled local disease.

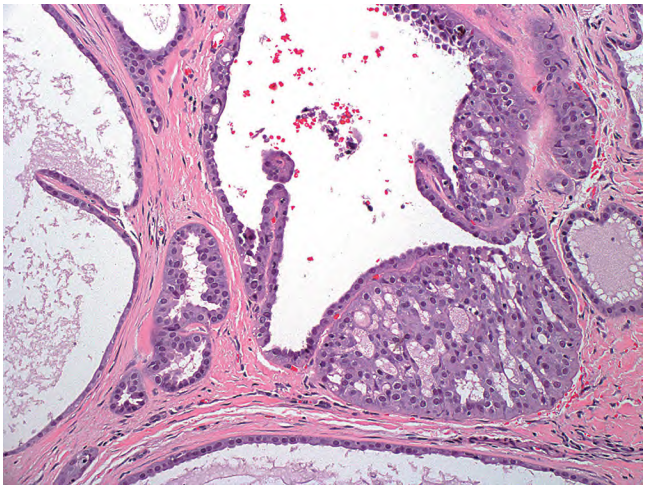
The acinic cell carcinoma is associated with one of the better prognoses of any of the malignant salivary gland tumors. Approximately 10% to 20% of patients have recurrences locally, and metastases develop in 8% to 11% of patients. About 10% of patients will die of their disease, with high-grade tumors showing a much worse prognosis than that for low-grade tumors. The outcome for minor gland tumors is better than that for tumors arising in the major glands.

◆ MAMMARY ANALOGUE SECRETORY CARCINOMA

Mammary analogue secretory carcinoma is a newly recognized salivary gland malignancy with histopathologic and molecular features that are similar to secretory carcinoma of the breast. Both of these tumors harbor a balanced chromosomal translocation, t(12;15)(p13;q25), which results in the formation of an ETV6-NTRK3 fusion gene. Prior to its recognition in 2010, many examples of mammary analogue secretory carcinoma probably were diagnosed as acinic cell carcinoma, which has overlapping light microscopic features (see legend for Fig. 11-66).

Clinical Features

The most common site of origin for the mammary analogue secretory carcinoma is the parotid gland, which accounts for 58% of reported cases. The minor salivary glands (31%) and submandibular gland (9%) are less frequent sites. The lips, soft palate, and buccal mucosa are the most common intraoral subsites (Fig. 11-66). The mean age is 47 years, and the tumor has been reported to occur slightly more often in males than in females. The lesion usually presents as a slowly growing, painless mass, which the patient may have noticed for months or many years. Occasional examples have been associated with some degree of discomfort.



• **Fig. 11-67 Mammary Analogue Secretory Carcinoma.** Medium-power view showing papillary-cystic spaces and small solid islands.

Histopathologic Features

Mammary analogue secretory carcinoma shows microscopic features that are similar to those of secretory carcinoma of the breast. The tumor cells exhibit bland, vesicular nuclei surrounded by slightly granular or vacuolated cytoplasm. These cells are variably arranged as solid, tubular, microcystic, or macrocystic structures. Larger cystic spaces may exhibit papillary infolding of tumor cells with a "hobnail" appearance (Fig. 11-67). Mitotic figures are rare.

The tumor cells show diffuse immunoreactivity for S-100 protein, vimentin, and mammaglobin. The chromosomal translocation can be confirmed via fluorescent *in situ*

hybridization (FISH) using the ETV6 break-apart probe, or by detection of the ETV6-NTRK3 fusion gene by reverse transcription-polymerase chain reaction (RT-PCR).

Treatment and Prognosis

Although data on treatment and outcome are limited, mammary analogue secretory carcinoma appears to be a low-grade malignancy with a generally favorable prognosis. However, local tumor recurrence and metastases occasionally have been documented, including several patients who died of tumor. Treatment most often has consisted of surgical resection, sometimes supplemented by adjuvant radiation therapy.

◆ MALIGNANT MIXED TUMORS (CARCINOMA EX PLEOMORPHIC ADENOMA; CARCINOMA EX MIXED TUMOR; CARCINOSARCOMA; METASTASIZING MIXED TUMOR)

Malignant mixed tumors represent malignant counterparts to the benign mixed tumor or pleomorphic adenoma. These uncommon neoplasms constitute 2% to 4% of all salivary tumors and can be divided into three categories:

1. Carcinoma ex pleomorphic adenoma (carcinoma ex mixed tumor)
2. Carcinosarcoma
3. Metastasizing mixed tumor

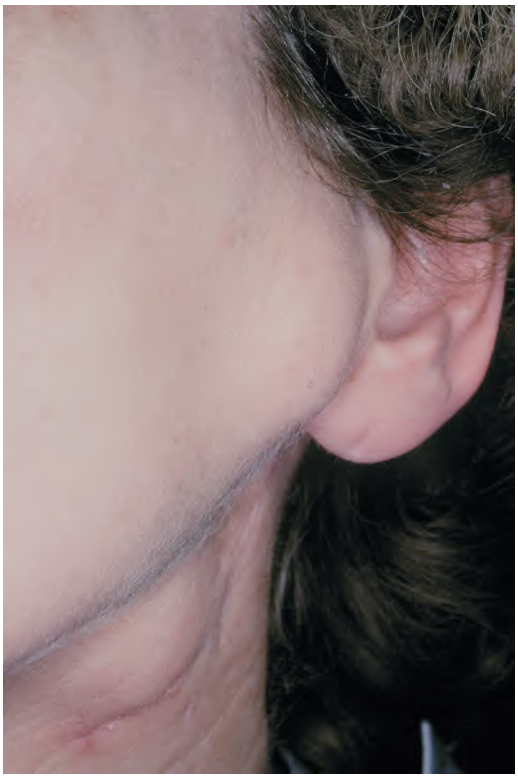
The most common of these is the **carcinoma ex pleomorphic adenoma,** which is characterized by malignant transformation of the epithelial component of a previously benign pleomorphic adenoma. The **carcinosarcoma** is a rare "mixed" tumor in which both carcinomatous and sarcomatous elements are present. The **metastasizing mixed tumor** has histopathologic features that are identical to the common pleomorphic adenoma (mixed tumor). In spite of its benign appearance, however, the lesion metastasizes. The metastatic tumor also has a benign microscopic appearance, usually similar to that of the primary lesion.

Clinical Features

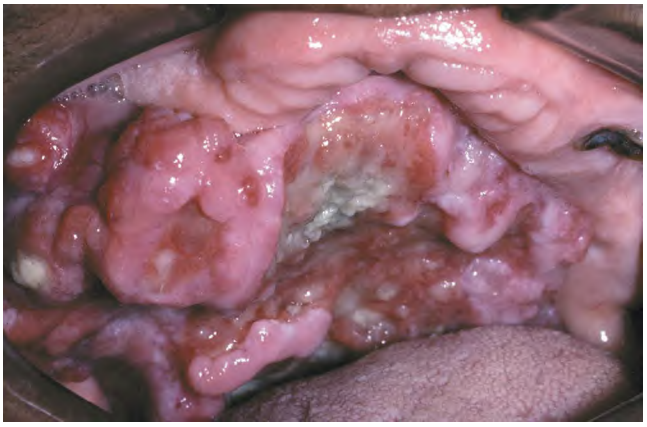
Carcinoma Ex Pleomorphic Adenoma

There is fairly convincing evidence that the carcinoma ex pleomorphic adenoma represents a malignant transformation within what was previously a benign neoplasm. First of all, the mean age of patients with this tumor is about 15 years older than that for the benign pleomorphic adenoma. It is most common in middle-aged and older adults, with peak prevalence in the sixth to eighth decades of life. In addition, patients may report that a mass has been present for many years, sometimes undergoing a recent rapid growth with associated pain or ulceration. However, some tumors may have a short duration. The histopathologic features, which are discussed later, also support malignant transformation of a benign pleomorphic adenoma. It has been noted that the risk for malignant change in a pleomorphic adenoma increases with the duration of the tumor.

More than 80% of cases of carcinoma ex pleomorphic adenoma are seen within the major glands, primarily the parotid gland (Fig. 11-68). Nearly two-thirds of minor salivary gland cases occur on the palate (Fig. 11-69). Although pain or recent rapid growth is not unusual, many cases present as a painless mass that is indistinguishable from a benign tumor. Parotid tumors may produce facial nerve palsy.



• **Fig. 11-68 Carcinoma Ex Pleomorphic Adenoma.** Mass of the parotid gland.



• **Fig. 11-69 Carcinoma Ex Pleomorphic Adenoma.** Granular exophytic and ulcerated mass filling the vault of the palate.

Carcinosarcoma

The carcinosarcoma is an extremely rare tumor. Most cases have been reported in the parotid gland, but the lesion also has been seen in the submandibular gland and minor salivary glands. The clinical signs and symptoms are similar to those of the carcinoma ex pleomorphic adenoma. Some patients have a previous history of a benign pleomorphic adenoma, although other cases appear to arise *de novo.*

Metastasizing Mixed Tumor

The metastasizing mixed tumor is also quite rare. As with other malignant mixed tumors, most cases originate in the parotid gland, but the primary tumor also may occur in the submandibular gland or minor salivary glands. Metastases have been found most frequently in the bones or lung, but they also can occur in other sites, such as regional lymph nodes, skin, or the liver. Most patients have a history of a benign mixed tumor, which may have been excised many years earlier. Many times the primary tumor exhibits multiple recurrences before metastasis occurs.

Histopathologic Features

Carcinoma Ex Pleomorphic Adenoma

The carcinoma ex pleomorphic adenoma shows a variable microscopic appearance. Areas of typical benign pleomorphic adenoma usually can be found and may constitute most or only a small portion of the lesion. However, extensive sampling may be required to identify the benign component in some cases. Within the tumor are areas of malignant degeneration of the epithelial component, characterized by cellular pleomorphism and abnormal mitotic activity (Fig. 11-70). This change is most often in the form of a poorly differentiated adenocarcinoma (such as, salivary duct carcinoma), but other patterns also can develop, including myoepithelial carcinoma, polymorphous low-grade adenocarcinoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma.

Based on the pattern of growth, carcinoma ex pleomorphic adenoma can be divided into three subcategories: *invasive, minimally invasive,* or *noninvasive.* Invasive carcinoma ex pleomorphic adenoma shows malignant cells penetrating greater than 1.5 mm from the tumor capsule into adjacent tissues. Minimally invasive tumors show extracapsular invasion that measures 1.5 mm or less. Noninvasive tumors may be discovered as a small malignant focus within the center of an encapsulated pleomorphic adenoma but without violation of the tumor capsule. Because such tumors have a markedly better prognosis than invasive tumors, they also have been designated as **carcinoma *in situ* ex mixed tumor** or **intracapsular carcinoma ex pleomorphic adenoma.**

Carcinosarcoma

The carcinosarcoma is a biphasic tumor, demonstrating both carcinomatous and sarcomatous areas. The epithelial component usually consists of a poorly differentiated adenocarcinoma or an undifferentiated carcinoma. The sarcomatous portion often predominates the tumor and is usually in the form of chondrosarcoma but also may show characteristics of osteosarcoma, fibrosarcoma, liposarcoma, rhabdomyosarcoma, or malignant fibrous histiocytoma. Some lesions have evidence of an origin from a benign mixed tumor.

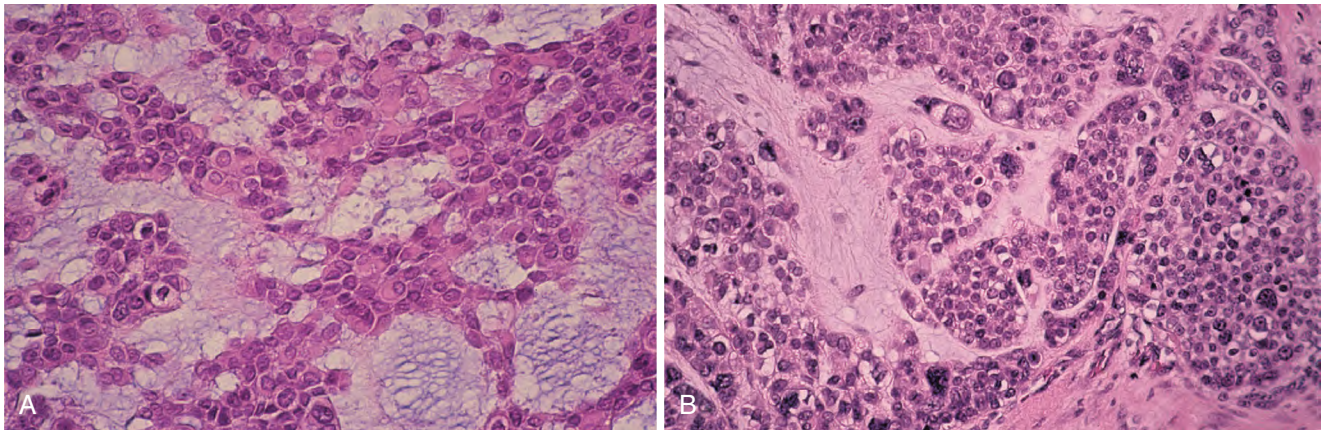
Metastasizing Mixed Tumor

The metastasizing mixed tumor has microscopic features of a benign pleomorphic adenoma, within both the primary and the metastatic sites. Malignant histopathologic changes are not observed.

Treatment and Prognosis

Carcinoma Ex Pleomorphic Adenoma

Invasive carcinoma ex pleomorphic adenoma usually is best treated by wide excision, possibly in conjunction with local lymph node dissection and adjunctive radiation therapy. The prognosis is guarded; the overall 5-year survival rate ranges from 25% to 65%, but this rate drops to 10% to



• **Fig. 11-70 Carcinoma Ex Pleomorphic Adenoma. A,** Medium-power view of the benign portion of the tumor showing sheets of plasmacytoid myoepithelial cells within a myxoid background. **B,** Malignant portion of the tumor showing epithelial cells with pleomorphic nuclei.

35% at 15 years. The prognosis is related to the histopathologic subtype of the malignant component. One study showed that well-differentiated carcinomas, such as polymorphous low-grade adenocarcinoma, have nearly a 90% 5-year survival rate. However, the outlook is much worse for patients with tumors that are poorly differentiated or that have invaded more than 8 mm beyond the residual capsule or benign residual tumor. In contrast, the prognosis for noninvasive or minimally invasive carcinoma ex pleomorphic adenoma approaches that for benign mixed tumor. However, rare examples of metastasis or tumor death have been documented in these latter groups.

Carcinosarcoma

Carcinosarcomas are treated by radical surgical excision, which may be combined with radiation therapy and chemotherapy. The prognosis is poor, with around 75% of patients either dying from their disease or developing recurrent local tumor or metastases.

Metastasizing Mixed Tumor

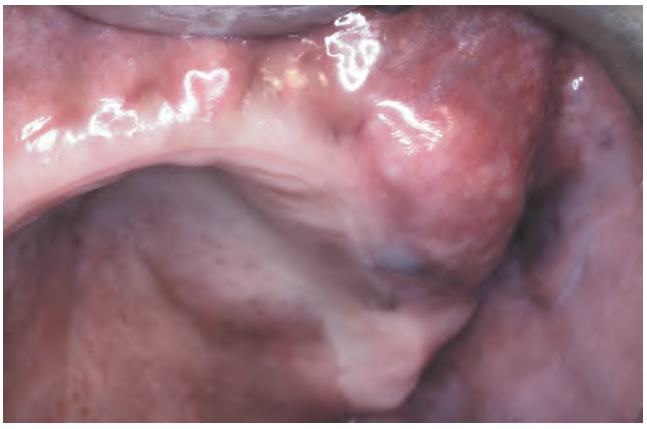
The treatment for a metastasizing mixed tumor consists of surgical excision of both the primary tumor and the metastatic sites. A mortality rate of 40% has been reported.

◆ ADENOID CYSTIC CARCINOMA

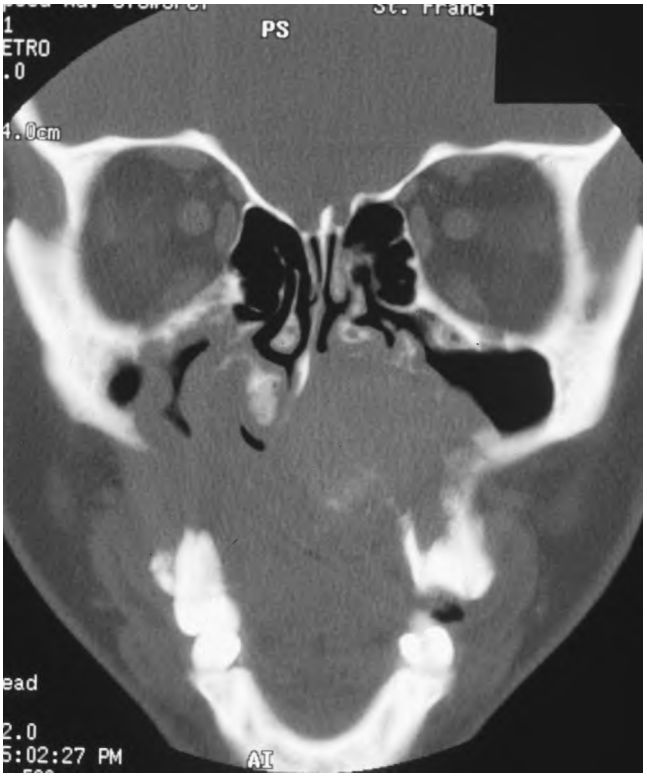
The **adenoid cystic carcinoma** is one of the more common and best-recognized salivary malignancies. Because of its distinctive histopathologic features, it was originally called a **cylindroma,** and this term still is heard sometimes as a synonym for this neoplasm. However, use of the term *cylindroma* should be avoided because it does not convey the malignant nature of the tumor, and also because this same term is used for a skin adnexal tumor that has a markedly different clinical presentation and prognosis.

Clinical and Radiographic Features

The adenoid cystic carcinoma can occur in any salivary gland site, but approximately 40% to 45% develop within the minor salivary glands. The palate is the most common site for minor gland tumors (Fig. 11-71). The remaining tumors are found mostly in the parotid and submandibular glands, with a fairly even distribution between these two sites. On an individual basis, however, a striking difference can be seen among the various glands. In the parotid gland, the adenoid cystic carcinoma is relatively rare, constituting only 2% of all tumors. In the submandibular gland, this tumor accounts for 11% to 17% of all tumors and is the most common malignancy. It is also relatively common among palatal salivary neoplasms; it represents 8% to 15% of all such tumors. The lesion is most common in middle-aged adults and is rare in people younger than age 20. Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2007 in the United States showed a male:female ratio of 1 : 1.4.



• **Fig. 11-71 Adenoid Cystic Carcinoma.** Painful mass of the hard palate and maxillary alveolar ridge. (Courtesy of Dr. George Blozis.)



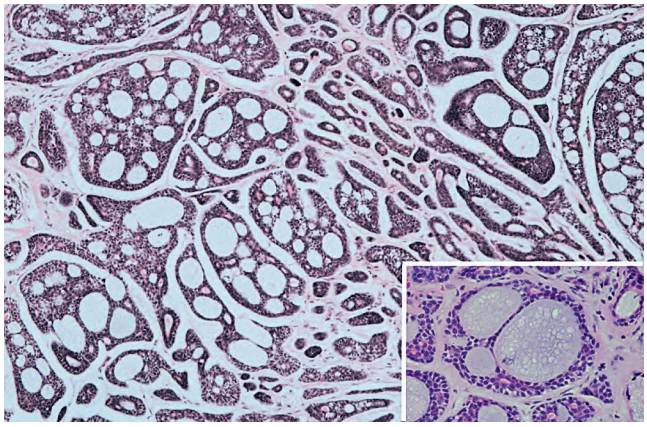
• **Fig. 11-72 Adenoid Cystic Carcinoma.** Computed tomography (CT) scan of this massive palatal tumor shows extensive destruction of the hard palate with extension of the tumor into the nasal cavity and both maxillary sinuses. (Courtesy of Dr. Kevin Riker.)

The adenoid cystic carcinoma usually appears as a slowly growing mass. Pain is a common and important finding, occasionally occurring early in the course of the disease before there is a noticeable swelling. Patients often complain of a constant, low-grade, dull ache, which gradually increases in intensity. Facial nerve paralysis may develop with parotid tumors. Palatal tumors can be smooth surfaced or ulcerated. Tumors arising in the palate or maxillary sinus often show radiographic evidence of bone destruction (Fig. 11-72).

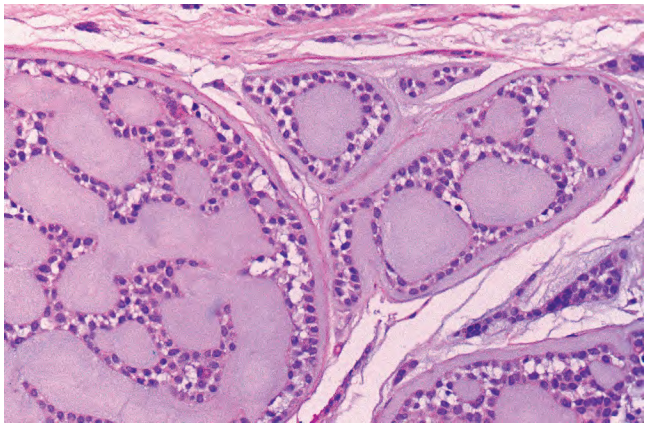
Histopathologic Features

The adenoid cystic carcinoma is composed of a mixture of myoepithelial cells and ductal cells that can have a varied arrangement (Fig. 11-73). Three major patterns are recognized: 1) cribriform, 2) tubular, and 3) solid. Usually a combination of these is seen, and the tumor is classified based on the predominant pattern.

The **cribriform pattern** is the most classic and best-recognized appearance, characterized by islands of basaloid epithelial cells that contain multiple cylindrical, cystlike spaces resembling Swiss cheese. These spaces often contain a mildly basophilic mucoid material, a hyalinized eosinophilic product, or a combined mucoid-hyalinized appearance. Sometimes the hyalinized material also surrounds these cribriform islands (Fig. 11-74), or small strands of tumor are found embedded within this hyalinized "stroma." The tumor cells are small and cuboidal, exhibiting deeply basophilic nuclei and little cytoplasm. These cells are fairly uniform in appearance, and mitotic activity is rarely seen. The pathologist should be mindful that other salivary tumors, especially polymorphous low-grade adenocarcinoma, also may exhibit areas with a cribriform pattern.



• **Fig. 11-73 Adenoid Cystic Carcinoma.** Islands of hyperchromatic cells forming cribriform and tubular structures. *Inset* shows a high-power view of a small cribriform island.



• **Fig. 11-74 Adenoid Cystic Carcinoma.** The tumor cells are surrounded by hyalinized material.

In the **tubular pattern,** the tumor cells are similar but occur as multiple small ducts or tubules within a hyalinized stroma. The tubular lumina can be lined by one to several layers of cells, and sometimes both a layer of ductal cells and myoepithelial cells can be discerned.

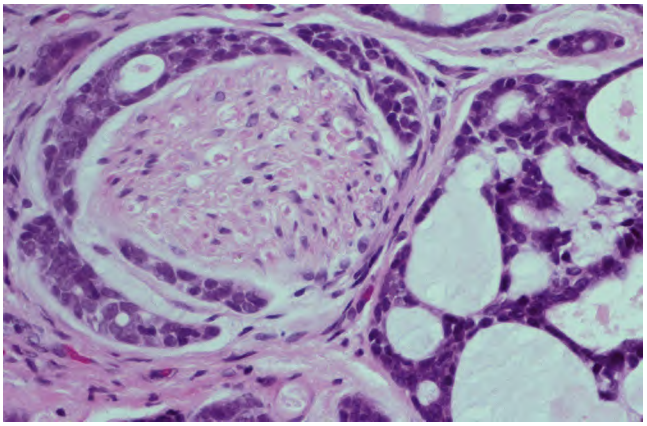
The **solid variant** consists of larger islands or sheets of tumor cells that demonstrate little tendency toward duct or cyst formation. Unlike the cribriform and tubular patterns, cellular pleomorphism and mitotic activity, as well as focal necrosis in the center of the tumor islands, may be observed.

A highly characteristic feature of adenoid cystic carcinoma is its tendency to show perineural invasion (Fig. 11-75), which probably corresponds to the common clinical finding of pain in these patients. Sometimes the cells appear to have a swirling arrangement around nerve bundles. However, perineural invasion is not pathognomonic for adenoid cystic carcinoma; it also may be seen in other salivary malignancies, especially polymorphous low-grade adenocarcinomas.

Positive immunostaining reactions for CD43 and c-kit (CD117) in adenoid cystic carcinoma have been reported to be useful diagnostic features that can help to distinguish this tumor from polymorphous low-grade adenocarcinoma, basal cell adenoma, and canalicular adenoma. In addition, the patterns of expression of a variety of other immunohistochemical markers have been suggested to be diagnostically relevant, including stains for vimentin, collagen IV, laminin, integrins, Ki-67, smooth muscle actin, and various cytokeratins.

Treatment and Prognosis

Adenoid cystic carcinoma is a relentless tumor that is prone to local recurrence and eventual distant metastasis. Surgical resection is usually the treatment of choice. Adjuvant radiation therapy may slightly improve patient survival in some cases, although recent SEER data suggest that radiation therapy does little to improve prognosis overall. Because metastasis to regional lymph nodes is uncommon (6% to 10% of cases), neck dissection usually is not indicated.



• **Fig. 11-75 Adenoid Cystic Carcinoma.** Perineural invasion.

Because the tumor is prone to late recurrence and metastasis, the 5-year survival rate has limited significance and does not equate to a cure. The 5-year survival rate may be as high as 77% to 82%, but this rate continues to decrease over time. The 10-year survival currently ranges from 60% to 68%, and by 20 years, only 35% to 52% of patients are still alive. Tumors with a solid histopathologic pattern are associated with a worse outlook than those with a cribriform or tubular arrangement. With respect to site, the prognosis is poorest for tumors arising in the maxillary sinus and submandibular gland. Better survival is observed in females, younger patients, and patients with localized disease at the time of diagnosis. Most studies have shown that microscopic identification of perineural invasion has little effect on the prognosis. Tumor DNA ploidy analysis may help to predict the prognosis of adenoid cystic carcinoma; patients with diploid tumors have been shown to have a significantly better outcome than patients with aneuploid tumors.

Death usually results from local recurrence or distant metastases. Tumors of the palate or maxillary sinus eventually may invade upward to the base of the brain. Metastases occur in approximately 35% of patients, most frequently involving the lungs, bone, and brain.

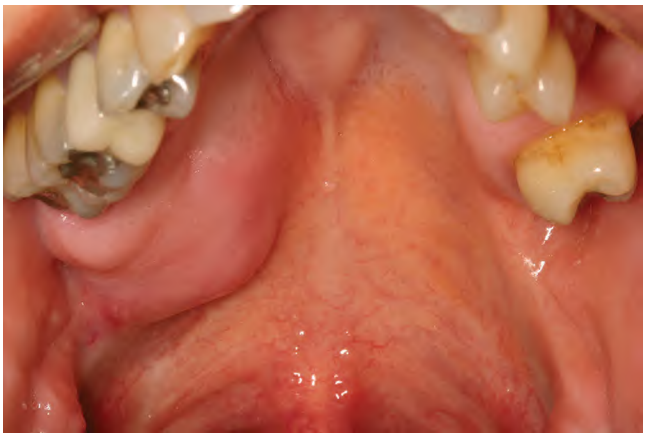
◆ POLYMORPHOUS LOW-GRADE ADENOCARCINOMA (LOBULAR CARCINOMA; TERMINAL DUCT CARCINOMA)

The **polymorphous low-grade adenocarcinoma** is a more recently recognized type of salivary malignancy that was first described in 1983. Before its identification as a distinct entity, examples of this tumor were categorized as pleomorphic adenoma, an unspecified form of adenocarcinoma, or sometimes as adenoid cystic carcinoma. Once recognized as a specific entity, however, it was realized that this tumor possesses distinct clinicopathologic features and is one of the more common minor salivary gland malignancies.

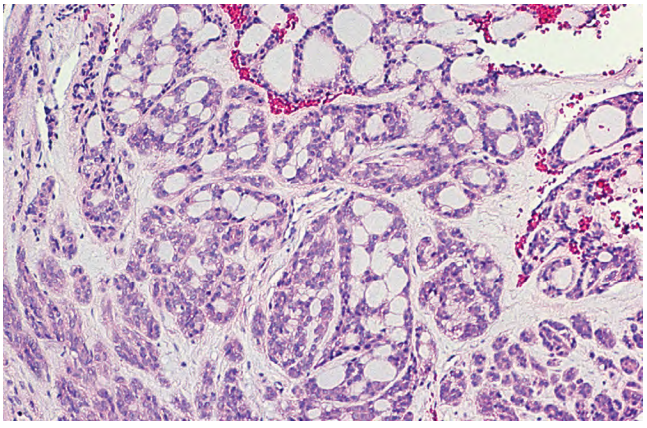
Clinical Features

The polymorphous low-grade adenocarcinoma is almost exclusively a tumor of the minor salivary glands. However, rare examples also have been reported in the major glands, either arising *de novo* or as the malignant component of a carcinoma ex pleomorphic adenoma. Sixty-five percent occur on the hard or soft palate (Fig. 11-76), with the upper lip and buccal mucosa being the next most common locations. It is most common in older adults, having peak prevalence in the sixth to eighth decades of life. Two-thirds of all cases occur in females.

The tumor most often appears as a painless mass that may have been present for a long time with slow growth. Occasionally, it is associated with bleeding or discomfort. Tumor can erode or infiltrate the underlying bone.



• **Fig. 11-76 Polymorphous Low-Grade Adenocarcinoma.** Slow-growing, firm mass of the right posterior lateral hard palate. (Courtesy of Dr. Kevin Riker.)

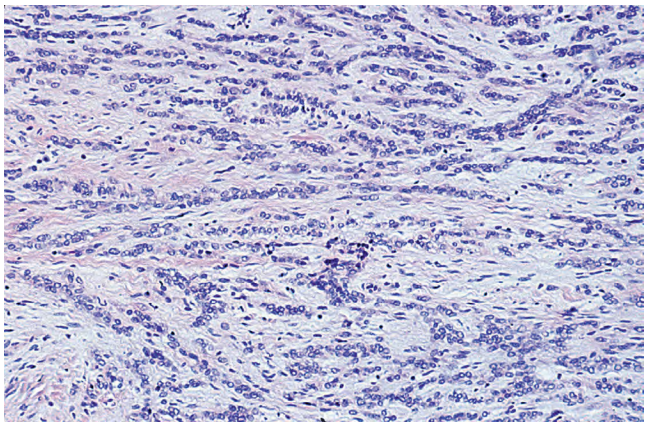


• **Fig. 11-77 Polymorphous Low-Grade Adenocarcinoma.** This medium-power view shows a cribriform arrangement of uniform tumor cells with pale-staining nuclei.

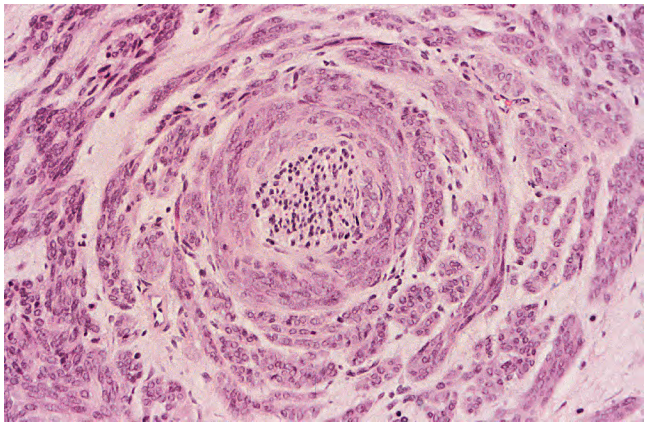
Histopathologic Features

The tumor cells of polymorphous low-grade adenocarcinomas have a deceptively uniform appearance. They are round to polygonal in shape, with indistinct cell borders and pale to eosinophilic cytoplasm. The nuclei may be round, ovoid, or spindled; these nuclei usually are pale staining, although they can be more basophilic in some areas. The cells can exhibit different growth patterns, hence, the *polymorphous* term. The cells may grow in a solid pattern or form cords, ducts, or larger cystic spaces. In some tumors, a cribriform pattern can be produced that mimics adenoid cystic carcinoma (Fig. 11-77). Mitotic figures are uncommon.

At low power, the tumor sometimes appears well circumscribed. However, the peripheral cells are usually infiltrative, invading the adjacent tissue in a single-file fashion (Fig. 11-78). Extension into underlying bone or skeletal muscle may be observed. The stroma is often mucoid in nature, or it may demonstrate hyalinization. Perineural invasion is



• **Fig. 11-78 Polymorphous Low-Grade Adenocarcinoma.** Pale-staining cells that infiltrate as single-file cords.



• **Fig. 11-79 Polymorphous Low-Grade Adenocarcinoma.** Perineural invasion.

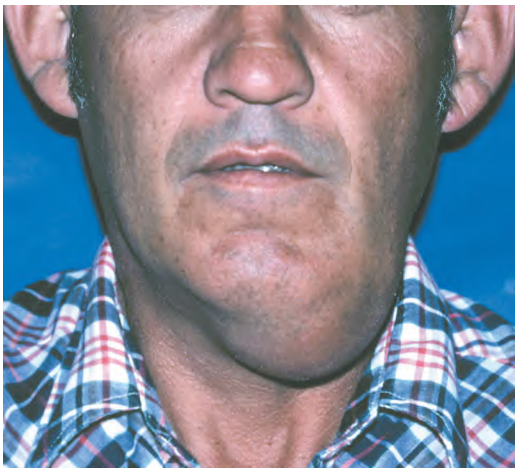
common—another feature that may cause the tumor to be mistaken for adenoid cystic carcinoma (Fig. 11-79). However, a distinction between these two tumors is important because of their vastly different prognoses.

Immunohistochemical staining can be helpful in distinguishing polymorphous low-grade adenocarcinoma from other salivary gland tumors that it may mimic. When compared with adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma exhibits significantly weaker expression of CD43 and c-kit (CD117). Likewise, lack of staining for glial fibrillary acidic protein (GFAP) can help to differentiate this tumor from pleomorphic adenoma, which is almost always strongly positive for GFAP.

Treatment and Prognosis

The polymorphous low-grade adenocarcinoma is best treated by wide surgical excision, sometimes including resection of the underlying bone. Metastasis to regional lymph nodes is relatively uncommon, occurring in 9% to 17% of patients. Therefore, neck dissection seems unwarranted in most cases unless there is clinical evidence of cervical metastases. However, tumors arising at the base of the tongue show a greater risk of regional metastasis. Distant metastasis is rare.

The overall prognosis is relatively good. Recurrent disease has been reported in 9% to 29% of all patients, but this usually can be controlled with reexcision. Death from tumor is rare but may occur secondary to direct extension into vital structures. Microscopic identification of perineural invasion does not appear to affect the prognosis.



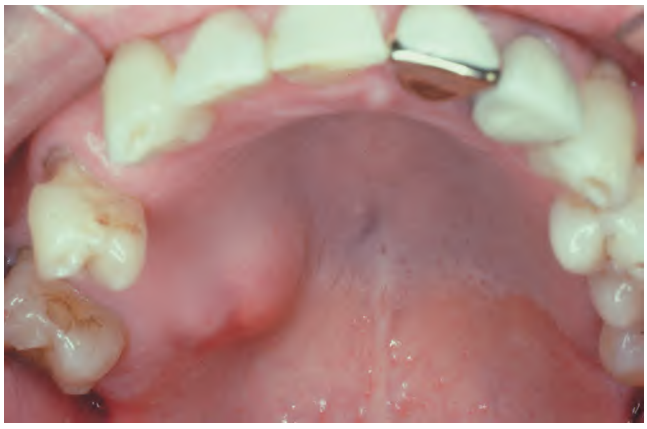
• **Fig. 11-80 Salivary Adenocarcinoma.** "Clear cell" adenocarcinoma of the submandibular gland.

◆ SALIVARY ADENOCARCINOMA, NOT OTHERWISE SPECIFIED

In spite of the wide variety of salivary gland malignancies that have been specifically identified and categorized, some tumors still defy the existing classification schemes. These tumors usually are designated as **salivary adenocarcinomas, not otherwise specified (NOS).**

Clinical and Histopathologic Features

Because these adenocarcinomas represent such a diverse group of neoplasms, it is difficult to generalize about their clinical and microscopic features. Like most salivary tumors, they appear to be most common in the parotid gland, followed by the minor glands and the submandibular gland (Figs. 11-80 and 11-81). They may present as asymptomatic masses or cause pain or facial nerve paralysis. The microscopic appearance is highly variable but demonstrates features of a glandular malignancy with evidence of cellular pleomorphism, an infiltrative growth pattern, or both. These tumors exhibit a wide spectrum of differentiation, ranging from well-differentiated, low-grade neoplasms to poorly differentiated, high-grade malignancies.



• **Fig. 11-81 Salivary Adenocarcinoma.** Mass of the posterior lateral hard palate.

As these tumors are studied more, it should be possible to classify some of them into separate, specific categories and allow more definitive analyses of their clinical and microscopic features.

Treatment and Prognosis

Because of their diversity, it is difficult to predict the prognosis for salivary adenocarcinoma (NOS), but patients with early-stage, well-differentiated tumors appear to have a better outcome. The survival rate is better for tumors of the oral cavity than for those in the major salivary glands. The reported 10-year survival rate for parotid tumors ranges from 26% to 55%; in contrast, one study reported a 10-year survival rate of 76% for intraoral tumors.

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12 Soft Tissue Tumors

◆ FIBROMA (IRRITATION FIBROMA; TRAUMATIC FIBROMA; FOCAL FIBROUS HYPERPLASIA; FIBROUS NODULE)

The **fibroma** is the most common "tumor" of the oral cavity. However, it is doubtful that it represents a true neoplasm in most instances; rather, it is a reactive hyperplasia of fibrous connective tissue in response to local irritation or trauma.

Clinical Features

Although the irritation fibroma can occur anywhere in the mouth, the most common location is the buccal mucosa along the bite line. Presumably, this is a consequence of trauma from biting the cheek (Figs. 12-1 and 12-2). The labial mucosa, tongue, and gingiva also are common sites (Figs. 12-3 and 12-4). It is likely that many gingival fibromas represent fibrous maturation of a preexisting pyogenic granuloma. The lesion typically appears as a smooth-surfaced pink nodule that is similar in color to the surrounding mucosa. In black patients, the mass may demonstrate gray-brown pigmentation. In some cases the surface may appear white as a result of hyperkeratosis from continued irritation. Most fibromas are sessile, although some are pedunculated. They range in size from tiny lesions that are only a couple of millimeters in diameter to large masses that are several centimeters across; however, most fibromas are 1.5 cm or less in diameter. The lesion usually produces no symptoms, unless secondary traumatic ulceration of the surface has occurred. Irritation fibromas are most common in the fourth to sixth decades of life, and the male-to-female ratio is almost 1 : 2 for cases submitted for biopsy.

The **frenal tag** is a commonly observed type of fibrous hyperplasia, which most frequently occurs on the maxillary labial frenum. Such lesions present as small, asymptomatic, exophytic growths attached to the thin frenum surface (Fig. 12-5).

Histopathologic Features

Microscopic examination of the irritation fibroma shows a nodular mass of fibrous connective tissue covered by stratified squamous epithelium (Figs. 12-6 and 12-7). This connective tissue is usually dense and collagenized, although in some cases, it is looser in nature. The lesion is not encapsulated; the fibrous tissue instead blends gradually into the surrounding connective tissues. The collagen bundles may be arranged in a radiating, circular, or haphazard fashion. The covering epithelium often demonstrates atrophy of the rete ridges because of the underlying fibrous mass. However, the surface may exhibit hyperkeratosis from secondary trauma. Scattered inflammation may be seen, most often beneath the epithelial surface. Usually this inflammation is chronic and consists mostly of lymphocytes and plasma cells.

Treatment and Prognosis

The irritation fibroma is treated by conservative surgical excision; recurrence is extremely rare. However, it is important to submit the excised tissue for microscopic examination because other benign or malignant tumors may mimic the clinical appearance of a fibroma.

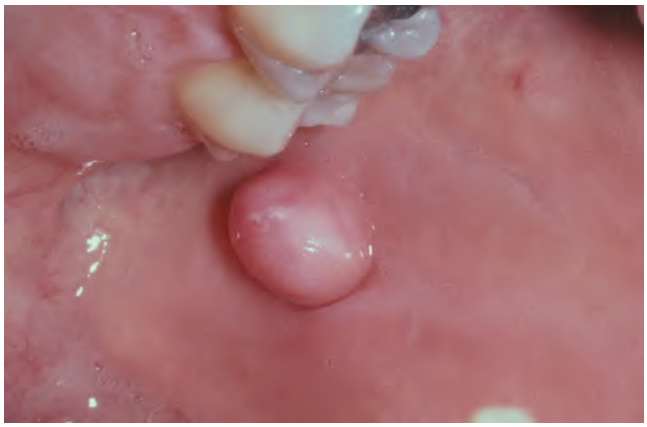
Because frenal tags are small, innocuous growths that are easily diagnosed clinically, no treatment is usually necessary.

◆ GIANT CELL FIBROMA

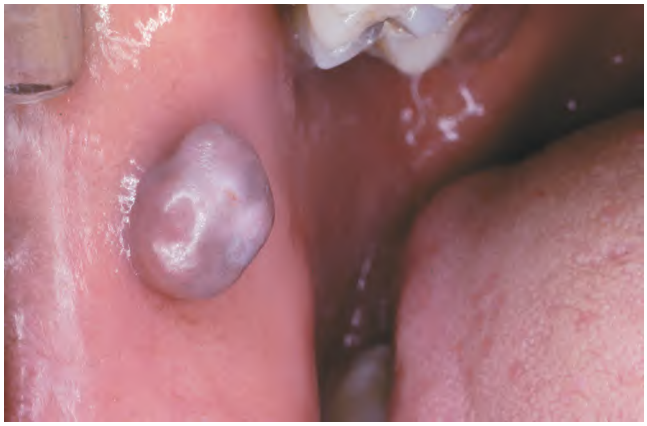
The **giant cell fibroma** is a fibrous tumor with distinctive clinicopathologic features. Unlike the traumatic fibroma, it does not appear to be associated with chronic irritation. The giant cell fibroma represents approximately 2% to 5% of all oral fibrous proliferations submitted for biopsy.

Clinical Features

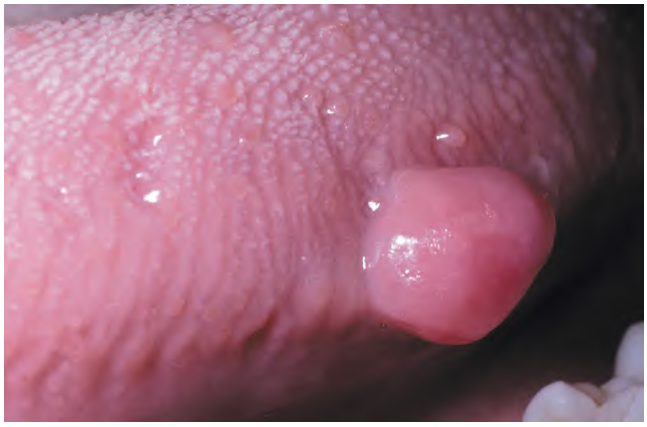
The giant cell fibroma is typically an asymptomatic sessile or pedunculated nodule, usually less than 1 cm in size



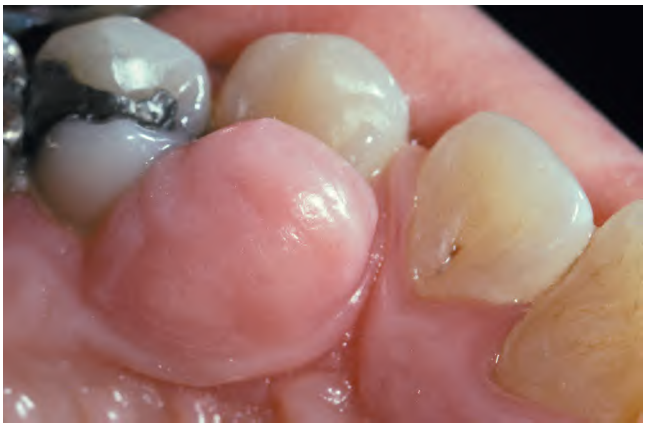
• **Fig. 12-1 Fibroma.** Pink nodule of the posterior buccal mucosa near the level of the occlusal plane.



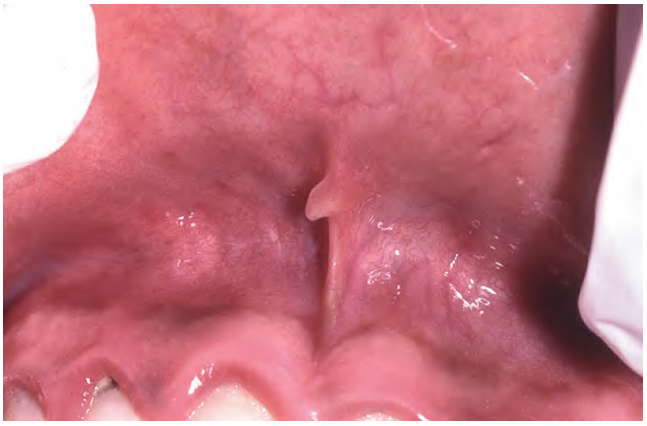
• **Fig. 12-2 Fibroma.** Black patient with a smooth-surfaced pigmented nodule on the buccal mucosa near the commissure.



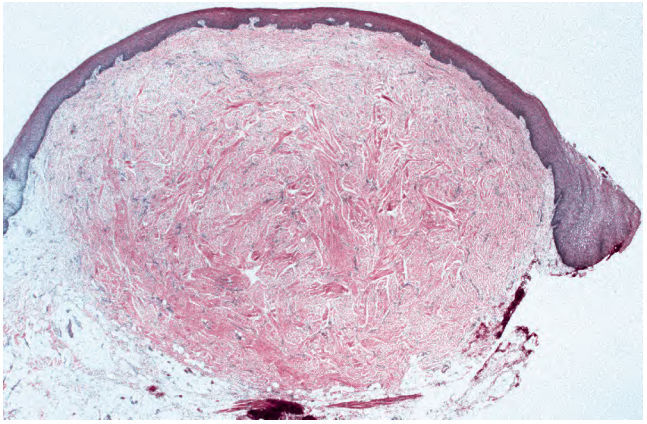
• **Fig. 12-3 Fibroma.** Lesion on the lateral border of the tongue.



• **Fig. 12-4 Fibroma.** Smooth-surfaced, pink nodular mass of the palatal gingiva between the cuspid and first bicuspid.



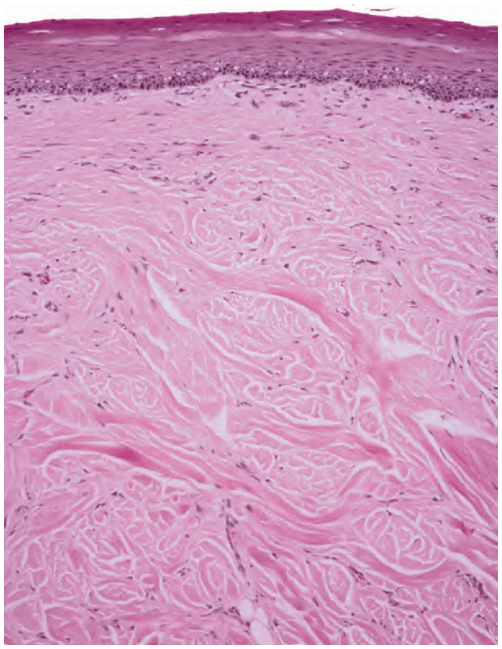
• **Fig. 12-5 Frenal tag.** A small fingerlike projection of tissue attached to the maxillary labial frenum.



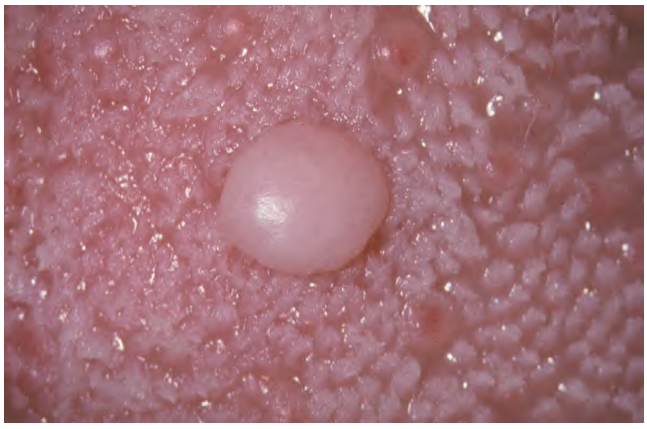
• **Fig. 12-6 Fibroma.** Low-power view showing an exophytic nodular mass of dense fibrous connective tissue.

(Fig. 12-8). The surface of the mass often appears papillary; therefore, the lesion may be clinically mistaken for a papilloma (Fig. 12-9). Compared with the common irritation fibroma, the lesion usually occurs at a younger age. In about 60% of cases, the lesion is diagnosed during the first three decades of life. Some studies have suggested a slight female predilection. Approximately 50% of all cases occur on the gingiva. The mandibular gingiva is affected twice as often as the maxillary gingiva. The tongue and palate also are common sites.

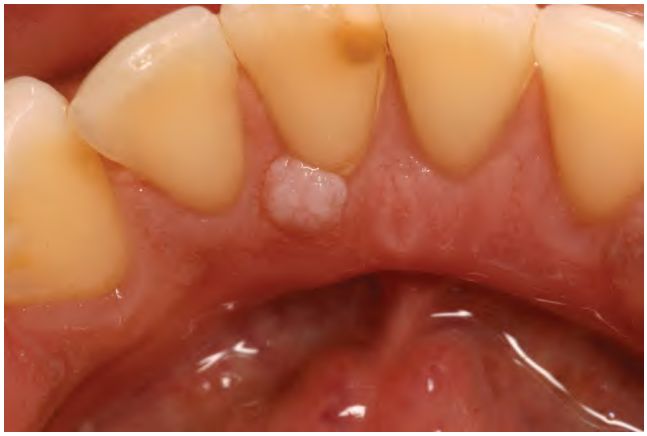
The **retrocuspid papilla** is a microscopically similar developmental lesion that occurs on the gingiva lingual to



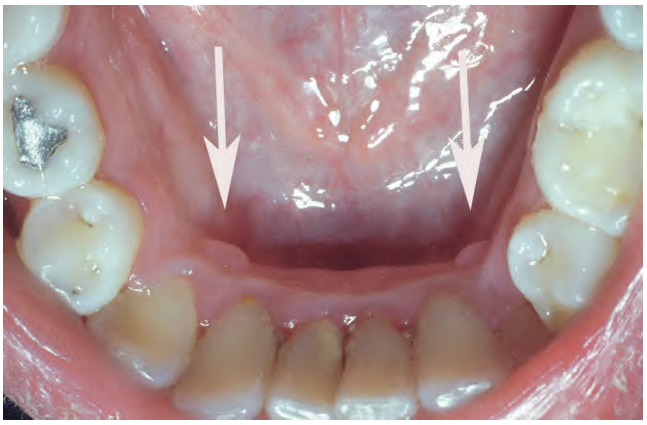
• **Fig. 12-7 Fibroma.** Higher-power view demonstrating dense collagen beneath the epithelial surface.



• **Fig. 12-8 Giant Cell Fibroma.** Exophytic nodule on the dorsum of the tongue.



• **Fig. 12-9 Giant Cell Fibroma.** Papillary growth on the lingual mandibular gingiva. Because of the rough surface, this lesion would be easily mistaken for a papilloma.



• **Fig. 12-10 Retrocuspid Papilla.** Bilateral papular lesions on the gingiva lingual to the mandibular canines *(arrows)*.

the mandibular cuspid. It is frequently bilateral and typically appears as a small, pink papule that measures less than 5 mm in diameter (Fig. 12-10). Retrocuspid papillae are quite common, having been reported in 25% to 99% of children and young adults. The prevalence in older adults drops to 6% to 19%, suggesting that the retrocuspid papilla represents a normal anatomic variation that disappears with age.

Histopathologic Features

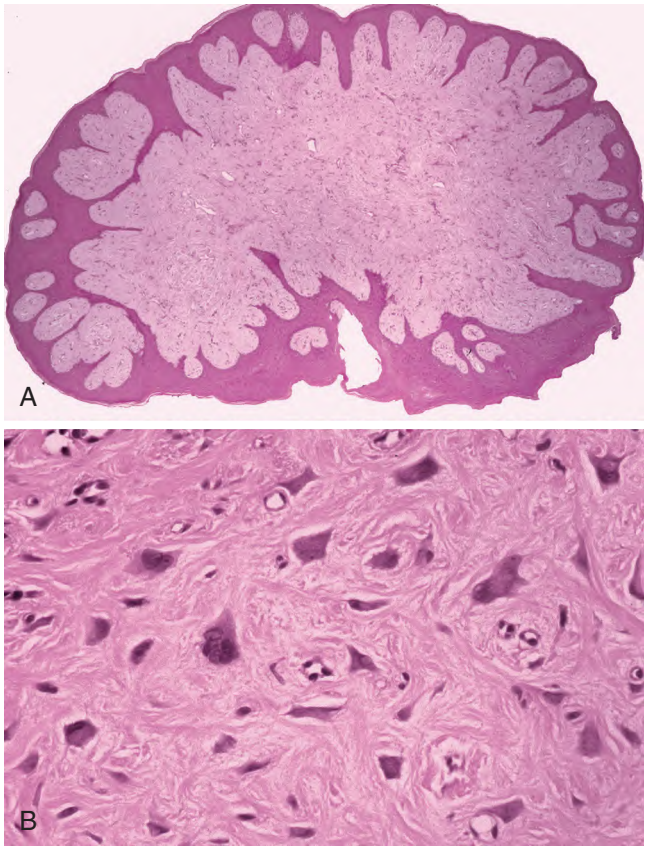
Microscopic examination of the giant cell fibroma reveals a mass of vascular fibrous connective tissue, which is usually loosely arranged (Fig. 12-11). The hallmark is the presence of numerous large, stellate fibroblasts within the superficial connective tissue. These cells may contain several nuclei. Frequently, the surface of the lesion is pebbly. The covering epithelium often is thin and atrophic, although the rete ridges may appear narrow and elongated.

Treatment and Prognosis

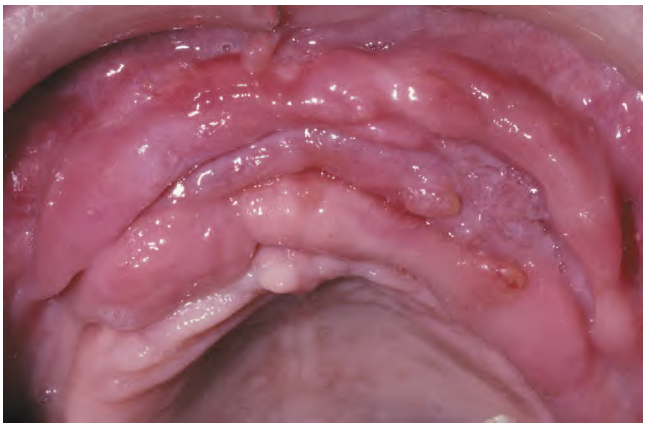
The giant cell fibroma is treated by conservative surgical excision. Recurrence is rare. Because of their characteristic appearance, retrocuspid papillae should be recognized clinically and do not need to be excised.

◆ EPULIS FISSURATUM (INFLAMMATORY FIBROUS HYPERPLASIA; DENTURE INJURY TUMOR; DENTURE EPULIS)

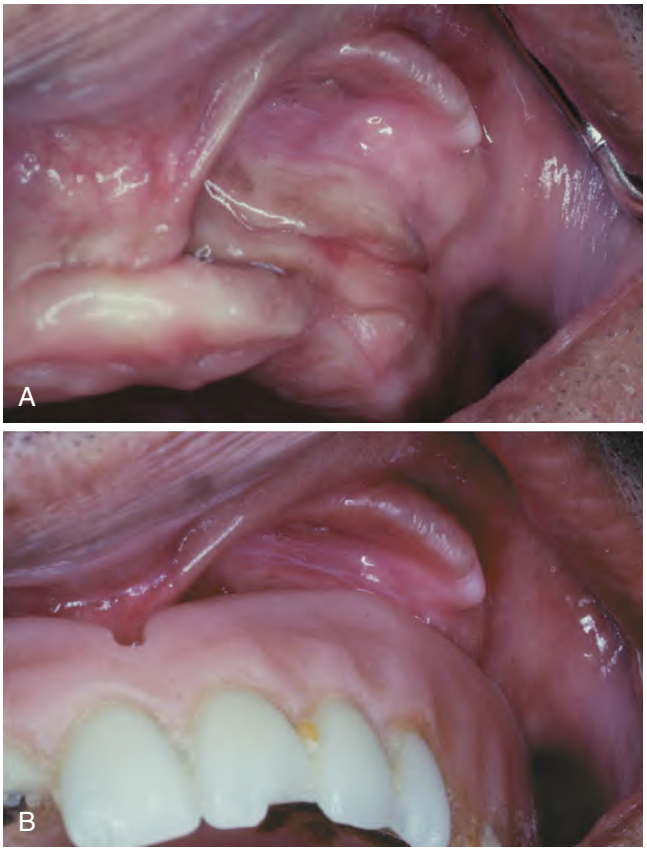
The **epulis fissuratum** is a tumorlike hyperplasia of fibrous connective tissue that develops in association with the flange of an ill-fitting complete or partial denture. Although the simple term *epulis* sometimes is used synonymously for epulis fissuratum, *epulis* is actually a generic term that can be applied to any tumor of the gingiva or alveolar mucosa. Therefore, some authors have advocated not using this term,



• **Fig. 12-11 Giant Cell Fibroma. A,** Low-power view showing a nodular mass of fibrous connective tissue covered by stratified squamous epithelium. Note the elongation of the rete ridges. **B,** High-power view showing multiple large stellate-shaped and multinucleated fibroblasts.



• **Fig. 12-12 Epulis Fissuratum.** Hyperplastic folds of tissue in the anterior maxillary vestibule.



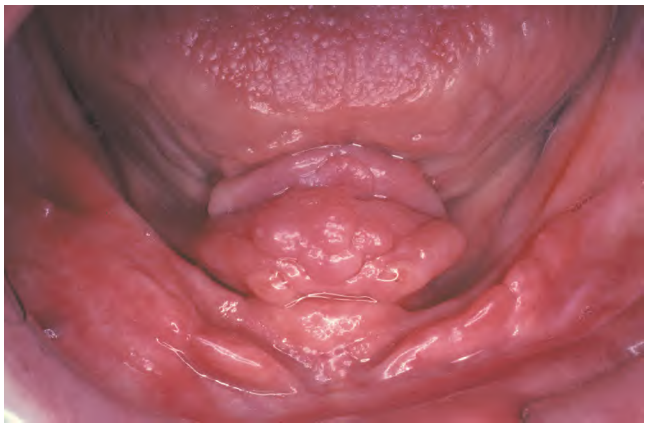
• **Fig. 12-13 Epulis Fissuratum. A,** Several folds of hyperplastic tissue in the maxillary vestibule. **B,** An ill-fitting denture fits into the fissure between two of the folds. (Courtesy of Dr. William Bruce.)

preferring to call these lesions *inflammatory fibrous hyperplasia* or other descriptive names. However, the term *epulis fissuratum* is still widely used today and is well understood by virtually all clinicians. Other examples of epulides include the **giant cell epulis (peripheral giant cell granuloma)** (see page 485), **ossifying fibroid epulis (peripheral ossifying fibroma)** (see page 487), and **congenital epulis** (see page 503).

Clinical Features

The epulis fissuratum typically appears as a single or multiple fold or folds of hyperplastic tissue in the alveolar vestibule (Figs. 12-12 and 12-13). Most often, there are two folds of tissue, and the flange of the associated denture fits conveniently into the fissure between the folds. The redundant tissue is usually firm and fibrous, although some lesions appear erythematous and ulcerated, similar to the appearance of a pyogenic granuloma. Occasional examples of epulis fissuratum demonstrate surface areas of inflammatory papillary hyperplasia (see page 478). The size of the lesion can vary from localized hyperplasias less than 1 cm in size to massive lesions that involve most of the length of the vestibule. The epulis fissuratum usually develops on the facial aspect of the alveolar ridge, although occasional lesions are seen lingual to the mandibular alveolar ridge (Fig. 12-14).

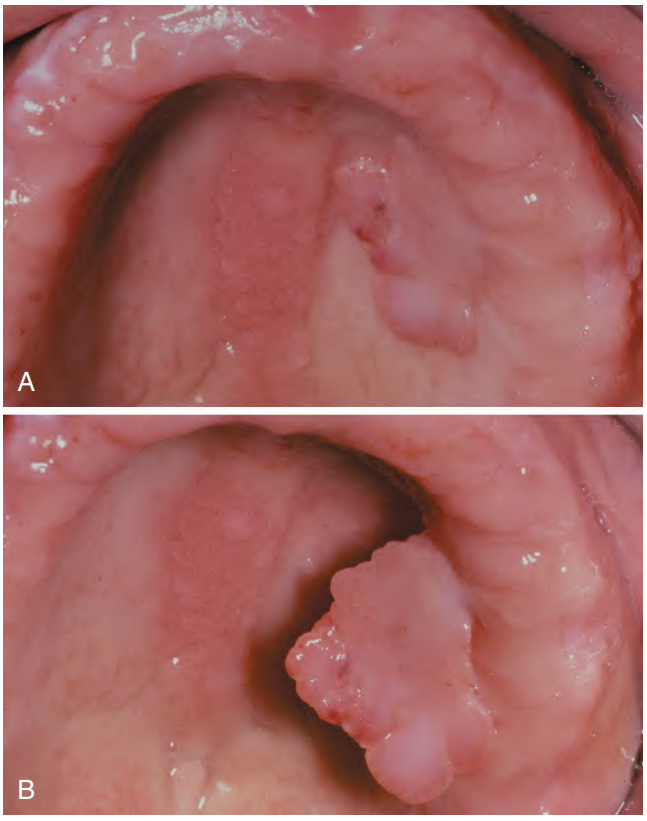
The epulis fissuratum most often occurs in middle-aged and older adults, as would be expected with a denture-related lesion. It may occur on either the maxilla or mandible. The anterior portion of the jaws is affected much



• **Fig. 12-14 Epulis Fissuratum.** Redundant folds of tissue arising in the floor of the mouth in association with a mandibular denture.

more often than the posterior areas. There is a pronounced female predilection; most studies show that two-thirds to three-fourths of all cases submitted for biopsy occur in women.

Another similar but less common fibrous hyperplasia, often called a **fibroepithelial polyp** or **leaflike denture fibroma,** occurs on the hard palate beneath a maxillary denture. This characteristic lesion is a flattened pink mass that is attached to the palate by a narrow stalk (Fig. 12-15). Usually, the flattened mass is closely applied to the palate and sits in a slightly cupped-out depression. However, it is easily lifted up with a probe, which demonstrates its pedunculated nature. The edge of the lesion often is serrated and resembles a leaf.



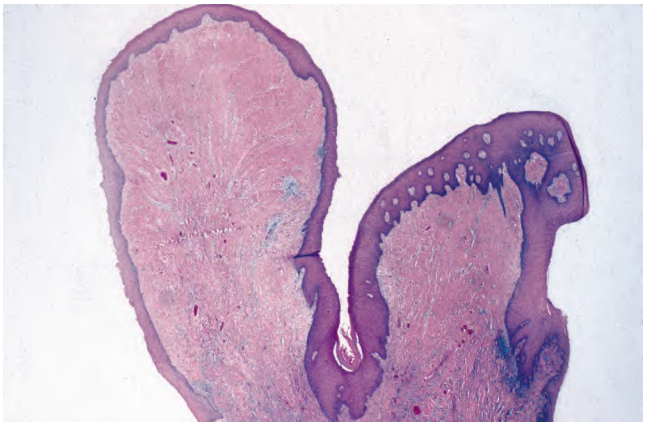
• **Fig. 12-15 Fibroepithelial Polyp.** Flattened mass of tissue arising on the hard palate beneath a maxillary denture; note its pedunculated nature. Because of its serrated edge, this lesion also is known as a *leaflike denture fibroma*. Associated inflammatory papillary hyperplasia is visible in the palatal midline.

Histopathologic Features

Microscopic examination of the epulis fissuratum reveals hyperplasia of the fibrous connective tissue. Often multiple folds and grooves occur where the denture impinges on the tissue (Fig. 12-16). The overlying epithelium is frequently hyperparakeratotic and demonstrates irregular hyperplasia of the rete ridges. In some instances, the epithelium shows inflammatory papillary hyperplasia (see page 478) or pseudoepitheliomatous (pseudocarcinomatous) hyperplasia. Focal areas of ulceration are not unusual, especially at the base of the grooves between the folds. A variable chronic inflammatory infiltrate is present; sometimes, it may include eosinophils or show lymphoid follicles. If minor salivary glands are included in the specimen, then they usually show chronic sialadenitis.

In rare instances, the formation of osteoid or chondroid is observed. This unusual-appearing product, known as **osseous and chondromatous metaplasia,** is a reactive phenomenon caused by chronic irritation by the ill-fitting denture (see page 292). The irregular nature of this bone or cartilage can be microscopically disturbing, and the pathologist should not mistake it for a sarcoma.

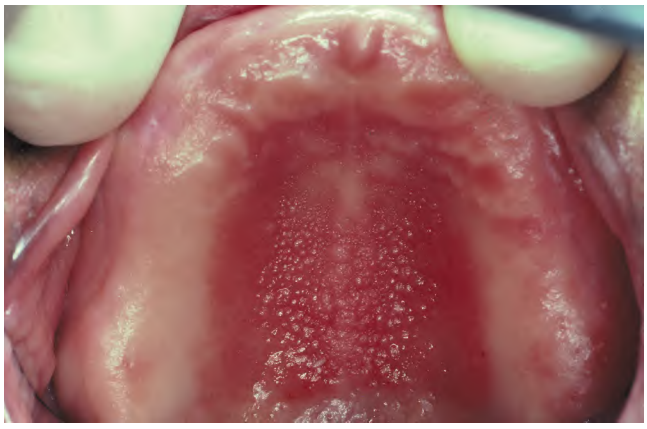
The denture-related fibroepithelial polyp has a narrow core of dense fibrous connective tissue covered by stratified squamous epithelium. Like the epulis fissuratum, the overlying epithelium may be hyperplastic.



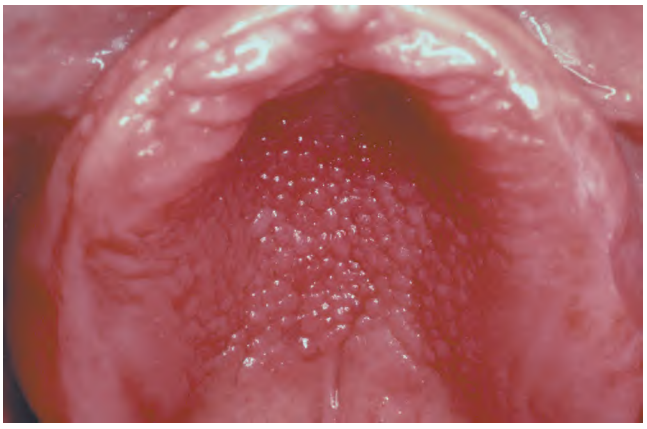
• **Fig. 12-16 Epulis Fissuratum.** Low-power photomicrograph demonstrating folds of hyperplastic fibrovascular connective tissue covered by stratified squamous epithelium.

Treatment and Prognosis

The treatment of the epulis fissuratum or fibroepithelial polyp consists of surgical removal, with microscopic



• **Fig. 12-17 Inflammatory Papillary Hyperplasia.** Erythematous, pebbly appearance of the palatal vault.



• **Fig. 12-18 Inflammatory Papillary Hyperplasia.** An advanced case exhibiting more pronounced papular lesions of the hard palate.

examination of the excised tissue. The ill-fitting denture should be remade or relined to prevent a recurrence of the lesion.

◆ INFLAMMATORY PAPILLARY HYPERPLASIA (DENTURE PAPILLOMATOSIS)

Inflammatory papillary hyperplasia is a reactive tissue growth that usually, although not always, develops beneath a denture. Some investigators classify this lesion as part of the spectrum of denture stomatitis (see page 194). Although the exact pathogenesis is unknown, the condition most often appears to be related to the following:

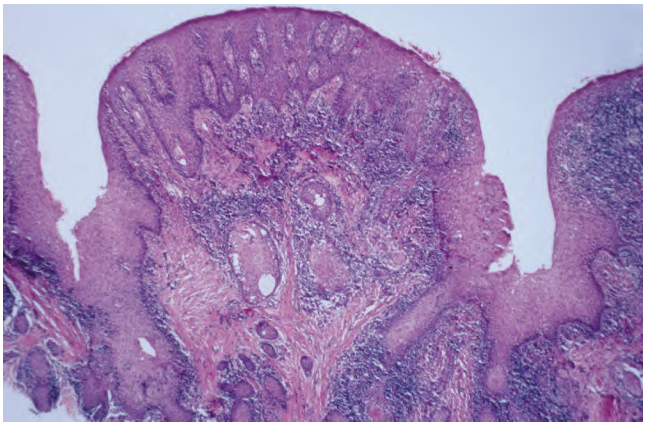
- An ill-fitting denture
- Poor denture hygiene
- Wearing the denture 24 hours a day

Approximately 20% of patients who wear their dentures 24 hours a day have inflammatory papillary hyperplasia. *Candida* organisms also have been suggested as a cause, but any possible role appears uncertain.

Clinical Features

Inflammatory papillary hyperplasia usually occurs on the hard palate beneath a denture base (Figs. 12-17 and 12-18). Early lesions may involve only the palatal vault, although advanced cases cover most of the palate. Less frequently, this hyperplasia develops on the edentulous mandibular alveolar ridge or on the surface of an epulis fissuratum. On rare occasions, the condition occurs on the palate of a patient without a denture, especially in people who habitually breathe through their mouth or have a high palatal vault. *Candida*-associated palatal papillary hyperplasia also has been reported in dentate patients with human immunodeficiency virus (HIV) infection.

Inflammatory papillary hyperplasia is usually asymptomatic. The mucosa is erythematous and has a pebbly or



• **Fig. 12-19 Inflammatory Papillary Hyperplasia.** Medium-power view showing fibrous and epithelial hyperplasia resulting in papillary surface projections. Heavy chronic inflammation is present.

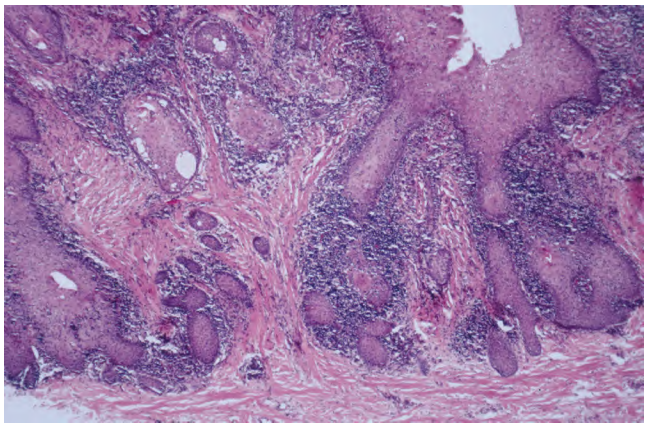
papillary surface. Many cases are associated with denture stomatitis.

Histopathologic Features

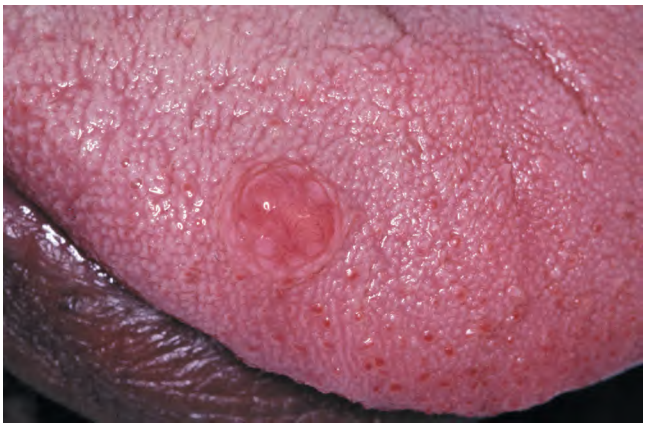
The mucosa in inflammatory papillary hyperplasia exhibits numerous papillary growths on the surface that are covered by hyperplastic, stratified squamous epithelium (Fig. 12-19). In advanced cases, this hyperplasia is pseudoepitheliomatous in appearance, and the pathologist should not mistake it for carcinoma (Fig. 12-20). The connective tissue can vary from loose and edematous to densely collagenized. A chronic inflammatory cell infiltrate is usually seen, which consists of lymphocytes and plasma cells. Less frequently, polymorphonuclear leukocytes are also present. If underlying salivary glands are present, then they often show sclerosing sialadenitis.

Treatment and Prognosis

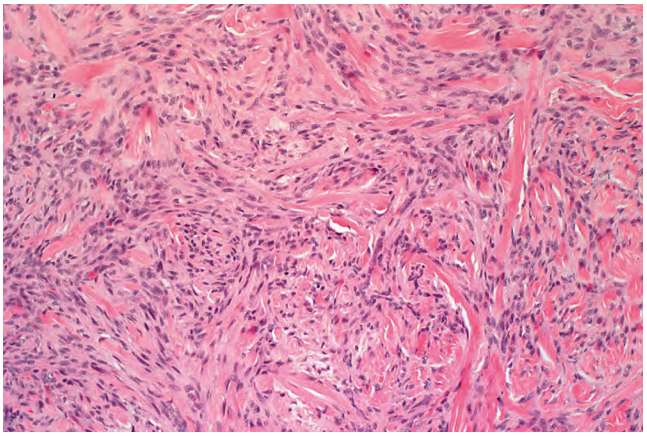
For very early lesions of inflammatory papillary hyperplasia, removal of the denture may allow the erythema and edema



• **Fig. 12-20 Inflammatory Papillary Hyperplasia.** Higher-power view showing pseudoepitheliomatous hyperplasia of the epithelium. This epithelium has a bland appearance that should not be mistaken for carcinoma.



• **Fig. 12-21 Fibrous Histiocytoma.** Nodular mass on the dorsum of the tongue.



• **Fig. 12-22 Fibrous Histiocytoma.** Medium-power view of a skin tumor *(dermatofibroma)* showing spindle-shaped cells arranged in a storiform pattern.

to subside, and the tissues may resume a more normal appearance. The condition also may show improvement after topical or systemic antifungal therapy. For more advanced and collagenized lesions, many clinicians prefer to excise the hyperplastic tissue before fabricating a new denture. Various surgical methods have been used, including the following:

- Partial-thickness or full-thickness surgical blade excision
- Curettage
- Electrosurgery
- Cryosurgery
- Laser surgery

After surgery, the existing denture can be lined with a temporary tissue conditioner that acts as a palatal dressing and promotes greater comfort. After healing, the patient should be encouraged to leave the new denture out at night and to keep it clean.

◆ FIBROUS HISTIOCYTOMA

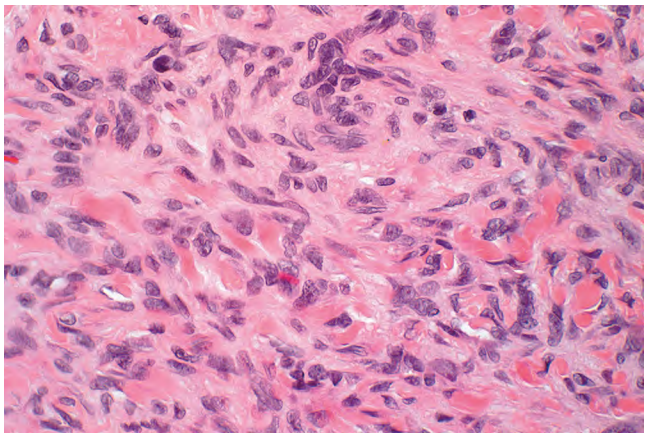
Fibrous histiocytomas are a diverse group of tumors that exhibit fibroblastic and histiocytic differentiation, although the cell of origin is uncertain. Because of the variable nature of these lesions, an array of terms has been used for them, including **dermatofibroma, sclerosing hemangioma, fibroxanthoma,** and **nodular subepidermal fibrosis.** Unlike other fibrous growths discussed previously in this chapter, the fibrous histiocytoma is generally considered to represent a true neoplasm.

Clinical Features

The fibrous histiocytoma can develop almost anywhere in the body. The most common site is the skin of the extremities, where the lesion is called a *dermatofibroma.* Tumors of the oral and perioral region are rare, and it is likely that many previously reported examples would be reclassified today as *solitary fibrous tumors* (see next topic). Rare intrabony lesions of the jaws also have been reported. Oral fibrous histiocytomas tend to occur in middle-aged and older adults; cutaneous examples are most frequent in young adults. The tumor is usually a painless nodular mass and can vary in size from a few millimeters to several centimeters in diameter (Fig. 12-21). Deeper tumors tend to be larger.

Histopathologic Features

Microscopically, the fibrous histiocytoma is characterized by a cellular proliferation of spindle-shaped fibroblastic cells with vesicular nuclei (Figs. 12-22 and 12-23). The margins of the tumor often are not sharply defined. The tumor cells are arranged in short, intersecting fascicles, known as a *storiform* pattern because of its resemblance to the irregular, whorled appearance of a straw mat. Rounded histiocyte-like cells, lipid-containing xanthoma cells, or multinucleated giant cells can be seen occasionally, as may scattered lymphocytes. The stroma may demonstrate areas of myxoid change or focal hyalinization.



• **Fig. 12-23 Fibrous Histiocytoma.** High-power view demonstrating spindle-shaped cells with vesicular nuclei.

Treatment and Prognosis

Local surgical excision is the treatment of choice. Recurrence is uncommon, especially for superficial tumors. Larger lesions of the deeper soft tissues have a greater potential to recur.

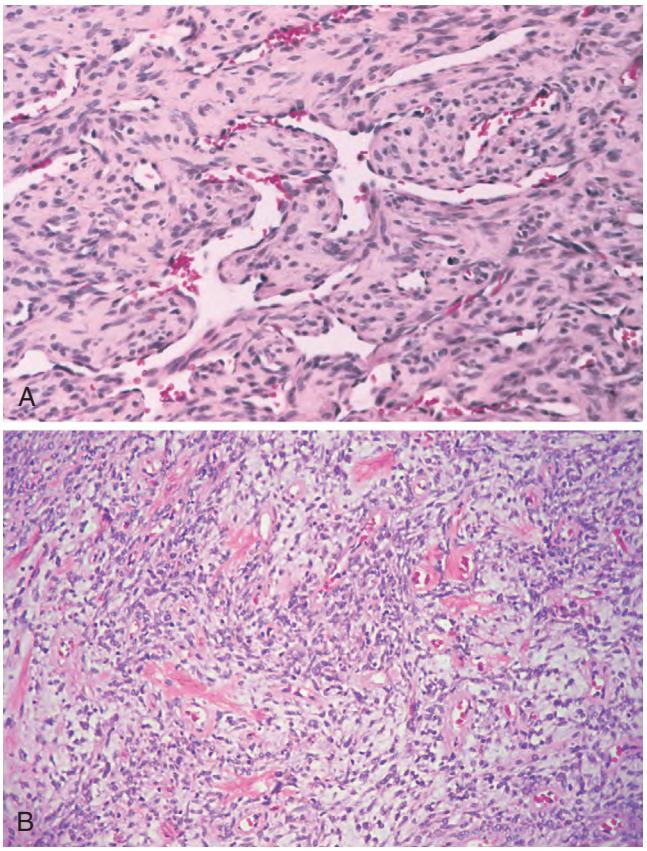
◆ SOLITARY FIBROUS TUMOR (HEMANGIOPERICYTOMA)

The **solitary fibrous tumor** was initially described as a pleural neoplasm that was believed to arise from either mesothelial cells or submesothelial fibroblasts. However, examples of this tumor were later identified in a number of other anatomic sites, including the head and neck region. The term **hemangiopericytoma** was originally used for a rare soft tissue neoplasm that presumably was derived from pericytes (i.e., cells with processes that encircled endothelial cells of capillaries). However, a pericytic origin appears doubtful, and there is a growing consensus that most so-called hemangiopericytomas represent cellular variants within the spectrum of solitary fibrous tumor.

In addition, a neoplasm microscopically similar to the hemangiopericytoma has been recognized in the sinonasal tract. This tumor does show myoid, pericyte-like differentiation and is thought to represent a separate entity known as a **sinonasal-type hemangiopericytoma (glomangiopericytoma; myopericytoma).**

Clinical Features

Solitary fibrous tumors have been reported primarily in adults and are rare in children. The tumor often is described as a slow-growing, painless, submucosal, or deep soft tissue mass that is easily removed from the surrounding tissues. Solitary fibrous tumors of the head and neck region are most common in the buccal mucosa, which accounts for approximately one-third of such cases.



• **Fig. 12-24 Solitary Fibrous Tumor. A,** "Staghorn" blood vessels surrounded by haphazardly arranged cells. **B,** Moderately cellular fibrous proliferation ("patternless pattern") with prominent vascularity, slightly myxoid areas, and scattered dense collagen bundles.

Sinonasal-type hemangiopericytoma occurs primarily in middle-aged and older adults. Common presenting symptoms include nasal obstruction and epistaxis.

Histopathologic Features

Solitary fibrous tumors are usually well-circumscribed lesions that exhibit a variable microscopic appearance. At one end of the spectrum, the lesional cells appear as tightly packed cells and surround endothelium-lined vascular channels—hence, the concept of hemangiopericytoma. The cells are haphazardly arranged and demonstrate round to ovoid nuclei and indistinct cytoplasmic borders. The blood vessels often show irregular branching, which results in a characteristic "staghorn" and "antlerlike" appearance (Fig. 12-24, *A*).

At the other end of the spectrum, the cells are more spindled and arranged in either short fascicles or in a disorganized fashion ("patternless pattern") (see Fig. 12-24, *B*). The tumor often demonstrates alternating hypercellular and hypocellular zones with a variable degree of myxoid background change. Prominent hyalinized collagen bundles are characteristically observed in the hypocellular areas. Immunohistochemical studies show the lesional cells to be positive for CD34 and bcl-2 in nearly all cases.

The identification of four or more mitoses per ten high-power fields suggests a rapidly growing tumor that is capable of metastasis. The presence of necrosis also suggests malignancy. However, it is difficult to predict microscopically whether a particular tumor will act in a benign or malignant fashion.

Sinonasal-type hemangiopericytomas have a more prominent spindle cell pattern, with the cells arranged in a more orderly fashion. Mitotic figures are rare or absent. The vascular component is less intricate, and less interstitial collagen is found among the tumor cells. Most examples will express myogenic markers, such as smooth muscle actin (92%) and muscle-specific actin (77%), but, in contrast to solitary fibrous tumor, the cells are usually negative for CD34 and bcl-2.

Treatment and Prognosis

For solitary fibrous tumors with a benign histopathologic appearance, local excision is the treatment of choice. More extensive surgery is required for tumors with malignant characteristics. Oral examples usually behave in a benign fashion, although approximately 10% of extrapleural solitary fibrous tumors have been reported to show malignant behavior. Therefore, long-term follow-up of patients with this tumor is recommended.

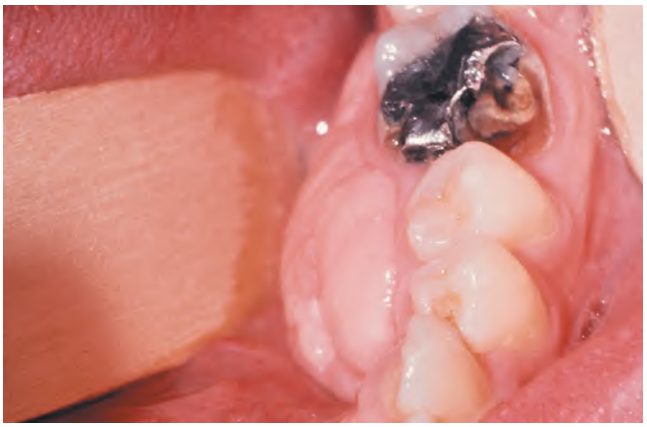
The sinonasal-type hemangiopericytoma usually has a favorable prognosis with a recurrence rate of approximately 17%. Rare examples of locally aggressive or metastatic tumors have been reported.

◆ FIBROMATOSIS

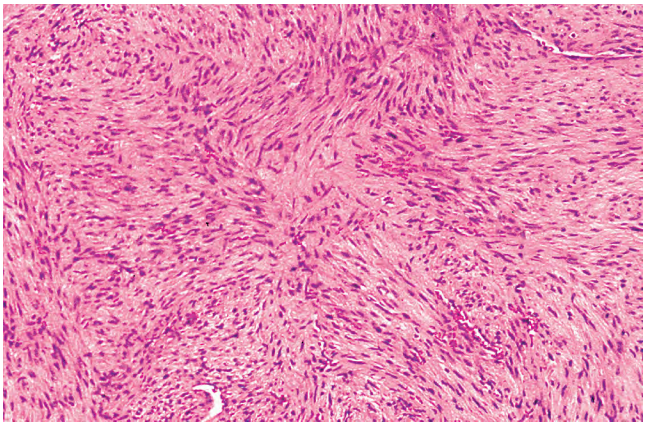
The **fibromatoses** are a broad group of fibrous proliferations that have a biologic behavior and histopathologic pattern that is intermediate between those of benign fibrous lesions and fibrosarcoma. A number of different forms of fibromatosis are recognized throughout the body, and they often are named based on their particular clinicopathologic features. In the soft tissues of the head and neck, these lesions are frequently called **juvenile aggressive fibromatoses** or **extraabdominal desmoids.** Similar lesions within the bone have been called **desmoplastic fibromas** (see page 613). Individuals with familial adenomatous polyposis and Gardner syndrome (see page 606) have a greatly increased risk for developing aggressive fibromatosis.

Clinical and Radiographic Features

Soft tissue fibromatosis of the head and neck is a firm, painless mass, which may exhibit rapid or insidious growth (Fig. 12-25). The lesion most frequently occurs in children or young adults; hence, the term **juvenile fibromatosis.** However, cases also have been seen in middle-aged adults. The most common oral site is the paramandibular soft tissue region, although the lesion can occur almost anywhere. The tumor can grow to considerable size, resulting in significant facial disfigurement. Destruction of adjacent bone may be observed on radiographs and other imaging studies.



• **Fig. 12-25 Fibromatosis.** Locally aggressive proliferation of fibrous connective tissue of the lingual mandibular gingival mucosa.



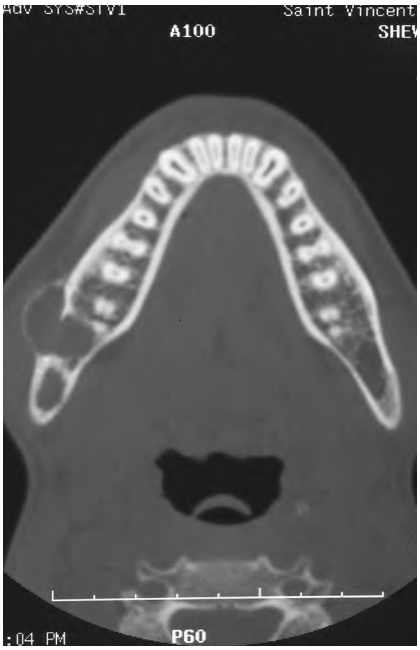
• **Fig. 12-26 Fibromatosis.** Streaming fascicles of fibroblastic cells that demonstrate little pleomorphism.

Histopathologic Features

Soft tissue fibromatosis is characterized by a cellular proliferation of spindle-shaped cells that are arranged in streaming fascicles and are associated with a variable amount of collagen (Fig. 12-26). The lesion is usually poorly circumscribed and infiltrates the adjacent tissues. Hyperchromatism and pleomorphism of the cells should not be observed.

Treatment and Prognosis

Because of its locally aggressive nature, the preferred treatment for soft tissue fibromatosis is wide excision that includes a generous margin of adjacent normal tissues. Adjuvant chemotherapy or radiation therapy sometimes has been used for incompletely resected or recurrent tumors. A 30% recurrence rate has been reported for aggressive fibromatosis of the head and neck. Metastasis does not occur.



• **Fig. 12-27 Myofibroma.** Computed tomography (CT) scan showing an expansile lytic mass of the posterior mandible on the left side of the illustration. (Courtesy of Dr. Timothy Armanini.)

◆ MYOFIBROMA (MYOFIBROMATOSIS)

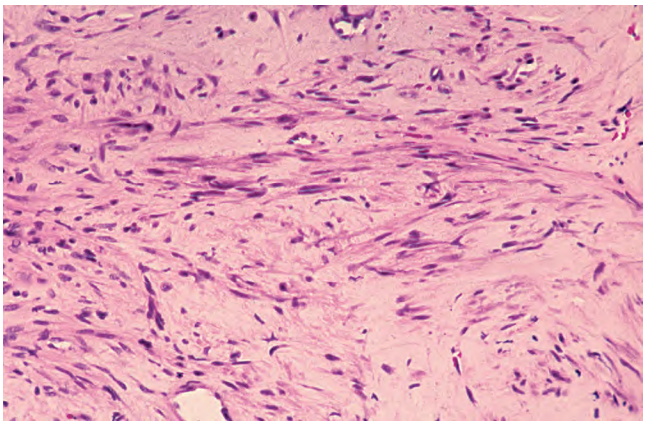
Myofibroma is a rare spindle cell neoplasm that consists of myofibroblasts (i.e., cells with both smooth muscle and fibroblastic features). Such cells are not specific for this lesion, however, because they also can be identified in other fibrous proliferations. Most myofibromas occur as solitary lesions, but some patients develop a multicentric tumor process known as **myofibromatosis.**

Clinical and Radiographic Features

Although myofibromas are rare neoplasms, they demonstrate a predilection for the head and neck region. Solitary tumors develop most frequently in the first four decades of life, with a mean age of 22 years. The most common oral location is the mandible, followed by the tongue and buccal mucosa. The tumor is typically a painless mass that sometimes exhibits rapid enlargement. Intrabony tumors create radiolucent defects that usually tend to be poorly defined, although some may be well defined or multilocular (Fig. 12-27). Multicentric myofibromatosis primarily affects neonates and infants who may have tumors of the skin, subcutaneous tissue, muscle, bone, and viscera. The number of tumors can vary from several to more than 100.

Histopathologic Features

Myofibromas are composed of interlacing bundles of spindle cells with tapered or blunt-ended nuclei and eosinophilic cytoplasm (Fig. 12-28). Nodular fascicles may alternate with more cellular zones, imparting a biphasic appearance to the tumor. Scattered mitoses are not uncommon. Centrally, the lesion is often more vascular with a hemangiopericytoma-like appearance. The tumor cells are positive for smooth muscle actin and muscle-specific actin with immunohistochemistry, but they are negative for desmin.



• **Fig. 12-28 Myofibromatosis.** Proliferation of spindle-shaped cells with both fibroblastic and smooth muscle features.

Treatment and Prognosis

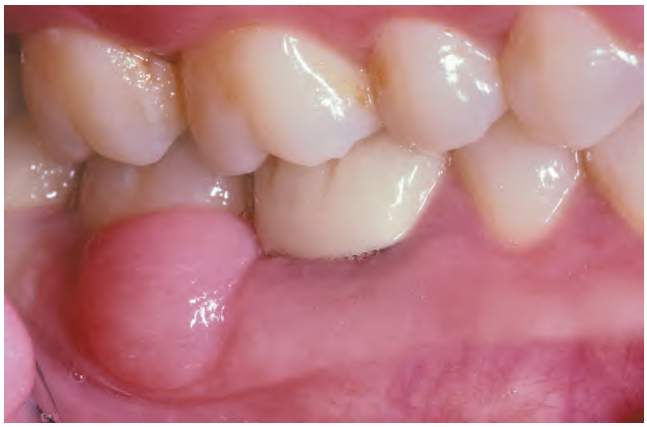
Solitary myofibromas are usually treated by surgical excision. A small percentage of tumors will recur after treatment, but typically, these can be controlled with reexcision. Multifocal tumors arising in soft tissues and bone rarely recur after surgical removal. Spontaneous regression may occur in some cases. However, myofibromatosis involving the viscera or vital organs in infants can act more aggressively and sometimes proves to be fatal within a few days after birth.

◆ ORAL FOCAL MUCINOSIS

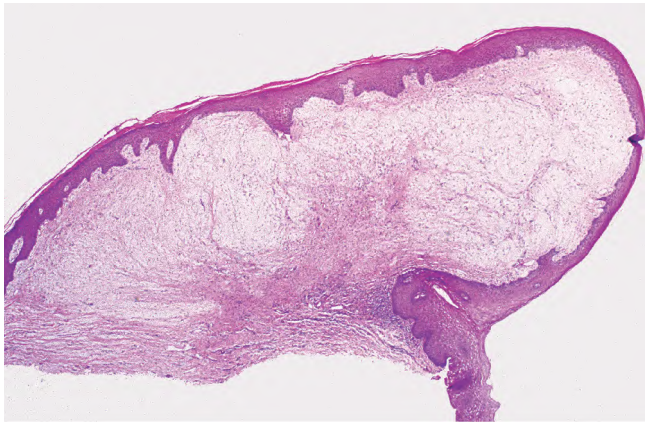
Oral focal mucinosis is an uncommon tumorlike mass that is believed to represent the oral counterpart of cutaneous focal mucinosis or a cutaneous myxoid cyst. The cause is unknown, although the lesion may result from overproduction of hyaluronic acid by fibroblasts.

Clinical Features

Oral focal mucinosis is most common in young adults and shows a 2:1 female-to-male predilection. The gingiva is the most common site; two-thirds to three-fourths of all cases are found there. The hard palate is the second most common location. The mass rarely appears at other oral sites. The lesion usually presents as a sessile or pedunculated, painless nodular mass that is the same color as the surrounding mucosa (Fig. 12-29). The surface is typically smooth and nonulcerated, although occasional cases exhibit



• **Fig. 12-29 Oral Focal Mucinosis.** Nodular mass arising from the gingiva between the mandibular first and second molars.

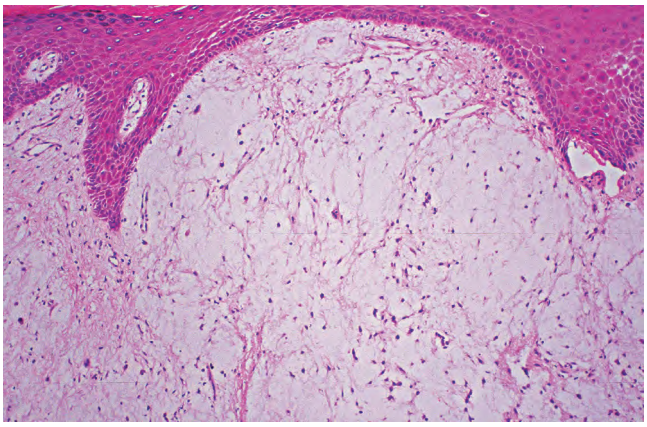


• **Fig. 12-30 Oral Focal Mucinosis.** Low-power view showing a nodular mass of loose, myxomatous connective tissue.

a lobulated appearance. The size varies from a few millimeters up to 2 cm in diameter. The patient often has been aware of the mass for many months or years before the diagnosis is made.

Histopathologic Features

Microscopic examination of oral focal mucinosis shows a well-localized but nonencapsulated area of loose, myxomatous connective tissue surrounded by denser, normal collagenous connective tissue (Figs. 12-30 and 12-31). The lesion is usually found just beneath the surface epithelium and often causes flattening of the rete ridges. The fibroblasts within the mucinous area can be ovoid, fusiform, or stellate, and they may demonstrate delicate, fibrillar processes. Few capillaries are seen within the lesion, especially compared with the surrounding denser collagen. Similarly, no significant inflammation is observed, although a perivascular lymphocytic infiltrate often is noted within the surrounding collagenous connective tissue. No appreciable reticulin is evident within the lesion, and special stains suggest that the mucinous product is hyaluronic acid.



• **Fig. 12-31 Oral Focal Mucinosis.** High-power view demonstrating the myxomatous change.

Treatment and Prognosis

Oral focal mucinosis is treated by surgical excision and does not tend to recur.

◆ PYOGENIC GRANULOMA (LOBULAR CAPILLARY HEMANGIOMA)

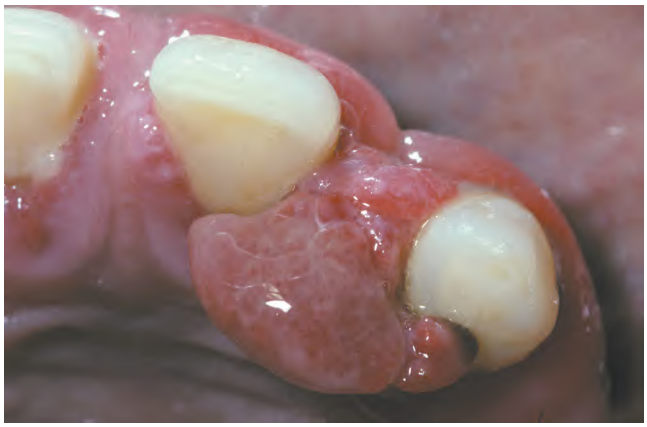
The **pyogenic granuloma** is a common tumorlike growth of the oral cavity that traditionally has been considered to be nonneoplastic in nature.* Although it was originally thought to be caused by pyogenic organisms, it is now believed to be unrelated to infection. Instead, the pyogenic granuloma is thought to represent an exuberant tissue response to local irritation or trauma. In spite of its name, it is not a true granuloma.

Clinical Features

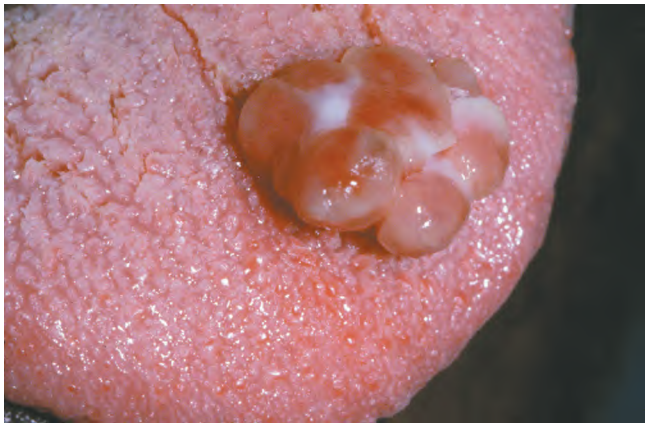
The pyogenic granuloma is a smooth or lobulated mass that is usually pedunculated, although some lesions are sessile (Figs. 12-32 to 12-34). The surface is characteristically ulcerated and ranges from pink to red to purple, depending on the age of the lesion. Young pyogenic granulomas are highly vascular in appearance; older lesions tend to become more collagenized and pink. They vary from small growths only a few millimeters in size to larger lesions that may measure several centimeters in diameter. Typically, the mass is painless, although it often bleeds easily because of its extreme vascularity. Pyogenic granulomas may exhibit rapid growth, which may create alarm for both the patient and the clinician, who may fear that the lesion might be malignant.

Oral pyogenic granulomas show a striking predilection for the gingiva, which accounts for approximately 75% to

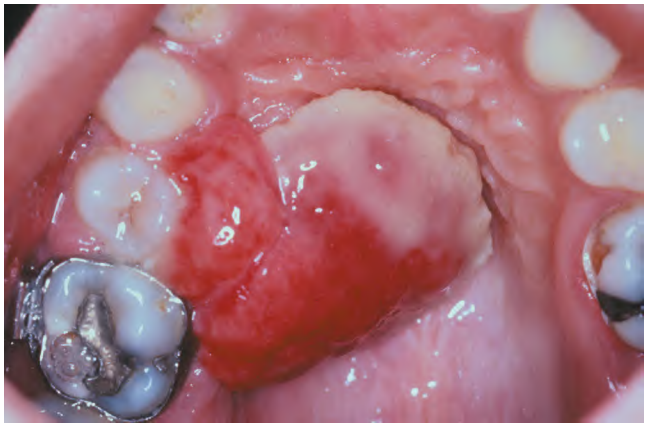
*However, some pyogenic granulomas (also known as *lobular capillary hemangiomas*) currently are categorized as *vascular tumors* under the classification scheme of the International Society for the Study of Vascular Anomalies (see Box 12-2, page 504).



• **Fig. 12-32 Pyogenic Granuloma.** Erythematous, hemorrhagic mass arising from the maxillary anterior gingiva.

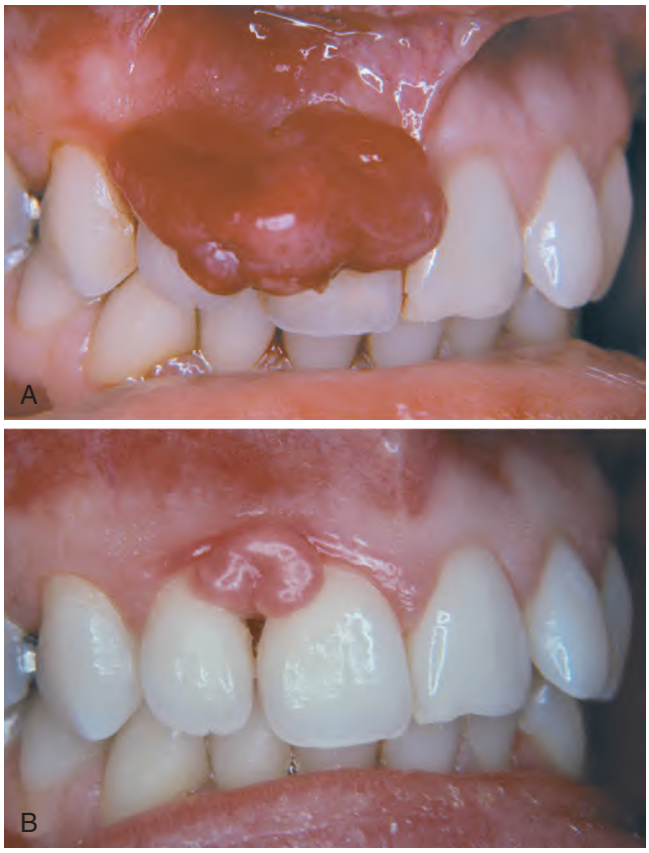


• **Fig. 12-33 Pyogenic Granuloma.** Ulcerated and lobulated mass on the dorsum of the tongue.



• **Fig. 12-34 Pyogenic Granuloma.** Unusually large lesion arising from the palatal gingiva in association with an orthodontic band. The patient was pregnant.

85% of all cases. Gingival irritation and inflammation that result from poor oral hygiene may be a precipitating factor in many patients. The lips, tongue, and buccal mucosa are the next most common sites. A history of trauma before the development of the lesion is not unusual, especially for

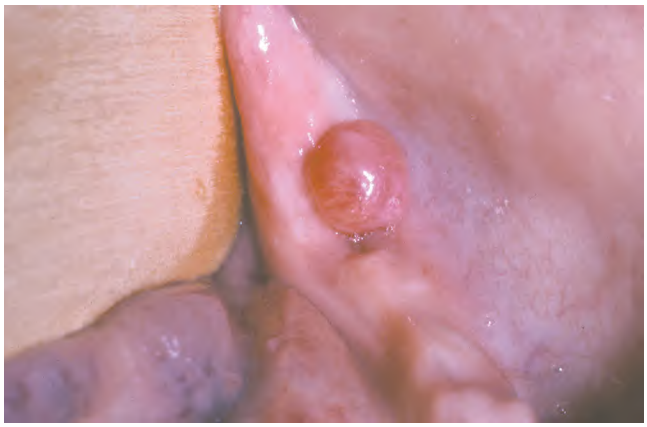


• **Fig. 12-35 Pyogenic Granuloma. A,** Large gingival mass in a pregnant woman just before childbirth. **B,** The mass has decreased in size and undergone fibrous maturation 3 months after childbirth. (Courtesy of Dr. George Blozis.)

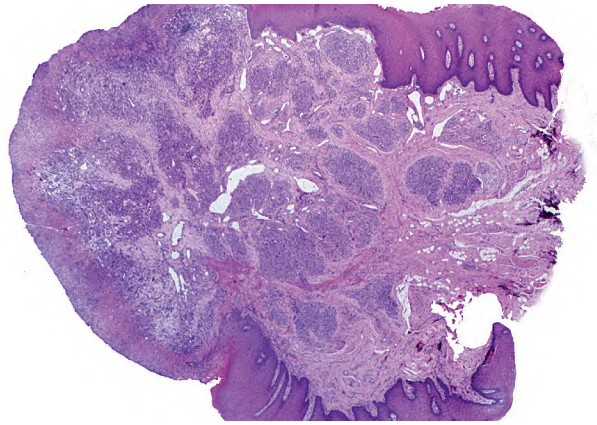
extragingival pyogenic granulomas. Lesions are slightly more common on the maxillary gingiva than the mandibular gingiva; anterior areas are more frequently affected than posterior areas. These lesions are much more common on the facial aspect of the gingiva than the lingual aspect; some extend between the teeth and involve both the facial and the lingual gingiva.

Although the pyogenic granuloma can develop at any age, it is most common in children and young adults. Most studies also demonstrate a definite female predilection, possibly because of the vascular effects of female hormones. Pyogenic granulomas of the gingiva frequently develop in pregnant women, so much so that the terms *pregnancy tumor* or *granuloma gravidarum* often are used. Such lesions may begin to develop during the first trimester, and their prevalence increases up through the seventh month of pregnancy. The gradual rise in development of these lesions throughout pregnancy may be related to the increasing levels of estrogen and progesterone as the pregnancy progresses. After pregnancy and the return of normal hormone levels, some of these pyogenic granulomas resolve without treatment or undergo fibrous maturation and resemble a fibroma (Fig. 12-35).

Epulis granulomatosa is a term used to describe hyperplastic growths of granulation tissue that sometimes arise in



• **Fig. 12-36 Epulis Granulomatosa.** Nodular mass of granulation tissue that developed in a recent extraction site.

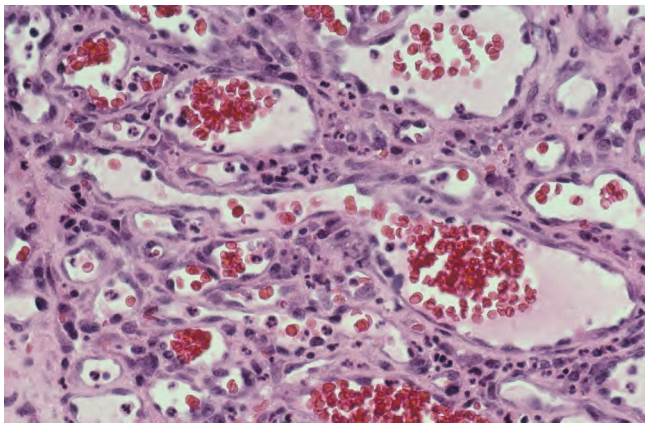


• **Fig. 12-37 Pyogenic Granuloma.** Low-power view showing an exophytic mass of granulation-like tissue with an ulcerated surface. Note the lobular endothelial proliferation in the deeper connective tissue.

healing extraction sockets (Fig. 12-36). These lesions resemble pyogenic granulomas and usually represent a granulation tissue reaction to bony sequestra in the socket.

Histopathologic Features

Microscopic examination of pyogenic granulomas shows a highly vascular proliferation that resembles granulation tissue (Figs. 12-37 and 12-38). Numerous small and larger endothelium-lined channels are formed that are engorged with red blood cells. These vessels sometimes are organized in lobular aggregates—hence, the term *lobular capillary hemangioma.* The surface is usually ulcerated and replaced by a thick fibrinopurulent membrane. A mixed inflammatory cell infiltrate of neutrophils, plasma cells, and lymphocytes is evident. Neutrophils are most prevalent near the ulcerated surface; chronic inflammatory cells are found deeper in the specimen. Older lesions may have areas with a more fibrous appearance. In fact, many gingival fibromas probably represent pyogenic granulomas that have undergone fibrous maturation.



• **Fig. 12-38 Pyogenic Granuloma.** Higher-power view showing capillary blood vessels and scattered inflammation.

Treatment and Prognosis

The treatment of patients with pyogenic granuloma consists of conservative surgical excision, which is usually curative. The specimen should be submitted for microscopic examination to rule out other more serious diagnoses. For gingival lesions, the excision should extend down to periosteum and the adjacent teeth should be thoroughly scaled to remove any source of continuing irritation. A recurrence rate of 3% to 15% has been reported in most studies. In rare instances, multiple recurrences have been noted.

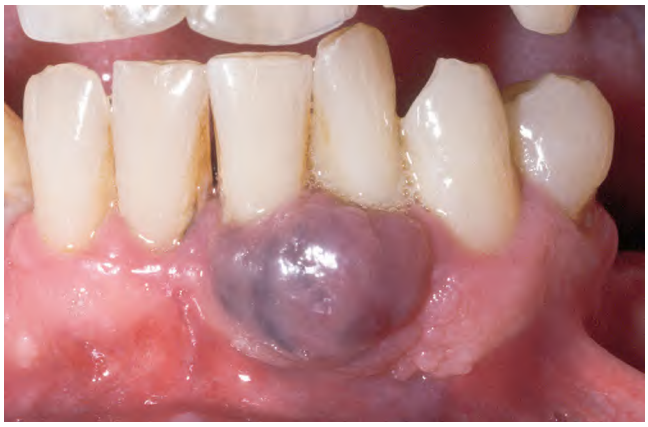
For lesions that develop during pregnancy, usually treatment should be deferred unless significant functional or aesthetic problems develop. The recurrence rate is higher for pyogenic granulomas removed during pregnancy, and some lesions will resolve spontaneously after parturition.

◆ PERIPHERAL GIANT CELL GRANULOMA (GIANT CELL EPULIS)

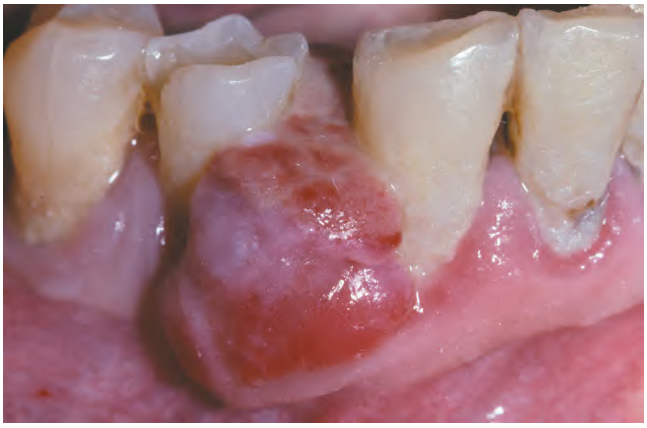
The **peripheral giant cell granuloma** is a relatively common tumorlike growth of the oral cavity. It probably does not represent a true neoplasm but rather is a reactive lesion caused by local irritation or trauma. In the past, it often was called a *peripheral giant cell reparative granuloma,* but any reparative nature appears doubtful. Some investigators believe that the giant cells show immunohistochemical features of osteoclasts, whereas other authors have suggested that the lesion is formed by cells from the mononuclear phagocyte system. The peripheral giant cell granuloma bears a close microscopic resemblance to the **central giant cell granuloma** (see page 584), and some pathologists believe that it may represent a soft tissue counterpart of this intraosseous lesion.

Clinical and Radiographic Features

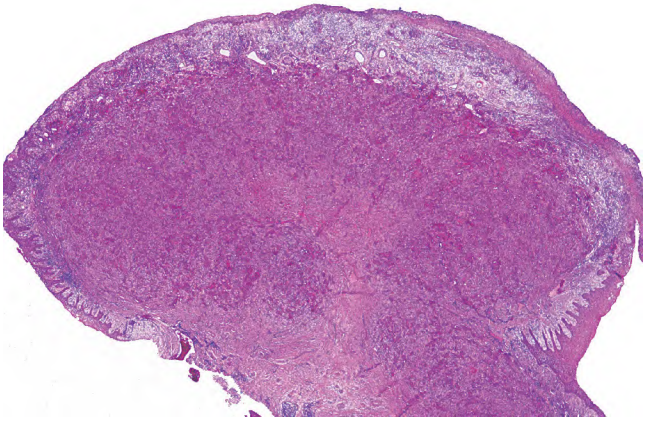
The peripheral giant cell granuloma occurs exclusively on the gingiva or edentulous alveolar ridge, presenting as a red or red-blue nodular mass (Figs. 12-39 and 12-40). Most



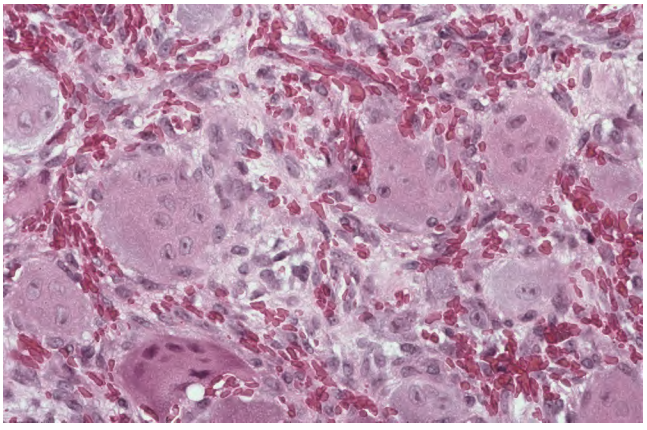
• **Fig. 12-39 Peripheral Giant Cell Granuloma.** Nodular blue-purple mass of the mandibular gingiva.



• **Fig. 12-40 Peripheral Giant Cell Granuloma.** Ulcerated mass of the mandibular gingiva.



• **Fig. 12-41 Peripheral Giant Cell Granuloma.** Low-power view showing a nodular proliferation of multinucleated giant cells within the gingiva.



• **Fig. 12-42 Peripheral Giant Cell Granuloma.** High-power view showing scattered multinucleated giant cells within a hemorrhagic background of ovoid and spindle-shaped mesenchymal cells.

lesions are smaller than 2 cm in diameter, although larger ones are seen occasionally. The lesion can be sessile or pedunculated and may or may not be ulcerated. The clinical appearance is similar to the more common pyogenic granuloma of the gingiva (see page 483), although the peripheral giant cell granuloma often is more blue-purple compared with the bright red of a typical pyogenic granuloma.

Peripheral giant cell granulomas can develop at almost any age, especially during the first through sixth decades of life. The mean age in several large series ranges from 31 to 46 years. Approximately 52% to 60% of cases occur in females. It may develop in either the anterior or posterior regions of the gingiva or alveolar mucosa, and the mandible is affected slightly more often than the maxilla. Although the peripheral giant cell granuloma develops within soft tissue, "cupping" resorption of the underlying alveolar bone sometimes is seen. On occasion, it may be difficult to determine whether the mass arose as a peripheral lesion or as a central giant cell granuloma that eroded through the cortical plate into the gingival soft tissues.

Histopathologic Features

Microscopic examination of a peripheral giant cell granuloma shows a proliferation of multinucleated giant cells within a background of plump ovoid and spindle-shaped mesenchymal cells (Figs. 12-41 and 12-42). The giant cells may contain only a few nuclei or up to several dozen. Some of these cells may have large, vesicular nuclei; others demonstrate small, pyknotic nuclei. Mitotic figures are fairly common in the background mesenchymal cells. Abundant hemorrhage is characteristically found throughout the mass, which often results in deposits of hemosiderin pigment, especially at the periphery of the lesion.

The overlying mucosal surface is ulcerated in about 50% of cases. A zone of dense fibrous connective tissue usually separates the giant cell proliferation from the mucosal surface. Adjacent acute and chronic inflammatory cells are frequently present. Areas of reactive bone formation or dystrophic calcifications are not unusual.

Treatment and Prognosis

The treatment of the peripheral giant cell granuloma consists of local surgical excision down to the underlying bone. The adjacent teeth should be carefully scaled to remove any source of irritation and to minimize the risk of recurrence. Approximately 10% to 18% of lesions are reported to recur,

and reexcision must be performed. On rare occasions, lesions indistinguishable from peripheral giant cell granulomas have been seen in patients with hyperparathyroidism (see page 781). They apparently represent the so-called osteoclastic brown tumors associated with this endocrine disorder. However, the brown tumors of hyperparathyroidism are much more likely to be intraosseous in location and mimic a central giant cell granuloma.

◆ PERIPHERAL OSSIFYING FIBROMA (OSSIFYING FIBROID EPULIS; PERIPHERAL FIBROMA WITH CALCIFICATION; CALCIFYING FIBROBLASTIC GRANULOMA)

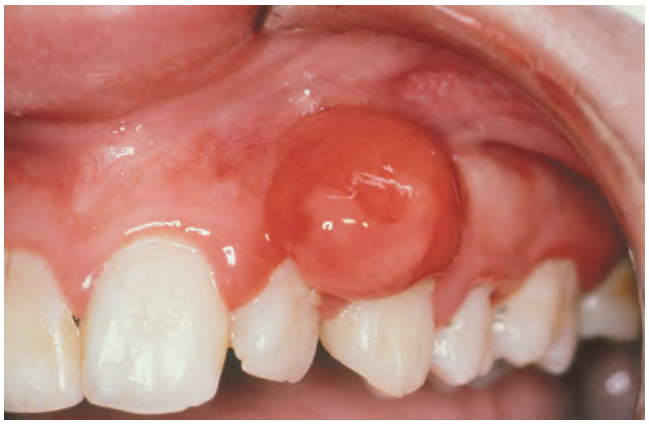
The **peripheral ossifying fibroma** is a relatively common gingival growth that is considered to be reactive rather than neoplastic in nature. The pathogenesis of this lesion is uncertain. Because of their clinical and histopathologic similarities, researchers believe that some peripheral ossifying fibromas develop initially as pyogenic granulomas that undergo fibrous maturation and subsequent calcification. However, not all peripheral ossifying fibromas may develop in this manner. The mineralized product probably has its origin from cells of the periosteum or periodontal ligament.

Considerable confusion has existed over the nomenclature of this lesion, and several terms have been used to describe its variable histopathologic features. In the past, the terms *peripheral odontogenic fibroma* (see page 678) and *peripheral ossifying fibroma* often were used synonymously, but the peripheral odontogenic fibroma is now considered to be a distinct and separate entity. In addition, in spite of the similarity in names, the peripheral ossifying fibroma does not represent the soft tissue counterpart of the central ossifying fibroma (see page 602).

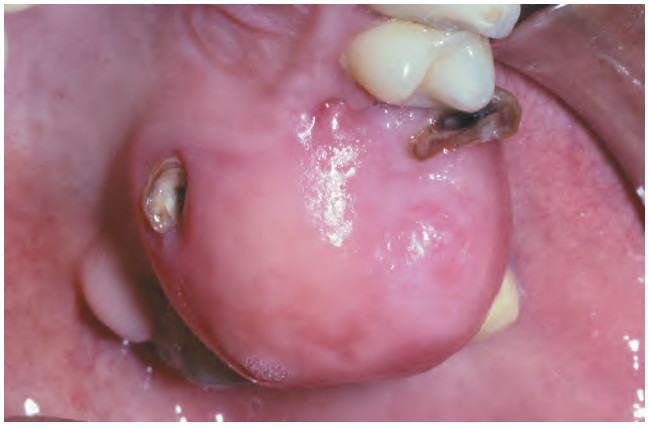
Clinical Features

The peripheral ossifying fibroma occurs exclusively on the gingiva. It appears as a nodular mass, either pedunculated or sessile, that usually emanates from the interdental papilla (Figs. 12-43 and 12-44). The color ranges from red to pink, and the surface is frequently, but not always, ulcerated. The growth probably begins as an ulcerated lesion; older ones are more likely to demonstrate healing of the ulcer and an intact surface. Red, ulcerated lesions often are mistaken for pyogenic granulomas; the pink, nonulcerated ones are clinically similar to irritation fibromas. Most lesions are less than 2 cm in size, although larger ones occasionally occur. The lesion often has been present for many weeks or months before the diagnosis is made.

The peripheral ossifying fibroma is predominantly a lesion of teenagers and young adults, with peak prevalence between the ages of 10 and 19. Almost two-thirds of all cases occur in females. There is a slight predilection for the maxillary arch, and more than 50% of all cases occur in the incisor-cuspid region. Usually, the teeth are unaffected; rarely, there can be migration and loosening of adjacent teeth.



• **Fig. 12-43 Peripheral Ossifying Fibroma.** This red, ulcerated mass of the maxillary gingiva has recurred twice. Such ulcerated lesions are easily mistaken for a pyogenic granuloma.

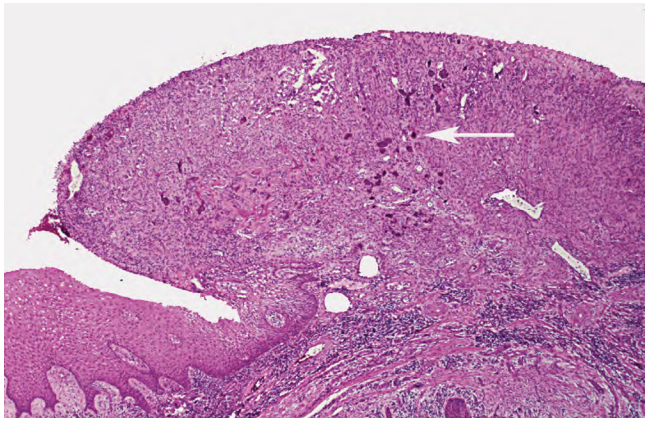


• **Fig. 12-44 Peripheral Ossifying Fibroma.** Pink, nonulcerated mass arising from the maxillary gingiva. The remaining roots of the first molar are present.

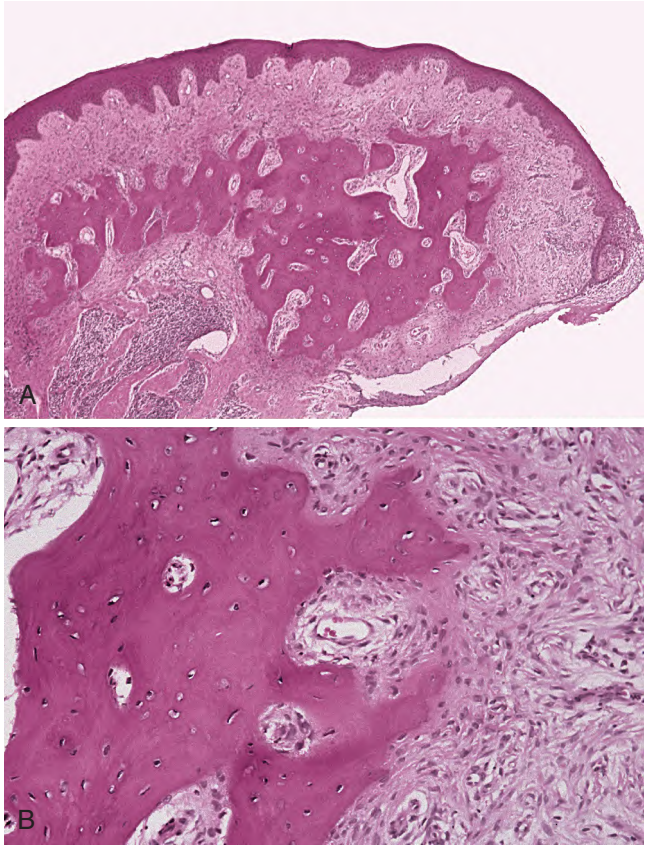
Histopathologic Features

The basic microscopic pattern of the peripheral ossifying fibroma is one of a fibrous proliferation associated with the formation of a mineralized product (Figs. 12-45 and 12-46). If the epithelium is ulcerated, then the surface is covered by a fibrinopurulent membrane with a subjacent zone of granulation tissue. The deeper fibroblastic component often is cellular, especially in areas of mineralization. In some cases, the fibroblastic proliferation and associated mineralization is only a small component of a larger mass that resembles a fibroma or pyogenic granuloma.

The type of mineralized component is variable and may consist of bone, cementum-like material, or dystrophic calcifications. Frequently, a combination of products is formed. Usually, the bone is woven and trabecular in type, although older lesions may demonstrate mature lamellar bone. Trabeculae of unmineralized osteoid are not unusual. Less

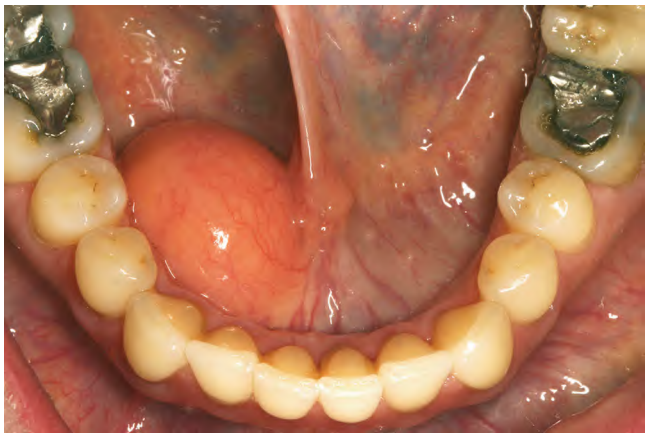


• **Fig. 12-45 Peripheral Ossifying Fibroma.** Ulcerated gingival mass demonstrating focal early mineralization *(arrow).*



• **Fig. 12-46 Peripheral Ossifying Fibroma. A,** Nonulcerated fibrous mass of the gingiva showing central bone formation. **B,** Higher-power view showing trabeculae of bone with adjacent fibrous connective tissue.

frequently, ovoid droplets of basophilic cementum-like material are formed. Dystrophic calcifications are characterized by multiple granules, tiny globules, or large, irregular masses of basophilic mineralized material. Such dystrophic calcifications are more common in early, ulcerated lesions; older, nonulcerated examples are more likely to demonstrate well-formed bone or cementum. In some cases, multinucleated giant cells may be found, usually in association with the mineralized product.



• **Fig. 12-47 Lipoma.** Soft, yellow nodular mass in the floor of the mouth. (Courtesy of Dr. Michael Tabor.)

Treatment and Prognosis

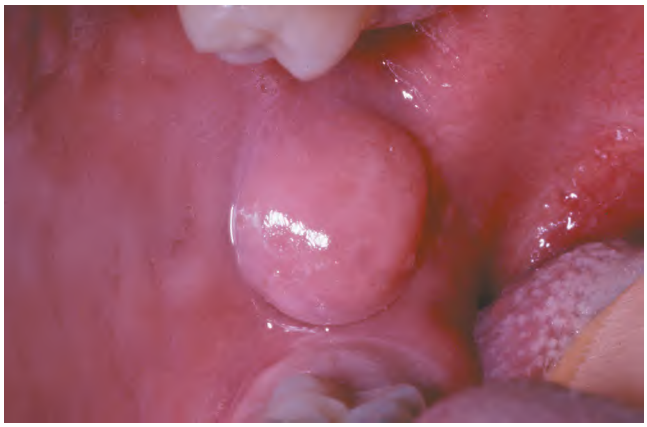
The treatment of choice for the peripheral ossifying fibroma is local surgical excision with submission of the specimen for histopathologic examination. The mass should be excised down to periosteum because recurrence is more likely if the base of the lesion is allowed to remain. In addition, the adjacent teeth should be thoroughly scaled to eliminate any possible irritants. Periodontal surgical techniques, such as repositioned flaps or connective tissue grafts, may be necessary to repair the gingival defect in an aesthetic manner. Although excision is usually curative, a recurrence rate of 8% to 16% has been reported.

◆ LIPOMA

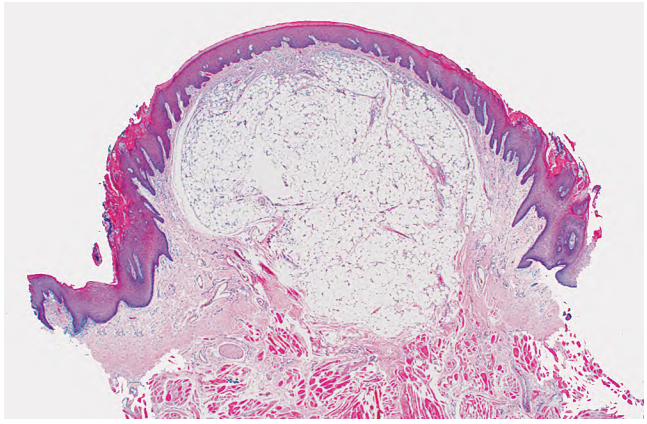
The **lipoma** is a benign tumor of fat. Although it represents by far the most common mesenchymal neoplasm, most examples occur on the trunk and proximal portions of the extremities. Lipomas of the oral and maxillofacial region are much less frequent, accounting for only 1% to 4% of all such tumors. The pathogenesis of lipomas is uncertain, but they appear to be more common in obese people. However, the metabolism of lipomas is completely independent of the normal body fat. If the caloric intake is reduced, then lipomas do not decrease in size, although normal body fat may be lost.

Clinical Features

Oral lipomas are usually soft, smooth-surfaced nodular masses that can be sessile or pedunculated (Figs. 12-47 and 12-48). Typically, the tumor is asymptomatic and often has been noted for many months or years before diagnosis. Most are less than 3 cm in size, but occasional lesions can become much larger. Although a subtle or more obvious yellow hue often is detected clinically, deeper examples may appear pink. The buccal mucosa and buccal vestibule are the most common intraoral sites and account for nearly 50% of all cases. Some buccal cases may not represent true



• **Fig. 12-48 Lipoma.** Nodular mass of the posterior buccal mucosa.



• **Fig. 12-49 Lipoma.** Low-power view of a tumor of the tongue demonstrating a mass of mature adipose tissue.

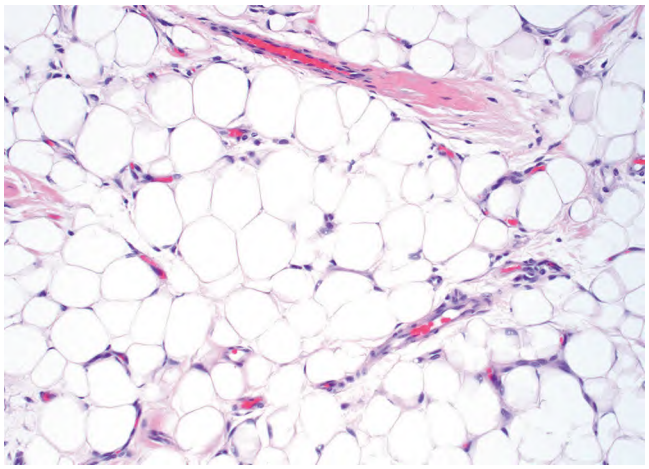
tumors, but rather herniation of the buccal fat pad through the buccinator muscle, which may occur after local trauma in young children or subsequent to surgical removal of third molars in older patients. Less common sites include the tongue, floor of the mouth, and lips. Most patients are 40 years of age or older; lipomas are uncommon in children. Lipomas of the oral and maxillofacial region have shown a fairly balanced sex distribution in most studies.

Histopathologic Features

Most oral lipomas are composed of mature fat cells that differ little in microscopic appearance from the surrounding normal fat (Figs. 12-49 and 12-50). The tumor is usually well circumscribed and may demonstrate a thin fibrous capsule. A distinct lobular arrangement of the cells often is seen. On rare occasions, central cartilaginous or osseous metaplasia may occur within an otherwise typical lipoma.

A number of microscopic variants have been described. The most common of these is the **fibrolipoma,** which is characterized by a significant fibrous component intermixed with the lobules of fat cells. The remaining variants are rare.

The **angiolipoma** consists of an admixture of mature fat and numerous small blood vessels. The **spindle cell lipoma**



• **Fig. 12-50 Lipoma.** High-power view showing the similarity of the tumor cells to normal fat.

demonstrates variable amounts of uniform-appearing spindle cells in conjunction with a more typical lipomatous component. Some spindle cell lipomas exhibit a mucoid background *(myxoid lipoma)* and may be confused with myxoid liposarcomas. **Pleomorphic lipomas** are characterized by the presence of spindle cells plus bizarre, hyperchromatic giant cells; they can be difficult to distinguish from a pleomorphic liposarcoma. **Intramuscular (infiltrating) lipomas** often are more deeply situated and have an infiltrative growth pattern that extends between skeletal muscle bundles. The term **sialolipoma** was coined to describe tumors that secondarily entrap salivary gland tissue.

Treatment and Prognosis

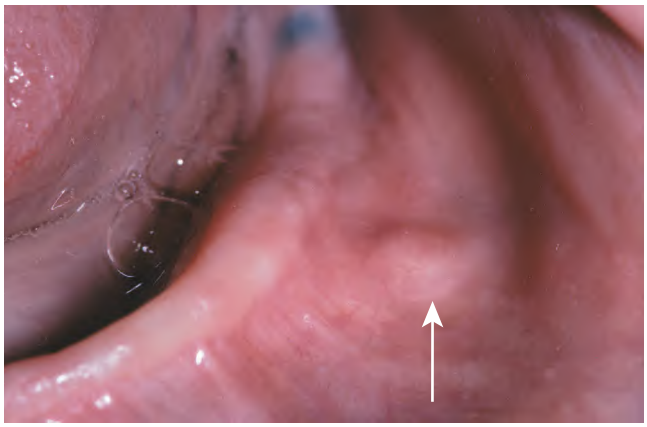
Lipomas are treated by conservative local excision, and recurrence is rare. Most microscopic variants do not affect the prognosis. Intramuscular lipomas have a higher recurrence rate because of their infiltrative growth pattern, but this variant is rare in the oral and maxillofacial region.

◆ TRAUMATIC NEUROMA (AMPUTATION NEUROMA)

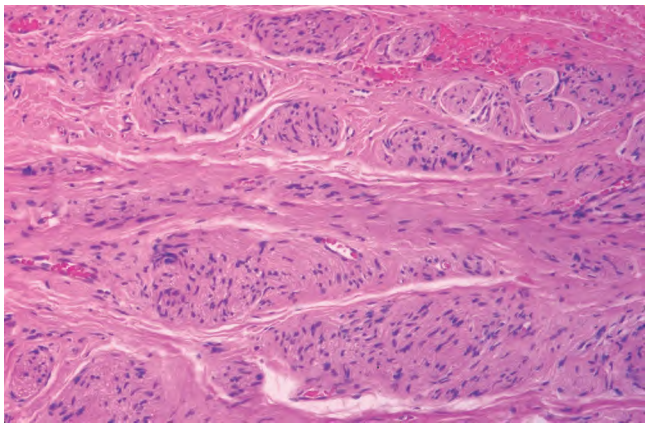
The **traumatic neuroma** is not a true neoplasm but a reactive proliferation of neural tissue after transection or other damage of a nerve bundle. After a nerve has been damaged or severed, the proximal portion attempts to regenerate and reestablish innervation of the distal segment by the growth of axons through tubes of proliferating Schwann cells. If these regenerating elements encounter scar tissue or otherwise cannot reestablish innervation, then a tumorlike mass may develop at the site of injury.

Clinical and Radiographic Features

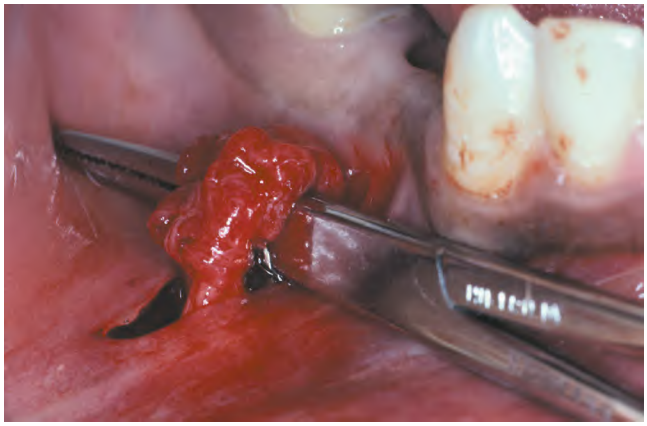
Traumatic neuromas of the oral mucosa are typically smooth-surfaced, nonulcerated nodules. They can develop



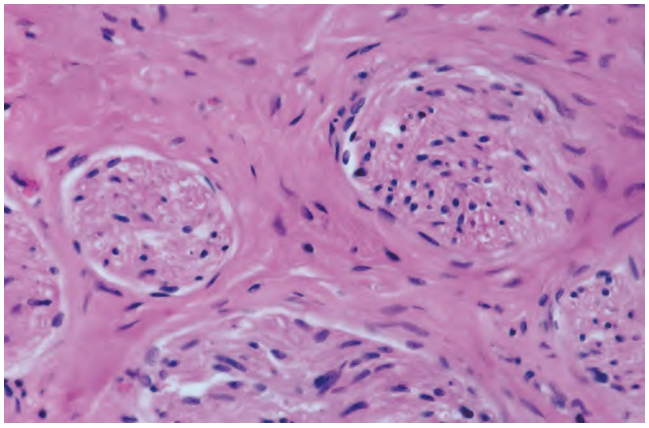
• **Fig. 12-51 Traumatic Neuroma.** Painful nodule of the mental nerve as it exits the mental foramen *(arrow).*



• **Fig. 12-53 Traumatic Neuroma.** Low-power view showing the haphazard arrangement of nerve bundles within the background fibrous connective tissue.



• **Fig. 12-52 Traumatic Neuroma.** Note the irregular nodular proliferation along the mental nerve that is being exposed at the time of surgery.



• **Fig. 12-54 Traumatic Neuroma.** High-power view showing cross-sectioned nerve bundles within dense fibrous connective tissue.

at any location but are most common in the mental foramen area, tongue, and lower lip (Figs. 12-51 and 12-52). A history of trauma often can be elicited; some lesions arise subsequent to tooth extraction or other surgical procedures. Intraosseous traumatic neuromas may demonstrate a radiolucent defect on oral radiographs. Examples also may occur at other head and neck sites; it has been estimated that traumatic neuromas of the greater auricular nerve develop in 5% to 10% of patients undergoing surgery for pleomorphic adenomas of the parotid gland.

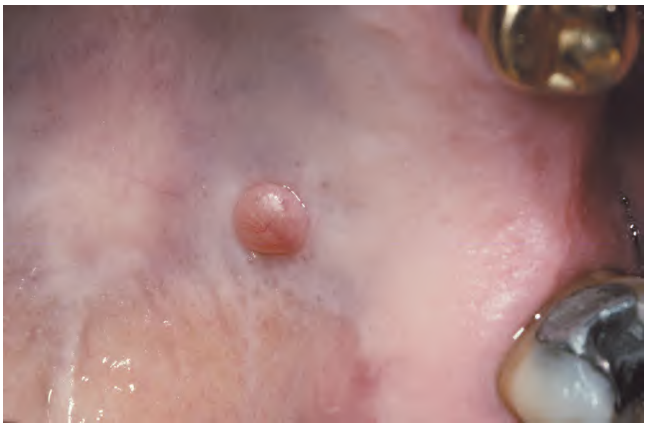
Traumatic neuromas can occur at any age, but they are diagnosed most often in middle-aged adults. They appear to be slightly more common in women. Many traumatic neuromas are associated with altered nerve sensations that can range from anesthesia to dysesthesia to overt pain. Although pain has been traditionally considered a hallmark of this lesion, studies indicate that only one-fourth to one-third of oral traumatic neuromas are painful. This pain can be intermittent or constant and ranges from mild tenderness or burning to severe radiating pain. Neuromas of the mental nerve are frequently painful, especially when impinged on by a denture or palpated.

Histopathologic Features

Microscopic examination of traumatic neuromas shows a haphazard proliferation of mature, myelinated and unmyelinated nerve bundles within a fibrous connective tissue stroma that ranges from densely collagenized to myxomatous in nature (Figs. 12-53 and 12-54). An associated mild chronic inflammatory cell infiltrate may be present. Traumatic neuromas with inflammation are more likely to be painful than those without significant inflammation.

Treatment and Prognosis

The treatment of choice for the patient with a traumatic neuroma is surgical excision, including a small portion of the involved proximal nerve bundle. Most lesions do not recur; in some cases, however, the pain persists or returns at a later date.



• **Fig. 12-55 Palisaded Encapsulated Neuroma.** Small, painless nodule of the lateral hard palate.

◆ PALISADED ENCAPSULATED NEUROMA (SOLITARY CIRCUMSCRIBED NEUROMA)

The **palisaded encapsulated neuroma** is a benign neural tumor with distinctive clinical and histopathologic features. It represents one of the more common superficial nerve tumors, especially in the head and neck region. The cause is uncertain, but some authors have speculated that trauma may play an etiologic role; the tumor is generally considered to represent a reactive lesion rather than a true neoplasm.

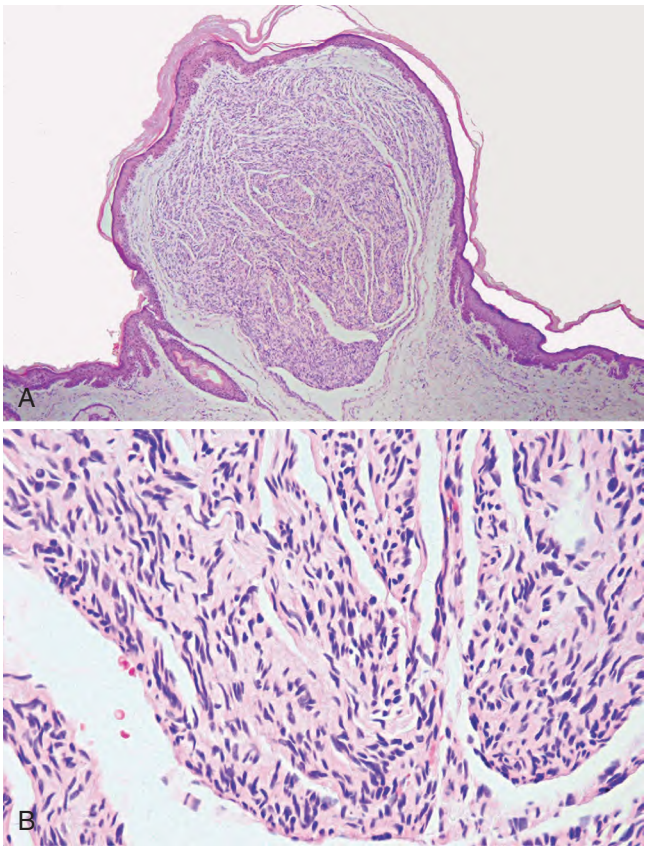
Clinical Features

The palisaded encapsulated neuroma shows a striking predilection for the face, which accounts for approximately 90% of reported cases. The nose and cheek are the most common specific sites. The lesion is most frequently diagnosed between the fifth and seventh decades of life, although the tumor often has been present for many months or years. It is a smooth-surfaced, painless, dome-shaped papule or nodule that is usually less than 1 cm in diameter.

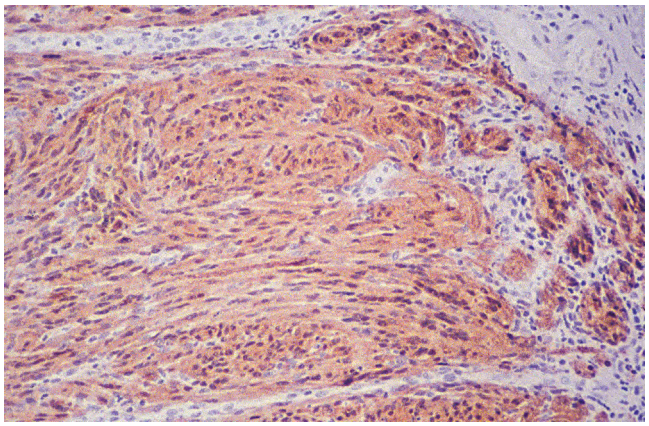
Oral palisaded encapsulated neuromas are not uncommon, although many are probably diagnosed microscopically as neurofibromas or schwannomas. The lesion appears most frequently on the hard palate (Fig. 12-55), gingiva, and labial mucosa, although it also may occur in other oral locations.

Histopathologic Features

Palisaded encapsulated neuromas appear well circumscribed and often encapsulated (Fig. 12-56), although this capsule may be incomplete, especially along the superficial aspect of the tumor. Some lesions have a lobulated appearance. The tumor consists of moderately cellular interlacing fascicles of spindle cells that are consistent with Schwann cells. The nuclei are characteristically wavy and pointed, with no significant pleomorphism or mitotic activity. Although the nuclei show a similar parallel orientation within the fascicles, the more definite palisading and Verocay bodies typical of the Antoni A tissue of a schwannoma are usually not seen. Special stains reveal the presence of numerous axons within the tumor (a feature not seen in schwannoma) and the cells show a positive immunohistochemical reaction for S-100 protein (Fig. 12-57). Negative immunoreactivity for



• **Fig. 12-56 Palisaded Encapsulated Neuroma. A,** Low-power view showing a well-circumscribed, nodular proliferation of neural tissue. **B,** Higher-power view demonstrating spindle cells with wavy nuclei.



• **Fig. 12-57 Palisaded Encapsulated Neuroma.** Immunohistochemical reaction demonstrating spindle-shaped cells that are strongly positive for S-100 protein.

glial fibrillary acidic protein (GFAP) may be helpful in distinguishing the palisaded encapsulated neuroma from other neural tumors. Because the tumor is not always encapsulated and the cells are usually not truly palisaded, some pathologists prefer **solitary circumscribed neuroma** as a better descriptive term for this lesion.

Treatment and Prognosis

The treatment for the palisaded encapsulated neuroma consists of conservative local surgical excision. Recurrence is rare. However, specific recognition of this lesion is important because it is not associated with neurofibromatosis or multiple endocrine neoplasia (MEN) type 2B.

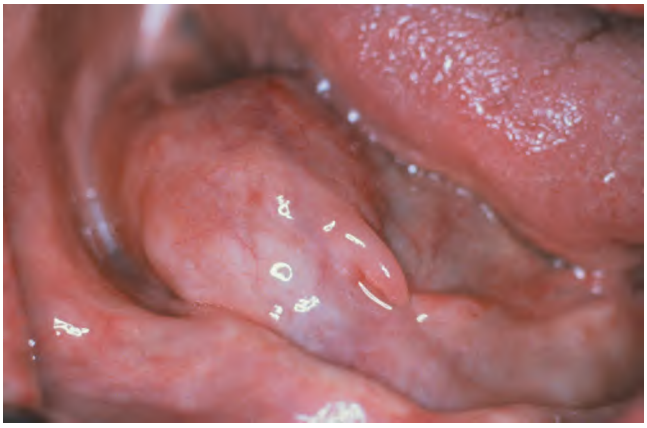
◆ SCHWANNOMA (NEURILEMOMA)

The **schwannoma** is a benign neural neoplasm of Schwann cell origin. It is relatively uncommon, although 25% to 48% of all cases occur in the head and neck region. Bilateral schwannomas of the auditory-vestibular nerve are a characteristic feature of the hereditary condition, **neurofibromatosis type II (NF2).** Multiple schwannomas also occur in another genetic disorder known as **schwannomatosis** (Table 12-1).

Clinical and Radiographic Features

The solitary schwannoma is a slow-growing, encapsulated tumor that typically arises in association with a nerve trunk. As it grows, it pushes the nerve aside. Usually, the mass is asymptomatic, although tenderness or pain may occur in some instances. The lesion is most common in young and middle-aged adults and can range from a few millimeters to several centimeters in size.

The tongue is the most common location for oral schwannomas, although the tumor can occur almost anywhere in the mouth (Fig. 12-58). On occasion, the tumor arises centrally within bone and may produce bony expansion. Intraosseous examples are most common in the posterior mandible and usually appear as either unilocular or multilocular radiolucencies on radiographs. Pain and paresthesia are not unusual for intrabony tumors.



• **Fig. 12-58 Schwannoma.** Nodular mass in the floor of the mouth. (Courtesy of Dr. Art A. Gonty.)

NF2 is an autosomal dominant condition caused by a mutation of a tumor suppressor gene *(NF2)* on chromosome 22, which codes for a protein known as *merlin.* In addition to bilateral schwannomas ("acoustic neuromas") of the vestibular nerve, patients also develop schwannomas of peripheral nerves, plus meningiomas and gliomas of the central nervous system (CNS). On occasion, neurofibromas and *café au lait* skin pigmentation may be observed. Characteristic symptoms include progressive sensorineural deafness, dizziness, and tinnitus.

Schwannomatosis is related to a mutation of the *SMARCB1* gene on chromosome 22. Patients develop multiple painful schwannomas at various sites but without involvement of the auditory-vestibular nerve.

Histopathologic Features

The schwannoma is usually an encapsulated tumor that demonstrates two microscopic patterns in varying amounts: 1) **Antoni A** and 2) **Antoni B.** Streaming fascicles of spindle-shaped Schwann cells characterize Antoni A tissue. These cells often form a palisaded arrangement around central acellular, eosinophilic areas known as **Verocay bodies** (Fig. 12-59). These Verocay bodies consist of reduplicated basement membrane and cytoplasmic processes. Antoni B tissue is less cellular and less organized; the spindle cells are randomly arranged within a loose, myxomatous stroma. Typically, neurites cannot be demonstrated within the tumor mass. The tumor cells will show a diffuse, positive immunohistochemical reaction for S-100 protein.

Degenerative changes can be seen in some older tumors **(ancient schwannomas).** These changes consist of hemorrhage, hemosiderin deposits, inflammation, fibrosis, and nuclear atypia. However, these tumors are still benign, and the pathologist must be careful not to mistake these alterations for evidence of a sarcoma. Another rare variant is the **plexiform schwannoma,** which is characterized grossly and microscopically by a multinodular, plexiform growth pattern. Such tumors occasionally are associated with NF2 or schwannomatosis.

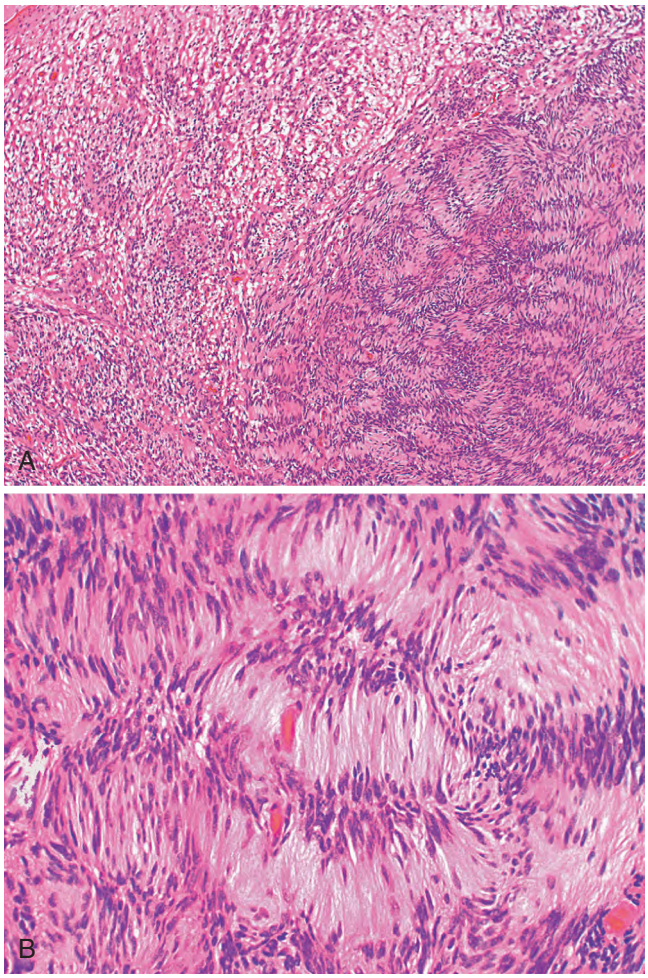
Treatment and Prognosis

The solitary schwannoma is treated by surgical excision, and the lesion should not recur. Malignant transformation does not occur or is extremely rare.

Vestibular schwannomas in patients with NF2 are difficult to manage. Surgical removal is indicated for large symptomatic tumors, but this often results in deafness and risks facial nerve damage. Stereotactic radiosurgery may be considered for older adult or frail patients, as well as for individuals who decline traditional surgery.

TABLE 12-1 Hereditary Neural and Neuroendocrine Syndromes

Syndrome	Inheritance Pattern	Gene Mutation	Frequency	Common or Significant Clinical Features
Neurofibromatosis type I (NF1)	Autosomal dominant	*NF1* gene (chromosome 17q11.2)	1 in 2,500 to 3,000 births	Neurofibromas (especially plexiform type) *Café au lait* pigmentation Axillary and groin freckling Lisch nodules of the iris Optic glioma Epilepsy Hypertension Malignant peripheral nerve sheath tumor (5% of patients)
Neurofibromatosis type II (NF2)	Autosomal dominant	*NF2* gene (chromosome 22q12.2)	1 in 25,000 to 87,000 births	Bilateral schwannomas ("acoustic neuromas") of the vestibular nerve (cranial nerve VIII) Cranial and spinal meningiomas Other cranial nerve and spinal schwannomas Cutaneous schwannomas Subcapsular cataracts *Café au lait* pigmentation (less common than in NF1) Cutaneous neurofibromas (uncommon)
Schwannomatosis	Autosomal dominant (although most cases have been sporadic)	*SMARCB1* gene (chromosome 22q11)	1 in 40,000 births	Multiple noncutaneous schwannomas (without involvement of cranial nerve VIII) Chronic pain associated with schwannomas
Multiple endocrine neoplasia type 1 (MEN 1)	Autosomal dominant	*MEN1* gene (chromosome 11q13)	1 in 20,000 to 40,000 births	Parathyroid tumors Pancreatic islet tumors Anterior pituitary tumors Adrenocortical tumors
Medullary thyroid carcinoma (MTC) syndrome	Autosomal dominant	*RET* proto-oncogene (chromosome 10q11.2; various codons)	1 in 114,000 to 1,000,000 births	MTC Low or no risk for other neuroendocrine tumors
Multiple endocrine neoplasia type 2A (MEN 2A)	Autosomal dominant	*RET* proto-oncogene (chromosome 10q11.2; most frequently codon 634)	1 in 40,000 to 72,000 births	MTC Pheochromocytoma Parathyroid adenoma
Multiple endocrine neoplasia type 2B (MEN 2B)	Autosomal dominant	*RET* proto-oncogene (chromosome 10q.11.2; most frequently codon 918)	1 in 400,000-4,000,000 births	MTC Pheochromocytoma Mucosal neuromas Marfanoid habitus



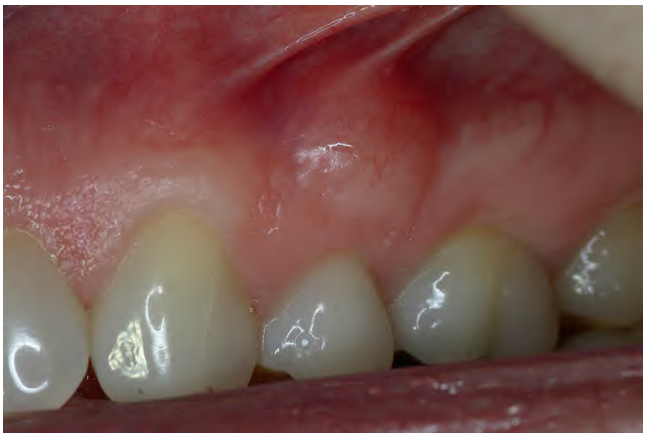
• **Fig. 12-59 Schwannoma. A,** Low-power view showing well-organized Antoni A tissue *(right)* with adjacent myxoid and less organized Antoni B tissue *(left).* **B,** The Schwann cells of the Antoni A tissue form a palisaded arrangement around acellular zones known as *Verocay bodies.*

◆ NEUROFIBROMA

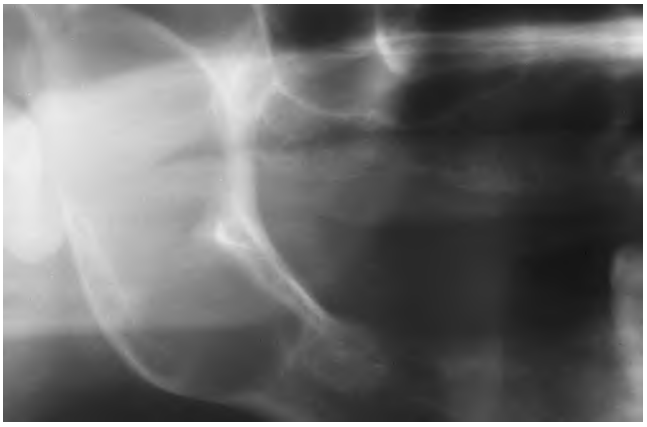
The **neurofibroma** is the most common type of peripheral nerve neoplasm. It arises from a mixture of cell types, including Schwann cells and perineural fibroblasts.

Clinical and Radiographic Features

Neurofibromas can arise as solitary tumors or be a component of neurofibromatosis (see page 495). Solitary tumors are most common in young adults and present as slow-growing, soft, painless lesions that vary in size from small nodules to larger masses. The skin is the most frequent location for neurofibromas, but lesions of the oral cavity are not uncommon (Fig. 12-60). The tongue and buccal mucosa are the most common intraoral sites. On rare occasions, the tumor can arise centrally within bone, where it may produce a well-demarcated or poorly defined unilocular or multilocular radiolucency (Fig. 12-61).



• **Fig. 12-60 Neurofibroma.** Smooth-surfaced, nodular mass of the maxillary gingiva and alveolar mucosa. (Courtesy of Dr. Neal Lemmerman.)



• **Fig. 12-61 Neurofibroma.** Intraosseous tumor filling the right mandibular ramus. (Courtesy of Dr. Paul Allen.)

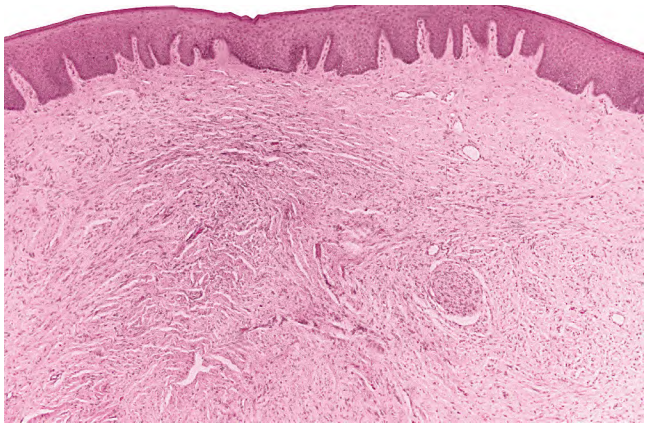
Histopathologic Features

The solitary neurofibroma often is well circumscribed, especially when the proliferation occurs within the perineurium of the involved nerve. Tumors that proliferate outside the perineurium may not appear well demarcated and tend to blend with the adjacent connective tissues.

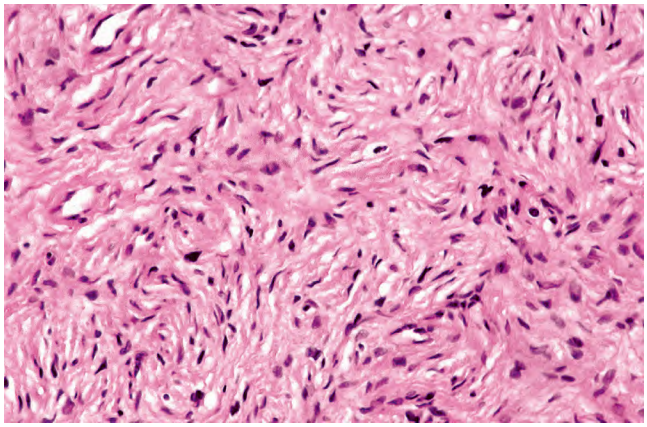
The tumor is composed of interlacing bundles of spindle-shaped cells that often exhibit wavy nuclei (Figs. 12-62 and 12-63). These cells are associated with delicate collagen bundles and variable amounts of myxoid matrix. Mast cells tend to be numerous and can be a helpful diagnostic feature. Sparsely distributed small axons usually can be demonstrated within the tumor tissue by using silver stains. Immunohistochemically, the tumor cells show a scattered, positive reaction for S-100 protein.

Treatment and Prognosis

The treatment for solitary neurofibromas is local surgical excision, and recurrence is rare. Any patient with a lesion that is diagnosed as a neurofibroma should be evaluated



• **Fig. 12-62 Neurofibroma.** Low-power view showing a cellular tumor mass below the epithelial surface.



• **Fig. 12-63 Neurofibroma.** High-power view showing spindle-shaped cells with wavy nuclei.

clinically for the possibility of **neurofibromatosis** (see next topic). Malignant transformation of solitary neurofibromas can occur, although the risk appears to be remote, especially compared with that in patients with neurofibromatosis.

◆ NEUROFIBROMATOSIS TYPE I (VON RECKLINGHAUSEN DISEASE OF THE SKIN)

Neurofibromatosis type I is a relatively common hereditary condition that is estimated to occur in one of every 2,500 to 3,000 births (see Table 12-1, page 493). At least eight forms of neurofibromatosis have been recognized, but the most common form is **neurofibromatosis type I (NF1),** which is discussed here. This form of the disease, also known as **von Recklinghausen disease of the skin,** accounts for 85% to 97% of neurofibromatosis cases and is inherited as an autosomal dominant trait (although 50% of all patients have no family history and apparently represent new mutations). It is caused by a variety of mutations of the *NF1* gene, which is located on chromosome region 17q11.2 and is responsible for a tumor suppressor protein product known as *neurofibromin.*

• BOX 12-1 Diagnostic Criteria for Neurofibromatosis Type I (NF1)

The diagnostic criteria are met if a patient has two or more of the following features:

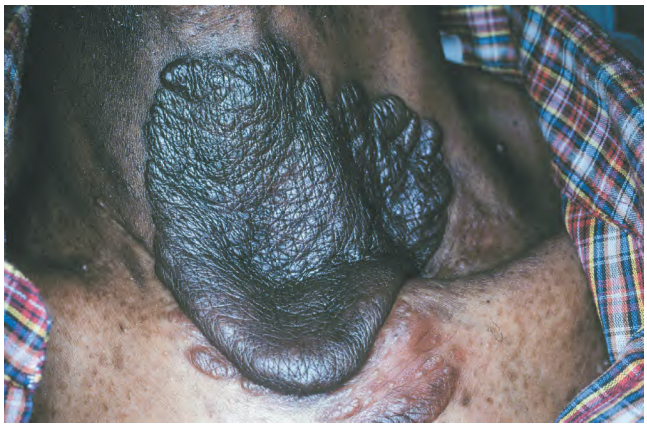
1. Six or more *café au lait* macules more than 5 mm in greatest diameter in prepubertal persons and more than 15 mm in greatest diameter in postpubertal persons
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, or offspring) with NF1, based on the previously mentioned criteria

• **Fig. 12-64 Neurofibromatosis Type I.** Multiple tumors of the trunk and arms.

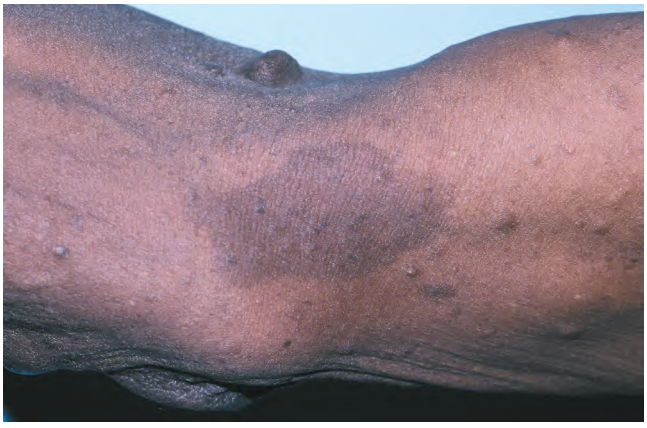
Clinical and Radiographic Features

The diagnostic criteria for NF1 are summarized in Box 12-1. Patients have multiple neurofibromas that can occur anywhere in the body but are most common on the skin. The clinical appearance can vary from small papules to larger soft nodules to massive baggy, pendulous masses **(elephantiasis neuromatosa)** on the skin (Figs. 12-64 and 12-65). The plexiform variant of neurofibroma, which feels like a "bag of worms," is considered pathognomonic for NF1. The tumors may be present at birth, but they often begin to appear during puberty and may continue to develop slowly throughout adulthood. Accelerated growth may be seen during pregnancy. There is a wide variability in the expression of the disease. Some patients have only a few neurofibromas; others have literally hundreds or thousands of tumors. However, two-thirds of patients have relatively mild disease.

Another highly characteristic feature is the presence of ***café au lait*** (coffee with milk) pigmentation on the skin (Fig. 12-66). These spots occur as yellow-tan to dark-brown



• **Fig. 12-65 Neurofibromatosis Type I.** Baggy, pendulous neurofibroma of the lower neck.

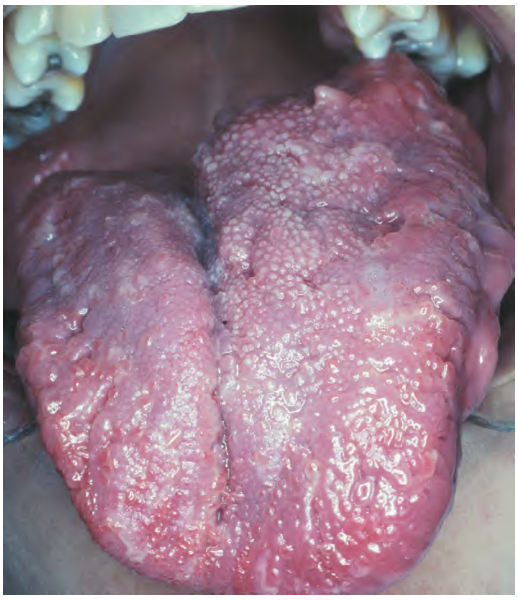


• **Fig. 12-66 Neurofibromatosis Type I.** Same patient as depicted in Fig. 12-64. Note the *café au lait* pigmentation on the arm.

macules that vary in diameter from 1 to 2 mm to several centimeters. In NF1, this pigmentation typically has a smooth edge ("coast of California"), in contrast to the irregular border ("coast of Maine") of the *café au lait* spots that may occur with polyostotic fibrous dysplasia (see page 593). The pigmentation usually is present at birth or it may develop during the first year of life. Freckling of the axilla **(Crowe sign)** or of other intertriginous zones is also a highly suggestive sign.

Lisch nodules, translucent brown-pigmented spots on the iris, are found in nearly all affected individuals. The most common general medical problem is hypertension, which may develop secondary to coarctation of the aorta, pheochromocytoma, or renal artery stenosis. Other possible abnormalities include CNS tumors, macrocephaly, mental deficiency, seizures, short stature, and scoliosis.

Studies indicate that oral manifestations may occur in as many as 72% to 92% of cases, especially if a detailed clinical and radiographic examination is performed. The most commonly described finding is enlargement of the fungiform papillae, which has been reported in up to 50% of patients; however, the specificity of this finding for neurofibromatosis is unknown. Only about 25% to 37% of patients will develop actual intraoral neurofibromas (Fig. 12-67). Radiographic findings may include enlargement of the mandibular foramen, enlargement or branching of the mandibular canal, increased bone density, concavity of the medial surface of the ramus, and increase in dimension of the coronoid notch. Cephalometric analysis often shows a short length of the mandible, maxilla, and cranial base.



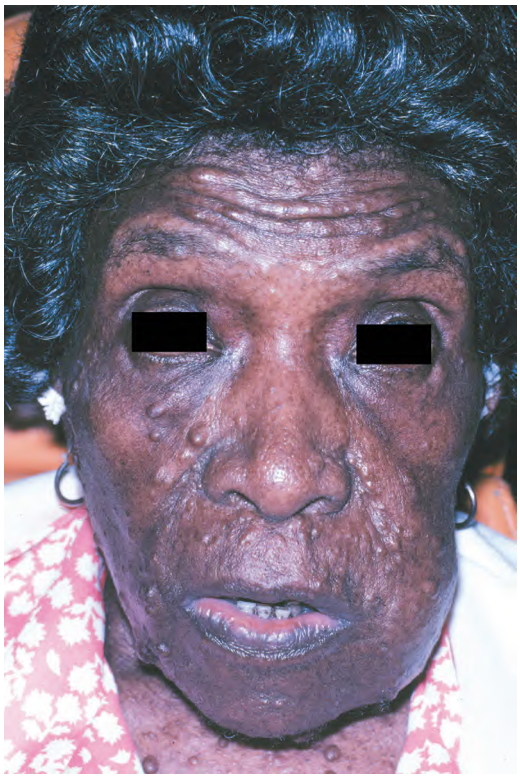
• **Fig. 12-67 Neurofibromatosis Type I.** Diffuse neurofibroma resulting in unilateral enlargement of the tongue.

Several unusual clinical variants of NF1 have been described. On occasion, the condition can include unilateral enlargement that mimics hemifacial hyperplasia (see page 35). In addition, several patients with NF1 have been described with associated Noonan syndrome or with central giant cell granulomas of the jaw.

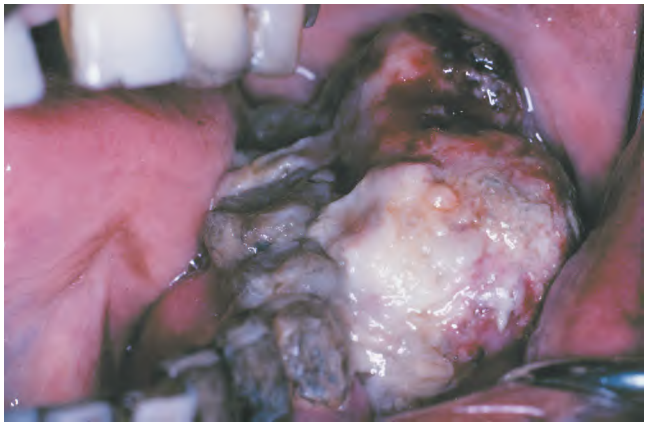
Treatment and Prognosis

There is no specific therapy for NF1, and treatment often is directed toward prevention or management of complications. Facial neurofibromas can be removed for cosmetic purposes. Carbon dioxide (CO_2) laser and dermabrasion have been used successfully for extensive lesions. NF1 patients with prominent hemifacial enlargement may require more significant cosmetic remodeling surgery.

One of the most feared complications is the development of cancer, most often a **malignant peripheral nerve sheath tumor (neurofibrosarcoma; malignant schwannoma),** which has been reported to occur in about 5% of cases. These tumors are most common on the trunk and extremities, although head and neck involvement is occasionally seen (Figs. 12-68 to 12-70). The 5-year survival rate for malignant peripheral nerve sheath tumors associated with NF1 is 35% to 54%. Other malignancies also have been associated with NF1, including CNS tumors, pheochromocytoma, leukemia, rhabdomyosarcoma, and Wilms tumor. The average lifespan of individuals with NF1 is 8 to 15 years



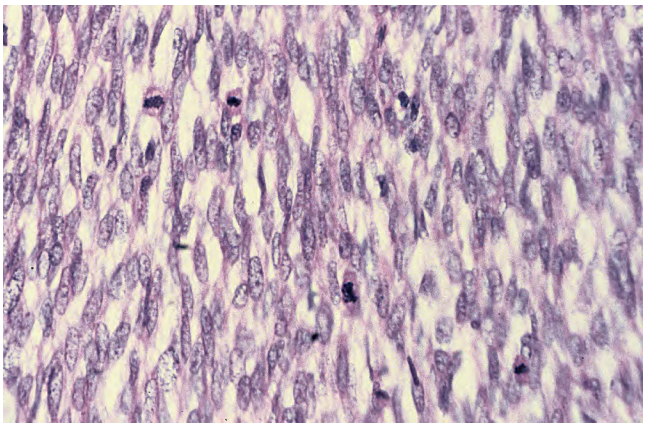
• **Fig. 12-68 Neurofibromatosis Type I.** Malignant peripheral nerve sheath tumor of the left cheek in a patient with type I neurofibromatosis. (From Neville BW, Hann J, Narang R, et al: Oral neurofibrosarcoma associated with neurofibromatosis type I, *Oral Surg Oral Med Oral Pathol* 72:456-461, 1991.)



• **Fig. 12-69 Neurofibromatosis Type I.** Same patient as depicted in Fig. 12-68. Note the intraoral appearance of malignant peripheral nerve sheath tumor of the mandibular buccal vestibule. The patient eventually died of this tumor. (From Neville BW, Hann J, Narang R, et al: Oral neurofibrosarcoma associated with neurofibromatosis type I, *Oral Surg Oral Med Oral Pathol* 72:456-461, 1991.)

less than the general population, mostly related to vascular disease and malignant neoplasms.

In recent years, there has been considerable interest in Joseph (not John) Merrick, the so-called Elephant Man. Although Merrick once was mistakenly considered to have NF1, it is now generally accepted that his horribly disfigured appearance was not because of neurofibromatosis, but



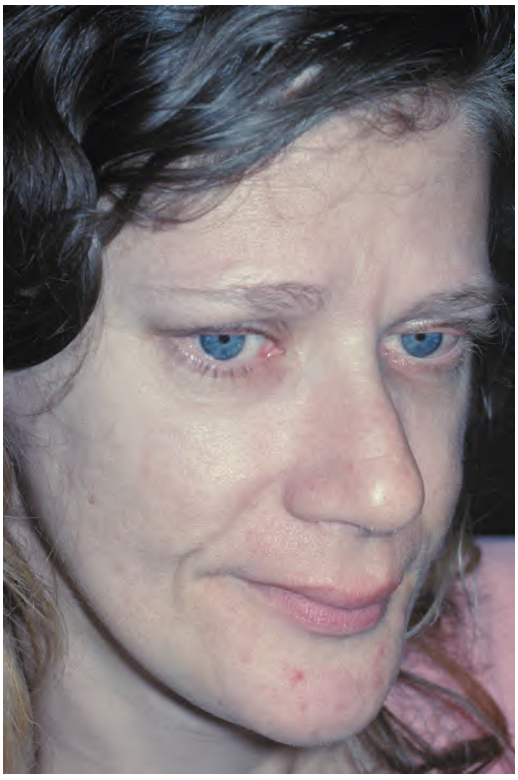
• **Fig. 12-70 Malignant Peripheral Nerve Sheath Tumor.** High-power view of an intraoral tumor that developed in a patient with neurofibromatosis type I. There is a cellular spindle cell proliferation with numerous mitotic figures.

that he most likely had a rare condition known as **Proteus syndrome.** Because patients with NF1 may fear acquiring a similar clinical appearance, they should be reassured that they have a different condition. The phrase "Elephant Man disease" is incorrect and misleading, and it should be avoided. Genetic counseling is extremely important for all patients with neurofibromatosis.

◆ MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

The **multiple endocrine neoplasia (MEN) syndromes** are a group of rare autosomal dominant conditions characterized by tumors or hyperplasias of the neuroendocrine tissues (see Table 12-1, page 493). MEN type 1 is caused by mutations of the *MEN1* gene located on chromosome 11. Affected individuals can develop a variety of tumors of the parathyroid glands, pancreatic islets, anterior pituitary gland, and adrenal cortex. MEN type 2 encompasses a family of disorders (familial medullary thyroid carcinoma [MTC] syndrome, MEN type 2A, and MEN type 2B) that are characterized by the development of MTC. These three conditions are caused by mutations at various sites of the RET proto-oncogene on chromosome 10. Patients with familial MTC syndrome develop MTC but are not at increased risk for other neuroendocrine tumors. Patients with MEN type 2A are at increased risk for MTC (over 95% of patients), adrenal pheochromocytomas (50% of patients), and primary hyperparathyroidism (20% to 30% of patients).

Over 95% of cases of MEN type 2B are caused by a germline mutation at codon 918 (M918T) of the RET proto-oncogene, although a few examples have been described with a mutation at codon 883 (A883F). In addition to MTC and pheochromocytomas, patients develop mucosal neuromas that especially involve the oral mucous membranes. Because oral manifestations are prominent



• **Fig. 12-71 Multiple Endocrine Neoplasia (MEN) Type 2B.** Note the narrow face and eversion of the upper eyelids.

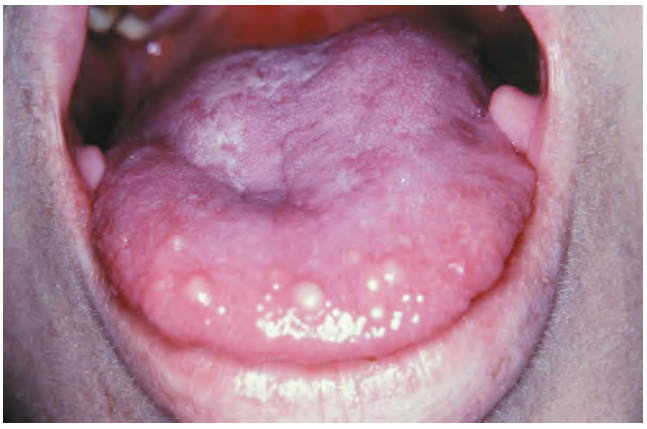
only in MEN type 2B, the remainder of the discussion is limited to this condition.

Clinical Features

Patients with MEN type 2B usually have a marfanoid body build characterized by thin, elongated limbs with muscle wasting. The face is narrow, but the lips are characteristically thick and protuberant because of the diffuse proliferation of nerve bundles. The upper eyelid sometimes is everted because of thickening of the tarsal plate (Fig. 12-71). Small, pedunculated neuromas may be observable on the conjunctiva, eyelid margin, or cornea.

Oral mucosal neuromas are usually the first sign of the condition and may be detectable during infancy. These neuromas appear as soft, painless papules or nodules that principally affect the lips and anterior tongue but also may be seen on the buccal mucosa, gingiva, and palate (Fig. 12-72). Bilateral neuromas of the commissural mucosa are highly characteristic.

Pheochromocytomas of the adrenal glands develop in at least 50% of all patients and become more prevalent with increasing age. These neuroendocrine tumors are frequently bilateral or multifocal. The tumor cells secrete catecholamines, which result in symptoms such as profuse sweating, intractable diarrhea, headaches, flushing, heart palpitations, and severe hypertension. Also, approximately 40% of patients with MEN type 2B will develop ganglioneuromatosis of the gastrointestinal tract, which can result in



• **Fig. 12-72 Multiple Endocrine Neoplasia (MEN) Type 2B.** Multiple neuromas along the anterior margin of the tongue and bilaterally at the commissures. (Courtesy of Dr. Emmitt Costich.)

abdominal distention, megacolon, constipation, and diarrhea.

The most significant aspect of this condition is the development of MTC, which occurs in virtually all cases. This aggressive tumor arises from the parafollicular cells (C cells) of the thyroid gland, which are responsible for calcitonin production. MTC silently develops early in life and, without prophylactic thyroidectomy before 1 year of age, most patients will develop metastatic tumor during childhood or adolescence.

Laboratory Values

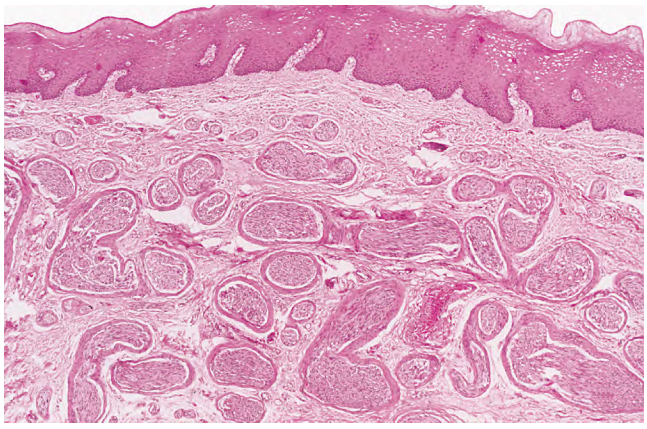
If MTC is present, then serum or urinary levels of calcitonin are elevated. An increase in calcitonin levels may herald the onset of the tumor, and calcitonin also can be monitored to detect local recurrences or metastases after treatment. Pheochromocytomas may result in increased levels of urinary vanillylmandelic acid (VMA) and increased epinephrine-to-norepinephrine ratios.

Histopathologic Features

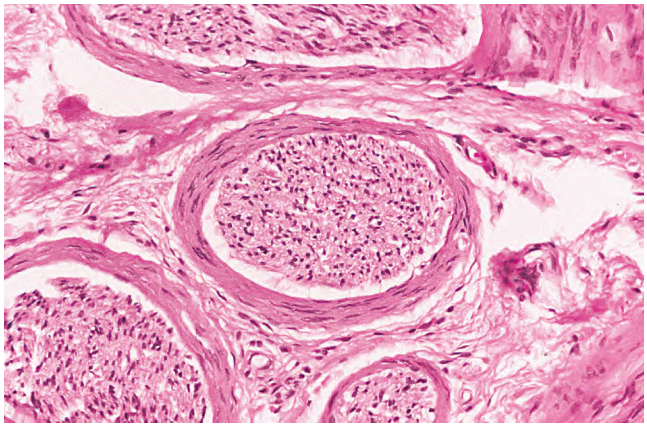
The mucosal neuromas are characterized by marked hyperplasia of nerve bundles in an otherwise normal or loose connective tissue background (Figs. 12-73 and 12-74). Prominent thickening of the perineurium is typically seen.

Treatment and Prognosis

The prognosis for patients with MEN type 2B centers on early recognition of the oral features. Because of the extremely poor prognosis for MTC, the thyroid gland should be removed as soon as possible—preferably within the first year of life. The average age of death from this neoplasm is 21 years. It has been suggested that patients with the A883F mutation of the RET proto-oncogene may develop a less aggressive form of MTC than patients with the M918T mutation. Patients also should be observed for the development of pheochromocytomas because they may



• **Fig. 12-73 Multiple Endocrine Neoplasia (MEN) Type 2B.** Low-power view of an oral mucosal neuroma showing marked hyperplasia of nerve bundles.



• **Fig. 12-74 Multiple Endocrine Neoplasia (MEN) Type 2B.** High-power view of the same neuroma as depicted in Fig. 12-73. Note the prominent thickening of the perineurium.

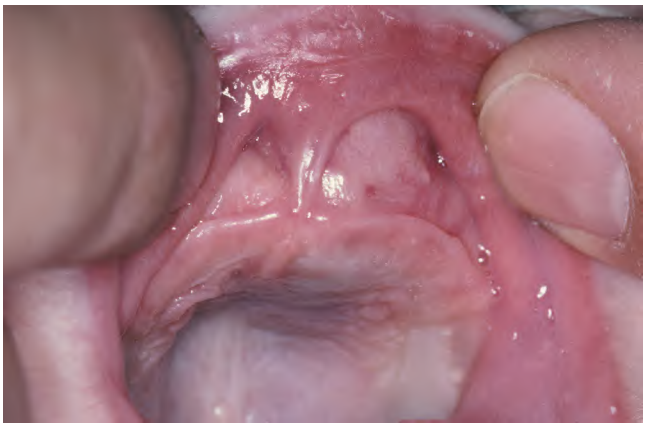
result in a life-threatening hypertensive crisis, especially if surgery with general anesthesia is performed.

◆ MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY

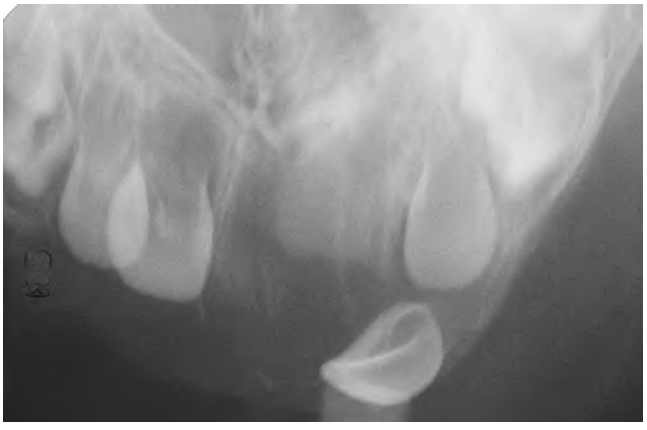
The **melanotic neuroectodermal tumor of infancy** is a rare pigmented neoplasm that usually occurs during the first year of life. It is generally accepted that this lesion is of neural crest origin. In the past, however, a number of tissues were suggested as possible sources of this tumor. These included odontogenic epithelium and retina, which resulted in various older terms for this entity, such as **pigmented ameloblastoma, retinal anlage tumor,** and **melanotic progonoma.** Because these names are inaccurate, however, they should no longer be used.

Clinical and Radiographic Features

Melanotic neuroectodermal tumor of infancy almost always develops in young children during the first year of life; only



• **Fig. 12-75 Melanotic Neuroectodermal Tumor of Infancy.** Infant with an expansile mass of the anterior maxilla. (From Steinberg B, Shuler C, Wilson S: Melanotic neuroectodermal tumor of infancy: evidence for multicentricity, *Oral Surg Oral Med Oral Pathol* 66:666-669, 1988.)



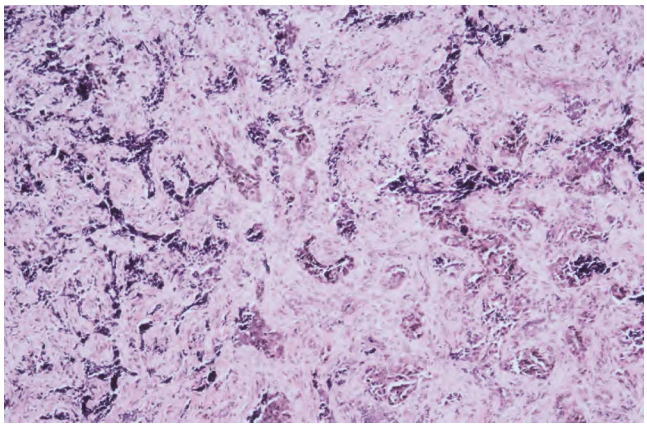
• **Fig. 12-76 Melanotic Neuroectodermal Tumor of Infancy.** Radiolucent destruction of the anterior maxilla associated with displacement of the developing teeth. (Courtesy of Dr. Len Morrow.)

9% of cases are diagnosed after the age of 12 months. There is a striking predilection for the maxilla, which accounts for 69% of reported cases. Less frequently reported sites include the skull (11%), epididymis and testis (9%), mandible (6%), and brain (4%). A slight male predilection has been noted.

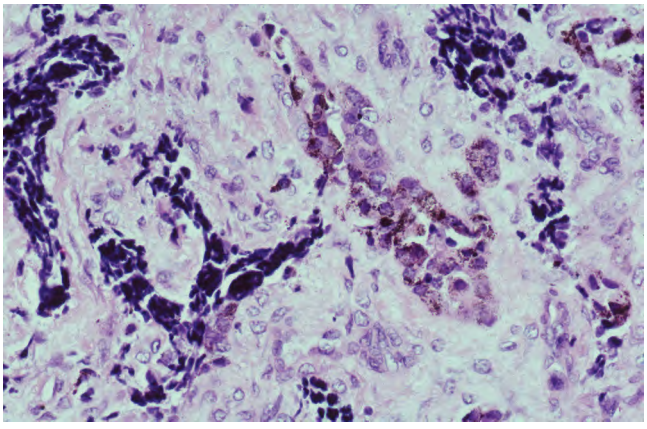
The lesion is most common in the anterior region of the maxilla, where it classically appears as a rapidly expanding mass that is frequently blue or black (Fig. 12-75). The tumor often destroys the underlying bone and may be associated with displacement of the developing teeth (Fig. 12-76). In some instances, there may be an associated osteogenic reaction, which exhibits a "sun ray" radiographic pattern that can be mistaken for osteosarcoma.

Laboratory Values

High urinary levels of vanillylmandelic acid (VMA) often are found in patients with melanotic neuroectodermal tumor of infancy. These levels may return to normal once



• **Fig. 12-77 Melanotic Neuroectodermal Tumor of Infancy.** Low-power view showing nests of epithelioid cells within a fibrous stroma.



• **Fig. 12-78 Melanotic Neuroectodermal Tumor of Infancy.** High-power view of a tumor nest demonstrating two cell types: 1) small, hyperchromatic round cells and 2) larger epithelioid cells with vesicular nuclei. Some stippled melanin pigment is also present.

the tumor has been resected. This finding supports the hypothesis of neural crest origin because other tumors from this tissue (e.g., pheochromocytoma and neuroblastoma) often secrete norepinephrine-like hormones that are metabolized to VMA and excreted in the urine.

Histopathologic Features

The tumor consists of a biphasic population of cells that form nests, tubules, or alveolar structures within a dense, collagenous stroma (Figs. 12-77 and 12-78). The alveolar and tubular structures are lined by cuboidal epithelioid cells that demonstrate vesicular nuclei and granules of dark-brown melanin pigment. The second cell type is neuroblastic in appearance and consists of small, round cells with hyperchromatic nuclei and little cytoplasm. These cells grow in loose nests and are frequently surrounded by the larger pigment-producing cells. Mitotic figures are rare.

Because of the tumor's characteristic microscopic features, immunohistochemistry usually is not essential to establish the diagnosis. However, the larger epithelioid cells typically are positive for cytokeratin, HMB-45, and neuron-specific enolase. In addition, the smaller cells usually are positive for neuron-specific enolase and CD56, and sometimes they will express other neuroendocrine markers such as synaptophysin.

Treatment and Prognosis

Despite their rapid growth and potential to destroy bone, most melanotic neuroectodermal tumors of infancy are benign. The lesion is best treated by surgical removal. Some clinicians prefer simple curettage, although others advocate that a 5-mm margin of normal tissue be included with the specimen. Recurrence of the tumor has been reported in about 20% of cases. In addition, about 7% of reported cases, mostly from the brain or skull, have acted in a malignant fashion, resulting in metastasis and death. Although this estimation of 7% is probably high (because unusual malignant cases are more likely to be reported), it underscores the potentially serious nature of this tumor and the need for careful clinical evaluation and follow-up of affected patients.

◆ PARAGANGLIOMA (CAROTID BODY TUMOR; CHEMODECTOMA; GLOMUS JUGULARE TUMOR; GLOMUS TYMPANICUM TUMOR)

The paraganglia are specialized tissues of neural crest origin that are associated with the autonomic nerves and ganglia throughout the body. Some of these cells act as chemoreceptors, such as the carotid body (located at the carotid bifurcation), which can detect changes in blood pH or oxygen tension and subsequently cause changes in respiration and heart rate. Tumors that arise from these structures are collectively known as **paragangliomas,** with the term preferably preceded by the anatomic site at which they are located. Therefore, tumors of the carotid body are appropriately known as **carotid body paragangliomas (carotid body tumors).** Other examples in the head and neck include **jugular paragangliomas (glomus jugulare tumors), tympanic paragangliomas (glomus tympanicum tumors),** and **vagal paragangliomas.**

Most head and neck paragangliomas occur as sporadic tumors, although 30% of cases are associated with heritable germline mutations of genes that encode for subunits or cofactors of succinate dehydrogenase (mitochondrial complex II). Four hereditary paraganglioma syndromes (PGL1-4) have been recognized, all of which show an autosomal dominant inheritance pattern. However, PGL1 and PGL2 exhibit an unusual "parent-of-origin—dependent effect" consistent with maternal imprinting of the disease gene. Although the gene can be inherited from either the father or mother, only paternal transmission will result in development of tumors in the offspring. Therefore, the trait may appear to skip generations within a family. Development of head and neck paragangliomas also has been

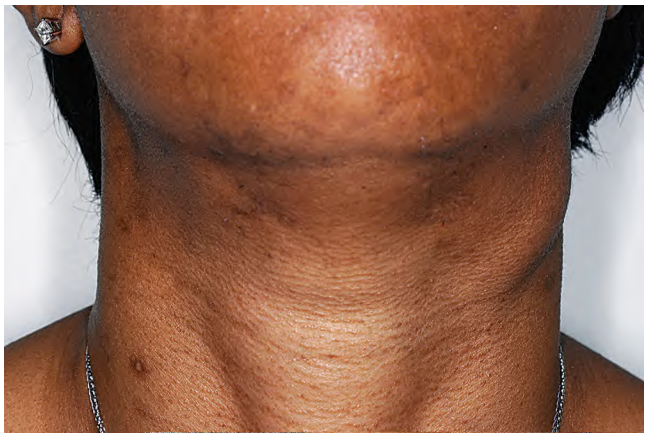


Fig. 12-79 Carotid Body Paraganglioma. Large tumor in the left neck producing a visible external swelling. (Courtesy of Dr. Terry Day.)

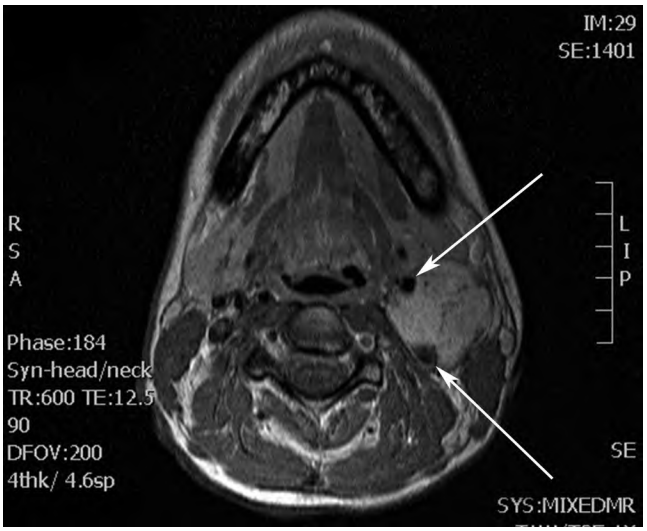


Fig. 12-80 Carotid Body Paraganglioma. Same patient as depicted in Fig. 12-79. The magnetic resonance image (MRI) shows a tumor mass at the carotid bifurcation. *Arrows* indicate the external and internal branches of the carotid artery. (Courtesy of Dr. Terry Day.)

described rarely in several other genetic conditions, such as neurofibromatosis type 1, multiple endocrine neoplasia type 2, and von Hippel-Lindau syndrome.

Clinical and Radiographic Features

Although paragangliomas are rare, the head and neck area is the most common site for these lesions. Isolated, mutation-negative tumors show a 4:1 female:male ratio, whereas mutation-positive examples have an equal sex distribution. The tumor usually occurs in middle-aged adults (mean age of 41 to 47 years), although inherited cases tend to develop in patients over a decade younger. Hereditary cases have a greater chance of being multicentric; about 37% of such patients will develop more than one tumor.

The most common type is the carotid body paraganglioma, which develops at the bifurcation of the internal and external carotid arteries (Figs. 12-79 and 12-80). Most often it is a slowly enlarging, painless mass of the upper lateral neck below the angle of the jaw. It is seen more frequently in patients who live at high altitudes, indicating that some cases may arise from chronic hyperplasia of the carotid body in response to lower oxygen levels. Angiography can help to localize the tumor and demonstrate its characteristic vascular nature.

Jugular and tympanic paragangliomas are the next most common types of these tumors. The most common symptoms include dizziness, tinnitus (a ringing or other noise in the ear), hearing loss, and cranial nerve palsies.

Histopathologic Features

The paraganglioma is characterized by round or polygonal epithelioid cells that are organized into nests or ***zellballen*** (Fig. 12-81). The overall architecture is similar to that of the normal paraganglia, except the *zellballen* are usually larger and more irregular in shape. These nests consist primarily of chief cells, which demonstrate centrally located, vesicular nuclei and somewhat granular, eosinophilic cytoplasm. These cells are positive for neuroendocrine markers, such as

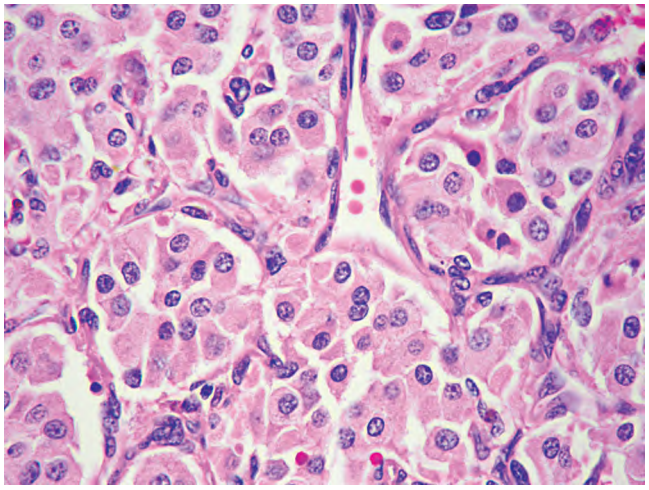


Fig. 12-81 Carotid Body Paraganglioma. Nested arrangement of tumor cells.

chromogranin and synaptophysin. The chief cells are surrounded by a flattened layer of sustentacular cells that are immunoreactive for S-100 protein. The tumor is typically vascular and may be surrounded by a thin fibrous capsule.

Treatment and Prognosis

The treatment of paragangliomas may include surgery, radiation therapy, or both, depending on the extent and location of the tumor. Localized carotid body paragangliomas often can be treated by surgical excision with maintenance of the vascular tree. If the carotid artery is encased by tumor, it also may need to be resected, followed by vascular grafting. Although most carotid body paragangliomas can be controlled with surgery, vascular complications can lead to considerable surgical morbidity, such as intraoperative hemorrhage, stroke, and blood pressure instability. Radiation

therapy may be used for unresectable tumors or as adjunctive treatment.

Because of their location near the base of the brain, jugular and tympanic paragangliomas are more difficult to manage. Hearing loss and other cranial nerve deficits are common postsurgical complications of jugular paragangliomas. Radiation therapy may be used in conjunction with surgery or as a primary treatment for unresectable tumors. Stereotactic radiosurgery (gamma knife treatment) has shown promise in the management of primary or recurrent jugular paragangliomas in patients who are poor surgical candidates. Tympanic paragangliomas are associated with a much lower risk of postsurgical problems.

Approximately 6% of paragangliomas will metastasize, either to regional lymph nodes or distant sites. Unfortunately, it is difficult to predict which tumors will act in a malignant fashion based on their microscopic features. However, the risk is much greater for patients with SDHB mutations (paraganglioma syndrome 4), where the rate of malignancy ranges from 13% to 23%.

◆ GRANULAR CELL TUMOR

The **granular cell tumor** is an uncommon benign soft tissue neoplasm that shows a predilection for the oral cavity. The histogenesis of this lesion continues to be debated. Originally, it was believed to be of skeletal muscle origin and was called the *granular cell myoblastoma.* However, more recent investigations point to a derivation from Schwann cells **(granular cell schwannoma/neurofibroma).** At present, it seems best to use the noncommittal term **granular cell tumor** for this lesion.

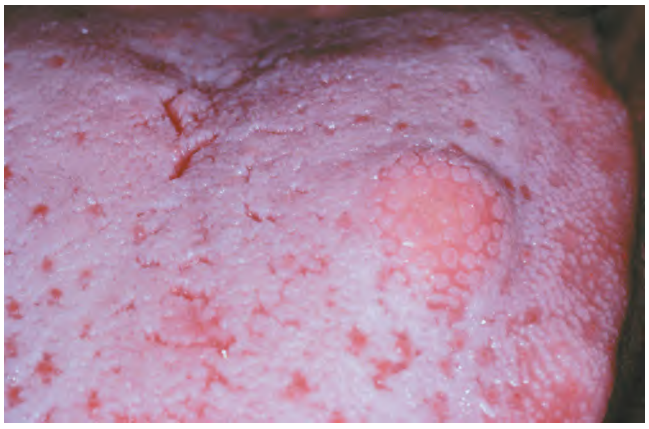
Clinical Features

Granular cell tumors are most common in the oral cavity and on the skin. The single most common site is the tongue, which accounts for one-third to half of all reported cases. Tongue lesions most often occur on the dorsal surface. The buccal mucosa is the second most common intraoral location. The tumor most frequently occurs in the fourth to sixth decades of life and is rare in children. There is a 2:1 female predilection.

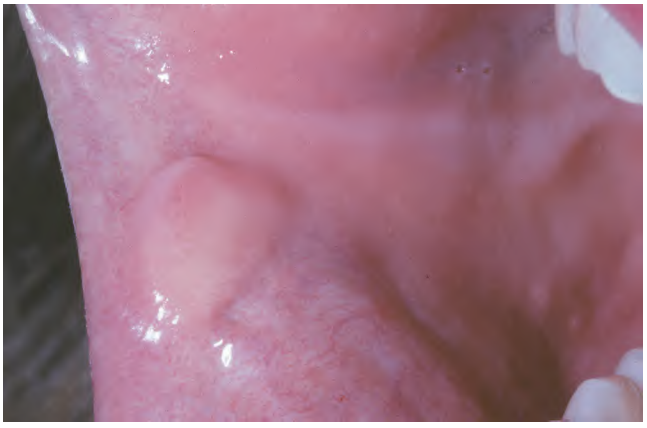
The granular cell tumor is typically an asymptomatic sessile nodule that is usually 2 cm or less in size (Figs. 12-82 and 12-83). The lesion often has been noted for many months or years, although sometimes the patient is unaware of its presence. The mass is typically pink, but some granular cell tumors appear yellow. The granular cell tumor is usually solitary, although multiple, separate tumors sometimes occur, especially in black patients.

Histopathologic Features

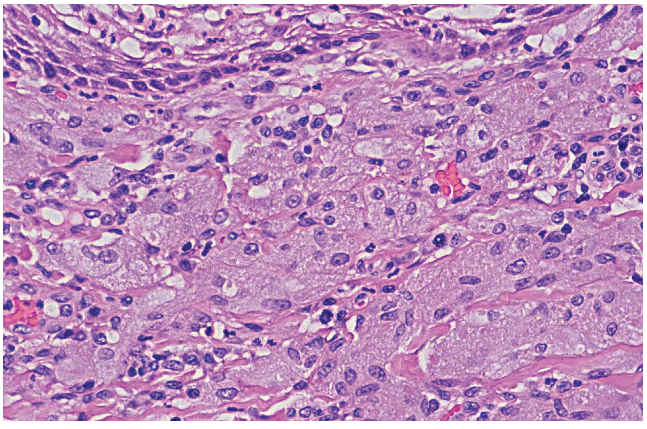
The granular cell tumor is composed of large, polygonal cells with abundant pale eosinophilic, granular cytoplasm and either dark or vesicular nuclei (Fig. 12-84). The cells



• **Fig. 12-82 Granular Cell Tumor.** Submucosal nodule on the dorsum of the tongue.

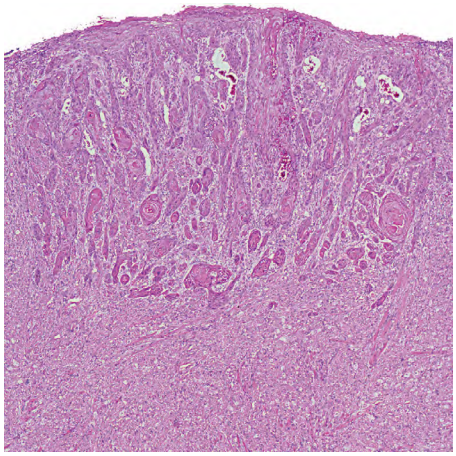


• **Fig. 12-83 Granular Cell Tumor.** Nodular mass of the buccal mucosa near the commissure.



• **Fig. 12-84 Granular Cell Tumor.** Medium-high–power view showing polygonal cells with abundant granular cytoplasm.

are usually arranged in sheets, but they also may be found in cords and nests. The cell borders often are indistinct, which results in a syncytial appearance. The lesion is not encapsulated and often intermingles with the adjacent connective tissues. Often, there appears to be a transition from normal adjacent skeletal muscle fibers to granular tumor



• **Fig. 12-85 Granular Cell Tumor.** Marked pseudoepitheliomatous hyperplasia overlying a granular cell tumor. Such cases may easily be mistaken for squamous cell carcinoma.

cells; this finding led earlier investigators to suggest a muscle origin for this tumor. Less frequently, one may see groups of granular cells that envelop small nerve bundles. Immunohistochemical analysis reveals positivity for S-100 protein within the cells—a finding that is supportive, but not diagnostic, of neural origin. The lesional cells also are positive for CD-68, calretinin, and neuron-specific enolase.

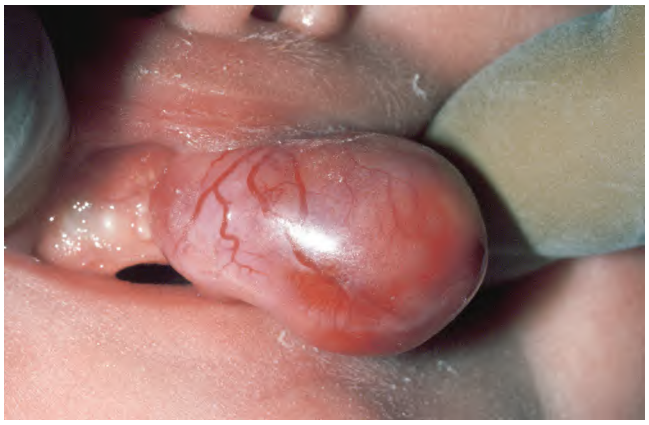
An unusual and significant microscopic finding is the presence of acanthosis or pseudoepitheliomatous (pseudocarcinomatous) hyperplasia of the overlying epithelium, which has been reported in up to 50% of all cases (Fig. 12-85). Although this hyperplasia is usually minor in degree, in some cases it may be so striking that it results in a mistaken diagnosis of squamous cell carcinoma and subsequent unnecessary cancer surgery. The pathologist must be aware of this possibility, especially when dealing with a superficial biopsy sample or a specimen from the dorsum of the tongue—an unusual location for oral cancer.

Treatment and Prognosis

The granular cell tumor is best treated by conservative local excision, and recurrence is uncommon, even when the lesion is not entirely removed. Extremely rare examples of malignant granular cell tumor have been reported.

◆ CONGENITAL EPULIS (CONGENITAL EPULIS OF THE NEWBORN; CONGENITAL GRANULAR CELL LESION)

The **congenital epulis** is an uncommon soft tissue tumor that occurs almost exclusively on the alveolar ridges of newborns. It is often known by the redundant term, **congenital epulis of the newborn.** Rare examples also have been described on the tongue; therefore, some authors prefer using the term **congenital granular cell lesion,** because not all cases present as an *epulis* on the alveolar ridge. It also has been called **gingival granular cell tumor of the newborn,** but this term should be avoided. Although it bears a slight microscopic resemblance to the granular cell tumor (discussed previously), it exhibits ultrastructural and immunohistochemical differences that warrant its classification as a distinct and separate entity. However, the histogenesis of this tumor is still uncertain.



• **Fig. 12-86 Congenital Epulis.** Polypoid mass of the anterior maxillary alveolar ridge in a newborn.

Clinical Features

The congenital epulis typically appears as a pink-to-red, smooth-surfaced, polypoid mass on the alveolar ridge of a newborn (Fig. 12-86). Most examples are 2 cm or less in size, although lesions as large as 7.5 cm have been reported. On occasion, the tumor has been detected *in utero* via ultrasound examination. Multiple tumors develop in 10% of cases. A few rare examples on the tongue have been described in infants who also had alveolar tumors.

The tumor is two to three times more common on the maxillary ridge than on the mandibular ridge. It most frequently occurs lateral to the midline in the area of the developing lateral incisor and canine teeth. The congenital epulis shows a striking predilection for females, which suggests a hormonal influence in its development, although estrogen and progesterone receptors have not been detected. Nearly 90% of cases occur in females.

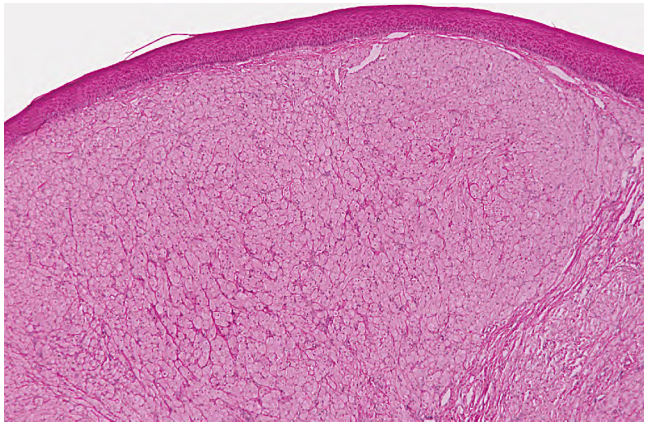
Histopathologic Features

The congenital epulis is characterized by large, rounded cells with abundant granular, eosinophilic cytoplasm and round to oval, lightly basophilic nuclei (Figs. 12-87 and 12-88). In older tumors, these cells may become elongated and separated by fibrous connective tissue. In contrast to the granular cell tumor, the overlying epithelium never shows pseudoepitheliomatous hyperplasia but typically demonstrates atrophy of the rete ridges. In addition, in contradistinction to the granular cell tumor, immunohistochemical analysis shows the tumor cells to be negative for S-100 protein.

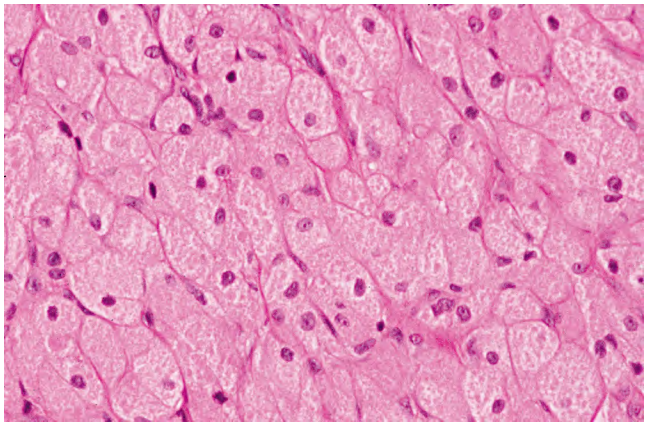
Treatment and Prognosis

The congenital epulis is usually treated by surgical excision. The lesion never has been reported to recur, even with incomplete removal.

After birth, the tumor appears to stop growing and may even diminish in size. Eventual complete regression has been reported in a few patients, even without treatment (Fig. 12-89).



• **Fig. 12-87 Congenital Epulis.** Low-power photomicrograph showing a nodular tumor mass. Note the atrophy of the rete ridges.



• **Fig. 12-88 Congenital Epulis.** High-power view of rounded cells with abundant granular cytoplasm.

◆ HEMANGIOMA AND VASCULAR MALFORMATIONS

In recent years, great progress has been made in the classification and understanding of tumors and tumorlike proliferations of vascular origin. A modified classification scheme for these vascular anomalies is presented in Box 12-2.

The term **hemangioma** traditionally has been used to describe a variety of developmental vascular anomalies. Currently, hemangiomas are considered to be benign tumors of infancy that display a rapid growth phase with endothelial cell proliferation, followed by gradual involution. Most hemangiomas cannot be recognized at birth, but arise subsequently during the first 8 weeks of life. On the other

• BOX 12-2 Classification of Vascular Anomalies

Vascular Tumors

Hemangiomas of infancy
- Superficial
- Deep
- Mixed

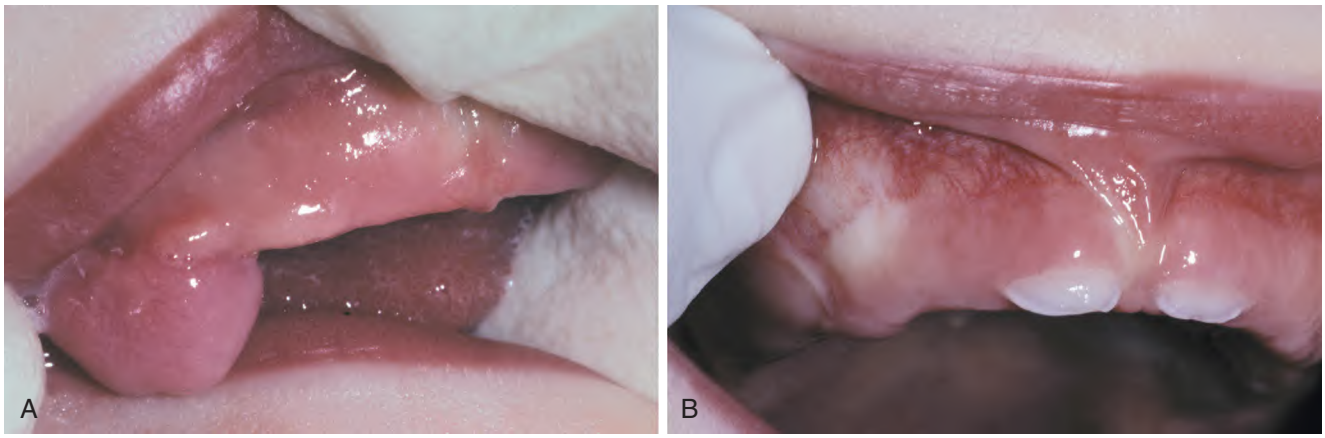
Congenital hemangiomas
- Noninvoluting congenital hemangioma (NICH)
- Rapidly involuting congenital hemangioma (RICH)

Kaposiform hemangioendothelioma
Tufted angioma
Pyogenic granuloma (lobular capillary hemangioma)

Vascular Malformations

Simple
- Capillary malformation
- Venous malformation
- Lymphatic malformation
- Arteriovenous malformation

Combined malformations



• **Fig. 12-89 Congenital Epulis. A,** Nodular mass on the maxillary alveolar ridge. Instead of being excised, the lesion was monitored clinically. **B,** Clinical appearance of the child at 1 year of age. The mass has disappeared without treatment. (Courtesy of Dr. Erwin Turner.)

hand, **vascular malformations** are structural anomalies of blood vessels with normal endothelial cell turnover. By definition, vascular malformations are present at birth and persist throughout life. They can be categorized according to the type of vessel involved (capillary, venous, or arteriovenous) and according to hemodynamic features (low flow or high flow).

Clinical and Radiographic Features

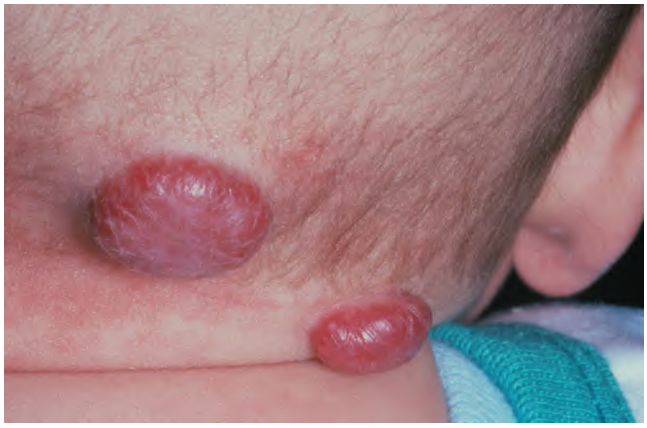
Hemangioma of Infancy

Hemangiomas are the most common tumors of infancy, occurring in 4% to 5% of 1-year-old children. They are much more common in females than in males (ratio of 3 : 1 to 5 : 1), and they occur more frequently in whites than in other racial groups. The most common location is the head and neck, which accounts for 60% of all cases. Eighty percent of hemangiomas occur as single lesions, but 20% of affected patients will have multiple tumors.

Infantile hemangiomas are rarely present at birth, although a pale macule with threadlike telangiectasias may be noted on the skin. During the first few weeks of life, the tumor will demonstrate rapid development that occurs at a faster pace than the infant's overall growth. Superficial tumors of the skin appear raised and bosselated with a bright-red color ("strawberry" hemangioma) (Fig. 12-90). They are firm and rubbery to palpation, and the blood cannot be evacuated by applying pressure. Deeper tumors may appear only slightly raised with a bluish hue.

The initial proliferative phase usually lasts for 6 to 12 months, after which the tumor grows proportionately with the child, followed by slow involution. The color gradually changes to a dull-purple hue, and the lesion feels less firm to palpation. By age 5, most of the red color is usually gone. About half of all hemangiomas will show complete resolution by 5 years of age, with 90% resolving by age 9. After tumor regression is complete, normal skin will be restored in about 50% of patients; however, up to 40% of affected individuals will show permanent changes such as atrophy, scarring, wrinkling, or telangiectasias.

Congenital hemangiomas, which are fully developed at birth, occur in two varieties. Rapidly involuting congenital hemangioma (RICH) shows early regression, with full involution by 9 to 14 months of age. Noninvoluting congenital hemangioma (NICH) grows proportionately with the child and does not undergo involution.



• **Fig. 12-90 Hemangioma.** Infant with two red, nodular masses on the posterior scalp and neck ("strawberry" hemangioma).

Complications occur in about 20% of hemangiomas. The most common problem is ulceration, which may occur with or without secondary infection. Although hemorrhage may be noted, significant blood loss does not usually occur. Hemangiomas that occur in crucial areas can be associated with significant morbidity. Periocular tumors often result in amblyopia (dimness of vision), strabismus, or astigmatism. Patients with multiple cutaneous hemangiomas or large facial hemangiomas are at increased risk for concomitant visceral hemangiomas. Tumors in the neck and laryngeal region can lead to airway obstruction.

Large, segmental cervicofacial hemangioma can be a component of a well-recognized hemangioma syndrome—**PHACE(S) syndrome.** This acronym stands for the following:

- **P**osterior fossa brain anomalies (usually Dandy-Walker malformation)
- **H**emangioma (usually cervical segmental hemangioma)
- **A**rterial anomalies
- **C**ardiac defects and **C**oarctation of the aorta
- **E**ye anomalies
- **S**ternal cleft or **S**upraumbilical raphe

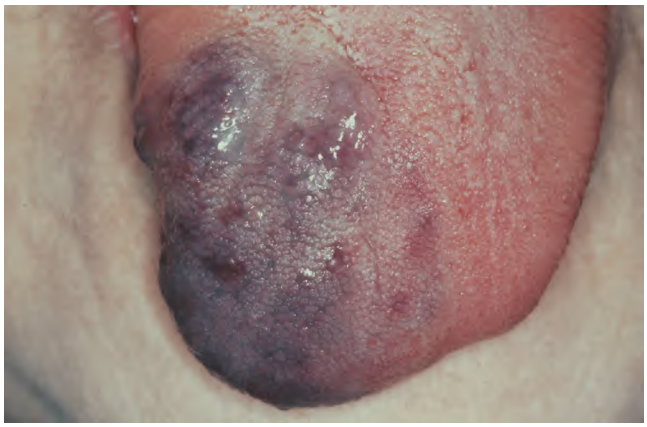
Kasabach-Merritt phenomenon is a serious coagulopathy that has been associated with two rare vascular tumors known as *tufted hemangioma* and *kaposiform hemangioendothelioma.* This disorder is characterized by severe thrombocytopenia and hemorrhage because of platelet trapping within the tumor. The mortality rate is as high as 20% to 30%.

Vascular Malformations

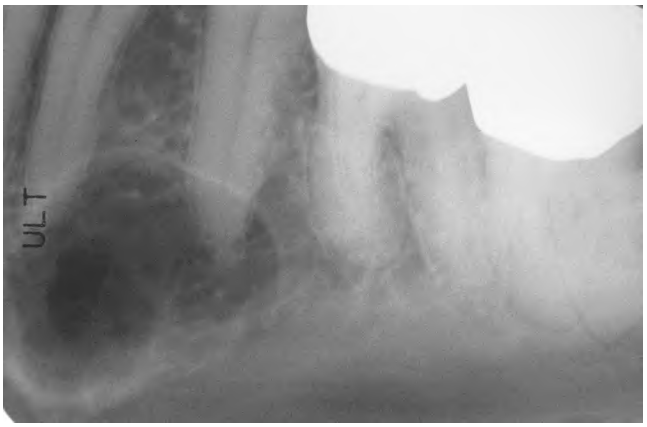
In contrast to hemangiomas, vascular malformations are present at birth and persist throughout life. Port wine stains are relatively common capillary malformations that occur in 0.3% of newborns and have been associated with somatic mutations in the *GNAQ* gene. They are most common on the face, particularly along the distribution of the trigeminal nerve. In Sturge-Weber syndrome, associated intracranial lesions are present (see page 508). Port wine stains are typically pink or purple macular lesions that grow commensurately with the patient. As the patient gets older, the lesion often darkens and becomes nodular because of vascular ectasia.

Low-flow **venous malformations** encompass a wide spectrum of lesions, from small isolated ectasias to complex growths that involve multiple tissues and organs. They are present at birth, although they may not always be immediately apparent. Typically, venous malformations are blue and are easily compressible (Fig. 12-91). They often grow proportionately with the patient, but they may swell when dependent or with increased venous pressure. Secondary thrombosis and phlebolith formation can occur.

Arteriovenous malformations are high-flow lesions that result from persistent direct arterial and venous



• **Fig. 12-91 Venous Malformation.** Blue-purple mass of the anterior tongue.



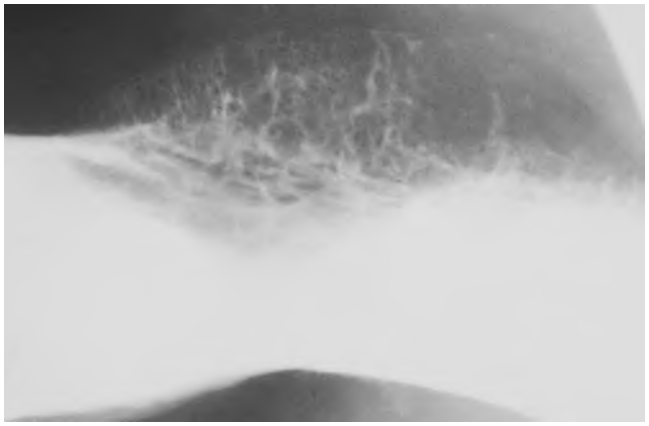
• **Fig. 12-92 Intrabony Venous Malformation.** Well-circumscribed radiolucency that contains fine trabeculations.

communication. Although they are present from birth, they may not become noticeable until later in childhood or adulthood. Because of the fast vascular flow through these lesions, a palpable thrill or bruit often is noticeable. The overlying skin typically feels warmer to touch. Presenting symptoms may include pain, bleeding, and skin ulceration.

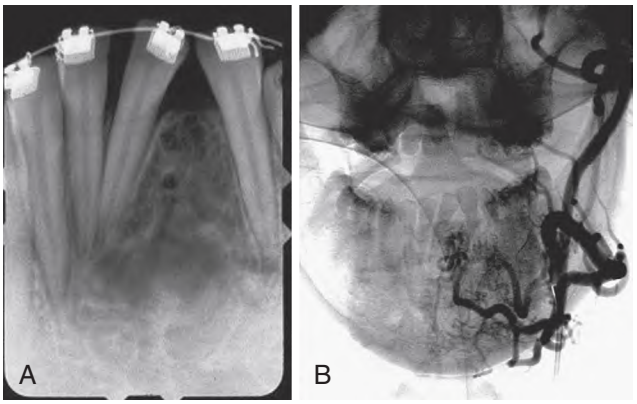
Intrabony Vascular Malformations

Intrabony "hemangiomas" also may occur and usually represent either venous or arteriovenous malformations. In the jaws, such lesions are detected most often during the first three decades of life. They are slightly more common in females than in males and occur three times more often in the mandible than the maxilla. The lesion may be completely asymptomatic, although some examples are associated with pain and swelling. Mobility of teeth or bleeding from the gingival sulcus may occur. A bruit or pulsation may be apparent on auscultation and palpation.

The radiographic appearance of intrabony vascular malformations is variable. Most commonly, the lesion shows a multilocular radiolucent defect. The individual loculations may be small (honeycomb appearance) or large (soap bubble appearance). In other cases the lesion may present as an ill-defined radiolucent area or a well-defined, cystlike radiolucency (Fig. 12-92). Large malformations may cause cortical expansion, and occasionally a "sunburst" radiographic pattern is produced (Fig. 12-93). Angiography can be helpful in demonstrating the vascular nature of the lesion (Fig. 12-94).



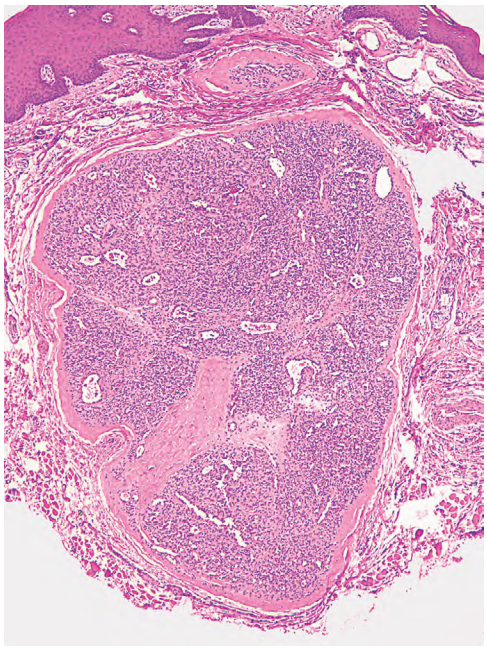
• **Fig. 12-93 Intrabony Venous Malformation.** Occlusal radiograph demonstrating cortical destruction and a "sunburst" periosteal reaction resembling osteosarcoma.



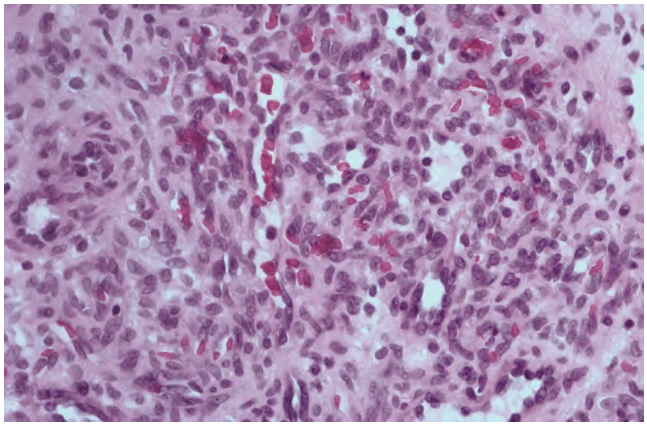
• **Fig. 12-94 Intrabony Arteriovenous Malformation. A,** Periapical radiograph showing an expansile, mottled radiolucency in the mandibular incisor region. Pulsatile hemorrhage was encountered when a biopsy of this lesion was attempted. **B,** Angiogram demonstrating a vascular proliferation between the mandibular incisors. (Courtesy of Dr. Larry Cunningham and Dr. Jason Ford.)

Histopathologic Features

Early hemangiomas of infancy are characterized by numerous plump endothelial cells and often-indistinct vascular lumina (Figs. 12-95 and 12-96). At this stage, such lesions often are known microscopically as *juvenile* or *cellular* hemangiomas. Because of their cellular nature, these lesions also have been called **juvenile hemangioendothelioma,** although this term should be avoided because



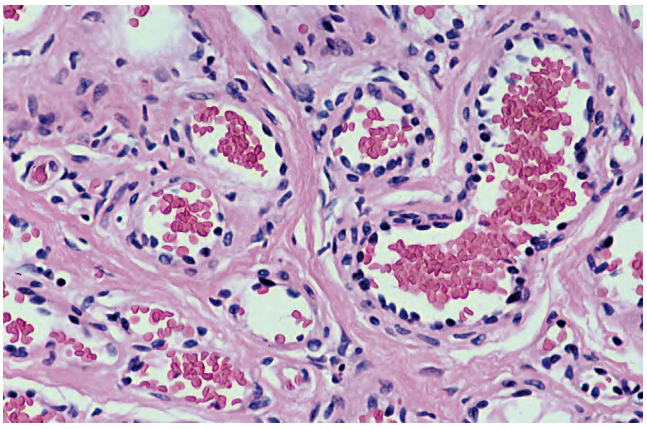
• **Fig. 12-95 Juvenile (Cellular) Hemangioma.** Low-power photomicrograph showing a circumscribed cellular mass of vascular endothelial cells arranged in lobular aggregates.



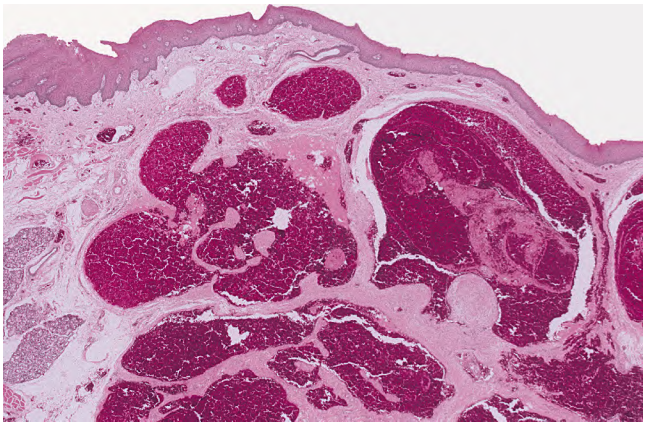
• **Fig. 12-96 Juvenile (Cellular) Hemangioma.** High-power view showing a highly cellular endothelial proliferation forming occasional indistinct vascular lumina.

hemangioendothelioma also is used to designate other vascular tumors of intermediate malignant potential. As the lesion matures, the endothelial cells become flattened, and the small, capillary-sized vascular spaces become more evident (Fig. 12-97). As the hemangioma undergoes involution, the vascular spaces become less prominent and are replaced by fibrofatty connective tissue.

Vascular malformations do not show active endothelial cell proliferation, and the channels resemble the vessels of origin. Therefore, capillary malformations may be similar to the capillary stage of hemangioma, whereas venous malformations may show more dilated vessels (Fig. 12-98). Because of their similar features, many vascular malformations are incorrectly categorized as *hemangiomas.* Arteriovenous



• **Fig. 12-97 Capillary Hemangioma.** High-power photomicrograph demonstrating well-formed capillary-sized vessels.



• **Fig. 12-98 Venous Malformation.** Low-power photomicrograph showing multiple large, dilated blood vessels.

malformations demonstrate a mixture of thick-walled arteries and veins, along with capillary vessels.

GLUT1 is an immunohistochemical marker that is consistently positive in the hemangioma of infancy. In contrast, this marker is negative in other developmental vascular tumors and anomalies listed in Box 12-2 (RICH, NICH, tufted angioma, kaposiform hemangioendothelioma, pyogenic granuloma, and vascular malformations).

Treatment and Prognosis

Because most hemangiomas of infancy undergo involution, management often consists of "watchful neglect." It is important to educate parents that although rapid growth may be seen, regression will occur. For problematic or life-threatening hemangiomas, pharmacologic therapy with the beta blocker propranolol has become the first-line treatment in recent years. Systemic corticosteroids also may help to reduce the size of the lesion, but this approach is associated with a greater risk potential than propranolol therapy. Intralesional and topical corticosteroids sometimes have been used for smaller localized, problematic lesions. Intravenous (IV) vincristine may be considered for complicated tumors

that are unresponsive to other therapies. Interferon α-2a is no longer widely used because of the reported risk of permanent spastic diplegia.

Surgical removal rarely is warranted for infantile hemangioma, although excision may be effective for localized, pedunculated tumors that demonstrate ulceration or recurrent bleeding. Surgical management early in childhood also might be a consideration in situations where eventual surgical repair would be required anyway and the scar can be easily hidden. Upper eyelid tumors that can affect vision also may be candidates for surgery.

Flashlamp pulsed dye lasers can be effective in the treatment of port wine stains. The management of venous malformations depends on the size, location, and associated complications of the lesion. Small, stable malformations may not require treatment. Larger, problematic lesions may be treated with a combination of sclerotherapy and surgical excision. Sclerotherapy involves the injection of sclerosing agents, such as 95% ethanol or sodium tetradecyl sulfate, directly into the lesion to induce fibrosis. Sclerotherapy alone may be sufficient for smaller lesions; for larger lesions, subsequent surgical resection can be accomplished with less risk of bleeding after sclerotherapy.

The treatment of arteriovenous malformations is more challenging and also depends on the size of the lesion and degree of involvement of vital structures. For cases that require resection, radiographic embolization often is performed 24 to 48 hours before surgery to minimize blood loss.

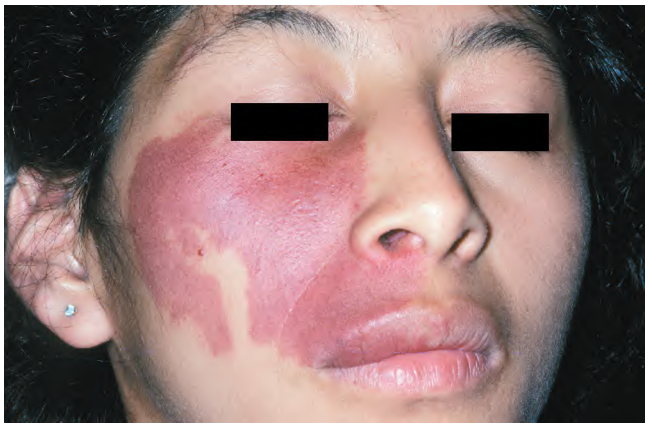
Vascular malformations of the jaws are potentially dangerous lesions because of the risk of severe bleeding, which may occur spontaneously or during surgical manipulation. Needle aspiration of any undiagnosed intrabony lesion before biopsy is a wise precaution to rule out the possibility of a vascular malformation. Severe and even fatal hemorrhages have occurred after incisional biopsy or extraction of teeth in the area of such lesions.

◆ STURGE-WEBER SYNDROME (ENCEPHALOTRIGEMINAL ANGIOMATOSIS; STURGE-WEBER ANGIOMATOSIS)

Sturge-Weber syndrome is a rare, nonhereditary developmental condition that is characterized by a hamartomatous vascular proliferation involving the tissues of the brain and face. This condition recently was shown to be related to a somatic activating mutation of the *GNAQ* gene on chromosome 9q21. It has been suggested that this embryologic mutation results in failure of the primitive cephalic venous plexus to regress and mature properly during the first trimester of pregnancy.

Clinical and Radiographic Features

Patients with Sturge-Weber syndrome are born with a dermal capillary vascular malformation of the face known as a **port wine stain** or **nevus flammeus** because of its deep-purple color. This port wine stain usually has a unilateral distribution along one or more segments of the trigeminal nerve. Occasionally, patients have bilateral involvement or additional port wine lesions elsewhere on the body. Only 8% to 10% patients with facial port wine nevi will have Sturge-Weber syndrome. Risk for the condition occurs primarily in patients with involvement along the distribution of the ophthalmic branch of the trigeminal nerve (V1) (Figs. 12-99 and 12-100). If the port-wine stain involves the entire distribution of V1, the risk for neurologic and ocular involvement is 78%.



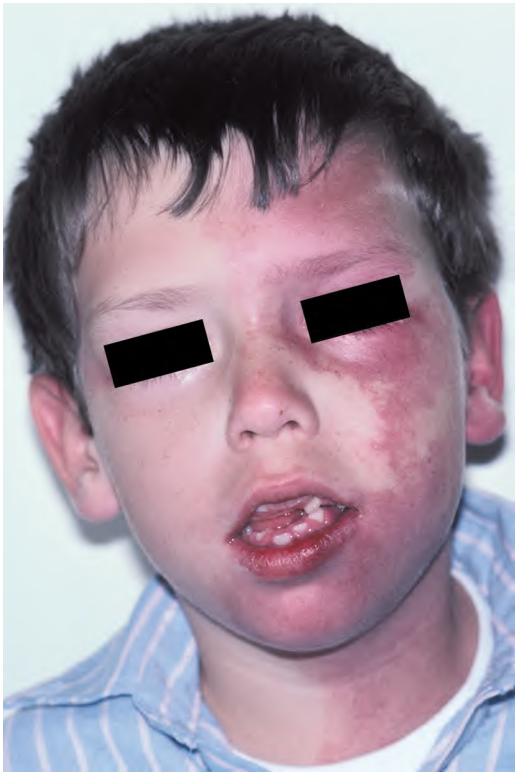
• **Fig. 12-99 Port Wine Stain.** Nevus flammeus of the malar area in a patient without Sturge-Weber syndrome. Unless the vascular lesion includes the region innervated by the ophthalmic branch of the trigeminal nerve, usually the patient does not have central nervous system (CNS) involvement.

In addition to the facial port wine nevus, individuals with Sturge-Weber syndrome have leptomeningeal angiomas that overlie the ipsilateral cerebral cortex. This meningeal angiomatosis usually is associated with a convulsive disorder and often results in intellectual disability or contralateral hemiplegia. Other potential problems include migraine headaches, stroke-like episodes, growth hormone deficiency, and central hypothyroidism. Imaging studies of the brain may reveal gyriform "tramline" calcifications on the affected side (Fig. 12-101). Ocular involvement may be manifested by glaucoma and vascular malformations of the conjunctiva, episclera, choroid, and retina.

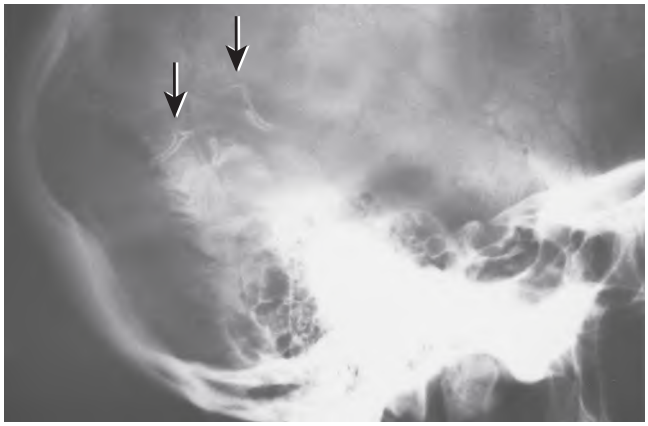
Intraoral involvement in Sturge-Weber syndrome is common, resulting in hypervascular changes to the ipsilateral mucosa (Fig. 12-102). The gingiva may exhibit slight vascular hyperplasia or a more massive hemangiomatous proliferation that can resemble a pyogenic granuloma. Such gingival hyperplasia may be attributable to the increased vascular component, anticonvulsant therapy used to control the epileptic seizures, or both. Destruction of the underlying alveolar bone has been reported in rare instances.

Histopathologic Features

The port wine nevus is characterized by excessive numbers of dilated blood vessels in the middle and deep dermis. The



• **Fig. 12-100 Sturge-Weber Syndrome.** Port wine stain of the left face, including involvement along the ophthalmic branch of the trigeminal nerve. The patient also was intellectually disabled and had a seizure disorder.

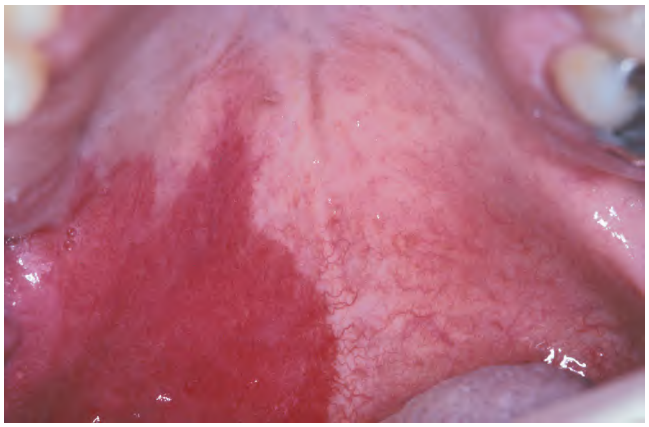


• **Fig. 12-101 Sturge-Weber Syndrome.** Skull film showing "tramline" calcifications *(arrows).* (Courtesy of Dr. Reg Munden.)

intraoral lesions show a similar vascular dilatation. Proliferative gingival lesions may resemble a pyogenic granuloma.

Treatment and Prognosis

The treatment and prognosis of Sturge-Weber syndrome depend on the nature and severity of the possible clinical features. Usually, facial port wine nevi can be improved by using flashlamp pulsed dye lasers. Cortical excision of angiomatous meningeal lesions may be necessary in some cases. Patients with intractable epilepsy and progressive intellectual disability eventually may require more extensive neurosurgical treatment, including lobectomy or hemispherectomy.



• **Fig. 12-102 Sturge-Weber Syndrome.** Unilateral vascular involvement of the soft palate.

Port wine nevi that affect the gingiva can make flossing and dental prophylaxis difficult. Great care must be taken when performing surgical procedures in affected areas of the mouth because significant hemorrhage may be encountered. Lasers also may be helpful in the removal of hyperplastic oral lesions.

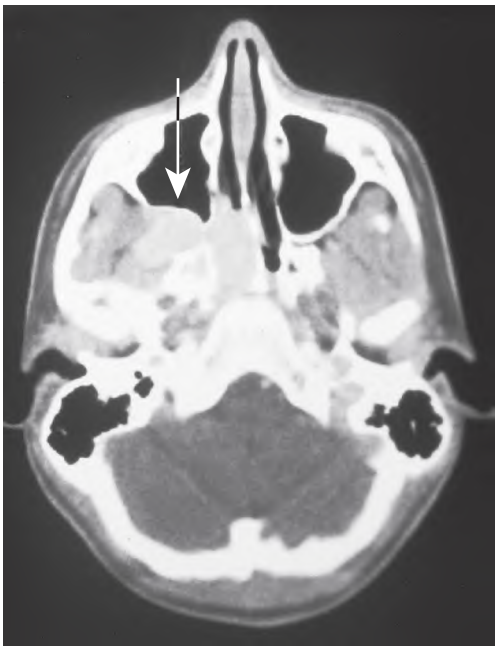
◆ NASOPHARYNGEAL ANGIOFIBROMA

The **nasopharyngeal angiofibroma** is a rare vascular and fibrous tumorlike lesion that occurs only in the nasopharynx. Although microscopically benign, it frequently exhibits locally destructive and aggressive behavior. It may represent a vascular malformation rather than a true neoplasm.

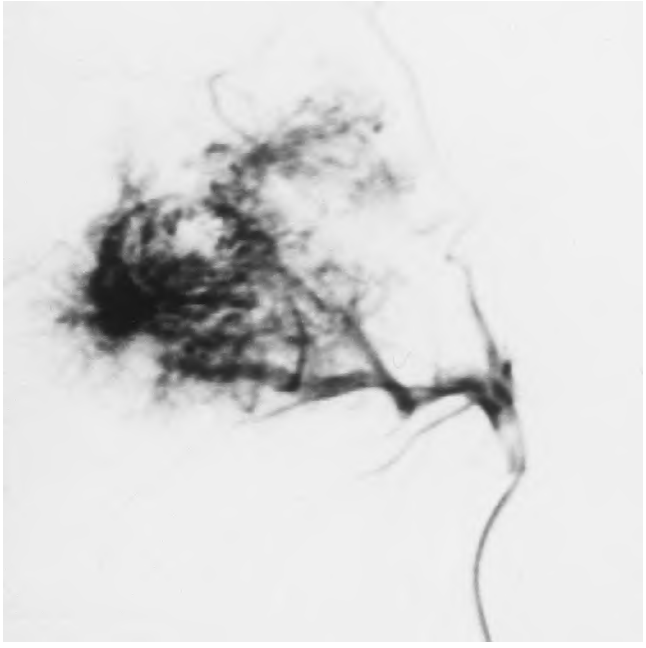
Clinical and Radiographic Features

Nasopharyngeal angiofibromas occur almost exclusively in males. The tumor is exceedingly rare in females—so much so that the diagnosis in a female patient should be viewed with skepticism and closely scrutinized. The lesion also shows a striking predilection for adolescents between the ages of 10 and 17 and often has been called the *juvenile nasopharyngeal angiofibroma.* However, rare examples also have been reported in slightly younger and older patients. Because of its almost exclusive occurrence in adolescent boys, a hormonal influence seems likely, although no endocrine abnormalities have been detected.

Nasal obstruction and epistaxis are common early symptoms. The lesion is currently presumed to arise in the pterygopalatine fossa and expands medially into the nasal cavity via the sphenopalatine foramen. Some cases show extension into the paranasal sinuses, orbits, or middle cranial fossa. Invasion into the oral cavity or cheek rarely has been reported. Computed tomography (CT) scans and magnetic resonance imaging (MRI) studies are helpful adjuncts in visualizing the extent of the lesion and degree of adjacent tissue destruction. Anterior bowing of the posterior wall of the maxillary sinus is a characteristic feature (Fig. 12-103).



• **Fig. 12-103 Nasopharyngeal Angiofibroma.** A contrasted computed tomography (CT) scan showing a tumor of the nasopharynx and pterygopalatine fossa, with characteristic anterior bowing of the posterior wall of the right maxillary sinus *(arrow).* (Courtesy of Dr. Pamela Van Tassel.)

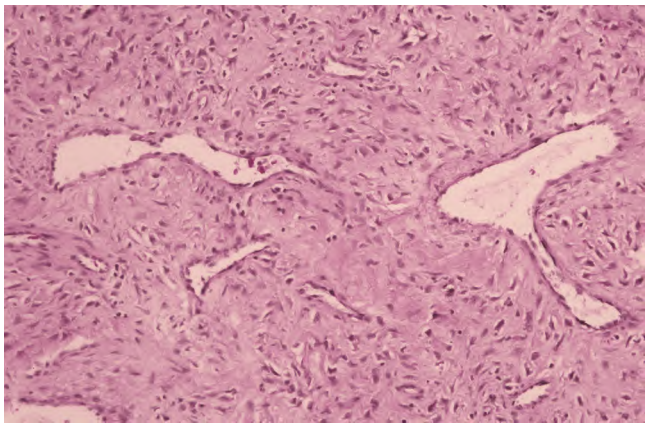


• **Fig. 12-104 Nasopharyngeal Angiofibroma.** A digital subtraction angiogram of the external carotid artery showing the intense vascular blush of the tumor. (Courtesy of Dr. Pamela Van Tassel.)

Angiograms can be used to confirm the vascular nature of the lesion (Fig. 12-104).

Histopathologic Features

The nasopharyngeal angiofibroma consists of dense fibrous connective tissue that contains numerous dilated, thin-walled blood vessels of variable size (Fig. 12-105). Typically, the vascular component is more prominent at the periphery of the tumor, especially in lesions from younger patients.



• **Fig. 12-105 Nasopharyngeal Angiofibroma.** Moderately cellular fibrous connective tissue with prominent blood vessels.

Treatment and Prognosis

The primary treatment of nasopharyngeal angiofibroma usually consists of surgical excision. Depending on the extent of the lesion, this may be accomplished via endoscopic surgery, lateral rhinotomy, midfacial degloving procedure, infratemporal fossa approach, or combined craniofacial resection. Preoperative embolization of the tumor is helpful in controlling blood loss. Radiation therapy usually is reserved for recurrent lesions and extensive tumors with unusual vascular supplies or intracranial extension.

The recurrence rate varies from 20% to 40% in most studies. Such recurrences usually are retreated with further surgery or radiation therapy. Malignant transformation into fibrosarcoma rarely has been reported and probably is associated with prior radiation therapy.

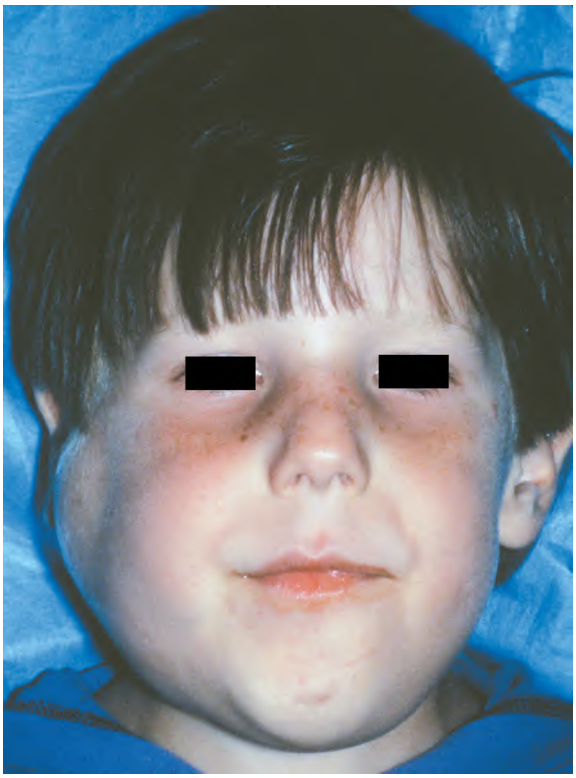
◆ LYMPHATIC MALFORMATIONS (LYMPHANGIOMA; CYSTIC HYGROMA)

Lymphatic malformations are benign, hamartomatous tumorlike growths of lymphatic vessels. Like other vascular malformations, it is doubtful that they are true neoplasms; instead, they most likely represent developmental anomalies that arise from sequestrations of lymphatic tissue that do not communicate normally with the rest of the lymphatic system.

Lymphatic malformations can be classified into three types:

1. **Macrocystic**—composed of cystlike spaces measuring 2 cm or greater in diameter
2. **Microcystic**—composed of smaller vascular channels measuring less than 2 cm in diameter
3. **Mixed**—composed of a combination of macrocystic and microcystic spaces

The subtypes are probably variants of the same pathologic process, and the size of the vessels may depend on the



• **Fig. 12-106 Lymphatic Malformation.** Young boy with a cystic hygroma primarily involving the right side of the face. (Courtesy of Dr. Frank Kendrick.)

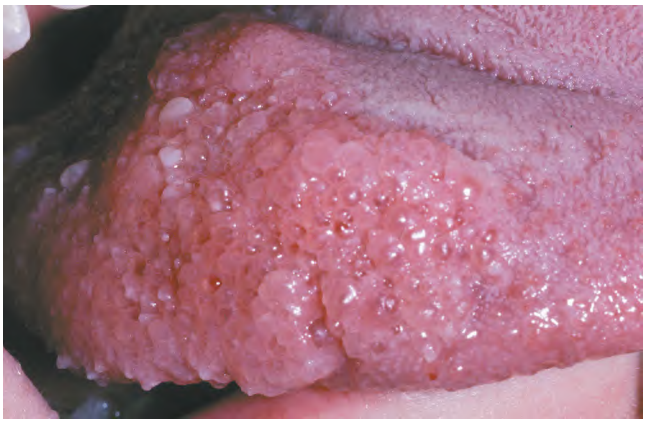
nature of the surrounding tissues. Macrocystic lymphatic malformations ("cystic hygroma") often occur in the neck, where the loose adjacent connective tissues allow for more expansion of the vessels. Microcystic lesions are more frequent in the mouth, where the denser surrounding connective tissue and skeletal muscle limit vessel expansion.

Clinical Features

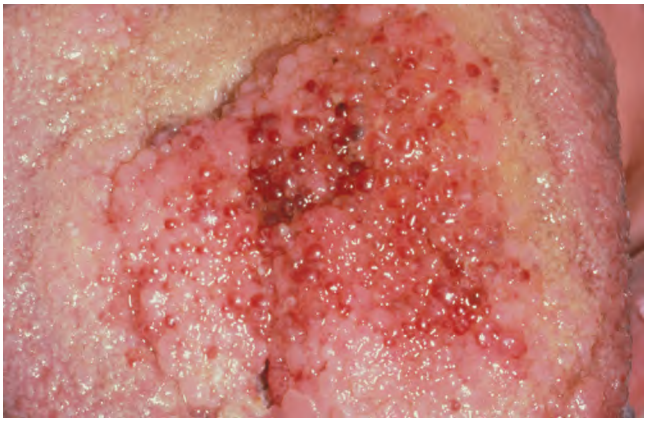
Lymphatic malformations have a marked predilection for the head and neck, which accounts for 50% to 75% of all cases (Fig. 12-106). About half of all lesions are noted at birth, and around 90% develop by 2 years of age.

Cervical lymphatic malformations are more common in the posterior triangle and are typically soft, fluctuant masses. They occur less frequently in the anterior triangle, although lesions in this location are more likely to result in respiratory difficulties or dysphagia if they grow large. Occasionally, cervical lesions will extend into the mediastinum or upward into the oral cavity. Such growths can become massive and can measure 15 cm or greater in size. Rapid enlargement may occur secondary to an upper respiratory tract infection, presumably because of increased lymph production, blocked lymphatic drainage, or secondary infection of the tumor.

Oral lymphatic malformations may occur at various sites but are most frequent on the anterior two thirds of the tongue, where they often result in macroglossia (Figs. 12-107 and 12-108). Usually, the lesion is superficial in



• **Fig. 12-107 Lymphatic Malformation.** Pebbly, vesicle-like appearance of a tumor of the right lateral tongue.



• **Fig. 12-108 Lymphatic Malformation.** Dorsal tongue lesion demonstrating a purple color, which can be caused by secondary hemorrhage or an associated hemangiomatous component.

location and demonstrates a pebbly surface that resembles a cluster of translucent vesicles. The surface has been likened to the appearance of frog eggs or tapioca pudding. Secondary hemorrhage into the lymphatic spaces may cause some of these "vesicles" to become purple. Deeper tumors present as soft, ill-defined masses.

Small lymphatic anomalies less than 1 cm in size occur on the alveolar ridge in around 4% of black neonates. These lesions often occur bilaterally on the mandibular ridge and show a 2:1 male-to-female distribution. Most of these alveolar lymphangiomas apparently resolve spontaneously because they are not observed in older people.

Histopathologic Features

Lymphatic malformations are composed of lymphatic vessels that may show mild dilatation (microcystic) (Figs. 12-109 and 12-110) or macroscopic cystlike structures (macrocystic) (Fig. 12-111). The vessels often diffusely infiltrate the adjacent soft tissues and may demonstrate lymphoid aggregates in their walls. The lining endothelium is typically thin, and the spaces contain proteinaceous fluid and occasional lymphocytes. Some channels also may

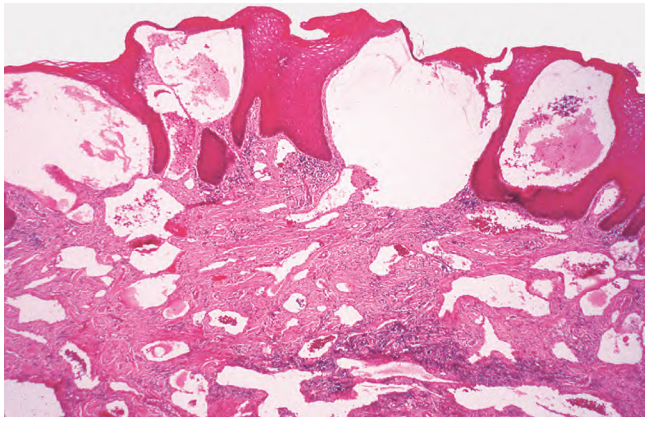


Fig. 12-109 Microcystic Lymphatic Malformation. Lesion of the tongue showing dilated lymphatic vessels beneath the epithelium and in the deeper connective tissues.

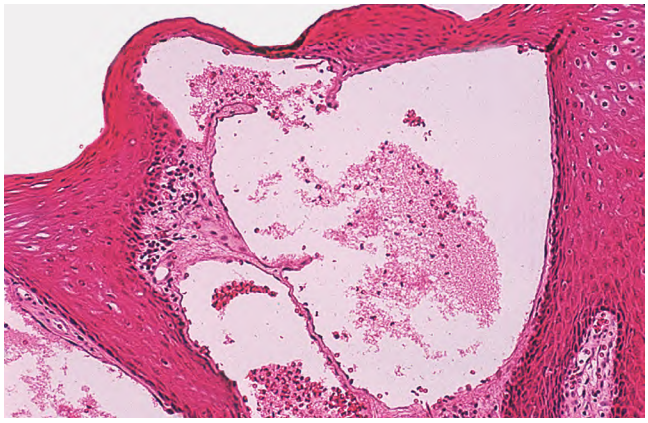


Fig. 12-110 Microcystic Lymphatic Malformation. High-power photomicrograph showing dilated, lymph-filled vessels immediately below the atrophic surface epithelium.

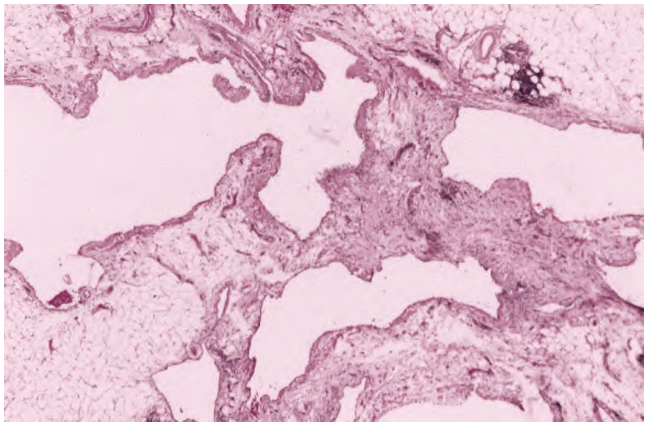


Fig. 12-111 Macrocystic Lymphatic Malformation. Lesion from the neck showing markedly dilated lymphatic vessels.

contain red blood cells, which creates uncertainty as to whether they are lymphatic or blood vessels. Although many of these likely represent secondary hemorrhage into a lymphatic vessel, some actually may be examples of mixed vascular malformations composed of both lymphatic and blood vessels.

In intraoral tumors, the lymphatic vessels are characteristically located just beneath the epithelial surface and often replace the connective tissue papillae. This superficial location results in the translucent, vesicle-like clinical appearance. However, extension of these vessels into the deeper connective tissue and skeletal muscle also may be seen.

Treatment and Prognosis

The treatment of lymphatic malformations of the head and neck depends on the size, location, and subtype of the anomaly. Smaller lesions not associated with significant functional or cosmetic problems may be managed best by observation alone. For example, some clinicians do not recommend treatment for nonenlarging lesions of the tongue because of the difficulty in removal and high recurrence rate. Spontaneous regression of lymphatic malformations is rare but has been reported in about 3% of cases.

When required, treatment usually consists of either surgical excision or percutaneous sclerotherapy. Total surgical removal may not be possible in all cases because of large size or involvement of vital structures. Recurrence after surgery is common, especially for microcystic lymphatic malformations of the oral cavity, because of their infiltrative nature. Macrocystic lesions of the cervical region are often well circumscribed and have a lower rate of recurrence.

In recent years, percutaneous sclerotherapy has proven to be a successful alternative to surgery for many lymphatic malformations. In the United States, the most widely used sclerosant currently is doxycycline. Other sclerosing agents that have been utilized include bleomycin, ethanol, acetic acid, sodium tetradecyl sulfate, and OK-432 (outside of the United States). Sclerotherapy is most successful in the management of macrocystic lesions, with most patients showing 75% to 100% clinical resolution. A lower success rate is achieved in mixed and microcystic subtypes.

The prognosis is good for most patients, although large tumors of the neck or tongue may result in airway obstruction and death.

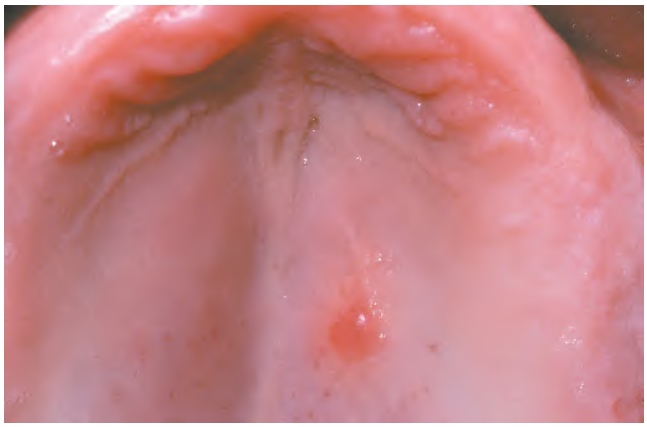
◆ LEIOMYOMA

Leiomyomas are benign tumors of smooth muscle that most commonly occur in the uterus, gastrointestinal tract, and skin. Leiomyomas of the oral cavity are rare. Most of these probably have their origin from vascular smooth muscle.

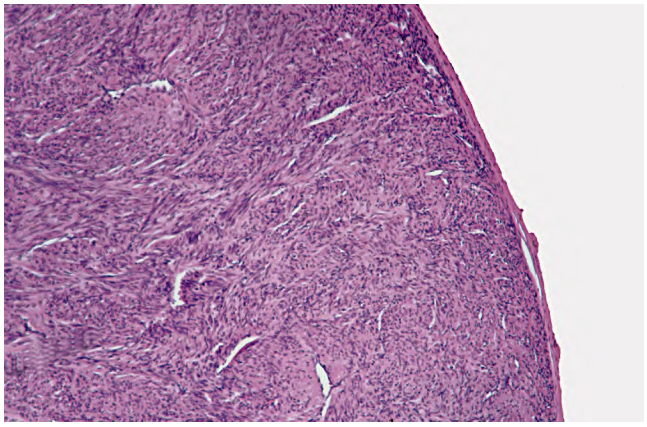
The three types are as follows:

1. Solid leiomyomas
2. Vascular leiomyomas (angiomyomas or angioleiomyomas)
3. Epithelioid leiomyomas (leiomyoblastomas)

Almost all oral leiomyomas are either solid or vascular in type; angiomyomas account for nearly 75% of all oral cases. Rare examples of developmental hamartomas composed primarily of smooth muscle (leiomyomatous hamartoma) also have been described in the oral cavity.



• **Fig. 12-112 Leiomyoma.** Small, pink-red nodule on the posterior hard palate lateral to the midline.



• **Fig. 12-113 Leiomyoma.** Low-power view showing a well-circumscribed cellular mass of spindle-shaped smooth muscle cells.

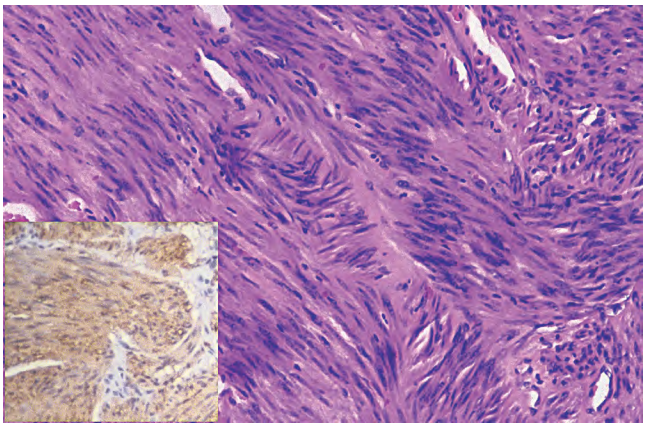
Clinical and Radiographic Features

The oral leiomyoma can occur at any age and is usually a slow-growing, firm, mucosal nodule (Fig. 12-112). Most lesions are asymptomatic, although occasional tumors can be painful. Solid leiomyomas are typically normal in color, although angiomyomas may exhibit a bluish hue. The most common sites are the lips, tongue, palate, and cheek, which together account for 80% of cases. Extremely rare intraosseous examples may present as unilocular radiolucencies of the jaws.

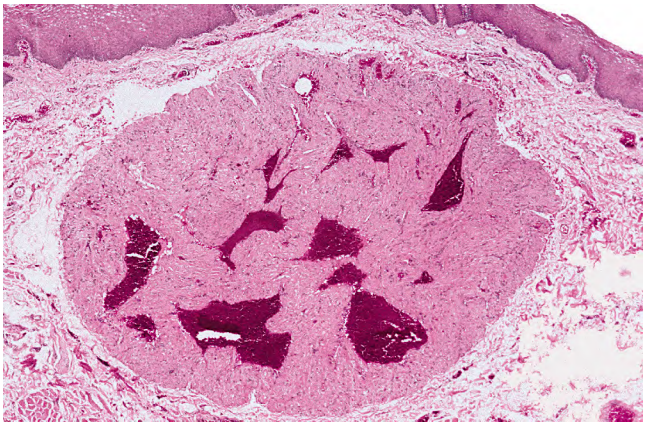
Histopathologic Features

Solid leiomyomas are well-circumscribed tumors that consist of interlacing bundles of spindle-shaped smooth muscle cells (Figs. 12-113 and 12-114). The nuclei are elongated, pale staining, and blunt ended. Mitotic figures are uncommon. Angiomyomas also are well-circumscribed lesions that demonstrate multiple tortuous blood vessels with thickened walls caused by hyperplasia of their smooth muscle coats (Fig. 12-115). Intertwining bundles of smooth muscle may be found between the vessels, sometimes with intermixed adipose tissue. As its name implies, the epithelioid leiomyoma is composed primarily of epithelioid cells rather than spindle cells.

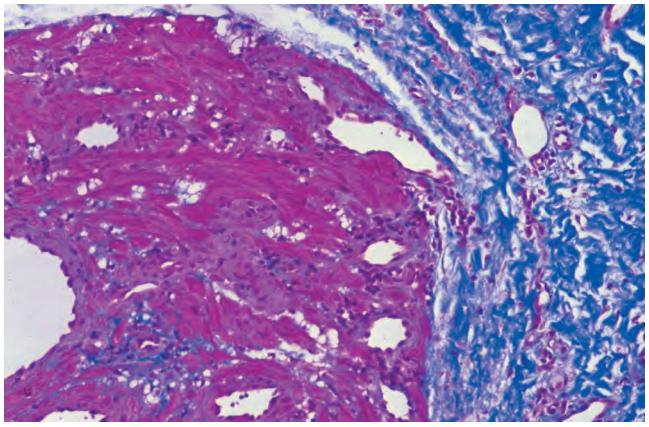
Special stains and immunohistochemistry may be helpful to confirm the smooth muscle origin if the diagnosis is in doubt. The smooth muscle stains bright red with the Masson trichrome stain (Fig. 12-116). Immunohistochemical



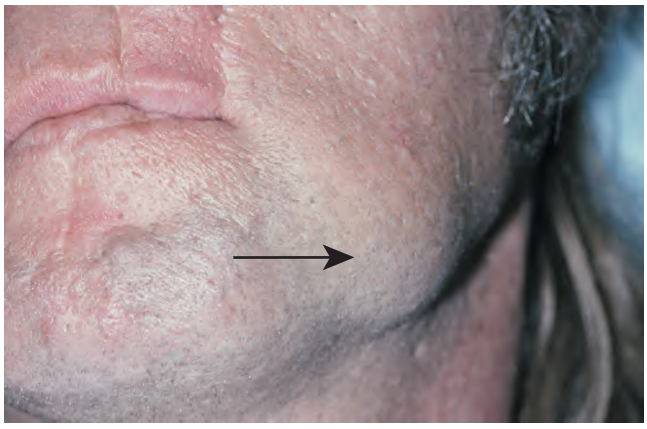
• **Fig. 12-114 Leiomyoma.** High-power view showing spindle-shaped cells with blunt-ended nuclei. Immunohistochemical analysis shows strong positivity for smooth muscle actin *(inset).*



• **Fig. 12-115 Angiomyoma.** Well-circumscribed tumor exhibiting prominent blood vessels surrounded by smooth muscle.



• **Fig. 12-116 Angiomyoma.** Masson trichrome stain demonstrating bundles of smooth muscle *(red)* with adjacent normal collagen *(blue).*



• **Fig. 12-117 Adult Rhabdomyoma.** Nodular mass *(arrow)* in the left cheek. (Courtesy of Dr. Craig Little.)

analysis usually reveals the tumor cells to be positive for vimentin, smooth muscle actin, and muscle-specific actin; desmin positivity also may be seen.

Treatment and Prognosis

Oral leiomyomas are treated by local surgical excision. The lesion should not recur.

◆ RHABDOMYOMA

Benign neoplasms of skeletal muscle are called **rhabdomyomas.** The term *rhabdomyoma* also is used to describe a hamartomatous lesion of the heart that often is associated with tuberous sclerosis (see page 705). Despite the great amount of skeletal muscle throughout the body, benign skeletal muscle tumors are extremely rare. However, these extracardiac rhabdomyomas show a striking predilection for the head and neck. Rhabdomyomas of the head and neck can be subclassified into two major categories: 1) adult rhabdomyomas and 2) fetal rhabdomyomas.

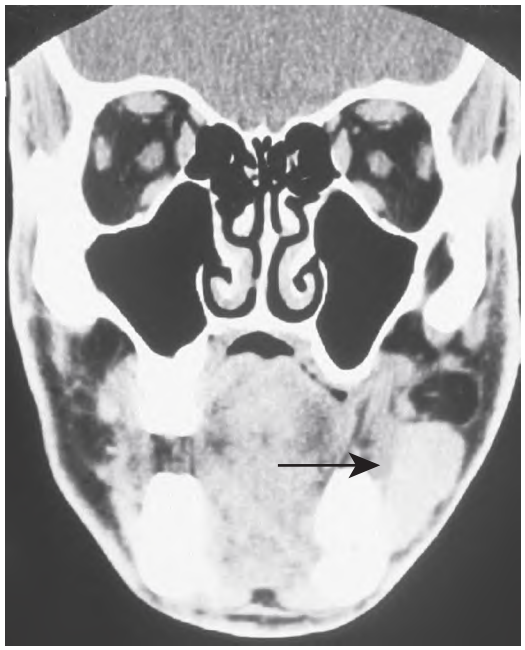
Clinical Features

Adult Rhabdomyomas

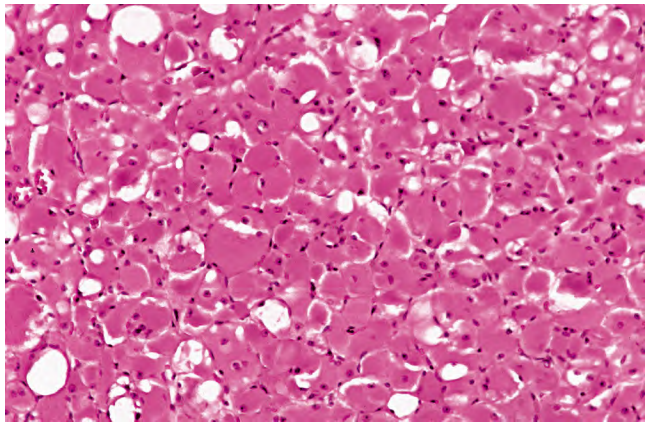
Adult rhabdomyomas of the head and neck occur primarily in middle-aged and older patients, with about 75% of cases found in men. The most frequent sites are the pharynx, oral cavity, and larynx; intraoral lesions are most common in the floor of the mouth, soft palate, and base of tongue. The tumor appears as a nodule or mass that can grow many centimeters before discovery (Figs. 12-117 and 12-118). Laryngeal and pharyngeal lesions often lead to airway obstruction. Sometimes, the tumor is multinodular in nature, with two or more discrete nodules found in the same anatomic location. From 3% to 10% of adult rhabdomyomas are multicentric, with separate, distinct tumors at different sites.

Fetal Rhabdomyomas

Fetal rhabdomyomas usually occur in young children, although some also develop in adults. A similar male predilection is noted. The most common locations are the face and periauricular region.



• **Fig. 12-118 Adult Rhabdomyoma.** Computed tomography (CT) scan of the same tumor depicted in Fig. 12-117. Note the mass *(arrow)* lateral to the left body of the mandible. (Courtesy of Dr. Craig Little.)

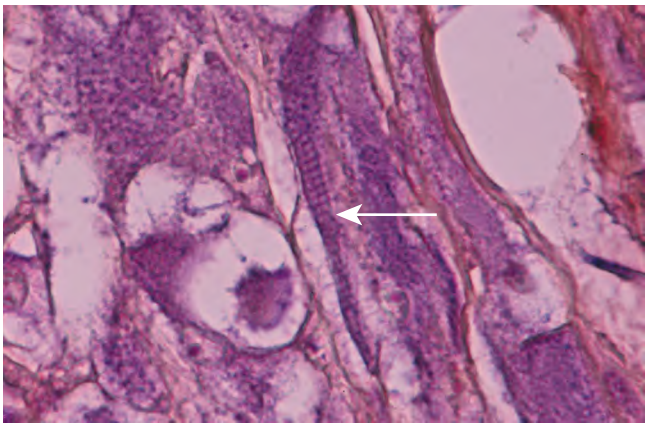


• **Fig. 12-119 Adult Rhabdomyoma.** Medium-power view showing a uniform tumor composed of rounded and polygonal cells with focal vacuolization.

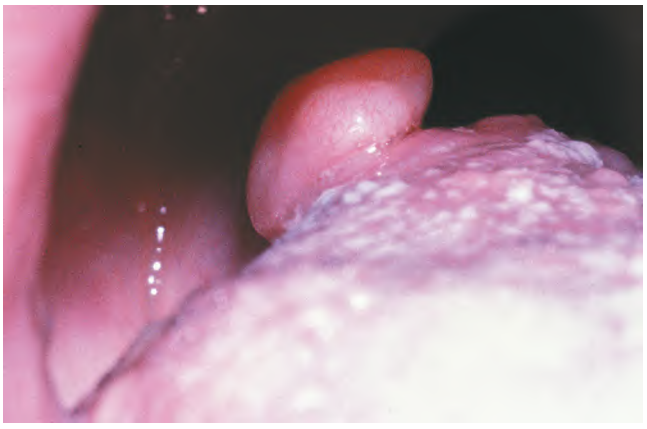
Histopathologic Features

Adult Rhabdomyomas

The adult rhabdomyoma is composed of well-circumscribed lobules of large, polygonal cells, which exhibit abundant granular, eosinophilic cytoplasm (Fig. 12-119). These cells often demonstrate peripheral vacuolization that results in a "spider web" appearance of the cytoplasm. Focal cells with cross striations can be identified in most cases (Fig. 12-120). Although rarely necessary for the diagnosis, immunohistochemical examination will show the tumor cells to be positive for myoglobin, desmin, and muscle-specific actin.



• **Fig. 12-120 Adult Rhabdomyoma.** Phosphotungstic acid hematoxylin (PTAH) stain that demonstrates focal cross striations in some cells *(arrow).*



• **Fig. 12-121 Osseous Choristoma.** Hard pedunculated nodule on the posterior dorsum of the tongue. (Courtesy of Dr. Michael Meyrowitz.)

Fetal Rhabdomyomas

The fetal rhabdomyoma has a less mature appearance and consists of a haphazard arrangement of spindle-shaped muscle cells that sometimes are found within a myxoid stroma. Some tumors may show considerable cellularity and mild pleomorphism, which makes them easily mistaken for rhabdomyosarcomas.

Treatment and Prognosis

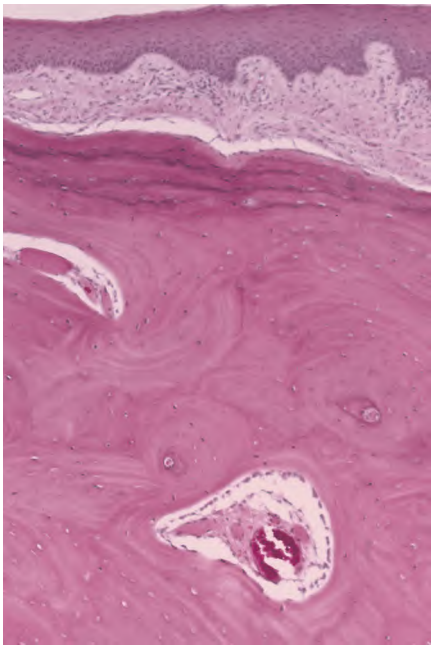
The treatment of both variants of rhabdomyoma consists of local surgical excision. Recurrence has been reported in 10% to 42% of cases, but this largely may be due to incomplete removal.

◆ OSSEOUS AND CARTILAGINOUS CHORISTOMAS

A **choristoma** is a tumorlike growth of microscopically normal tissue in an abnormal location. Several different tissue types may occur in the mouth as choristomas. These include gastric mucosa, glial tissue, and tumorlike masses of sebaceous glands. However, the most frequently observed choristomas of the oral cavity are those that consist of bone, cartilage, or both. These lesions sometimes have been called **soft tissue osteomas** or **soft tissue chondromas,** but *choristoma* is a better term because they do not appear to be true neoplasms.

Clinical Features

Osseous and cartilaginous choristomas show a striking predilection for the tongue, which accounts for 85% of cases. The most common location is the posterior tongue near the foramen cecum, although rare examples also have been reported elsewhere on the tongue and at other oral locations. The lesion is usually a firm, smooth-surfaced, sessile or pedunculated nodule between 0.5 and 2.0 cm in diameter (Fig. 12-121). Many patients are unaware of the lesion, although some complain of gagging or dysphagia.



• **Fig. 12-122 Osseous Choristoma.** Mass of dense lamellar bone beneath the surface epithelium.

Histopathologic Features

Microscopic examination of choristomas shows a well-circumscribed mass of dense lamellar bone or mature cartilage that is surrounded by dense fibrous connective tissue (Fig. 12-122). Sometimes a combination of bone and cartilage is formed. The bone has a well-developed Haversian canal system and occasionally demonstrates central fatty or hematopoietic marrow.

Treatment and Prognosis

Osseous and cartilaginous choristomas are best treated by local surgical excision. Recurrence has not been reported.

SOFT TISSUE SARCOMAS

Fortunately, soft tissue sarcomas are rare in the oral and maxillofacial region and account for less than 1% of the cancers in this area. Because of their relative rarity, it is beyond the scope of this book to give a complete, detailed discussion of each of these tumors. However, a review of these entities is included in the following section.

◆ FIBROSARCOMA

The **fibrosarcoma** is a malignant tumor of fibroblasts. At one time, it was considered one of the most common soft tissue sarcomas. However, the diagnosis of fibrosarcoma is made much less frequently today because of the recognition and separate classification of other spindle cell lesions that have similar microscopic features. The tumor is most common in the extremities; only 10% to 19% occur in the head and neck region.

Clinical Features

Fibrosarcomas most often present as slow-growing masses that may reach considerable size before they produce pain (Fig. 12-123). They can develop at any age and occur anywhere in the head and neck region. A number of cases have been reported in the nose and paranasal sinuses, where they often result in obstructive symptoms.

Histopathologic Features

Fibrosarcoma is often a diagnosis of exclusion, which is used for spindle cell sarcomas that do not fit microscopically into other recognized categories. Well-differentiated examples consist of fascicles of spindle-shaped cells that classically form a "herringbone" pattern (Fig. 12-124). The cells often show little variation in size and shape, although variable numbers of mitotic figures can usually be identified. In more poorly differentiated tumors, the cells are less organized and may appear rounder or ovoid. Mild pleomorphism along with more frequent mitotic activity may be seen. Higher grade tumors tend to produce less collagen than do well-differentiated tumors. Immunohistochemical markers should be negative except for vimentin and minimal smooth muscle actin.

Treatment and Prognosis

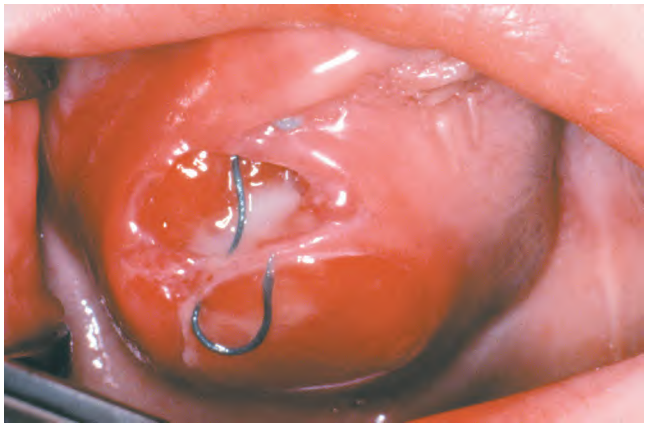
The treatment of choice is usually surgical excision, including a wide margin of adjacent normal tissue. Recurrence is noted in about half of cases, and 5-year survival rates range from 40% to 70%.

◆ UNDIFFERENTIATED PLEOMORPHIC SARCOMA (MALIGNANT FIBROUS HISTIOCYTOMA)

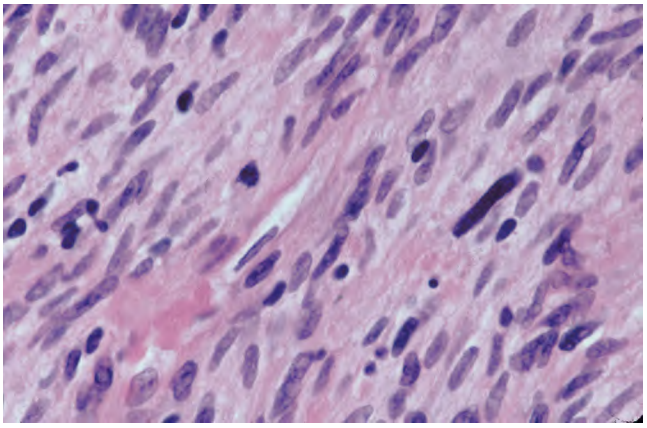
The term **malignant fibrous histiocytoma** was introduced in the 1960s to describe a group of sarcomas that were considered to show both fibroblastic and histiocytic features. This concept rapidly gained acceptance and malignant fibrous histiocytoma soon became the most commonly diagnosed soft tissue sarcoma in adults. However, experts today have questioned this concept because, with the help of immunohistochemistry and other ancillary studies, most tumors formerly diagnosed as malignant fibrous histiocytoma can now be reclassified into other categories, such as liposarcoma, leiomyosarcoma, rhabdomyosarcoma, myxofibrosarcoma, melanoma, and anaplastic carcinoma. However, there still remains a heterogeneous group of tumors from this former family, whose line of differentiation cannot be determined. The term **undifferentiated pleomorphic sarcoma** is now recommended for these lesions.

Clinical Features

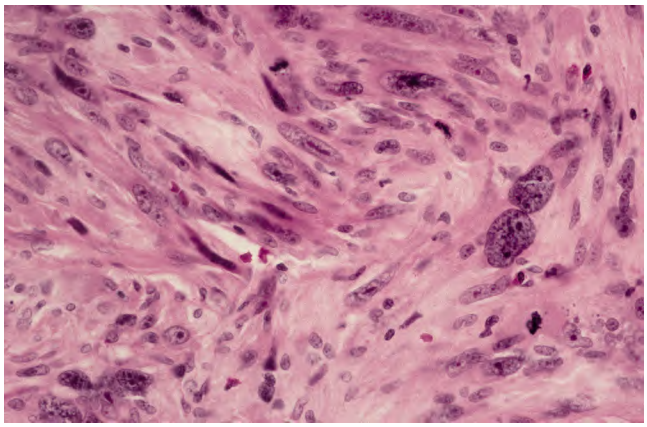
Undifferentiated pleomorphic sarcomas occur primarily in older age groups. The most common complaint is an expanding mass that may or may not be painful or ulcerated. The deep tissues of the trunk and extremities are the



• **Fig. 12-123 Fibrosarcoma.** Child with a large mass of the hard palate and maxillary alveolar ridge. (Courtesy of Dr. John McDonald.)



• **Fig. 12-124 Fibrosarcoma.** Cellular mass of spindle-shaped cells demonstrating mild pleomorphism.



• **Fig. 12-125 Undifferentiated Pleomorphic Sarcoma.** Spindle cell neoplasm demonstrating marked pleomorphism and scattered mitoses.

most frequent locations. Tumors of the nasal cavity and paranasal sinuses produce obstructive symptoms.

Histopathologic Features

Several histopathologic patterns have been described. The most classic variety is the storiform-pleomorphic type, which is characterized by short fascicles of plump spindle cells arranged in a storiform pattern, admixed with areas of pleomorphic giant cells (Fig. 12-125).

Treatment and Prognosis

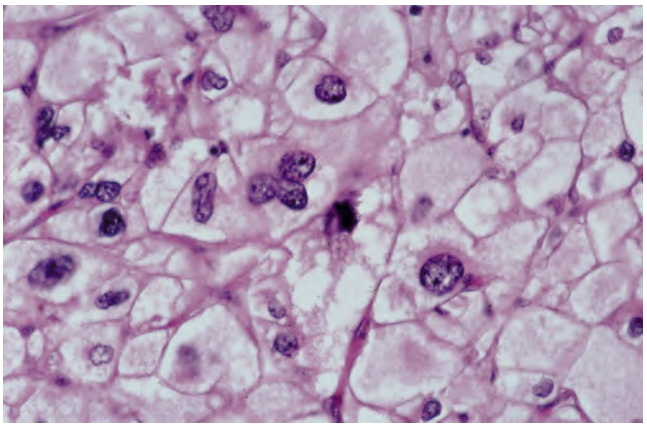
Undifferentiated pleomorphic sarcoma is considered to be an aggressive tumor that is usually treated by radical surgical resection. Approximately 40% of patients with head and neck tumors will have local recurrence, and almost 30% will develop metastases. The overall 5-year survival rate is 52% to 55%.

◆ LIPOSARCOMA

The **liposarcoma** is a malignant neoplasm of fatty origin. It currently is considered to be the most common soft tissue sarcoma and accounts for 17% to 30% of all soft tissue malignancies in adults. The most common sites are the thigh, retroperitoneum, and inguinal region. Liposarcomas of the head and neck are rare, comprising only 3% of all such tumors.

Clinical Features

Liposarcomas are seen primarily in adults; the mean age for head and neck tumors is 57 years. The tumor is typically a soft, slow-growing, ill-defined mass that may appear normal in color or yellow. Pain or tenderness is uncommon; when present, it is usually a late feature. The neck is the most common site for liposarcomas of the head and neck region. The most frequent intraoral locations are the tongue and cheek.



• **Fig. 12-126 Liposarcoma.** High-power view showing vacuolated lipoblasts with pleomorphic nuclei.

Histopathologic Features

Most liposarcomas can be divided into several major categories:

1. Well-differentiated liposarcoma/atypical lipomatous tumor
2. Myxoid/round cell liposarcoma
3. Pleomorphic liposarcoma
4. Dedifferentiated liposarcoma

The most common of these variants in the oral cavity is the **well-differentiated liposarcoma,** which accounts for 55% to 90% of all cases. These tumors resemble benign lipomas but demonstrate scattered lipoblasts and atypical, hyperchromatic stromal cells (Fig. 12-126).

Myxoid liposarcomas demonstrate proliferating lipoblasts within a myxoid stroma that contains a rich capillary network. The **round cell liposarcoma** is a more aggressive form of myxoid liposarcoma with less differentiated, rounded cells.

Pleomorphic liposarcomas exhibit extreme cellular pleomorphism and bizarre giant cells. **Dedifferentiated liposarcomas** are characterized by the combination of well-differentiated liposarcoma with poorly differentiated, non-lipogenic sarcomatous changes. These features may coexist in the same neoplasm, or the dedifferentiated changes may develop in a recurrent tumor or metastasis.

Treatment and Prognosis

Radical excision is the treatment of choice for most liposarcomas throughout the body. In spite of this, around 50% of all tumors recur. The overall 5-year survival rate ranges from 59% to 70%. There is a 10-year survival rate of approximately 50%. The histopathologic subtype is extremely important in predicting the prognosis; the outlook for pleomorphic liposarcomas is much worse than for myxoid and well-differentiated tumors.

In contrast, the prognosis for oral liposarcoma is more favorable because of the predominance of well-differentiated subtypes and because most tumors are small when

diagnosed. Local recurrence has been reported in 15% to 20% of cases, but metastasis and death as a result of tumor is rare.

◆ MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MALIGNANT SCHWANNOMA; NEUROFIBROSARCOMA; NEUROGENIC SARCOMA)

The principal malignancy of peripheral nerve origin is preferably called a **malignant peripheral nerve sheath tumor.** These tumors account for 3% to 10% of all soft tissue sarcomas, with nearly half of such cases occurring in patients with neurofibromatosis type I (see page 495). The lesion is most common on the proximal portions of the extremities and the trunk; 14% to 19% of cases occur in the head and neck.

Clinical and Radiographic Features

Malignant peripheral nerve sheath tumors are most common in young adults. The mean age in patients with neurofibromatosis (29 to 36 years) is about one decade younger than in those without this condition (40 to 46 years). The tumor is an enlarging mass that sometimes exhibits rapid growth. Associated pain or a nerve deficit is common.

Oral tumors may occur anywhere, but the most common sites are the mandible, lips, and buccal mucosa (see Figs. 12-68 and 12-69, page 497). Radiographic examination of intraosseous tumors of the mandible may reveal widening of the mandibular canal or the mental foramen, with or without irregular destruction of the surrounding bone.

Histopathologic Features

The malignant peripheral nerve sheath tumor shows fascicles of atypical spindle-shaped cells, which often resemble the cells of fibrosarcoma (see Fig. 12-70, page 516). However, these cells frequently are more irregular in shape with wavy or comma-shaped nuclei. In addition to streaming fascicles, less cellular myxoid areas also may be present. With some tumors, there can be heterologous elements, which include skeletal muscle differentiation **(malignant Triton tumor)**, cartilage, bone, or glandular structures.

A definitive diagnosis of neural origin often is difficult, especially in the absence of neurofibromatosis. Positive immunostaining for S-100 protein can be a helpful clue, but this is found in only about 50% of all cases and may be focal.

Treatment and Prognosis

The treatment of malignant peripheral nerve sheath tumors consists primarily of radical surgical excision, possibly along with adjuvant radiation therapy and chemotherapy. The prognosis is generally poor, with disease-specific survival ranging from 39% to 60% at 5 years, and 26% to 45% at 10 years. A number of studies have suggested that patients with neurofibromatosis type I have a worse prognosis than sporadic cases, although other studies have shown no significant difference between these two groups. One recent study reported that tumors negative for S-100 protein were associated with a significantly worse prognosis.

◆ OLFACTORY NEUROBLASTOMA (ESTHESIONEUROBLASTOMA)

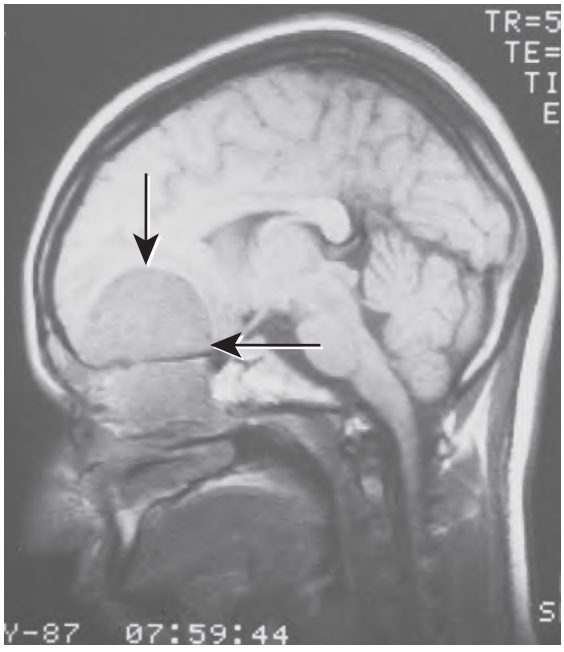
The **olfactory neuroblastoma** is a rare neuroectodermal neoplasm of the upper nasal vault that shows some similarities to neuroblastomas seen elsewhere in the body. It is believed to arise from sensory olfactory neuroepithelial cells.

Clinical and Radiographic Features

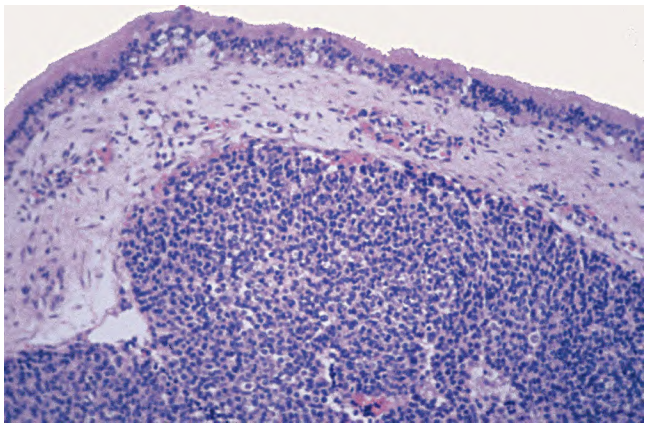
Unlike the usual neuroblastoma, the olfactory neuroblastoma is rare in patients younger than the age of 10 years. Instead, it is more common in adults, with a mean age at diagnosis of 45 to 56 years. The tumor arises high in the nasal cavity close to the cribriform plate. From there it may extend into the adjacent paranasal sinuses (especially the ethmoid sinus), the orbit, and the anterior cranial fossa (Fig. 12-127). The most common symptoms are nasal obstruction, epistaxis, pain, and anosmia.

Histopathologic Features

Olfactory neuroblastomas consist of small, round to ovoid basophilic cells that are arranged in sheets and lobules



• **Fig. 12-127 Olfactory Neuroblastoma.** A T1-weighted sagittal magnetic resonance image (MRI) showing a tumor filling the superior nasal cavity and ethmoid sinus, with extension into the anterior cranial fossa *(arrows).* (Courtesy of Dr. Pamela Van Tassel.)



• **Fig. 12-128 Olfactory Neuroblastoma.** Sheet of small, basophilic cells adjacent to the sinonasal epithelium *(top)*.

(Fig. 12-128). Rosette and pseudorosette formation and areas of delicate neurofibrillary material may be seen.

Treatment and Prognosis

The treatment of olfactory neuroblastoma consists of surgical excision, often with adjuvant radiation therapy. A combined craniofacial surgical approach frequently is used. Chemotherapy also has been administered, especially in advanced cases.

The prognosis depends on the stage of the disease. For patients with stage A lesions (tumor confined to the nasal cavity), the 5-year survival rate ranges from 75% to 91%. The 5-year survival rate drops to 68% to 71% for stage B disease (tumor extending into the paranasal sinuses). For stage C disease (tumor extending beyond the nasal cavity and sinuses), the 5-year survival rate ranges from 41% to 47%. Death is usually a result of local recurrence; metastasis occurs in approximately 20% to 37% of cases.

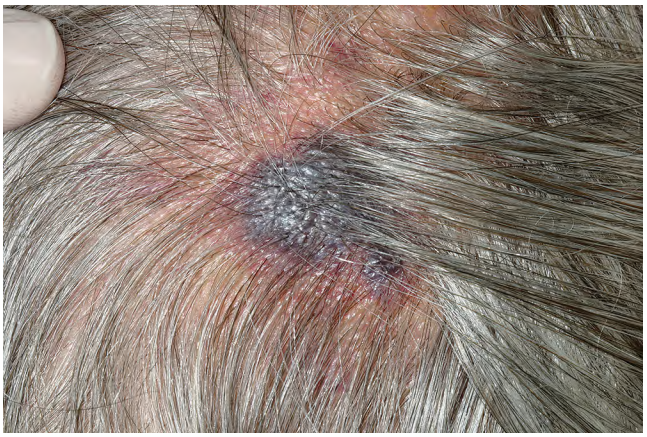
◆ ANGIOSARCOMA

Angiosarcoma is a rare malignancy of vascular endothelium, which may arise from either blood or lymphatic vessels. More than 50% of all cases occur in the head and neck region, with the scalp and forehead being the most common sites. Oral lesions are quite rare.

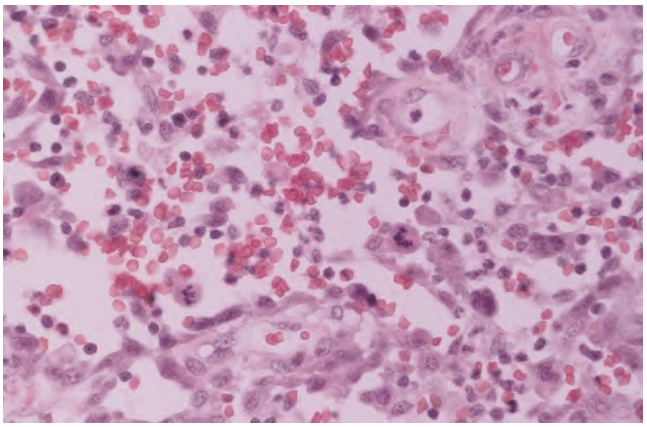
The term **hemangioendothelioma** is used to describe vascular tumors with microscopic features intermediate between those of hemangiomas and angiosarcomas. Such tumors also are rare and are considered to be of intermediate malignancy.

Clinical Features

Cutaneous angiosarcomas of the head and neck are most common in older adult patients. Early lesions often resemble a simple bruise, which may lead to a delay in diagnosis. However, the lesion continues to enlarge, which results in an elevated, nodular, or ulcerated surface (Fig. 12-129).



• **Fig. 12-129 Angiosarcoma.** Slightly elevated, bluish purple lesion on the scalp. (Courtesy of Dr. Terry Day.)



• **Fig. 12-130 Angiosarcoma.** Sinusoidal vascular spaces lined by pleomorphic endothelial cells.

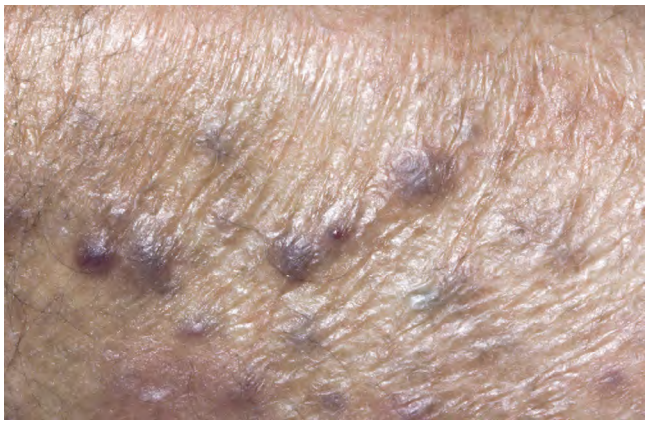
Many examples appear multifocal in nature. Oral angiosarcomas have been reported in various locations; the tongue and mandible are two of the more common sites.

Histopathologic Features

Angiosarcoma is characterized by an infiltrative proliferation of endothelium-lined blood vessels that form an anastomosing network (Fig. 12-130). The endothelial cells appear hyperchromatic and atypical; they often tend to pile up within the vascular lumina. Increased mitotic activity may be seen. Immunohistochemical studies show the tumor cells to be positive for CD31 and factor VIII–related antigen in most cases, whereas CD34 positivity is observed less consistently.

Treatment and Prognosis

Treatment usually consists of radical surgical excision, radiation therapy, or both. The prognosis for angiosarcoma of the face and scalp is poor, with a reported 10-year survival rate of only 14% to 21%. However, angiosarcomas of the oral cavity and salivary glands appear to have a better



• **Fig. 12-131 Kaposi Sarcoma.** Classic Kaposi sarcoma in an older man presenting as multiple purple macules and plaques on the lower leg.

outcome. One study showed 11 of 14 patients with oral and salivary angiosarcoma to be free of tumor on follow-up (mean follow-up period of 8.6 years).

◆ KAPOSI SARCOMA

Kaposi sarcoma is an unusual vascular neoplasm that was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist. Before the advent of the acquired immunodeficiency syndrome (AIDS) epidemic, it was a rare tumor; however, beginning in the early 1980s, Kaposi sarcoma became quite common because of its propensity to develop in individuals infected by HIV. Since the introduction of combination antiretroviral therapy (cART) in the mid- to late 1990s, the prevalence of AIDS-related Kaposi sarcoma in the Western world has declined.

Kaposi sarcoma is caused by infection with human herpesvirus 8 (HHV-8; Kaposi sarcoma-associated herpesvirus [KSHV]). The lesion most likely arises from endothelial cells, which may express markers for both lymphatic and blood vessel differentiation. Four clinical presentations are recognized:

1. Classic
2. Endemic (African)
3. Iatrogenic (transplant-associated)
4. Epidemic (AIDS-related)

The first three forms are discussed here; AIDS-related Kaposi sarcoma is covered in the section on HIV disease (see page 244).

Clinical Features

Classic Type

Classic (chronic) Kaposi sarcoma is primarily a disease of late adult life, and 70% to 95% of cases occur in men. It mostly affects individuals of Italian, Jewish, or Slavic ancestry. Multiple blue-purple macules and plaques are present on the skin of the lower extremities (Fig. 12-131). These lesions grow slowly over many years and develop into painless tumor nodules. Oral lesions are rare and most frequently involve the palate. Some studies have suggested that patients with classic Kaposi sarcoma have an increased prevalence of lymphoreticular malignancies, but other reports have questioned any significant association.

Endemic Type

Prior to the advent of HIV/AIDS, endemic Kaposi sarcoma was already recognized as a relatively common neoplasm of younger adults and children in sub-Saharan Africa. The course of the disease can vary widely; some patients develop indolent skin lesions similar to the pattern observed in classic Kaposi sarcoma, whereas others exhibit more aggressive tumors that involve deeper tissues, bone, and viscera. A particularly aggressive lymphadenopathic form also is recognized in young children, which is characterized by rapidly growing tumors of the lymph nodes, occasional visceral organ lesions, and sparse skin involvement. Although endemic Kaposi sarcoma used to be the most common form of the disease seen in Africa, epidemic (AIDS-related) Kaposi sarcoma is seen more frequently now.

Iatrogenic Type

Iatrogenic (transplant-associated) Kaposi sarcoma occurs in recipients of solid organ transplants. It affects 0.5% of renal transplant patients, usually several months to a few years after the transplant. It is probably related to the loss of cellular immunity from immunosuppressive therapy given to prevent organ rejection. Like classic Kaposi sarcoma, iatrogenic cases are more common in individuals of Italian, Jewish, and Slavic ancestry; however, the disease may run a more aggressive course.

Histopathologic Features

Kaposi sarcoma typically evolves through three stages:

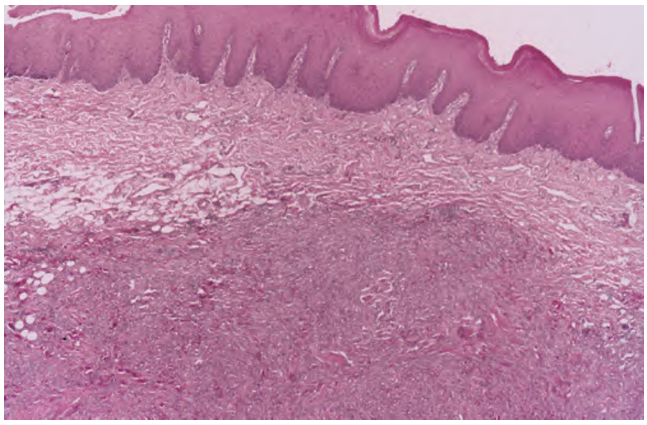
1. Patch (macular)
2. Plaque
3. Nodular

A proliferation of miniature vessels characterizes the **patch stage.** This results in an irregular, jagged vascular network that surrounds preexisting vessels. Sometimes normal structures, such as hair follicles or preexisting blood vessels, may appear to protrude into these new vessels (promontory sign). The lesional endothelial cells have a bland appearance and may be associated with scattered lymphocytes and plasma cells.

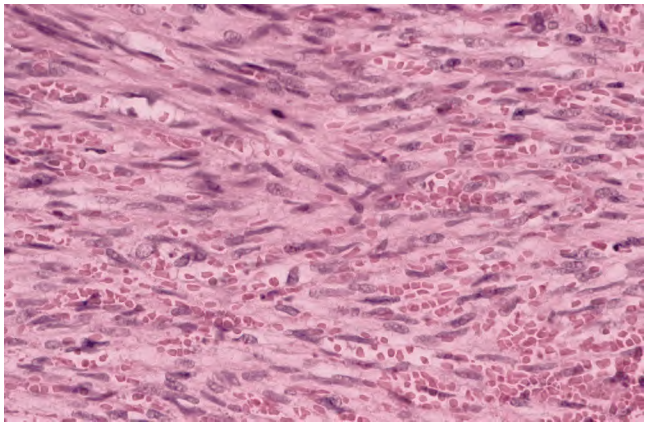
The **plaque stage** demonstrates further proliferation of these vascular channels along with the development of a significant spindle cell component.

In the **nodular stage,** the spindle cells increase to form a nodular tumorlike mass that may resemble a fibrosarcoma or other spindle cell sarcomas (Figs. 12-132 and 12-133). However, numerous extravasated erythrocytes are present, and slitlike vascular spaces may be discerned.

Other microscopic variants of Kaposi sarcoma include lymphangioma-like, telangiectatic, desmoplastic, lymphangiectatic, ecchymotic, and anaplastic subtypes.



• **Fig. 12-132 Kaposi Sarcoma.** Low-power photomicrograph showing a cellular spindle cell tumor within the connective tissue.

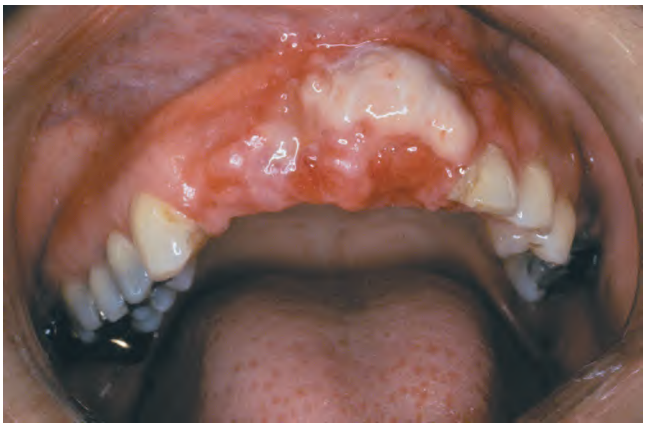


• **Fig. 12-133 Kaposi Sarcoma.** High-power photomicrograph showing spindle cells and poorly defined vascular slits.

Treatment and Prognosis

The treatment of Kaposi sarcoma depends on the clinical subtype and stage of the disease. For skin lesions in the classic form of the disease, radiation therapy (especially electron beam) often is used. Radiation therapy for oral lesions must be approached with caution, because an unusually severe mucositis can develop. Surgical excision can be performed for the control of individual lesions of the skin or mucosa. Systemic chemotherapy also may be helpful. Intralesional injection of vinblastine is used to control individual lesions.

The prognosis is variable, depending on the form of the disease and the patient's immune status. The classic form of the disease is slowly progressive; only 10% to 20% of patients develop disseminated lesions. The mean survival time is 10 to 15 years, and patients often die from unrelated causes. Some patients with the endemic form of the disease develop indolent lesions similar in behavior to classic non-African Kaposi sarcoma. However, the other endemic African forms are more aggressive and the prognosis is poorer. The lymphadenopathic form runs a particularly fulminant course, usually resulting in the death of the patient within 2 to 3 years. In transplant patients, the disease also may be somewhat more aggressive, although the tumors may regress if immunosuppressive therapy is discontinued or reduced.



• **Fig. 12-134 Leiomyosarcoma.** Ulcerated mass of the anterior maxillary alveolar ridge. (Courtesy of Dr. Jim Weir.)

LEIOMYOSARCOMA

The **leiomyosarcoma** is a malignant neoplasm of smooth muscle differentiation, which accounts for 7% of all soft tissue sarcomas. The most common sites are the uterine wall and gastrointestinal tract. Leiomyosarcomas of the oral cavity are rare.

Clinical Features

In general, leiomyosarcomas are most common in middle-aged and older adults. However, tumors in the oral and maxillofacial region occur over a wide age range without a predilection for any age group. They have been reported at various sites, but half of all oral cases occur in the jawbones. The clinical appearance is nonspecific; there is usually an enlarging mass that may or may not be painful (Fig. 12-134). Secondary ulceration of the mucosal surface may occur.

Histopathologic Features

The microscopic examination of a leiomyosarcoma shows fascicles of spindle-shaped cells with abundant eosinophilic cytoplasm and blunt-ended, cigar-shaped nuclei (Fig. 12-135). Some tumors may be composed primarily of rounded epithelioid cells that have either eosinophilic or clear cytoplasm (epithelioid leiomyosarcoma). The degree of pleomorphism varies from one tumor to the next, but smooth muscle tumors with the presence of five or more mitoses per ten high-power fields should be considered malignant. Glycogen usually can be demonstrated within the cells with a periodic acid-Schiff (PAS) stain, and the cell cytoplasm appears bright red with a Masson trichrome stain. Immunohistochemical analysis usually reveals the presence of one or more of the following myogenic markers:

desmin, muscle-specific actin (HHF 35), smooth muscle myosin (SMMS), and smooth muscle actin.

Treatment and Prognosis

The treatment of leiomyosarcoma primarily consists of radical surgical excision, sometimes with adjunctive chemotherapy or radiation therapy. The prognosis for oral tumors is guarded, with the potential for local recurrence and distant metastasis. Although few cases are available for analysis, a 5-year survival rate of 55% has been estimated.

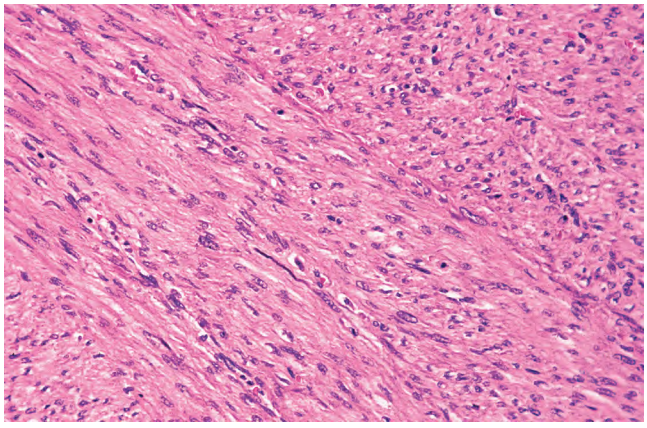
◆ RHABDOMYOSARCOMA

Rhabdomyosarcoma is a malignant neoplasm that is characterized by skeletal muscle differentiation. These tumors are much more common in young children, accounting for 50% of soft tissue sarcomas in childhood. In contrast, rhabdomyosarcoma comprises only 2% to 5% of soft tissue sarcomas in adults. The most frequent site is the head and neck, which accounts for 35% of all cases. The genitourinary tract is the second most common location. Several microscopic patterns of pediatric rhabdomyosarcoma are recognized (Table 12-2), although discussion here will be limited primarily to the embryonal and alveolar subtypes.

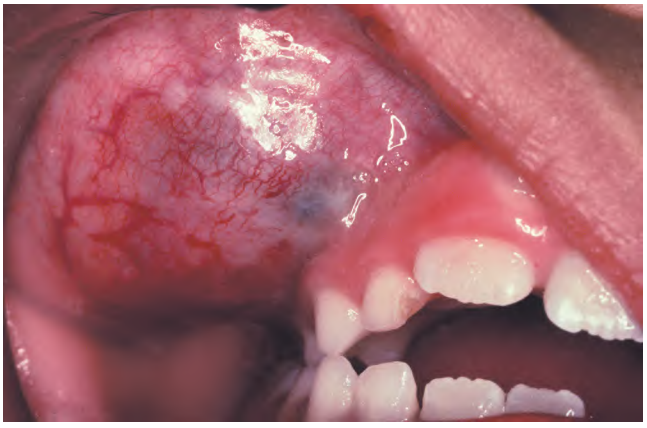
Clinical Features

Rhabdomyosarcoma primarily occurs during the first decade of life but also may occur in teenagers and young adults. It is rare in people older than 45 years, and approximately 60% of all cases occur in males. Embryonal rhabdomyosarcomas are most common in the first 10 years of life and account for about 60% of all cases. Alveolar rhabdomyosarcomas occur most often in persons between 10 and 25 years of age; they account for 20% to 30% of all tumors. Pleomorphic rhabdomyosarcomas represent less than 5% of all cases and show peak prevalence in patients older than 40 years of age. Most head and neck lesions are embryonal or alveolar types; pleomorphic rhabdomyosarcomas primarily occur on the extremities.

The tumor is most often a painless, infiltrative mass that may grow rapidly (Figs. 12-136 and 12-137). In the head and neck region, the face and orbit are the most frequent



• **Fig. 12-135 Leiomyosarcoma.** Medium-high–power view of a pleomorphic spindle cell proliferation.

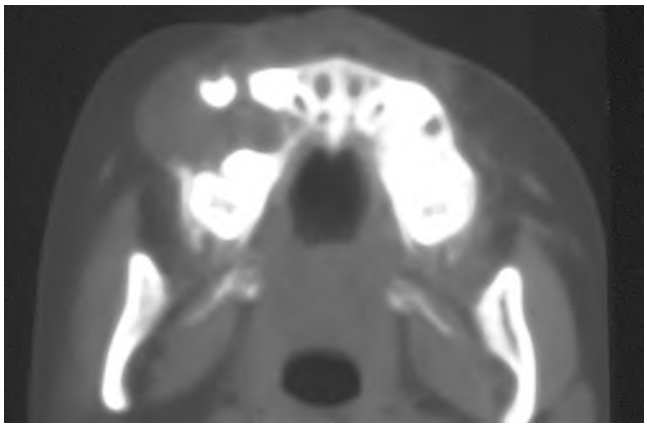


• **Fig. 12-136 Embryonal Rhabdomyosarcoma.** Young child with a mass of the right maxilla. (Courtesy of Dr. Robert Achterberg.)

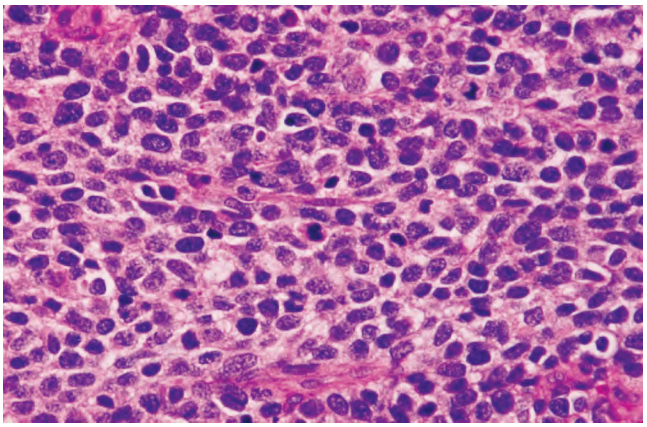
TABLE 12-2 Pediatric Rhabdomyosarcomas

Major Types	Distribution	Five-Year Survival	Relative Prognosis
Embryonal rhabdomyosarcoma			
NOS	49%	66%	Intermediate
Botryoid	6%	95%	Excellent
Spindle	3%	88%	Excellent
Alveolar rhabdomyosarcoma	31%	53%	Poor
Undifferentiated sarcoma	3%	44%	Poor
Anaplastic rhabdomyosarcoma	2%	45%	Poor

Adapted from Hicks J, Flaitz C: Rhabdomyosarcoma of the head and neck in children, *Oral Oncol* 38:450-459, 2002.
NOS, Not otherwise specified.



• **Fig. 12-137 Embryonal Rhabdomyosarcoma.** Computed tomography (CT) scan of patient from Fig. 12-136 showing expansile lytic lesion of the maxilla. (Courtesy of Dr. Robert Achterberg.)



• **Fig. 12-138 Embryonal Rhabdomyosarcoma.** Medium-power view showing a sheet of small, round cells with hyperchromatic nuclei.

locations, followed by the nasal cavity. The palate is the most frequent intraoral site, and some lesions may appear to arise in the maxillary sinus and break through into the oral cavity. Some embryonal rhabdomyosarcomas that arise within a cavity, such as the vagina or oropharynx, demonstrate an exophytic, polypoid growth pattern that resembles a cluster of grapes. The term *botryoid* (grapelike) *rhabdomyosarcoma* has been used for these lesions.

Histopathologic Features

Embryonal Type

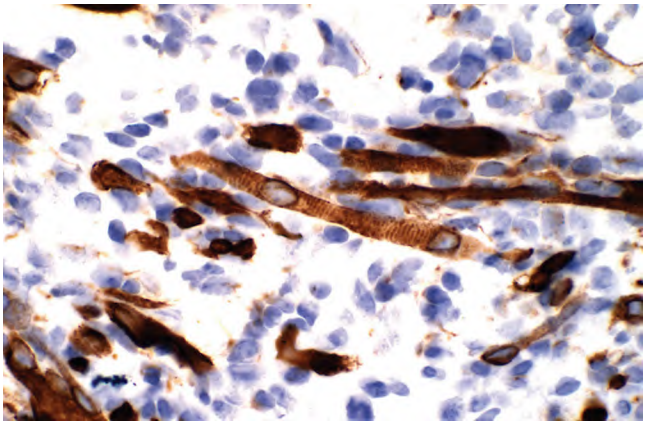
The embryonal rhabdomyosarcoma resembles various stages in the embryogenesis of skeletal muscle. Poorly differentiated examples may be difficult to diagnose and consist of small round or oval cells with hyperchromatic nuclei and indistinct cytoplasm (Fig. 12-138). Alternating hypercellular and myxoid zones may be seen. Better-differentiated lesions show round to ovoid rhabdomyoblasts with distinctly eosinophilic cytoplasm and fibrillar material around the nucleus. Some tumors contain elongated, strap-shaped rhabdomyoblasts, but cross striations rarely are found (Fig. 12-139).

The **botryoid** subtype of embryonal rhabdomyosarcoma is sparsely cellular and has a pronounced myxoid stroma. Increased cellularity, or a so-called *cambium layer,* is usually seen just beneath the mucosal surface.

Immunohistochemical analysis for the presence of desmin, myogenin, and muscle-specific actin can be helpful in supporting the muscular nature of the tumor. However, the intensity of the immunostaining can vary depending on the degree of rhabdomyoblastic differentiation.

Alveolar Type

Both classic and solid variants of alveolar rhabdomyosarcoma are recognized. The classic pattern is characterized by aggregates of poorly differentiated round to oval cells separated by fibrous septa. These cells demonstrate a central loss of cohesiveness, which results in an alveolar pattern. The peripheral cells of these aggregates adhere to the septal walls



• **Fig. 12-139 Embryonal Rhabdomyosarcoma.** This tumor shows strap-shaped rhabdomyoblasts that are positive for desmin with immunohistochemical staining. Note the cross striations.

in a single layer. The central cells appear to float freely within the alveolar spaces. Mitoses are common, and multinucleated giant cells also may be seen. In contrast, solid alveolar rhabdomyosarcoma demonstrates cellular fields of small round basophilic cells without fibrovascular septa.

Cytogenetic and molecular studies play an important role in the diagnosis of rhabdomyosarcoma. Two distinct chromosomal translocations have been identified in alveolar rhabdomyosarcoma: *PAX3-FKHR (FOXO1)* and *PAX7-FKHR (FOXO1).* Embryonal rhabdomyosarcoma usually is characterized by loss of heterozygosity with loss of imprinting at chromosome 11p15.5.

Treatment and Prognosis

Before 1960 the prognosis for a patient with rhabdomyosarcoma was extremely poor, with more than 90% of patients dying. With the advent of multimodal therapy, the prognosis has improved dramatically.

Treatment typically consists of local surgical excision followed by multiagent chemotherapy (vincristine, actinomycin D, and cyclophosphamide). Postoperative radiation therapy also is used, except for localized tumors that have

been completely resected at initial surgery. The 5-year survival rate for embryonal rhabdomyosarcoma (not otherwise specified [NOS]) of the head and neck is around 66% to 72%, although the figures for botryoid (95%) and spindle cell variants (88%) are much better. The 5-year survival rate for alveolar rhabdomyosarcoma is only 44% to 53%.

◆ SYNOVIAL SARCOMA

Synovial sarcoma is an uncommon malignancy that represents 5% to 10% of all soft tissue sarcomas. The tumor occurs primarily near large joints and bursae, especially in the extremities, but authorities now agree that this lesion probably does not arise from the synovium. Although it is often para-articular in location, the tumor rarely occurs within the joint capsule. In some instances, it arises in areas without any obvious relationship to synovial structures. Synovial sarcomas of the head and neck are rare (only 1.9% to 3.7% of all cases), and many of these are unrelated to joint areas.

Over 90% of synovial sarcomas exhibit a specific balanced reciprocal translocation between the X chromosome and chromosome 18: t(X;18)(p11.2;q11.2), which results in an SS18-SSX fusion gene. Detection of this translocation can be helpful in making the diagnosis and confirming the presence of metastatic disease.

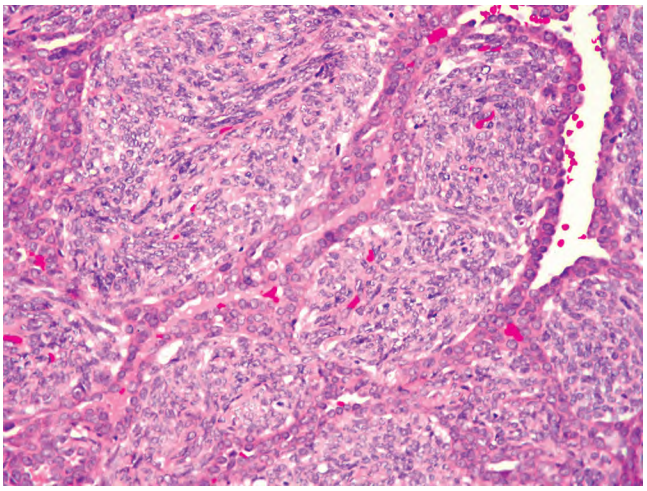
Clinical Features

Synovial sarcomas most frequently occur in teenagers and young adults, and there is a slight male predilection. The most common presentation is a gradually enlarging mass that often is associated with pain or tenderness. Tumors in the head and neck region are most common in the paravertebral and parapharyngeal areas. Often, they produce symptoms of dysphagia, dyspnea, or hoarseness. One recent series of head and neck synovial sarcomas showed a predilection for the parotid and temporal regions. Oral tumors most often have been reported in the tongue and cheek.

Histopathologic Features

Classic synovial sarcoma is a biphasic tumor that consists of a combination of spindle cells and epithelial cells (Fig. 12-140). The spindle cells usually predominate and produce a pattern that is similar to fibrosarcoma. Within this spindle cell background are groups of cuboidal to columnar epithelial cells that surround glandlike spaces or form nests, cords, or whorls. Calcifications are seen in around 30% of cases.

Frequently the tumor is monophasic and consists primarily or entirely of spindle cells. The diagnosis of these tumors is difficult, but most lesions demonstrate at least focal positive immunostaining of spindle cells for cytokeratin or epithelial membrane antigen. Molecular genetic testing for the SS18-SSX fusion gene transcript is especially helpful in confirming the diagnosis. Rare examples of monophasic epithelial synovial sarcomas also have been reported.



• **Fig. 12-140 Synovial Sarcoma.** Biphasic tumor consisting of spindle cells intermixed with cuboidal to columnar epithelial cells that line glandlike spaces.

Treatment and Prognosis

Treatment of synovial sarcoma usually consists of radical surgical excision, possibly with adjunctive radiation therapy or chemotherapy. The prognosis is poor because the tumor has a high rate of recurrence and metastasis. The reported 5-year survival rate ranges from 36% to 64%. However, the 10-year survival rate drops to 20% to 38% because of the high rate of late metastases.

◆ ALVEOLAR SOFT-PART SARCOMA

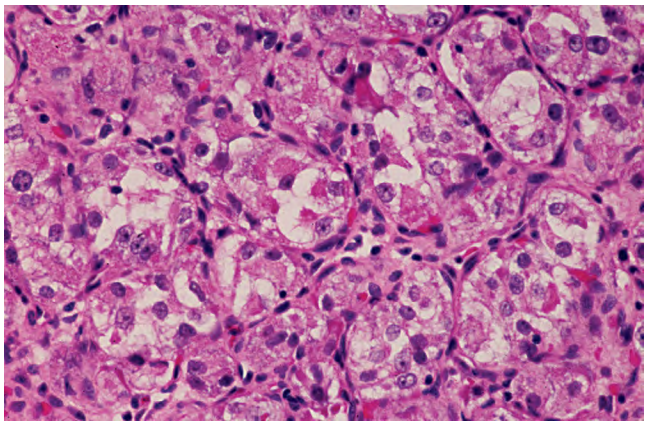
The **alveolar soft-part sarcoma** is a rare neoplasm of uncertain histogenesis, which accounts for 0.5% to 1% of all soft tissue sarcomas. About 5% to 12% of all cases occur in the head and neck. Molecular analysis of this tumor shows a characteristic genetic translocation, der(17)t(X;17)(p11.2;q25), which results in an *ASPL-TFE3* fusion gene.

Clinical Features

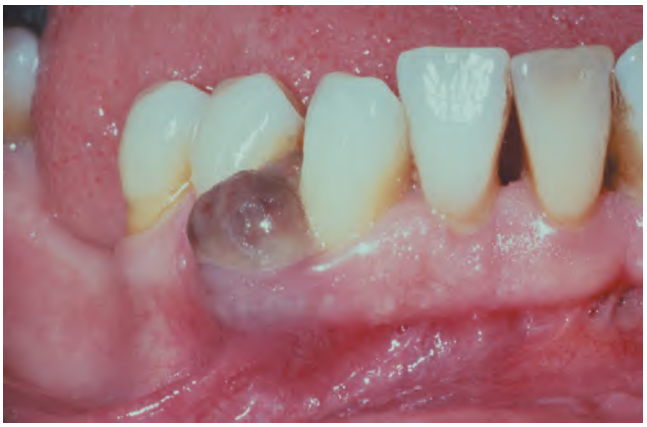
The alveolar soft-part sarcoma is usually a slow-growing, painless mass that is most common in young adults and children. The lower extremity is the most frequent location. The orbit and tongue are the most common head and neck sites, and the median age for lingual tumors is only 5 to 8 years. During the first two decades of life, the tumor shows nearly a 2:1 female predilection. However, cases that develop after the age of 30 are more common in men.

Histopathologic Features

Alveolar soft-part sarcomas are composed of groups of large, polygonal cells that are arranged around central alveolar



• **Fig. 12-141 Alveolar Soft-Part Sarcoma.** Alveolar collections of large, polygonal cells containing abundant granular cytoplasm.



• **Fig. 12-142 Metastatic Melanoma.** Pigmented nodule of the mandibular gingiva.

spaces (Fig. 12-141). These cells have abundant granular, eosinophilic cytoplasm and one to several vesicular nuclei. Mitoses are rare. Special stains will reveal PAS-positive, diastase-resistant crystals that are highly characteristic for this tumor. Under the electron microscope, these crystals appear as rhomboid, polygonal, or rod-shaped structures with a regular latticework pattern.

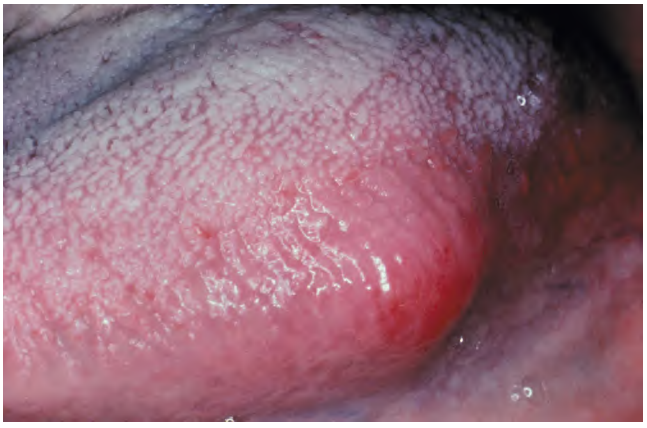
Immunohistochemical analysis will demonstrate strong positivity for TFE3 transcription factor in the tumor nuclei. The diagnosis can be confirmed by identification of the *ASPL-TFE3* fusion gene with reverse-transcription polymerase chain reaction (RT-PCR).

Treatment and Prognosis

Most patients with alveolar soft-part sarcomas are treated by radical surgical excision, possibly in conjunction with radiation therapy and chemotherapy. The prognosis is generally poor, often as a result of late metastasis. One study reported a 5-year survival rate of 60%, but the 20-year survival rate dropped to only 15%. Another series showed a 5-year disease-free survival of 71% for patients with localized disease, compared with only 20% for patients who presented with metastatic disease. However, the prognosis for children appears to be better than for adults. Lingual and orbital tumors have much higher survival rates, possibly because of smaller tumor size at diagnosis and younger patient age.

◆ METASTASES TO THE ORAL SOFT TISSUES

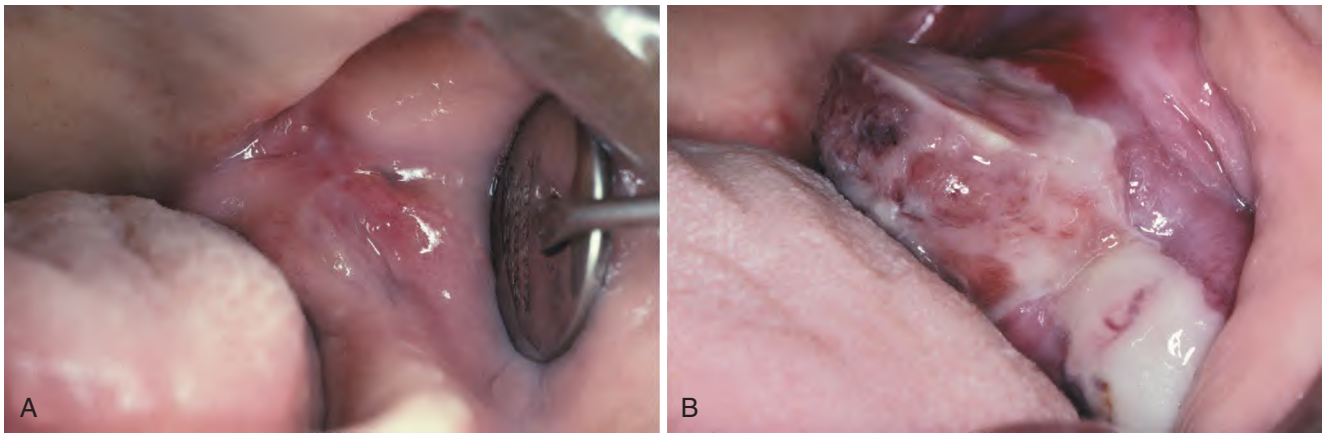
Metastatic tumors to the oral cavity are uncommon and represent approximately 1% of all oral malignancies. Such metastases can occur to bone (see page 622) or to the oral soft tissues. The mechanism by which tumors can spread to the oral cavity is poorly understood. Primary malignancies from immediately adjacent tissues might be able to spread by a lymphatic route; however, such a mechanism cannot explain metastases from tumors from lower parts of the body, which are almost certainly blood-borne and should be filtered out by the lungs. One possible explanation for blood-borne metastases to the head and neck, especially in the absence of pulmonary metastases, is **Batson plexus,** a valveless vertebral venous plexus that might allow retrograde spread of tumor cells, bypassing filtration through the lungs.



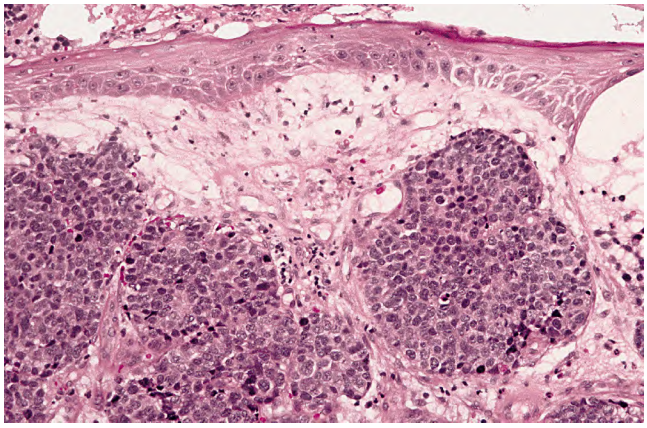
• **Fig. 12-143 Metastatic Renal Carcinoma.** Nodular mass of the left lateral border of the tongue. (Courtesy of Dr. Mark Bowden.)

Clinical Features

The most common site for oral soft tissue metastases is the gingiva, which accounts for 54% of all cases. The next most common site is the tongue, which accounts for 22.5% of cases. The lesion usually appears as a nodular mass that often resembles a hyperplastic or reactive growth, such as a pyogenic granuloma (Figs. 12-142 to 12-144). Occasionally, the lesion appears as a surface ulceration. Adjacent teeth may become loosened by an underlying destruction of the alveolar bone. The presence of teeth may play an important role in the preference of metastases for the gingiva. Once malignant cells reach the oral cavity, the rich vascular network of inflamed gingival tissues may serve as a fertile site for further growth.



• **Fig. 12-144 Metastatic Adenocarcinoma of the Colon. A,** Focal swelling of the left retromolar pad area. **B,** Same patient 4 weeks later. Note the marked enlargement of the lesion. (Courtesy of Dr. George Blozis.)



• **Fig. 12-145 Metastatic Carcinoma of the Lung.** Aggregates of malignant epithelial cells below the surface epithelium.

Oral soft tissue metastases are more common in males and are seen most frequently in middle-aged and older adults. Almost any malignancy from any body site is capable of metastasis to the oral cavity, and a wide variety of tumors have been reported to spread to the mouth. (However, there is probably a bias in the literature toward reporting more unusual cases.) In the cases reported, lung cancer is responsible for nearly one-third of all oral soft tissue metastases in men, followed by renal carcinoma and melanoma. Although prostate cancer is common in men, metastases from these tumors have an affinity for bone and rarely occur in soft tissues. For women, breast cancer accounts for almost 25% of all cases, followed by malignancies of the genital organs, kidney, lung, and bone.

In most cases the primary tumor already is known when the metastatic lesion is discovered. In 25% of patients, however, the oral lesion is the first sign of the malignant disease.

Histopathologic Features

The microscopic appearance of the metastatic neoplasm should resemble the tumor of origin (Fig. 12-145). Most cases represent carcinomas; metastatic sarcomas to the oral region are rare.

Treatment and Prognosis

The prognosis for patients with metastatic tumors is generally poor because other metastatic sites also are frequently present. Management of the oral lesion is usually palliative and should be coordinated with the patient's overall treatment.

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13 Hematologic Disorders

LYMPHOID HYPERPLASIA

The lymphoid tissue of the body plays an important role in the recognition and processing of foreign antigens, such as viruses, fungi, and bacteria. In addition, the lymphoid tissue has a protective function through a variety of direct and indirect mechanisms. In responding to antigenic challenges, lymphoid cells proliferate, thus increasing their numbers, to combat the offending agent more effectively. This proliferation results in enlargement of the lymphoid tissue, which is seen clinically as **lymphoid hyperplasia.**

Clinical Features

Lymphoid hyperplasia may affect the lymph nodes, the lymphoid tissue of Waldeyer ring, or the aggregates of lymphoid tissue that are normally scattered throughout the oral cavity, particularly in the oropharynx, the soft palate, the lateral tongue, and the floor of the mouth. When lymphoid hyperplasia affects the lymph nodes, usually the site that the lymph node drains can be identified as a source of active or recent infection. In the head and neck region, the anterior cervical chain of lymph nodes is most commonly involved, although any lymph node in the area may be affected.

With acute infections, the lymphadenopathy appears as enlarged, tender, relatively soft, freely movable nodules. Chronic inflammatory conditions produce enlarged, rubbery firm, nontender, freely movable nodes. Sometimes these chronic hyperplastic lymph nodes may be difficult to distinguish clinically from lymphoma, and a history of a preceding inflammatory process and lack of progressive enlargement are helpful clues that are consistent with a reactive process. Another condition, however, that should be considered in the differential diagnosis of multiple, persistently enlarged, nontender lymph nodes is human immunodeficiency virus (HIV) infection (see page 245).

Tonsillar size is variable from one person to the next, but lymphoid tissue is normally more prominent in younger individuals, usually reaching its peak early during the second decade of life and gradually diminishing thereafter. Some patients have such large tonsils that it seems as if they would occlude the airway (so-called kissing tonsils). Often, however, these patients have no symptoms and are unaware of a problem. As long as the large tonsils are symmetrical and asymptomatic (Fig. 13-1), it is likely that they are normal for that particular patient. Tonsillar asymmetry is a potentially serious sign that should be evaluated further to rule out the presence of a metastatic tumor or lymphoma.

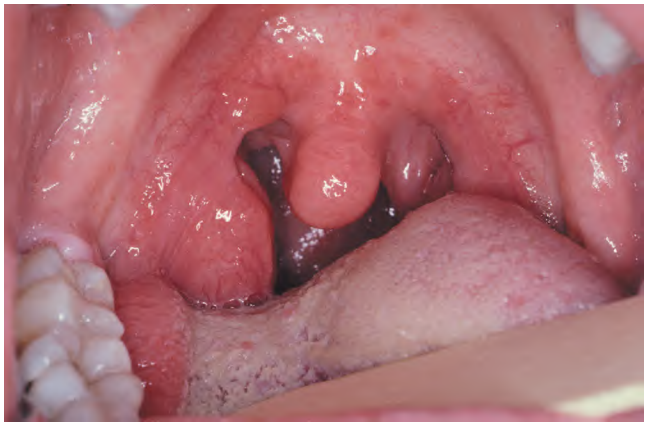
Hyperplastic intraoral lymphoid aggregates appear as discrete, nontender, submucosal swellings, usually less than 1 cm in diameter, which may appear normal or dark pink in color if the aggregate is deeper; they may have a creamy yellow-orange to amber hue if the collection of lymphocytes is closer to the surface (Figs. 13-2 and 13-3). Lymphoid hyperplasia commonly involves the posterior lateral tongue, where it may appear somewhat ominous. The enlargement is usually bilaterally symmetrical, however, which helps to distinguish the condition from a malignancy. The buccal lymph node may also become hyperplastic and appear as a nontender, solitary, freely movable nodule, usually less than 1 cm in diameter, within the substance of the cheek. Infrequently, a more diffuse lymphoid hyperplasia involves the posterior hard palate, producing a slowly growing, nontender, boggy swelling with an intact mucosal surface and little color change. These palatal lesions may be clinically impossible to distinguish from extranodal lymphoma and would, therefore, necessitate biopsy.

Histopathologic Features

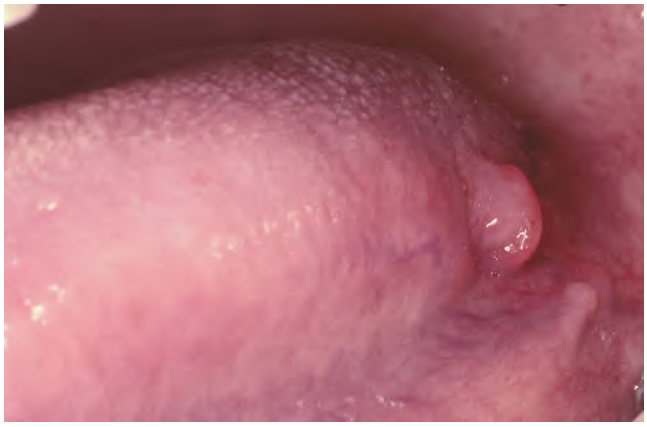
The microscopic features of lymphoid hyperplasia include sheets of small, well-differentiated lymphocytes with numerous interspersed, sharply demarcated collections of reactive lymphoblasts called **germinal centers.** The cells that comprise the germinal centers are primarily transformed B lymphocytes that may demonstrate numerous mitoses. Macrophages can also be identified by the presence of phagocytized material **(tingible bodies)** in their cytoplasm as they engulf nuclear debris from the proliferating lymphocytes. In some instances, immunohistochemical studies and clonality assays must be performed to rule out the possibility of follicular lymphoma.

Treatment and Prognosis

Once the diagnosis of lymphoid hyperplasia is confirmed, no treatment is usually required because it is a completely benign process. For those patients with palatal lymphoid hyperplasia that may interfere with a dental prosthesis, complete excision of the lesion is recommended.



• **Fig. 13-1 Lymphoid Hyperplasia.** The large tonsil observed in this patient represents a benign hyperplasia of the lymphoid cells. If significant asymmetry is observed, further investigation may be warranted to rule out the possibility of lymphoma.



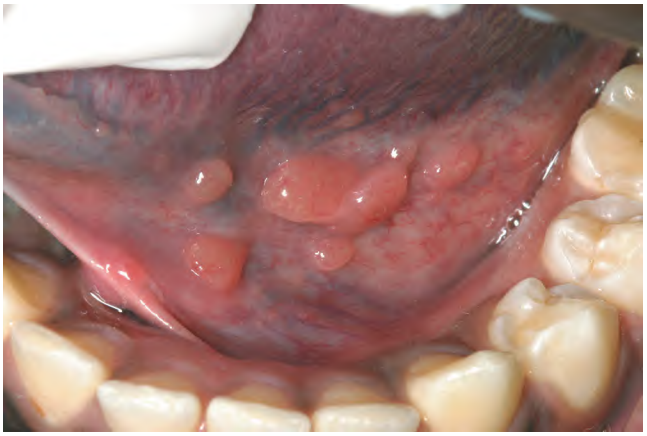
• **Fig. 13-2 Lymphoid Hyperplasia.** The smooth-surfaced papule of the posterior lateral tongue represents an enlarged lymphoid aggregate. The lesion exhibits a lighter color as a result of the accumulation of lymphocytes, which are white blood cells. (Courtesy of Dr. Dean White.)

◆ HEMOPHILIA

Hemophilia (*hemo* = blood; *philia* = loving) represents a variety of bleeding disorders associated with a genetic deficiency of any one of the clotting factors of the blood (Table 13-1). This condition was common in certain European royal families, with the initial mutation of the gene for factor IX affecting Queen Victoria of England, who then passed it on to her descendants. DNA analysis of the remains of the Russian royal family (Tsarina Alexandra was a granddaughter of Queen Victoria) confirmed a factor IX gene mutation that resulted in hemophilia B. Because this is an X-linked hereditary condition, a significant proportion of the male members of these families had hemophilia.

In the days before blood transfusions and clotting factor replacement therapy, many of these patients died as a direct result of, or from the complications of, uncontrolled hemorrhage. Because **hemophilia A** (factor VIII deficiency) is the most significant and widely recognized form of hemophilia and accounts for 80% to 85% of the bleeding diatheses associated with a specific clotting factor deficiency, most of this discussion centers on that entity. Its estimated prevalence in the United States is 1 in 10,000 persons (or 1 in 5000 males).

As previously mentioned, a deficiency of factor IX or **hemophilia B (Christmas disease)** also may be encountered. Hemophilia B is similar to hemophilia A in its



• **Fig. 13-3 Lymphoid Hyperplasia.** Multiple prominent lymphoid aggregates in the floor of the mouth.

TABLE 13-1 Comparison of the Most Commonly Encountered Inherited Bleeding Disorders

Type	Defect	Inheritance	Findings
Hemophilia A (classic hemophilia)	Factor VIII deficiency	X-linked recessive	Abnormal PTT
Hemophilia B (Christmas disease)	Factor IX deficiency	X-linked recessive	Abnormal PTT
von Willebrand disease	Abnormal von Willebrand factor, abnormal platelets	Autosomal dominant	Abnormal PFA, abnormal PTT

PFA, Platelet function assay (replaces bleeding time test); *PTT*, partial thromboplastin time.

presentation, being transmitted in an X-linked fashion. Hemophilia B is much less common than hemophilia A, occurring with a prevalence of 1 in 60,000 (or 1 in 30,000 males). The term *Christmas disease* was obtained from the surname of the first person, a Canadian boy, who was identified as having hemophilia B in 1952.

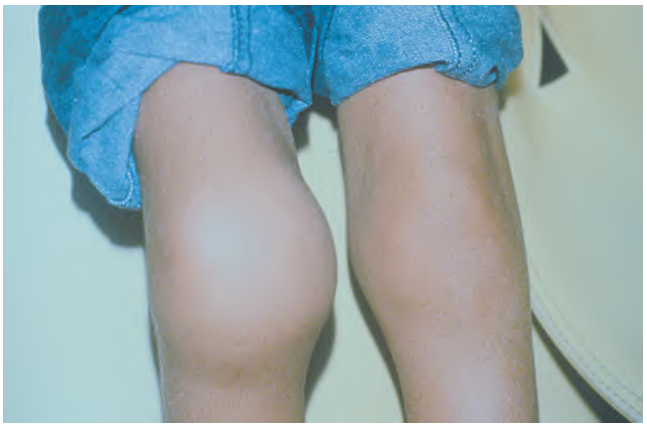
Another clotting disorder that is sometimes seen, **von Willebrand disease**, is the result of a genetic deficiency of a plasma glycoprotein called **von Willebrand factor**. This glycoprotein aids in the adhesion of platelets at a site of bleeding, and it also binds to factor VIII, acting as a transport molecule. Von Willebrand disease is a genetically heterogeneous condition, with several subtypes currently identified, and it may be transmitted in an autosomal dominant or recessive pattern. It is the most common of the inherited bleeding disorders, affecting an estimated 1 in 800 to 1000 persons. However, many cases of von Willebrand disease are mild and may be clinically insignificant.

Clinical Features

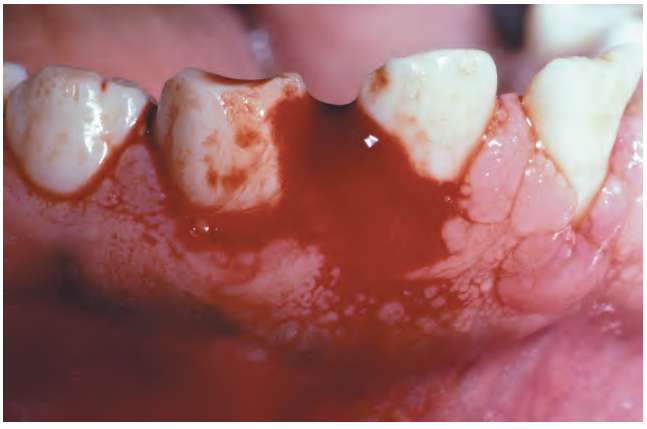
Hemophilia A is an X-linked disorder. Females typically carry the trait, but it is expressed primarily in males. Approximately 1 in 5000 males is born with this genetic disease, with about 30% of the cases representing new mutations. Failure of normal hemostasis after circumcision is typically one of the first signs that a bleeding disorder is present.

The severity of the bleeding disorder depends on the extent of the clotting factor deficiency. Hemophilia A is a heterogeneous disorder that is caused by any one of a variety of mutations associated with the gene for factor VIII. Because the mutations occur at different sites in the factor VIII gene (more than 900 different mutations have been identified), a clinical spectrum of deficiency of factor VIII is seen. This results in varying degrees of disease expression, with those mutations affecting more significant or larger portions of the factor VIII gene causing more severe clinical disease. Not all patients have an absolute lack of the particular clotting factor; rather, the deficiency may be a percentage of the normal value in a given patient. For example, a patient with only 25% of normal factor VIII levels may be able to function normally under most circumstances; one with less than 5% commonly manifests a marked tendency to bruise with only minor trauma.

In infants, oral lacerations and ecchymoses that involve the lips and tongue are a frequent occurrence as a result of the common falls and bumps experienced by this age group. If not treated appropriately, then such lacerations may result in significant blood loss in more severely affected patients. Sometimes deep hemorrhage occurs during normal activity and may involve the muscles, soft tissues, and weight-bearing joints **(hemarthrosis),** especially the knees (Fig. 13-4). The result of such uncontrolled bleeding is the formation of scar tissue as the body removes the extravasated blood. This often causes a crippling deformity of the knee joints secondary to arthritis and ankylosis. Sometimes the



• **Fig. 13-4 Hemophilia.** The enlargement of the knees of this patient with factor VIII deficiency is due to repeated episodes of bleeding into the joints (hemarthrosis). Inflammation and scarring have resulted.



• **Fig. 13-5 Hemophilia.** Hemorrhage in a patient with factor IX deficiency occurred after routine periodontal curettage.

tissue hemorrhage results in the formation of a tumorlike mass, which has been called **pseudotumor of hemophilia.** Such lesions have been reported in the oral regions.

An increased coagulation time (delay in blood clotting), of course, is the hallmark feature of this group of conditions. Uncontrollable or delayed hemorrhage may result from any laceration; this includes surgical incisions, dental extractions, and periodontal curettage (Fig. 13-5). Measurements of the platelet count, platelet function assay (PFA—an *in vitro* test of platelet function that has replaced the bleeding time test), prothrombin time (PT), and partial thromboplastin time (PTT) should be ordered as screening tests for any patient with a possible bleeding disorder.

Treatment and Prognosis

The treatment of clotting factor deficiencies essentially consists of replacement therapy with the appropriate clotting factor. Whether treatment is instituted depends on the severity of the clotting factor deficiency.

Patients who have greater than 25% of normal values of factor VIII may function normally. For patients with mild hemophilia (5% to 40% of normal levels of factor VIII),

no special treatment is typically required for normal activities. If surgery is to be performed, then clotting factor replacement therapy may be indicated.

For patients with severe deficiencies (less than 1% of normal levels of factor VIII), injections with the clotting factor must be performed as soon as a hemorrhagic episode occurs to prevent such complications as the crippling joint deformities of the knees.

The use of aspirin is strictly contraindicated because of its adverse effect on blood platelet function. Severe hemorrhage may result if these patients use aspirin-containing medications.

Genetic counseling should be provided to these patients and their families to help them understand the mechanism of inheritance. Using molecular techniques, women who are carriers can be confirmed. In addition, affected male fetuses can now be identified, and the severity of the factor VIII mutation can be assessed.

Optimal dental care is strongly encouraged for these patients to prevent oral problems that might require surgery. If oral or periodontal surgery is necessary, then consultation with the patient's physician is mandatory. The patient is usually prepared for the procedure by the administration of clotting factor just before the surgery. With an extensive surgical procedure, additional doses of clotting factor may be needed subsequently. In addition, epsilon-aminocaproic acid (EACA), an antifibrinolytic agent that inhibits clot degradation, should be given 1 day before the surgery and continued for 7 to 10 days afterward. Alternative therapy for patients who have levels of factor VIII greater than 5% of normal is desmopressin (1-deamino-8-D-arginine; DDAVP), which can be given just before surgery, either intravenously, subcutaneously, or intranasally. This drug causes the release of bound factor VIII, producing a temporary increase in the plasma levels of the clotting factor. Desmopressin may also be used to manage most patients affected by type 1 von Willebrand disease, which represents approximately 70% to 80% of the cases of that disorder.

Although it saved many lives, clotting factor replacement therapy has also resulted in a tragic complication for many of these patients. Cryoprecipitation, the traditional method of concentrating clotting factors from the plasma, also resulted in the concentration of several viruses, including the hepatitis viruses and HIV. More than 40% of hemophilia A and B patients in the United States were estimated to be infected with hepatitis C virus. In addition, as many as 80% to 90% of hemophiliac patients treated with multiple doses of factor VIII cryoprecipitate were infected with HIV, and many of these patients eventually developed acquired immunodeficiency syndrome (AIDS). The methods of preparing the clotting factors from pooled human plasma have been modified to eliminate or inactivate HIV; hepatitis A, B, and C; and parvovirus. Recombinant DNA technology also now provides a source of factor VIII that is manufactured by inserting the human factor VIII gene into bacteria that then synthesize the protein. Therefore, this product can now be manufactured without contamination by any viral organisms. Young people affected by hemophilia currently have minimal risk of contracting these infections as a result of their clotting factor replacement therapy.

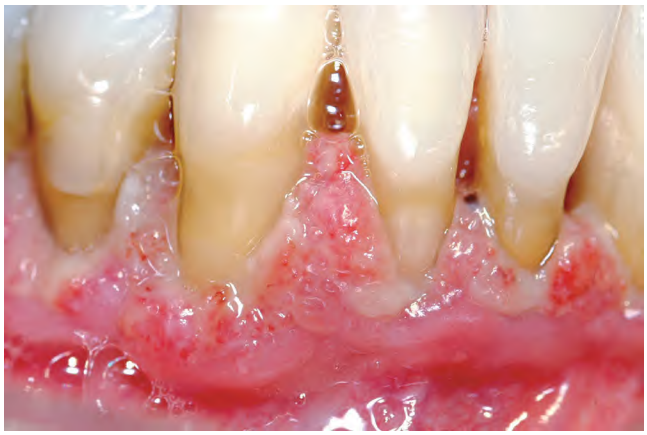
Other problems must occasionally be confronted, however. Approximately 25% to 30% of patients with severe hemophilia A may develop antibodies directed against factor VIII, and this is a very serious complication. Because the antibodies react with the factor VIII molecule, the result is an inhibition of the activity of the clotting factor, and these patients are once more faced with the prospect of uncontrolled bleeding. Patients with factor IX deficiency can develop similar inhibitory antibodies to factor IX, but this appears to occur much less frequently. Attempts to induce immune tolerance may help some individuals, although more immediate care has generally centered on bypassing the factor VIII–related portion of the clotting cascade by administration of recombinant factor VIIa or activated prothrombin complex. Research has shown this approach to be effective, although costly.

◆ PLASMINOGEN DEFICIENCY (LIGNEOUS CONJUNCTIVITIS; HYPOPLASMINOGENEMIA)

Plasminogen deficiency is a rare autosomal recessive condition that is caused by any one of several mutations of the gene responsible for the production of plasminogen, the precursor to plasmin. In the clotting cascade, factors are activated that lead to the development of a clot; however, simultaneously serum proteins such as plasminogen are converted to plasmin, which is responsible for degrading the clot. Without the formation of plasmin, the clot tends to grow and persist despite having performed its original hemostatic function. The result of plasminogen deficiency is a buildup of fibrin, deposited as irregular plaques and nodules that primarily affect mucosal surfaces. Involvement of the conjunctival mucosa is characterized by the formation of thick, firm plaques, for which the term *ligneous conjunctivitis* has been used (*ligneous* means "woodlike"). Even though this condition was initially described in the nineteenth century, it was during the late 1990s that an explanation for the majority of these cases was provided. Similar lesions have been produced in mice that have been genetically manipulated to create knock-out mutations of the plasminogen gene.

Clinical Features

The most striking aspect of plasminogen deficiency is the development of thick, creamy yellow to erythematous, firm plaques and nodules involving primarily the conjunctival mucosa of the upper eyelid. Typically the condition is detected during the first decade of life, but lesions can develop later as well. Even though this is an autosomal recessive condition, there is a tendency for the disease to present more often in women, although the reason for this is unknown.



• **Fig. 13-6 Plasminogen Deficiency.** The ulcerated plaques and papules seen on the gingiva of this patient with plasminogen deficiency represent accumulations of fibrin. (Courtesy of Dr. Kenneth Rasenberger.)

In addition to the conjunctival lesions, other mucosal surfaces can be affected, including the oral mucosa, laryngeal mucosa, and vaginal mucosa. In a recent series of 50 patients with this condition, ocular lesions were documented in 80%, gingival lesions in 34%, respiratory tract lesions in 16%, and vaginal lesions in 8%. Laryngeal mucosal involvement often includes the vocal cords, which typically results in a raspy, hoarse voice. Occlusion of the airway by a fibrin mass has been described rarely.

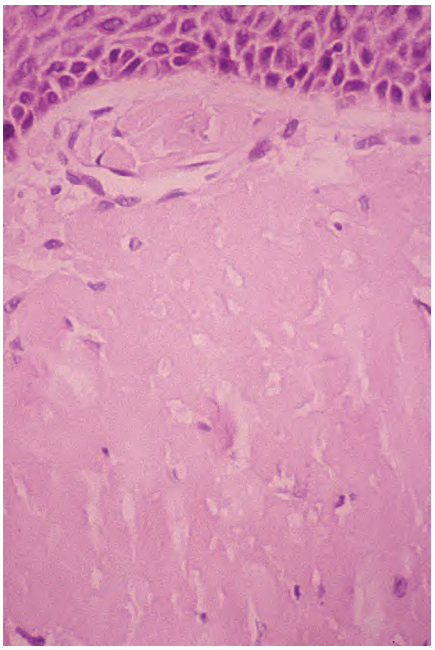
Oral lesions of plasminogen deficiency primarily involve the gingivae, presenting as patchy ulcerated papules and nodules with a very irregular surface (Fig. 13-6). These lesions may be few in number or distributed diffusely in all quadrants, and they tend to wax and wane in severity.

Histopathologic Features

The microscopic features of the lesions associated with this condition can be very confusing for the pathologist who is not familiar with the disease. The accumulation of fibrin appears as diffuse sheets of acellular eosinophilic material that bears a close resemblance to amyloid (Fig. 13-7). Special stains for amyloid (such as, Congo red) are negative, however, because this material represents fibrin. Confirmation that the eosinophilic material is fibrin can be done using the Fraser-Lendrum histochemical staining method. Variable numbers of inflammatory cells are seen, and granulation tissue is usually seen adjacent to the fibrin deposits.

Treatment and Prognosis

Treatment of plasminogen deficiency remains a problem. Damage to the mucosal tissues, including surgical trauma, should be minimized to reduce the likelihood of fibrin accumulation. Careful, thorough oral hygiene practices should be encouraged to diminish the effect of local inflammation. Sporadic reports describe resolution of the conjunctival lesions with either topical or systemic plasminogen; however, this agent is not available commercially. Some patients have experienced spontaneous regression of their lesions over time. Topical heparin combined with prednisone has helped control the gingival lesions in some patients. Alternatively, surgical excision of the gingival nodules, followed by low-dose systemic doxycycline, topical chlorhexidine mouth rinse, and systemic warfarin has also reportedly been effective in managing the lesions. These may be the two most reasonable approaches for treating the oral lesions until replacement plasminogen is marketed or gene therapy is feasible. Interestingly, these patients do not have any unusual problems with intravascular thrombus formation, and their lifespan does not appear to be shortened.



• **Fig. 13-7 Plasminogen Deficiency.** This high-power photomicrograph shows attenuated surface epithelium and a collection of relatively acellular eosinophilic material that superficially resembles amyloid, but is actually fibrin.

◆ ANEMIA

Anemia is a general term for either a decrease in the volume of red blood cells (hematocrit) or in the concentration of hemoglobin. This problem can result from a number of factors, including a decreased production of erythrocytes or an increased destruction or loss of erythrocytes. Laboratory studies, such as the red blood cell (RBC) count, hematocrit, hemoglobin concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), can help indicate the probable cause of the anemia.

Rather than being a disease itself, anemia is often a sign of an underlying disease, such as renal failure, liver disease, chronic inflammatory conditions, malignancies, or vitamin or mineral deficiencies. The diverse causes and complexity of the problem of anemia are presented in Box 13-1.

• BOX 13-1 Causes of Anemia

Anemias with Disturbed Iron Metabolism

- Iron deficiency anemia
- Sideroblastic anemias

Megaloblastic Anemias

- Cobalamin (B_{12}) deficiency (pernicious anemia)
- Folic acid deficiency

Anemia Associated with Chronic Disorders

- Anemia of chronic infection (infective endocarditis, tuberculosis, osteomyelitis, lung abscess, and pyelonephritis)
- Anemia of inflammatory connective tissue disorders (rheumatoid arthritis, lupus erythematosus, sarcoidosis, temporal arteritis, and regional enteritis)
- Anemia associated with malignancy
  - Secondary to chronic bleeding
  - Myelophthisic anemia
- Anemia of uremia
- Anemia of endocrine failure
- Anemia of liver disease

Hemolytic Anemias

- Extrinsic causes
  - Splenomegaly
  - Red cell antibodies
  - Trauma in the circulation
  - Direct toxic effects (various microorganisms, copper salts, and venom of certain snakes)
- Membrane abnormalities
  - Spur cell anemia
  - Paroxysmal nocturnal hemoglobinuria
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
- Disorders of the interior of the red cell
  - Defects in the Embden-Meyerhof pathway
  - Defects in the hexose monophosphate shunt

Disorders of Hemoglobin

- Sickle cell anemia
- Thalassemias

Clinical Features

The symptoms of anemia are typically related to the reduced oxygen-carrying capacity of the blood, which is a result of the reduced numbers of erythrocytes. Symptoms such as tiredness, headache, shortness of breath, or lightheadedness are often present.

Pallor of the mucous membranes may be observed in severe cases of anemia. The palpebral conjunctiva is often the site where this paleness is most easily appreciated, but the oral mucosa may show similar signs.

Treatment and Prognosis

The treatment of anemia depends on determining the underlying cause of the anemia and correcting that problem, if possible.

◆ SICKLE CELL ANEMIA

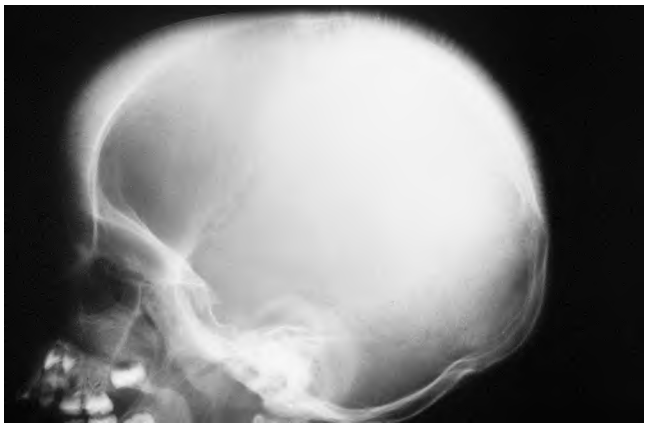
Sickle cell anemia is one of the more severe genetic disorders of hemoglobin synthesis **(hemoglobinopathies).** Because of the mutational substitution of a thymine molecule for an adenine in DNA, the codon is altered to code for the amino acid valine rather than glutamic acid in the β-globin chain of hemoglobin. This results in a hemoglobin molecule that, in the deoxygenated state, is prone to molecular aggregation and polymerization. Consequently, the red blood cells (RBCs) of patients with sickle cell anemia have a marked tendency to undergo deformation from the normal biconcave disk shape to a rigid-and-curved (sickle) shape. Because the genes for hemoglobin synthesis are codominant, if only one allele is affected, then only 40% to 50% of that patient's hemoglobin will be abnormal. Such a patient is simply a carrier and is said to have **sickle cell trait,** a condition that has no significant clinical manifestations in most everyday circumstances. Some sickling may be precipitated under certain conditions, such as dehydration or low-oxygen tensions related to either exercise or high altitudes.

This abnormal gene has persisted in the human race perhaps because it confers a degree of resistance to the malarial organism. As a result, the gene is seen most frequently in populations, such as African, Mediterranean, and Asian, who reside in areas where malaria is endemic. In the United States, nearly 2.5 million people (approximately 8% of the black population) carry this trait.

Unfortunately, in patients who inherit two alleles that code for sickle hemoglobin, the RBCs contain primarily sickle hemoglobin, which results in the condition called **sickle cell disease.** In the United States, about 1 of every 350 to 400 blacks is born with this disease. Such patients are often susceptible to the problems associated with abnormal RBC morphology. The sickled erythrocytes are more fragile than normal, lasting only 12 to 16 days in the circulation (about one-tenth of the lifespan of a normal RBC), and they tend to block the capillaries because of their shape and adherence properties. As a result, these patients have a chronic hemolytic anemia and many difficulties related to reduced blood flow to organs and tissues, which produces ischemia, infarction, and tissue death.

Clinical and Radiographic Features

Virtually any tissue or organ may be affected in sickle cell disease. The clinical spectrum of involvement can vary tremendously, with approximately one-third of patients exhibiting severe manifestations. Perhaps the most dramatic sign of this disease is the **sickle cell crisis,** a situation in which the sickling of the erythrocytes becomes severe. Hypoxia, infection, hypothermia, or dehydration may precipitate a crisis; however, for most crises there is no identifiable predisposing factor. Patients who experience a crisis suffer extreme pain from ischemia and infarction of the affected tissue. The long bones, lungs, and abdomen are among the most commonly affected sites, and each episode lasts 3 to



• **Fig. 13-8 Sickle Cell Anemia.** Lateral skull radiograph reveals an altered trabecular pattern, including a slight degree of "hair-on-end" appearance of the cranial bones. (Courtesy of Dr. Reg Munden.)

10 days. Pulmonary involvement, known as **acute chest syndrome,** is particularly serious, and one large study indicated that this is frequently precipitated by fat embolism or community-acquired pneumonia. Some patients may experience such crises monthly; others may go for 1 year or longer without problems. Often fever accompanies the crisis; therefore, infection must be considered in the differential diagnosis.

Patients with sickle cell disease are susceptible to infections, especially those caused by *Streptococcus pneumoniae,* probably because of the destruction of the spleen at an early age by repeated infarctions. Such infections are the most common cause of death among children affected by sickle cell disease in the United States.

Other problems include delayed growth and development in most patients. Impaired kidney function and ocular abnormalities develop secondary to the damage caused by vaso-occlusive episodes in the capillary networks of those organs. If the patient lives long enough, then renal failure may eventually develop. In addition, approximately 5% to 8% of these patients will experience central nervous system (CNS) damage in the form of a stroke, which occurs at an average age of about 8 years.

The oral radiographic features of sickle cell disease are relatively nonspecific. They consist of a reduced trabecular pattern of the mandible because of increased hematopoiesis occurring in the marrow spaces. Occasionally, a "hair-on-end" appearance is seen on the skull radiograph, although this is less prominent than that seen in thalassemia (Fig. 13-8). Other oral problems that have been reported include an increased prevalence of osteomyelitis of the mandible, mandibular bone infarction, prolonged paresthesia of the mandibular nerve, and asymptomatic pulpal necrosis.

Histopathologic Features

In homozygous sickle cell disease, a peripheral blood smear shows a peculiar curved distortion of the erythrocytes, resembling a sickle or boomerang shape.

Treatment and Prognosis

The patient experiencing a sickle cell crisis should be managed with supportive care, including fluids, rest, and appropriate analgesic therapy (usually narcotic preparations). It is important, but often difficult, to rule out the possibility of infection. Acute chest syndrome or cerebral infarct may require treatment with RBC transfusions.

All 50 states now screen for this hemoglobin disorder as part of their newborn infant health care system to identify affected individuals as soon as possible so that appropriate therapy can be instituted. For children with a diagnosis of sickle cell disease, continuous prophylactic penicillin therapy is indicated until at least 5 years of age. In addition, the child should be given polyvalent pneumococcal vaccinations. Situations that might precipitate a crisis, such as strenuous exercise, dehydration, or exposure to cold, should be avoided. For adults with relatively severe disease, hydroxyurea has been approved for treatment. This drug increases the fetal form of hemoglobin (hemoglobin F), which may inhibit polymerization of hemoglobin S and may also reduce the adherence of erythrocytes to the vessel walls. Unfortunately, hydroxyurea has a number of potential side effects and should be used judiciously. Bone marrow transplantation is curative, but this is a procedure with multiple potential complications and is used primarily for severely affected patients having a histocompatibility antigen (HLA)-matched donor sibling. Only about 1% of sickle cell anemia patients currently meet these criteria.

When surgery is necessary, local anesthesia, if possible, is usually preferred. If general anesthesia is indicated, then precautions should be taken to avoid conditions that might induce a crisis, such as hypoxia, vascular stasis, acidosis, infection, reduced body temperature, or dehydration.

For patients who have the sickle cell trait or the disease, genetic counseling is appropriate. DNA diagnostic techniques have been used for several years to assess whether a fetus is affected by sickle cell disease, permitting consideration of termination of the pregnancy. Molecular evaluation of the DNA from a single cell obtained from an embryo that was fertilized *in vitro* has allowed selection of a nonaffected embryo for uterine implantation. For parents who are carriers of the sickle cell trait, this is one method to ensure that their offspring do not have sickle cell disease.

Although the mortality rate for sickle cell disease in developed countries has improved dramatically over the past few years, the prognosis is variable because of the wide spectrum of disease activity. Those who are severely affected, however, often are quite disabled because of the many complications of the disease and have a decreased life span.

◆ THALASSEMIA

Thalassemia represents a group of disorders of hemoglobin synthesis that are characterized by reduced synthesis of either the α-globin or β-globin chains of the hemoglobin molecule. As in those with sickle cell trait, people who carry the trait for one of the forms of thalassemia seem to be more

resistant to infection by the malarial organism; an increased frequency of these genes is seen in Mediterranean, African, Indian, and Southeast Asian populations. Because the original cases were reported from the region of the Mediterranean Sea, the name *thalassemia* was given, derived from the Greek word *thalassa,* meaning "sea." The thalassemias are considered to be among the most common inherited conditions that affect humans.

An understanding of the structure and synthesis of hemoglobin is helpful in explaining the pathophysiology of these conditions. The hemoglobin molecule is a tetramer that is composed of two α chains and two β chains; if one of the chains is not being made in adequate quantities, then the normal amount of hemoglobin cannot be made. Furthermore, the excess globin chains accumulate within the erythrocyte, further compromising the structure and function of the cell. These abnormal erythrocytes are recognized by the spleen and selected for destruction **(hemolysis).** In addition, there is evidence of ineffective erythropoiesis caused by premature cell death of erythrocyte precursors in the bone marrow because of activation of apoptotic mechanisms. The net result is that the patient has hypochromic, microcytic anemia.

Because two genes code for the β chain and four genes code for the α chain, the degree of clinical severity in these conditions can vary considerably. The severity depends on which specific genetic alteration is present and whether it is heterozygous or homozygous. In the heterozygous state, an adequate amount of normal hemoglobin can be made and the affected patient experiences few signs or symptoms. In the homozygous state, however, the problems are often severe or even fatal. In addition, variations in the severity of the clinical presentation may be a reflection of the specific alteration in the genetic code, because more than 200 different mutations have been documented for β-thalassemia alone.

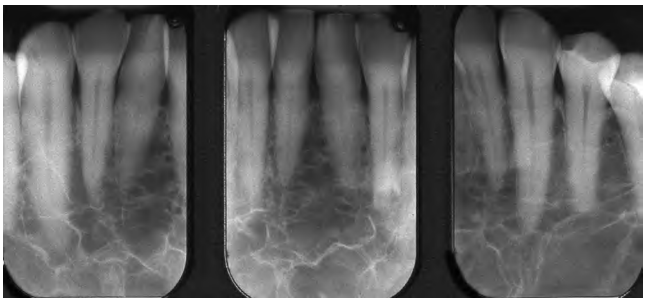
Clinical and Radiographic Features

β-Thalassemia

If only one defective gene for the β-globin molecule is inherited **(thalassemia minor)**, no significant clinical manifestations are usually present.

When two defective genes for the β-globin molecule are inherited, the patient typically is affected with **thalassemia major**, also called **Cooley anemia** or **Mediterranean anemia.** The disease is usually detected during the first year of life because a severe microcytic, hypochromic anemia develops when fetal hemoglobin synthesis ceases after 3 to 4 months of age. The red blood cells (RBCs) that are produced are extremely fragile and survive for only a few days in the peripheral circulation.

In an attempt to maintain adequate oxygenation, the rate of hematopoiesis (despite being ineffective) is greatly increased (up to 30 times normal), resulting in massive bone marrow hyperplasia, as well as hepatosplenomegaly and lymphadenopathy because of extramedullary hematopoiesis. The bone marrow hyperplasia may affect the jaws especially, producing an altered trabecular pattern and marked, painless enlargement of the mandible and maxilla (Fig. 13-9). This results in a characteristic "chipmunk" facies and causes reduced size or obliteration of the paranasal sinuses. Frontal bossing is also present, and a skull radiograph may show a prominent "hair-on-end" appearance of the calvaria (Fig. 13-10). Generalized maturational delay of the patient is typically seen. Delayed development of the dentition also has been described, with the teeth showing a mean delay of approximately 1 year compared with a matched population.



• **Fig. 13-9 Thalassemia.** Periapical radiographs of the anterior mandible showing reduced trabeculation because of increased hematopoiesis. (Courtesy of Dr. José Luis Tapia.)

• **Fig. 13-10 Thalassemia.** Lateral skull radiograph depicting the characteristic "hair-on-end" appearance in a patient with thalassemia.

Without therapy, tissue hypoxia worsens and serious bacterial infections with pneumococcal organisms often develop. Eventually, high-output cardiac failure occurs; many patients die by 1 year of age as a result of infection or heart problems.

α-Thalassemia

Because four α-globin genes may be affected, **α-thalassemia** has a broader spectrum of involvement than does β-thalassemia. The condition is caused by deletion at the α-globin gene locus.

When only one deleted gene is inherited, no disease can be detected. With the inheritance of two deleted genes, the condition is known as **α-thalassemia trait**. These patients have a mild degree of anemia and microcytosis that is

usually not clinically significant. With three deleted genes, the term **hemoglobin H (HbH) disease** is applied. Patients have problems with hemolytic anemia and splenomegaly. For patients with severe hemolysis, splenectomy may be indicated.

The homozygous state, in which all four genes are deleted, causes severe generalized fetal edema, a condition that has been termed **hydrops fetalis.** Hydrops fetalis is not specific for α-thalassemia and can be seen as a manifestation of other diseases, such as severe Rh incompatibility. Infants with α-thalassemia who are affected by this problem typically die within a few hours of birth.

Treatment and Prognosis

Thalassemia major is treated today primarily by means of blood transfusions. These should be administered every 2 to 3 weeks to simulate the normal hematologic state. Unfortunately, with repeated blood transfusions, iron overload inevitably develops because of the constant infusion of exogenous RBCs. This is a serious problem, and often death is due to **hemochromatosis,** an abnormal deposition of iron throughout the tissues of the body. The heart, liver, and endocrine glands are particularly affected by the toxic accumulation of iron. To combat this problem, an iron-chelating agent, deferoxamine (also known as *desferrioxamine*), must be given. If such therapy is used steadfastly, patients with β-thalassemia may have a relatively normal life span; however, problems may arise with patient compliance because this medication must be infused parenterally over several hours for at least 250 nights each year. Two oral iron chelators, deferiprone and deferasirox, are now available and appear to be good therapeutic additions. Deferiprone used alone is not as effective as deferoxamine, but the number of weekly infusions of the latter drug can be reduced when combined with deferiprone. Hematologic studies are done weekly due to agranulocytosis developing in 1% of patients taking deferiprone. Deferasirox does not seem to have significant side effects. All of these iron chelators are expensive, although the oral medications are more cost effective because patient compliance is better and infusion-related costs are eliminated. Hematopoietic stem cell transplantation has also been used with considerable success for individuals who are relatively young, have little organ damage, and have an HLA-matched donor.

Clinicians can now identify α-thalassemia, with its attendant hydrops fetalis (historically considered a fatal condition), *in utero* by molecular testing, and the fetus can be given intrauterine umbilical vein transfusions. An 80% survival rate has been reported for these infants, although they will require either lifelong transfusion therapy or hematopoietic stem cell transplantation. Prenatal diagnosis is also available for β-thalassemia.

For patients who have developed an abnormal facial appearance caused by thalassemia, surgical correction can be performed in many cases. Prevention of thalassemia also is desirable, either by screening for carriers of the genetic trait and providing genetic counseling, or by prenatal diagnosis.

APLASTIC ANEMIA

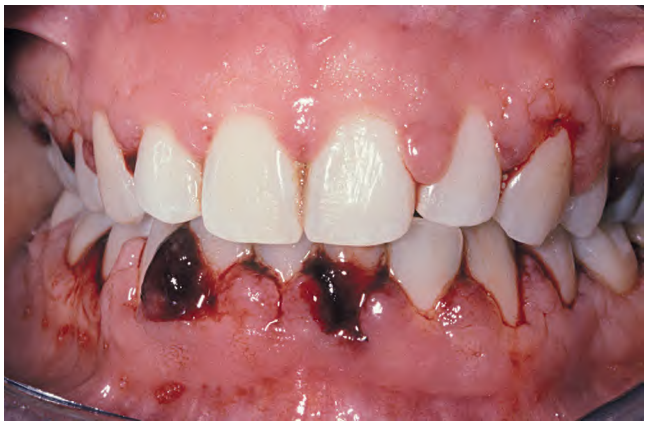
Aplastic anemia is a rare, life-threatening hematologic disorder that is characterized by failure of the hematopoietic precursor cells in the bone marrow to produce adequate numbers of all types of blood cells (pancytopenia). A significant amount of evidence supports the concept that most cases of aplastic anemia represent an immune-mediated disease caused by cytotoxic T lymphocytes that target differentiating hematopoietic cells in the marrow. As a result, the hematopoietic stem cells do not seem to undergo normal maturation despite normal or increased levels of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which normally induce the production and maturation of several types of white blood cells.

Although the underlying trigger for the immune-mediated destruction of the hematopoietic cells is unknown, some cases of aplastic anemia are associated with exposure to certain environmental toxins (e.g., benzene), treatment with certain drugs (especially the antibiotic chloramphenicol), or infection with certain viruses (particularly non-A, non-B, non-C, or non-G hepatitis). It is possible that the abnormal immune response is perhaps initiated by such exogenous stimuli in certain instances. A few genetic disorders, such as **Fanconi anemia** and **dyskeratosis congenita** (see page 695), also are associated with an increased frequency of aplastic anemia.

Clinical Features

Because all of the formed elements of the blood are decreased in patients with aplastic anemia, the initial symptoms may be related to any one or several of the deficiencies. The erythrocyte deficiency produces signs and symptoms related to a decreased oxygen-carrying capacity of the blood; therefore, patients may experience fatigue, lightheadedness, tachycardia, or weakness. The platelet deficiency (thrombocytopenia) is seen as a marked tendency for bruising and bleeding, which affects a variety of sites. Retinal and cerebral hemorrhages are some of the more devastating manifestations of this bleeding tendency. Deficiency of white blood cells (neutropenia, leukopenia, or granulocytopenia) is the most significant complication of this disease, predisposing the patient to bacterial and fungal infections that often are the cause of death.

The oral findings related to thrombocytopenia include gingival hemorrhage (Fig. 13-11), oral mucosal petechiae, purpura, and ecchymoses. The oral mucosa may appear pale because of the decreased numbers of red blood cells (RBCs). Oral ulcerations associated with infection due to neutropenia, particularly those that involve the gingival tissues, may be present. Minimal erythema is usually associated with the periphery of the ulcers. Gingival hyperplasia has also been reported in association with aplastic anemia.



• **Fig. 13-11 Aplastic Anemia.** Diffuse gingival hyperplasia with sulcular hemorrhage.

Histopathologic Features

A bone marrow biopsy specimen usually demonstrates a relatively acellular marrow with extensive fatty infiltration. The histopathologic features of an oral ulceration in a patient with aplastic anemia show numerous microorganisms in addition to a remarkable lack of inflammatory cells in the ulcer bed.

Diagnosis

The diagnosis of aplastic anemia is usually established by laboratory studies. A pancytopenia is characterized by at least two of the following findings:

- Fewer than 500 granulocytes/μL
- Fewer than 20,000 platelets/μL
- Fewer than 20,000 reticulocytes/μL

Treatment and Prognosis

The course for patients with aplastic anemia is unpredictable. For the milder forms of the disease, spontaneous recovery of the marrow may occur in some instances; progression to severe aplastic anemia may be seen in others. Generally, in severe cases, the chances of spontaneous recovery are slim. If a particular environmental toxin or drug is associated with the process, then withdrawal of the offending agent may sometimes result in recovery.

The treatment is initially supportive. Appropriate antibiotics are given for the infections that develop, and transfusions of packed RBCs or platelets are administered for symptomatic treatment of anemia and bleeding problems, respectively.

Definitive therapy for aplastic anemia is to replace the defective marrow with normal marrow, either by bone marrow transplantation or peripheral blood stem cell transplantation from a matched donor. Patients must be carefully selected; patients younger than 50 years of age and those with an HLA-matched donor (usually a sibling) have the best prognosis, but unfortunately only about 30% of patients meet these criteria.

For those patients who would not be a good prospect for bone marrow transplantation because of their advanced age or no matched donor, immunosuppressive therapy is recommended. Antithymocyte globulin combined with cyclosporine produces a response in the majority of these patients. Compared with treatment results from only 25 years ago, the prognosis for this condition has markedly improved. In the past, for patients with severe aplastic anemia treated with only antibiotics and transfusions, the mortality rate was greater than 80% in the first year after the diagnosis. Currently, an overall long-term survival of 75% of these patients can be achieved with either bone marrow transplant or immunosuppressive therapy. However, even if the disease is controlled, then these patients remain at risk for recurrent marrow aplasia and are at increased risk for acute leukemia.

◆ NEUTROPENIA

Neutropenia refers to a decrease in the number of the circulating neutrophils below 1500/mm^3 in an adult. It is often associated with an increased susceptibility of the patient to bacterial infections. Clinicians must be aware of this disorder because infection of the oral mucosa may be the initial sign of the disease. Interestingly, several ethnic groups, including patients of African and Middle Eastern background, will consistently have neutrophil counts that would qualify as neutropenia (as low as 1200/mm^3), yet these individuals are otherwise healthy. This finding has been termed **benign ethnic neutropenia,** and it appears to have no effect on the health of the patient because neutrophil counts respond to bacterial challenge.

A decrease in neutrophils may be precipitated by several mechanisms, most of which involve decreased production or increased destruction of these important inflammatory cells. When infections are noted in infancy and neutropenia is detected, the problem is usually the result of a congenital or genetic abnormality, such as **Schwachman-Diamond syndrome, dyskeratosis congenita** (see page 695), **cartilage-hair syndrome,** or **severe congenital neutropenia.** If the neutropenia is detected later in life, it usually represents one of the acquired forms. Many acquired neutropenia conditions have an unknown cause; however, others are clearly associated with various causes. A decreased production of neutrophils and the other formed elements of the blood may result from the destruction of the bone marrow by malignancies, such as leukemia (see page 547), or by metabolic diseases, such as Gaucher disease (see page 763), and osteopetrosis (see page 574).

Many drugs may affect neutrophil production, either through direct toxic effects on the bone marrow progenitor cells or by unknown idiosyncratic mechanisms. These drugs include the following:

- Anticancer chemotherapeutic agents (e.g., nitrogen mustard, busulfan, chlorambucil, and cyclophosphamide)
- Antibiotics (e.g., penicillins and sulfonamides)
- Phenothiazines

- Tranquilizers
- Diuretics

Neutropenia can also be a late manifestation of rituximab therapy, occurring 4 to 5 weeks after treatment on average. Nutritional deficiencies of vitamin B_{12} or folate, which may be a consequence of malabsorption syndromes, can inhibit neutrophil production as well.

A variety of viral and bacterial infections not only may reduce production of neutrophils but also seem to increase their destruction, typically at the sites of infection. Viral infections that have been implicated include the following:

- Hepatitis A and B
- Rubella
- Measles
- Respiratory syncytial virus
- Varicella
- HIV

Numerous bacterial infections, such as typhoid, tuberculosis, brucellosis, and tularemia, may also cause neutropenia. The increased destruction of neutrophils by an autoimmune mechanism also occurs in such disorders as systemic lupus erythematosus (SLE), in which autoantibodies directed against the neutrophil are produced.

Clinical Features

Most patients with neutropenia have some form of bacterial infection rather than a viral or fungal infection, particularly if the other elements of the immune system (lymphocytes, plasma cells, and monocytes) are still intact. *Staphylococcus aureus* and gram-negative organisms seem to cause the most problems for patients with neutropenia. The suppuration and abscess formation normally associated with such infections may be markedly reduced because of the lack of neutrophils. The most common sites of infection include the middle ear, the oral cavity, and the perirectal area. When neutrophil counts drop below 500/mm^3, however, pulmonary infections often develop.

The oral lesions of neutropenia consist of ulcerations that usually involve the gingival mucosa, probably because of the heavy bacterial colonization of this area and the chronic trauma that it receives. These ulcers characteristically lack an erythematous periphery, although this finding has been variable. Premature periodontal bone loss with exfoliation of the deciduous dentition has been described.

Histopathologic Features

A biopsy specimen of neutropenic ulceration usually shows a reduced number or the absence of neutrophils. Bacterial invasion of the host tissue may be apparent in some instances.

Treatment and Prognosis

Infections related to neutropenia are managed with appropriate antibiotic therapy. The patient should be encouraged to maintain optimal oral hygiene to decrease the bacterial load in the oral cavity. Studies using recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim; pegfilgrastim), a cytokine that promotes the growth and differentiation of neutrophils, have shown remarkable results. Patients with severe neutropenia have a significant increase in neutrophil counts and resolution of infections after treatment with this agent. Prophylactic use of filgrastim or pegfilgrastim reduces the risk of febrile neutropenia in patients who are receiving certain antineoplastic chemotherapeutic regimens. Patients who do not respond to G-CSF may have to be considered for hematopoietic stem cell transplantation, depending on the severity of the neutropenia and subsequent infections.

AGRANULOCYTOSIS

Agranulocytosis is a condition in which the cells of the granulocytic series, particularly neutrophils, are absent. As in other disorders of the formed elements of the blood, agranulocytosis may occur as a result of decreased production or increased destruction or use of these cells. Although some cases are idiopathic, most are induced by exposure to one of several drugs. Some drugs, such as the anticancer chemotherapeutic agents, induce agranulocytosis by inhibiting the normal mitotic division and maturation of the hematopoietic stem cells. In other instances, the drugs trigger an immunologic reaction that results in the destruction of granulocytes. Rarely, agranulocytosis may be a congenital syndrome **(congenital agranulocytosis, Kostmann syndrome)** that results from a decreased level of the cytokine granulocyte colony-stimulating factor (G-CSF).

Clinical Features

Agranulocytosis typically develops within a few days after a person ingests the offending drug. Because of the lack of granulocytes (especially neutrophils), bacterial infections often develop and patients may show signs and symptoms of malaise, sore throat, swelling, fever, chills, bone pain, pneumonia, and shock. The erythrocyte and platelet counts are usually normal or only slightly depressed.

Oral lesions are common and include necrotizing, deep, punched-out ulcerations of the buccal mucosa, tongue, and palate. The gingivae are especially susceptible to infection, often resembling the pattern of necrotizing ulcerative gingivitis (NUG) (see page 143).

Histopathologic Features

Microscopic examination of a biopsy specimen from one of the oral ulcerations in agranulocytosis characteristically shows abundant bacterial organisms, both on the surface and within the tissue. The host inflammatory response is relatively sparse, with few granulocytes, particularly neutrophils, seen in the ulcer bed.

Treatment and Prognosis

If the clinician believes that a particular drug has caused the agranulocytosis, the medication should be discontinued as soon as is reasonably possible. In many instances, the granulocyte count returns to normal within 10 to 14 days after cessation of the offending agent. For patients who have agranulocytosis secondary to cancer chemotherapy, oral hygiene should be meticulous to foster an immaculate oral environment. In addition, the use of chlorhexidine-containing mouth rinses seems to reduce the severity of the oral lesions. Active infections are treated with appropriate antibiotic medications.

If the agranulocytosis is related to cancer treatment, the white blood cell count usually returns to normal after a period of weeks. For patients whose granulocyte counts do not recover, administration of G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be beneficial. The overall mortality rate for this condition in the past was 20% to 30%, although cytokine therapy and the newer broad-spectrum antibiotics have improved the outlook for these patients.

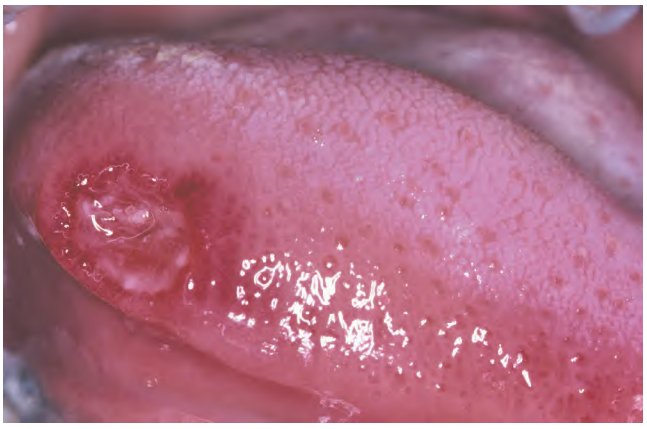
◆ CYCLIC NEUTROPENIA (CYCLIC HEMATOPOIESIS)

Cyclic neutropenia is a rare idiopathic hematologic disorder that is characterized by regular periodic reductions in the neutrophil population of the affected patient. The underlying cause seems to be a mutation of the neutrophil elastase *(ELA-2* or *ELANE)* gene, resulting in arrested development of neutrophils at the promyelocyte stage within the marrow. This mutation is also associated with premature apoptosis of these myeloid precursor cells. The best estimated frequency of this disease in the population is about 1 in 1 million. Although an autosomal dominant pattern of inheritance has been described in a few cases, most examples of cyclic neutropenia are isolated.

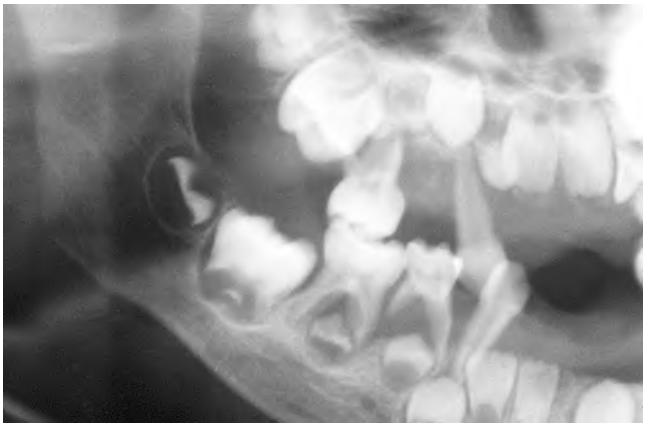
Symptoms usually begin in childhood and tend to correlate with the neutrophil counts. When the neutrophil count is at its nadir (i.e., lowest point), the patient experiences problems with infection. As the neutrophil count rises toward normal, the signs and symptoms abate. Very low neutrophil counts usually are present for 3 to 6 days, and blood monocyte and eosinophil levels are typically increased when the neutrophil count is depressed. Even when the neutrophil count is at its peak, the levels are often less than normal.

Clinical and Radiographic Features

The signs and symptoms of cyclic neutropenia occur in rather uniformly spaced episodes, which usually have a 21-day cycle. Patients typically complain of recurrent episodes of fever, anorexia, cervical lymphadenopathy, malaise, pharyngitis, and oral mucosal ulcerations. Other gastrointestinal mucosal areas, including the colon, rectum, and anus, may be affected by recurrent ulcerations.



• **Fig. 13-12 Cyclic Neutropenia.** Ulceration of the lateral tongue is typical of the lesions associated with cyclic neutropenia. (From Allen CM, Camisa C: Diseases of the mouth and lips. In Sams WM, Lynch P, editors: *Principles and practice of dermatology,* ed 2, New York, 1996, Churchill Livingstone.)



• **Fig. 13-13 Cyclic Neutropenia.** Cyclic neutropenia is one of several conditions that may produce premature bone loss, as shown in the interradicular regions of the mandibular deciduous molar teeth.

The oral ulcerations develop on any oral mucosal surface that is exposed to even minor trauma, particularly the lips, tongue, buccal mucosa, and oropharynx (Fig. 13-12). An erythematous halo is variably present at the periphery of the ulcers. The gingiva is the most severely affected region of the oral cavity. Severe periodontal bone loss with marked gingival recession and tooth mobility also is characteristic (Fig. 13-13).

Diagnosis

The diagnosis of cyclic neutropenia should be established by sequential complete blood counts (typically three times per week for 6 to 8 weeks) to determine whether cycling of the neutrophil levels occurs. The neutrophil count should be less than 500/mm^3 for 3 to 5 days during each of at least three successive cycles to make this diagnosis.

Histopathologic Features

The histopathologic features of cyclic neutropenia are similar to those of the other neutropenic and granulocytopenic ulcerations if the biopsy is performed during the nadir of the neutrophil count.

Treatment and Prognosis

Supportive care for the patient with cyclic neutropenia includes antibiotic therapy for significant infections that might occur while the neutrophil count is at its lowest. Unfortunately, this approach cannot be considered a permanent treatment. Other methods that have been used with marginal success include splenectomy, corticosteroid therapy, and nutritional supplementation. Administration of the cytokine granulocyte colony-stimulating factor (G-CSF) several times weekly seems to correct the lack of production of neutrophils. This treatment results in a decrease in the time of neutropenia from 5 days to 1 day, which improves the clinical course of the disease. The cycles are reduced from 18 to 21 days to 11 to 13 days, and the severity of mucositis and infection are reduced.

Supportive care in the form of optimal oral hygiene should be maintained to reduce the number and severity of oral infections and improve the prognosis of the periodontal structures. Fortunately, for many of these patients, the severity of symptoms related to cyclic neutropenia seems to diminish after the second decade of life, despite the fact that the cycling of the neutrophils continues.

◆ THROMBOCYTOPENIA

Thrombocytopenia is a hematologic disorder that is characterized by a markedly decreased number of circulating blood platelets (formed elements derived from megakaryocyte precursors in the bone marrow). Platelets are necessary for hemostasis and clot formation. A platelet count of 200,000 to 400,000/mm^3 is considered normal. The decrease in platelets may be the result of the following:

- Reduced production
- Increased destruction
- Sequestration in the spleen

REDUCED PLATELET PRODUCTION

Reduced production of platelets may be the result of various causes, such as infiltration of the bone marrow by malignant cells or the toxic effects of cancer chemotherapeutic drugs. In such instances, decreases in the other formed elements of the blood are also seen.

INCREASED PLATELET DESTRUCTION

Increased destruction of platelets may be caused by an immunologic reaction, which is often precipitated by any one of more than 100 different drugs; heparin is one of the most common offending agents. This type of reaction is typically idiosyncratic and, therefore, not related to the dose of the drug. Similarly, autoantibodies directed against platelets, specifically certain surface glycoproteins, may on rare occasions be induced by viral infection or vaccination. In addition, certain systemic diseases may have thrombocytopenia as a component, such as systemic lupus erythematosus (SLE) and HIV infection. Increased destruction may also occur because of increased consumption of platelets associated with abnormal blood clot formation. This occurs in patients with conditions, such as **thrombotic thrombocytopenic purpura (TTP).** This serious disorder of coagulation is caused by a deficiency of a von Willebrand factor-cleaving metalloprotease (ADAMTS13), which triggers the formation of numerous thrombi within the small blood vessels of the body. The condition is usually caused by antibodies directed against ADAMTS13, but TTP can also rarely be inherited as an autosomal recessive condition when mutations of the ADAMTS13 gene are present.

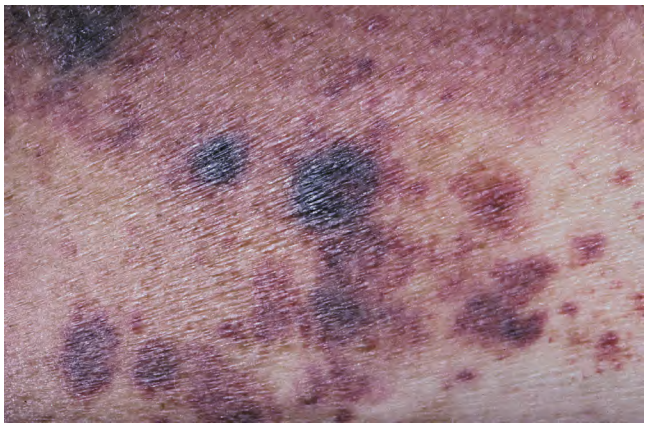
SEQUESTRATION IN THE SPLEEN

Under normal conditions, one-third of the platelet population is sequestered in the spleen. Consequently, conditions that cause splenomegaly (e.g., portal hypertension secondary to liver disease, splenic enlargement secondary to tumor infiltration, and splenomegaly associated with Gaucher disease) also cause larger numbers of platelets to be taken out of circulation. Regardless of the cause, the result for the patient is a bleeding problem because normal numbers of platelets are not available for proper hemostasis.

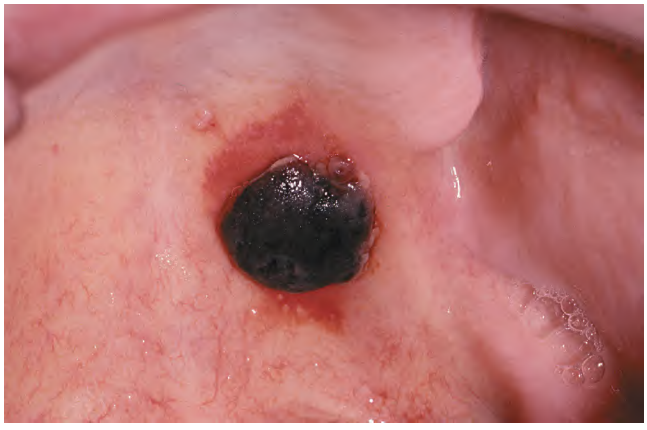
Clinical Features

Clinical evidence of thrombocytopenia is not usually seen until the platelet levels drop below 100,000/mm^3. The severity of involvement is directly related to the extent of platelet reduction. The condition often is initially detected because of the presence of oral lesions. Minor traumatic events are continuously inflicted on the oral mucosa during chewing and swallowing of food. The small capillaries that are damaged during this process are normally sealed off with microscopic thrombi. In a patient with thrombocytopenia, however, the thrombi do not form properly. This results in a leakage of blood from the small vessels. Clinically, this usually produces pinpoint hemorrhagic lesions known as **petechiae.** If a larger quantity of blood is extravasated, then an **ecchymosis** or bruise results (Fig. 13-14). With even larger amounts of extravasated blood, a **hematoma** (*hemat* = blood; *oma* = tumor) will develop (Fig. 13-15). Spontaneous gingival hemorrhage often occurs in these patients, as does bleeding from sites of minor trauma.

Similar hemorrhagic events occur throughout the body. With severe thrombocytopenia (<10,000 platelets/mm^3), massive bleeding from the gastrointestinal or urinary tract may be fatal. Epistaxis is often present in these patients, and hemoptysis indicates significant pulmonary hemorrhage.



• **Fig. 13-14 Thrombocytopenia.** The bruising (purpura) seen on this patient's forearm is a result of reduced platelet count secondary to myelodysplasia, a preleukemic bone marrow disorder.



• **Fig. 13-15 Thrombocytopenia.** This dark palatal lesion represents a hematoma caused by a lack of normal coagulation, characteristic of thrombocytopenia.

Intracranial hemorrhage is also a potentially fatal complication of severe thrombocytopenia.

Immune thrombocytopenic purpura (ITP), which used to be known as idiopathic thrombocytopenic purpura, can present as either an acute or chronic process. Acute ITP usually occurs during childhood, classically after a nonspecific viral infection. The symptoms of thrombocytopenia appear quickly and may be severe. Most cases, however, resolve spontaneously within 4 to 6 weeks, and 90% of patients recover by 3 to 6 months. Chronic ITP most frequently affects women between 20 and 40 years. Autoantibodies directed against antigens on the platelet surface result in sequestration and destruction of the platelets in the spleen. Consequently many of these patients may respond to splenectomy.

Histopathologic Features

Gingival biopsy may be performed for diagnostic purposes in patients with suspected TTP. Approximately 30% to 40% of such biopsy specimens show the presence of fibrin deposits in the small vessels. These deposits are more readily appreciated after staining the tissue section using the periodic acid-Schiff (PAS) method.

Treatment and Prognosis

If the clinician believes the thrombocytopenia to be drug-related, the drug should be discontinued immediately. In most instances, the platelet count returns to normal after several days. Platelet transfusions and corticosteroid therapy may be necessary if life-threatening hemorrhage occurs. As mentioned earlier, ITP often resolves spontaneously, but those cases that are more severe may require corticosteroid therapy or intravenous immunoglobulin (IVIG) therapy. Refractory ITP has been treated with splenectomy, but newer medical treatments, such as rituximab (targeting B lymphocytes) and thrombopoietin-receptor agonists, are now available. For some forms of thrombocytopenia, such as TTP, the patient's prognosis is relatively guarded. In the past, the condition was almost uniformly fatal, although the outlook has greatly improved since therapy with plasma exchange transfusions, combined with corticosteroids or rituximab, became available. More than 70% of these patients now survive with proper treatment.

◆ POLYCYTHEMIA VERA (PRIMARY POLYCYTHEMIA; POLYCYTHEMIA RUBRA VERA; PRIMARY ACQUIRED ERYTHROCYTOSIS)

Polycythemia vera is a rare idiopathic hematologic disorder that is best thought of as an increase in the mass of the red blood cells (RBCs). Uncontrolled production of platelets and granulocytes, however, is often seen concurrently, and most authorities feel that this condition represents a relatively nonaggressive myeloproliferative disorder. Researchers believe the overproduction is related to the abnormal behavior of a single progenitor marrow stem cell, which begins multiplying without regard to the normal regulatory hormones, such as erythropoietin. This gives rise to a group or clone of unregulated cells that then produce the excess numbers of these formed elements of the blood at two to three times the normal rate. These cells generally function in a normal fashion.

Clinical Features

Polycythemia vera typically affects older adults. The median age at diagnosis is 60 years. Only 5% of cases are diagnosed before the age of 40 years. No sex predilection is seen, and the annual incidence in the United States is estimated to be approximately 20 cases per million population. An acquired mutation of one of the tyrosine kinase genes, Janus kinase 2 *(JAK2),* plays a significant role in the development of this

disorder, and more than 95% of patients with polycythemia vera have been shown to have this mutation.

The initial symptoms of the disease are nonspecific and include the following:

- Headache
- Weakness
- Dizziness
- Drowsiness
- Visual disturbances
- Sweating
- Weight loss
- Dyspnea
- Epigastric pain

A ruddy complexion may be evident on physical examination. One relatively characteristic complaint, described in about 40% of affected patients, is that of generalized pruritus (itching), particularly after bathing, without evidence of a rash.

The problems caused by thrombus formation, which would be expected with the increased viscosity of the blood and the increased platelet numbers, include transient ischemic attacks, cerebrovascular accidents, and myocardial infarctions. Hypertension and splenomegaly are also common.

A peculiar peripheral vascular event called **erythromelalgia** affects the hands and feet. Patients experience a painful burning sensation accompanied by erythema and warmth. This may eventually lead to thrombotic occlusion of the vessels that supply the digits. Digital gangrene and necrosis may result. Erythromelalgia is probably caused by excessive platelets, and its onset seems to be precipitated by exercise, standing, or warm temperatures.

Strangely enough, these patients may also have problems with excess hemorrhage. Epistaxis and ecchymoses are sometimes a problem, and gingival hemorrhage has been described.

Treatment and Prognosis

With the initial diagnosis of polycythemia vera, an immediate attempt is made to reduce the RBC mass. The first treatment is usually phlebotomy, with as much as 500 mL of blood removed every other day until a hematocrit of less than 45% is achieved. If thrombotic events are an immediate problem, then treatment with low-dose aspirin should be started. To control the platelet levels, anagrelide hydrochloride, a selective inhibitor of megakaryocyte maturation and platelet production, may be prescribed. Antihistamines are used to help control the symptoms of pruritus.

Long-term management may include intermittent phlebotomy, although myelosuppressive therapy has also been advocated. An increased risk of leukemia is associated with some chemotherapeutic drugs. Hydroxyurea is one chemotherapeutic agent that may not pose an increased risk of leukemia, however, because it acts as an antimetabolite and does not appear to have any mutagenic properties. Nevertheless, in 2% to 10% of patients with polycythemia vera, acute leukemia ultimately develops.

Overall, the prognosis is fair; patients with polycythemia vera survive an average of 10 to 12 years after the diagnosis, if treated. Given the fact that the median age at diagnosis is 60 years, the majority of affected patients do not seem to have a markedly higher death rate compared with their unaffected peers.

LEUKEMIA

Leukemia represents several types of malignancies of hematopoietic stem cell derivation. The disease begins with the malignant transformation of one of the stem cells, which initially proliferates in the bone marrow and eventually overflows into the peripheral blood of the affected patient. Problems arise when the leukemic cells crowd out the normal defense cell and erythrocyte precursors. In the United States, approximately 2.9% of all cancers are leukemia, and 4.1% of deaths from cancer can be attributed to this disease.

Leukemias are usually classified according to their histogenesis and clinical behavior. Therefore, the broad categories would be **acute** or **chronic** (referring to the clinical course) and **myeloid** or **lymphocytic/lymphoblastic** (referring to the histogenetic origin). Myeloid leukemias can differentiate along several different pathways; thus they produce malignant cells that usually show features of granulocytes or monocytes, and less frequently, erythrocytes or megakaryocytes.

Acute leukemias, if untreated, run an aggressive course and often result in the death of the patient within a few months. Chronic leukemias tend to follow a more indolent course, although the end result is the same. One of the greatest successes in cancer treatment has been achieved in acute lymphoblastic leukemia of childhood, a condition that used to be uniformly fatal but now is often capable of being controlled.

Leukemias are probably the result of a combination of environmental and genetic factors. Certain syndromes are associated with an increased risk. These genetic disorders include the following:

- Down syndrome
- Bloom syndrome
- Neurofibromatosis type I
- Schwachman syndrome
- Ataxia-telangiectasia syndrome
- Klinefelter syndrome
- Fanconi anemia
- Wiskott-Aldrich syndrome

In addition, certain types of leukemia show specific chromosomal abnormalities. The first chromosomal abnormality to be detected was found in patients with **chronic myeloid leukemia,** and this malignancy was characterized by a genetic alteration called the **Philadelphia chromosome.** This abnormality represents a translocation of the

chromosomal material between the long arms of chromosomes 22 and 9. This rearrangement of the genetic material occurs in such a fashion as to fuse the breakpoint cluster region *(BCR)* gene with the Abelson *(ABL)* oncogene, producing an entirely new gene: *BCR-ABL.* This gene is continuously transcribed, and the resulting protein product, a tyrosine kinase, causes the uncontrolled proliferation of the leukemic cells. Identifying such pathogenetic mechanisms has opened up an entirely new field of chemotherapy that targets specific molecular mechanisms of carcinogenesis. A variety of other genetic alterations in the bone marrow stem cells has been associated with the **myelodysplasia syndromes,** a group of disorders that appear to represent early stages in the evolution of **acute myeloid leukemia.** As the genetic alterations accumulate in the stem cells, the chances of the patient developing leukemia increase.

Some environmental agents are associated with an increased risk of leukemia, but their overall contribution to the leukemia problem is thought to be less than 5%. Exposure to pesticides, benzene, and benzene-like chemicals has been associated with an increased risk of developing leukemia. Ionizing radiation has also been implicated; this was documented by the increased frequency of chronic myeloid leukemia in the survivors of the atomic bomb blasts at Hiroshima and Nagasaki during World War II. Viruses have also been shown to produce leukemia, although this is not a common finding. The most thoroughly studied is the retrovirus known as *human T-cell leukemia/lymphoma virus type 1 (HTLV-1),* which is transmitted by contaminated blood from infected to uninfected individuals. This virus can cause a relatively rare form of malignancy of T lymphocytes, which may present as a leukemia or non-Hodgkin lymphoma (see page 555). Most cases have been identified in parts of the Caribbean, central Africa, and southwestern Japan.

As knowledge about this group of diseases increases, the fact that the leukemias are diverse and complex cannot be overlooked. For example, at least eight distinct subtypes of acute myeloid leukemia have now been identified, and each subtype has a different treatment approach and prognosis. Because of the complexity of this area, the discussion is limited to those aspects of leukemia that are more directly related to the oral or head and neck region.

Clinical Features

If all types of leukemia are considered, this condition occurs at a rate of 13 cases per 100,000 population annually. Slightly more males than females are affected. The myeloid leukemias generally affect an adult population; **acute myeloid leukemia** affects a broader age range, which includes children. **Chronic myeloid leukemia** shows peak prevalence during the third and fourth decades of life. **Acute lymphoblastic leukemia,** in contrast, occurs predominantly in children and represents one of the more common childhood malignancies. **Chronic lymphocytic leukemia,** the most common type of leukemia, primarily affects older adults.

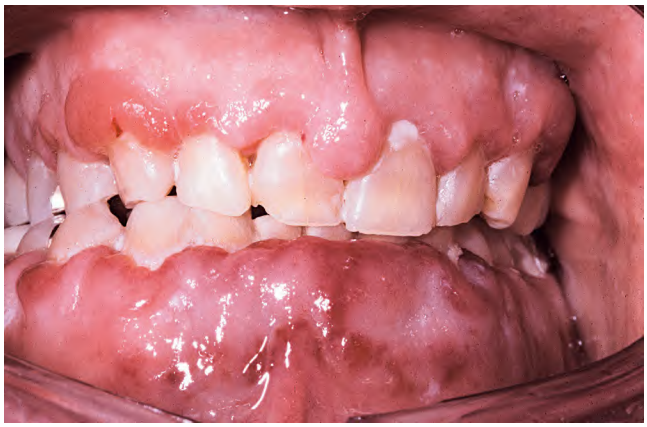
Many of the clinical signs and symptoms of leukemia are related to the marked reduction in the numbers of normal white and red blood cells, a phenomenon that results from the crowding out of the normal hematopoietic stem cells by the malignant proliferation **(myelophthisic anemia).** Because of the reduced red blood cell (RBC) count and subsequent reduction in oxygen-carrying capacity of the blood, patients complain of fatigue, easy tiring, and dyspnea on mild exertion. The malignant cells may also infiltrate other organs and often cause splenomegaly, hepatomegaly, and lymphadenopathy.

Leukemic patients may also complain of easy bruising and bleeding, problems that are caused by a lack of blood platelets **(thrombocytopenia),** the result of megakaryocytes being crowded out of the marrow. Petechial hemorrhages of the posterior hard palate and the soft palate may be observed, and these may be accompanied by spontaneous gingival hemorrhage, especially with platelet counts less than 10,000 to 20,000/mm^3. Because disturbances in stem cell differentiation accompany the myelodysplasia syndromes, thrombocytopenia is often present in these patients, and gingival hemorrhage has been reported in this setting. Serious hemorrhagic complications may result from bleeding into the CNS or the lungs.

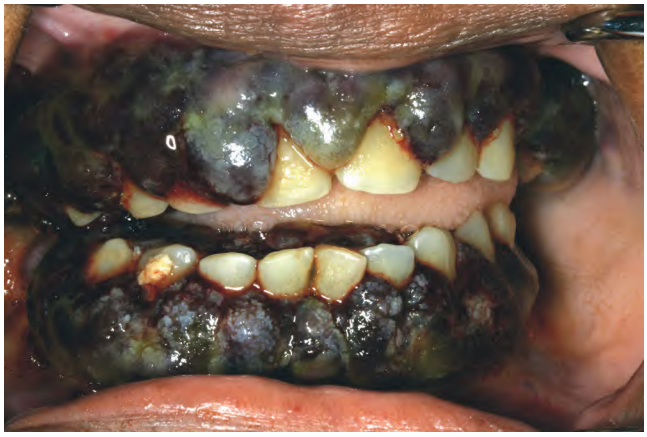
A fever associated with infection may be the initial sign of the leukemic process. Perirectal infections, pneumonia, urinary tract infections, and septicemia are common infectious complications. The microorganisms that are typically involved include gram-negative bacteria, gram-positive cocci, and certain *Candida* species.

Ulceration of the oral mucosa is often present as a result of the impaired ability of the host to combat the normal microbial flora. Usually, the gingival mucosa is the most severely affected because of the abundant bacteria normally present around the teeth. The neutropenic ulcers that are produced are typically deep, punched-out lesions with a gray-white necrotic base. Oral candidiasis is often a complication of leukemia, involving the oral mucosa diffusely. Herpetic infections are the most common viral lesions, and these may involve any area of the oral mucosa rather than being confined to the keratinized mucosa, as in immunocompetent patients.

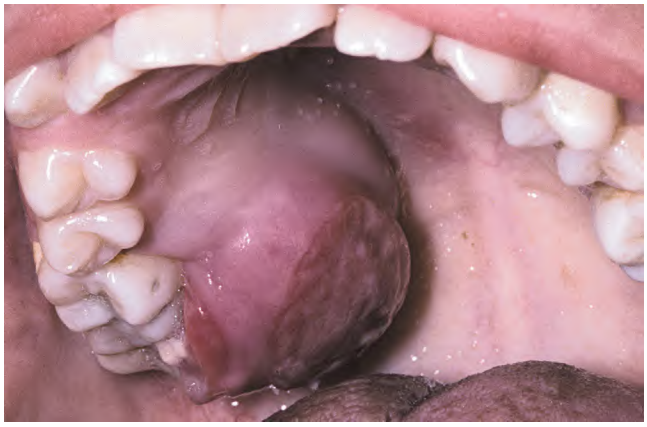
Occasionally, the leukemic cells infiltrate the oral soft tissues and produce a diffuse, boggy, nontender swelling that may or may not be ulcerated. This occurs most frequently with the myelomonocytic types of leukemia, and it may result in diffuse gingival enlargement (Figs. 13-16 and 13-17) or a prominent tumorlike growth (Fig. 13-18). The tumorlike collection of leukemic cells is known as **myeloid sarcoma,** a designation that has replaced the older terms, **granulocytic sarcoma** and **extramedullary myeloid tumor.** Historically the proliferation of leukemic cells was called *chloroma* because it is often greenish (*chlor* = green; *oma* = tumor) on fresh-cut sections. Other oral manifestations include infiltration of the periapical tissues, simulating periapical inflammatory disease both clinically and radiographically.



• **Fig. 13-16 Leukemia.** Diffuse gingival enlargement, as depicted in this photograph, may occur in leukemic patients, particularly in those with monocytic leukemia. This older man had a history of myelodysplasia for several years before the development of leukemia.



• **Fig. 13-17 Leukemia.** Extensive hemorrhagic enlargement of the maxillary and mandibular gingivae. (Courtesy of Dr. Michael Tabor.)



• **Fig. 13-18 Leukemia.** The ulcerated soft tissue nodule of the hard palate represents leukemic cells that have proliferated in this area.

Histopathologic Features

Microscopic examination of leukemia-affected tissue shows diffuse infiltration and destruction of the normal host tissue by sheets of poorly differentiated cells with either myelomonocytic characteristics or lymphoid features.

Diagnosis

The diagnosis is usually established by confirming the presence of poorly differentiated leukemic cells in the peripheral blood and bone marrow. Bone marrow biopsy is normally performed in conjunction with the peripheral blood studies because some patients may go through an aleukemic phase in which the atypical cells are absent from the circulation. Classifying the type of leukemia requires establishing the immunophenotype by using immunohistochemical markers to identify cell surface antigens expressed by the tumor cells. Immunohistochemical confirmation of certain characteristic enzymes (e.g., myeloperoxidase and lysozyme) is necessary to identify and classify the myeloid leukemias. In addition, cytogenetic and molecular characterization of the lesional cells is typically necessary. In many cases, the results of these various studies will be significant because the patient's prognosis is directly affected.

Treatment and Prognosis

The treatment of a patient with leukemia consists of various forms of chemotherapy; the type of leukemia dictates the chemotherapeutic regimen. In most cases the purpose of chemotherapy is to destroy as many of the atypical cells as possible in a short time, thus inducing a remission. For this reason, this technique has been termed **induction chemotherapy.** Usually, this phase of chemotherapy requires high doses of toxic chemotherapeutic agents; often, the patient experiences a number of unpleasant side effects during treatment. Once remission has been induced, this state must be maintained. This is the purpose of **maintenance chemotherapy,** which typically requires lower doses of chemotherapeutic drugs given over a longer period.

If the *BCR-ABL* fusion is identified in the leukemic cells of a patient with chronic myeloid leukemia, then treatment with a tyrosine kinase inhibitor is appropriate. The first tyrosine kinase inhibitor to be developed and marketed was imatinib mesylate, and at least half of these patients will respond dramatically to this therapy. Imatinib must be taken continuously, because relapses develop quickly if the drug is stopped. Unfortunately over 100 different mutations have been identified in this fused gene; consequently, 33% of chronic myelogenous leukemia patients will be resistant to imatinib. More potent BCR-ABL tyrosine kinase inhibitors, such as dasatinib and nilotinib, have now been developed and can be used as first- or second-line therapy. Chronic lymphocytic leukemia is considered curable only by treatment with allogeneic hematopoietic stem cell transplantation, a procedure that has its own risks and can be considered in patients less than 60 years of age. Most patients achieve a significant response when treated with traditional chemotherapeutic agents that are combined with monoclonal antibodies directed against one of the B-lymphocyte cell surface antigens. Rituximab, which is a CD20 antibody, has been effective in managing this disease; however, other monoclonal B-cell surface antibodies are

being investigated. Drug therapy may be combined with radiation therapy to the CNS because the chemotherapeutic drugs often do not cross the blood-brain barrier effectively. Therefore, the leukemic cells may survive in this site and cause a relapse of the leukemia. Direct intrathecal infusion of the chemotherapeutic agent may be performed to circumvent the problem of the blood-brain barrier. If this strategy succeeds in inducing a remission, then a bone marrow transplant may be considered as a therapeutic option, particularly for the types of leukemia that tend to relapse. This option often is reserved for patients younger than 45 years of age because the success rate is less favorable in older patients.

Supportive care is often necessary if these patients are to survive their leukemia. For patients with bleeding problems, transfusions with platelets may be necessary. If severe anemia is present, packed RBCs may be required. Infections, of course, should be evaluated with respect to the causative organism, and appropriate antibiotics must be prescribed. Support must be maintained from an oral perspective because many of these patients experience infections of the oral mucosa during the course of their disease. Optimal oral hygiene should be encouraged, and aggressive investigation of any oral complaint should be performed as soon as possible to prevent potentially serious oral infectious complications.

The prognosis of a particular patient depends on a number of variables, including the type of leukemia, the age of the patient, and the cytogenetic alterations associated with the disease. In children with **acute lymphoblastic leukemia,** nearly 90% of these patients are now considered to be cured after appropriate treatment. In an adult with the same diagnosis, even though the rate of initial remission induction is 80%, the 5-year survival rate is generally much lower in most reported series.

Patients younger than 60 years of age with **acute myeloid leukemia** have a 5-year survival rate of approximately 40% today. This form of leukemia in a patient older than 60 years, however, has a much poorer prognosis, with less than a 10% chance of survival seen in that population. Similarly, patients with a previous history of myelodysplasia have an unfavorable prognosis.

Even though an indolent period is experienced with **chronic myeloid leukemia,** eventually the neoplastic cells undergo a process known as **blast transformation,** in which they become less differentiated, proliferate wildly, and cause the patient's death within 3 to 6 months. In the past, the 5-year survival rate for chronic myeloid leukemia was in the 20% range. Today, most centers are reporting 5-year survival rates of approximately 80%, a dramatic improvement presumably because of the effect of tyrosine kinase inhibitor therapy. Additional factors that may play a role in improved survival include diagnosis of the disease at an earlier stage and the availability of better supportive care. Attempts to control chronic myeloid leukemia by bone marrow transplantation from an HLA-matched donor have resulted in 5-year survival rates of 60% to 70% in younger patients with this disease. This may be an option for those patients who do not respond to tyrosine kinase inhibitor therapy.

Chronic lymphocytic leukemia is considered to be incurable, but its course is highly variable and depends on the stage of the disease. Patients with limited disease have an average survival time of more than 10 years. Those with more advanced disease survive an average of only 2 years.

◆ LANGERHANS CELL HISTIOCYTOSIS (HISTIOCYTOSIS X; LANGERHANS CELL DISEASE; IDIOPATHIC HISTIOCYTOSIS; EOSINOPHILIC GRANULOMA; LANGERHANS CELL GRANULOMA; LANGERHANS CELL GRANULOMATOSIS)

The term *histiocytosis X* was introduced as a collective designation for a spectrum of rare clinicopathologic disorders characterized by proliferation of histiocyte-like cells that are accompanied by varying numbers of eosinophils, lymphocytes, plasma cells, and multinucleated giant cells. The distinctive histiocytic cells present in this lesion have been identified as Langerhans cells, and the condition is now designated as **Langerhans cell histiocytosis.** Estimates of its incidence in the general population range from 1 to 4 cases per million annually.

Langerhans cells are dendritic mononuclear cells normally found in the epidermis, mucosa, lymph nodes, and bone marrow. These cells process and present antigens to T lymphocytes. For many years, researchers have debated whether Langerhans cell histiocytosis represents a nonneoplastic condition or a true neoplasm. Studies examining the clonality of the lesional cells of this condition have shown this to be a monoclonal proliferation, a finding that is more consistent with a neoplastic process. *BRAF* mutations have been identified in 40% to 60% of Langerhans cell histiocytosis lesions, and this oncogene has been implicated in uncontrolled cell division related to several other neoplasms.

Clinical and Radiographic Features

The clinicopathologic spectrum traditionally considered under the designation of Langerhans cell histiocytosis includes the following:

- Monostotic or polyostotic eosinophilic granuloma of bone—solitary or multiple bone lesions without visceral involvement
- Chronic disseminated histiocytosis—a disease involving bone, skin, and viscera **(Hand-Schüller-Christian disease)**
- Acute disseminated histiocytosis—a disease with prominent cutaneous, visceral, and bone marrow involvement occurring mainly in infants **(Letterer-Siwe disease)**

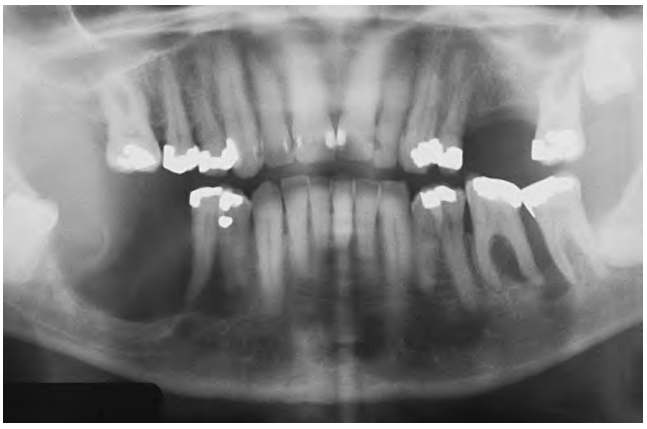
It is difficult to categorize many patients into one of these classic designations because of overlapping clinical features. The often-cited Hand-Schüller-Christian triad—bone lesions, exophthalmos, and diabetes insipidus—is present in only a few patients with chronic disseminated disease. It is widely believed that the traditional designations of Hand-Schüller-Christian and Letterer-Siwe disease serve no useful purpose and should be discontinued. Many cases reported as Letterer-Siwe disease in the older literature probably included obscure infections, immunodeficiency syndromes, and malignant histiocytic lesions. Pulmonary Langerhans cell histiocytosis has also been described, but this probably is unrelated to the condition that affects the jaws. Patients who develop pulmonary Langerhans cell histiocytosis are usually adults with a history of smoking, and clonality studies suggest that this is probably a reactive process. The Histiocyte Society, in order to better define prognostic categories of Langerhans cell histiocytosis, has proposed the following classification:

- Single organ involvement—typically bone or skin
  - Unifocal disease
  - Multifocal disease
- Multi-organ involvement
  - No organ dysfunction
  - Organ dysfunction
    - Low-risk (skin, bone, lymph nodes, and/or pituitary gland)
    - High-risk (lung, liver, spleen, and/or bone marrow)

Although Langerhans cell histiocytosis may be encountered in patients over a wide age range, more than 50% of all cases are seen in patients younger than age 15. Although some series have reported a male predilection, overall the sexes appear to be equally affected. Bone lesions, either solitary or multiple, are the most common clinical presentation. Lesions may be found in almost any bone, but the skull, ribs, vertebrae, and mandible are among the most frequent sites. Children younger than age 10 most often have skull and femoral lesions; patients older than age 20 more often have lesions in the ribs, shoulder girdle, and mandible. Adult patients with solitary or multiple bone lesions may have lymphadenopathy but usually do not have significant visceral involvement.

The jaws are affected in 10% to 20% of all cases. Dull pain and tenderness often accompany bone lesions. Radiographically, the lesions often appear as sharply punched-out radiolucencies without a corticated rim, but occasionally an ill-defined radiolucency is seen. Bone involvement in the mandible usually occurs in the posterior areas, and a characteristic "scooped out" appearance may be evident when the superficial alveolar bone is destroyed. The resulting bone destruction and loosening of the teeth clinically may resemble severe periodontitis (Fig. 13-19). Extensive alveolar involvement causes the teeth to appear as if they are "floating in air" (Fig. 13-20).

Ulcerative or proliferative mucosal lesions or a proliferative gingival mass may develop if the disease breaks out of bone (Fig. 13-21). Occasionally, this process may involve only the oral soft tissues. Lesions also can occur within the body of the mandible or maxilla, where they may simulate a periapical inflammatory condition.



• **Fig. 13-19 Langerhans Cell Histiocytosis.** Severe bone loss in the mandibular molar regions that resembles advanced periodontitis. (Courtesy of Dr. James White.)

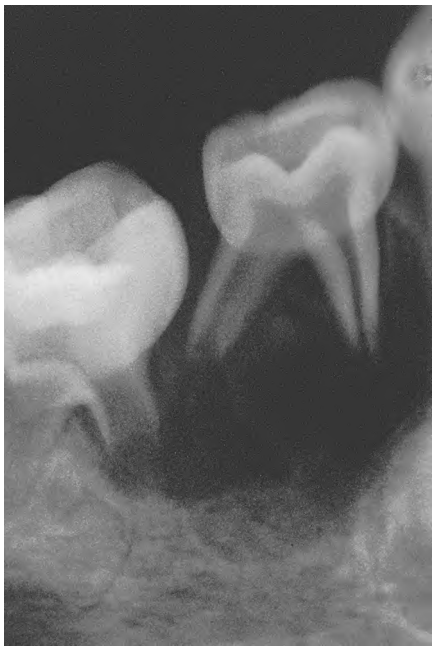
Histopathologic Features

The bone lesions of patients with Langerhans cell histiocytosis show a diffuse infiltration of large, pale-staining mononuclear cells that resemble histiocytes. These cells have indistinct cytoplasmic borders and rounded or indented vesicular nuclei. Varying numbers of eosinophils are typically interspersed among the histiocyte-like cells (Fig. 13-22). Plasma cells, lymphocytes, and multinucleated giant cells are often seen, and areas of necrosis and hemorrhage may be present.

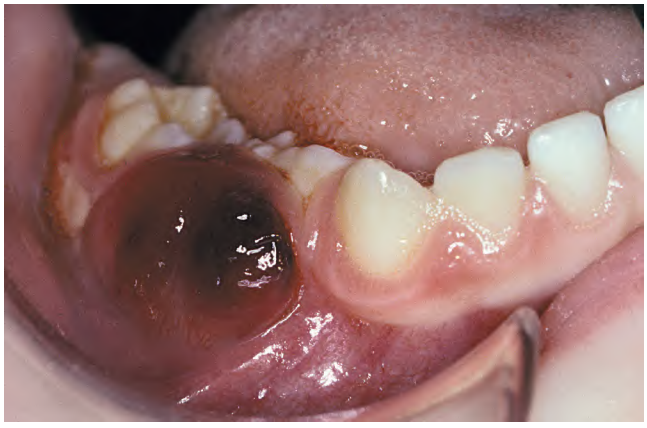
The identification of lesional Langerhans cells is necessary to confirm the diagnosis. Because Langerhans cells cannot be differentiated from other histiocytes by routine histologic staining, additional diagnostic methods are required. Electron microscopic evaluation of lesional tissue was the gold standard for many years because, ultrastructurally, Langerhans cells contain rod-shaped cytoplasmic structures known as **Birbeck granules,** which differentiate them from other mononuclear phagocytes (Fig. 13-23). Immunohistochemical procedures are now used to identify the lesional Langerhans cells because of their immunoreactivity with antibodies directed against either CD-1a or CD-207 (langerin), and both markers are specific for Langerhans cell histiocytosis when seen in the correct clinical setting.

Treatment and Prognosis

Because this condition is relatively rare, treatment recommendations are often based on anecdotal experience, rather than randomized controlled trials. Most patients with oral involvement have single organ disease affecting the jaws, although other skeletal lesions may be present. Accessible bone lesions, such as those in the maxilla and mandible, are usually treated by curettage. Low doses of radiation may be



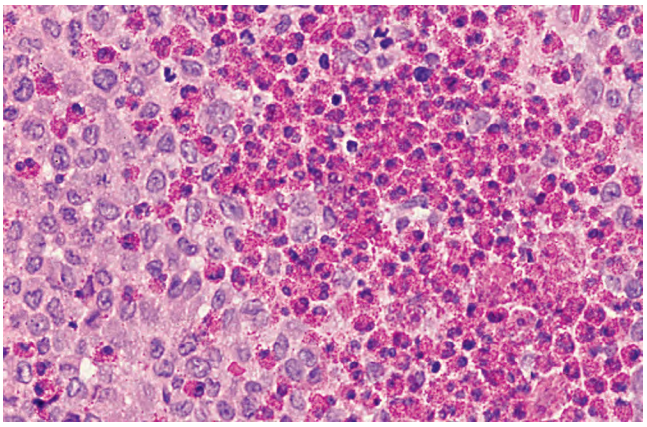
• **Fig. 13-20 Langerhans Cell Histiocytosis.** Periapical radiograph showing marked bone loss involving the mandibular teeth in a young girl, resulting in a "floating-in-air" appearance of the teeth.



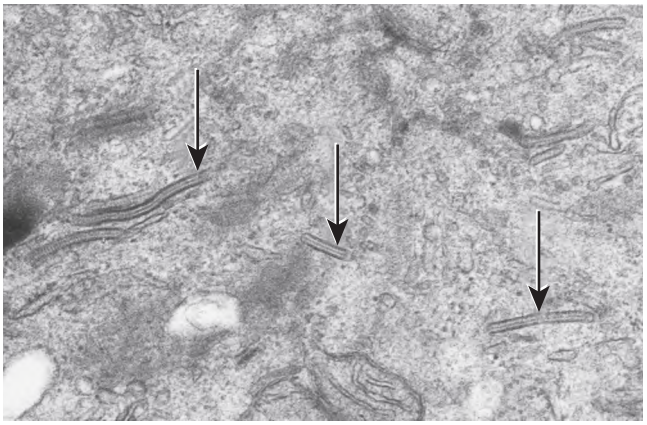
• **Fig. 13-21 Langerhans Cell Histiocytosis.** Clinical photograph of the same patient shown in Fig. 13-20. The lesion has broken out of bone and produced this soft tissue mass.

used for less accessible bone lesions, although the potential for induction of malignancy secondary to this treatment is a concern in younger patients. Intralesional injection with corticosteroid agents has also been reported to be effective in some patients with localized bone lesions. Infrequently, the apparent spontaneous regression of localized Langerhans cell histiocytosis has been reported. The prognosis for bone lesions in the absence of significant visceral involvement is generally good; however, progression or dissemination of the disease may occur, particularly for patients who have three or more bones affected.

When multiple organs are involved, the low-risk pattern is often associated with considerable morbidity, but the mortality is considerably less than that of patients with



• **Fig. 13-22 Langerhans Cell Histiocytosis.** There is a diffuse infiltrate of pale-staining Langerhans cells intermixed with numerous red granular eosinophils.

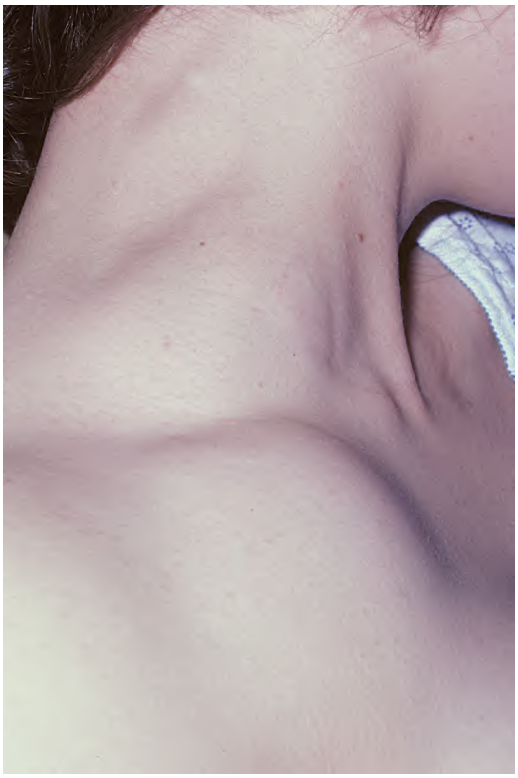


• **Fig. 13-23 Langerhans Cell Histiocytosis.** Electron micrograph showing rod-shaped Birbeck bodies *(black arrows)* in the cytoplasm of a Langerhans cell. (Courtesy of Richard Geissler.)

high-risk organ involvement. Because of the relative rarity of disseminated cases, the ideal treatment has yet to be identified. Single-agent chemotherapy using prednisolone, etoposide, vincristine, or cyclosporine has produced a good response in a significant percentage of such patients, although recurrence is typically seen in over half of the cases. A combination of vincristine and prednisone seems to reduce this risk of recurrence, particularly in children. Lesions in adults, however, respond much better to low-dose cytosine arabinoside (ARA-C), which is also less toxic. Multiple high-risk organ involvement seen in infants and young children may not respond to these more conservative approaches, and multiple chemotherapeutic agents are given in that situation. Patients who improve significantly with induction chemotherapy during the first 6 weeks have a much better prognosis (nearly 90% survival) compared to those who do not respond. In that group, only 20% to 35% survive. In general, the prognosis is poorer for patients in whom the first sign of the disease develops at a very young age and somewhat better for patients who are older at the time of onset.

HODGKIN LYMPHOMA (HODGKIN DISEASE)

Hodgkin lymphoma represents a malignant lymphoproliferative disorder, although for many years the exact nature of the process was poorly understood. The difficulty in comprehending the character of the condition is reflected in the relatively noncommittal term *Hodgkin disease*, which was used for decades and still may be heard today. Perhaps one reason why Hodgkin lymphoma was not easily understood is that, unlike most malignancies, the neoplastic cells **(Reed-Sternberg cells)** make up only about 0.1% to 2% of the cells in the enlarged lymph nodes that characterize this condition. Current evidence regarding the histogenesis of the Reed-Sternberg cell points to a B-lymphocyte origin. Certainly, the disease can cause death if appropriate therapy is not instituted, although the treatment of this malignancy is one of the few major success stories in cancer therapy during the past 30 years. In the United States, Hodgkin lymphoma is about one sixth as common as non-Hodgkin lymphoma; approximately 9000 cases are diagnosed annually. Although the cause of this disease is unknown, epidemiologic and molecular studies have linked Epstein-Barr virus (EBV) infection to a significant percentage of these lesions.



• **Fig. 13-24 Hodgkin Lymphoma.** The prominent supraclavicular and cervical masses represent Hodgkin lymphoma.

Clinical Features

Hodgkin lymphoma almost always begins in the lymph nodes, and any lymph node group is susceptible. The most common sites of initial presentation are the cervical and supraclavicular nodes (70% to 75%) or the axillary and mediastinal nodes (5% to 10% each). The disease initially appears less than 5% of the time in the abdominal and inguinal lymph nodes.

Overall, a male predilection is observed, and a bimodal pattern is noted with respect to the patient's age at diagnosis. One peak is observed between 15 and 35 years of age; another peak is seen after the age of 50.

The usual presenting sign is the identification by the patient of a persistently enlarging, nontender, discrete mass or masses in one lymph node region (Fig. 13-24). In the early stages, the involved lymph nodes are often rather movable; as the condition progresses, the nodes become more matted and fixed to the surrounding tissues. If it is untreated, then the condition spreads to other lymph node groups and eventually involves the spleen and other extralymphatic tissues, such as bone, liver, and lung. Oral involvement has been reported, but it is rare. In about 30% to 40% of patients with Hodgkin disease, other systemic signs and symptoms may be present, such as weight loss, fever, night sweats, and generalized pruritus (itching). The absence of these systemic signs and symptoms is considered to be better in terms of the patient's prognosis, and this information is used in staging the disease. Patients who have no systemic signs are assigned to category A and those with systemic signs to category B.

The staging of Hodgkin lymphoma is important for planning treatment and estimating the prognosis for a given patient. The staging procedure typically includes confirmation of the pathologic diagnosis, careful history and physical examination, abdominal and thoracic computed tomography (CT) scans or magnetic resonance imaging (MRI) studies, chest radiographs, and routine hematologic studies (e.g., complete blood count, serum chemistries, and erythrocyte sedimentation rate). Evaluation of the extent of disease involvement using positron emission tomography (PET) scans is becoming part of the standard protocol, particularly at large institutions. Lymphangiography, gallium scan, bone marrow biopsy, exploratory laparotomy, and splenectomy may be necessary if the information that they would provide might have an effect on staging or treatment. A summary of the staging system for Hodgkin lymphoma is presented in Table 13-2.

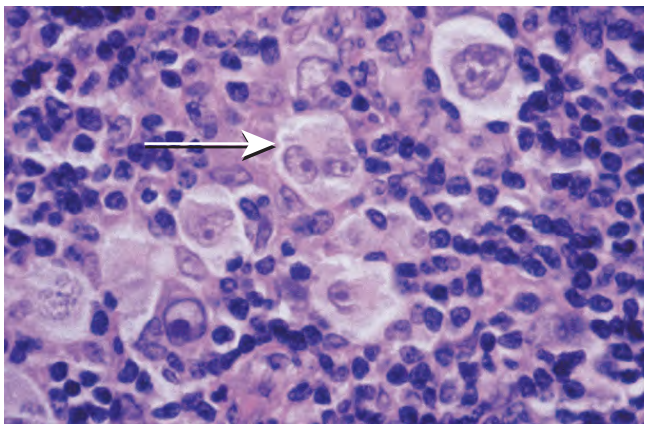
Histopathologic Features

Hodgkin lymphoma is recognized to comprise two main forms, 1) nodular lymphocyte–predominant Hodgkin lymphoma and 2) classical Hodgkin lymphoma, the latter of which is divided into five subtypes. Although this group of diseases has certain features in common, current immunohistochemical and molecular biologic techniques have

TABLE 13-2 Ann Arbor System for Classification of Hodgkin Lymphoma

Stage	Defining Features
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or one or more lymph node regions with an extralymphatic site (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), possibly with an extralymphatic organ or site (III_E), the spleen (III_S), or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs (identified by symbols), with or without associated lymph node involvement A: Absence of systemic signs B: Presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight during the 6-month period before diagnosis

Adapted from Gobbi PG, Ferreri AJM, Ponzoni M, et al: Hodgkin lymphoma, *Crit Rev Oncol Hematol* 85:216-237, 2013.



• **Fig. 13-25 Hodgkin Lymphoma.** This high-power photomicrograph shows the characteristic Reed-Sternberg cell *(arrow)* of Hodgkin lymphoma, identified by its "owl-eye" nucleus.

allowed distinctions to be made among the various types. The common features include effacement of the normal nodal architecture by a diffuse, often mixed, infiltrate of inflammatory cells that is interspersed with large, atypical neoplastic lymphoid cells. In the case of classical Hodgkin lymphoma, this atypical cell is known as a **Reed-Sternberg cell** (Fig. 13-25). The Reed-Sternberg cell is typically binucleated ("owl-eye" nuclei), although it may be multinucleated ("pennies on a plate"), with prominent nucleoli. The malignant cell in nodular lymphocyte–predominant Hodgkin lymphoma is the "popcorn cell," which is so-named because of the resemblance of the nucleus to a kernel of popped corn. The pathologist must see one of these types of distinctive atypical cells to make a diagnosis of Hodgkin lymphoma, although their presence does not automatically imply that diagnosis, because similar cells may be seen in certain viral infections, especially infectious mononucleosis. To summarize, Hodgkin lymphoma is currently classified in the following manner:

- Nodular lymphocyte–predominant Hodgkin lymphoma, or
- Classical Hodgkin lymphoma (comprising five histopathologic subtypes):
  1. Lymphocyte rich
  2. Nodular sclerosis
  3. Mixed cellularity
  4. Lymphocyte depletion
  5. Unclassifiable

These names describe the most prominent histopathologic feature of each type, and specific epidemiologic and prognostic characteristics are associated with each type.

Nodular lymphocyte–predominant Hodgkin lymphoma constitutes 4% to 5% of all cases of Hodgkin lymphoma in the United States. In the past, this form was probably combined with the lymphocyte-rich subtype, but the presence of the characteristic popcorn cells is a significant clue to the diagnosis.

Lymphocyte-rich classical Hodgkin lymphoma represents about 6% of all cases. Sheets of small lymphocytes with few Reed-Sternberg cells characterize this form.

The **nodular sclerosis** subtype makes up 60% to 80% of cases and occurs more frequently in females during the second decade of life. This type gets its name from the broad fibrotic bands that extend from the lymph node capsule into the lesional tissue. Reed-Sternberg cells in the nodular sclerosis form appear to reside in clear spaces and, therefore, are referred to as *lacunar cells.*

The **mixed cellularity** form accounts for about 15% to 30% of the cases and is characterized by a mixture of small lymphocytes, plasma cells, eosinophils, and histiocytes with abundant Reed-Sternberg cells.

The **lymphocyte depletion** subtype, the most aggressive type, makes up less than 1% of the cases in recent reports. Before modern immunohistochemical techniques, many examples of large cell lymphoma or anaplastic T-cell lymphoma were undoubtedly included in this category. In this form of Hodgkin lymphoma, numerous bizarre giant Reed-Sternberg cells are present, with few lymphocytes.

Occasionally, examples of Hodgkin lymphoma are encountered that really do not fit the criteria for any of the known subtypes, and these are designated as **unclassifiable.**

Treatment and Prognosis

The treatment of Hodgkin lymphoma depends on the stage of involvement. In the past, patients who had limited disease (stages I and II) often were managed by local radiation therapy alone. Recent treatment trends, however,

combine less extensive radiotherapy fields with milder multiagent chemotherapy regimens to maximize disease control and minimize long-term complications of therapy. Patients with stage III or IV disease require chemotherapy; radiation therapy is used conjointly if significant mediastinal involvement or residual disease is detected. For many years a regimen known as **MOPP** (mechlorethamine, Oncovin, procarbazine, prednisone) was widely used to treat Hodgkin lymphoma. Because significant long-term side effects can be associated with this chemotherapy, another regimen known as **ABVD** (Adriamycin, bleomycin, vinblastine, dacarbazine [DTIC]) is now used most often because it has fewer complications.

Before modern cancer therapy was developed for Hodgkin lymphoma, the 5-year survival rate was only 5%. The prognosis for this disease is fairly good today; the best treatment results occur in those who present in the early stages. Patients with stage I and II disease often have an 80% to 90% relapse-free 10-year survival rate; those with stage III and IV disease have a 55% to 75% 10-year survival rate.

The histopathologic subtype of Hodgkin lymphoma appears to have minimal impact on the response to therapy. In the past, researchers believed that the lymphocyte depletion form had a poorer prognosis than the other subtypes. However, with newer immunohistochemical studies, clinicians now realize that many of these cases were misdiagnosed. In most instances, the stage of disease now plays a more important role in determining the patient's prognosis than does the histopathologic subtype.

After 15 years posttreatment, patient mortality is due more often to the complications of therapy: either secondary malignancy or cardiovascular disease. Currently, research is focused on the development of treatment regimens that continue to have a superior cure rate, while simultaneously decreasing the risk of treatment-related complications.

◆ NON-HODGKIN LYMPHOMA

The **non-Hodgkin lymphomas** include a diverse and complex group of malignancies of lymphoreticular histogenesis and differentiation. In most instances, they initially arise within lymph nodes and tend to grow as solid masses. This is in contrast to lymphocytic leukemias (see page 547), which begin in the bone marrow and are characterized by a large proportion of malignant cells that circulate in the peripheral blood. The non-Hodgkin lymphomas most commonly originate from cells of the B-lymphocyte series, with an estimated 85% of European and American lymphoid neoplasms having this derivation. Tumors with a T-lymphocyte derivation are less common, whereas true histiocyte-derived lymphomas are even rarer.

The microscopic appearance of the lesional cells was used in the past to classify the tumors as either *lymphocytic* or *histiocytic*. With the development of modern immunologic techniques, however, it is now known that many of the lesions that had been classified as *histiocytic* were in fact neoplasms composed of transformed B lymphocytes. In the early 1980s, a group of American pathologists devised a classification scheme, known as the *Working Formulation for Clinical Use,* which may still be referred to in the United States. Based on this classification, lymphomas were broadly grouped into three categories:

1. Low grade
2. Intermediate grade
3. High grade

Unfortunately, the Working Formulation has been shown to be somewhat limited in its utility and accuracy. Many lesions that have been recently defined are not included in this classification. For these reasons, an international study group in the early 1990s devised a new method of categorizing the lymphomas, known as the *REAL (revised European-American lymphoma) classification.* With this system, a combination of histopathologic features, immunologic cell surface markers, and gene rearrangement studies are used to organize this group of neoplasms. Further revisions to the World Health Organization (WHO) lymphoma classification system appear periodically as knowledge about this challenging area of pathology accumulates (Box 13-2). This classification is more precise than the Working Formulation, and currently most pathologists in the United States categorize lymphomas according to the modified REAL system, although some of the more sophisticated molecular studies may not be available at smaller laboratories.

Approximately 70,000 cases of non-Hodgkin lymphoma are diagnosed in the United States annually; approximately one-third of this number will die of the disease each year. For reasons that are currently unclear, the incidence of this malignancy seems to be rising in the United States. The prevalence of lymphoma is increased in patients who have immunologic problems, such as congenital immunodeficiencies (e.g., Bloom syndrome, Wiskott-Aldrich syndrome, and common variable immunodeficiency), AIDS, organ transplantation, and autoimmune disease (e.g., Sjögren syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis).

Viruses may play a role in the pathogenesis of at least some of these lesions. For example, Epstein-Barr virus (EBV) has been implicated, but not proven, to be an etiopathogenic agent in Burkitt lymphoma (see page 560), a type of high-grade, small, noncleaved B-cell lymphoma. EBV is more convincingly related to the development of various lymphoproliferative conditions (known as **EBV-associated lymphoproliferative disorders**) that range from benign, reactive processes through overt malignancies. Some of these occur in the setting of immune senescence (decreased function of the immune system with aging), whereas others are related to immunosuppressive medications (Fig. 13-26), immunosuppression after solid organ or bone marrow transplant, or in association with AIDS (see page 245). Human herpesvirus 8 (HHV-8) has not only been associated with Kaposi sarcoma but also with primary body cavity lymphoma and some cases of plasmablastic

• BOX 13-2 Classification of Hematopoietic and Lymphoid Neoplasms, Modified from the Revised European-American Lymphoma (REAL)/ World Health Organization (WHO) Classification

B-Cell Neoplasms

I. Precursor B-cell neoplasm: Precursor B-acute lymphoblastic leukemia/LBL
II. Peripheral (mature) B-cell neoplasms
  A. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  B. B-cell prolymphocytic leukemia
  C. Lymphoplasmacytic lymphoma/immunocytoma
  D. Mantle cell lymphoma
  E. Follicular lymphoma
  F. Extranodal marginal zone B-cell lymphoma of MALT type
  G. Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
  H. Splenic marginal zone lymphoma (± villous lymphocytes)
  I. Hairy cell leukemia
  J. Plasmacytoma/plasma cell myeloma
  K. Diffuse large B-cell lymphoma
  L. Burkitt lymphoma

T-Cell and Putative NK-Cell Neoplasms

I. Precursor T-cell neoplasm: Precursor T-acute lymphoblastic leukemia/LBL
II. Peripheral (mature) T-cell and NK-cell neoplasms
  A. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
  B. T-cell granular lymphocytic leukemia
  C. Mycosis fungoides/Sézary syndrome
  D. Peripheral T-cell lymphoma, not otherwise characterized
  E. Hepatosplenic gamma/delta T-cell lymphoma
  F. Subcutaneous panniculitis-like T-cell lymphoma
  G. Angioimmunoblastic T-cell lymphoma
  H. Extranodal T-/NK-cell lymphoma, nasal type
  I. Enteropathy-type intestinal T-cell lymphoma
  J. Adult T-cell lymphoma/leukemia (HTLV 1+)
  K. Anaplastic large cell lymphoma, primary systemic type
  L. Anaplastic large cell lymphoma, primary cutaneous type
  M. Aggressive NK-cell leukemia

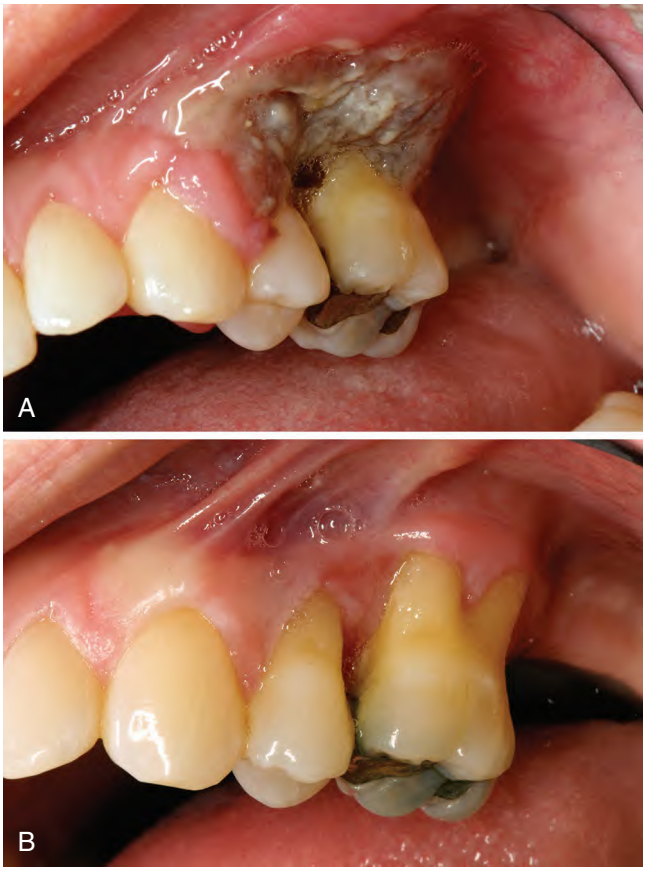
HTLV, Human T-lymphotropic virus; *LBL,* lymphoblastic lymphoma; *MALT,* mucosa-associated lymphoid tissue; *NK*, natural killer.

lymphoma. The blood-borne human retrovirus, human T-cell leukemia/lymphoma virus type I (HTLV-1), has been shown to cause an aggressive form of peripheral T-cell lymphoma among certain populations in the Caribbean, central Africa, and southwest Japan.

Even bacteria have been shown to induce the formation of so-called **mucosa-associated lymphoid tissue (MALT) lymphoma** of the stomach. Antibiotic treatment of *Helicobacter pylori* infection of the stomach lining often results in complete regression of this low-grade lymphoma.

Clinical and Radiographic Features

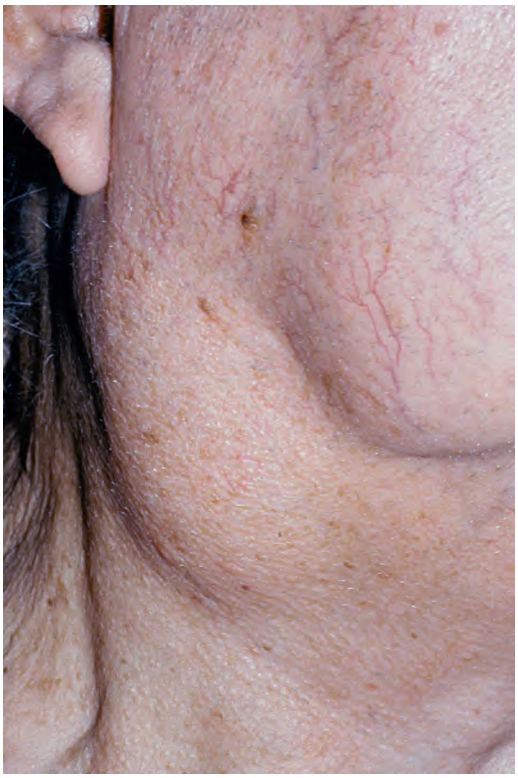
Non-Hodgkin lymphoma occurs primarily in adults, although children may be affected, particularly by the more aggressive intermediate- and high-grade lymphomas. The condition most commonly develops in the lymph nodes, but so-called extranodal lymphomas are also found. In the United States, approximately 20% to 40% of lymphomas develop in an extranodal site, but in Asian countries such as Korea and Japan, nearly half of all lymphomas are extranodal.



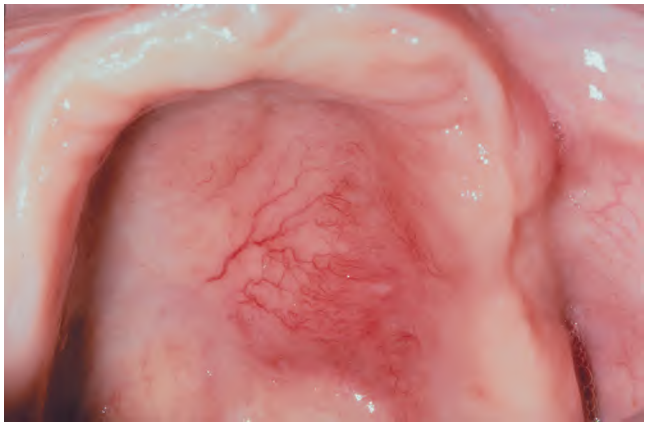
• Fig. 13-26 Epstein-Barr Virus (EBV)-Associated Lymphoproliferative Disorder. A, This 42-year-old woman, treated for autoimmune hepatitis with mycophenolate mofetil, developed painful gingival ulcers. **B,** Resolution of the lesion after immune suppression was stopped and rituximab therapy was initiated.

With a nodal presentation, the patient usually is aware of a nontender mass that has been slowly enlarging for months. The lesion typically involves a local lymph node collection, such as the cervical, axillary, or inguinal nodes; one or two freely movable nodules are noticed initially. As the malignancy progresses, the nodes become more numerous and are fixed to adjacent structures or matted together (Fig. 13-27). Gradually, the process involves other lymph node groups, and invasion of adjoining normal tissues occurs.

In the oral cavity, lymphoma usually appears as extranodal disease. Although the oral lesions of lymphoma are often a component of more widely disseminated disease, at times the lymphoma begins in the oral tissues and has not spread to other sites. The malignancy may develop in the oral soft tissues or centrally within the jaws. Soft tissue lesions appear as nontender, diffuse swellings; they most



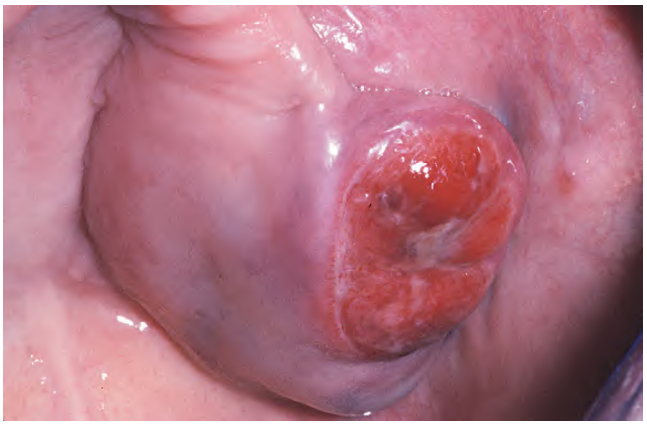
• **Fig. 13-27 Non-Hodgkin Lymphoma.** The matted, nontender lymph node enlargement in the lateral cervical region represents a common presentation of lymphoma.



• **Fig. 13-28 Non-Hodgkin Lymphoma.** One of the frequent locations of extranodal lymphoma in the head and neck area is the palate, where the tumor appears as a nontender, boggy swelling. Note the overlying telangiectatic blood vessels, a feature often seen with malignancy.

commonly affect the buccal vestibule, posterior hard palate, or gingiva (Figs. 13-28 and 13-29). Such swellings characteristically have a boggy consistency. The lesion may appear erythematous or purplish, and it may or may not be ulcerated. Patients who wear a denture that contacts the lesional site often complain that their denture does not fit because it feels too tight.

Lymphoma of bone may cause vague pain or discomfort, which might be mistaken for a toothache. The patient may



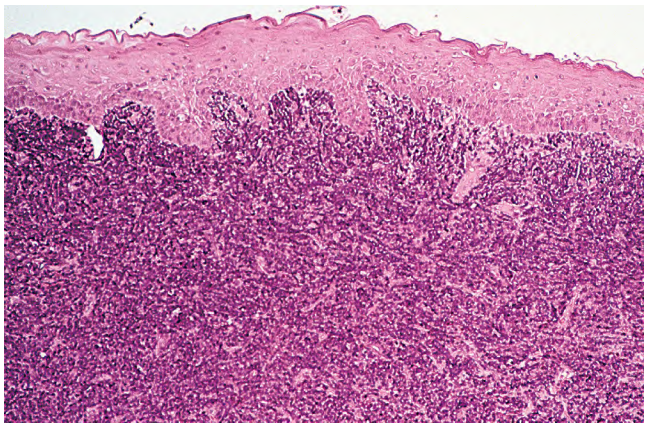
• **Fig. 13-29 Non-Hodgkin Lymphoma.** Ulcerated mass of the left posterior maxilla.

complain of paresthesia, particularly with a mandibular lesion (so-called numb chin syndrome). Radiographs usually show an ill-defined or ragged radiolucency, although in the early stages, the radiographic changes may be subtle or nonexistent. If untreated, then the process typically causes expansion of the bone, eventually perforating the cortical plate and producing a soft tissue swelling. Such lesions have been mistaken for a dental abscess, although a significant amount of pain is not present in most cases.

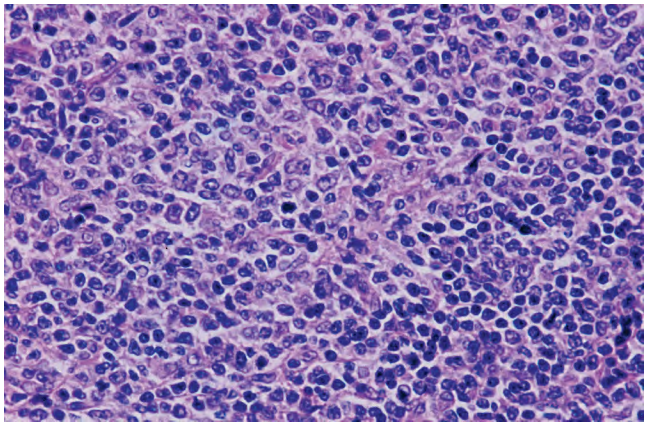
Clinical staging to determine the extent to which the disease has spread is an important factor in assessing the prognosis for a particular patient. The staging evaluation should include a history, physical examination, complete blood count, liver function studies, CT scans of the thoracic, pelvic and abdominal regions, and bone marrow biopsy. Because of the information obtained with CT imaging, studies such as chest radiographs, lymphangiography and staging laparotomy are not routinely performed. PET scans are also useful in staging, but this technique may not be available at all medical centers. In some cases it is employed to assess response to treatment, rather than for staging. The staging system for Hodgkin lymphoma (see Table 13-2) has been widely adopted for use with the non-Hodgkin lymphomas.

Histopathologic Features

Non-Hodgkin lymphomas are histopathologically characterized by a proliferation of lymphocytic-appearing cells that may show varying degrees of differentiation, depending on the type of lymphoma. Low-grade lesions consist of well-differentiated small lymphocytes. High-grade lesions tend to be composed of less differentiated cells. All lymphomas grow as infiltrative, broad sheets of relatively uniform neoplastic cells that usually show little or no evidence of lesional tissue necrosis (Figs. 13-30 and 13-31). In some lesions, particularly those of B-lymphocyte origin, a vague semblance of germinal center formation may be seen (i.e., a *nodular* or *follicular* pattern). Other lymphomas show no evidence of such differentiation, and this pattern is termed



• **Fig. 13-30 Non-Hodgkin Lymphoma.** This low-power photomicrograph shows a diffuse infiltration of the subepithelial connective tissue by lymphoma.



• **Fig. 13-31 Non-Hodgkin Lymphoma.** This high-power photomicrograph shows lesional cells of lymphoma, consisting of a population of poorly differentiated cells of the lymphocytic series with minimal cytoplasm.

diffuse. If the lymphoma arises in a lymph node, then the tumor destroys the normal architecture of the node. An extranodal lymphoma destroys the normal adjacent host tissue by infiltrating throughout the area. In the oral cavity, diffuse large B-cell lymphoma, which is considered to be a high-grade lymphoma, is the most common diagnosis, comprising approximately 60% of the cases.

Standard of care demands that appropriate immunohistochemical and cytogenetic studies be performed for a tumor diagnosed as lymphoma. In general, these studies can become quite involved and, therefore, are beyond the scope of this text.

Treatment and Prognosis

The treatment of a patient with non-Hodgkin lymphoma is based on several factors, including the stage and grade of the lymphoma, the overall health of the patient, and the patient's pertinent past medical history. The patient's health must be considered because many of the chemotherapeutic regimens are quite debilitating. Surgical management is not usually indicated.

Because most non-Hodgkin lymphomas are of B-cell differentiation, many treatment strategies now incorporate monoclonal antibodies directed against CD20, a B-cell surface antigen, as part of the chemotherapeutic regimen for both low-grade and high-grade lymphomas. Rituximab is one of the more commonly used agents (see Fig. 13-26), although others are now available. Novel monoclonal antibodies to CD20 and other lymphoid cell surface antigens are continually being developed and examined in clinical trials.

Low-grade (indolent) lymphomas are perhaps the most controversial in terms of treatment. Some authorities recommend no particular treatment because these tumors are slow growing and tend to recur despite chemotherapy. Given the fact that low-grade lymphomas arise in older adults and the median survival without treatment is 8 to 10 years, many oncologists opt for a "watch and wait" strategy, treating the patient only if symptoms develop. Unfortunately, approximately 40% of low-grade lymphomas eventually transform to a high-grade lymphoma, leading to the patient's demise. Because these low-grade lymphomas have been considered "incurable," new treatments are being investigated.

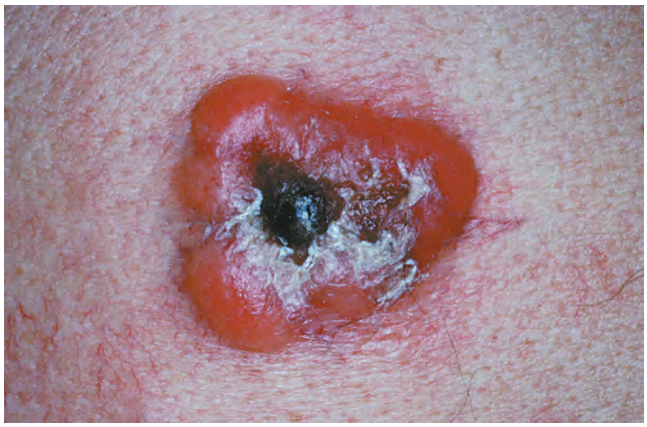
For **high-grade** (aggressive) lymphomas, the treatment of localized disease consists of radiation plus chemotherapy. With more advanced and disseminated disease, chemotherapy alone usually is implemented. Multiagent chemotherapy is used routinely, and new combinations are being evaluated continuously. Unfortunately, although the response rate of many lesions is good and much progress has been made in this area, the cure rate is not high. High-grade lymphomas are associated with a 60% mortality rate at 5 years after diagnosis and treatment.

◆ MYCOSIS FUNGOIDES (CUTANEOUS T-CELL LYMPHOMA)

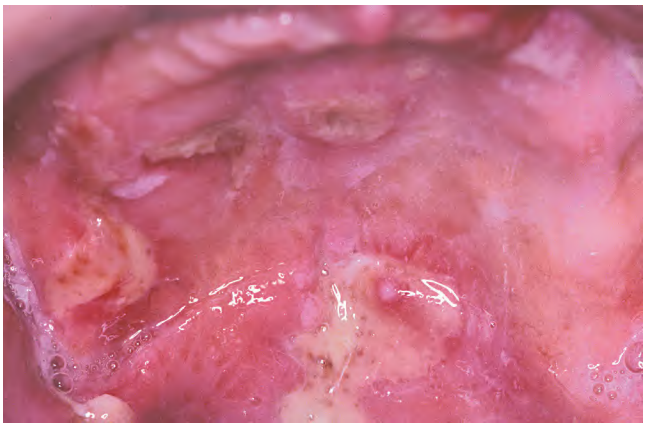
From its name, one might think that **mycosis fungoides** is a fungal infection. The early dermatologists who first recognized mycosis fungoides knew that this was not the case; however, they still thought the disease resembled a fungal condition. Thus this term has persisted. This condition, in fact, represents a lymphoma that is derived from T lymphocytes, specifically the T-helper (CD4+) lymphocyte. With modern diagnostic techniques, clinicians now know that there are several types of cutaneous lymphomas, each having specific T-lymphocyte or B-lymphocyte differentiation patterns. Even though mycosis fungoides is the most common of these cutaneous lymphomas, it is still a relatively rare malignancy; only about 1,200 new cases are diagnosed in the United States annually. This condition exhibits a peculiar property called **epidermotropism** (i.e., a propensity to invade the epidermis of the skin). Oral involvement, although infrequent, may also be present.

Clinical Features

Mycosis fungoides is a condition that usually affects middle-aged adult men; there is a 2:1 male-to-female ratio and a



• **Fig. 13-32 Mycosis Fungoides.** In the tumor stage of the disease, patients with mycosis fungoides have ulcerated nodules of the skin. (From Damm DD, White DK, Cibull ML, et al: Mycosis fungoides: initial diagnosis via palatal biopsy with discussion of diagnostic advantages of plastic embedding, *Oral Surg Oral Med Oral Pathol* 58:413-419, 1984.)



• **Fig. 13-33 Mycosis Fungoides.** The ulcerated palatal lesions represent a rare example of oral mucosal involvement by mycosis fungoides.

mean age at diagnosis of 55 to 60 years. African-Americans appear to be affected approximately 1.5 times more frequently than other ethnic groups. The disease progresses through three stages, usually over the course of several years.

The first stage, known as the **eczematous (erythematous) stage,** is often mistaken for psoriasis of the skin because of the well-demarcated, scaly, erythematous patches that characterize these lesions. Patients may complain of pruritus. With time, the erythematous patches evolve into slightly elevated, red lesions **(plaque stage).** These plaques tend to grow and become distinct papules and nodules. At this time, the disease has entered the **tumor stage** (Fig. 13-32). Visceral involvement is also seen at this point.

Approximately 35 cases of mycosis fungoides with oral involvement have been reported. The most commonly affected sites are the tongue, palate, and gingiva (Fig. 13-33). The buccal mucosa, tonsils, lips, sinuses, and nasopharynx may also be affected. The oral lesions present as erythematous, indurated plaques or nodules that are typically ulcerated. Generally, these lesions appear late in the course of the disease and develop after the cutaneous lesions.

Sézary syndrome is an aggressive expression of mycosis fungoides that essentially represents a dermatopathic T-cell leukemia. The patient has a generalized exfoliative erythroderma, as well as lymphadenopathy, hepatomegaly, and splenomegaly. The lung, kidneys, and CNS can also be involved. This condition follows a fulminant course and typically results in the patient's death within a short period of time; the median survival for this form of the disease is 2 to 3 years.

Histopathologic Features

Eczematous Stage

The early stages of mycosis fungoides may be difficult to diagnose histopathologically because of the subtle changes that characterize the initial lesions. A psoriasiform pattern of epithelial alteration is seen, with parakeratin production and elongation of the epithelial rete ridges. Scattered, slightly atypical lymphocytic cells may be seen in the connective tissue papillae, but such features are often mistaken for an inflammatory process.

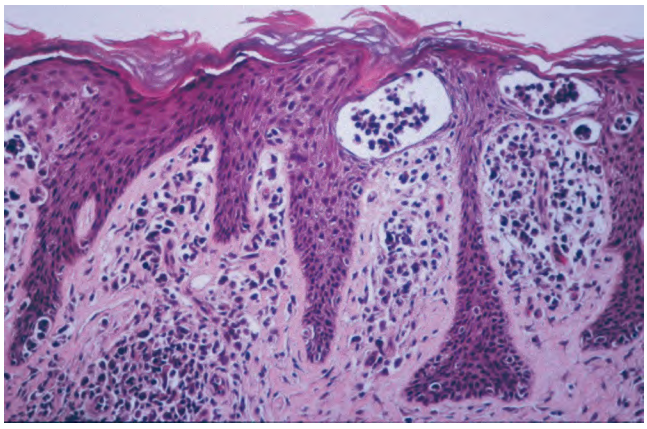
Plaque Stage

With the development of the plaque stage, a more readily identifiable microscopic pattern emerges. Examination of the surface epithelium reveals infiltration by atypical lymphocytic cells, which are sometimes referred to as *mycosis cells* or *Sézary cells.* These atypical lymphocytes classically form small intraepithelial aggregates termed *Pautrier microabscesses* (Fig. 13-34). The lesional cells have an extremely unusual nucleus because of the marked infolding of the nuclear membrane, which results in what is termed a *cerebriform nucleus.* This feature can best be appreciated when viewed in special semithin, plastic-embedded microscopic sections (Fig. 13-35). The diagnosis of mycosis fungoides can be confirmed by demonstrating positivity for CD4 (a cell surface marker for T-helper cells) in the lesional cell population. In addition, T-cell receptor gene rearrangement analysis should identify a monoclonal population of T lymphocytes. A mixed infiltrate of eosinophils, histiocytes, and plasma cells may be observed in the subepithelial connective tissue.

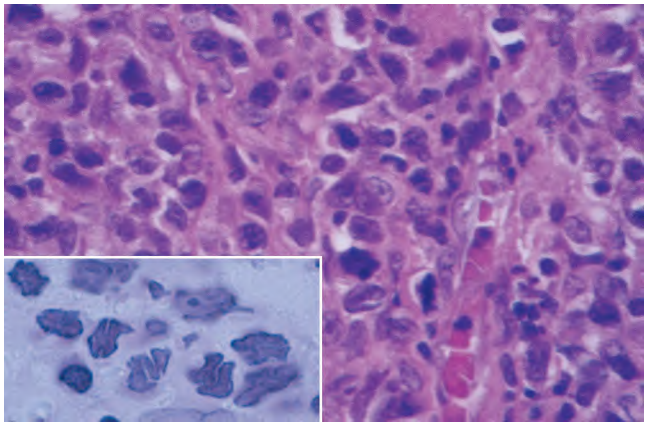
Tumor Stage

As the condition progresses to the tumor stage, the diffuse infiltration of the dermis and epidermis by atypical lymphocytic cells makes it easier to identify as a malignant process. Other types of lymphoma would enter into the histopathologic differential diagnosis.

Immunohistochemical studies demonstrating a T-helper phenotype, combined with the T-cell receptor gene rearrangement studies, would help to distinguish the malignant infiltrate from other lymphomas and establish the diagnosis of mycosis fungoides. Examination of the peripheral blood of a patient with Sézary syndrome shows circulating atypical lymphoid cells.



• **Fig. 13-34 Mycosis Fungoides.** This medium-power photomicrograph of a cutaneous lesion of mycosis fungoides shows infiltration of the epithelium by the malignant infiltrate that forms Pautrier microabscesses.



• **Fig. 13-35 Mycosis Fungoides.** This high-power photomicrograph of an oral biopsy specimen reveals the atypical, malignant lymphoid cells of mycosis fungoides that exhibit cerebriform morphology *(inset).*

Treatment and Prognosis

Topical nitrogen mustard, topical carmustine, superpotent topical corticosteroids, topical bexarotene (a synthetic retinoid), electron beam therapy, or photochemotherapy **(PUVA** [8-methoxy-**p**soralen + **u**ltra**v**iolet **A**]**)** are effective in controlling mycosis fungoides during the early stages. Ultimately, the topical forms of therapy fail, and aggressive chemotherapy is necessary, particularly if there is visceral involvement. Newer agents that may be added to the chemotherapy regimen include monoclonal antibodies directed against the cell surface marker CD52, certain retinoid compounds (including systemic bexarotene), and specific interferon compounds. Another new agent that may be used for advanced disease is known as *denileukin diftitox,* which is derived from diphtheria toxin and targets the interleukin-2 receptor on the neoplastic lymphocytes. If Sézary syndrome develops, then extracorporeal photopheresis or chemotherapy is used as a treatment modality. Extracorporeal photopheresis involves removing of a small amount of the patient's blood and separating the red and white blood cells. The red blood cells are returned to the patient immediately. The white blood cells are mixed with the photoactive drug 8-methoxypsoralen, and are irradiated outside the body (extracorporeal) with ultraviolet A. These altered white cells are then infused back into the patient. Many of the altered white cells undergo apoptosis, but the procedure also may help generate an immunologic response to the patient's own abnormal lymphocytes.

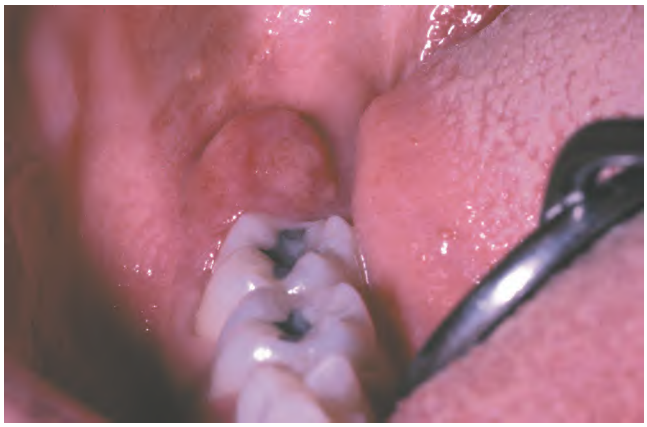
Although mycosis fungoides is not considered to be curable, the disease is usually slowly progressive. As a result, there is a median survival time of 8 to 10 years, and patients may die of causes unrelated to their lymphoma. Once the disease progresses beyond the cutaneous involvement, the course becomes much worse. The patient usually dies of organ failure or sepsis within 1 year.

◆ BURKITT LYMPHOMA

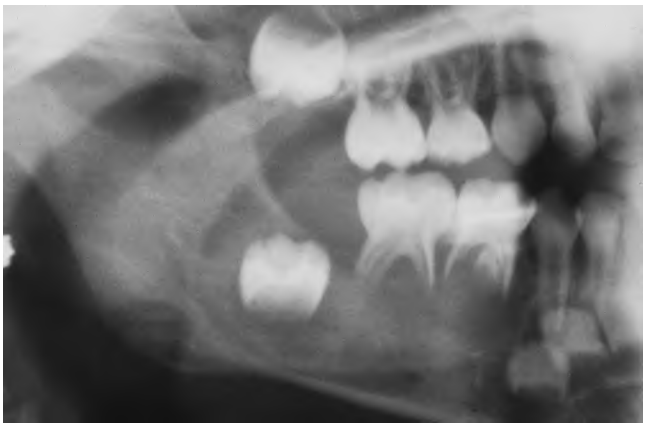
Burkitt lymphoma is a malignancy of B-lymphocyte origin that represents an undifferentiated lymphoma. It was named after the missionary doctor, Denis Burkitt, who first documented the process. In the original report, this type of lymphoma was described in young African children, and it seemed to have a predilection for the jaws. Because it was seen frequently in sub-Saharan Africa, the term **African Burkitt lymphoma** has been applied to the disease. It is now known to have increased prevalence in areas of the world where malaria is also seen, such as northeastern Brazil and New Guinea, and some investigators now refer to such tumors arising in these areas of increased prevalence as **endemic Burkitt lymphoma.** Examination of tumor tissue from the African cases led to the discovery of Epstein-Barr virus (EBV) by virologists in 1964. Although the mechanism is unknown, the pathogenesis of endemic Burkitt lymphoma is undoubtedly related to EBV because more than 90% of the tumor cells show expression of EBV nuclear antigen, and affected patients have elevated antibody titers to EBV. Malarial infection somehow plays a role in endemic Burkitt lymphoma as well, because patients with the highest antibody titers to *Plasmodium falciparum,* the causative organism of malaria, are most likely to develop the malignancy. Characteristic cytogenetic chromosomal translocations, which may also be responsible for neoplastic transformation, have also been described. Tumors with a similar histomorphology, commonly referred to as **sporadic** or **American Burkitt lymphoma,** have been observed in other countries, where the neoplasm is usually first detected as an abdominal mass. EBV is much less frequently identified in the sporadic tumors, however. Some HIV-related lymphomas may also have the microscopic features of Burkitt lymphoma, and these lesions have been designated **immunodeficiency-associated Burkitt lymphoma.** Similar tumors have been reported in other immunodeficiency settings, such as in patients who have received allografts or have a congenital immunodeficiency syndrome.

Clinical and Radiographic Features

As many as 50% to 70% of the cases of endemic Burkitt lymphoma present in the jaws. The malignancy usually



• **Fig. 13-36 Burkitt Lymphoma.** This patient had documented American Burkitt lymphoma involving the abdominal region. The retromolar swelling represents oral involvement with the malignancy.



• **Fig. 13-37 Burkitt Lymphoma.** This 4-year-old child had evidence of bone destruction with tooth mobility in all four quadrants of his jaws. Note the patchy, ill-defined loss of bone. (Courtesy of Dr. Gregory Anderson.)

affects children (peak prevalence, about 7 years of age) who live in Central Africa, and a male predilection is usually reported. The posterior segments of the jaws are more commonly affected, and the maxilla is involved more often than the mandible (a 2:1 ratio). Sometimes all four quadrants of the jaws show tumor involvement.

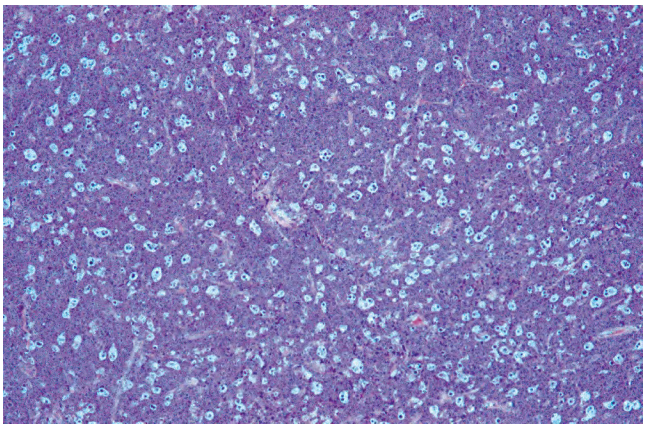
The tendency for jaw involvement seems to be age related; nearly 90% of 3-year-old patients have jaw lesions, in contrast to only 25% of patients older than age 15. Sporadic Burkitt lymphoma tends to affect patients over a greater age range than is noted for the African tumor. Although the abdominal region is typically affected, jaw lesions have been reported in sporadic Burkitt lymphoma (Fig. 13-36).

The growth of the tumor mass may produce facial swelling and proptosis. Pain, tenderness, and paresthesia are usually minimal, although marked tooth mobility may be present because of the aggressive destruction of the alveolar bone. Premature exfoliation of deciduous teeth and enlargement of the gingiva or alveolar process may also be seen.

The radiographic features are consistent with a malignant process and include a radiolucent destruction of the bone with ragged, ill-defined margins (Fig. 13-37). This process may begin as several smaller sites, which eventually enlarge and coalesce. Patchy loss of the lamina dura has been mentioned as an early sign of Burkitt lymphoma.

Histopathologic Features

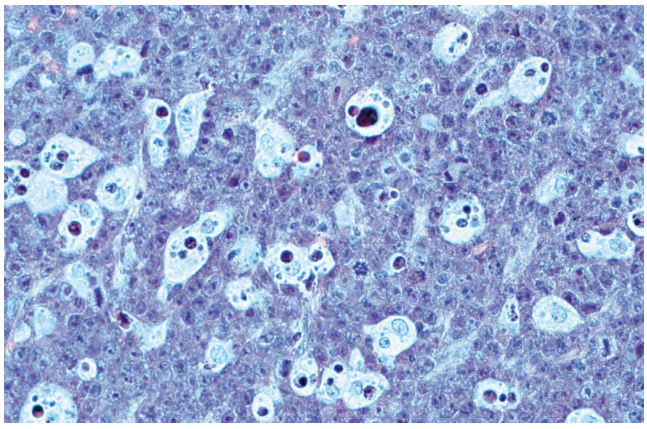
Burkitt lymphoma histopathologically represents an undifferentiated, small, noncleaved B-cell lymphoma. The lesion invades as broad sheets of tumor cells that exhibit round nuclei with minimal cytoplasm. Each tumor nucleus often has several prominent nucleoli, and numerous mitoses are seen. Immunohistochemical studies using markers that identify proliferating cells (e.g., Ki-67) typically indicate that almost 100% of the tumor cells are in the process of replicating. On viewing the lesion on low-power magnification, a classic "starry-sky" pattern is often appreciated—a



• **Fig. 13-38 Burkitt Lymphoma.** This low-power photomicrograph shows the classic "starry-sky" appearance, a pattern caused by interspersed histiocytic cells with abundant cytoplasm ("stars") set against a background of malignant, darkly staining lymphoma cells ("night sky").

phenomenon that is caused by the presence of macrophages within the tumor tissue (Fig. 13-38). These macrophages have abundant cytoplasm, which microscopically appears less intensely stained in comparison with the surrounding process. Thus these cells tend to stand out as "stars" set against the "night sky" of deeply hyperchromatic neoplastic lymphoid cells (Fig. 13-39).

Because the histopathologic features of Burkitt lymphoma can appear similar to some cases of diffuse large B-cell lymphoma, standard of care now dictates that, in addition to immunohistochemical studies, molecular genetic analysis of the tumor tissue should be performed. This distinction is important because these two malignancies are treated differently. Burkitt lymphoma is characterized by one of several specific translocations, the most common being t(8;14)(q24;q32), that results in overexpression of the oncogene *c-myc,* an event that presumably drives the neoplastic proliferation.



• **Fig. 13-39 Burkitt Lymphoma.** This high-power photomicrograph demonstrates the undifferentiated, small, dark lesional cells with numerous histiocytes.

Treatment and Prognosis

Burkitt lymphoma is an aggressive malignancy that usually results in the death of the patient within 4 to 6 months after diagnosis if it is not treated. Treatment generally consists of an intensive chemotherapeutic regimen, which emphasizes the use of high doses of cyclophosphamide. More than 90% of the patients respond to this treatment.

The prognosis for Burkitt lymphoma in the past was poor, with a median survival time of only $10^1/_2$ months. More recent trials with more intensive, multi-agent chemotherapeutic protocols have shown an 85% to 95% event-free (no evidence of recurrence) survival rate 3 to 5 years after treatment for patients with stage I or II disease. Even for advanced stage (III and IV) Burkitt lymphoma, the event-free survival has improved to 75% to 85%.

◆ EXTRANODAL NK/T-CELL LYMPHOMA, NASAL-TYPE (ANGIOCENTRIC T-CELL LYMPHOMA; MIDLINE LETHAL GRANULOMA; IDIOPATHIC MIDLINE DESTRUCTIVE DISEASE; POLYMORPHIC RETICULOSIS; MIDLINE MALIGNANT RETICULOSIS; ANGIOCENTRIC IMMUNOPROLIFERATIVE LESION)

Extranodal NK/T-cell lymphoma, nasal-type is a rare malignancy that is characterized clinically by aggressive, non-relenting destruction of the midline structures of the palate and nasal fossa. For many decades, the nature of this process was controversial, a fact that can readily be appreciated by the wide variety of terms by which it has been called. In actuality, many of the cases reported as "midline lethal granuloma" in the past represented a wide variety of immunologic (e.g., Wegener granulomatosis) and infectious (e.g., tertiary syphilis) diseases. The term **midline lethal granuloma** should be used only as a descriptive designation of a destructive midline condition, and thorough diagnostic evaluation, including biopsy and culture, is necessary to make a definitive diagnosis. Once the other causes of midline destruction have been eliminated, in most cases this disorder can be identified as a *natural killer (NK)/T-cell lymphoma,* based on modern cytogenetic, immunologic, and molecular studies. Epstein-Barr virus (EBV) is thought to play a significant role in the pathogenesis of this malignancy, and by the WHO criteria, *in situ* evidence of EBV in the lesional cells is necessary to make this diagnosis. The difficulty in distinguishing among these destructive disorders can be appreciated by the fact that **lymphomatoid granulomatosis,** which had been considered part of this T-cell lymphoma spectrum, is now known to be an EBV-driven proliferation of B lymphocytes.

Even though extranodal NK/T-cell lymphoma often does not have the classic histopathologic features of lymphoma microscopically, it behaves in a malignant fashion and responds to the same treatments to which lymphomas respond. For reasons that are unclear, this condition is seen with greater frequency in Asian, Guatemalan, and Peruvian populations.

Clinical Features

Extranodal NK/T-cell lymphoma is typically observed in adults, and a male predilection is noted in most case series. The initial signs and symptoms are often localized to the nasal region and include nasal stuffiness or epistaxis. Pain may accompany the nasal symptoms. Swelling of the soft palate or posterior hard palate may precede the formation of a deep, necrotic ulceration, which usually occupies a midline position. This ulceration enlarges and destroys the palatal tissues, which typically creates an oronasal fistula (Fig. 13-40). Secondary infection may complicate the course of the disease, and life-threatening hemorrhage is a potential problem in some instances.

Histopathologic Features

Histopathologic examination of one of these lesions shows a mixed infiltrate of a variety of inflammatory cells, often arranged around blood vessels (angiocentric) (Fig. 13-41). The lesional process appears to invade and destroy the normal tissue in the area. Necrosis is often present in some areas of the lesion, presumably secondary to infiltration of the blood vessels by the tumor cells. Medium to large, angular, lymphocytic cells with an atypical appearance are usually identified as a component of the cellular infiltrate. Immunohistochemical evaluation of this infiltrate shows that the atypical cells mark with antibodies directed against either NK-cell antigens (such as CD56) or T-lymphocyte antigens (such as CD3). Probes for EBV-encoded RNA (EBER) should label nearly all of the tumor cells as well. Molecular genetic studies may show monoclonal gene rearrangements of the T-lymphocyte receptor, consistent with

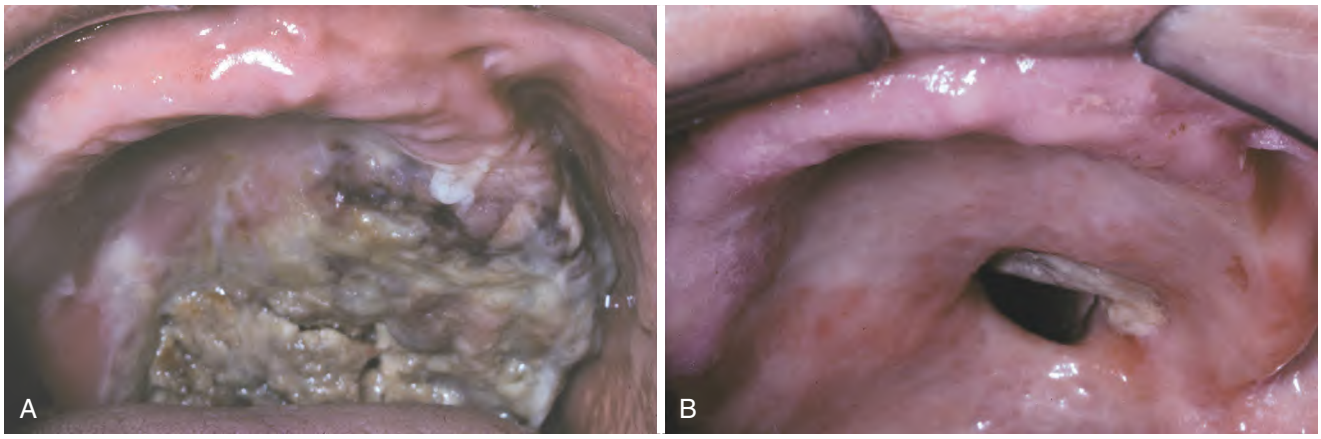


Fig. 13-40 Extranodal NK/T-Cell Lymphoma, Nasal-Type. A, This 62-year-old man had a destructive palatal lesion that proved to be a T-cell lymphoma, and evaluation showed cervical lymph node involvement as well. **B,** Resolution of the lesion 1 month later, after multiagent chemotherapy.

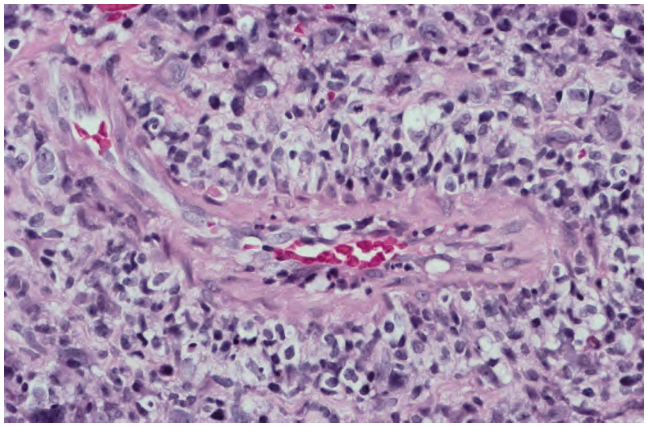


Fig. 13-41 Extranodal NK/T-Cell Lymphoma, Nasal-Type. This medium-power photomicrograph shows atypical lymphoid cells infiltrating the wall and filling the lumen of a blood vessel. Such a pattern is termed *angiocentric* (i.e., around blood vessels).

a lymphoreticular malignancy, in those tumors that have T-cell, rather than NK-cell, differentiation.

Treatment and Prognosis

Without treatment, extranodal NK/T-cell lymphoma is a relentlessly progressive, highly destructive process that ultimately leads to the patient's death by secondary infection, massive hemorrhage, or infiltration of vital structures in the area. Lesions that are localized usually respond to radiation therapy, a feature that is similar to that of T-cell lymphomas of other sites. Treatment with 40 to 50 Gy will appear to control the disease, although dissemination of the lesion develops in approximately 30% of these patients. Concurrent or sequential treatment with a multidrug chemotherapeutic regimen is now recommended. Five-year survival rates are usually reported to be in the range of 70% to 80%. For patients with more disseminated disease, combination chemotherapy is indicated, and a less favorable prognosis can be expected, with 30% to 50% 5-year survival generally reported.

MULTIPLE MYELOMA

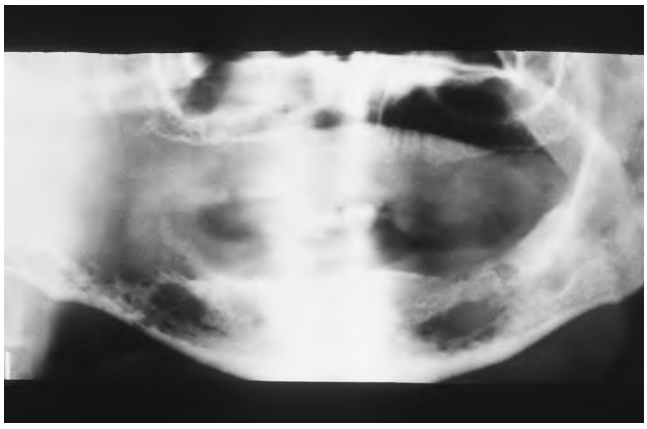
Multiple myeloma is a relatively uncommon malignancy of plasma cell origin that often appears to have a multicentric origin within bone. The cause of the condition is unknown, although sometimes a plasmacytoma (see page 565) may evolve into multiple myeloma. This disease makes up about 1% of all malignancies and 10% to 15% of hematologic malignancies. If metastatic disease is excluded, then multiple myeloma accounts for nearly 50% of all malignancies that involve the bone. Over 22,000 cases are diagnosed annually in the United States.

The abnormal plasma cells that compose this tumor are typically monoclonal. The abnormal cells probably arise from a single malignant precursor that has undergone uncontrolled mitotic division and has spread throughout the body. Because the neoplasm develops from a single cell, all of the daughter cells that comprise the lesional tissue have the same genetic makeup and produce the same proteins. These proteins are the immunoglobulin components that the plasma cell would normally produce, although in the case of this malignant tumor the immunoglobulins are not normal or functional. The signs and symptoms of this disease result from the uncontrolled proliferation of the tumor cells and the uncontrolled manufacture of their protein products.

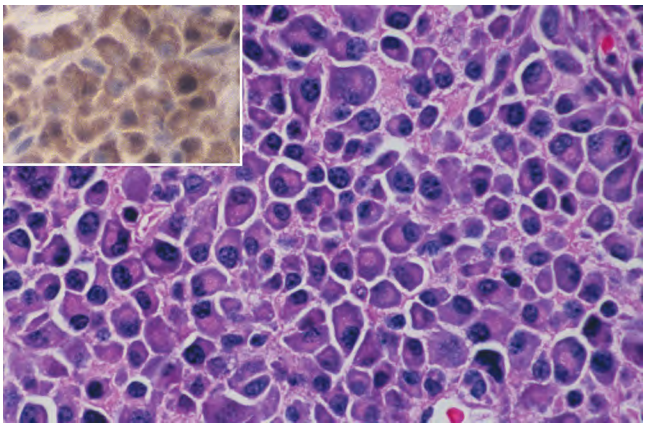
Clinical and Radiographic Features

Multiple myeloma is typically a disease of adults, with men being affected slightly more often than women. The median age at diagnosis is between 60 and 70 years, and it is rarely diagnosed before age 40. For reasons that are not understood, the disease occurs twice as frequently in blacks as whites, making this the most common hematologic malignancy among black persons in the United States.

Bone pain, particularly in the lumbar spine, is the most characteristic presenting symptom. Some patients experience pathologic fractures caused by tumor destruction of



• **Fig. 13-42 Multiple Myeloma.** Multiple myeloma affecting the mandible. The disease produced several radiolucencies with ragged, ill-defined margins. (Courtesy of Dr. Joseph Finelli.)



• **Fig. 13-43 Multiple Myeloma.** This high-power photomicrograph reveals sheets of malignant plasma cells with eccentric nuclei and stippled nuclear chromatin. Immunohistochemical studies *(inset)* show a uniform reaction of the lesional cells for antibodies directed against kappa light chains, indicating a monoclonal neoplastic proliferation.

bone. They may also complain of fatigue as a consequence of myelophthisic anemia. Petechial hemorrhages of the skin and oral mucosa may be seen if platelet production has been affected. Fever may be present as a result of neutropenia with increased susceptibility to infection. Metastatic calcifications may involve the soft tissues and are thought to be caused by hypercalcemia secondary to tumor-related osteolysis.

Radiographically, multiple well-defined, punched-out radiolucencies or ragged radiolucent lesions may be seen in multiple myeloma (Fig. 13-42). These may be especially evident on a skull film. Although any bone may be affected, the jaws have been reported to be involved in as many as 30% of cases. The radiolucent areas of the bone contain the abnormal plasma cell proliferations that characterize multiple myeloma.

Renal failure may be a presenting sign in these patients because the kidneys become overburdened with the excess circulating light chain proteins of the tumor cells. These light chain products, which are found in the urine of 30% to 50% of patients with multiple myeloma, are called **Bence Jones proteins,** after the British physician who first described them in detail.

Approximately 10% to 15% of patients with multiple myeloma show deposition of amyloid (see page 766) in various soft tissues of the body, and this may be the initial manifestation of the disease. Amyloid deposits are due to the accumulation of the abnormal light chain proteins. Sites that are classically affected include the oral mucosa, particularly the tongue. The tongue may show diffuse enlargement and firmness or may have more of a nodular appearance. Sometimes the nodules are ulcerated. Another area that is commonly affected is the periorbital skin, with the amyloid deposits appearing as waxy, firm, plaquelike lesions (see Fig. 17-7 on page 767).

Histopathologic Features

Histopathologic examination of the lesional tissue in multiple myeloma shows diffuse, monotonous sheets of neoplastic, variably differentiated, plasmacytoid cells that invade and replace the normal host tissue (Fig. 13-43). Mitotic activity may be seen with some frequency. The monoclonality of the plasma cell population can be demonstrated using antibodies directed against the lambda and kappa light chain components of the immunoglobulin molecule. In a neoplastic proliferation of plasma cells, virtually all of the lesional cells will mark with only one of these antibodies. In contrast, a reactive plasma cell infiltrate will show a mixture of lambda- and kappa-producing plasma cells. Occasionally, deposition of amyloid may be observed in association with the neoplastic cells. Like other types of amyloid, this material appears homogeneous, eosinophilic, and relatively acellular. It stains metachromatically with crystal violet and shows an affinity for Congo red, demonstrating apple-green birefringence on viewing with polarized light. A biopsy specimen of bone marrow from a patient with multiple myeloma should show at least 10% atypical plasma cells making up the marrow cell population.

Diagnosis

Although the histopathologic and radiographic findings may strongly suggest a diagnosis of multiple myeloma, screening of the serum or urine by protein electrophoresis should be performed. If an abnormality is detected, then this should be confirmed by protein immunoelectrophoresis, which is a more sensitive test, as an additional parameter to establish the diagnosis. The serum and urine protein immunoelectrophoresis should show the presence of myeloma protein (M-protein). This represents the massive overproduction of one abnormal immunoglobulin by the neoplastic clone of plasma cells, thus this feature is termed **monoclonal gammopathy.** This monoclonal protein consists of two heavy chain polypeptides of the same immunoglobulin (Ig) class (IgA, IgG, IgM, IgD, or IgE) and one of two light chain polypeptides of the same class (kappa or

lambda). Occasionally, the neoplastic cells produce only the light chain component.

Treatment and Prognosis

The goals of treatment related to multiple myeloma include not only controlling the malignancy but also making the patient comfortable and prolonging the patient's survival. Initial attempts to control multiple myeloma generally consist of chemotherapy. Several combinations of chemotherapeutic agents are available, including a corticosteroid (usually dexamethasone) in addition to one or two other drugs, such as an alkylating agent (melphalan or cyclophosphamide), an immune-modulating agent (thalidomide or lenalidomide), a proteasome inhibitor (bortezomib), and/or an anthracycline (doxorubicin). More aggressive chemotherapeutic regimens, as well as stem cell or bone marrow transplantation (either autologous or allogeneic), may be considered in otherwise healthy patients under the age of 55 to 65 years, but these individuals comprise a minority of multiple myeloma patients. Radiation therapy is useful only as palliative treatment for painful bone lesions. Any one of several bisphosphonate medications (clodronate, pamidronate, or zoledronic acid) can be prescribed to reduce the possibility of myeloma-related fracture with its attendant pain, but these medications do not increase survival. A small percentage of these patients may experience the complication of medication-related osteonecrosis of the jaws (see page 271).

While it is unlikely that multiple myeloma can be cured, the prognosis varies considerably among affected individuals. A variety of factors play a role in predicting prognosis, with younger patients tending to do better than older ones. Patients with other systemic diseases have a worse prognosis, as do patients who present with more widespread lesions. The prognosis is dependent on certain chromosomal and molecular genetic features, with hyperdiploid lesions being more aggressive, as well as those with certain chromosomal translocations. Multiple myeloma that does not respond well to initial therapy also has a worse prognosis. Hematologists often categorize the tumor as being "standard risk," "intermediate risk," or "high risk," depending on these various features. The treatment regimen will depend on the patient's risk category.

Patients who fall in the standard-risk category can expect to have a median survival rate of 6 to 7 years following diagnosis, whereas those who are high-risk can expect a median survival of 2 to 3 years. These figures, while not encouraging at first glance, are much improved compared to just one or two decades ago, when a 10% 5-year survival was typical.

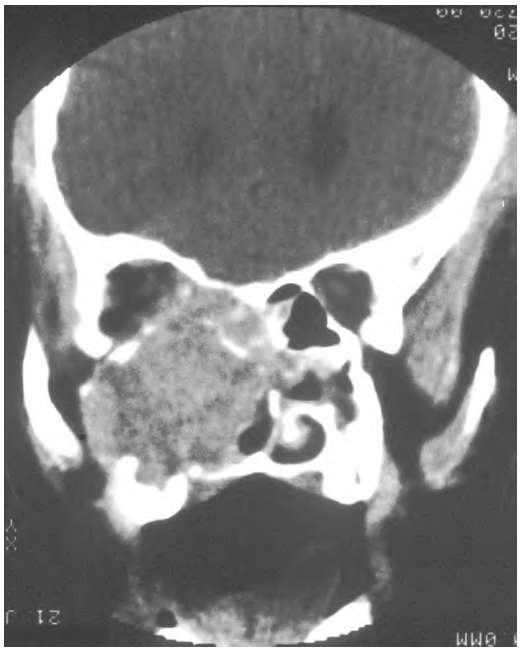
◆ PLASMACYTOMA

The **plasmacytoma** is a unifocal, monoclonal, neoplastic proliferation of plasma cells that usually arises within bone. Infrequently, it is seen in soft tissue, in which case, the term **extramedullary plasmacytoma** is used. Some investigators believe that this lesion represents the least aggressive part of a spectrum of plasma cell neoplasms that extends to **multiple myeloma.** Therefore, the plasmacytoma is important because it may ultimately give rise to the more serious problem of multiple myeloma.

Clinical and Radiographic Features

The plasmacytoma usually is detected in an adult male, with an average age at diagnosis of 55 years. The male-to-female ratio is approximately 2:1. Most of the lesions present centrally within a single bone, and the spine is the most commonly involved site. About one-third of the cases are reported in that location. The initial symptoms often relate to swelling or bone pain; occasionally, however, this lesion is detected on routine radiographic examination. The extramedullary plasmacytoma appears as a relatively nondescript, well-circumscribed, nontender soft tissue mass. A slightly stronger male predilection is seen with this lesion, approaching a 3:1 male-to-female ratio. Approximately 25% of extramedullary plasmacytomas develop in the head and neck region, and such lesions have been reported in the tonsils, the nasopharynx, the paranasal sinuses, the nose, and the parotid gland.

Radiographically, the lesion may be seen as a well-defined, unilocular radiolucency with no evidence of sclerotic borders or as a ragged radiolucency similar to the appearance of multiple myeloma (Fig. 13-44). No other lesions should be identifiable by a skeletal survey or careful physical examination, however.



• **Fig. 13-44 Plasmacytoma.** This computed tomography (CT) scan depicts a solitary plasmacytoma involving the left maxillary sinus and nasal cavity.

Histopathologic Features

The histopathologic features of the plasmacytoma are identical to those of multiple myeloma. Sheets of plasma cells show varying degrees of differentiation. Immunohistochemical studies demonstrate that these plasma cells are monoclonal. As many as 25% to 50% of these patients also show a monoclonal gammopathy on evaluation by serum protein immunoelectrophoresis, although the amount of abnormal protein is much less than that seen with multiple myeloma. Solitary plasmacytoma also differs from multiple myeloma in that no evidence of plasma cell infiltration should be seen by a random bone marrow biopsy, and the patient should not show signs of anemia, hypercalcemia, or renal failure. Immunohistochemically, extramedullary plasmacytoma appears to differ from its intrabony counterparts in that it shows a marked decrease or lack of immunoreactivity for antibodies directed against cyclin D1 and CD56.

Treatment and Prognosis

Plasmacytomas are usually treated with radiation therapy, and typically a dose of at least 40 Gy is delivered to the tumor site. A few lesions have been surgically excised with good results, although this is not the preferred treatment in most instances. Unfortunately, when patients with plasmacytoma of bone are observed on a long-term basis, most will eventually develop multiple myeloma. About 50% show evidence of disseminated disease within 2 to 3 years. However, one third of these patients will not have symptoms of multiple myeloma for as long as 10 years. Extramedullary plasmacytoma seems to have a much better prognosis, with less than 30% of these patients showing progression to multiple myeloma and 70% having a 10-year disease-free period after treatment.

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14 Bone Pathology

OSTEOGENESIS IMPERFECTA ("BRITTLE BONE DISEASE")

Osteogenesis imperfecta comprises a heterogeneous group of heritable disorders characterized by osteopenia (low bone density) and bone fragility. This condition represents one of the most common heritable bone diseases, with a worldwide prevalence of approximately 6 to 7 per 100,000 population.

More than 90% of cases exhibit an autosomal dominant inheritance pattern with mutations in one of two type I collagen genes: *COL1A1* and *COL1A2.* In addition, there are numerous other variants (mainly autosomal recessive) caused by recently discovered mutations in genes related to type I collagen processing, bone mineralization, and other functions. Sporadic cases are possible as well.

Type I collagen is a major constituent of bone, dentin, sclerae, ligaments, and skin; osteogenesis imperfecta may affect any of these tissue types. Type I collagen is a triple helical molecule composed of peptide chains encoded by *COL1A1* and *COL1A2.* Defects in the complex process of synthesis, posttranslational modification (including hydroxylation, crosslinking, and terminal propeptide cleavage), and chaperone-guided protein folding result in abnormal type I collagen with low tensile strength. Consequently, the bone is brittle; upon fracture, healing will occur but may be associated with exuberant callus formation.

Classification of the various forms of osteogenesis imperfecta continues to evolve as molecular genetic discoveries are made. Table 14-1 summarizes a proposed classification scheme based on phenotypic and genetic findings.

Clinical and Radiographic Features

Severity varies widely by disease type, and mutations in even a single gene locus may produce extensive phenotypic variation. Disease characterization as mild, moderate, or severe generally is based on the number of bone fractures, degree of long bone and spine deformity, degree of growth impairment, and age at which abnormalities initially become evident. For example, osteogenesis imperfecta type I—the mildest and most common form—is characterized by a variable number of bone fractures, minimal bone deformity, and essentially normal growth. Typically, fractures first occur when the patient begins to walk and decrease in frequency after puberty. In contrast, osteogenesis type II is the most severe form, characterized by extreme bone fragility and deformity. Most patients with this disease type die *in utero* or shortly after birth; death often results from respiratory distress due to multiple rib fractures and a small thorax.

Additional clinical findings may include blue sclerae (Fig. 14-1), hearing loss, and joint hyperextensibility or contractures. The radiographic hallmarks include osteopenia, bowing deformity of the long bones, multiple fractures, and an increased number of Wormian bones in the skull. Wormian bones are small sutural bones arranged in a mosaic pattern; they also can be seen in other processes, such as cleidocranial dysplasia.

Dental alterations that appear clinically and radiographically identical to dentinogenesis imperfecta (see page 99) may be evident—especially in osteogenesis imperfecta types III and IV. Both dentitions demonstrate blue, yellow, or brown translucence (Fig. 14-2, *A*); however, this finding may be less prominent in the permanent teeth. The underlying dentinal defects often lead to severe attrition, resulting in loss of vertical dimension and potential tooth loss. Radiographs typically reveal premature pulpal obliteration, although shell teeth rarely may be seen (see Fig. 14-2, *B*). The tooth roots may appear narrow or corncob-shaped. Despite exhibiting similar tooth alterations, osteogenesis imperfecta and dentinogenesis imperfecta are distinct diseases resulting from different mutations. Therefore, the dental defects associated with the systemic disorder osteogenesis imperfecta should be designated **opalescent teeth,** whereas the term *dentinogenesis imperfecta* should be reserved for patients with alterations isolated to the teeth.

Craniofacial findings in osteogenesis imperfecta may include triangular facies, frontal bossing, relative macrocephaly, a flattened vertex and skull base, and a prominent occiput. In addition, there is an increased prevalence of Class III malocclusion (caused by maxillary hypoplasia, with or without mandibular hyperplasia), crossbite, and open bite.

There are a few reported families exhibiting generalized bone fractures combined with diffuse radiolucent, radiopaque, or radiolucent-radiopaque lesions of the jaws

TABLE 14-1 Osteogenesis Imperfecta Classification Scheme

Type		Mode of Inheritance	Phenotype	Mutated Gene
Classical types	I	AD	Mild phenotype, minimal bone deformity, bone fractures, normal or near normal stature, blue sclerae, joint laxity, hearing loss, rarely opalescent teeth	*COL1A1* (null allele*)
	II	AD	Perinatal lethal, multiple fractures of ribs and long bones, respiratory distress, limb deformities, dark blue sclerae	*COL1A1* *COL1A2*
	III	AD	Severely deforming, very short stature, frequent fractures, wheelchair-dependent at an early age, triangular facies, coxa vara,† "popcorn calcifications" of femoral head, blue-gray sclerae, often opalescent teeth, most patients die during childhood secondary to complications of kyphoscoliosis	*COL1A1* *COL1A2*
	IV	AD	Mild to moderate bone fragility and deformity, white to gray sclerae, often opalescent teeth	*COL1A1* *COL1A2*
COL1-mutation negative	V	AD	Moderate to severe bone fragility, radial head dislocation, forearm interosseous membrane calcification, radiopaque metaphyseal bands at growth plates of long bones, hypertrophic calluses, white sclerae, no opalescent teeth, hypodontia	*IFITM5*
Mineralization defect	VI	AR	Moderate to severe skeletal changes, early-onset fractures, distinct histopathology (osteoid accumulation, "fish-scale" lamellar bone under polarized light), no opalescent teeth	*SERPINF1*
3-hydroxylation defects	VII	AR	Severe to perinatal lethal, shortened long bones, severe growth deficiency, "popcorn calcifications" of femoral head, coxa vara, white or light gray sclerae, no opalescent teeth	*CRTAP*
	VIII	AR	Severe to perinatal lethal, white sclerae, bowing of long bones, Wormian bones, severe growth deficiency, bulbous metaphyses	*LEPRE1*
	IX	AR	Moderate to perinatal lethal, white or gray sclerae, opalescent teeth possible	*PPIB*
Chaperone defects	X	AR	Severe phenotype, bone deformities and fractures, growth deficiency, triangular facies, blue sclerae, opalescent teeth rare	*SERPINH1*
	XI	AR	Moderate to severe phenotype, progressive kyphoscoliosis, joint hypermobility, grayish white sclerae, some cases associated with Bruck syndrome I (severe osteogenesis imperfecta and congenital contractures), no opalescent teeth	*FKBP10*
C-propeptide cleavage defect	XII	AR	Severe phenotype, long bone deformity, kyphoscoliosis, joint hypermobility, high bone mass, light blue sclerae, no opalescent teeth	*BMP1*

AD, Autosomal dominant; *AR,* autosomal recessive; *BMP1,* bone morphogenetic protein 1 gene; *COL1A1,* collagen, type 1, alpha 1 gene; *COL1A2,* collagen, type 1, alpha 2 gene; *FKBP10,* FK506 binding protein 10 gene; *PPIB,* peptidylprolyl isomerase B gene; *SERPINH1,* serpin peptidase inhibitor gene.
*Null allele results in a reduced amount of normal type I collagen (and, thus, a mild phenotype).
†Coxa vara: Inward hip curvature caused by reduced angle between the femoral head and shaft.

(similar to florid cemento-osseous dysplasia or gigantiform cementoma). However, it is unclear whether such cases represent variants of osteogenesis imperfecta. Instead, they may belong to a distinct category known as *gnatho-diaphyseal dysplasia* (see page 602).

Diagnosis

Diagnosis requires correlation of the clinical features, radiographic and/or prenatal ultrasound findings, and family history. For diagnostic confirmation, genetic testing is more sensitive than electrophoresis for type I collagen secreted by cultured dermal fibroblasts. Bone biopsy may be helpful in select cases. Serum concentrations of vitamin D, calcium, phosphorus, and alkaline phosphatase usually are normal, although occasionally the latter may be slightly elevated.

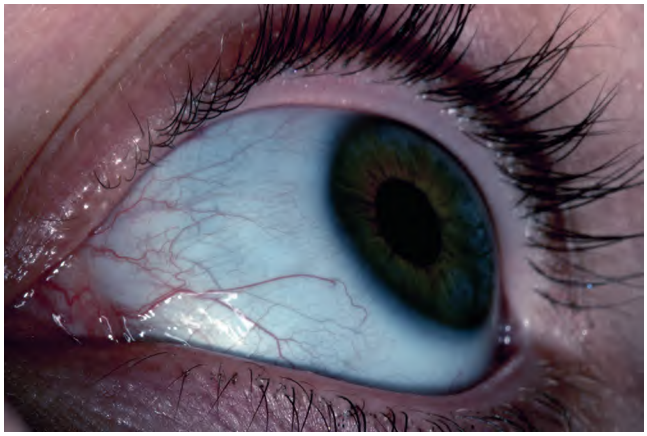
Treatment and Prognosis

Management of bone fractures and deformity may be difficult. The mainstays of treatment are physiotherapy, rehabilitation, and orthopedic surgery. In addition, intravenous (IV) bisphosphonates typically are administered to children with moderate to severe disease; such therapy may decrease

pain, reduce fracture rates, and improve mobility. The benefits of bisphosphonate therapy for adult or mild childhood disease and the long-term safety of bisphosphonate therapy require further study. There is limited evidence that recombinant growth hormone—alone or in combination with bisphosphonates—may increase growth rate in some patients. Targeted therapies (e.g., bone morphogenetic protein modulators, receptor activator of nuclear factor-kappa B ligand [RANKL] inhibitors), gene therapy, and stem cell therapy hold some promise for the future but remain in the early stages of development.

Treatment of the dentition is similar to that for dentinogenesis imperfecta (see page 102). Successful implant placement has been reported in a few cases, although the impact of the altered bone on osseointegration is not well studied. In patients with significant malocclusion, orthognathic surgery and orthodontic treatment may be performed. Alternatively, osteodistraction may be considered to reduce the risk of atypical fractures from conventional orthognathic procedures (e.g., Le Fort I osteotomy). Presurgical planning should take into account an increased risk for bleeding disorders, cardiac malformations, and hyperthermia. Intubation may be difficult because of a short neck, kyphoscoliosis, and fragility of the mandible and cervical vertebrae. Also, patients previously treated with bisphosphonates may exhibit delayed healing after osteotomy.

The prognosis varies by disease type. Patients with mild disease exhibit a normal life span, whereas those with especially severe disease die *in utero* or in the perinatal period.



• **Fig. 14-1 Osteogenesis Imperfecta.** Blue sclera in a patient with osteogenesis imperfecta.

◆ OSTEOPETROSIS (ALBERS-SCHÖNBERG DISEASE; MARBLE BONE DISEASE)

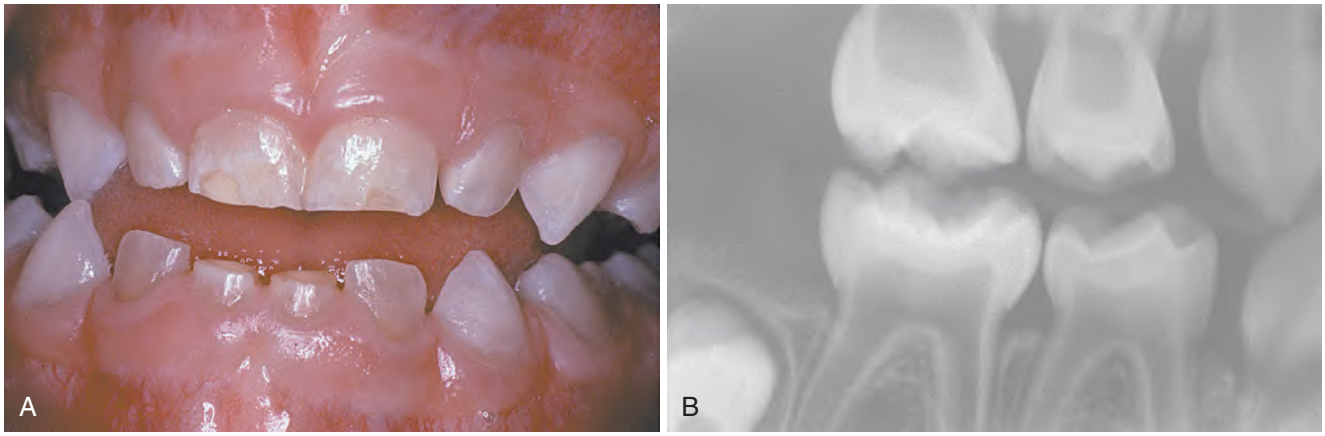
Osteopetrosis is a group of rare hereditary skeletal disorders characterized by markedly increased bone density. This condition results from a failure of osteoclast function or differentiation. Decreased osteoclastic bone resorption results in sclerotic bone. The disease affects approximately 1 per 100,000 to 500,000 persons.

The underlying genetic abnormality is unknown in about 30% of patients. Mutations discovered thus far primarily cause defects in osteoclastic proteins necessary for acidification of resorption lacunae, regulation of ionic charge across the osteoclast cell membrane, and subsequent resorption of the bone matrix. In some cases, mutations in genes encoding the cell-surface receptor RANK (receptor activator of nuclear factor-kappa B) or RANK ligand interfere with osteoclastogenesis.

Although several disease subtypes have been identified, there are three major clinical patterns:

1. **Autosomal recessive infantile ("malignant") type**
2. **Autosomal recessive intermediate type**
3. **Autosomal dominant adult ("benign") type**

Table 14-2 summarizes a classification system based on phenotype and corresponding genetic defects. Disease severity varies widely, potentially even among patients with the same disease subtype.



• **Fig. 14-2 Osteogenesis Imperfecta. A,** Opalescent dentin in a patient with osteogenesis imperfecta. **B,** Bite-wing radiograph of the same patient showing shell teeth with thin dentin and enamel of normal thickness. (Courtesy of Dr. Tom Ison.)

TABLE 14-2 Classification Scheme for Major Forms of Osteopetrosis

Inheritance Pattern/Subtype		Phenotype	Mutated Gene	Normal Gene Product and/or Function
Autosomal recessive	1	Malignant neonatal or infantile	*TCIRG1*	Proton pump subunit
	2	Intermediate	*RANKL (TNFSF11)*	Ligand that binds RANK receptor to induce osteoclastic differentiation
	3	Intermediate	*CAII*	Enzyme that catalyzes a proton-releasing reaction
	4	Malignant infantile	*CLCN7*	Chloride channel
	5	Malignant infantile	*OSTM1*	Chloride channel function
	6	Variable, often intermediate	*PLEKHM1*	Vesicle trafficking and acidification
	7	Severe	*RANK (TNFRSF11A)*	Cell-surface receptor involved in osteoclastic differentiation
Autosomal dominant	1	Adult	*LRP5*	Bone formation by osteoblasts*
	2	Adult	*CLCN7*	Chloride channel

CAII, Carbonic anhydrase II gene; *CLCN7,* chloride channel 7 gene; *LRP5,* low-density lipoprotein receptor-related protein gene; *OSTM1,* osteopetrosis-associated transmembrane protein 1 gene; *PLEKHM1,* pleckstrin homology domain gene; *RANK,* receptor activator of nuclear factor-kappa B gene; *RANKL,* receptor activator of nuclear factor-kappa B ligand gene; *TCIRG1,* T-cell immune regulator 1 gene; *TNFRSF11A,* tumor necrosis factor receptor superfamily, member 11A gene (also known as *RANK*); *TNFSF11,* tumor necrosis factor ligand superfamily member 11 gene (also known as *RANKL*).
*Interestingly, autosomal dominant osteopetrosis type 1 is caused by dysfunction of osteoblasts rather than osteoclasts; therefore, some authorities have reclassified this condition as "high bone mass disease" and no longer consider it a subtype of osteopetrosis.

Clinical and Radiographic Features

Autosomal Recessive Infantile Osteopetrosis

This severe form usually is diagnosed at birth or in early infancy. Typical findings include a diffusely sclerotic skeleton, bone marrow failure, frequent fractures, cranial nerve compression, and growth impairment.

The initial signs often are normocytic anemia with hepatosplenomegaly resulting from compensatory extramedullary hematopoiesis. Granulocytopenia causes increased susceptibility to infection. Affected children often exhibit a broad face, hypertelorism, snub nose, and frontal bossing. Failure of resorption and remodeling of the skull produces narrow skull foramina and cranial nerve compression, which may result in blindness, deafness, and facial paralysis. The bone is dense but prone to pathologic fracture. Osteomyelitis of the jaws is a frequent complication of tooth extraction (Fig. 14-3).

Radiographically, there is a widespread increase in skeletal density with defects in metaphyseal remodeling. The radiographic distinction between cortical and cancellous bone is lost (Fig. 14-4). On dental radiographs, tooth roots often are difficult to visualize because of the density of the surrounding bone. In addition, failure of tooth eruption is common.

Autosomal Recessive Intermediate Osteopetrosis

Affected patients often are asymptomatic at birth but exhibit fractures by the end of the first decade. Mild to moderate anemia and extramedullary hematopoiesis are common, but bone marrow failure is rare. Short stature, mandibular prognathism, unerupted teeth, and osteomyelitis also have been reported.

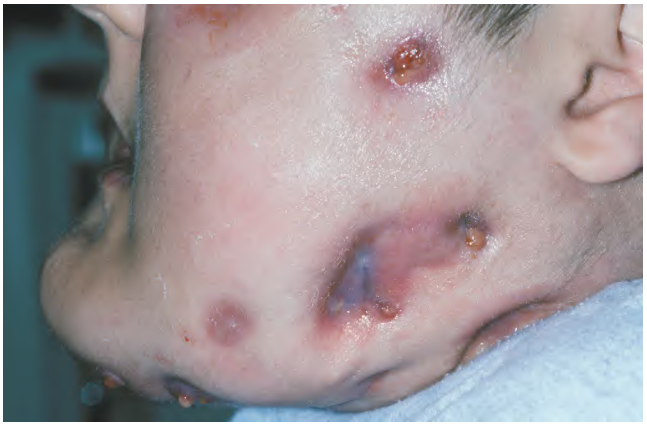
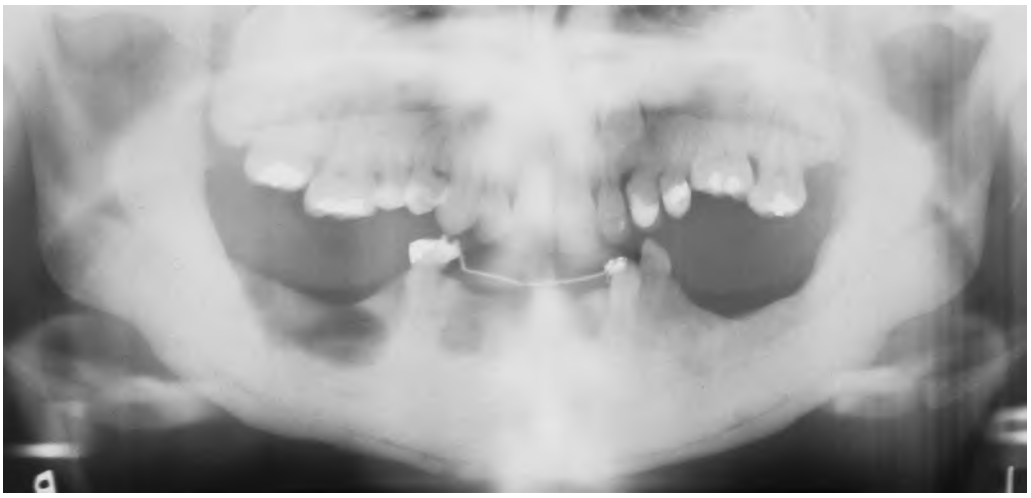


Fig. 14-3 Osteopetrosis. This 24-year-old white man has the infantile form of osteopetrosis. He has mandibular osteomyelitis, and multiple draining fistulae are present on his face. (Courtesy of Dr. Dan Sarasin.)

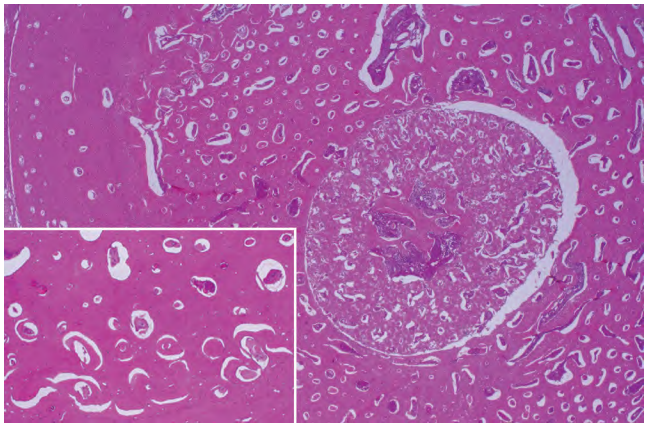
Autosomal Dominant Adult Osteopetrosis

This most common type usually is discovered in adolescence or adulthood and exhibits less severe manifestations. Sclerosis mainly affects the axial skeleton, with relative sparing of the long bones. Marrow failure is rare, and approximately 40% of affected patients are asymptomatic. Among symptomatic patients, bone pain is frequent. In some cases, cranial nerve compression is the major finding, whereas in other cases frequent fractures predominate.

Occasionally, the diagnosis is discovered initially on review of dental radiographs that reveal diffusely increased radiopacity of the medullary bone. Mandibular involvement may be associated with an increased risk for fracture and osteomyelitis following tooth extraction.



• **Fig. 14-4 Osteopetrosis.** Extensive mandibular involvement is apparent in this radiograph of a 31-year-old woman. She received a diagnosis of osteopetrosis as a child. There is a history of multiple fractures and osteomyelitis of the jaws. (Courtesy of Dr. Dan Sarasin.)



• **Fig. 14-5 Osteopetrosis.** Low-power photomicrograph showing sclerotic bone that is replacing the normal cancellous bone. The *inset* shows a nodular pattern of the dense bone obliterating the marrow spaces.

Other rare conditions causing widespread osteosclerosis should be considered in the differential diagnosis. Such diseases include autosomal dominant osteosclerosis (endosteal hyperostosis, Worth type), sclerosteosis, and van Buchem disease.

Histopathologic Features

Several patterns of abnormal endosteal bone formation have been described. These include the following:

- Tortuous lamellar trabeculae replacing the cancellous portion of the bone
- Globular amorphous bone deposition in the marrow spaces (Fig. 14-5)
- Osteophytic bone formation

Osteoclasts may be increased, decreased, or normal in number; however, they do not appear to be functional because Howship lacunae are not visible. In osteoclast-rich disease forms, there may be a concurrent increase in the number of activated osteoblasts.

Treatment and Prognosis

Adult osteopetrosis usually is associated with long-term survival. Other than management of disease complications, no specific treatment is indicated.

In contrast, the prognosis for untreated infantile osteopetrosis is poor, with most patients dying during the first decade of life. For patients with certain disease subtypes, bone marrow transplantation potentially may cure bone marrow failure and may improve the phenotype. The rationale for this procedure is based on the hematopoietic origin of osteoclasts. However, finding an appropriate donor can be difficult, and the procedure is associated with considerable risk. The search for alternative therapies is ongoing. Interferon gamma-1b—often combined with calcitriol and restricted calcium intake—has been shown to reduce bone mass, decrease the prevalence of infections, and lower the frequency of nerve compression. Other options include corticosteroids (to stimulate bone resorption and increase circulating red blood cells and platelets) and erythropoietin.

Supportive measures include transfusions and antibiotic therapy. Osteomyelitis of the jaws requires rapid intervention to minimize osseous destruction; management typically includes drainage and surgical débridement, bacterial culture with sensitivity testing, and prolonged IV antibiotic therapy. Hyperbaric oxygen may be a useful adjunct in recalcitrant cases, and surgical reconstruction may be necessary.

◆ CLEIDOCRANIAL DYSPLASIA (CLEIDOCRANIAL DYSOSTOSIS)

Best known for its dental and clavicular abnormalities, **cleidocranial dysplasia** is a generalized bone disorder caused

by mutations in the *RUNX2* (or *CBFA1*) gene on chromosome 6p21. This gene normally guides osteoblastic differentiation, chondrocyte maturation, and appropriate bone formation. This condition initially was thought to involve only membranous bones (e.g., clavicles, skull, and flat bones), but it is now known to affect endochondral ossification as well. Studies suggest that *RUNX2* additionally plays an important role in odontogenesis via participation in odontoblast differentiation, enamel organ formation, and dental lamina proliferation. Disruption of these functions might explain the distinct dental anomalies associated with this disorder. The estimated worldwide prevalence is 1:1,000,000. There is an autosomal dominant inheritance pattern, although as many as 40% of cases may represent spontaneous mutations. In addition, investigators have proposed that an autosomal recessive form and germline mosaicism are possible.

Clinical and Radiographic Features

The bone defects chiefly involve the clavicles and skull, although various other skeletal anomalies may be present (Table 14-3). The clavicles typically are hypoplastic or discontinuous, either unilaterally or bilaterally; in about 10% of cases, the clavicles are completely absent. The patient's neck appears long, and the shoulders are narrow with marked drooping. The clavicular abnormalities result in unusual hypermobility, and many patients can approximate their shoulders anteriorly (Fig. 14-6).

Additional features include short stature, enlarged skull, brachycephaly, and pronounced frontal and parietal bossing. Ocular hypertelorism and a broad-based nose with a depressed bridge often are noted. On skull radiographs, the sutures and fontanels show delayed closure or may remain open throughout life. Secondary centers of ossification appear in the suture lines, and many Wormian bones may be seen. Abnormal development of the temporal bone and eustachian tube may lead to conductive or sensorineural hearing loss and recurrent ear infections.

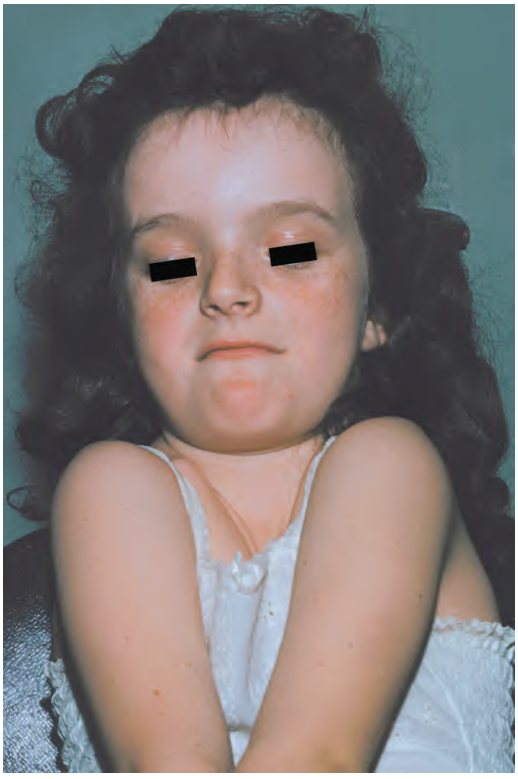
The gnathic and dental manifestations are distinctive and may lead to the initial diagnosis. Patients often have a narrow, high-arched palate, and there is an increased prevalence of cleft palate. Over-retained deciduous teeth and delay or complete failure of permanent tooth eruption are

TABLE 14-3 Major Clinical and Radiographic Features of Cleidocranial Dysplasia

Anatomic Region	Features
Craniofacial/oral region	• Large skull • Frontal and parietal bossing • Brachycephaly • Ocular hypertelorism • Nose with depressed bridge and broad base • Delayed closure of sutures and fontanels • Wormian bones • Small or absent paranasal sinuses • Narrow, high-arched palate; cleft palate • Numerous unerupted/variably misshapen permanent and supernumerary teeth • Retention of primary dentition; delayed eruption of permanent dentition • Mandible: Prognathism, coarse trabeculation, narrow and parallel-sided rami, slender and pointed coronoid processes with distal curvature, patent symphysis • Hypoplastic maxilla
Thorax	• Hypoplastic, discontinuous, or absent clavicles • Hypoplastic scapulae • Narrow upper thorax • Absent ribs
Pelvis	• Hypoplastic iliac wings • Widening of the pubic symphysis and sacroiliac joints • Delayed ossification of the pubic bone
Extremities	• Genus valgus (knock knees) • Pes planus (flat feet) • Brachydactyly • Tapered fingers and short, broad thumbs • Short terminal phalanges • Long second metacarpals • Short and deformed middle phalanges
Other	• Short stature • Scoliosis

characteristic features. There may be abnormal spacing in the mandibular incisor area because of widening of the alveolar bone. On dental radiographs, the most dramatic finding is the presence of numerous unerupted permanent and supernumerary teeth, often exhibiting distorted crown and root shapes (Fig. 14-7). Dentigerous cysts occasionally may arise in association with these unerupted teeth. The number of supernumerary teeth can be impressive, with some patients demonstrating more than 60 such teeth. In addition, the mandible often demonstrates coarse trabeculation with areas of increased density; narrow rami with nearly parallel anterior and posterior borders; and slender, pointed coronoid processes with a distal curvature. In some cases, the mandibular symphysis remains patent. There may be a thin zygomatic arch and small or absent maxillary sinuses. Generalized hypoplasia of the paranasal sinuses may predispose the patient to recurrent sinus infections.

As the patient ages, a short lower face height, acute gonial angle, anterior inclination of the mandible, and mandibular prognathism develop. These changes may result from inadequate vertical growth of the maxilla and hypoplastic alveolar ridge development caused by delay or lack of permanent tooth eruption.



• **Fig. 14-6 Cleidocranial Dysplasia.** Patient can almost approximate her shoulders in front of her chest. (Courtesy of Dr. William Bruce.)

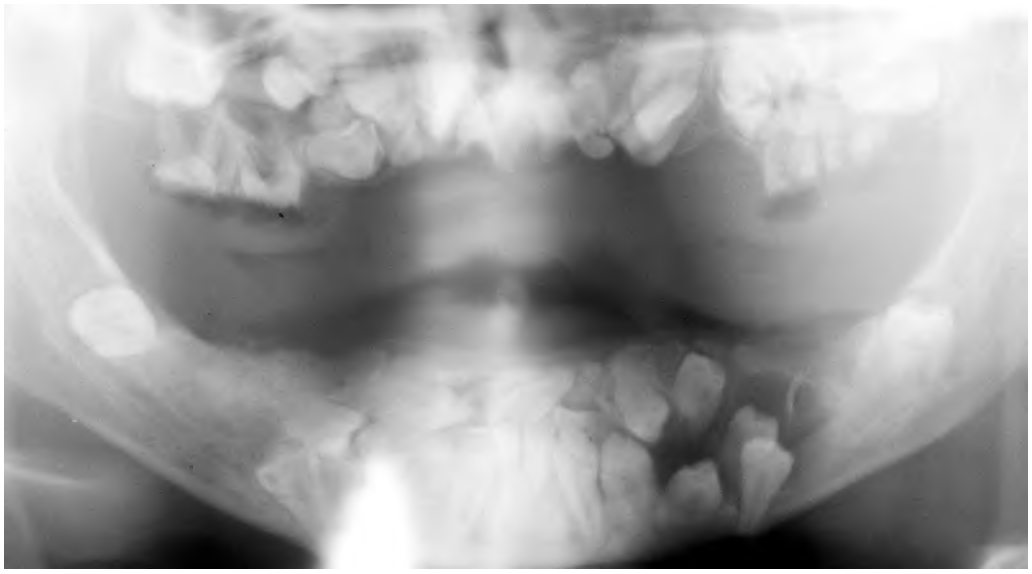
Histopathologic Features

The reason for failure of permanent tooth eruption in cleidocranial dysplasia is poorly understood. Some microscopic studies have reported a lack of secondary cementum in unerupted teeth, although other studies have disputed this finding. Additional proposed hypotheses include increased jawbone density and insufficient alveolar bone resorption—possibly resulting from altered periodontal ligament cells with reduced capacity to induce osteoclastogenesis.

Treatment and Prognosis

Most patients function well. An affected individual may be unaware of the disease until a professional calls it to his or her attention.

The dental problems may be difficult to address. The preferred treatment involves removal of primary and



• **Fig. 14-7 Cleidocranial Dysplasia.** Panoramic radiograph showing multiple unerupted teeth. (Courtesy of Dr. John R. Cramer.)

supernumerary teeth followed by exposure and orthodontic extrusion of permanent teeth. The extractions may be conducted in stages (according to the extent of root development of the unerupted permanent dentition) or in a single procedure. If completed before adulthood, then such treatment may prevent short lower face height and mandibular prognathism. Orthognathic surgery also may be considered after growth completion. Additional treatment options include full-mouth extractions or autotransplantation of selected impacted teeth followed by fabrication of an appropriate prosthesis. In a few reported cases, dental implants have been placed successfully; however, further studies are needed to assess whether the altered bone might compromise osseointegration.

◆ FOCAL OSTEOPOROTIC MARROW DEFECT

The **focal osteoporotic marrow defect** is an area of hematopoietic marrow that is sufficient in size to produce a radiolucency. This entity does not represent a pathologic process, but its radiographic features may be confused with an intraosseous neoplasm or other pathosis. The pathogenesis is unknown, although the following theories have been proposed:

- Aberrant bone regeneration after tooth extraction
- Persistence of fetal marrow
- Marrow hyperplasia in response to increased demand for erythrocytes

Clinical and Radiographic Features

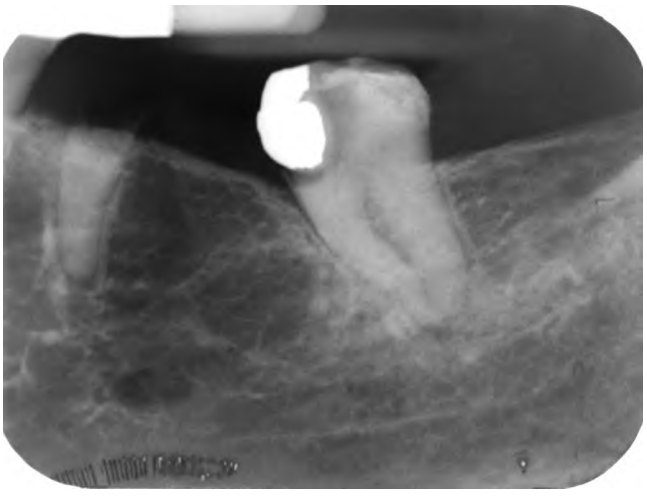
Approximately 75% of cases occur in adult females, and about 70% involve the posterior mandible, most often in edentulous areas. The defect is typically asymptomatic and nonexpansile. Most cases are detected incidentally during radiographic examination, which shows a radiolucency ranging from several millimeters to several centimeters in diameter. The borders typically appear well-circumscribed on panoramic radiographs; however, more detailed periapical radiographs may exhibit ill-defined borders and fine central trabeculation (Fig. 14-8).

Histopathologic Features

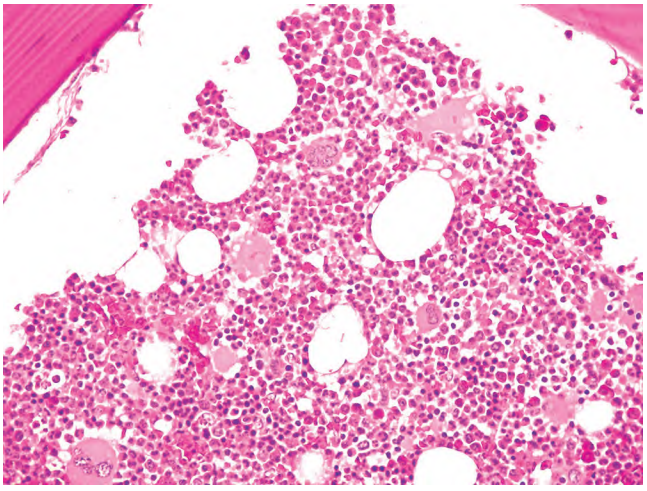
Microscopically, the defect contains cellular hematopoietic and/or fatty marrow (Fig. 14-9). The associated bony trabeculae show no evidence of abnormal osteoblastic or osteoclastic activity.

Treatment and Prognosis

The radiographic findings are often suggestive of the diagnosis but are nonspecific. Incisional biopsy, therefore, often is necessary to establish the diagnosis. Once the diagnosis is made, no further treatment is needed. The prognosis is excellent, and there appears to be no significant association with anemia or other hematologic disorders.



• **Fig. 14-8 Focal Osteoporotic Marrow Defect.** Fairly well-circumscribed radiolucency with fine central trabeculation in the extraction site of a mandibular molar. (Courtesy of Dr. R. Sidney Jones.)



• **Fig. 14-9 Focal Osteoporotic Marrow Defect.** Photomicrograph showing normal hematopoietic bone marrow.

◆ IDIOPATHIC OSTEOSCLEROSIS

Idiopathic osteosclerosis represents focally increased bone density of unknown cause. It cannot be attributed to any inflammatory, dysplastic, neoplastic, or systemic disorder. Idiopathic osteosclerosis also has been termed *dense bone island, bone eburnation, bone whorl, bone scar, enostosis*, and *focal periapical osteopetrosis.* The following discussion focuses on jaw lesions, although similar sclerotic areas may occur in other bones.

In addition, similar radiopaque foci may develop in the periapical areas of teeth with nonvital or inflamed pulps; these lesions most likely represent a response to

inflammation. Such reactive foci are termed **condensing osteitis** or **focal chronic sclerosing osteomyelitis** (see page 134) and should not be designated *idiopathic osteosclerosis.* Because past studies did not distinguish between idiopathic and inflammatory lesions, confusion in terminology has resulted.

Clinical and Radiographic Features

The estimated prevalence is 5%, with some investigators suggesting a slightly increased frequency in blacks and Asians. Most authors report no significant sex predilection. According to several long-term studies, most areas of idiopathic osteosclerosis arise in the late first or early second decade. The lesion may remain static or slowly increase in size. In almost all cases, once the patient reaches full maturity, the sclerotic area stabilizes. In a smaller percentage, the lesion diminishes or undergoes complete regression. The peak prevalence is in the third decade, with peak bone mass in the fourth decade.

Idiopathic osteosclerosis is invariably asymptomatic and nonexpansile. The condition typically is detected incidentally during routine radiographic examination. About 90% of cases occur in the mandible, most often in the first molar area. The second premolar and second molar areas also are common sites. In most patients, only one sclerotic focus is present, although some patients have two to four foci. For patients with multiple lesions, the possibility of multiple osteomas within the setting of Gardner syndrome (see page 606) should be excluded.

Radiographically, idiopathic osteosclerosis typically appears as a well-defined radiopacity, ranging from 0.2 cm to 2.0 cm in diameter. The radiopacity may be round, elliptical, or irregular and does not exhibit a radiolucent rim. Most lesions are uniformly radiopaque, although large lesions occasionally demonstrate a nonhomogeneous appearance. Most examples are associated with a root apex, but interradicular lesions and lesions unrelated to teeth also are possible (Fig. 14-10). Rarely, the sclerotic bone may surround an impacted tooth. Root resorption and tooth movement have been noted infrequently.

Histopathologic Features

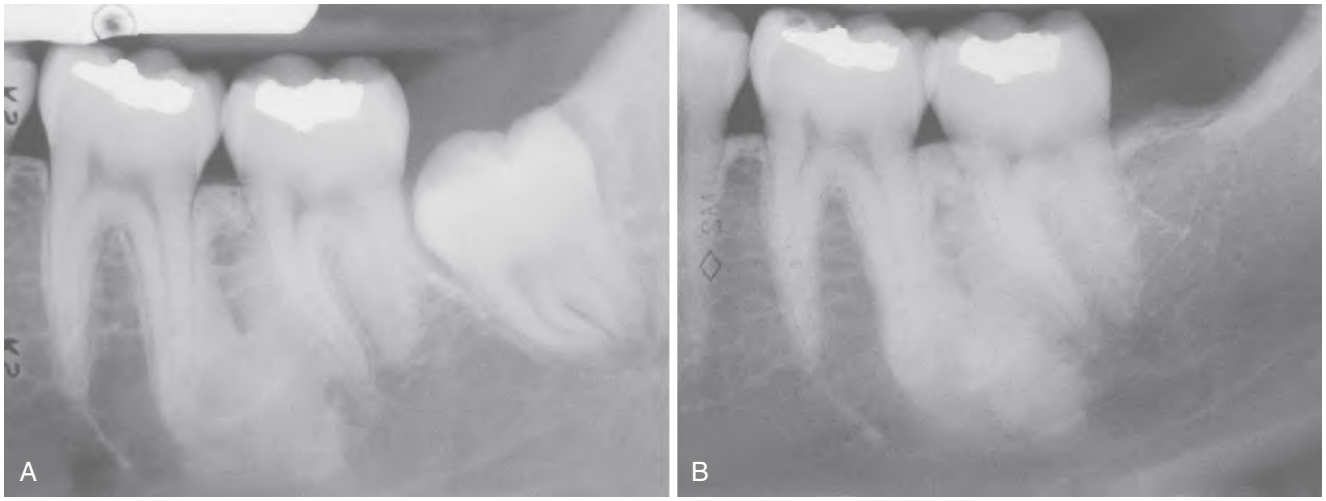
Microscopic examination shows dense lamellar bone with scant fibrofatty marrow. Inflammatory cells are inconspicuous or absent.

Diagnosis

Usually a diagnosis of idiopathic osteosclerosis may be made with confidence, based on history, clinical features, and radiographic findings. Biopsy is warranted if there are symptoms or significant cortical expansion. Although idiopathic osteosclerosis demonstrates radiographic and histopathologic similarities with a compact osteoma (see page 605), lack of cortical expansion and failure of continued growth rule against a neoplastic process. Tooth vitality and the absence of a deep restoration or caries help to distinguish idiopathic osteosclerosis from condensing osteitis.

Treatment and Prognosis

If the lesion is discovered during adolescence, periodic radiographs appear prudent until the area stabilizes. After that point, no treatment is indicated, because there is little or no tendency for the lesions to progress or change in adulthood.



• **Fig. 14-10 Idiopathic Osteosclerosis. A,** An asymptomatic area of bone sclerosis is seen between and apical to the roots of the first and second mandibular molars. **B,** No appreciable change can be seen on this radiograph taken 10 years later. (Courtesy of Dr. Michael Quinn.)

◆ MASSIVE OSTEOLYSIS (GORHAM DISEASE; GORHAM-STOUT SYNDROME; VANISHING BONE DISEASE; PHANTOM BONE DISEASE; IDIOPATHIC OSTEOLYSIS)

Massive osteolysis is a rare disease characterized by spontaneous and usually progressive destruction of one or more bones. The destroyed bone is replaced by a vascular proliferation and, ultimately, dense fibrous tissue without bone regeneration.

The etiopathogenesis is unknown. There is no evidence of underlying metabolic or endocrine imbalance. Proposed pathogenetic mechanisms include the following:

- Trauma-induced proliferation of vascular granulation tissue
- Trauma-induced activation of a previously silent hamartoma
- Increased osteoclastic activity mediated by interleukin-6 (IL-6)
- Lymphangiogenesis mediated by vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)
- Agenesis or dysfunction of thyroid C cells

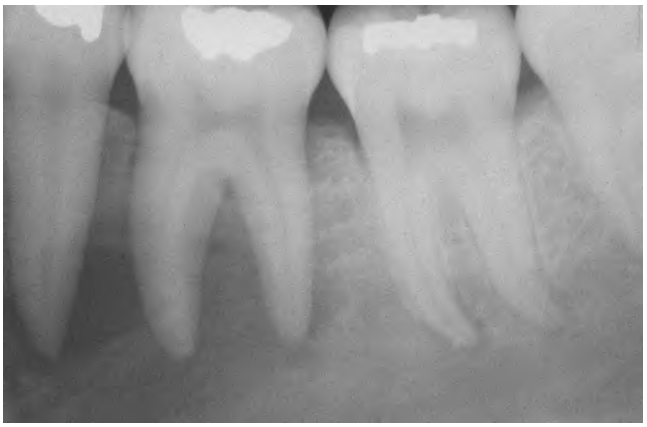
In addition, some investigators hypothesize that slow blood flow through dilated lesional vessels causes local hypoxia and reduced pH, thereby favoring activation of hydrolytic enzymes that contribute to bone resorption.

Clinical and Radiographic Features

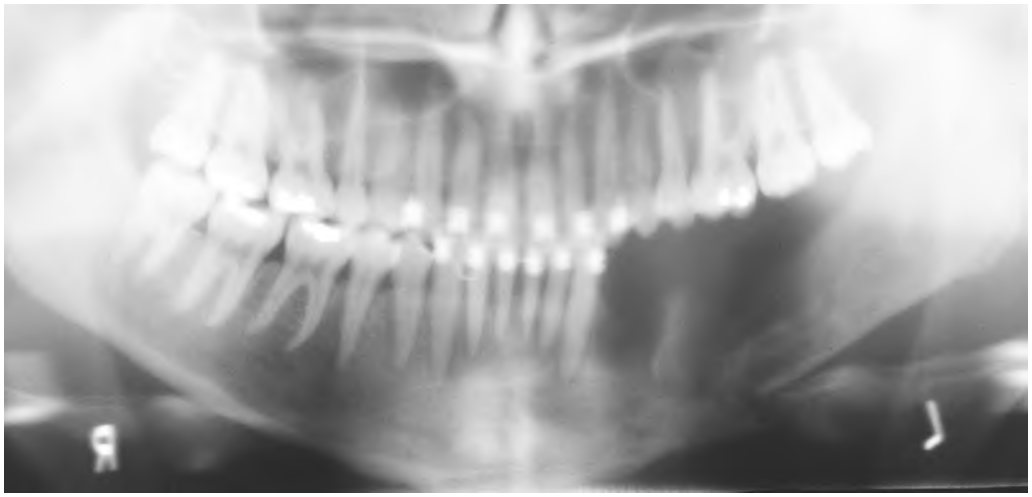
The disease occurs over a broad age range (1 month to 75 years), with a predilection for children and young adults. About 50% of patients recall prior trauma, albeit often trivial in nature. Reported sites of involvement include bones of the extremities, maxillofacial region, trunk, and pelvis. Multicentric involvement and extension into soft tissue may be evident.

Gnathic lesions most often involve the mandible. Simultaneous involvement of both jaws and extension to contiguous extragnathic sites are possible. Signs and symptoms include mobile teeth, pain, malocclusion, deviation of the mandible, and clinically obvious deformity. Potential sequelae include pathologic fracture and obstructive sleep apnea; the latter may occur secondary to posterior mandibular displacement after extensive osteolysis. Temporomandibular joint (TMJ) involvement may be confused with other conditions that can cause TMJ dysfunction.

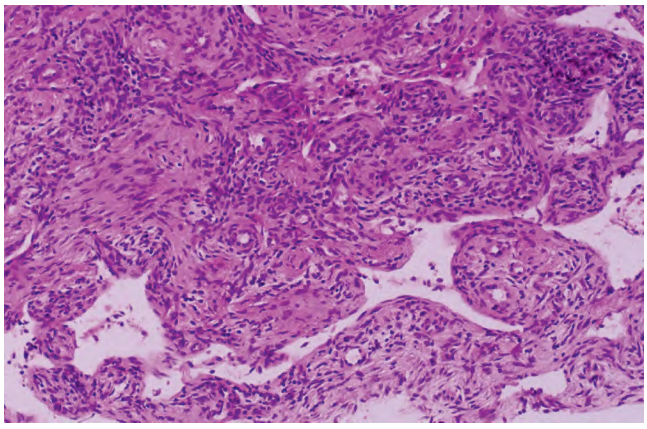
The results of laboratory studies are generally within normal limits. Radiographically, the earliest changes consist of intramedullary radiolucent foci of varying size with indistinct margins (Fig. 14-11). These foci coalesce, enlarge, and extend to the cortical bone. Eventually, large portions of bone disappear (Fig. 14-12). Loss of the lamina dura and



• **Fig. 14-11 Massive Osteolysis.** Periapical radiograph showing an ill-defined radiolucency associated with vital mandibular teeth. Note the loss of lamina dura. (Courtesy of Dr. John R. Cramer.)



• **Fig. 14-12 Massive Osteolysis.** Panoramic radiograph of the same patient shown in Fig. 14-11, showing extensive bone loss and a pathologic fracture of the left mandible. This destruction occurred over an 8-month period. (Courtesy of Dr. John R. Cramer.)



• **Fig. 14-13 Massive Osteolysis.** Biopsy specimen from the same patient shown in Figs. 14-11 and 14-12. The loose, highly vascular connective tissue shows a diffuse chronic inflammatory cell infiltrate.

thinning of the cortical plates often precede development of obvious radiolucency. In some cases, the bone destruction may mimic periodontitis or periapical inflammatory disease.

Histopathologic Features

Microscopically, early lesions exhibit a nonspecific vascular proliferation intermixed with fibrous connective tissue and chronic inflammatory cells (Fig. 14-13). Blood vessels and/or lymphatic vessels may be present, although current evidence suggests the latter predominate. Immunohistochemistry with the D2-40 antibody may be performed to highlight lymphatic endothelium. The vascular channels are thin-walled and may vary in size. Despite theories regarding their potential pathogenetic role, osteoclasts may not be evident in the adjacent bone. In later stages, there is fibrosis without bone regeneration.

Treatment and Prognosis

The clinical course of massive osteolysis is variable and unpredictable. In most cases, bone destruction progresses over months to a few years and results in complete loss of the affected bone or bones. Some patients, however, experience spontaneous arrest of the process without complete loss of the affected bone. Uncommonly, death results from respiratory compromise due to severe thoracic involvement or from spinal cord compression due to vertebral destruction.

Treatment is not particularly satisfactory. Maxillofacial lesions most commonly are treated by surgical resection and/or radiation therapy. However, particularly in young patients, there are concerns regarding the potential for post-irradiation sarcoma and radiation-induced developmental defects. Surgical reconstruction may be complicated by bone graft resorption and inadequate bone for fixation; therefore, it is advisable to delay reconstruction until arrest of the osteolytic disease phase.

Alternatively, some investigators have reported disease stabilization with administration of bisphosphonates and/or alpha-2b interferon, although additional studies are needed. Current clinical trials are evaluating rapamycin therapy. Unfortunately, limited or no improvement has been reported with various other treatments, including estrogens, magnesium, calcium, vitamin D, fluoride, calcitonin, cisplatin, actinomycin D, etoposide, and imatinib. The effectiveness of any therapeutic intervention is difficult to evaluate, because the disease is so rare and the condition may arrest spontaneously in some patients.

◆ PAGET DISEASE OF BONE (OSTEITIS DEFORMANS)

Paget disease of bone is characterized by abnormal, anarchic resorption and deposition of bone, resulting in skeletal distortion and weakening. It represents the second most common metabolic bone disorder after osteoporosis and primarily affects older adults of Anglo-Saxon ancestry. There is marked variation in reported prevalence by geographic region, with the highest rates in the United Kingdom. The disease also frequently occurs in Australia, New Zealand, Western and Southern Europe, and North America. In the United States, the disease affects approximately 1% to 2% of the general population. For reasons unclear, significant declines in disease incidence and severity have been observed in recent decades in many high-prevalence regions.

The etiology is unknown, but both genetic and environmental factors have been proposed. Approximately one-third of patients have a first-degree relative with the disease. In about 40% of familial cases and 8% of sporadic cases, germline mutations in the sequestosome 1 gene *(SQSTM1)* (also known as *p62*) have been identified. Patients with *SQSTM1* mutations tend to have more severe disease than those without such mutations. *SQSTM1* activates osteoclasts via the nuclear factor-kappa B (NF-κB) signaling pathway. In addition, genomic studies have identified polymorphisms in several other genes that appear to confer increased susceptibility to Paget disease.

The possibility that Paget disease results from a slow virus infection has received considerable attention but remains controversial. Inclusion bodies resembling nucleocapsids from a paramyxovirus have been detected in osteoclasts from affected individuals; however, attempts to demonstrate mRNA and proteins from paramyxoviruses in patient tissue samples have yielded variable results. In animal models, interactions between measles virus infection and *SQSTM1* mutations can produce a pagetic phenotype. Additional circumstantial evidence is provided by epidemiologic studies that have noted an association with rural living, thereby suggesting possible transmission of an infectious agent via contact with farm animals.

Cell culture studies suggest that increased bone resorption in Paget disease may result from increased vitamin D receptor binding affinity among osteoclasts. Also, increased

osteoclastogenesis may be caused by hyperresponsiveness of osteoclast precursors to RANKL (receptor activator of nuclear factor kappa B ligand) and decreased inhibition of RANK signaling. Additionally, recent findings suggest that Paget disease may be associated with dysregulation of autophagy (a controlled protein degradation process) in osteoclasts. Some studies suggest that underlying defects may reside not only in osteoclasts but also in osteoblasts.

Clinical and Radiographic Features

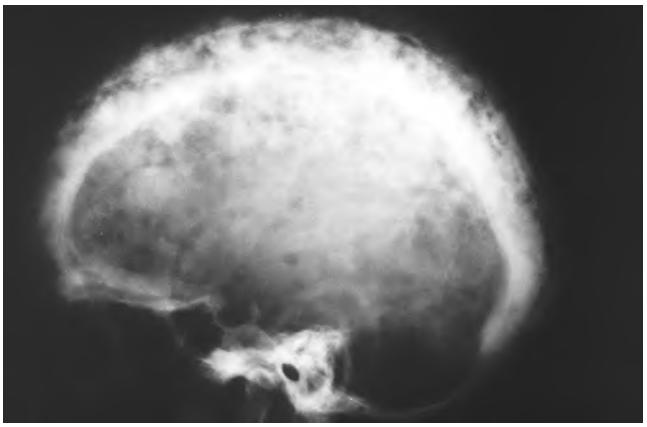
Paget disease of bone primarily affects older patients. Disease frequency increases with age, and the mean age at diagnosis has been increasing in many populations. The condition is rare in patients younger than 40 years. Most studies report a male predilection.

At diagnosis many patients are asymptomatic, although up to 40% of patients initially present with bone pain. Asymptomatic disease may be discovered incidentally when radiographic examination or serum alkaline phosphatase measurement is performed for unrelated reasons. Bone pain may result from either increased bone turnover or secondary complications (e.g., osteoarthritis, spinal stenosis, pathologic fracture, and pseudofracture).

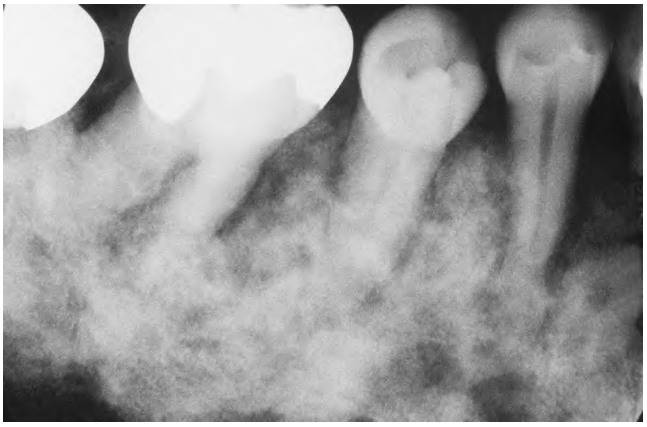
The disease arises in one or more bones simultaneously, and involvement typically remains restricted to these original sites throughout the disease course. The pelvis, femur, lumbar vertebrae, skull, and tibia are involved most commonly. Affected bones become thickened, enlarged, and weakened, with an increased risk for fracture. Involvement of weight-bearing bones often leads to bowing deformity, resulting in a "simian (monkeylike) stance." Skull involvement generally causes a progressive increase in head circumference. Deafness and visual impairment may result from nerve compression or other mechanisms. Cardiovascular complications, including arterial calcifications and high-output congestive heart failure, also are possible.

Jaw involvement is present in about 17% of patients, with a predilection for the maxilla (approximate 2:1 maxilla-to-mandible ratio). Maxillary disease produces enlargement of the middle third of the face and may result in nasal obstruction, enlarged turbinates, obliterated sinuses, and deviated septum. In extreme cases, there is a lion-like facial deformity **(leontiasis ossea).** The alveolar ridges tend to remain symmetrical but become grossly enlarged. Alveolar enlargement may cause spacing between teeth, and edentulous patients may complain that their dentures feel too tight.

Radiographically, in early disease stages, the affected bone exhibits decreased radiodensity and a coarse trabecular pattern. Particularly in the skull, large circumscribed radiolucencies may be present **(osteoporosis circumscripta).** In later disease stages, patchy areas of bone sclerosis form and tend to become confluent. The patchy sclerotic areas characteristically exhibit a "cotton wool" appearance (Figs. 14-14 and 14-15). In addition, the teeth may demonstrate generalized hypercementosis.



• **Fig. 14-14 Paget Disease.** Lateral skull film shows marked enlargement of the cranium with new bone formation above the outer table of the skull and a patchy, dense, "cotton wool" appearance. (Courtesy of Dr. Reg Munden.)

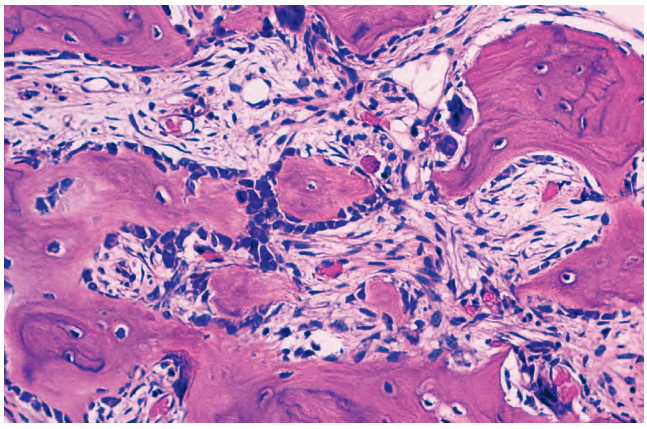


• **Fig. 14-15 Paget Disease.** Periapical film showing the "cotton wool" appearance of the bone.

Radiographic findings of Paget disease may resemble those of cemento-osseous dysplasia (see page 596). Patients with presumed cemento-osseous dysplasia who develop significant jaw expansion should be evaluated further to rule out Paget disease.

Histopathologic Features

Microscopic examination shows uncontrolled resorption and formation of bone. In the resorptive phase, numerous hyperactive osteoclasts surround the bone trabeculae; these osteoclasts tend to be enlarged with an increased number of nuclei. In addition, highly vascular fibrous connective tissue replaces the marrow. Behind the "leading edge" of osteoclastic activity, there is a gradual conversion from predominantly osteoclastic to osteoblastic activity. The osteoblasts form osteoid rims around the bone trabeculae, and the bone lacks an organized lamellar pattern. Basophilic reversal lines, which indicate the junction between alternating bone resorption and formation, result in a characteristic "jigsaw puzzle" or "mosaic" appearance (Fig. 14-16). In the



• **Fig. 14-16 Paget Disease.** Prominent osteoblastic and osteoclastic activity surround the bone trabeculae. Note the resting and reversal lines.

sclerotic phase, there are large masses of dense bone with prominent reversal lines.

Diagnosis

Diagnosis typically requires correlation of the clinical and radiographic findings with laboratory test results. In addition, bone scintigraphy may help to determine the extent of involvement. Histopathologic examination can be confirmatory but often is unnecessary for diagnosis.

Laboratory testing typically shows elevated serum alkaline phosphatase levels with normal blood calcium and phosphorus levels. Although serum bone-specific alkaline phosphatase is considered the most sensitive marker of bone formation, total serum alkaline phosphatase is more widely available and, thus, typically used in routine clinical practice. When measuring total serum alkaline phosphatase, liver enzymes also should be assessed in order to exclude elevated alkaline phosphatase of hepatic origin.

In patients with limited disease extent, total serum alkaline phosphatase may be within normal range. In such cases, it may be helpful to assess specialized markers of bone formation (e.g., serum N-terminal propeptide of type 1 collagen) or resorption (e.g., urinary N-terminal telopeptide of type 1 collagen).

Treatment and Prognosis

Paget disease is chronic and slowly progressive but seldom fatal. Asymptomatic patients with limited disease do not require treatment. Patients with symptomatic or extensive disease typically receive bisphosphonate therapy (i.e., single infusion of zoledronic acid; oral risedronate or alendronate administered daily for several months). Studies have demonstrated that such treatment can reduce bone turnover, induce normalization of alkaline phosphatase levels, decrease bone pain, and improve quality of life. In particular, single-infusion therapy with zoledronic acid is highly effective in achieving sustained disease remission. However, there is currently insufficient evidence regarding whether bisphosphonates may reduce the risk for long-term complications, such as osteoarthritis, bone deformity, and deafness. Analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) may be useful for controlling pain caused by secondary osteoarthritis. Management of Paget disease also may include orthotics, canes or other mobility devices, and orthopedic surgery (e.g., hip or joint replacement). Prior to orthopedic surgery involving an active disease site, bisphosphonates may be administered in order to reduce the risk for excessive blood loss.

Potential dental complications include difficulties in extracting teeth with hypercementosis and/or ankylosis; extensive hemorrhage from oral surgical procedures performed during the vascular lytic phase; and poor wound healing with increased susceptibility to osteomyelitis during the avascular sclerotic phase. Edentulous patients may require new dentures periodically to compensate for progressive alveolar enlargement. Pagetic bone and a history of bisphosphonate therapy generally are considered unfavorable factors for osseointegration of dental implants, although successful implant placement has been reported in a few cases.

Malignant transformation of pagetic bone into osteosarcoma or other sarcomas is a rare disease complication, with an estimated lifetime risk of less than 1%. A sudden increase in bone pain or swelling should raise suspicion of possible underlying malignancy. Osteosarcoma in adults older than 40 years is quite uncommon in individuals who do not have Paget disease. Most Paget-related osteosarcomas develop in the pelvis and long bones of the extremities—the skull and jaws are affected only rarely. Osteosarcoma in Paget disease is very aggressive and associated with a poor prognosis. Another rare complication of Paget disease is the development of benign and malignant giant cell tumors (see page 586), most often involving the craniofacial skeleton.

◆ CENTRAL GIANT CELL GRANULOMA (GIANT CELL LESION; GIANT CELL TUMOR)

The **central giant cell granuloma** is an intraosseous lesion of unknown etiology. There is much debate regarding whether this entity represents a reactive process or a benign neoplasm. In the past, it was hypothesized to represent a reparative response to trauma-induced hemorrhage—hence, its former designation *giant cell reparative granuloma.* However, there is little evidence to support a reparative response; therefore, most oral and maxillofacial pathologists today prefer the term *giant cell granuloma* or the more noncommittal term *giant cell lesion.* In fact, some examples demonstrate locally aggressive behavior similar to that of a benign neoplasm. Recent genetic studies suggest that some giant cell lesions of the jaws are monoclonal, and reciprocal chromosomal translocations have been identified in two cases involving the jaws thus far. Somatic mutation of

SH3BP2 has been detected in only one case; germline mutations in this gene cause cherubism (see page 587).

Clinical and Radiographic Features

Central giant cell granulomas of the jaws occur over a broad age range (2 to 80 years), although more than 60% of cases occur before age 30. There is a female predilection, and approximately 70% of cases arise in the mandible. Lesions are more common in the anterior portions of the jaws, and mandibular lesions frequently cross the midline. Although central giant cell granulomas also have been reported in various extragnathic sites, it is uncertain whether such cases actually represent true **giant cell tumors** (see next topic).

Based on the clinical and radiographic features, central giant cell granulomas of the jaws may be divided into two categories:

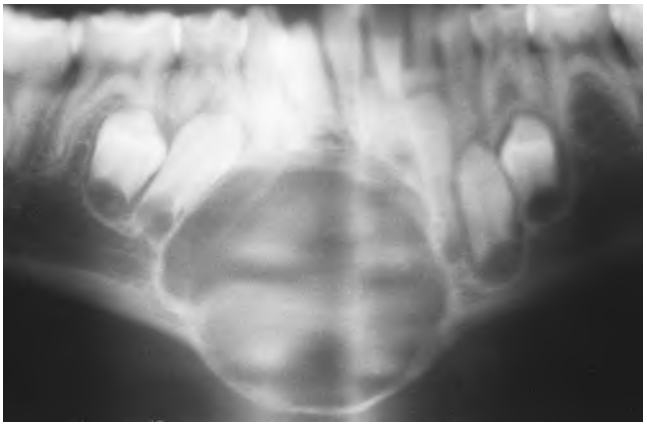
1. **Nonaggressive lesions** comprise most cases. They are relatively small, exhibit few or no symptoms, grow slowly, and do not cause cortical perforation or root resorption. Such lesions typically are discovered during routine radiographic examination or as a result of painless jaw expansion.
2. **Aggressive lesions** are characterized by pain, rapid growth, cortical perforation, root resorption, tooth displacement, and/or paresthesia. Extension into soft tissue and ulceration of the overlying mucosal surface also are possible (Fig. 14-17). Compared to nonaggressive lesions, aggressive lesions tend to be larger at diagnosis, develop in somewhat younger patients, and exhibit a greater recurrence potential.

Radiographically, the central giant cell granuloma appears as a unilocular or multilocular radiolucency, with well-delineated but generally non-corticated borders. The lesion may vary from a 5 mm incidental radiographic finding to a destructive lesion greater than 10 cm (Fig. 14-18). Small unilocular lesions may be confused with periapical granulomas or cysts (Fig. 14-19), and multilocular lesions may appear similar to ameloblastomas.

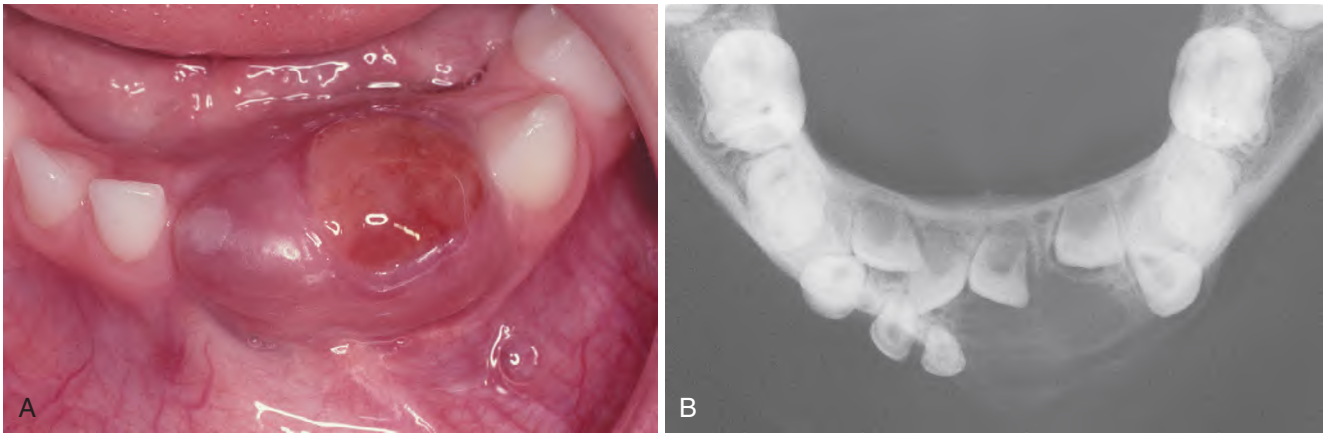
Areas histopathologically identical to central giant cell granuloma have been noted in aneurysmal bone cysts (see page 591) and intermixed with central odontogenic fibromas (see page 676). Because giant cell granulomas are also histopathologically identical to brown tumors, hyperparathyroidism (see page 781) should be ruled out in all instances. Furthermore, multifocal giant cell lesions of the jaws may occur rarely as an isolated finding or in association with certain heritable conditions, including cherubism (see page 587), Noonan-like/multiple giant cell lesion syndrome, Ramon syndrome, Jaffe-Campanacci syndrome, and neurofibromatosis type 1 (see page 495).

Histopathologic Features

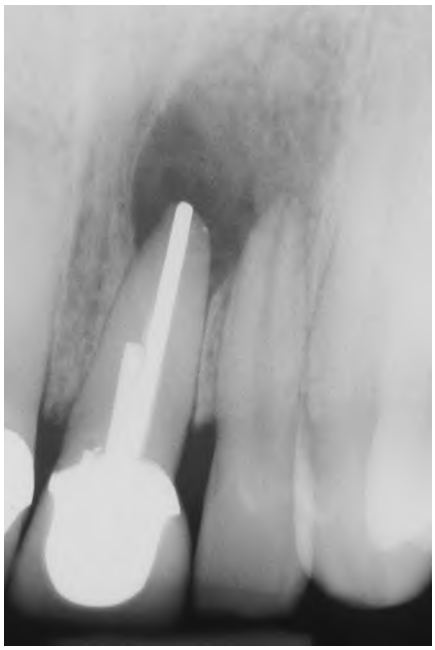
Microscopically, giant cell lesions of the jaws exhibit few to many multinucleated giant cells in a background of ovoid to spindle-shaped mononuclear stromal cells (Fig. 14-20). Investigators have proposed that the spindle cell component is the proliferating cell population and recruits monocyte-macrophage precursors, inducing them to differentiate into



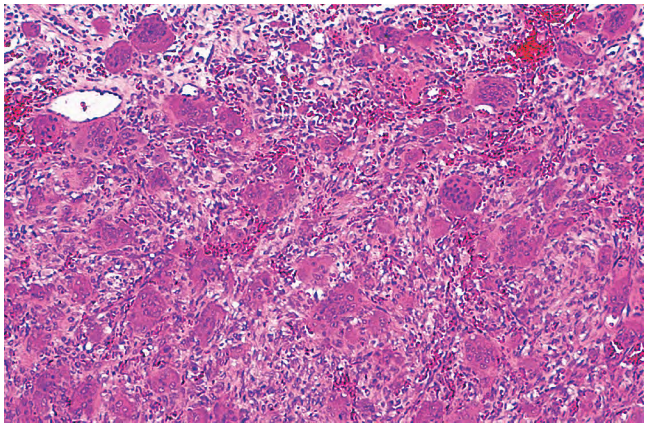
• **Fig. 14-18 Central Giant Cell Granuloma.** Panoramic radiograph showing a large, expansile radiolucent lesion in the anterior mandible. (Courtesy of Dr. Gregory R. Erena.)



• **Fig. 14-17 Central Giant Cell Granuloma. A,** A blue-purple, ulcerated mass is present on the anterior alveolar ridge of this 4-year-old white boy. **B,** The occlusal radiograph shows a radiolucent lesion with cortical expansion.



• **Fig. 14-19 Central Giant Cell Granuloma.** The periapical radiograph shows a radiolucent area involving the apex of an endodontically treated tooth. This was considered preoperatively to represent a periapical granuloma or periapical cyst.



• **Fig. 14-20 Central Giant Cell Granuloma.** Numerous multinucleated giant cells within a background of plump proliferating mesenchymal cells. Note extensive red blood cell extravasation.

osteoclastic giant cells by activation of the RANK/RANKL signaling pathway. The giant cells may be aggregated focally in the lesional tissue or may be present diffusely throughout the lesion. These cells vary considerably in size and shape from case to case. Some are small and irregular in shape with only a few nuclei, whereas others are large and round with 20 or more nuclei.

The stroma may be loosely arranged and edematous or more cellular. Older lesions may show considerable stromal fibrosis. Erythrocyte extravasation and hemosiderin deposition are often prominent. Focal bone or osteoid formation may be present.

Correlation of the histopathologic features with clinical behavior remains debatable. There are conflicting reports regarding whether more aggressive giant cell lesions of the jaws may be associated with an increased number of giant cells, larger giant cells, a greater fractional surface area occupied by giant cells, and a higher mitotic index. A few studies suggest that increased vascular density, increased expression of markers of angiogenesis, and increased expression of matrix metalloproteinases might correlate with aggressive clinical behavior.

Treatment and Prognosis

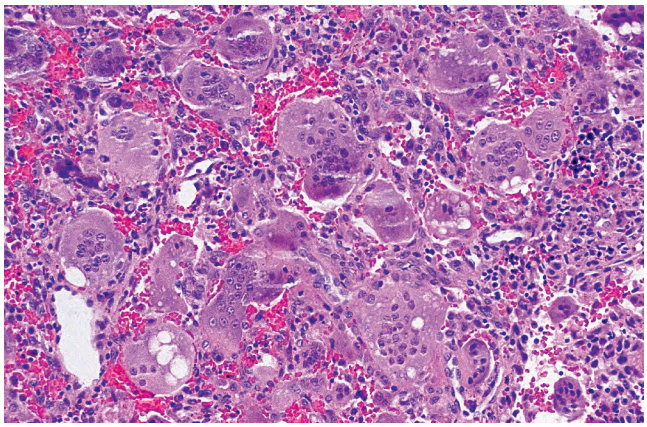
Central giant cell granulomas of the jaws usually are treated by thorough curettage. Recurrent lesions may require further curettage (at times combined with peripheral ostectomy) or *en bloc* resection. Alternative treatments include intralesional corticosteroid injections, subcutaneous or nasal calcitonin, subcutaneous interferon alpha-2a, imatinib, and bisphosphonates. Although further studies are needed, nonsurgical approaches may be desirable when surgical removal of a large tumor would result in significant deformity.

Reported overall recurrence rates range from about 11% to 49%, with most studies noting recurrence in approximately 20% of cases. Lesions with aggressive clinicoradiographic features exhibit increased recurrence potential. In spite of the potential for recurrence, the long-term prognosis is good.

◆ GIANT CELL TUMOR ("TRUE GIANT CELL TUMOR")

The relationship between **giant cell tumors** of the extragnathic skeleton and giant cell lesions of the jaws is uncertain and controversial. Some authors regard these two groups of lesions as distinct entities, based on differences in clinical findings, histopathologic features, and biologic behavior. Extragnathic giant cell tumors most often occur in the epiphyses of long bones. Compared to giant cell lesions of the jaws, extragnathic tumors are more likely to cause pain and tend to be diagnosed in patients who are 1 to 2 decades older on average, without a significant gender predilection. Some microscopic studies suggest that extragnathic giant cell tumors tend to exhibit more stromal cellularity and larger, more uniformly distributed giant cells, with a greater number of nuclei. Nonetheless, jaw lesions occasionally may exhibit microscopic features that are indistinguishable from typical extragnathic giant cell tumors (Fig. 14-21). In terms of biologic behavior, compared to jaw lesions, extragnathic lesions tend to be more aggressive, with higher recurrence rates after curettage. Malignant degeneration has been reported in 15% to 30% of true giant cell tumors, with pulmonary metastases in about 3% of extragnathic cases.

On the other hand, others have suggested that giant cell granulomas of the jaws and giant cell tumors of the



• **Fig. 14-21 Giant Cell Tumor.** This photomicrograph shows large giant cells that are distributed in a cellular mesenchymal tissue. This specimen was from an aggressive lesion that had destroyed most of the maxilla.

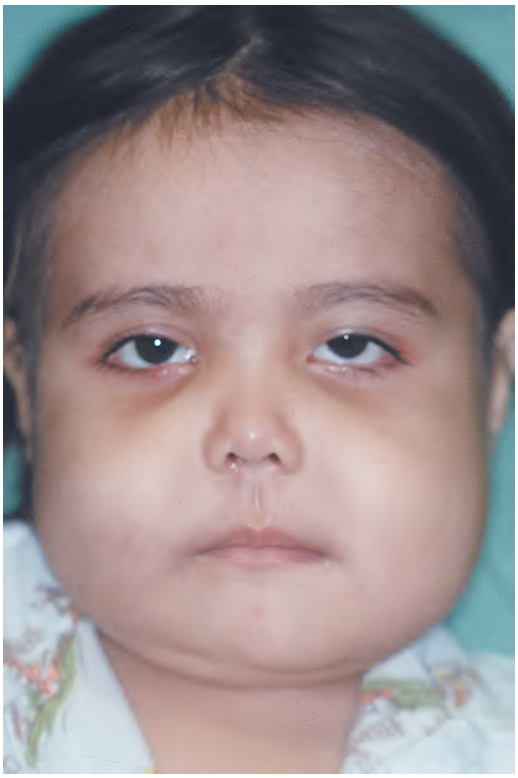
extragnathic skeleton represent the same disease entity or members of a single disease spectrum. One study has found that the two groups of lesions are similar in most respects when substratification by clinical behavior is taken into account. These investigators hypothesize that giant cell lesions tend to be diagnosed earlier in the jaws compared to other sites simply because of frequent routine dental examinations and readily apparent changes in facial appearance.

◆ CHERUBISM

Cherubism is a rare developmental jaw condition that can be inherited as an autosomal dominant trait with variable expressivity. However, many cases appear to represent *de novo* mutations. Some investigators have reported a higher penetrance in males than in females, but others have questioned this finding.

Most cases are caused by gain-of-function mutations in the *SH3BP2* gene on chromosome 4p16. These mutations lead to enhanced stability of the 3BP2 adaptor protein and consequent upregulation of various signal transduction pathways. As a result, enhanced osteoclastogenesis and hyperactive osteoclasts produce lytic bone lesions. In addition, mouse model studies demonstrating increased production of tumor necrosis factor-alpha (TNF-α) by macrophages suggest a role for inflammation in this disorder. However, it is unclear why the lesions in cherubism primarily affect the jaws. Investigators hypothesize that rapid bone remodeling during childhood tooth eruption and oral commensal bacteria may play a role.

The name *cherubism* was applied to this condition because the facial appearance is similar to that of the plump-cheeked little angels (cherubs) depicted in Renaissance paintings. Although cherubism also has been called *familial fibrous dysplasia,* this term should be avoided because cherubism has no relationship to fibrous dysplasia of bone (see page 592).



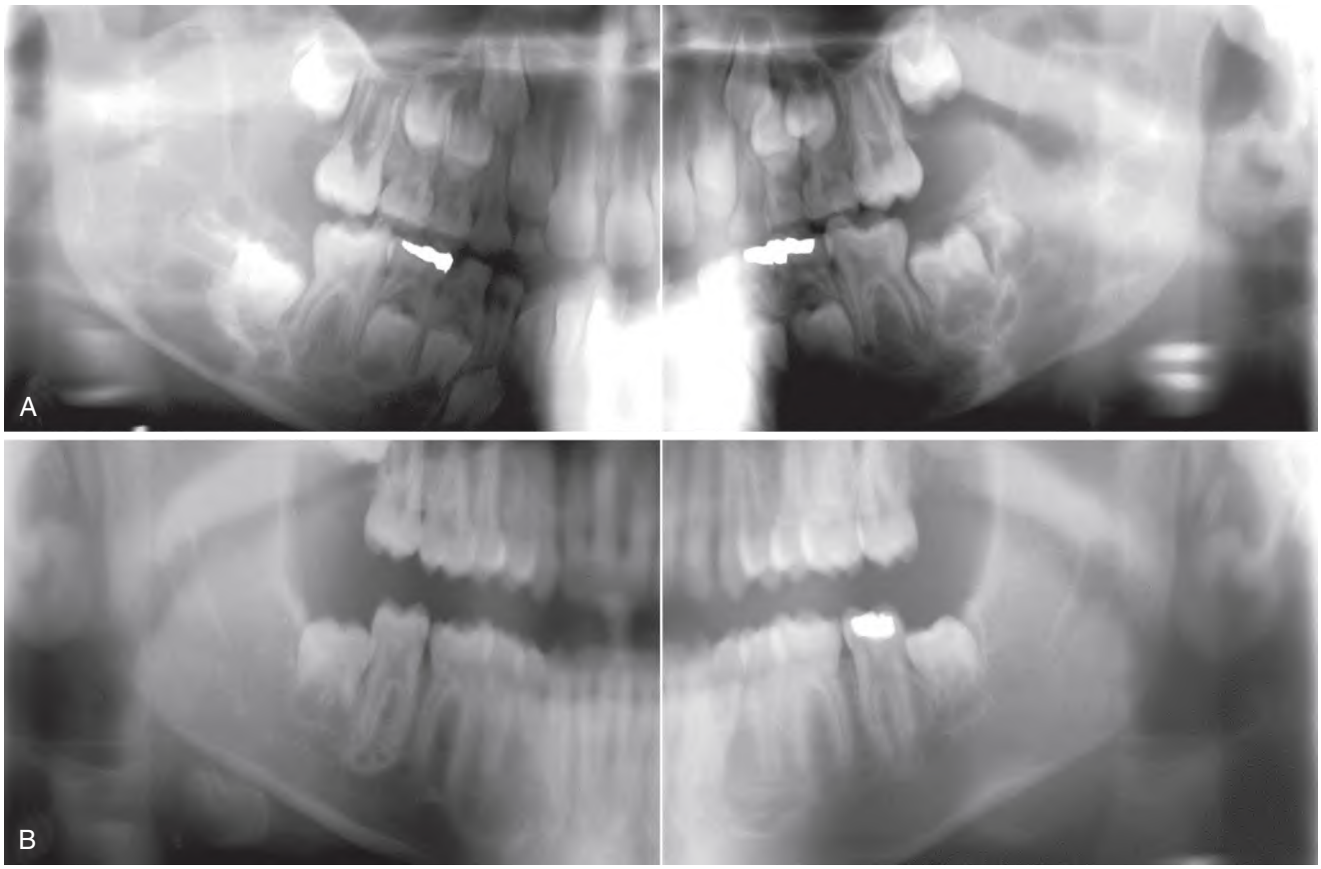
• **Fig. 14-22 Cherubism.** This young girl shows the typical cherubic facies resulting from bilateral expansile mandibular and maxillary lesions. (Courtesy of Dr. Román Carlos.)

Clinical and Radiographic Features

The condition usually first becomes evident at around 2 to 5 years of age, although in mild cases the diagnosis may not be made until 10 to 12 years. The clinical alterations typically progress until puberty, then stabilize and slowly regress.

The plump, cherub-like cheeks result from painless, bilaterally symmetric expansion of the posterior mandible (Fig. 14-22). In early disease, cervical lymphadenopathy also may contribute to the apparent fullness. In severe cases, involvement of the inferior and/or lateral orbital walls may tilt the eyeballs upward and retract the lower eyelid, thereby exposing the sclera below the iris to produce an "eyes upturned to heaven" appearance. Rare reports of unilateral cherubism are difficult to accept as true examples of this disease unless there is a strong family history or genetic confirmation.

In the mandible, lesions frequently develop in the angles, ascending rami, and coronoid processes, but the condyles usually are spared. In severe cases, most of the mandible is affected. Involvement of the maxillary tuberosities or entire maxilla also is possible, and there may be a V-shaped palatal arch. Extensive jaw involvement causes marked widening and distortion of the alveolar ridges. In addition to aesthetic compromise, the lesions may cause tooth displacement, tooth mobility, failure of tooth eruption, impaired mastication, speech difficulties, upper airway obstruction, and vision or hearing loss.



• **Fig. 14-23 Cherubism. A,** Panoramic radiograph of a 7-year-old white boy. Bilateral multilocular radiolucencies can be seen in the posterior mandible. **B,** Same patient 6 years later. The lesions in the mandibular rami demonstrate significant resolution, but areas of involvement are still present in the body of the mandible. (Courtesy of Dr. John R. Cramer.)

Radiographic examination typically shows bilateral, multilocular, expansile radiolucencies (Fig. 14-23). This radiographic presentation is virtually diagnostic. Less commonly, the lesions may appear unilocular. Additional findings may include resorption of adjacent tooth roots and thinning or perforation of the cortical bone. Although cherubism primarily is limited to the craniofacial region, rib involvement also has been reported in a few cases.

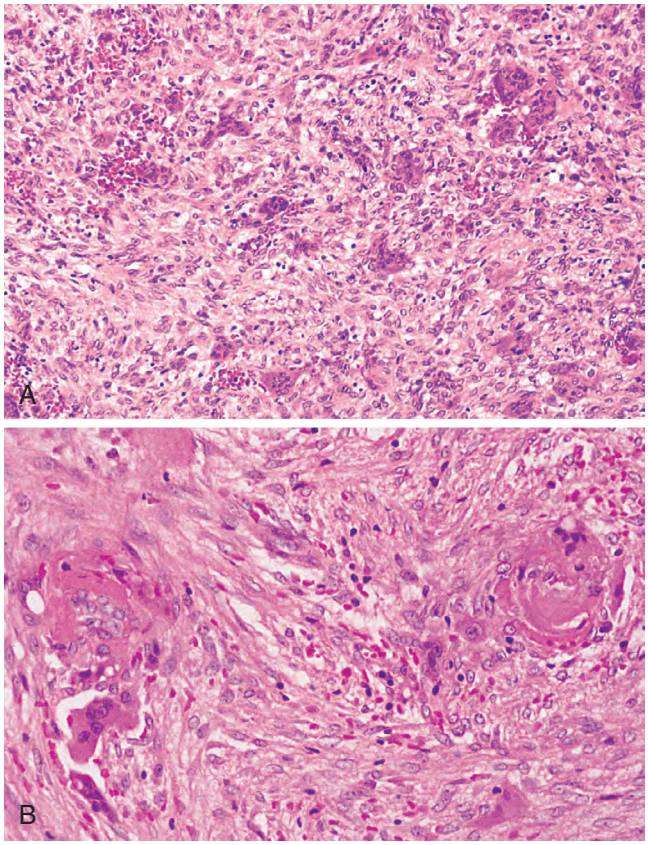
Biochemical findings typically are normal in patients with cherubism. If laboratory results do not suggest hyperparathyroidism, then most children with bilaterally symmetric giant cell lesions of the jaws represent examples of cherubism. However, multiple giant cell lesions may be seen in association with other conditions, including Ramon syndrome, Jaffe-Campanacci syndrome, Noonan-like/multiple giant cell lesion syndrome, and neurofibromatosis type 1.

Histopathologic Features

Because the microscopic findings of cherubism are similar to those of isolated giant cell granulomas, correlation with the clinical and radiographic findings is essential for diagnosis. Microscopic examination shows vascular fibrous tissue with variable numbers of multinucleated giant cells and scattered hemorrhage. The giant cells tend to be small and aggregated focally (Fig. 14-24). Like the giant cells in central giant cell granulomas, the giant cells in cherubism express markers suggestive of osteoclastic origin. The stroma in cherubism tends to be more loosely arranged than that in giant cell granulomas. In some cases, cherubism reveals eosinophilic, cuff-like deposits surrounding small blood vessels. This eosinophilic cuffing appears to be specific for cherubism but is present in only a small proportion of cases. In older, resolving lesions of cherubism, the tissue becomes more fibrous, the number of giant cells decreases, and new bone formation is seen.

Treatment and Prognosis

In most instances, the lesions regress spontaneously after puberty (see Fig. 14-23). By the fourth decade, the facial features of most patients approach normalcy. Nevertheless, the prognosis in any given case is difficult to predict, and persistent facial deformity or continued disease progression is possible.



• **Fig. 14-24 Cherubism. A,** Photomicrograph showing scattered giant cells within a background of cellular, hemorrhagic mesenchymal tissue. **B,** High-power view showing perivascular eosinophilic cuffing.

Because most cases regress over time, a conservative treatment approach generally is preferred. Mild cases may require only observation. However, treatment typically is indicated for patients with aggressive lesions, severe functional impairment, or marked facial deformity. Surgical intervention may consist of curettage, recontouring, partial resection, or complete resection. The surgical defects may be filled with autogenous cancellous bone and bone marrow grafts. Outcomes of surgery performed during the active disease phase are variable, with some investigators reporting excellent results and others reporting aggressive regrowth. Generally, it is preferable to delay surgery until the disease has become quiescent, although severe aesthetic and functional compromise may demand earlier intervention. Alternative treatment with calcitonin or interferon has been reported anecdotally but requires further study. Attempts to treat cherubism with adalimumab (a TNF-α antagonist)—alone or in combination with bisphosphonates—have yielded disappointing results thus far. Radiation therapy is contraindicated because of the risk for postirradiation sarcoma.

Dental management may include extraction or orthodontic extrusion of impacted teeth; orthodontics for malocclusion; and prostheses for missing teeth. Placement of dental implants and autotransplantation of teeth also have been reported in a few cases.

◆ SIMPLE BONE CYST (TRAUMATIC BONE CYST; HEMORRHAGIC BONE CYST; SOLITARY BONE CYST; IDIOPATHIC BONE CAVITY; UNICAMERAL BONE CYST)

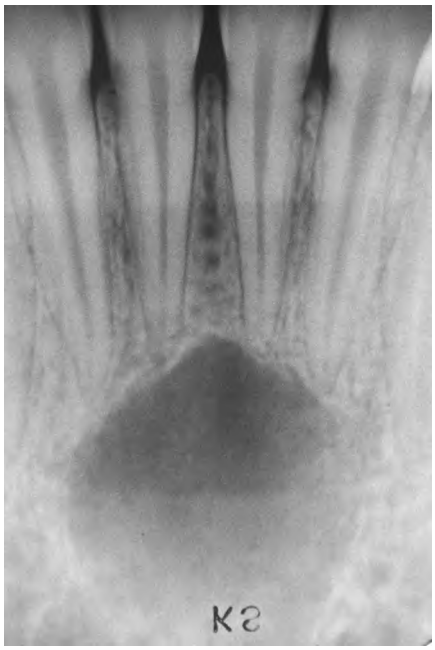
The **simple bone cyst** is an empty or fluid-containing bone cavity. Because this lesion lacks an epithelial lining, it represents a pseudocyst rather than a true cyst.

The etiopathogenesis is uncertain, and several theories have been proposed. In particular, the **trauma-hemorrhage theory** has many advocates, as evidenced by the widely used designation **traumatic bone cyst.** According to this theory, trauma that is insufficient to cause a bone fracture results in an intraosseous hematoma. If the hematoma does not undergo organization and repair, it may liquefy and result in a pseudocystic defect. However, a history of trauma to the affected area and the presence of blood within the cavity have been inconsistent findings. Other proposed theories include venous obstruction, local disturbance in bone growth, altered calcium metabolism, ischemic marrow necrosis, aberrant synovial development, and degeneration of a bone tumor or cyst.

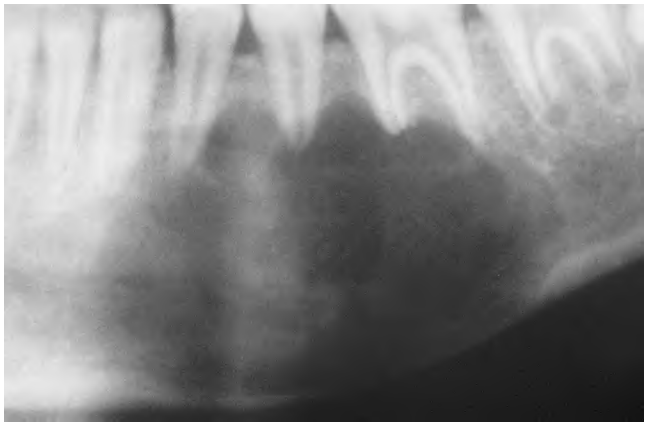
Clinical and Radiographic Features

Simple bone cysts have been reported in almost every bone of the body. Most cases involve the metaphyses of long bones, with a predilection for the proximal humerus and proximal femur. In addition, solitary bone cysts may arise in the jaws, with a marked mandibular predominance. Although any area of the mandible may be involved, the premolar, molar, and symphyseal regions are affected most commonly. Most solitary bone cysts are diagnosed in young patients, with a peak in the second decade. Jaw lesions exhibit no significant gender bias, whereas extragnathic lesions exhibit a male predilection. Unlike extragnathic lesions, jaw lesions tend to lack clinical signs or symptoms; thus, the true frequency of jaw lesions is undoubtedly greater than the literature would suggest. About 20% of patients, however, have a painless jaw swelling. Pain and paresthesia are noted infrequently.

Simple bone cysts of the jaws often are discovered incidentally during radiographic examination for some other reason. The lesion typically appears as a well-delineated, unilocular radiolucency. However, ill-defined and multilocular lesions also are possible. The defect may range from 1 to 10 cm in diameter. Occasionally, the radiolucent defect shows domelike projections that scallop upward between the roots of adjacent teeth. This feature is highly suggestive but not diagnostic of a simple bone cyst (Figs. 14-25 and 14-26). In many cases, a cone-shaped outline (pointed at one or both ends in the anterior-posterior direction) may be noted, particularly when the lesion is large. Oval, irregular, or rounded borders are possible as well. The adjacent teeth are generally vital. Root resorption, loss of lamina dura, cortical expansion, and cortical thinning are evident



• **Fig. 14-25 Simple Bone Cyst.** Periapical radiograph showing a radiolucent area in the apical region of the anterior mandible. The incisor teeth responded normally to vitality testing, and no restorations are present.



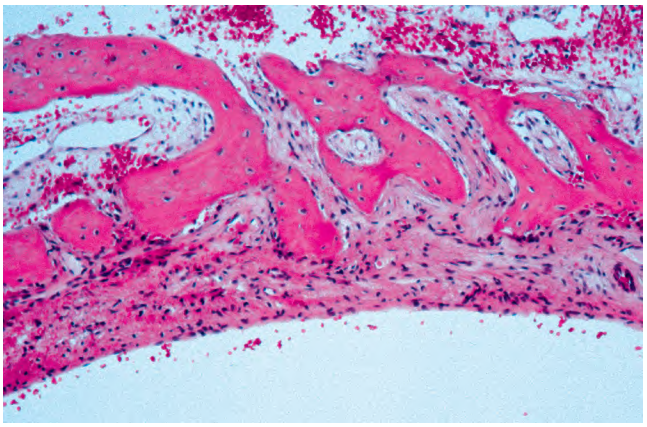
• **Fig. 14-26 Simple Bone Cyst.** Panoramic film showing a large simple bone cyst of the mandible in a 12-year-old girl. The scalloping superior aspect of the cyst between the roots of the teeth is highly suggestive of, but not diagnostic for, a simple bone cyst. (Courtesy of Dr. Lon Doles.)

in a minority of cases. Most lesions are solitary, but multifocal involvement has been reported occasionally. Extensive lesions involving a substantial portion of the mandibular body and ascending ramus also are possible.

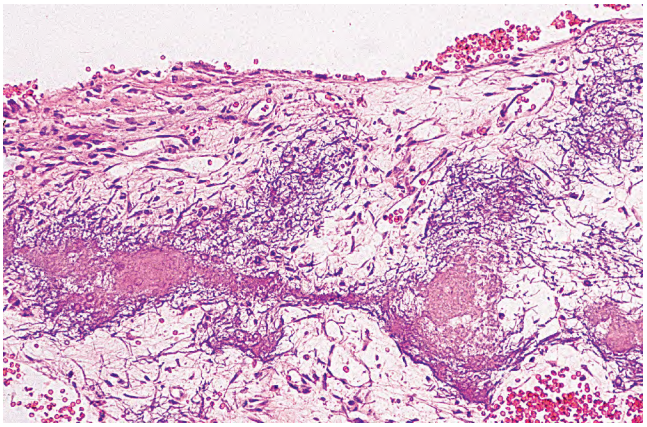
Simple bone cysts at times may arise in association with cemento-osseous dysplasia (see page 596) and other fibro-osseous proliferations. Such cases tend to occur in older females.

Histopathologic Features

There is never an epithelial lining. Instead, the walls of the defect are lined by a thin band of vascular fibrous connective tissue (Fig. 14-27) or a thickened myxofibromatous proliferation with reactive bone. In addition, there may be fibrin, scattered erythrocytes, occasional giant cells, and lacelike dystrophic calcifications (Fig. 14-28). Some authors also have noted amorphous, cementum-like material, which may represent osteoid. The bony surface next to the cavity may show resorptive areas (Howship lacunae) indicative of past osteoclastic activity.



• **Fig. 14-27 Simple Bone Cyst.** Photomicrograph of the bony wall of a simple bone cyst. A thin, vascular connective tissue membrane is adjacent to the bone, and no epithelial lining is identified.



• **Fig. 14-28 Simple Bone Cyst.** Loose vascular connective tissue exhibiting areas of basophilic lacelike calcification in the wall of a simple bone cyst.

Diagnosis

The radiographic features of the simple bone cyst are not entirely specific and may be confused with a wide variety of odontogenic and nonodontogenic radiolucent jaw lesions. Surgical exploration is necessary to establish the diagnosis.

Typically, little to no tissue is obtained at the time of surgery; therefore, the diagnosis is based primarily on the clinical, radiographic, and intraoperative findings. In about one-third of cases, there is an empty cavity with smooth, shiny bony walls. In about two-thirds of cases, the cavity contains small amounts of serosanguineous fluid. The

mandibular neurovascular bundle may be seen lying free in the cavity.

Treatment and Prognosis

Simple bone cysts of the long bones often are treated aggressively, with various combinations of curettage, cryosurgery, decompression, intralesional steroid injections, bone substitute or autologous bone marrow injection, and bone grafting. Reported recurrence rates are relatively high (mean 29%, range 12% to 48%).

In contrast, simple bone cysts of the jaws typically are managed by surgical exploration and curettage. Intraoperatively, the bony walls of the cavity usually appear smooth and shiny, although it is wise to curette them and submit the small amount of tissue obtained for microscopic examination to rule out more serious diseases. Surgical exploration with or without curettage usually induces bone regeneration; normal radiographic findings typically are evident 12 to 17 months after surgery. Periodic radiographic examination should be performed until complete resolution has been confirmed. Most studies report very low recurrence rates (approximately 1% to 2%), although some report recurrence rates as high as 27%. There is an increased potential for recurrence when there are multiple lesions or with lesions arising in association with cemento-osseous dysplasia. In addition, one study reported an increased recurrence potential among jaw lesions exhibiting scalloped margins, resorption of the lamina dura, nodular bone expansion, and multiple cavities. Some authors suggest that the use of packing materials may decrease recurrence, but further studies are needed. Overall, the prognosis is excellent.

◆ ANEURYSMAL BONE CYST

The **aneurysmal bone cyst** is an intraosseous accumulation of variable-sized, blood-filled spaces surrounded by cellular fibrous connective tissue and reactive bone. Because the lesion lacks an epithelial lining, it represents a pseudocyst rather than a true cyst. Aneurysmal bone cysts may be classified as *primary* (i.e., arising *de novo*) or *secondary* (i.e., arising in association with another bone lesion).

The etiopathogenesis is poorly understood. Traditionally, the aneurysmal bone cyst has been considered a reactive lesion. Many authors have theorized that a traumatic event, vascular malformation, or neoplasm may disrupt normal osseous hemodynamics, resulting in an enlarging area of hemorrhage and osteolysis. Consistent with this hypothesis is the observation that approximately 20% to 30% of aneurysmal bone cysts form in association with other lesions.

In contrast, cytogenetic evidence suggests that primary aneurysmal bone cysts may be neoplastic in nature. The majority of primary lesions analyzed exhibit recurrent translocations and consequent transcriptional upregulation of the ubiquitin-specific protease 6 *(USP6)* (also known as *Tre-2* or *TRE17*) oncogene on chromosome 7p13. However, *USP6* translocations have been detected in very few craniofacial lesions thus far. The underlying mechanisms by which *USP6* upregulation leads to tumor formation remain poorly understood, although studies suggest that nuclear factor-kappa B (NF-κB)-mediated induction of matrix metalloproteinases and inflammatory cytokines may play a role.

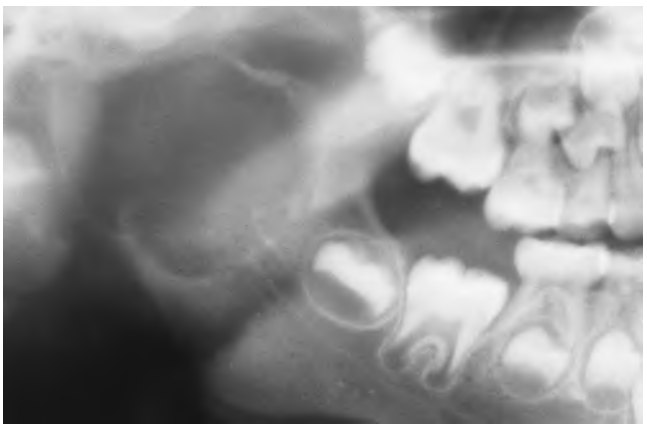
Clinical and Radiographic Features

Aneurysmal bone cysts arise primarily in the long bones or vertebrae of patients younger than 30 years. Only about 2% of cases involve the jaws. Gnathic lesions mainly affect young patients (peak in the second decade) but may occur over a broad age range. Most authors report either no significant sex predilection or a slight female predilection. The lesions arise more often in the mandible than the maxilla, and the vast majority arises in the posterior segments of the jaws. Within the mandible, involvement of the ascending ramus and posterior body is common, whereas involvement of the condylar and coronoid processes is infrequent.

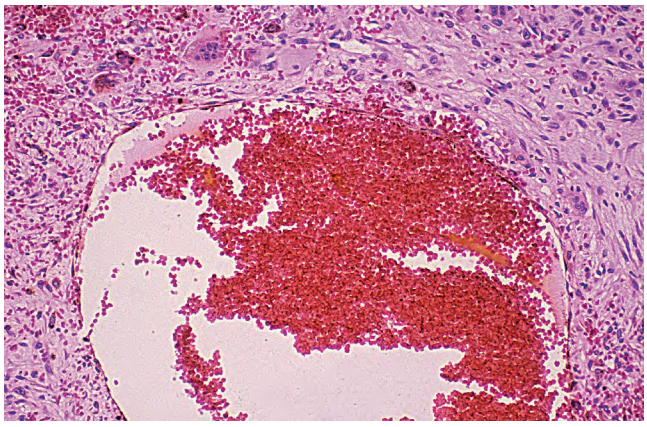
The most common clinical manifestation is a rapidly enlarging swelling. Pain is a variable finding; paresthesia and crepitus have been noted rarely. Malocclusion, mobility, migration, or resorption of involved teeth may be present. Maxillary lesions often bulge into the adjacent sinus and occasionally cause nasal obstruction, nasal bleeding, proptosis, and diplopia.

Radiographic examination shows a unilocular or multilocular radiolucency, often with marked cortical expansion and thinning (Fig. 14-29). The radiographic borders may be well defined or poorly defined. There is frequently a ballooning or "blow-out" distention of the affected bone. Uncommonly, small radiopaque foci, thought to be small trabeculae of reactive bone, are noted within the radiolucency.

Intraoperatively, intact periosteum and a thin shell of bone typically are evident overlying the lesion, although cortical perforation is possible. When the periosteum and



• **Fig. 14-29 Aneurysmal Bone Cyst.** A large radiolucent lesion involves most of the ascending ramus in a 5-year-old white boy. (Courtesy of Dr. Samuel McKenna.)



• **Fig. 14-30 Aneurysmal Bone Cyst.** Photomicrograph showing a blood-filled space surrounded by fibroblastic connective tissue. Scattered multinucleated giant cells are seen adjacent to the vascular space.

bony shell are removed, the lesion exhibits dark venous-like bleeding with a "blood-soaked sponge" appearance.

Histopathologic Features

Microscopically, the aneurysmal bone cyst is characterized by blood-filled spaces of varying size. These blood-filled spaces lack an endothelial or epithelial lining (Fig. 14-30). The surrounding cellular fibroblastic tissue contains multinucleated giant cells, osteoid, and woven bone. Similar to the multinucleated giant cells in giant cell granulomas, the multinucleated giant cells in aneurysmal bone cysts exhibit an osteoclastic phenotype, as evidenced by immunohistochemical and *in situ* hybridization studies. Osteoid deposits may appear linear, nodular, or lacelike. As noted earlier, aneurysmal bone cysts may be associated with other pathoses, most commonly fibro-osseous lesions or giant cell granulomas.

Treatment and Prognosis

Aneurysmal bone cysts of the jaws usually are treated by curettage or enucleation, sometimes supplemented with cryosurgery. *En bloc* resection is reserved for extensive or recurrent lesions. Preoperative embolization may be considered to control bleeding but often is unnecessary, because most gnathic lesions exhibit low-flow vascularity. Typically, the surgical defect heals within 6 months to 1 year and does not necessitate bone grafting. Irradiation generally is contraindicated.

Reported recurrence rates range from 8% to 70%. According to one comprehensive review of the literature, approximately 13% of reported jaw lesions have recurred within 2 years. Most reported recurrences actually represent persistence after incomplete removal. Occasionally, recurrence also may be related to incomplete removal of a coexisting lesion, such as an ossifying fibroma or osteoblastoma. Overall, despite recurrences, the long-term prognosis is favorable.

FIBRO-OSSEOUS LESIONS OF THE JAWS

Fibro-osseous lesions are a diverse group of processes that are characterized by replacement of normal bone by fibrous tissue containing a newly formed mineralized product. The term *fibro-osseous lesion* is descriptive and does not constitute a specific diagnosis. Lesions belonging to this category may be developmental (hamartomatous), reactive, dysplastic, or neoplastic.

Fibro-osseous lesions of the jaws include the following:

- Fibrous dysplasia
- Cemento-osseous dysplasia
  - Focal cemento-osseous dysplasia
  - Periapical cemento-osseous dysplasia
  - Florid cemento-osseous dysplasia
- Ossifying fibroma

Although these conditions differ in etiology, they may exhibit very similar histopathologic features. Therefore, correlation of the histopathologic findings with the clinical and radiographic features typically is essential for establishing a specific diagnosis. (However, in some cases of cemento-osseous dysplasia, a presumptive diagnosis may be made based on the clinical and radiographic findings.) A specific diagnosis is critical because the treatment, biologic behavior, and prognosis of these pathoses vary greatly. Some fibro-osseous lesions only require monitoring, whereas others necessitate surgical recontouring or complete removal.

◆ FIBROUS DYSPLASIA

Fibrous dysplasia is a developmental tumorlike condition, characterized by replacement of normal bone by a proliferation of cellular fibrous connective tissue with irregular bony trabeculae. This sporadic condition results from postzygotic, activating mutations in the *GNAS* gene, which encodes the alpha subunit of a stimulatory G protein. Such mutations have not been detected in ossifying fibroma or cemento-osseous dysplasia.

Clinically, fibrous dysplasia may involve one bone or multiple bones; in some cases, involvement of multiple bones may occur in conjunction with cutaneous and endocrine abnormalities. The extent of disease depends on when the *GNAS* mutation occurs. During early embryonic development, mutation of a pluripotent stem cell can cause abnormalities in multiple cell types, including osteoblasts, melanocytes, and endocrine cells. In contrast, if the mutation occurs in a skeletal progenitor cell in a later stage of embryonic development, then only osteoblasts will be affected. Alternatively, if the mutation occurs during postnatal life, then osteoblasts in only a single bone will be affected. Furthermore, the parental origin of the mutated *GNAS* allele may affect the phenotype, because in certain cell types (such as pituitary somatotrophs) genomic imprinting results in expression of only the maternal allele.

Constitutive activation of G-protein signaling impairs osteoblastic differentiation in skeletal progenitor cells,

stimulates melanin production in melanocytes, and causes hyperplasia and hyperfunction of various endocrine cell types. In addition, mutated osteoblasts overexpress interleukin (IL)-6, which stimulates osteoclastic activity and may contribute to bone lesion expansion.

Clinical and Radiographic Features

Monostotic Fibrous Dysplasia

About 70% to 85% of patients with fibrous dysplasia have disease limited to a single bone **(monostotic fibrous dysplasia).** Monostotic fibrous dysplasia is diagnosed most often during the second and third decades of life. Males and females are affected with about equal frequency. Commonly involved sites include the craniofacial bones, ribs, femur, and tibia.

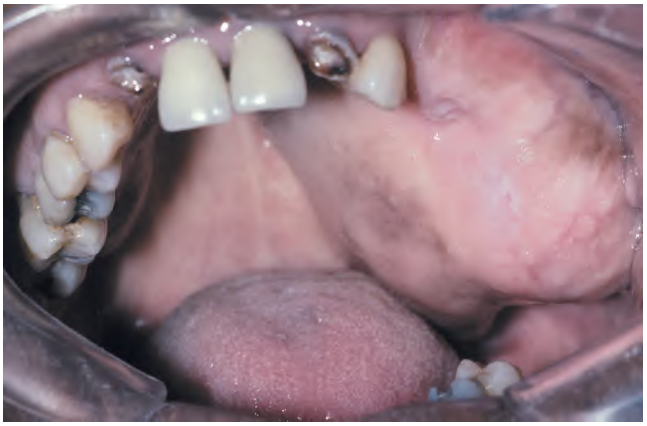
Among cases involving the jaws, the maxilla is affected more often than the mandible. There is a predilection for the posterior region. Although mandibular lesions are truly monostotic, maxillary lesions often extend to involve adjacent bones (e.g., zygoma, sphenoid, ethmoid, frontal bone, temporal bone, occiput)—in which case the term **craniofacial fibrous dysplasia** is appropriate. Painless, unilateral swelling is the most common clinical finding (Fig. 14-31). Growth is generally slow, and it is common for the patient to be aware of the condition for several years before seeking professional evaluation. Occasionally, however, the growth may be fairly rapid. Adjacent teeth may be displaced by the bony mass but usually remain firm.

The classic radiographic finding is a fine "ground-glass" opacification with poorly defined margins (Figs. 14-32 through 14-34). However, some lesions may appear radiolucent or mixed radiolucent-radiopaque. Mandibular lesions often exhibit buccolingual expansion and bulging of the inferior border. There may be superior displacement of the inferior alveolar canal. Periapical radiographs of the adjacent dentition may demonstrate narrowing of the periodontal ligament space and an ill-defined lamina dura that blends with the abnormal bone. Maxillary lesions often cause superior displacement of the sinus floor and obliteration of the antrum. In addition, extensive skull involvement may be evident (Fig. 14-35). Bone scintigraphy may aid in determining the extent of involvement and ruling out polyostotic disease.

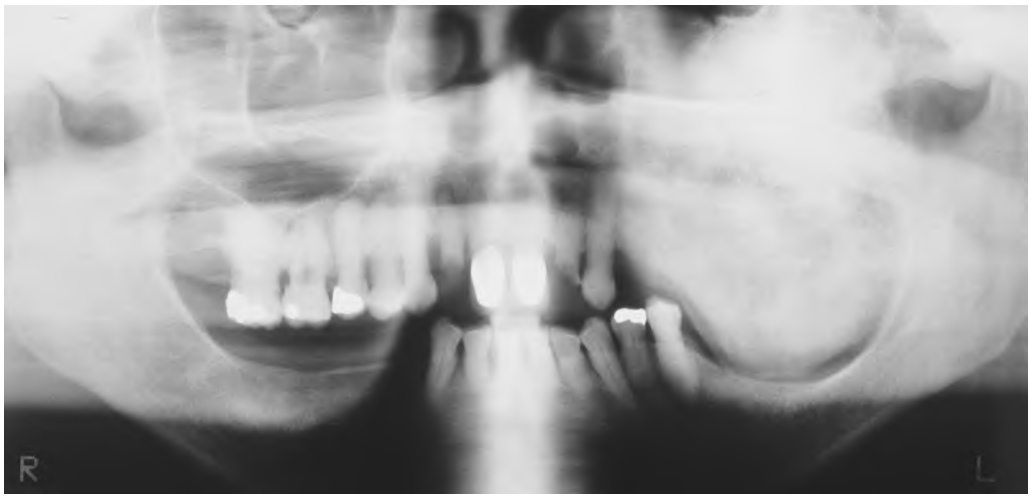
Polyostotic Fibrous Dysplasia; Jaffe-Lichtenstein Syndrome; McCune-Albright Syndrome

A minority of patients with fibrous dysplasia exhibits involvement of two or more bones **(polyostotic fibrous dysplasia).** Most patients with polyostotic disease are diagnosed before 10 years of age, and there is a female predilection. The number of involved bones varies from a few to 75% of the entire skeleton.

Presenting signs and symptoms typically are related to long bone involvement and include pain, pathologic fracture, limping, leg length discrepancy, and bowing deformity. Radiographic examination may reveal malformation



• **Fig. 14-31 Fibrous Dysplasia.** Expansile mass of the left maxilla in a 45-year-old woman. This lesion was known to have been present for at least 20 years.



• **Fig. 14-32 Fibrous Dysplasia.** Panoramic radiograph of the patient shown in Fig. 14-31. A diffuse "ground-glass" radiopacity is evident. (Courtesy of Dr. Richard Brock.)

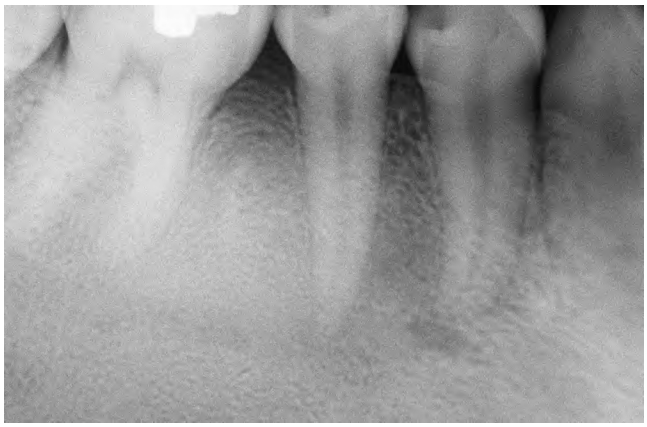


Fig. 14-33 Fibrous Dysplasia. Periapical radiograph showing a diffuse "ground-glass" radiographic appearance.

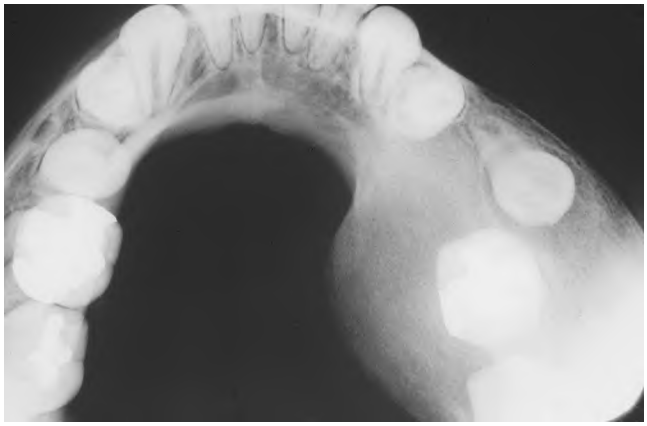


Fig. 14-34 Fibrous Dysplasia. Occlusal radiograph showing localized expansion of the mandible and the "ground-glass" radiographic appearance. The margins of the lesion are not well defined and blend into the adjacent bone. (From Waldron CA, Giansanti JS: Benign fibro-osseous lesions of the jaws: a clinical-radiologic-histologic review of 65 cases. I. Fibrous dysplasia of the jaws, *Oral Surg Oral Med Oral Pathol* 35:190–201, 1973.)

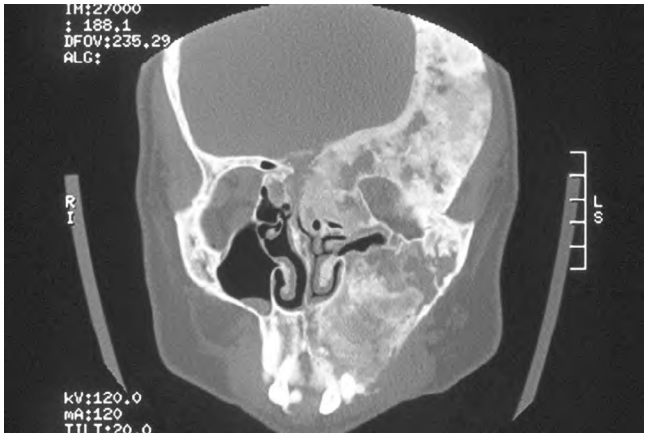


Fig. 14-35 Fibrous Dysplasia. Computed tomography (CT) image showing extensive involvement of the maxilla and skull.

of the proximal femur (known as *coxa vara, shepherd's crook deformity,* or *hockey stick deformity*). Involvement of the skull and jaws may result in facial asymmetry (Fig. 14-36). Craniofacial involvement may cause vision changes, hearing impairment, sinonasal congestion, and airway obstruction. Hypophosphatemia caused by renal phosphate wasting is a fairly common finding, which appears to be related to the release of fibroblast growth factor 23 *(FGF23)* by the affected bones.

A small subset of patients may exhibit polyostotic fibrous dysplasia in association with the following syndromes:

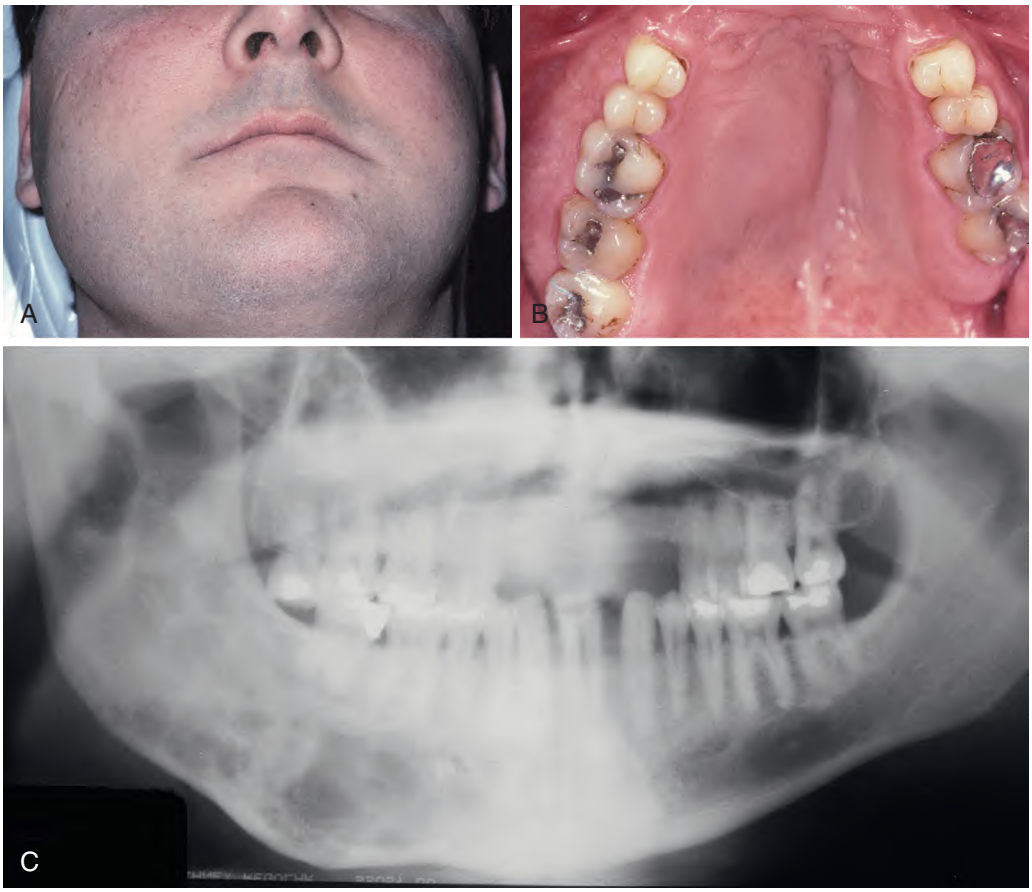
- **Jaffe-Lichtenstein syndrome**, characterized by polyostotic fibrous dysplasia and *café au lait* (coffee with milk) pigmentation
- **McCune-Albright syndrome**, characterized by polyostotic fibrous dysplasia, *café au lait* pigmentation, and multiple endocrinopathies
- **Mazabraud syndrome**, characterized by fibrous dysplasia and intramuscular myxomas

The *café au lait* pigmentation may be congenital and consists of well-defined, tan macules. The macules are generally unilateral and most commonly affect the skin, although oral mucosal involvement also is possible. The margins of the *café au lait* spots are typically very irregular, resembling a map of the coastline of Maine (Fig. 14-37). In contrast, the *café au lait* spots of neurofibromatosis (see page 495) tend to exhibit smooth borders (like the coast of California).

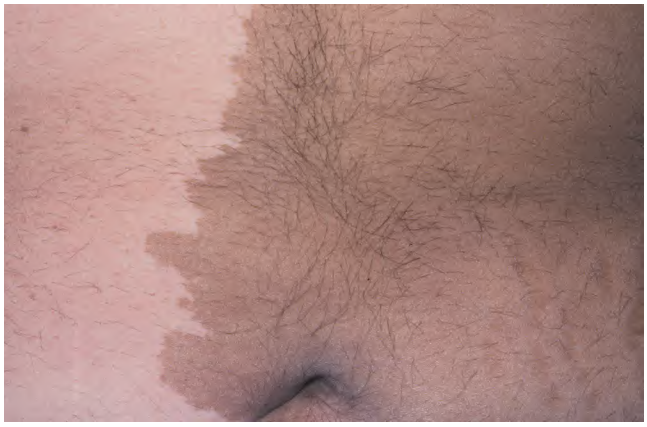
In McCune-Albright syndrome, the most common endocrine abnormality is sexual precocity, particularly in females. Menstrual bleeding, breast development, and pubic hair may be apparent within the first few months or years of life. Other possible endocrinopathies include hyperthyroidism, hyperparathyroidism, hypercortisolism, and excess growth hormone. In addition, in one study of craniofacial fibrous dysplasia mainly occurring in McCune-Albright syndrome, investigators have reported various dental anomalies, including tooth displacement, oligodontia, enamel hypoplasia, enamel hypomineralization, taurodontism, and retained deciduous teeth.

Histopathologic Features

Microscopic examination shows irregularly shaped trabeculae of immature (woven) bone in a cellular fibrous stroma (Fig. 14-38). At the periphery, the lesional bone fuses with normal bone, without a capsule or line of demarcation. The abnormal bony trabeculae tend to be thin and disconnected, with curvilinear shapes likened to Chinese characters. Osteoblastic rimming is usually absent or minimal, and peritrabecular clefting (artifactual retraction of the stroma from the bony trabeculae) is common. In addition, tiny calcified spherules rarely may be seen but are never numerous. In later stages, the woven bone is replaced by lamellar bone with roughly parallel trabeculae (Fig. 14-39). The rather monotonous pattern of calcification in fibrous dysplasia differs from the more haphazard mixture of woven



• **Fig. 14-36 Polyostotic Fibrous Dysplasia.** Jaffe-Lichtenstein syndrome. **A,** Young man exhibiting enlargement of the right maxilla and mandible. **B,** Intraoral photograph showing unilateral maxillary expansion. **C,** Panoramic radiograph showing ill-defined lesions of the right side of both jaws.



• **Fig. 14-37 Polyostotic Fibrous Dysplasia.** Jaffe-Lichtenstein syndrome. *Café au lait* pigmentation of the abdomen. This is the same patient as shown in Fig. 14-36.

bone, lamellar bone, and spheroid particles characteristic of ossifying fibroma and cemento-osseous dysplasia.

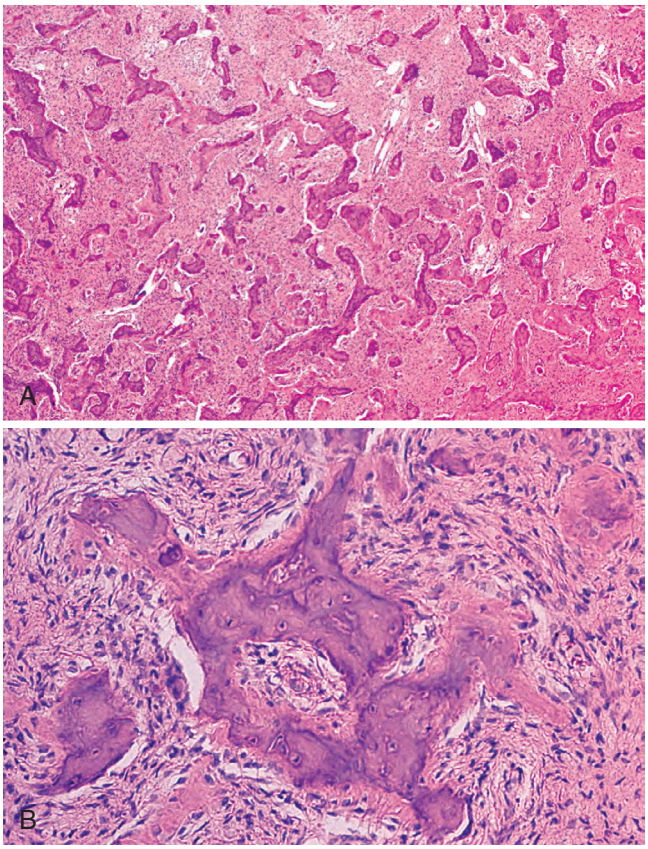
Fibrous dysplasia may appear more sclerotic in the jaw and skull than other sites. Microscopic variations include a pagetoid pattern (characterized by thick, interconnected bone trabeculae) and a hypercellular pattern (characterized by parallel bone trabeculae with numerous osteocytes and polarized osteoblastic rimming). Secondary aneurysmal bone cyst formation has been reported as well.

Genetic testing for *GNAS* mutations can be performed on lesional tissue or, possibly, peripheral blood samples. Such testing may be helpful when there is diagnostic uncertainty, but it exhibits low sensitivity and is not performed routinely.

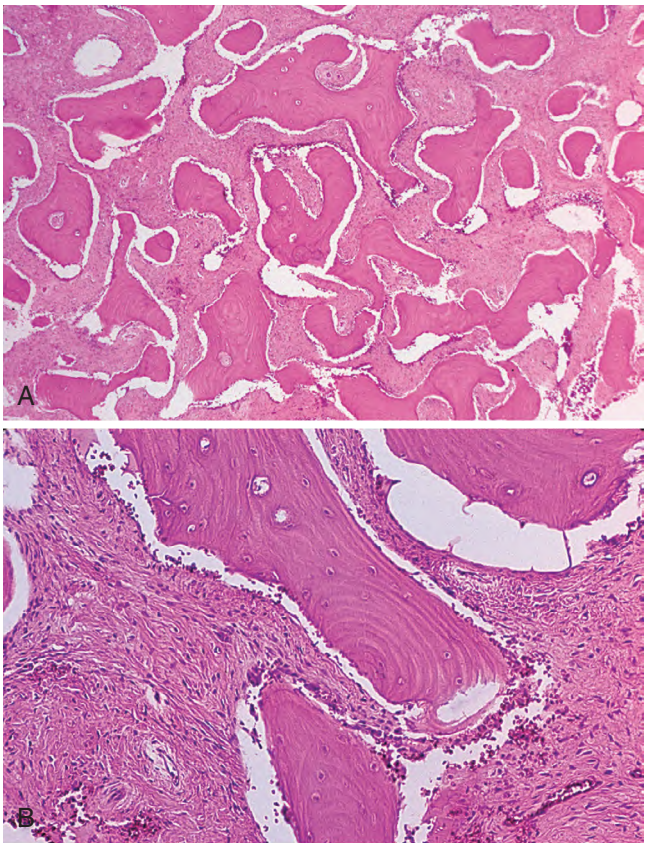
Treatment and Prognosis

Fibrous dysplasia tends to stabilize upon skeletal maturation, and spontaneous regression even has been reported in a few cases. Therefore, conservative management is preferred. Some lesions, nevertheless, exhibit continued growth into adulthood. The risk for severe deformity and complications is particularly elevated among patients with widespread polyostotic fibrous dysplasia—especially in the setting of McCune-Albright syndrome with uncontrolled growth hormone excess.

Patients with minimal cosmetic and functional disturbances may not require surgical treatment. For young patients with significant problems due to large or extensive lesions, surgical contouring, shaving, or other debulking



• **Fig. 14-38 Fibrous Dysplasia. A,** Irregularly shaped trabeculae of woven bone in a fibrous stroma. **B,** Medium-power view showing peripheral osteoid without osteoblastic rimming.



• **Fig. 14-39 Mature Fibrous Dysplasia. A,** This long-standing lesion shows separate, broad trabeculae of bone within fibrous connective tissue. **B,** Note the lamellar maturation of the bone.

procedures may be performed. However, subsequent regrowth may require additional surgery. Approximately 20% to 50% of patients show some regrowth after surgical debulking, and the risk for regrowth is greater among younger than older patients. Therefore, if possible, many authorities prefer to delay surgery until the disease is quiescent. Some investigators have proposed that serum alkaline phosphatase levels after incomplete surgical removal may be predictive of disease progression, although validation studies are needed.

Alternatively, complete surgical removal may be considered in some cases, such as monostotic lesions, very aggressive lesions, or lesions refractory to repeated debulking. Combined orthodontic treatment and orthognathic surgery may be performed to correct malocclusion. Successful placement of dental implants has been reported in a few cases, but additional studies are needed. Several reports suggest that bisphosphonates (e.g., IV pamidronate, oral alendronate) may help to relieve bone pain in fibrous dysplasia. However, well-designed studies are needed to confirm these findings, to assess the potential for inducing disease stabilization, and to evaluate the long-term safety of such treatment in young patients. Radiation therapy is contraindicated because of the risk for postirradiation bone sarcoma.

Transformation into malignancy, usually an osteosarcoma, is estimated to occur in less than 1% of patients with fibrous dysplasia. The risk for sarcomatous transformation is greatest among those with a history of radiation therapy, McCune-Albright syndrome, or Mazabraud syndrome. Rapid lesion growth, sudden onset of pain, neurosensory changes, or marked changes in radiographic appearance should alert the clinician to rule out malignant transformation.

◆ CEMENTO-OSSEOUS DYSPLASIAS (OSSEOUS DYSPLASIA)

Cemento-osseous dysplasia occurs in the tooth-bearing areas of the jaws and is probably the most common fibro-osseous lesion encountered in clinical practice. Because the histopathologic features share many similarities with fibrous dysplasia and ossifying fibroma, correct diagnosis can be problematic but is critical for appropriate management.

Some investigators have suggested that cemento-osseous dysplasia originates from the periodontal ligament, because of microscopic similarity and lesion proximity to this structure. Others believe this condition represents a defect in extraligamentary bone remodeling that may be triggered by local injury or, possibly, an underlying hormonal imbalance.

Clinical and Radiographic Features

Based on clinical and radiographic features, cemento-osseous dysplasia includes the following variants: (1) **focal,** (2) **periapical,** and (3) **florid.**

Focal Cemento-Osseous Dysplasia

Focal cemento-osseous dysplasia involves a single site. Before the concept of focal cemento-osseous dysplasia was clarified in the mid-1990s, most cases were misdiagnosed as a variant of ossifying fibroma.

About 90% of cases of focal cemento-osseous dysplasia occur in females, with an approximate mean age of 41 years and a predilection for the third to sixth decades. The lesion has been reported across ethnic groups—most often American blacks followed by East Asians and whites. In contrast to the periapical and florid variants, the focal variant seems to affect a greater proportion of whites, although this finding may be due to study population bias.

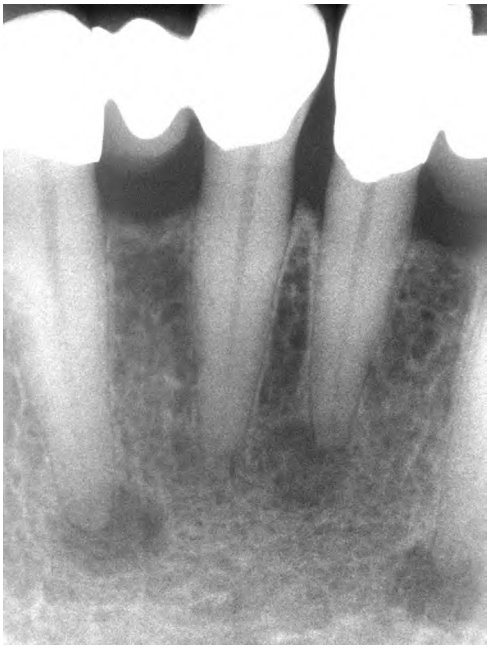
Focal cemento-osseous dysplasia most commonly involves the posterior mandible. The disease typically is asymptomatic and is detected incidentally by radiographic examination. Most lesions are smaller than 1.5 cm in diameter.

Radiographically, the lesion varies from completely radiolucent to densely radiopaque with a thin peripheral radiolucent rim. Most commonly, however, there is a mixed radiolucent and radiopaque pattern (Fig. 14-40). The borders tend to be well defined but slightly irregular. The lesions typically occur around tooth apices or in extraction sites. A focal lesion occasionally may represent an early stage in the transition to multifocal involvement, especially in black females.

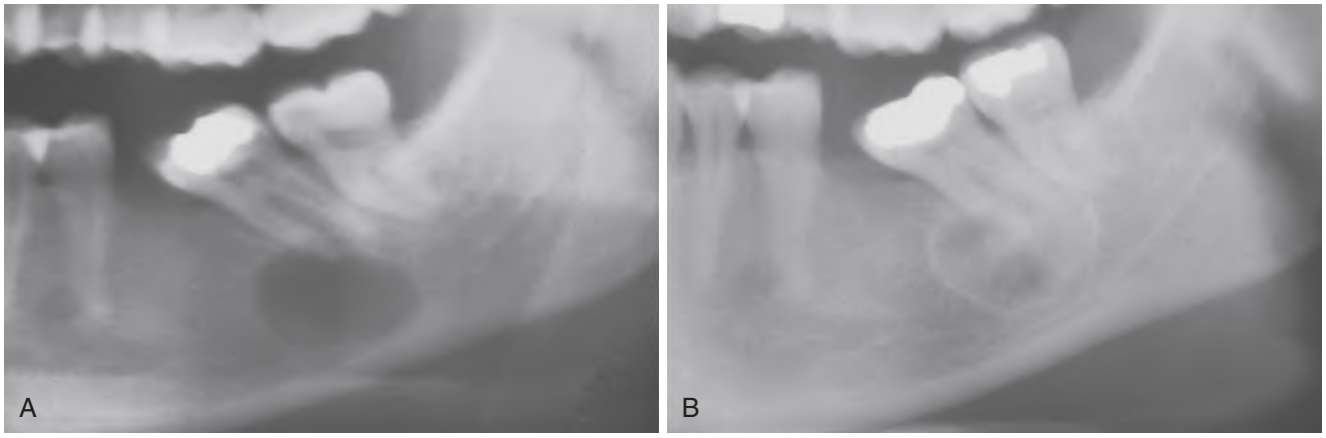
Periapical Cemento-Osseous Dysplasia (Osseous Dysplasia; Periapical Cemental Dysplasia; Periapical Cementoma)

Periapical cemento-osseous dysplasia predominantly involves the periapical region of the anterior mandible. Solitary lesions may occur, but multiple foci typically are present. There is a marked female predilection (female-to-male ratio ranging from 10:1 to 14:1), and approximately 70% of cases affect blacks. Most patients are diagnosed initially between 30 and 50 years of age, with the diagnosis almost never made in individuals younger than 20 years. The associated teeth are usually vital and seldom have restorations.

Periapical cemento-osseous dysplasia is an asymptomatic condition that often is discovered when radiographs are taken for other purposes. Early lesions appear as circumscribed periapical radiolucencies, similar to periapical granulomas or periapical cysts (Fig. 14-41). Adjacent lesions may fuse to form a linear radiolucency that envelops the



• **Fig. 14-41 Periapical Cemento-Osseous Dysplasia.** Periapical radiograph showing multiple radiolucent lesions at the apices of the anterior mandibular teeth. (Courtesy of Dr. Aaron Carner.)

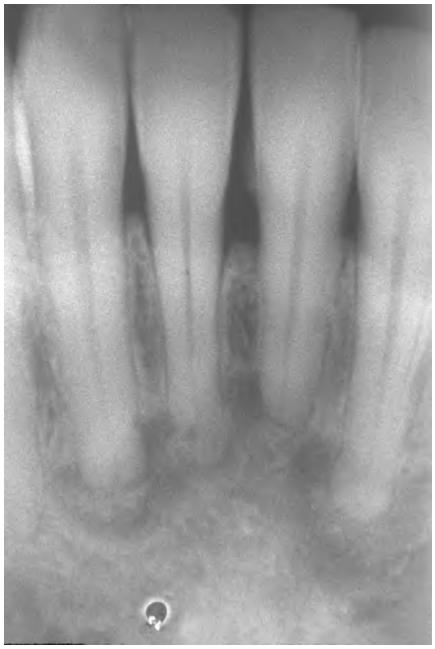


• **Fig. 14-40 Focal Cemento-Osseous Dysplasia. A,** A radiolucent area involves the edentulous first molar area and the apical area of the second molar. **B,** Radiograph of the same patient taken 9 years later showing a mixed radiolucent and radiopaque pattern.

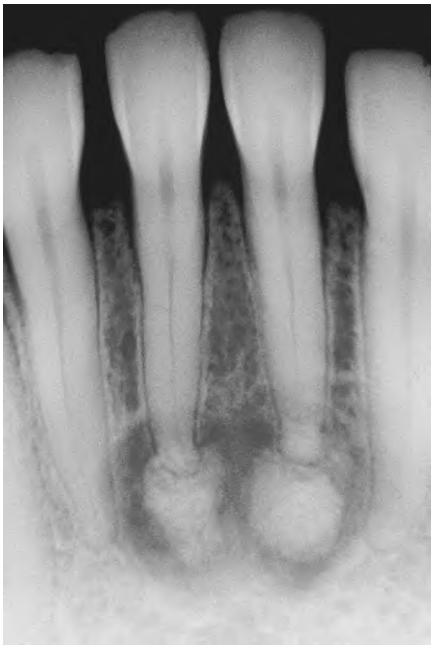
apices of several teeth (Fig. 14-42). Over time, the lesions tend to "mature" and become mixed radiolucent-radiopaque (Fig. 14-43). In the end stage, the lesions appear as circumscribed, dense radiopacities surrounded by narrow radiolucent rims. The periodontal ligament space usually appears intact, and fusion to the tooth is rare. Most lesions are nonexpansile with self-limiting growth; individual lesions seldom exceed 1.0 cm in diameter.

Florid Cemento-Osseous Dysplasia

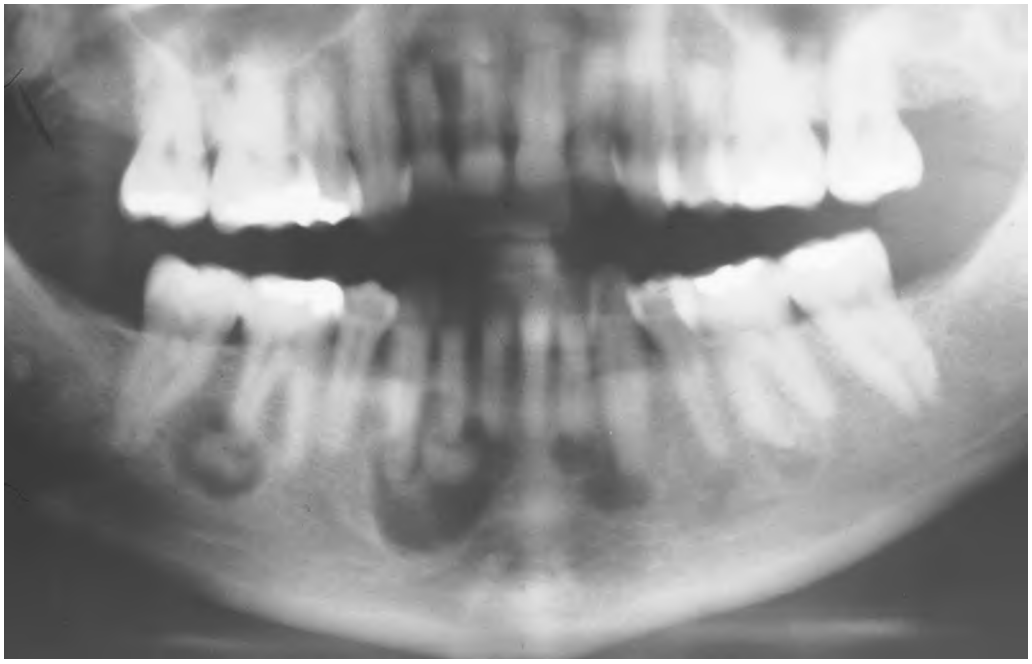
Florid cemento-osseous dysplasia exhibits multifocal involvement not limited to the anterior mandible. Although many cases affect only the posterior portions of the jaws, synchronous involvement of the anterior mandible may be observed as well (Fig. 14-44). Like the periapical pattern, this form predominantly affects black females (in some series, more than 90% of patients), with a marked



• **Fig. 14-42 Periapical Cemento-Osseous Dysplasia.** Later-stage lesions exhibiting significant mineralization.



• **Fig. 14-43 Periapical Cemento-Osseous Dysplasia.** Later-stage lesions exhibiting significant mineralization.



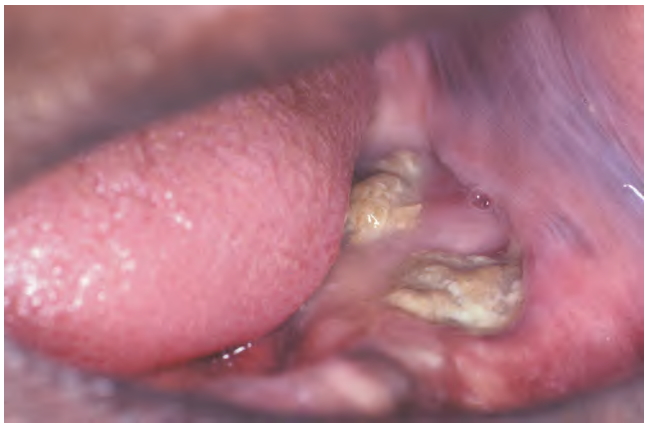
• **Fig. 14-44 Florid Cemento-Osseous Dysplasia.** Multiple mixed radiolucent and radiopaque lesions involving the anterior and posterior regions of the mandible.

predilection for middle-aged to older adults. An intermediate frequency among East Asian populations also has been described.

The lesions show a tendency for bilateral and fairly symmetrical involvement of the mandible, and occasionally there may be extensive involvement in all four quadrants. At times the disease may be asymptomatic and discovered only when radiographs are taken for unrelated reasons. In other cases, patients may have dull pain, alveolar sinus tracts, and exposure of yellowish, avascular bone to the oral cavity (Fig. 14-45). Although rarely prominent, some jaw expansion may be evident.

Radiographically, the lesions demonstrate a maturation pattern similar to that noted in the other forms of cemento-osseous dysplasia. Initially, the lesions are predominantly radiolucent but with time become mixed, then predominantly radiopaque with only a thin radiolucent rim (Fig. 14-46). On occasion, a lesion can become almost totally radiopaque and blend with the adjacent normal-appearing bone. Typically, the radiopacities remain separated from adjacent teeth with an intervening, intact periodontal ligament space. However, in some end-stage lesions, the cemento-osseous material may fuse with the tooth root surface to produce thickened root apices surrounded by radiolucency (or a "hypercementosis-like" appearance).

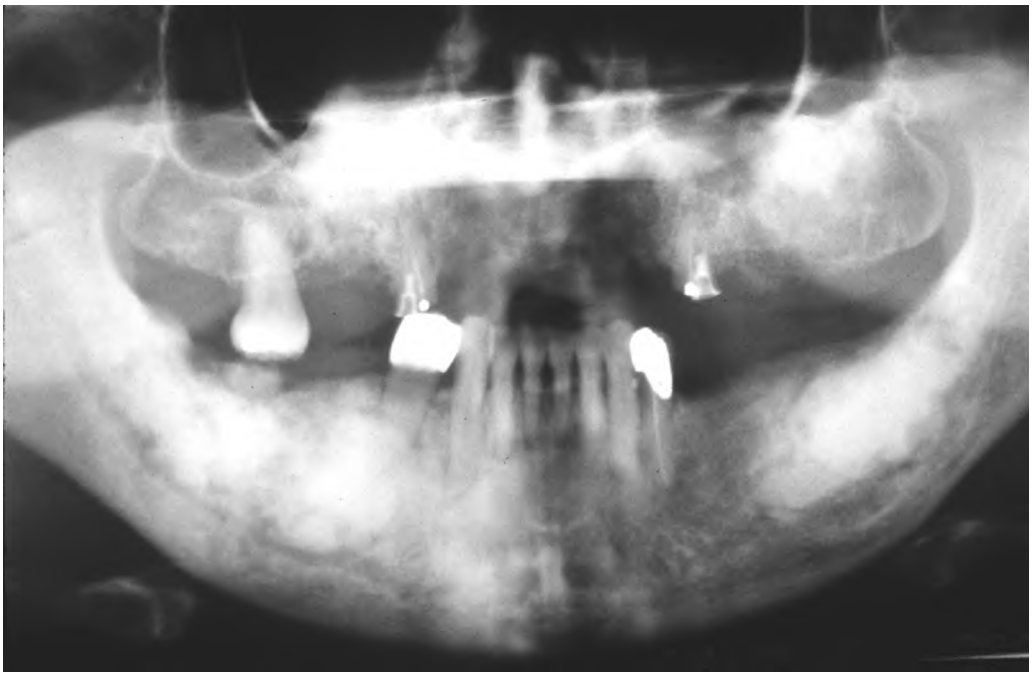
Both dentulous and edentulous areas may be affected, and involvement appears to be unrelated to the presence or absence of teeth. Sharply defined radiolucent areas, which on surgical exploration prove to be simple bone cysts (see page 589), may be intermixed with the other lesional elements. Investigators have suggested that these simple bone cysts may result from interstitial fluid obstruction by the fibro-osseous proliferation.



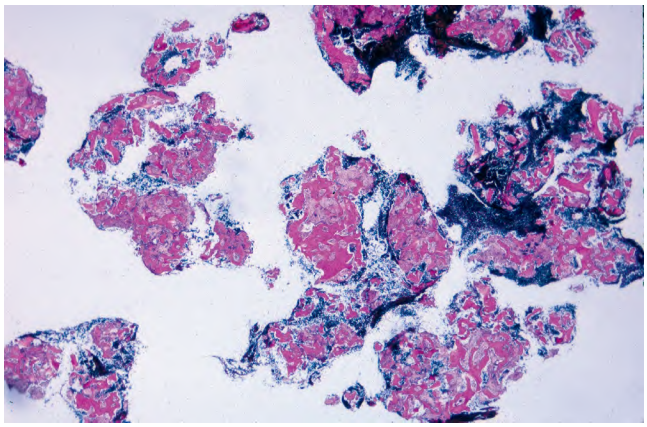
• **Fig. 14-45 Florid Cemento-Osseous Dysplasia.** Yellowish, avascular cementum-like material is beginning to exfoliate through the oral mucosa.

Histopathologic Features

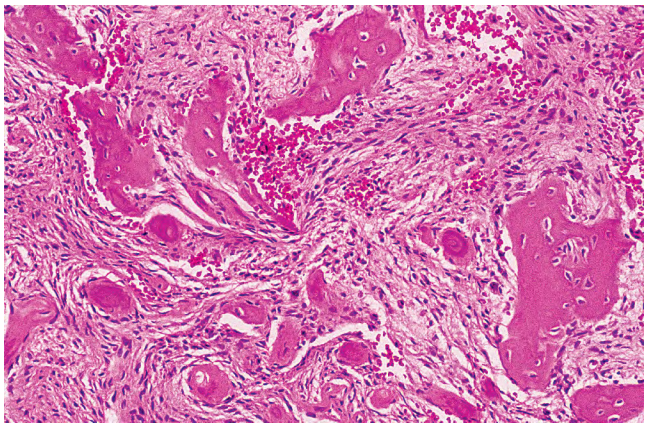
All three patterns of cemento-osseous dysplasia demonstrate similar histopathologic features. There are typically fragments of cellular fibrovascular connective tissue with scattered hemorrhage and a variable mixture of woven bone, lamellar bone, and cementum-like particles (Figs. 14-47 and 14-48). As the lesions mature, the ratio of fibrous connective tissue to mineralized material decreases. Over time, the bony trabeculae become thick and curvilinear, with shapes likened to ginger roots. In the final radiopaque stage,



• **Fig. 14-46 Florid Cemento-Osseous Dysplasia.** Multifocal radiopaque lesions of the posterior areas of the jaws. (Courtesy of Dr. Solomon Israel.)



• **Fig. 14-47 Cemento-Osseous Dysplasia.** Low-power photomicrograph showing fragments of cellular fibrous connective tissue containing scattered trabeculae of bone.



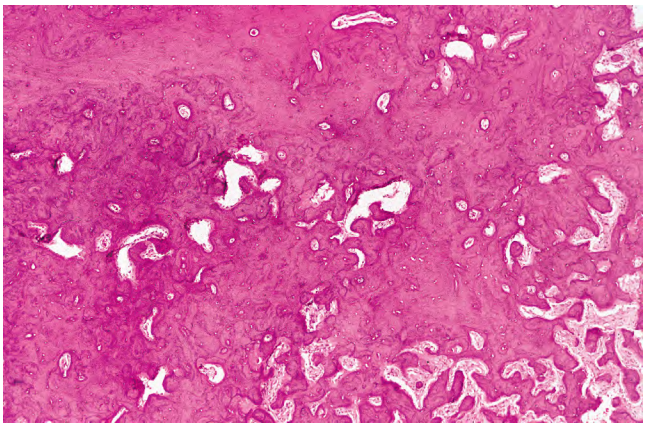
• **Fig. 14-48 Cemento-Osseous Dysplasia.** High-power photomicrograph showing spicules of bone and cementum-like hard tissue within moderately cellular fibrous connective tissue. Note the hemorrhage around the bony trabeculae.

the individual trabeculae fuse to form sheetlike or globular masses of sclerotic, disorganized cemento-osseous material (Fig. 14-49).

Diagnosis

In most instances of periapical or florid cemento-osseous dysplasia, the distinctive clinical and radiographic findings (e.g., a black female patient with multiquadrant involvement or multiple lesions involving vital lower incisor teeth) allow a strong presumptive diagnosis. In contrast, the features of focal cemento-osseous dysplasia tend to be less specific, and biopsy often is needed for diagnosis.

In particular, distinguishing focal cemento-osseous dysplasia from ossifying fibroma can be difficult. However, the findings at surgery may be helpful in discriminating between these two lesions. Before the final sclerotic stage, cemento-osseous dysplasia consists of gritty tissue that the surgeon typically curettes into small fragments during biopsy. In contrast, ossifying fibromas tend to separate cleanly and are removed in one or several large masses. Microscopically,



• **Fig. 14-49 Cemento-Osseous Dysplasia.** Late-stage lesion showing a sclerotic mass of cemento-osseous material.

both lesion types demonstrate a mixture of bone and cementum-like particles, although subtle histopathologic differences may be appreciated. The bony trabeculae in ossifying fibroma tend to be more delicate and show more prominent osteoblastic rimming compared to those in cemento-osseous dysplasia. Also, the cementum-like particles in cemento-osseous dysplasia are irregularly shaped and often exhibit retraction from the adjacent stroma, whereas those in ossifying fibroma are more ovoid and often demonstrate brush borders in intimate association with the adjacent stroma. Although ossifying fibroma can exhibit peripheral hemorrhage, cemento-osseous dysplasia typically reveals hemorrhage throughout the lesion and sinusoidal vascularity in close association with the bony trabeculae.

Treatment and Prognosis

Cemento-osseous dysplasia does not appear to be neoplastic and, therefore, generally does not require removal. During the predominantly radiolucent phase, the lesions cause few problems. However, in the sclerotic phase, the lesions tend to be hypovascular and prone to necrosis and secondary infection with minimal provocation. For the asymptomatic patient, the best management consists of regular recall examinations with prophylaxis and oral hygiene reinforcement to control periodontal disease and prevent tooth loss.

Because the onset of symptoms usually is associated with exposure of the sclerotic masses to the oral cavity, surgical procedures (e.g., biopsy, elective tooth extraction) should be avoided. In some instances, symptoms begin after lesion exposure resulting from progressive alveolar atrophy under a denture. Therefore, affected patients should be encouraged to retain their teeth. Dental implant placement in an area of cemento-osseous generally is not recommended. Management of the symptomatic patient who has developed secondary osteomyelitis is more difficult. Antibiotics may be indicated but often are not effective. Sequestration of the sclerotic cementum-like masses occurs slowly and is followed by healing. Saucerization of dead bone may speed healing. When simple bone cysts arise within foci of

cemento-osseous dysplasia, surgical exploration is necessary to establish the diagnosis. These simple bone cysts often do not heal as rapidly as those noted in younger patients without cemento-osseous dysplasia. In some cases the cysts persist or enlarge after surgical intervention; when they fill in, the bone retains an abnormal radiographic appearance. Thorough curettage of the cyst and the surrounding fibro-osseous proliferation may assist healing.

Some investigators have noted a rare subset of cases (termed *expansive osseous dysplasia*) that exhibit progressive growth but otherwise typical clinicopathologic features of cemento-osseous dysplasia. Such lesions have been reported most often in the anterior mandible of African black females and typically require surgical removal.

Overall, the prognosis is good. Development of a sarcoma within an area of cemento-osseous dysplasia has been reported but is extremely rare.

◆ FAMILIAL GIGANTIFORM CEMENTOMA

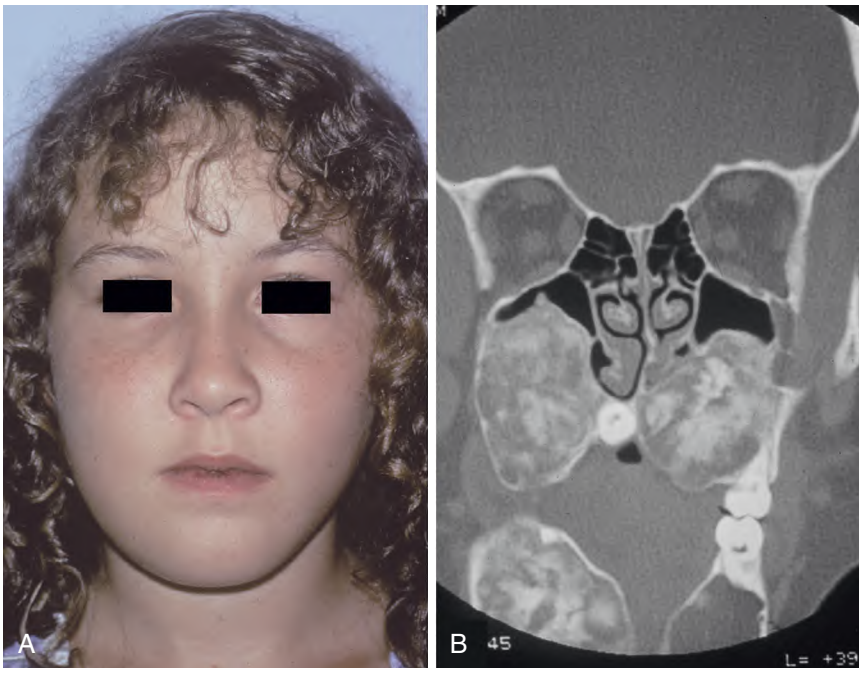
Although the term *gigantiform cementoma* has been used in the past as a synonym for florid cemento-osseous dysplasia, most authorities now restrict use of this term to a rare hereditary disorder known as **familial gigantiform cementoma.** This disorder exhibits an autosomal dominant pattern of transmission with high penetrance and variable expressivity. It is characterized by a cemento-osseous proliferation involving multiple quadrants of the jaws and often resulting in massive expansion.

Based on microscopic similarities, some authors consider familial gigantiform cementoma to be a variant of cemento-osseous dysplasia. However, a tendency for progressive lesion growth suggests a truly neoplastic process; thus, many authors prefer to regard familial gigantiform cementoma as a distinct neoplasm or a subtype of ossifying fibroma.

Sporadic cases with clinical and radiographic features similar to those of familial gigantiform cementoma also have been reported using various terms, including *nonfamilial gigantiform cementoma, multiple (cemento-) ossifying fibromas, bilateral ossifying fibromas,* and *expansive osseous dysplasia.* Whether such cases represent spontaneous mutations, multiple ossifying fibromas, or unusual progressive forms of cemento-osseous dysplasia remains unclear. Molecular genetic studies are needed to improve the understanding and appropriate classification of this problematic disease spectrum.

Clinical and Radiographic Findings

Unlike florid cemento-osseous dysplasia, familial gigantiform cementoma exhibits neither a predilection for blacks nor a significant gender predilection. Although blacks may be affected, most reported families are white or Asian. Radiographic alterations may begin to develop during the first decade of life. By adolescence, most patients exhibit clinically obvious expansion of the jaws (Fig. 14-50). The lesions affect multiple quadrants, often with simultaneous involvement of the maxilla and mandible. Lesion growth may be rapid or slow. In a few reported cases, especially rapid growth has been noted during pregnancy. Although the course is variable, many patients develop significant facial deformity,



• **Fig. 14-50 Familial Gigantiform Cementoma.** Young woman with massive lesions involving all four quadrants of the jaws. (**A,** From Abdelsayed RA, Eversole LR, Singh BS, et al: Gigantiform cementoma: clinicopathologic presentation of 3 cases, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 91:438–444, 2001; **B,** Courtesy of Dr. Rafik Abdelsayed.)

as well as impaction, malposition, and malocclusion of the involved dentition. If not treated, then the osseous enlargement eventually ceases during the fifth decade.

Radiographically, the lesions initially may appear as multiple periapical radiolucencies, resembling cemento-osseous dysplasia. With progression, the affected sites expand to replace much of the normal bone within the involved quadrant and develop a mixed radiolucent and radiopaque pattern. With further maturation, the lesions become predominantly radiopaque but often maintain a thin radiolucent rim. As noted in cemento-osseous dysplasia, the affected bone during the final radiopaque stage is very sensitive to inflammatory stimuli and becomes necrotic with minimal provocation.

Some investigators have reported elevated serum alkaline phosphatase that subsequently declines after surgical removal of the osseous proliferations. Anemia also has been reported in a number of affected females in different kindreds. In one family, two affected females demonstrated multifocal polypoid adenomas of the uterus that were associated with chronic hemorrhage and apparently caused anemia.

Furthermore, in a few kindreds diagnosed with familial gigantiform cementoma, bone fragility and a tendency for long bone fractures have been noted. However, such cases actually may represent examples of another entity known as *gnatho-diaphyseal dysplasia* (a heritable autosomal dominant condition characterized by *GDD1* [or *TMEM16E*] mutations, diffuse fibro-osseous lesions of the jaws with a prominent psammomatoid body component, bone fragility, and bowing/cortical sclerosis of long bones).

Histopathologic Features

Histopathologically, familial gigantiform cementoma shows the same spectrum of changes seen in florid cemento-osseous dysplasia, and the two cannot be distinguished microscopically.

Treatment and Prognosis

Before the final sclerotic stage, shave-down surgical procedures typically are unsuccessful because the dysplastic tissue rapidly regrows. Once the lesions are predominantly radiopaque, partial removal may lead to sequestration of the remaining affected bone. Therefore, if feasible, complete resection and reconstruction are recommended. Because familial gigantiform cementoma might be associated with polypoid adenomas of the uterus, gynecologic evaluation is prudent for female patients—especially those with anemia.

◆ OSSIFYING FIBROMA (CEMENTIFYING FIBROMA; CEMENTO-OSSIFYING FIBROMA)

Although it can resemble focal cemento-osseous dysplasia radiographically and histopathologically, **ossifying fibroma** is a true neoplasm with significant growth potential. Ossifying fibromas are relatively rare. Many examples reported in the older literature actually represent cases of focal cemento-osseous dysplasia.

The neoplasm is composed of fibrous tissue with a variable mixture of bony trabeculae and cementum-like spherules. In the past, investigators have suggested that the origin of these tumors is odontogenic or from periodontal ligament. However, such an origin is questionable, because microscopically identical neoplasms with cementum-like differentiation also have been reported in the orbital, frontal, ethmoid, sphenoid, and temporal bones. Today, many authorities regard the cementum-like material in ossifying fibromas as a variation of bone. Indeed, some contend that bone and cementum are essentially the same mineralized product and only can be distinguished based on anatomic location (i.e., presence of cementum along root surfaces). Although various terms (including *ossifying fibroma, cemento-ossifying fibroma,* and *cementifying fibroma*) continue to be used for this tumor, most authorities consider it to be an osteogenic neoplasm. In this section, all of these variations are combined under the term *ossifying fibroma.*

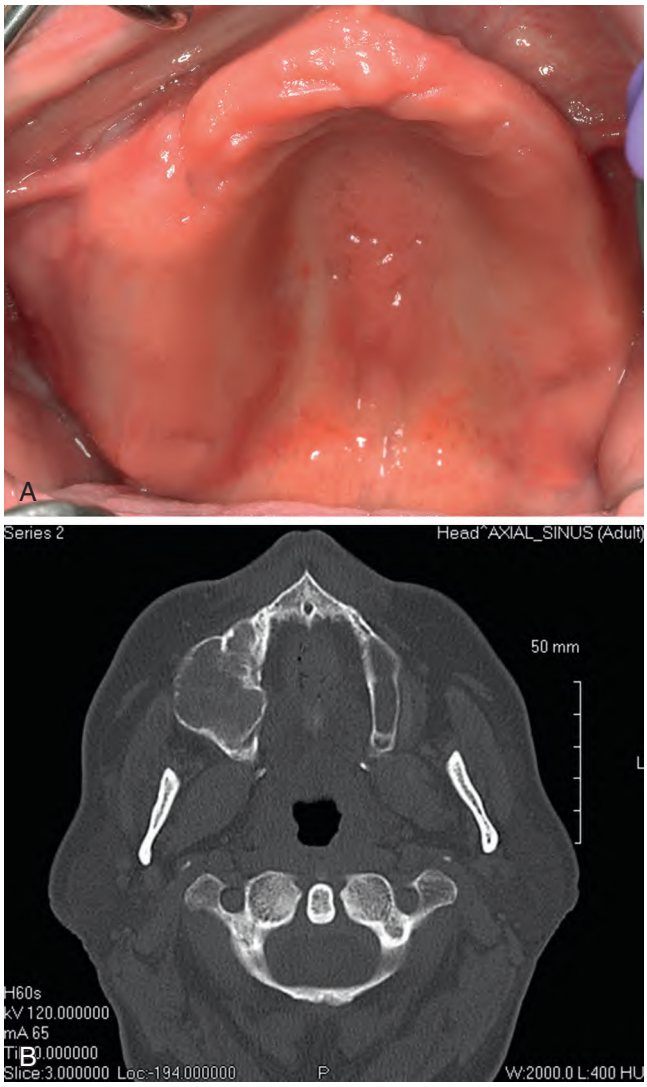
Mutations in the tumor suppressor gene *HRPT2* (which encodes the parafibromin protein) have been identified in patients with *hyperparathyroidism-jaw tumor syndrome.* This rare syndrome is characterized by parathyroid adenoma or carcinoma, ossifying fibromas of the jaws, renal cysts, and Wilms tumors. In addition, investigators have found *HRPT2* gene mutations in a few sporadic cases of ossifying fibroma of the jaws. However, the potential pathogenetic role of *HRPT2* mutations in ossifying fibroma remains poorly understood.

Clinical and Radiographic Features

Ossifying fibromas occur over a broad age range, with a peak in the third and fourth decades of life. There is a female predilection, with the mandible involved far more often than the maxilla. The mandibular premolar and molar area is the most common site. Maxillary lesions tend to involve the antrum.

Small lesions are often asymptomatic and may be detected only by radiographic examination. Larger tumors may produce painless jaw swelling (Fig. 14-51) and obvious facial asymmetry. Some lesions may become massive and cause considerable deformity. Pain and paresthesia are rare. Most examples are solitary; however, multiple synchronous lesions have been reported very rarely—either as an isolated finding or as a component of hyperparathyroidism-jaw tumor syndrome.

Depending on the amount of calcification, radiographic examination typically shows a well-defined, unilocular radiolucency or mixed radiolucency and radiopacity. Some examples show a sclerotic border. Multilocular lesions comprise only a minority of cases. True ossifying fibromas that appear largely radiopaque with only a thin radiolucent periphery are infrequent; many reported examples with this



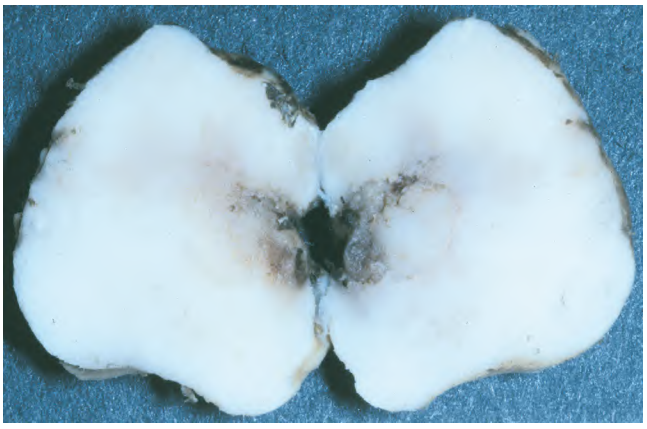
• **Fig. 14-51 Ossifying Fibroma.** Clinical image **(A)** and computed tomography (CT) scan **(B)** showing a large, expansile lesion of the posterior maxilla. (Courtesy of Dr. Greg Cobetto.)

radiographic pattern likely represent end-stage focal cemento-osseous dysplasia. Buccolingual bony expansion is common; in addition, large mandibular lesions often demonstrate a characteristic downward bowing of the inferior cortex. The adjacent teeth may exhibit root divergence or root resorption.

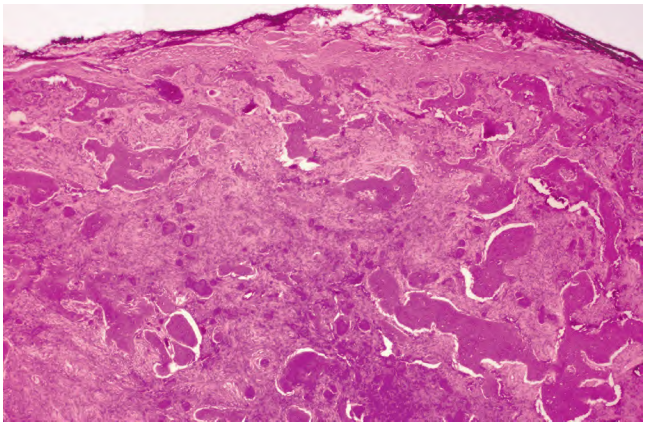
Histopathologic Features

At surgery, the lesion tends to separate easily from the surrounding bone; thus, the tumor usually is submitted as one mass or a few large pieces (Fig. 14-52). Grossly and microscopically, most lesions are well demarcated but unencapsulated. However, a fibrous capsule may be present in some cases.

Microscopic examination shows cellular fibrous tissue with mineralized product (Fig. 14-53). The mineralized component may include a variable admixture of osteoid,



• **Fig. 14-52 Ossifying Fibroma.** Gross specimen showing a well-circumscribed tumor that shelled out in one piece and subsequently was hemisected.

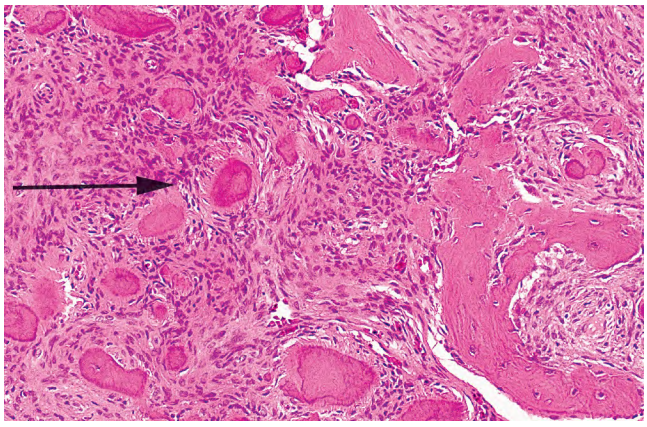


• **Fig. 14-53 Ossifying Fibroma.** This low-magnification photomicrograph shows a well-circumscribed solid tumor mass. Trabeculae of bone and droplets of cementum-like material can be seen forming within a background of cellular fibrous connective tissue.

bone, and basophilic acellular (or "cementum-like") spherules. The bony trabeculae vary in size and frequently demonstrate both woven and lamellar patterns. Peripheral osteoid and osteoblastic rimming are usually present. The cementum-like spherules often demonstrate brush borders that blend into the adjacent connective tissue (Fig. 14-54). Significant intralesional hemorrhage is unusual. The heterogeneous mineralized product characteristic of ossifying fibroma differs from the more uniform osseous pattern of fibrous dysplasia. Rarely, a lesion may exhibit combined features of ossifying fibroma and central giant cell granuloma.

Treatment and Prognosis

The circumscribed nature of the ossifying fibroma generally permits enucleation of the tumor with relative ease. Large lesions that have caused considerable bone destruction may necessitate surgical resection and bone grafting. Recurrence after complete removal is uncommon; one systematic review of the literature has reported a 12% recurrence rate. Overall,



• **Fig. 14-54 Ossifying Fibroma.** High-power photomicrograph showing a mixture of woven bone and cementum-like material. Note the spherules demonstrating peripheral brush borders *(arrow).*

the prognosis is very good, and there is no apparent potential for malignant transformation.

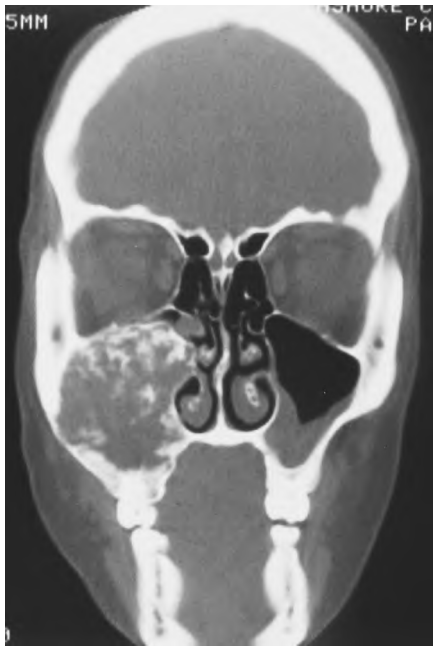
◆ JUVENILE OSSIFYING FIBROMA (JUVENILE ACTIVE OSSIFYING FIBROMA; JUVENILE AGGRESSIVE OSSIFYING FIBROMA)

The **juvenile ossifying fibroma** is a controversial lesion that has been distinguished from conventional ossifying fibroma on the basis of patient age, site predilection, and clinical behavior. The term includes two distinct clinicopathologic variants: 1) **trabecular** and 2) **psammomatoid.** Among lesions involving the craniofacial skeleton, the psammomatoid variant has been reported more frequently than the trabecular variant.

The etiopathogenesis is poorly understood. In a small number of orbital psammomatoid ossifying fibromas, investigators have demonstrated nonrandom chromosomal breakpoints at Xq26 and 2q33 resulting in (X;2) translocation. Among studies conducted thus far, failure to detect *GNAS* or *HRPT2* mutations in juvenile ossifying fibromas suggests that these lesions are distinct from fibrous dysplasia and conventional ossifying fibromas.

Clinical and Radiographic Features

Juvenile ossifying fibromas most often arise in children, adolescents, and young adults; however, a broader age range has been reported for the psammomatoid variant (3 months to 72 years) than the trabecular variant (2 to 33 years). Among various reported case series, the average age at diagnosis is somewhat younger for the trabecular variant (range from 8½ to 12 years) than the psammomatoid variant (range from 16 to 33 years). Most authors report either a slight male predilection or no significant gender predilection. The trabecular variant arises primarily in the jaws, whereas the psammomatoid variant predominantly involves



• **Fig. 14-55 Juvenile Ossifying Fibroma.** Computed tomography (CT) scan showing a large tumor involving the left maxilla and maxillary sinus of a 12-year-old girl. Clinically, the tumor was growing rapidly.

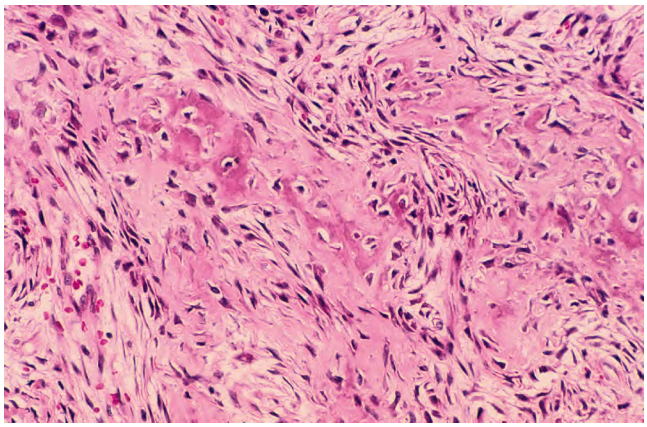
the paranasal sinuses and orbital region. In both variants, gnathic involvement favors the maxilla.

Although some cases exhibit slow, progressive enlargement, others exhibit rapid, aggressive growth. Small lesions may be discovered incidentally during routine radiographic examination, whereas larger lesions tend to cause painless swelling and obvious facial enlargement. Pain and paresthesia are infrequent findings. Tumors arising in the paranasal sinuses may penetrate the orbital, nasal, and cranial cavities. Nasal obstruction, epistaxis, sinusitis, headaches, proptosis, diplopia, and blindness may result. Rarely, intracranial extension may cause encephalitis and meningitis.

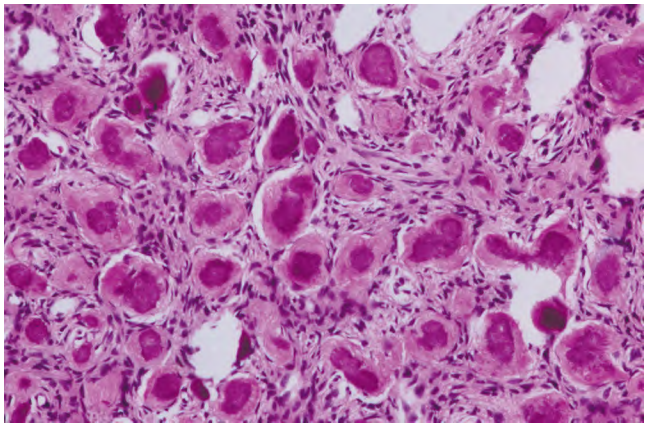
Radiographic examination typically shows a well-circumscribed radiolucency or mixed radiolucency and radiopacity (Fig. 14-55). A sclerotic border may be evident in some cases. "Ground-glass" opacification or a multilocular "honeycomb" pattern also may be observed. Aggressive lesions often cause expansion and cortical thinning or perforation. Similar to conventional ossifying fibromas, juvenile ossifying fibromas may produce downward bowing of the inferior cortex of the mandible. Jaw lesions also can cause tooth displacement, root resorption, and failure of tooth development. Sinus involvement may appear radiographically as cloudy opacification mimicking sinusitis.

Histopathologic Features

Both patterns are typically well demarcated but unencapsulated. The fibrous stromal component exhibits variable degrees of cellularity and collagenization. Some zones may be so hypercellular that the cytoplasm of individual cells is hard to discern. Other areas may appear myxomatous with



• **Fig. 14-56 Juvenile Ossifying Fibroma, Trabecular Variant.** Trabeculae of cellular woven bone are present in a cellular fibrous stroma.



• **Fig. 14-57 Juvenile Ossifying Fibroma, Psammomatoid Variant.** Cellular fibrous connective tissue containing spherical ossicles with basophilic centers and peripheral eosinophilic rims.

a tendency for pseudocystic degeneration. Hemorrhage and small clusters of multinucleated giant cells are common. Mitotic figures may be present but are neither numerous nor atypical. In the trabecular variant, microscopic zones of hemorrhage, giant cells, and pseudocystic degeneration may correlate with grossly evident brown, curvilinear strands on the tumor's cut surface.

The mineralized component differs between the two variants. The trabecular variant shows irregular strands of highly cellular osteoid encasing plump and irregular osteocytes (Fig. 14-56). These strands often are lined by plump osteoblasts and multinucleated osteoclasts. In contrast, the psammomatoid variant exhibits concentric lamellated ossicles that vary in size and may be round, ovoid, or crescentic in shape. The ossicles typically appear basophilic with peripheral eosinophilic osteoid rims and brush borders that blend into the surrounding stroma (Fig. 14-57).

Secondary formation of a simple bone cyst or aneurysmal bone cyst also is possible. The latter may manifest clinically with rapid, aggressive growth.

Treatment and Prognosis

For small lesions, complete local excision or thorough curettage appears adequate. For large or aggressive lesions, wider resection may be required.

In contrast to the negligible recurrence rate for conventional ossifying fibromas, recurrence rates of 30% to 58% have been reported for juvenile ossifying fibromas. Many reported recurrences actually may represent tumor persistence after incomplete surgical removal. Malignant transformation has not been documented. Tumor-related deaths are extremely rare and primarily result from complications caused by direct intracranial extension.

◆ OSTEOMA

Osteomas are benign tumors composed of mature compact or cancellous bone. Osteomas primarily involve the craniofacial skeleton and rarely, if ever, are diagnosed in other bones. They may arise on the bone surface **(periosteal, peripheral,** or **exophytic osteomas)** or within medullary bone **(endosteal** or **central osteomas). Extraskeletal osteomas,** typically located within muscle or the dermis of the skin **(osteoma cutis),** also are possible.

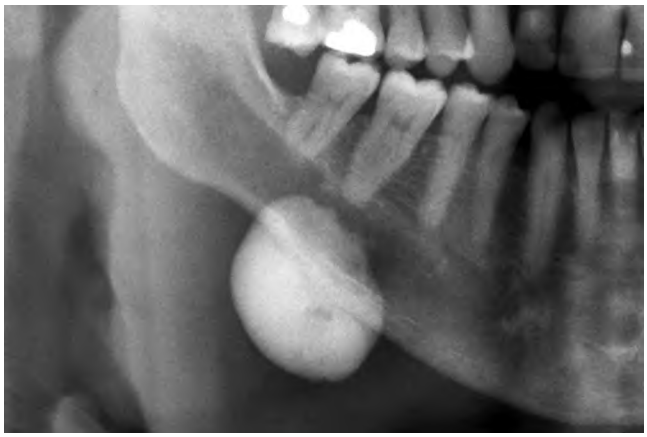
There is some question whether osteomas represent true neoplasms, and not all lesions designated as osteomas may represent a single entity. Some likely represent the end stage of an injury, inflammatory process, or hamartomatous process, such as fibrous dysplasia. Because some osteomas arise in areas where muscle attaches to bone, investigators have hypothesized that muscle traction may be a contributory factor. Common palatal tori, mandibular tori, and buccal exostoses (see page 18) are not considered to be osteomas, although they are histopathologically identical. Because many osteomas are small and asymptomatic, there is little reliable information regarding their frequency and demographic distribution.

Clinical and Radiographic Features

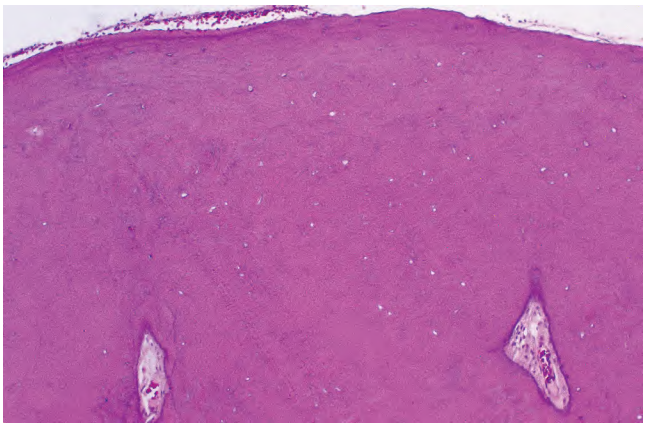
Osteomas of the jaws most often are detected in adults, with a predilection for the mandibular body and condyle. Lesions involving the mandibular body frequently are found on the lingual surface adjacent to the premolars or molars. Less common mandibular locations include the angle (particularly at the inferior border), coronoid process, and ramus.

Most examples are solitary and asymptomatic with very slow growth. Pain, tooth displacement, and tooth impaction have been reported in a minority of cases. Rarely, a lesion may become especially large and produce marked facial deformity. Periosteal osteomas appear as polypoid or sessile masses on the bone surface, whereas endosteal osteomas may not be evident clinically unless they are large enough to cause expansion. Multifocal lesions may arise in association with Gardner syndrome (see page 606).

Osteomas involving the mandibular condyle may limit mouth opening or cause malocclusion, with deviation of



• **Fig. 14-58 Osteoma.** Panoramic radiograph showing a uniformly sclerotic mass arising from the surface of the posterior mandible. (Courtesy of Dr. James Lemon.)



• **Fig. 14-59 Osteoma.** This compact osteoma is composed of dense bone, with only minimal marrow elements.

the dental midline and chin toward the unaffected side. Pain and facial swelling also are possible. Some authorities consider condylar osteomas to be true neoplasms, whereas others designate them as *hyperostoses.* Distinguishing this process from condylar hyperplasia can be difficult; however, a condylar osteoma typically is lobulated, whereas a hyperplastic condyle usually retains its original shape.

Paranasal sinus osteomas are even more common than gnathic lesions. The frontal sinus is most often involved, followed by the ethmoid and maxillary sinuses. Such lesions are usually asymptomatic, although pain, swelling, sinusitis, and nasal discharge are possible. In rare cases, paranasal sinus osteomas may expand into orbital structures and may result in proptosis, diplopia, and decreased visual acuity. Infrequently, intracranial extension can cause meningitis, cerebral abscesses, and intracranial mucoceles.

Radiographically, osteomas appear as circumscribed sclerotic masses. Periosteal osteomas may show a uniformly sclerotic pattern or may demonstrate a sclerotic periphery with central trabeculation (Fig. 14-58). Smaller endosteal osteomas are difficult, if not impossible, to differentiate radiographically from condensing osteitis, focal chronic sclerosing osteomyelitis, or idiopathic osteosclerosis. The true nature of these osteomas can be confirmed only by documentation of continued growth.

Histopathologic Features

Compact osteomas are composed of normal-appearing, dense bone with minimal marrow (Fig. 14-59). **Cancellous** osteomas are composed of bony trabeculae and fibrofatty marrow. Osteoblastic activity may be fairly prominent.

Treatment and Prognosis

Small, asymptomatic osteomas may not require treatment but should be observed periodically. Conservative excision is appropriate for large or symptomatic osteomas of the mandibular body. Because they are frequently symptomatic, condylar osteomas usually are removed by local resection or condylectomy. Symptomatic paranasal sinus osteomas may be removed endoscopically or via an open surgical approach. Recurrence after excision is extremely rare, and there are no reports of malignant transformation.

GARDNER SYNDROME

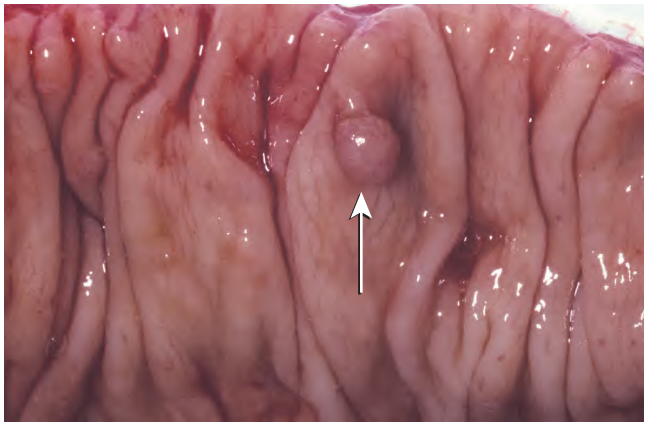
Gardner syndrome is a rare disorder, characterized by intestinal polyps as well as various abnormalities of bone, teeth, skin, soft tissue, and other sites. This syndrome represents a variant of *familial adenomatous polyposis*—an inherited condition in which patients develop hundreds to thousands of intestinal adenomatous polyps, with nearly 100% progression to colorectal cancer if left untreated. Both classical familial adenomatous polyposis and the Gardner syndrome variant are highly penetrant autosomal dominant disorders caused by mutations in the adenomatous polyposis coli *(APC)* tumor suppressor gene on chromosome 5q21. Most affected individuals have a family history of the disease, although approximately 30% of cases appear to represent new mutations. The severity of gastrointestinal disease and the prominence of extraintestinal findings correlate with the specific position of mutations within the *APC* gene. The term *Gardner syndrome* generally refers to cases in which the extraintestinal manifestations are especially prominent. The estimated frequency of Gardner syndrome ranges from about 1 : 8,300 to 1 : 16,000 live births.

Clinical and Radiographic Features

Colorectal polyps typically develop by the second decade of life (Fig. 14-60). The lesions often are asymptomatic but may cause diarrhea, constipation, rectal bleeding, anemia, and abdominal pain. The colorectal polyps are adenomatous (i.e., precancerous with varying degrees of dysplasia) and, if untreated, ultimately transform into adenocarcinoma. In addition, polyps often arise in the small intestine or stomach,

although only a small percentage of polyps in these sites undergo carcinomatous transformation.

Up to 90% of patients with Gardner syndrome demonstrate skeletal abnormalities, the most common of which are osteomas. The osteomas usually are noted around puberty and often become evident before the intestinal polyps; indeed, the presence of multiple osteomas may lead to an early diagnosis of Gardner syndrome. Although the osteomas may affect any part of the skeleton, they most commonly involve the skull, paranasal sinuses, and mandible. Mandibular lesions often occur at the angle and may cause marked facial deformity. Occasionally, osteomas of the condyle may limit mouth opening. Most patients demonstrate between three and six osseous lesions. The osteomas appear as radiopacities that vary from a few millimeters to several centimeters in diameter (Fig. 14-61).



• **Fig. 14-60 Gardner Syndrome.** A segment of resected large bowel showing polyp formation *(arrow).*

Dental abnormalities occur in about 22% to 30% of patients and include odontomas, supernumerary teeth, and impacted teeth. The frequency of supernumerary teeth in Gardner syndrome is not nearly as high as that noted in cleidocranial dysplasia.

Most patients show one or several epidermoid cysts of the skin (Fig. 14-62). Other cutaneous findings may include lipomas, fibromas, neurofibromas, and leiomyomas. Desmoid tumors (locally aggressive fibrous neoplasms of soft tissue) arise in approximately 12% to 18% of patients. These lesions are more frequent in females than males and often develop in the abdominal scar that forms after colectomy. In addition, numerous other extraintestinal neoplasms have been reported in Gardner syndrome, including thyroid carcinoma, adrenal adenoma or adenocarcinoma, hepatoblastoma, pancreatic adenocarcinoma, nasopharyngeal angiofibroma, and brain tumors.

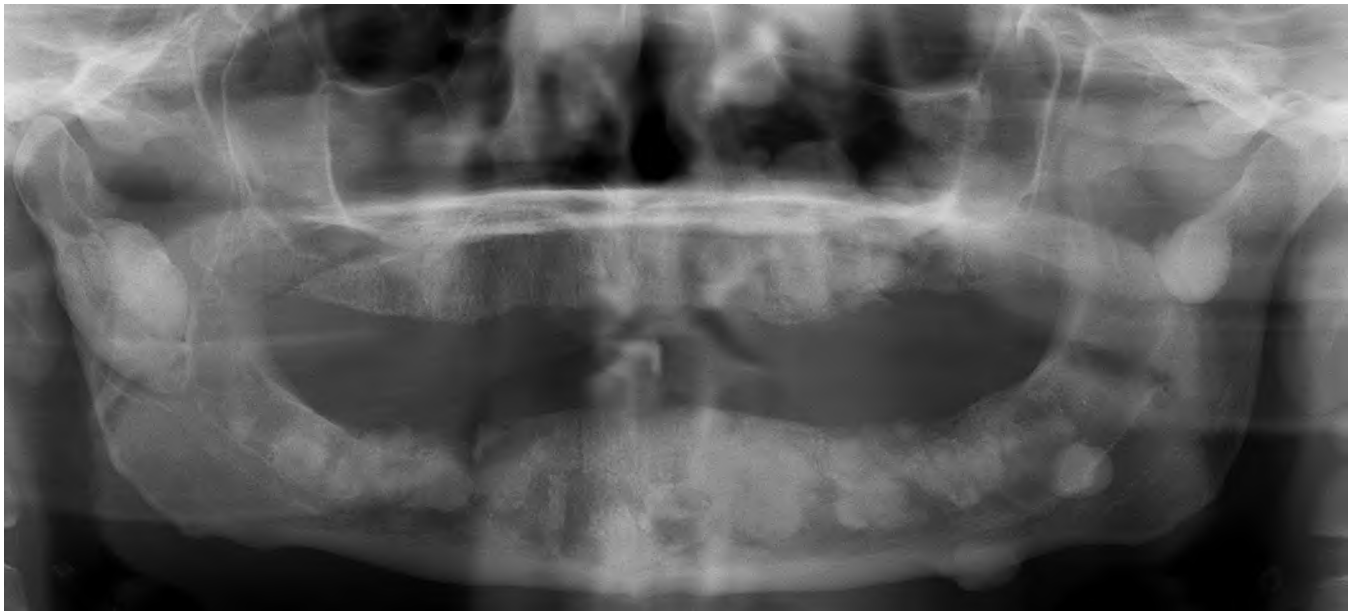
Furthermore, pigmented lesions of the ocular fundus (also known as *congenital hypertrophy of the retinal pigment epithelium*) are evident in about 58% to 88% of patients with familial adenomatous polyposis. This ocular abnormality correlates with specific mutated loci within the *APC* gene.

Histopathologic Features

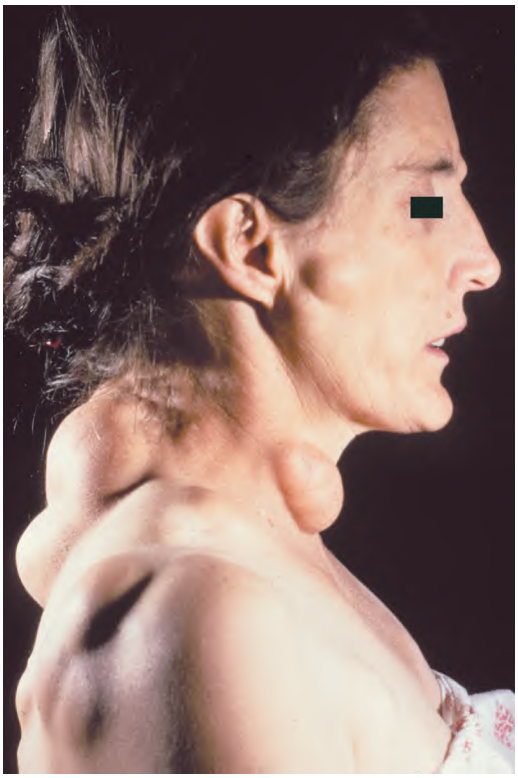
Histopathologically, the osteomas are generally of the compact type. An individual lesion cannot be differentiated microscopically from a solitary osteoma.

Treatment and Prognosis

The major problem for patients with Gardner syndrome is the high risk for transformation of colorectal polyps into



• **Fig. 14-61 Gardner Syndrome.** Panoramic radiograph showing multiple osteomas of the jaws. (Courtesy of Dr. Terry Day.)



• **Fig. 14-62 Gardner Syndrome.** This patient has multiple, large epidermoid cysts. (Courtesy of Dr. William Welton.)

adenocarcinoma. Without treatment, approximately 50% of patients will develop colorectal cancer by 30 years of age, and the frequency of malignant change approaches 100% by the fifth decade. Therefore, prophylactic colectomy usually is recommended. Clinical trials have shown some regression of polyps with celecoxib or sulindac, but further chemoprevention studies are needed.

Patients also should be monitored for development of extracolonic malignancies or desmoid tumors. Genetic counseling is indicated as well. Osteomas and epidermoid cysts may be removed if they cause functional or cosmetic problems. Dental management typically involves surgical extraction of impacted teeth, removal of odontomas, and prosthodontic treatment. Orthodontic tooth movement may be difficult due to increased bone density from the osteomas.

◆ OSTEOBLASTOMA (GIANT OSTEOID OSTEOMA) AND OSTEOID OSTEOMA

Osteoblastoma and **osteoid osteoma** are closely related benign bone tumors that arise from osteoblasts. They exhibit very similar histopathologic features, and some authors regard them as variants of the same lesion. However, most authorities currently recognize them as two distinct clinicopathologic entities. In particular, the osteoid osteoma exhibits a unique tumor nidus with a high concentration of peripheral nerves and prostaglandins; these findings apparently form the basis for characteristic nocturnal pain relieved by nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, the osteoid osteoma exhibits more limited growth potential than osteoblastoma. Classically, the distinction depends on lesion size, with osteoid osteomas measuring less than a threshold of 1.5 cm or 2 cm in diameter, whereas osteoblastomas are larger.

Most investigators consider these lesions to be true neoplasms, although some have proposed that the limited growth of osteoid osteoma suggests an inflammatory or unusual healing process. In support of a neoplastic nature, cytogenetic studies have identified recurrent alterations on the long arm of chromosome 22 in some osteoid osteomas and aggressive osteoblastomas.

Clinical and Radiographic Features

Osteoblastoma

Osteoblastomas are rare and represent approximately 1% of all primary bone tumors. The most frequently affected sites are the vertebral column, long bones, pelvis, talus, facial bones, and small bones of the hands and feet. Among gnathic lesions, there is a mandibular predilection, with most examples involving the posterior regions. Approximately 85% of gnathic osteoblastomas occur before 30 years of age, and there is a slight female predominance.

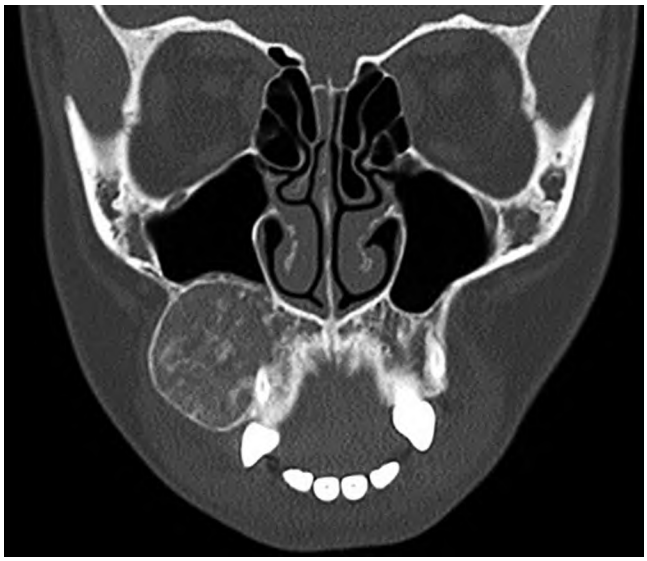
Most osteoblastomas are between 2 and 4 cm, but they may be as large as 10 cm. Dull pain, tenderness, and swelling are common presenting features. Unlike the pain associated with osteoid osteoma, the pain associated with osteoblastoma usually is not relieved by NSAIDs. Painful jaw lesions may be misinterpreted as odontogenic infections. Gnathic tumors also may cause tooth mobility, root resorption, or tooth displacement.

Radiographically, the osteoblastoma typically appears as a well- or ill-defined, round to oval radiolucency with patchy areas of mineralization (Fig. 14-63). Some examples demonstrate considerable mineralization. Surrounding reactive sclerosis is less prominent in osteoblastoma than osteoid osteoma. Most osteoblastomas arise within medullary bone, although a periosteal or intracortical origin also is possible.

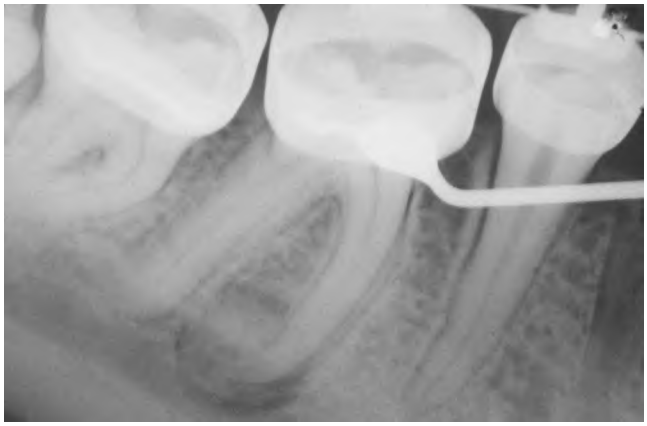
A small subset of osteoblastomas **(aggressive osteoblastomas)** is characterized by atypical histopathologic features and locally aggressive behavior. These tumors usually occur in patients older than 30 years. A variety of bones, including the mandible, may be involved. Pain is common and may be severe. Aggressive osteoblastomas exhibit radiographic findings similar to those of conventional osteoblastoma but tend to be larger (typically greater than 4 cm in diameter).

Osteoid Osteoma

Osteoid osteoma comprises about 3% of all primary bone tumors. The lesion occurs most often in the femur and tibia but is very rare in the jaws. Among reported gnathic tumors, there is a slight mandibular predominance, with most



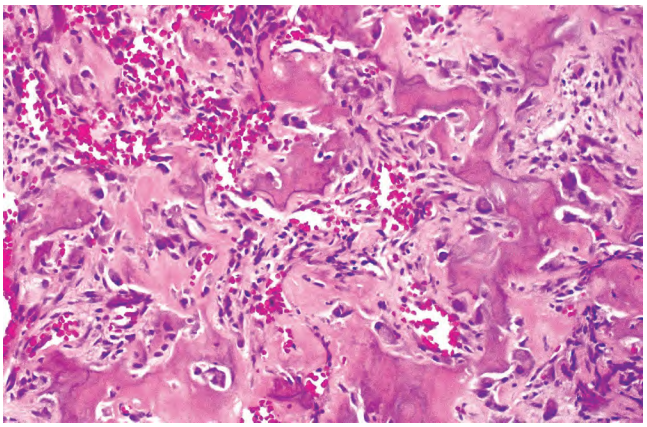
• **Fig. 14-63 Osteoblastoma.** Computed tomography (CT) image showing an expansile, mixed radiolucent and radiopaque lesion of the maxilla. (Courtesy of Dr. Michael Zetz.)



• **Fig. 14-64 Osteoid Osteoma.** A circumscribed, mixed radiolucent and radiopaque lesion near the apex of mesial root of mandibular first molar. The patient had dull, nocturnal pain that was relieved by aspirin. (Courtesy of Dr. Ellen Eisenberg.)

patients diagnosed during the second and third decades of life (mean age 25 years). Although extragnathic lesions demonstrate a male predilection, jaw lesions exhibit no significant gender predilection. The most prominent clinical symptom is pain that is most severe at night and alleviated by NSAIDs. However, nocturnal pain relieved by NSAIDs has been documented more often among extragnathic lesions than jaw lesions.

Radiographically, the osteoid osteoma typically appears as a well-circumscribed, round to ovoid radiolucency (or "nidus") with a variable degree of surrounding reactive sclerosis. The radiolucent nidus may contain a small, central radiopacity, resulting in a target-like appearance (Fig. 14-64). The nidus typically measures less than 1.5 cm in diameter and most commonly arises within cortical bone, although a medullary or periosteal origin also is possible. A periosteal reaction occasionally may be seen.



• **Fig. 14-65 Osteoblastoma.** High-power photomicrograph showing irregular bony trabeculae with prominent osteoblastic rimming and osteoclasts.

Histopathologic Features

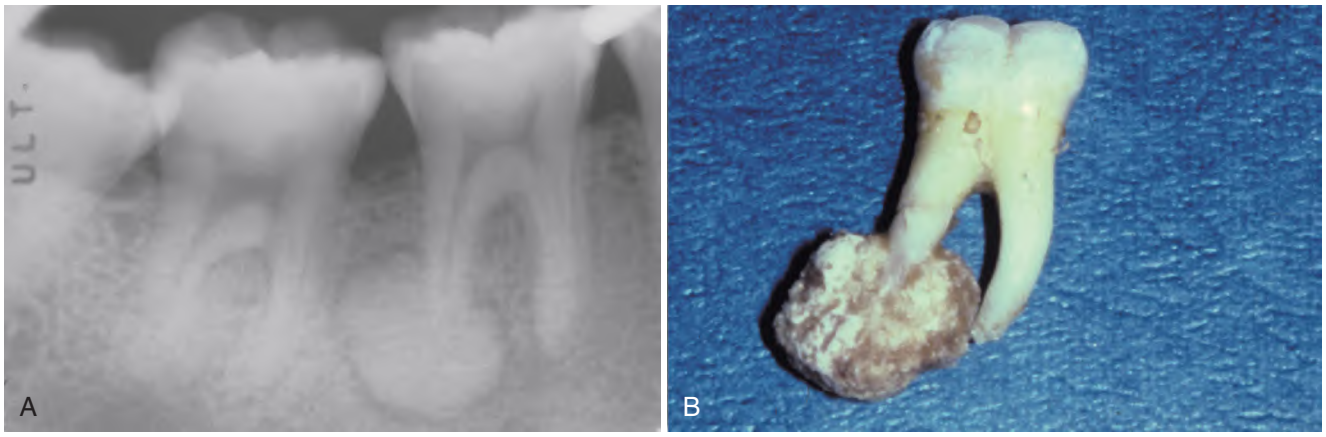
Microscopically, both osteoid osteoma and osteoblastoma centrally exhibit irregular trabeculae of osteoid or woven bone, which are surrounded by numerous osteoblasts and scattered osteoclasts. The osteoblasts have ample cytoplasm and hyperchromatic nuclei (Fig. 14-65). The loose fibrous stroma includes dilated vessels and occasional hemorrhage. The vascularity tends to be more prominent in osteoblastoma than osteoid osteoma. At the periphery, there is typically a more prominent zone of dense, sclerotic bone in osteoid osteoma than osteoblastoma.

Aggressive osteoblastomas are characterized by large (epithelioid) osteoblasts with increased mitotic activity and sheets or lacelike areas of osteoid production. Differentiation between aggressive osteoblastoma and low-grade osteosarcoma may be very difficult, although infiltrative growth, marked cytologic atypia, and atypical mitotic figures favor the latter.

Treatment and Prognosis

Most osteoid osteomas and osteoblastomas of the jaws are treated by local excision or curettage. Some osteoid osteomas may regress spontaneously; however, most clinicians prefer surgical removal over long-term observation and pain management with NSAIDs. For extragnathic lesions, minimally invasive techniques (e.g., computed tomography [CT]-guided excision and radiofrequency ablation) have gained popularity recently.

Recurrence after complete removal is uncommon; many reported recurrences may be attributed to incomplete excision. Osteoid osteoma exhibits no potential for malignant transformation, and osteoblastoma only rarely transforms into osteosarcoma. Whether aggressive osteoblastoma exhibits a greater recurrence potential than conventional osteoblastoma is controversial, although metastasis or death from aggressive osteoblastoma has not been reported.



• **Fig. 14-66 Cementoblastoma. A,** A densely mineralized mass is seen at the apex of the distal root of the first molar. The root is partially resorbed. **B,** The surgical specimen shows that the mass is attached to the root. (Courtesy of Dr. John Wright.)

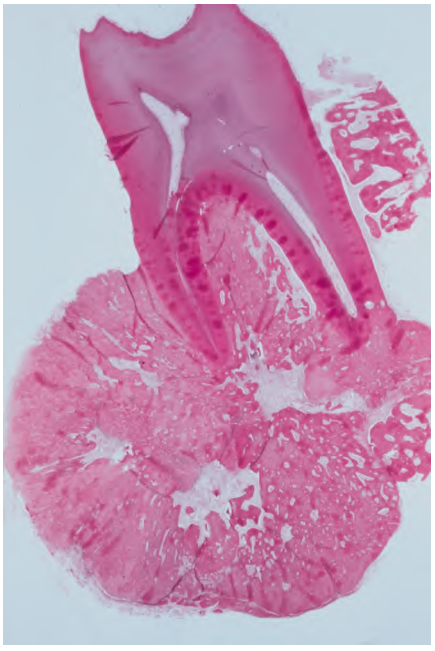
◆ CEMENTOBLASTOMA (TRUE CEMENTOMA)

Cementoblastoma is a benign neoplasm of cementoblasts and represents less than 1% of all odontogenic tumors. Many authorities believe this lesion represents the only true neoplasm of cementum. Alternatively, because cementoblastoma bears a close histopathologic resemblance to osteoblastoma (see previous section), others consider cementoblastoma to be a variant of osteoblastoma. The primary distinguishing factor is whether or not the lesion is fused to a tooth root. Because of its similarity to osteoblastoma, cementoblastoma is discussed here rather than in Chapter 15.

Clinical and Radiographic Features

Approximately 80% of cases arise in the mandible, primarily in the molar and premolar region. In particular, almost 50% of cases involve the mandibular first permanent molar. Impacted, unerupted, or deciduous teeth rarely may be affected as well. There is no definite sex predilection. The neoplasm predominantly affects young patients, with about 50% arising by 20 years of age and 75% by 30 years. Pain and swelling are present in approximately two-thirds of reported cases. The associated tooth usually responds normally to vitality tests. Most investigators consider this lesion rather innocuous; however, signs of locally aggressive behavior may be observed, including bony expansion, cortical erosion, displacement of adjacent teeth, envelopment of multiple teeth, maxillary sinus involvement, and infiltration into the pulp chamber and root canals.

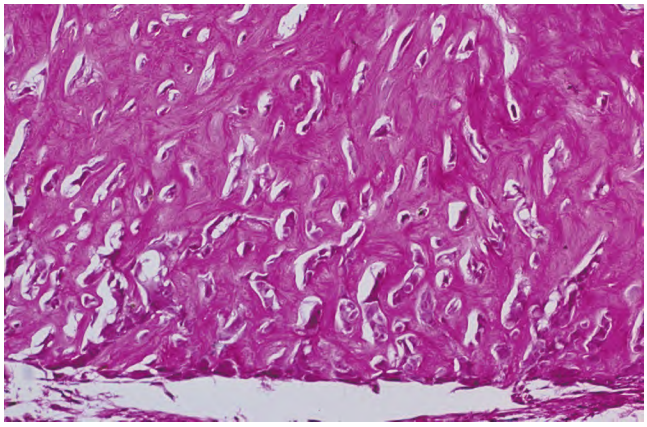
Radiographically, the tumor appears as a radiopaque mass that is fused to one or more tooth roots and is surrounded by a thin radiolucent rim (Fig. 14-66). The outline of the root or roots of the involved tooth usually is obscured by root resorption and fusion of the tumor with the tooth.



• **Fig. 14-67 Cementoblastoma.** Low-power photomicrograph showing the tumor attached to the roots of the tooth.

Histopathologic Features

The histopathologic features of cementoblastoma closely resemble those of osteoblastoma. However, the primary distinguishing feature of cementoblastoma is fusion with the involved tooth (Fig. 14-67). Microscopic examination shows sheets and thick trabeculae of mineralized material with irregularly placed lacunae and prominent basophilic reversal lines. The background stroma is comprised of cellular fibrovascular tissue. Multinucleated giant cells often are present, and prominent blast-like cells frequently line the mineralized trabeculae (Fig. 14-68). Radiating columns of uncalcified matrix typically are seen at the periphery, corresponding to the radiolucent rim seen radiographically.



• **Fig. 14-68 Cementoblastoma.** Mineralized tissue containing numerous plump cementoblasts.

In few instances, the lesion may infiltrate the pulp chamber and root canals of the involved tooth.

Treatment and Prognosis

Treatment usually consists of surgical extraction of the tooth and the attached calcified mass. A potential alternative is excision of the mass with root amputation followed by endodontic treatment of the remaining tooth. Some investigators suggest that supplementing extraction or excision with osseous curettage may decrease the risk for recurrence. Historically, most authorities have considered the recurrence potential to be very low; however, one large series with an extensive literature review has reported an overall recurrence rate of 22%. Completeness of removal is most closely related to recurrence.

◆ CHONDROMA

Chondromas are benign tumors of mature hyaline cartilage. They comprise about 16% of benign bone tumors and most often arise in the small bones of the hands and feet. However, a diagnosis of chondroma in the craniofacial bones should be viewed with great skepticism because many purported cases have recurred and exhibited malignant behavior. There are only a few individual reports and small series of gnathic chondromas, with most examples thought to arise from cartilage or cartilaginous rests in the condyle, anterior maxilla, mandibular symphysis, and coronoid process. Recent studies have shown that chondromas frequently harbor somatic mutations in the isocitrate dehydrogenase 1 *(IDH1)* gene.

Clinical and Radiographic Features

Approximately 50% of chondromas are diagnosed in the second, third, and fourth decades of life, and there is a female predilection. Most gnathic examples occur in the condyle or anterior maxilla of adult patients. Usually, the lesions are painless and grow slowly. However, condylar tumors may cause pain, limited mouth opening, and deviation of the mandible from the midline. Lesions arising adjacent to teeth may cause tooth mobility and root resorption. Radiographically, the chondroma typically appears as a well-defined radiolucency with central opacification. Most cases arise within medullary bone *(enchondromas),* but some may arise just beneath the periosteum *(periosteal chondromas).* Most chondromas are solitary, although multiple lesions may develop in **Ollier disease** (sporadic chondromatosis with a unilateral tendency) or **Maffucci syndrome** (sporadic chondromatosis with soft tissue angiomas).

Histopathologic Features

Histopathologically, a chondroma appears as a well-circumscribed, lobular mass of mature hyaline cartilage. The cartilage typically demonstrates well-formed lacunae containing small chondrocytes with pale cytoplasm and small, round nuclei. Microscopic distinction between a chondroma and a low-grade chondrosarcoma of the jaws may be difficult (see page 618).

Treatment and Prognosis

It is wise to consider any jaw lesion diagnosed as a chondroma to represent a potential chondrosarcoma. Treatment typically consists of complete surgical removal.

◆ CHONDROMYXOID FIBROMA

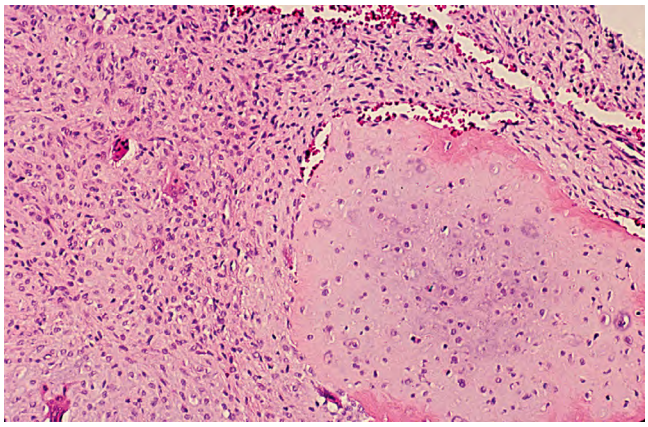
The **chondromyxoid fibroma** is a rare, benign cartilaginous neoplasm that represents less than 1% of all primary bone tumors. Cytogenetic studies are limited but have detected frequent abnormalities in chromosome 6, where a number of candidate cartilage-related and tumor suppressor genes are located.

Clinical and Radiographic Features

Chondromyxoid fibromas most commonly involve the metaphyseal region of long bones, especially the tibia. Only about 2% of cases arise in the craniofacial bones.

Among reported jaw lesions, the average age at diagnosis is 28 years (range 9 to 67 years), with a peak in the second and third decades. There is no significant sex predilection. Approximately three-quarters occur in the mandible. Initial signs and symptoms often include swelling (65%) and pain (22%). However, some cases are asymptomatic and detected incidentally by radiographic examination.

Radiographically, chondromyxoid fibromas of the jaws typically appear as well-circumscribed radiolucencies with sclerotic or scalloped margins. The maximum diameter may range from 1.0 to 6.5 cm (average 3.3 cm). Cortical destruction is common, but the periosteum usually remains intact. Central radiopacities are evident in about 10% of cases.



• **Fig. 14-69 Chondromyxoid Fibroma.** Myxoid connective tissue with scattered giant cells and foci of cartilaginous differentiation.

Histopathologic Features

Microscopic examination shows lobules of spindle-shaped or stellate cells with abundant myxoid or chondroid intercellular substance. The lobules characteristically exhibit increased cellularity at the periphery. Between the lobules there is cellular fibrous tissue with spindle-shaped or round cells and varying numbers of multinucleated giant cells (Fig. 14-69). Focal calcifications and residual bone spicules also may be present. Occasionally, large pleomorphic cells may cause confusion with chondrosarcoma; however, chondrosarcoma typically shows hypercellularity throughout the tumor lobules and lacks a benign radiographic appearance.

Treatment and Prognosis

There is controversy regarding the most appropriate treatment for chondromyxoid fibroma. Many authors advocate conservative surgical removal, whereas others prefer wide resection. In general, relatively small lesions of the jaws are treated by local enucleation or curettage, but larger lesions often necessitate resection. In addition, some investigators have reported that filling the surgical defect with bone graft material following curettage results in a lower recurrence rate than curettage alone. Radiation therapy is contraindicated because of the risk for inducing malignant transformation or osteoradionecrosis.

Although the chondromyxoid fibroma is a benign tumor, approximately 25% of cases in the long bones recur after curettage alone. Among reported jaw tumors, the overall recurrence rate is about 10%.

◆ SYNOVIAL CHONDROMATOSIS (CHONDROMETAPLASIA)

Synovial chondromatosis is a rare, benign arthropathy characterized by development of cartilaginous nodules within the synovial membrane. The etiopathogenesis is poorly understood. Traditionally, synovial chondromatosis has been regarded as a reactive, metaplastic process. However, recent cytogenetic studies and transgenic mouse model studies suggest that it might represent a true, benign neoplasm. Examples may be subclassified as *primary synovial chondromatosis* (i.e., cases with no identifiable etiologic factors) or, more commonly, *secondary synovial chondromatosis* (i.e., cases associated with trauma, joint overuse, inflammatory joint disease, or noninflammatory arthropathy).

The condition typically proceeds through three stages. In the first stage, cartilaginous or osteocartilaginous nodules develop in the synovial lining. Subsequently, these nodules begin to detach, with some lying free in the joint space and others remaining in the synovial membrane. In the final stage, the nodules are found only in the joint space. The detached particles are called **loose bodies** (or "joint mice").

Clinical and Radiographic Features

The disease most commonly affects large joints, such as the knee, elbow, hip, and shoulder. Temporomandibular joint (TMJ) involvement is uncommon, although in recent years there has been an increase in reported cases, possibly because of improved imaging techniques and increased disease awareness.

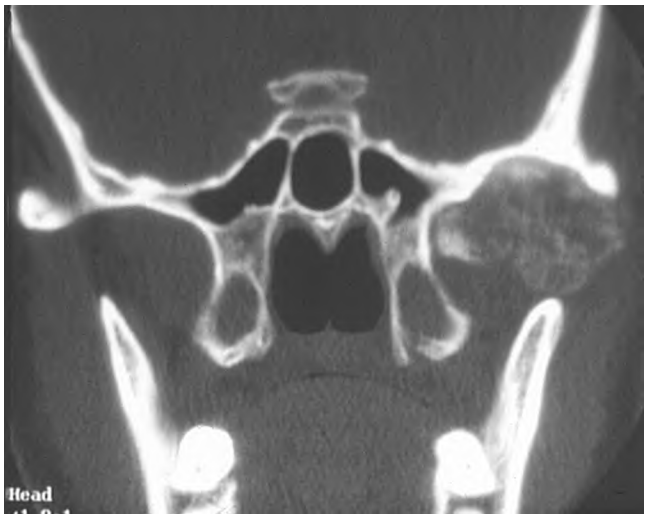
Synovial chondromatosis of the TMJ occurs over a broad age range (12 to 82 years), with a peak in the fourth and fifth decades of life. In contrast to the findings in other joints, there is a predilection for females. The clinical presentation is nonspecific and, thus, delay in diagnosis is common. Typical findings include periarticular swelling, pain, crepitus, and limitation of joint motion. Headache, sensory disturbances, and facial nerve paralysis are infrequent. In rare instances, the disease may produce no symptoms.

The process usually is confined to a single joint. However, bilateral involvement and extraarticular extension (e.g., TMJ lesions with erosion of the condylar head, skull base, or intracranial structures) have been reported in a few cases. Within the TMJ, the disease primarily involves the superior compartment, although involvement of the inferior compartment also is possible.

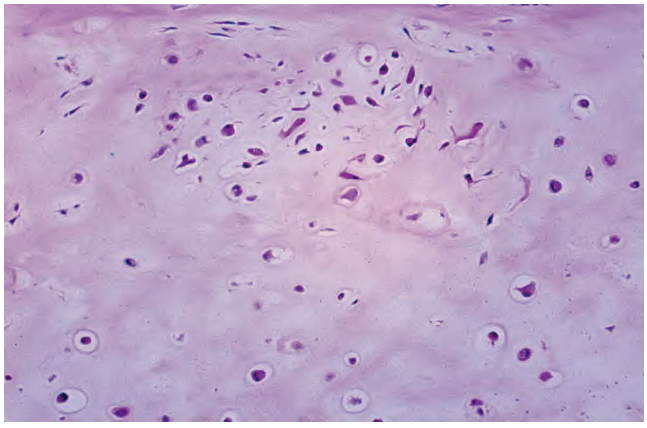
Radiographically, the loose bodies in the joint may appear as round to irregular, radiopaque structures of variable size (Fig. 14-70). Other findings may include irregularity of the joint surface, widening of the joint space, and sclerosis or hyperostosis of the glenoid fossa or condyle. Similar features, however, may be seen in other degenerative joint diseases. Likewise, failure to detect loose bodies on imaging studies does not preclude a diagnosis of synovial chondromatosis. CT and magnetic resonance imaging (MRI) are more sensitive than plain radiography for demonstrating many of the characteristic features of synovial chondromatosis.

Histopathologic Features

Nodules of hyaline cartilage are present within the synovium and lie loose in the joint space. There may be anywhere from



• **Fig. 14-70 Synovial Chondromatosis.** Computed tomography (CT) scan showing opacites of variable size within the temporomandibular joint (TMJ) region. (Courtesy of Dr. K. Krishnan Unni.)



• **Fig. 14-71 Synovial Chondromatosis.** Photomicrograph from one of many nodules removed at the time of synovectomy. The cartilage shows some degree of atypia, and in a different clinical setting this histopathology could be interpreted to represent a low-grade chondrosarcoma.

1 to more than 200 loose bodies. The cartilaginous nodules often become calcified or ossified. Particularly in primary lesions, the chondrocytes may appear atypical with enlarged, hyperchromatic nuclei and binucleation (Fig. 14-71). However, correlation with the clinical and radiographic findings may aid in distinguishing synovial chondromatosis from chondrosarcoma.

Treatment and Prognosis

Synovial chondromatosis of the TMJ typically is treated by partial or complete synovectomy and removal of all loose bodies, at times combined with meniscectomy. Condylectomy is reserved for unusual cases with severe condylar destruction. Surgery is performed most commonly via open arthrotomy, although arthroscopy or arthrocentesis may be used for biopsy and, in select cases, for treatment. A wider approach is typically necessary for rare cases with extensive extraarticular involvement.

The prognosis is good, with an overall low frequency of recurrence after surgical excision. However, some investigators have noted more aggressive behavior and a higher recurrence rate among primary lesions compared to secondary lesions. Thus periodic follow-up examinations would appear to be prudent. Malignant transformation of synovial chondromatosis of the TMJ is extremely rare.

◆ DESMOPLASTIC FIBROMA

The **desmoplastic fibroma** of bone is a benign, locally aggressive, myofibroblastic neoplasm that comprises less than 1% of primary bone tumors. Clinicopathologic, ultrastructural, and immunohistochemical findings suggest that this tumor represents the osseous counterpart of soft tissue fibromatosis (desmoid tumor) (see page 481). Thus far, however, limited genetic studies of desmoplastic fibromas of bone have not identified mutations in the *CTTNB1* gene, which encodes beta-catenin and often is mutated in soft tissue fibromatosis. In a few cases, desmoplastic fibroma-like lesions of the jaws have been reported in association with tuberous sclerosis.

Clinical and Radiographic Features

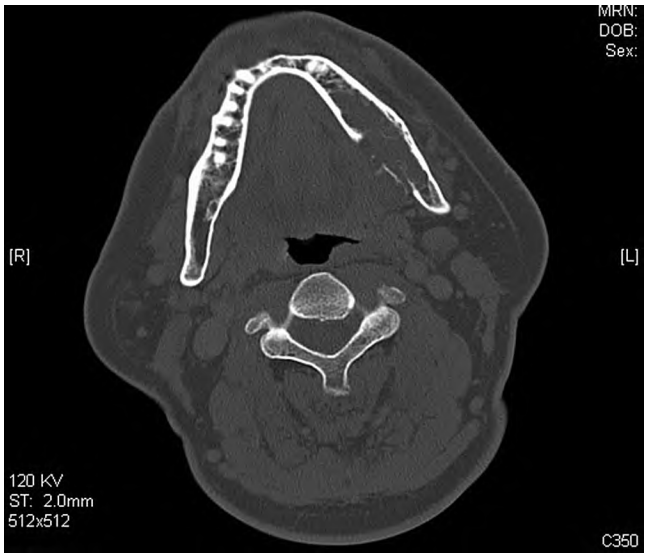
Most desmoplastic fibromas of bone arise in patients younger than 30 years old. The most common locations are the mandible, femur, tibia, radius, humerus, and pelvis.

Among jaw lesions reported in the English literature, the age range is 10 months to 60 years, with a mean of approximately 14 years. There is no significant sex predilection. More than 80% of cases affect the mandible—most often the posterior body, the angle, and the ramus. Most patients exhibit a painless swelling with slow to rapid growth, although pain has been reported in some examples. Limited opening, malocclusion, tooth mobility, tooth displacement, proptosis, concurrent infection, and dysesthesia also are possible.

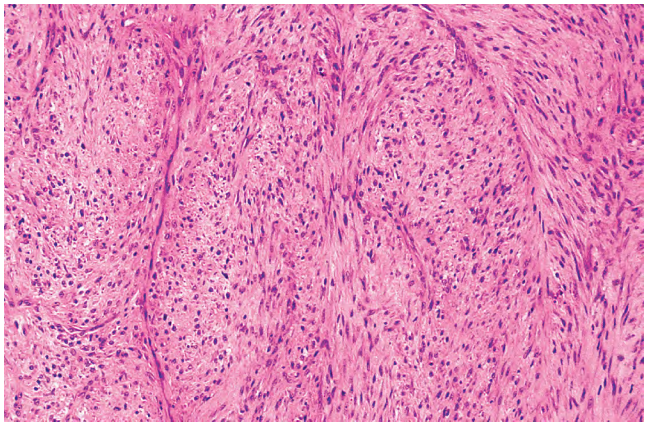
Radiographically, the lesion appears as a multilocular or unilocular radiolucency with well- or ill-defined margins (Fig. 14-72). The bone is expanded, and the cortex is thinned; cortical reaction mimicking the appearance of an osteosarcoma is rare. Erosion through the cortex and extension into soft tissue may be evident. In such cases, it may be difficult to determine whether the lesion is a desmoplastic fibroma of bone with soft tissue extension or a soft tissue fibromatosis with extension into bone.

Histopathologic Findings

The tumor is composed of small, elongated fibroblasts and abundant collagen fibers (Fig. 14-73). The degree of cellularity may vary within a given lesion, and the cellular areas may show plump fibroblasts. However, the fibroblasts are not atypical, and mitoses are absent or sparse. Bone spicules



• **Fig. 14-72 Desmoplastic Fibroma.** Ill-defined, destructive radiolucency of the left mandible.



• **Fig. 14-73 Desmoplastic Fibroma.** The tumor consists of a cellular proliferation of fibroblasts arranged in interlacing fascicles.

may be present at the interface between the tumor and adjacent bone but are never an integral part of the lesion. This reactive bone at the periphery may be mistaken for osteoid production, which may lead to a misdiagnosis of a benign fibro-osseous lesion or osteosarcoma. Therefore, diagnostic biopsies should be sampled generously from the center rather than the periphery of the lesion.

Treatment and Prognosis

Although the desmoplastic fibroma is a benign tumor, it often behaves in a locally aggressive fashion, with extensive bone destruction and soft tissue extension; thus, radical surgery may be required to control the disease. Most cases are treated by resection, although curettage may be adequate for localized lesions without cortical perforation or soft tissue extension. The recurrence rate is approximately 30% for lesions treated by curettage or enucleation, compared with about 5% for those treated by resection. Given the potential for recurrence, patients should be monitored postoperatively for at least 3 years. The long-term prognosis is good, but there may be considerable morbidity. Malignant transformation is rare.

It may be very difficult to distinguish desmoplastic fibroma of bone from well-differentiated fibrosarcoma. Some authorities suggest that all desmoplastic fibromas of bone be considered potentially malignant.

◆ OSTEOSARCOMA (OSTEOGENIC SARCOMA)

Osteosarcoma is a malignancy of mesenchymal cells that have the ability to produce osteoid or immature bone. Excluding hematopoietic neoplasms, osteosarcoma is the most common malignancy to originate within bone. In the United States, the age-adjusted annual incidence is approximately 3 cases per million population.

The etiology of osteosarcoma is largely unknown. A strong association with the adolescent growth spurt and the metaphyses of long bones suggests that rapid bone growth and hormonal factors may play a role. Additional risk factors include radiation exposure, alkylating agents, Paget disease of bone, Li-Fraumeni syndrome, hereditary retinoblastoma, and Rothmund-Thompson syndrome. Studies have demonstrated a complex genetic profile among osteosarcomas, with alterations frequently detected in *p53, RB1,* and chromosome 21q.

Osteosarcomas may be classified as *central* (arising within the medullary cavity), *surface* (arising in the juxtacortical region), or, vary rarely, *extraskeletal* (arising within soft tissue) (Table 14-4). The vast majority of cases are central. Surface osteosarcomas are discussed in the next section (see page 617). In addition, some authors regard gnathic osteosarcomas as a separate entity, because these lesions exhibit somewhat distinctive clinical features and biologic behavior.

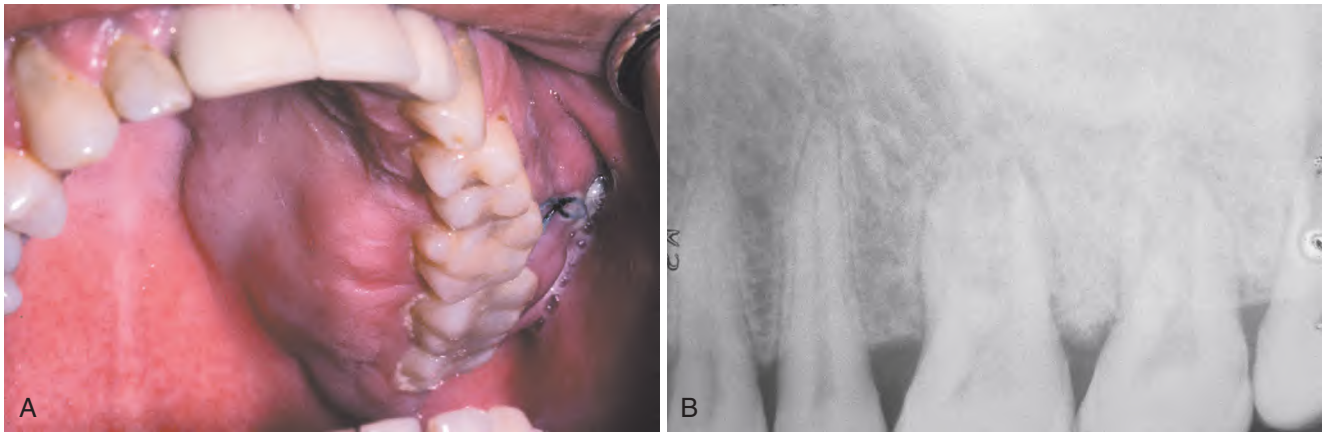
Clinical and Radiographic Features

Extragnathic osteosarcoma demonstrates a bimodal age distribution, with a major peak during adolescence and a lesser peak among adults older than 60 years. The initial peak occurs during the period of greatest bone growth; accordingly, most of these osteosarcomas arise in the distal femoral and proximal tibial metaphyses. In older patients, osteosarcoma often is attributed to Paget disease of bone or previous irradiation, and the axial skeleton and flat bones are involved most frequently.

About 6% of all osteosarcomas arise in the jaws. Jaw lesions occur over a broad age range, with a peak in the third through fifth decades of life. The mean age is approximately 33 to 39 years, which is about 1 to 2 decades older than the mean age for osteosarcomas of the long bones. Both gnathic and extragnathic osteosarcomas exhibit a slight male predilection.

TABLE 14-4 Osteosarcoma Types

Type		Grade
Central (intramedullary)	Conventional: • Osteoblastic • Chondroblastic • Fibroblastic	High
	Other rare variants (e.g., telangiectatic, small cell, epithelioid, giant cell-rich, osteoblastoma-like, and chondroblastoma-like)	High
	Low-grade central	Low
Surface (juxtacortical)	Parosteal	Low
	Periosteal	Intermediate
	High-grade surface	High
Extraskeletal		Low to high



• **Fig. 14-74 Osteosarcoma. A,** This patient shows a firm, painful swelling of the left maxilla of recent onset. **B,** The periapical radiograph shows a dense sclerotic change in the bone pattern. (Courtesy of Dr. Len Morrow.)

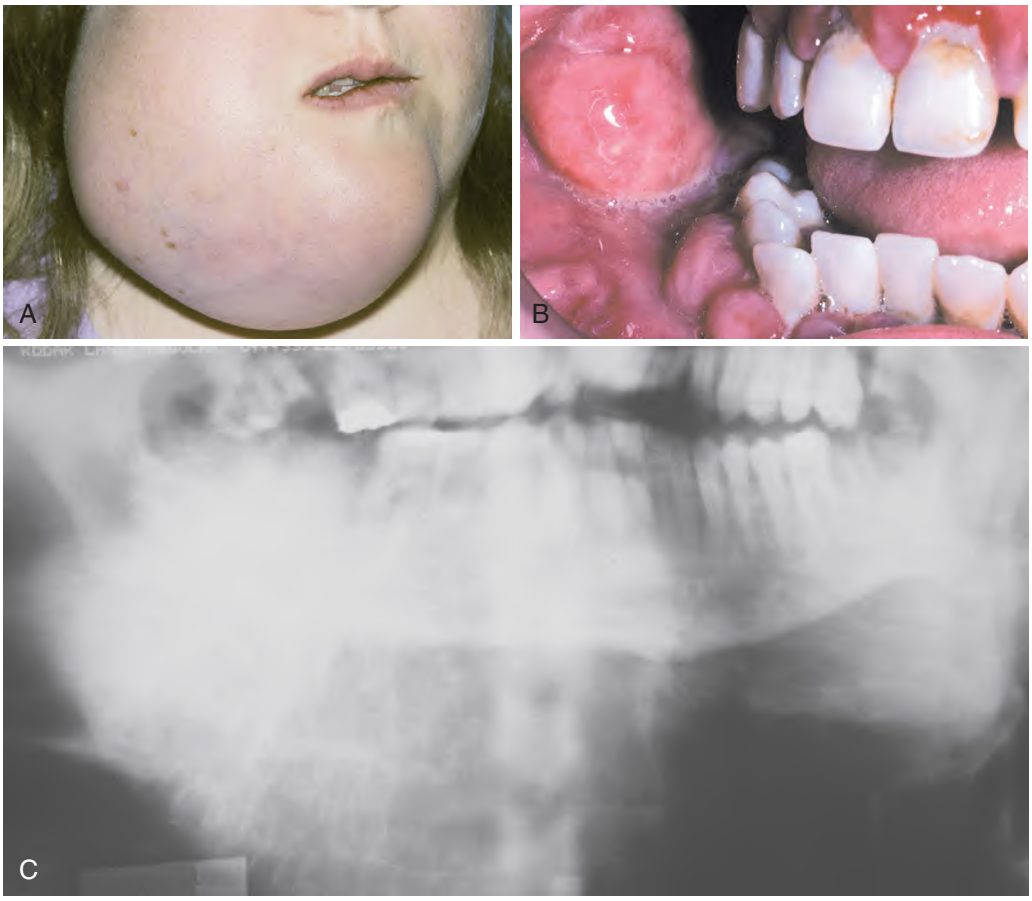
Most studies report either a fairly even distribution between the mandible and maxilla or a slight mandibular predilection. Mandibular tumors arise most frequently in the body, followed by the angle, symphysis, and ramus. Maxillary lesions develop more often in the inferior portion (alveolar ridge, sinus floor, and/or palate) than the superior aspect (zygoma and orbital rim).

Swelling and pain are the most common clinical findings (Figs. 14-74 and 14-75). Tooth mobility, paresthesia, and nasal obstruction (in the case of maxillary tumors) also may be noted. Some patients report symptoms for relatively long periods before diagnosis, which suggests that some osteosarcomas of the jaws grow rather slowly.

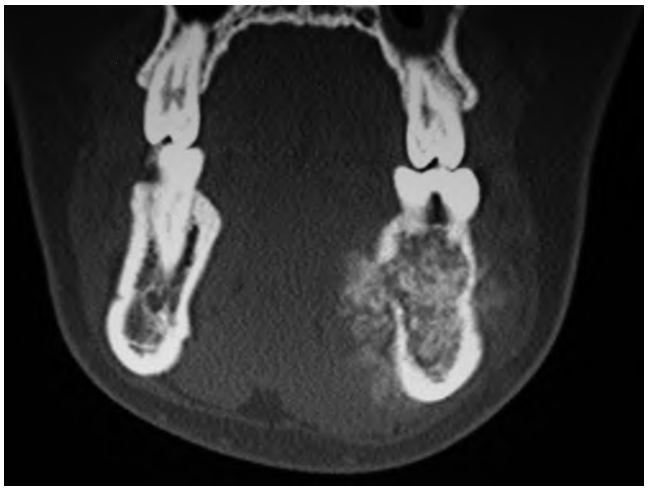
Radiographic examination may show a radiopaque, mixed radiolucent-radiopaque, or entirely radiolucent lesion with ill-defined borders (Figs. 14-74, *B,* 14-75, *B,* and 14-76). Cortical destruction, cortical expansion, and a periosteal reaction also may be evident. The latter may appear as a "classic" sunburst pattern (present in about 25% of jaw osteosarcomas) or a triangular elevation of the periosteum (*Codman triangle*). Occasionally, the adjacent teeth exhibit "spiking" root resorption (with tapered narrowing of the root). Symmetrical widening of the periodontal ligament space (Fig. 14-77) may be an important clue for diagnosis of early osteosarcoma, although this feature also may be seen in other malignancies. At times an extensive osteosarcoma may show only subtle variation in the trabecular pattern. Plain radiography often is used for initial evaluation. However, MRI is superior for assessment of primary tumor extent, and CT is important for detection of pulmonary metastasis.

Histopathologic Features

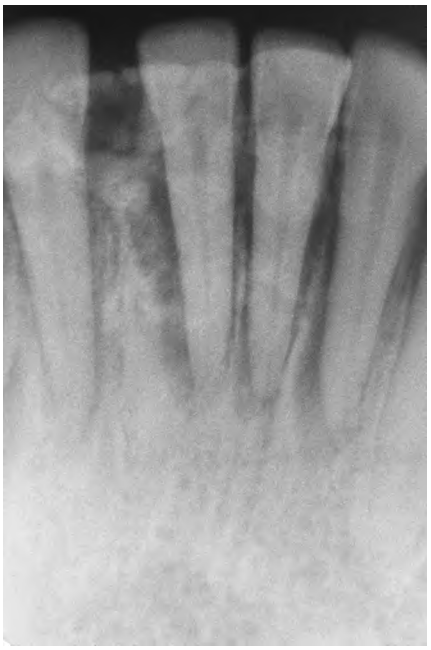
Although osteosarcomas exhibit considerable histopathologic variation, the essential microscopic criterion is direct production of osteoid by malignant mesenchymal cells (Fig. 14-78). In addition to osteoid, the tumor cells may produce chondroid and fibrous connective tissue. The tumor cells may vary from relatively uniform, round or spindle-shaped



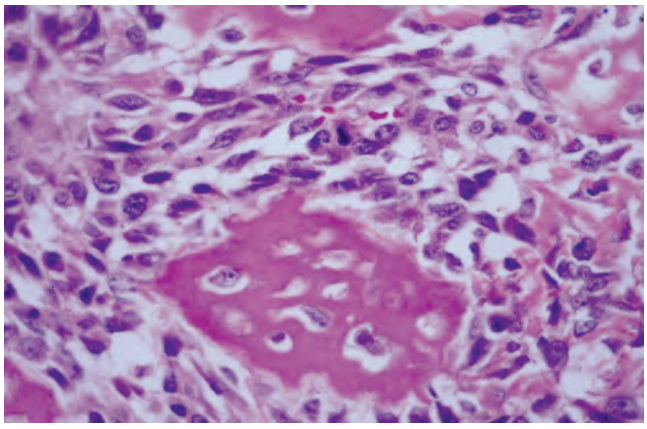
• **Fig. 14-75 Osteosarcoma. A,** This massive tumor had been present for many months before the patient sought treatment. **B,** Intraoral photograph of the tumor mass. **C,** The panoramic radiograph shows a "sunburst" pattern of trabeculation.



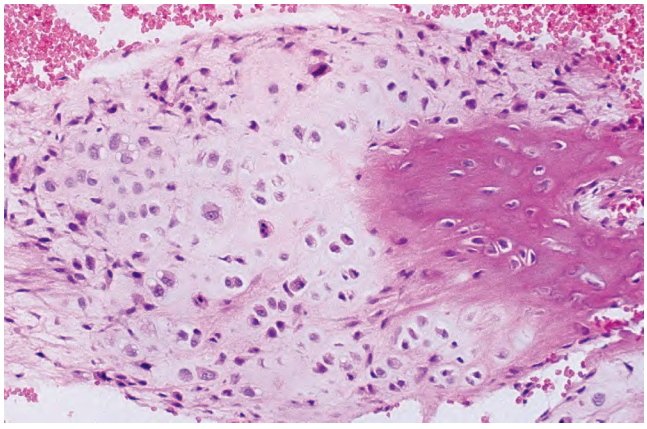
• **Fig. 14-76 Osteosarcoma.** Computed tomography (CT) scan showing a mottled radiopacity of the mandible with cortical destruction and a focal "sunburst" periosteal reaction. (Courtesy of Dr. Steve Anderson.)



• **Fig. 14-77 Osteosarcoma.** This 26-year-old woman had a 6-cm painful tumor of the anterior mandible. The periapical radiograph shows widening of the periodontal ligament spaces and a mottled radiopacity superimposed on the teeth. (Courtesy of Dr. Charles Ferguson.)



• **Fig. 14-78 Osteosarcoma.** Anaplastic tumor cells forming cellular disorganized bone.



• **Fig. 14-79 Osteosarcoma.** This tumor produced a combination of malignant cartilage and bone.

cells to highly pleomorphic cells with bizarre nuclear and cytoplasmic shapes. The amount of matrix produced by the tumor may vary considerably. In some instances, osteoid production may be very minimal and difficult to demonstrate.

Depending on the relative amounts of osteoid, cartilage, or collagen produced by the tumor, many pathologists subclassify conventional osteosarcomas into the following types:

- Osteoblastic
- Chondroblastic
- Fibroblastic

These histopathologic types, however, do not have any great bearing on the prognosis. Less common variants are listed in Table 14-4.

Chondroblastic osteosarcomas constitute a substantial proportion of all osteosarcomas of the jaws. Some examples may be composed almost entirely of malignant cartilage growing in lobules with only small foci of direct osteoid production by tumor cells (Fig. 14-79). Such lesions, however, should be classified as osteosarcomas rather than chondrosarcomas. Interestingly, one recent study has shown that chondroblastic osteosarcomas lack *IDH1* mutations, whereas such mutations are frequent among chondrosarcomas.

Low-grade osteosarcomas show minimal cellular atypia and abundant bone formation. On microscopic examination, these lesions may be difficult to differentiate from benign bone lesions, such as fibrous dysplasia or ossifying fibroma. Correlation with imaging studies is essential for accurate diagnosis. Immunohistochemical expression of MDM2 and CDK4 also may help to distinguish low-grade osteosarcoma from benign fibro-osseous lesions and other benign bone tumors.

Treatment and Prognosis

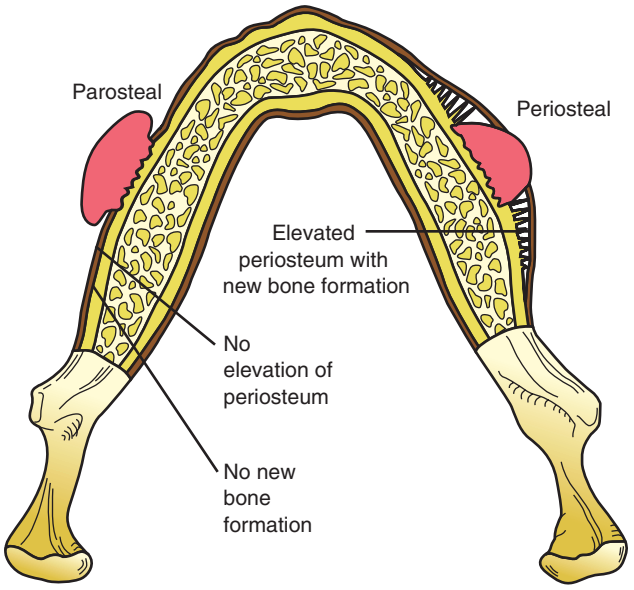
The treatment of choice for osteosarcoma of the jaws is wide surgical resection. The additional use of chemotherapy and/or radiotherapy for gnathic osteosarcomas is controversial but may be considered in some cases (e.g., tumors of questionable resectability, surgical margins positive for tumor, and recurrent tumors). For high-grade osteosarcomas of the long bones, management usually consists of neoadjuvant (preoperative) chemotherapy followed by radical surgery and adjuvant (postoperative) chemotherapy. Among patients with localized disease at diagnosis, such treatment has resulted in 5-year survival rates of approximately 60% to 80%, compared to only about 20% with surgery alone. However, for patients with gnathic osteosarcomas, such protocols have yielded variable outcomes, and further studies are needed.

The most important prognostic factor is the ability to achieve initial complete surgical removal. Compared to mandibular lesions, maxillary lesions often are more difficult to resect and exhibit a worse prognosis. Additional adverse factors include prior radiation exposure and underlying Paget disease of bone. Interestingly, some investigators have reported a better prognosis for osteosarcoma of the jaws than osteosarcoma of the long bones. This observation may be related to a tendency for gnathic osteosarcomas to exhibit a low rate of metastasis despite often high-grade histopathologic features. However, other studies have shown no significant survival advantage among patients with gnathic osteosarcoma.

For patients with osteosarcoma of the jaws, death results more often from uncontrolled local disease than from distant metastases. Most deaths from uncontrolled local disease occur within 2 years of initial treatment. Metastases most often affect the lungs. In recent years, most large series of jaw tumors have reported 5-year overall survival rates of approximately 60% to 70%, and some centers have reported greater than 80% survival.

SURFACE (JUXTACORTICAL) OSTEOSARCOMAS

Although most osteosarcomas arise within the medullary cavity of bone, some cases originate in the periosteal or



• **Fig. 14-80 Peripheral (Juxtacortical) Osteosarcoma.** Illustration comparing different types of peripheral osteosarcoma. Parosteal osteosarcoma presents as a lobulated nodule without a peripheral periosteal reaction. Periosteal osteosarcoma presents as a sessile mass associated with significant periosteal new bone formation.

cortical region with little or no medullary involvement. Such surface lesions typically involve the long bones, although gnathic cases rarely have been reported. Surface osteosarcoma includes the following subtypes:

- Parosteal osteosarcoma
- Periosteal osteosarcoma
- High-grade surface osteosarcoma

Parosteal osteosarcoma appears as a lobulated, exophytic nodule attached to the cortex by a short, broad stalk (Fig. 14-80). There is no elevation of the periosteum and no peripheral periosteal reaction. Radiographs may demonstrate a radiolucent line ("string sign") that corresponds to the periosteum between the sclerotic tumor and the underlying cortex. Histopathologic examination shows a spindle cell fibroblast-like proliferation with well-developed, elongated bony trabeculae, often arranged in a parallel streaming or "pulled steel wool" pattern. A cartilaginous component also may be evident in some cases. Parosteal osteosarcomas are low-grade tumors, with a low risk for recurrence and metastasis following radical excision. However, long-standing or inadequately excised tumors may become higher grade osteosarcomas.

Periosteal osteosarcoma appears as a sessile lesion that arises between the cortex and the inner (or cambium) layer of the periosteum (see Fig. 14-80). Thus, a periosteal reaction often is evident radiographically. The tumor frequently perforates the periosteum and extends into the surrounding soft tissue. Histopathologically, the tumor demonstrates primitive sarcomatous cells with chondroblastic differentiation. Close inspection reveals focal osteoid or immature bone formation. Radical surgical excision is the therapy of choice. Periosteal osteosarcoma is an intermediate-grade tumor, with a prognosis better than conventional intramedullary osteosarcoma but worse than parosteal osteosarcoma.

High-grade surface osteosarcoma is extremely rare. This variant is similar to conventional intramedullary osteosarcoma in terms of microscopic features and biologic behavior.

POSTIRRADIATION BONE SARCOMA

Sarcoma arising in bone previously subjected to radiation therapy is an uncommon but well-recognized phenomenon. The jaws and craniofacial bones are among the more common sites for such tumors. Bone sarcomas have been reported to develop 3 to 55 years after radiation exposure, with a mean latency period of about 4 to 17 years. Studies estimate that 0.03% to 0.2% of irradiated patients develop postirradiation bone or soft tissue sarcomas. The risk appears to increase with increasing radiation dose. Reported mean and median radiation doses for postirradiation bone sarcomas vary from 43 to 64 Gy. Some investigators have suggested that the risk is negligible with a dose less than 10 Gy; however, a recent prospective study of atomic bomb survivors in Japan suggests an increased risk for bone sarcoma with a radiation dose as low as 0.85 Gy. **Osteosarcoma** is the most common postirradiation bone sarcoma type, accounting for 49% to 85% of cases. Other reported types include undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma), fibrosarcoma, and chondrosarcoma. The lesions tend to be poorly differentiated, and the prognosis is generally poor.

◆ CHONDROSARCOMA

Chondrosarcoma is a malignant neoplasm in which the tumor cells form cartilage but not bone. Chondrosarcoma is about half as common as osteosarcoma and twice as common as Ewing sarcoma. Chondrosarcomas comprise about 11% of all primary malignant bone tumors but involve the jaws only rarely. Approximately 1% to 12% of all chondrosarcomas arise in the head and neck, and such lesions comprise only 0.1% of all head and neck malignancies.

Chondrosarcoma may develop *de novo (primary chondrosarcoma)* or from a preexisting benign cartilaginous tumor *(secondary chondrosarcoma).* The histogenesis is controversial; investigators have hypothesized that the tumor may originate from chondrocytes, embryonal chondroid, or pluripotential mesenchymal stem cells. Interestingly, there is an increased risk for chondrosarcoma among patients with Ollier disease and Maffucci syndrome (see page 611). These forms of chondromatosis are associated with somatic mutations in isocitrate dehydrogenase 1 *(IDH1)* gene and isocitrate dehydrogenase 2 *(IDH2)* gene; likewise, chondromas and chondrosarcomas of bone frequently exhibit *IDH1* mutations.

Clinical and Radiographic Findings

Although chondrosarcoma develops over a broad age range, most affected patients are older. In the United States, the mean age at diagnosis is approximately 51 years, and there is a slight male predilection. The most frequently involved sites are the ilium, femur, humerus, and ribs.

Gnathic chondrosarcomas exhibit a predilection for the anterior maxilla. In contrast, mandibular tumors tend to favor the posterior region. Other possible sites of involvement in the head and neck include the paranasal sinuses, nasal septum, skull base, and cervical vertebrae. Most head and neck chondrosarcomas develop within bone, but approximately one-third of cases originate in either laryngotracheal cartilage or soft tissue. According to one large case series, chondrosarcomas of gnathic and facial bones occur over a broad age range with peak prevalence in the seventh decade and a mean age at diagnosis of approximately 42 years. Some studies have noted a greater proportion of young patients with craniofacial chondrosarcomas compared to chondrosarcomas in other sites; however, other studies have not confirmed this finding.

A painless swelling is the most common presenting sign. In contrast to osteosarcoma, pain is an unusual complaint. Jaw lesions may cause separation or loosening of teeth. Maxillary tumors may cause nasal obstruction, congestion, epistaxis, photophobia, or visual loss.

Radiographically, chondrosarcoma usually appears as an ill-defined radiolucency with radiopaque foci (Fig. 14-81). These radiopaque foci correspond to calcification or ossification of the cartilage matrix. Some cases show extensive calcification and primarily appear radiopaque. Infrequently, there is lobular growth with minimal or no calcification; such lesions may appear as multilocular radiolucencies that mimic a benign process. Penetration of the cortex can result in a sunburst pattern similar to that seen in some osteosarcomas. Jaw tumors may cause root resorption or symmetrical widening of the periodontal ligament space of adjacent teeth.

Chondrosarcomas tend to be highly infiltrative. Although plain radiography typically is used for initial evaluation, MRI is the best method for assessing tumor extent. In addition, CT may help to demonstrate calcifications.

Histopathologic Features

Chondrosarcomas are composed of cartilage showing varying degrees of maturation and cellularity. In most cases, lacunar formation within the chondroid matrix is evident, although this feature may be scarce in poorly differentiated tumors. The tumor often shows a lobular growth pattern. The central areas of the lobules demonstrate the greatest degree of maturation, whereas the peripheral areas tend to exhibit immature cartilage and mesenchymal tissue consisting of round or spindle-shaped cells. Calcification or ossification may occur within the chondroid matrix. Neoplastic cartilage may be replaced by bone in a manner similar to normal endochondral ossification. Distinction between metaplastic bone formation and malignant osteoid production is important for differentiating chondrosarcoma from chondroblastic osteosarcoma.

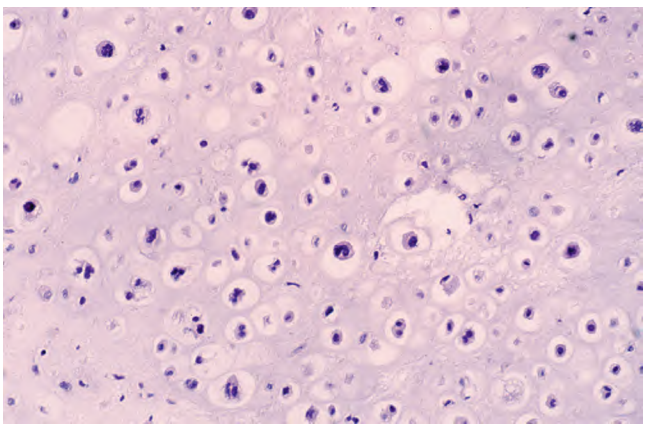
Chondrosarcomas may be assigned a histopathologic grade of I through III. Low-grade tumors closely resemble normal cartilage and may be very difficult to distinguish from chondromas. With increasing tumor grade, there is a decreased amount of cartilaginous matrix but increased cellularity, nuclear size, nuclear pleomorphism, binucleated or multinucleated chondrocytes, cellular spindling, mitotic activity, and necrosis. Most chondrosarcomas of the jaws are grade I or II (Fig. 14-82).

Variants

Uncommon microscopic variants of chondrosarcoma include the following:

- **Clear cell chondrosarcoma** is a low-grade variant exhibiting cells with abundant clear cytoplasm. This variant may be difficult to differentiate from metastatic clear cell carcinoma.

• **Fig. 14-81 Chondrosarcoma.** Ill-defined radiolucent lesion of posterior mandible containing radiopaque foci. (Courtesy of Dr. Ben B. Henry.)



• **Fig. 14-82 Chondrosarcoma.** This grade II chondrosarcoma shows a variation in size of chondrocyte nuclei. Occasional double nuclei are seen in the lacunae.

- **Dedifferentiated chondrosarcoma** is a high-grade variant that shows an admixture of well-differentiated chondrosarcoma and a high-grade sarcoma. This variant is exceedingly rare in the jaws.
- **Myxoid chondrosarcoma** classically is described as a soft tissue tumor, although intraosseous lesions are possible. This variant is characterized by a proliferation of cells with clear, vacuolated, or eosinophilic cytoplasm within a background of mucoid material.
- **Mesenchymal chondrosarcoma** is discussed in the next section.

Treatment and Prognosis

Surgical resection is the mainstay of treatment for chondrosarcoma. Curettage followed by cryosurgery may be an alternative for grade I chondrosarcomas confined within bone, although this technique mainly is used for long bone tumors. Radiation and chemotherapy are less effective for chondrosarcoma than osteosarcoma and are used primarily for high-grade chondrosarcomas. Radiation also may be considered for residual, recurrent, or unresectable disease.

Major prognostic factors for chondrosarcoma include clinical stage, histopathologic grade, and adequacy of resection. In the United States, the relative 5-year survival rate is approximately 75%. The 30-year disease-specific survival rates for patients with localized disease, regional metastasis, and distant metastasis are 43%, 22%, and less than 10%, respectively. Because recurrence often is a late sequela, patients must be followed for their lifetime.

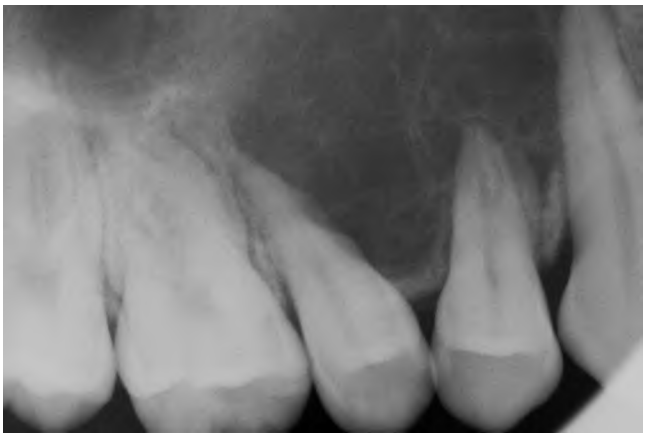
Head and neck chondrosarcomas typically are locally aggressive with low metastatic potential. Metastasis mainly is seen among rare high-grade tumors. Nevertheless, death may occur by direct extension into vital structures. In particular, maxillary tumors often are large at diagnosis, occur adjacent to the central nervous system, and are difficult to resect; therefore, they are difficult to cure. In the National Cancer Database series of 400 head and neck chondrosarcomas, the overall 5- and 10-year disease-specific survival rates were 87.2% and 70.6%, respectively. In the Mayo Clinic series of 56 chondrosarcomas of the jaws and facial bones, the 5-, 10-, and 15-year survival rates were 67.6%, 53.7%, and 43.9%, respectively.

MESENCHYMAL CHONDROSARCOMA

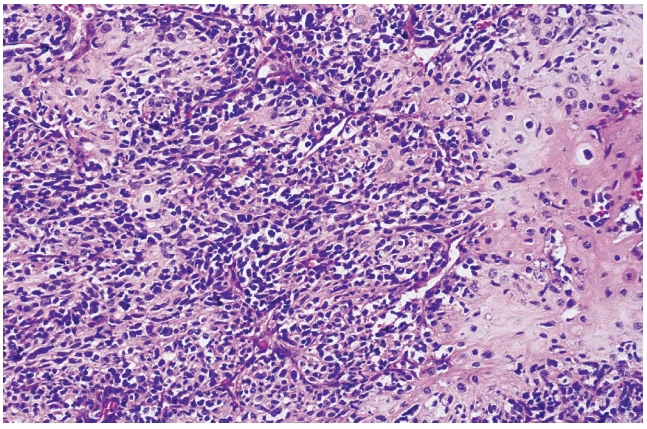
Mesenchymal chondrosarcoma is an aggressive variant of chondrosarcoma with a distinctive biphasic histopathologic pattern. It is considered high-grade based on clinical behavior rather than histopathologic features. This variant represents only about 1% to 9% of all chondrosarcomas.

Clinical and Radiographic Features

In contrast to other chondrosarcoma types, the mesenchymal variant is unusual in that it most frequently affects individuals in the second and third decades of life and most often arises in the jaws (22% to 27% of cases). Other commonly affected sites are the ribs, shoulder, pelvic girdle, and vertebrae. In addition, about one-third of cases arise in soft tissue rather than bone.



• **Fig. 14-83 Mesenchymal Chondrosarcoma.** Periapical radiograph showing an ill-defined radiolucency with associated root resorption. (Courtesy of Dr. Michael Robinson.)



• **Fig. 14-84 Mesenchymal Chondrosarcoma.** Medium-power photomicrograph showing sheets of small basophilic cells with focal areas of cartilaginous differentiation *(right).*

Swelling and pain, often of fairly short duration, are the most common symptoms. Radiographically, the tumor typically appears as an ill-defined radiolucency with or without stippled calcification (Fig. 14-83). However, some examples may appear predominantly radiopaque, particularly within the maxilla.

Histopathologic Features

Microscopic examination shows two distinct elements: well-differentiated cartilaginous nodules and sheets of small, undifferentiated, spindled or round cells (Fig. 14-84). The degree of cellularity and atypia within the cartilaginous component may vary from that of a benign chondroma to a low-grade chondrosarcoma. The undifferentiated component may exhibit a branching vascular pattern that mimics hemangiopericytoma. In addition, the undifferentiated

component may appear similar to rhabdomyosarcoma, Ewing sarcoma, lymphoma, or metastatic small cell carcinoma.

Treatment and Prognosis

Surgical excision with wide margins is the mainstay of therapy. Some studies have suggested that supplemental radiation therapy and/or chemotherapy may be beneficial, although further investigation is needed. Close long-term follow-up is recommended, because local recurrence and metastasis are common and may be discovered more than 20 years after initial therapy. Metastasis most frequently develops in the lungs. Reported overall 5- and 10-year survival rates range from 35% to 65% and 20% to 40%, respectively. Some authors have suggested that jaw lesions exhibit a favorable prognosis with a 5-year survival rate of 82%, although a recent review of maxillary lesions reported a 5-year survival rate of only 59%.

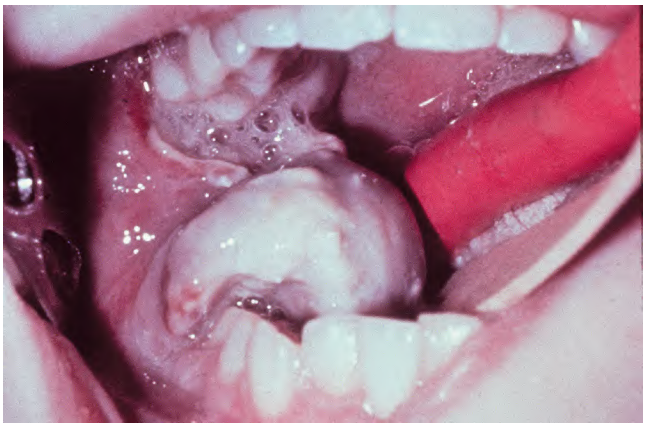
◆ EWING SARCOMA

Ewing sarcoma is a malignant neoplasm composed of small, undifferentiated round cells. In the United States, the annual incidence is approximately 1 per million population. Although rare, Ewing sarcoma is the second most common primary malignant bone tumor in pediatric patients after osteosarcoma. The term *Ewing sarcoma* (or the *Ewing sarcoma family of tumors*) includes classical Ewing sarcoma of bone, extraosseous Ewing sarcoma, primitive neuroectodermal tumor (Ewing sarcoma with neuronal differentiation), and Askin tumor (small round cell tumor of the chest wall). Based on shared histologic, immunohistochemical, and genetic characteristics, authorities currently consider these entities to represent the same tumor type.

The histogenesis of Ewing sarcoma is unknown. Investigators previously have hypothesized that the tumor originates from the neural crest. However, current evidence favors an origin from mesenchymal stem cells with potential for limited neural differentiation. At the molecular level, Ewing sarcoma is defined by balanced chromosomal translocations that result in fusion of the RNA-binding protein EWS (or the closely related FUS protein) with ETS family transcription factors (e.g., FLI1, ERG, ETV1, ETV4, and FEV). In particular, more than 85% of cases demonstrate the translocation t(11;22) (q24;q12), which encodes the EWS-FLI1 fusion protein.

Clinical and Radiographic Features

Most patients with Ewing sarcoma are adolescents, and the median age at diagnosis is 15 years. However, advances in molecular diagnosis have led to a recent increase in the number of cases diagnosed in young adults. There is a slight male predominance, and the majority of patients are white. Osseous lesions most frequently involve the long bones, pelvis, and ribs. Only 1% to 2% of cases arise in the gnathic or craniofacial bones. Primary extraosseous lesions are also possible but very rare.



• **Fig. 14-85 Ewing Sarcoma.** A rapidly growing, ulcerated tumor of the right posterior mandible. (Courtesy of Dr. George Blozis.)

The most common clinical findings are pain and swelling. Fever, leukocytosis, and an elevated erythrocyte sedimentation rate also may be present in advanced disease. The tumor often penetrates the cortex, resulting in a soft tissue mass overlying the affected area of the bone (Fig. 14-85). Jaw involvement is more common in the mandible than the maxilla and may result in paresthesia and tooth mobility. The nonspecific clinicoradiographic presentation may lead to a misdiagnosis of odontogenic infection or osteomyelitis.

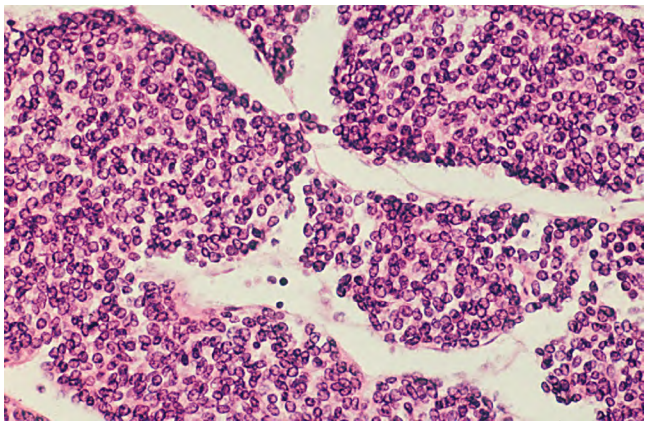
Radiographically, most osseous lesions appear as ill-defined radiolucencies, although a mixed radiolucent and radiopaque pattern also is possible. Cortical destruction or expansion may or may not be present. The characteristic "onionskin" periosteal reaction, commonly observed in Ewing sarcoma of long bones, seldom is seen in jaw lesions. Although plain radiography often is used for initial evaluation, CT and MRI are superior for assessing lesion extent.

Histopathologic Features

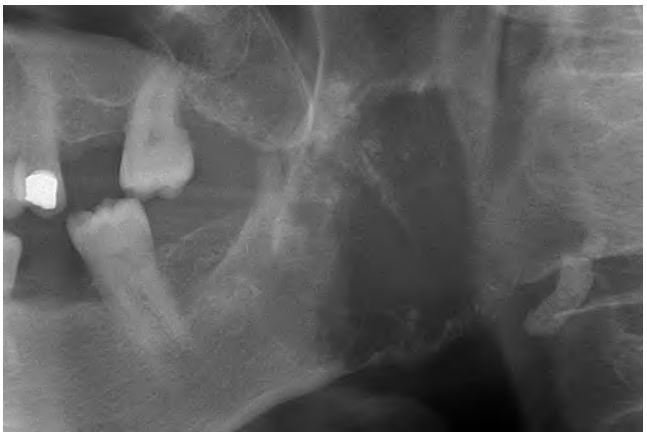
Ewing sarcoma typically is composed of broad sheets of small, monotonous, round cells with well-delineated nuclear outlines and ill-defined cellular borders (Fig. 14-86). In some cases, variable-sized nests of tumor cells are separated by fibrovascular septa, creating a lobular pattern. Extensive necrosis and hemorrhage are common.

Diagnosis may be difficult. Ewing sarcoma must be differentiated from other pediatric small round cell tumors, such as metastatic neuroblastoma, malignant lymphoma, small cell osteosarcoma, and alveolar rhabdomyosarcoma. Metastatic small cell carcinoma also may be considered in the differential diagnosis of a suspected Ewing sarcoma in an older patient.

Ewing sarcomas typically exhibit cytoplasmic periodic acid-Schiff (PAS)-positive glycogen granules and membranous immunoreactivity for CD99 (MIC2), although these findings are nonspecific. Immunohistochemical expression



• **Fig. 14-86 Ewing Sarcoma.** Broad sheets of small round cells with well-defined nuclear outlines and ill-defined cytoplasmic borders.



• **Fig. 14-87 Thyroid Carcinoma Metastatic to the Jaws.** Radiograph showing an ill-defined, destructive radiolucency with irregular borders at the angle of the mandible. (Courtesy of Dr. Terry Day.)

of Fli1 also has been described, although with variable sensitivity and specificity. Identification of characteristic chromosomal translocations by reverse transcription polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybridization (FISH) may aid in confirming the diagnosis.

Treatment and Prognosis

Treatment usually consists of multidrug chemotherapy with surgery and/or radiotherapy. Systemic chemotherapy typically is indicated, because seemingly localized disease often is associated with occult micrometastases. Investigational treatments include insulin-like growth factor-1 receptor (IGF1R) blocking agents and myeloablative stem cell transplantation.

With the development of modern multimodal therapy, the prognosis for patients with Ewing sarcoma has improved dramatically in recent decades. Current 5-year survival rates for patients with apparently localized versus metastatic disease at presentation are approximately 70% and 25%, respectively. The presence of metastasis is the most important prognostic factor, and metastasis is evident at initial diagnosis in about 25% of patients. The most common sites of metastasis are the lungs and bones; for reasons unknown, patients with extrapulmonary metastasis tend to fare worse than those with metastasis confined to the lungs. There is limited data regarding gnathic Ewing sarcoma, although lesions arising in the jaws appear to exhibit a more favorable prognosis compared to those arising in the long bones and pelvis.

◆ METASTATIC TUMORS TO THE JAWS

Metastatic carcinoma is the most common form of cancer involving bone. The most common primary sites for carcinomas that metastasize to bone are the breast, lung, thyroid, prostate, and kidney. The bones that most frequently exhibit metastasis include the vertebrae, ribs, pelvis, and skull.

Jaw metastasis is rare but may occur more often than generally appreciated. In an autopsy study of mandibles from patients with various extraoral primary carcinomas, microscopic examination revealed metastasis in 16% of cases, with most of these metastases found to be clinically, radiographically, and grossly undetectable. Metastatic spread of a carcinoma to the jaws usually occurs by the hematogenous route. Sarcomas arising in soft tissues or other bones metastasize to the jaws only very rarely.

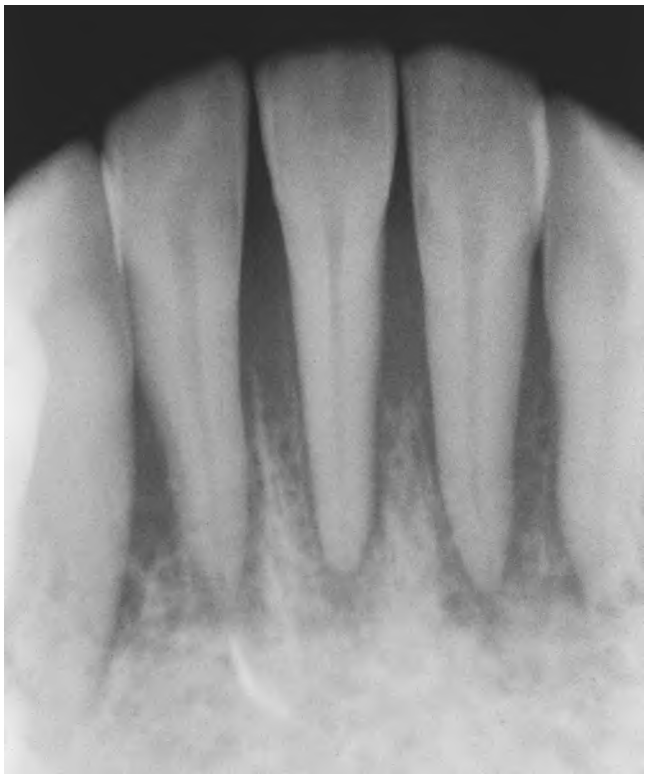
Clinical and Radiographic Features

Jaw metastases have been reported over a broad age range but most often affect older adults; the mean age is approximately 43 to 52 years, with no significant gender bias. There is a marked predilection for the mandible, especially the molar region.

Clinical signs and symptoms of jaw metastasis may include pain, swelling, tooth mobility, trismus, and paresthesia. In particular, mandibular metastasis with involvement of the mental nerve may produce paresthesia in the lower lip and chin **(numb-chin syndrome).** The rarity of jaw metastases and the nonspecific clinical presentation may lead to a mistaken impression of an inflammatory process. Sometimes an osseous metastasis is discovered in a nonhealing extraction site from which a tooth was removed because of local pain or significant mobility. In other instances, the patient may be completely asymptomatic, and the lesion is discovered incidentally by radiographic examination.

Occasionally, diagnosis of a jaw metastasis is the first indication that the patient has a primary malignancy at some other anatomic site. Location of the occult primary tumor may be difficult and may require extensive evaluation.

Most radiographically evident jaw metastases appear as ill-defined or "moth-eaten" radiolucencies (Fig. 14-87). However, some examples—particularly metastatic prostate and breast carcinomas—may appear radiopaque or mixed radiocent-radiopaque. *Osteolytic* (bone-resorbing) and/or *osteoblastic* (bone-forming) activity may result from various growth factors and other substances produced by tumor



• **Fig. 14-88 Carcinoma Metastatic to the Jaws.** Periapical radiograph showing widening of the periodontal ligament spaces.

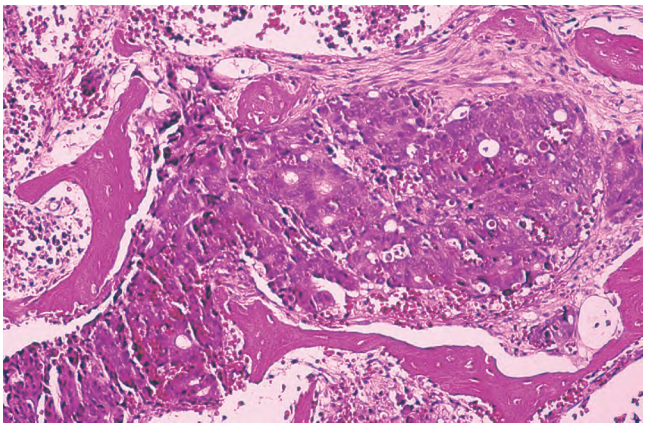
cells. Some lesions may mimic periapical inflammatory disease or periodontal disease. Cortical erosion, pathologic fracture, and widening of the periodontal ligament space may be noted as well (Fig. 14-88). Compared to plain radiography, bone scintigraphy is more sensitive for detecting osseous metastases.

Histopathologic Features

The microscopic appearance of metastatic carcinoma in bone varies. In some instances, the metastasis exhibits well-differentiated features that suggest an origin from a specific site, such as the kidney, colon, or thyroid. More often, however, metastatic carcinomas are poorly differentiated, and the tumor origin is not readily apparent (Fig. 14-89). Poorly differentiated metastatic carcinoma may be difficult to differentiate from lymphoma, melanoma, or anaplastic sarcoma. In such cases, immunohistochemistry may aid in diagnosis. Definitive diagnosis requires correlation of laboratory studies with a thorough medical history, complete physical examination, and imaging studies.

Treatment and Prognosis

Although a solitary metastatic focus may be treated by excision or radiation therapy, jaw metastasis almost always is associated with widely disseminated disease. Management depends on the specific underlying tumor type and often is palliative in nature. Administration of bisphosphonates may help to slow progression of bone metastases, decrease bone pain, and reduce the risk for pathologic fracture. By definition, osseous metastasis constitutes stage IV disease. Accordingly, the prognosis for metastatic carcinoma to the jaws is poor, and most patients survive less than 1 year.



• **Fig. 14-89 Carcinoma Metastatic to the Jaws.** Islands of malignant cells can be seen filling the marrow spaces.

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15 Odontogenic Cysts and Tumors

Odontogenic cysts and tumors constitute an important aspect of oral and maxillofacial pathology. Odontogenic cysts are encountered relatively commonly in dental practice. Odontogenic tumors, by contrast, are uncommon lesions. Even in the specialized oral and maxillofacial pathology laboratory, less than 1% of all specimens received are odontogenic tumors.

ODONTOGENIC CYSTS

With rare exceptions, epithelium-lined cysts in bone are seen only in the jaws. Other than a few cysts that may result from the inclusion of epithelium along embryonic lines of fusion, most jaw cysts are lined by epithelium that is derived from odontogenic epithelium. These are referred to as **odontogenic cysts.** (Nonodontogenic jaw cysts are discussed in Chapter 1.)

Odontogenic cysts are subclassified as developmental or inflammatory in origin. The inciting factors that initiate the formation of **developmental cysts** are unknown, but these lesions do not appear to be the result of an inflammatory reaction. **Inflammatory cysts** are the result of inflammation. Box 15-1 presents categories of odontogenic cysts modified from the 2005 World Health Organization (WHO) classification. (The periapical cyst is discussed in Chapter 3.)

◆ DENTIGEROUS CYST (FOLLICULAR CYST)

The **dentigerous cyst** is defined as a cyst that originates by the separation of the follicle from around the crown of an unerupted tooth. This is the most common type of developmental odontogenic cyst, making up about 20% of all epithelium-lined cysts of the jaws. The dentigerous cyst encloses the crown of an unerupted tooth and is attached to the tooth at the cementoenamel junction (Fig. 15-1). The pathogenesis of this cyst is uncertain, but apparently it develops by accumulation of fluid between the reduced enamel epithelium and the tooth crown.

Although most dentigerous cysts are considered to be developmental in origin, there are some examples that appear to have an inflammatory pathogenesis. For example, it has been suggested that, on occasion, a dentigerous cyst may develop around the crown of an unerupted permanent tooth as a result of periapical inflammation from an overlying primary tooth. Another scenario involves a partially erupted mandibular third molar that develops an inflamed cystlike lesion along the distal or buccal aspect. Although many such lesions probably are due to inflammation associated with recurrent pericoronitis, these lesions are usually diagnosed as examples of dentigerous cyst, especially because it is impossible to determine histopathologically whether the inflammatory component is primary or secondary in nature. The term **paradental cyst** sometimes has been applied to these lesions, but the use of this term in the literature is confusing because it also has been used to describe examples of what is known as the *buccal bifurcation cyst* (see page 650).

Clinical and Radiographic Features

Although dentigerous cysts may occur in association with any unerupted tooth, most often they involve mandibular third molars, accounting for approximately 65% of all cases. Other relatively frequent sites include maxillary canines, maxillary third molars, and mandibular second premolars. Dentigerous cysts rarely involve unerupted deciduous teeth. Occasionally, they are associated with supernumerary teeth or odontomas. Multiple dentigerous cysts have been reported, although this is an infrequent finding.

Although dentigerous cysts may be encountered in patients across a wide age range, they are discovered most frequently in patients between 10 and 30 years of age. There is a slight male predilection, and the prevalence is higher for whites than for blacks. Small dentigerous cysts are usually completely asymptomatic and are discovered only on a routine radiographic examination or when films are taken to determine the reason for the failure of a tooth to erupt. Dentigerous cysts can grow to a considerable size, and large cysts may be associated with a painless expansion of the bone in the involved area. Extensive lesions may result in facial asymmetry. Large dentigerous cysts are uncommon, and most lesions that are considered to be large dentigerous cysts on radiographic examination prove to be odontogenic keratocysts (OKCs) or ameloblastomas. Dentigerous cysts may become infected and be associated with

• BOX 15-1 Classification of Odontogenic Cysts

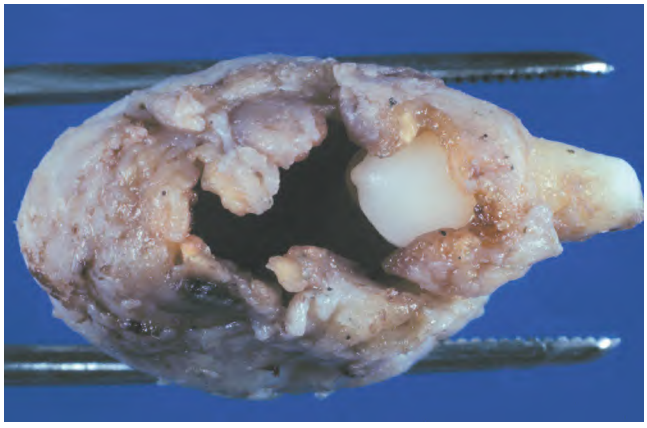
Developmental

- Dentigerous cyst
- Eruption cyst
- Odontogenic keratocyst (OKC)*
- Orthokeratinized odontogenic cyst
- Gingival (alveolar) cyst of the newborn
- Gingival cyst of the adult
- Lateral periodontal cyst
- Calcifying odontogenic cyst†
- Glandular odontogenic cyst

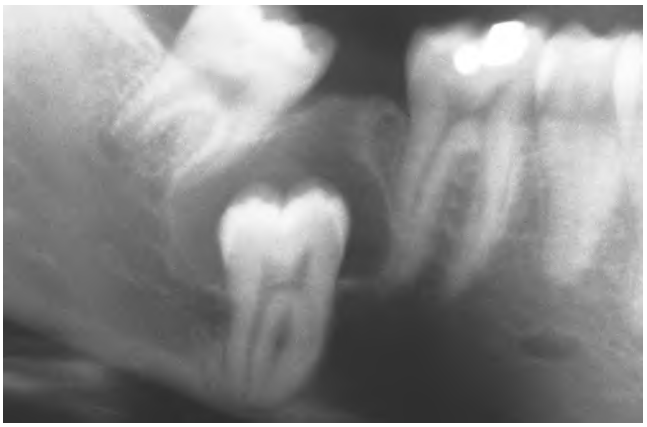
Inflammatory

- Periapical (radicular) cyst
- Residual periapical (radicular) cyst
- Buccal bifurcation cyst

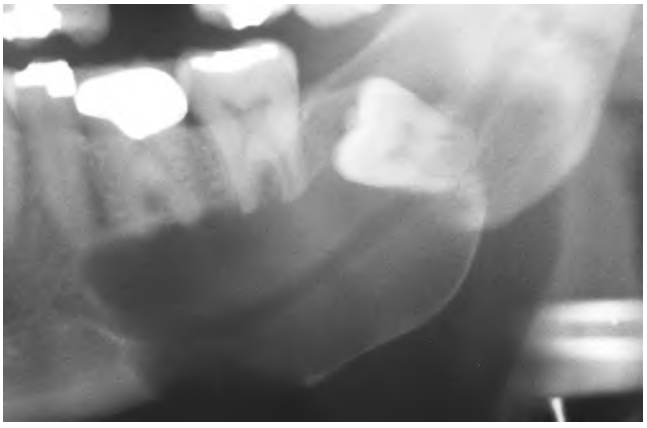
*Although the OKC is included with the odontogenic tumors in the 2005 World Health Organization (WHO) classification ("keratocystic odontogenic tumor"), the authors still favor including it in the odontogenic cyst category.
†Although the calcifying odontogenic cyst is included with odontogenic tumors in the 2005 WHO classification ("calcifying cystic odontogenic tumor"), it is discussed with the odontogenic cysts in this chapter.



• **Fig. 15-1 Dentigerous Cyst.** Gross specimen of a dentigerous cyst involving a maxillary canine tooth. The cyst has been cut open to show the cyst-to-crown relationship.



• **Fig. 15-2 Dentigerous Cyst.** Central type showing the crown projecting into the cystic cavity. (Courtesy of Dr. Stephen E. Irwin.)

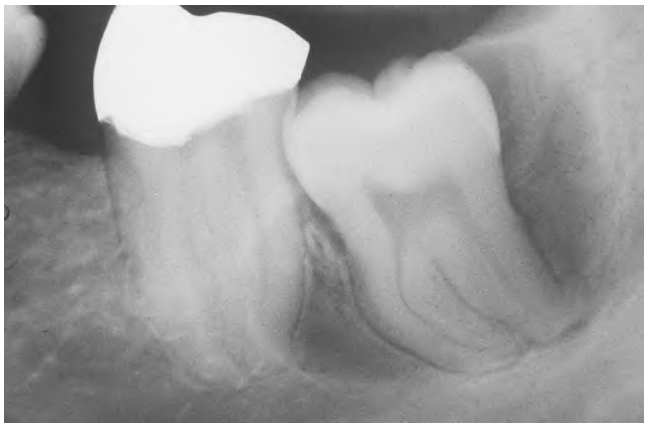


• **Fig. 15-3 Dentigerous Cyst.** Lateral variety showing a large cyst along the mesial root of the unerupted molar. This cyst exhibited mucous cell prosoplasia. (Courtesy of Dr. John R. Cramer.)

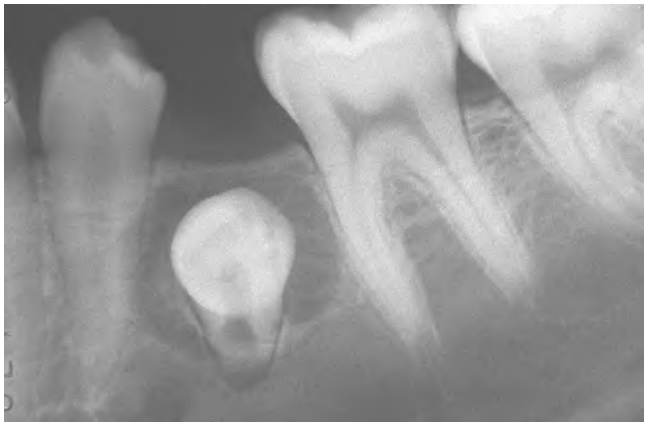
pain and swelling. Such infections may arise in a dentigerous cyst that is associated with a partially erupted tooth or by extension from a periapical or periodontal lesion that affects an adjacent tooth.

Radiographically, the dentigerous cyst typically shows a unilocular radiolucent area that is associated with the crown of an unerupted tooth. The radiolucency usually has a well-defined and often corticated border, but an infected cyst may show ill-defined borders. A large dentigerous cyst may give the impression of a multilocular process because of the persistence of bone trabeculae within the radiolucency. The cyst-to-crown relationship shows several radiographic variations. In the **central** variety, which is the most common, the cyst surrounds the crown of the tooth and the crown projects into the cyst (Fig. 15-2). The **lateral** variety is usually associated with mesioangular impacted mandibular third molars that are partially erupted. The cyst grows laterally along the root surface and partially surrounds the crown (Fig. 15-3). In the **circumferential** variant, the cyst surrounds the crown and extends for some distance along the root so that a significant portion of the root appears to lie within the cyst (Fig. 15-4). Rarely, a third molar may be displaced to the lower border of the mandible or higher up into the ascending ramus. Maxillary anterior teeth may be displaced into the floor of the nose, and other maxillary teeth may be moved through the maxillary sinus to the floor of the orbit. Dentigerous cysts may displace the involved tooth for a considerable distance. Root resorption of adjacent erupted teeth can occur.

Radiographic distinction between a small dentigerous cyst and an enlarged follicle about the crown of an unerupted tooth is difficult and may be largely an academic exercise (Fig. 15-5). For the lesion to be considered a dentigerous cyst, some investigators believe that the radiolucent space surrounding the tooth crown should be at least 3 to 4 mm in diameter. Radiographic findings are not diagnostic for a dentigerous cyst, however, because OKCs, unilocular ameloblastomas, and many other odontogenic and nonodontogenic tumors may have



• **Fig. 15-4 Dentigerous Cyst.** Circumferential variety showing cyst extension along the mesial and distal roots of the unerupted tooth. (Courtesy of Dr. Richard Marks.)



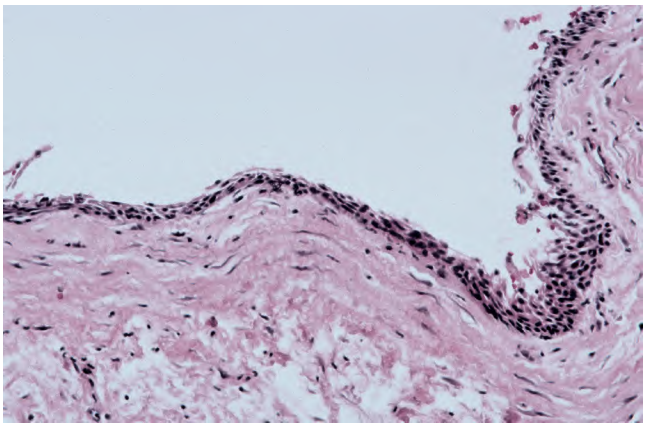
• **Fig. 15-5 Dentigerous Cyst or Enlarged Follicle.** Radiolucent lesion involving the crown of an unerupted mandibular premolar. Distinction between a dentigerous cyst and an enlarged follicle for a lesion of this size by radiographic and even histopathologic means is difficult, if not impossible. (Courtesy of Dr. Wally Austelle.)

radiographic features that are essentially identical to those of a dentigerous cyst.

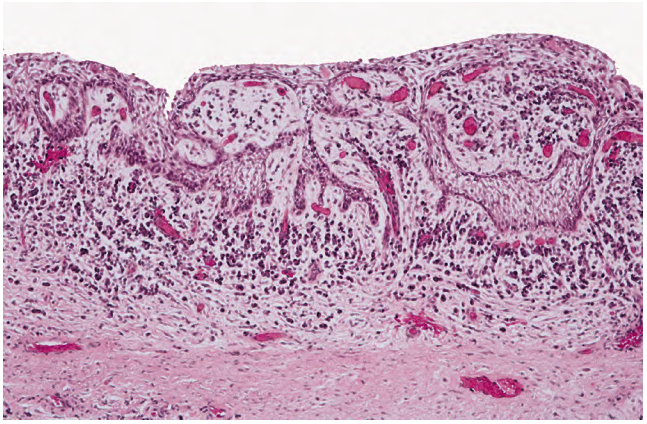
Histopathologic Features

The histopathologic features of dentigerous cysts vary, depending on whether the cyst is inflamed or not inflamed. In the **noninflamed dentigerous cyst,** the fibrous connective tissue wall is loosely arranged and contains considerable glycosaminoglycan ground substance. Small islands or cords of inactive-appearing odontogenic epithelial rests may be present in the fibrous wall. Occasionally these rests may be numerous, and at times pathologists who are not familiar with oral lesions have misinterpreted this finding as ameloblastoma. The epithelial lining consists of two to four layers of flattened nonkeratinizing cells, and the epithelium and connective tissue interface is flat (Fig. 15-6).

In the fairly common **inflamed dentigerous cyst,** the fibrous wall is more collagenized, with a variable infiltration of chronic inflammatory cells. The epithelial lining may show varying amounts of hyperplasia with the development



• **Fig. 15-6 Dentigerous Cyst.** This noninflamed dentigerous cyst shows a thin, nonkeratinized epithelial lining.

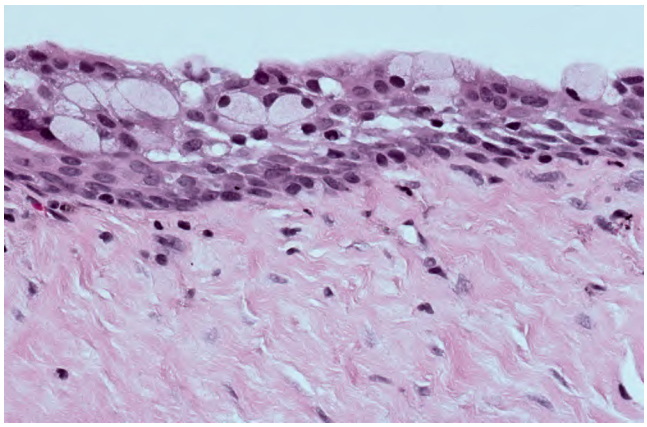


• **Fig. 15-7 Dentigerous Cyst.** This inflamed dentigerous cyst shows a thicker epithelial lining with hyperplastic rete ridges. The fibrous cyst capsule shows a diffuse chronic inflammatory infiltrate.

of rete ridges and more definite squamous features (Fig. 15-7). A keratinized surface is sometimes seen, but these changes must be differentiated from those observed in the OKC. Focal areas of mucous cells may be found in the epithelial lining of dentigerous cysts (Fig. 15-8). Rarely, ciliated columnar cells are present. Small nests of sebaceous cells rarely may be noted within the fibrous cyst wall. These mucous, ciliated, and sebaceous elements are believed to represent the multipotentiality of the odontogenic epithelial lining in a dentigerous cyst.

Gross examination of the wall of a dentigerous cyst may reveal one or several areas of nodular thickening on the luminal surface. These areas must be examined microscopically to rule out the presence of early neoplastic change.

Because a thin layer of reduced enamel epithelium normally lines the dental follicle surrounding the crown of an unerupted tooth, it can be difficult to distinguish a small dentigerous cyst from simply a normal or enlarged dental follicle based on microscopic features alone. Again, this distinction often represents largely an academic exercise; the most important consideration is ensuring that the lesion does not represent a more significant pathologic process (e.g., OKC or ameloblastoma).



• **Fig. 15-8 Dentigerous Cyst.** Scattered mucous cells can be seen within the epithelial lining.

Treatment and Prognosis

The usual treatment for a dentigerous cyst is careful enucleation of the cyst together with removal of the unerupted tooth. If eruption of the involved tooth is considered feasible, then the tooth may be left in place after partial removal of the cyst wall. Patients may need orthodontic treatment to assist eruption. Large dentigerous cysts also may be treated by marsupialization. This permits decompression of the cyst, with a resulting reduction in the size of the bone defect. The cyst can then be excised at a later date, with a less extensive surgical procedure.

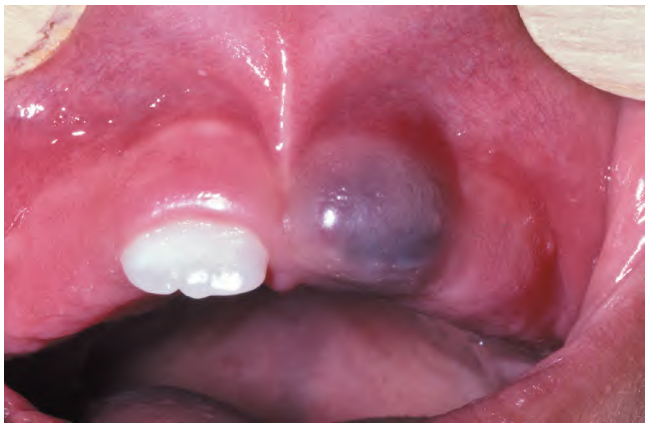
The prognosis for most dentigerous cysts is excellent, and recurrence seldom is noted after complete removal of the cyst. However, several potential complications must be considered. Much has been written about the possibility that the lining of a dentigerous cyst might undergo neoplastic transformation to an **ameloblastoma.** Although undoubtedly this can occur, the frequency of such neoplastic transformation is low. Rarely, a **squamous cell carcinoma** may arise in the lining of a dentigerous cyst (see page 651). It is likely that some **intraosseous mucoepidermoid carcinomas** (see page 457) develop from mucous cells in the lining of a dentigerous cyst.

◆ ERUPTION CYST (ERUPTION HEMATOMA)

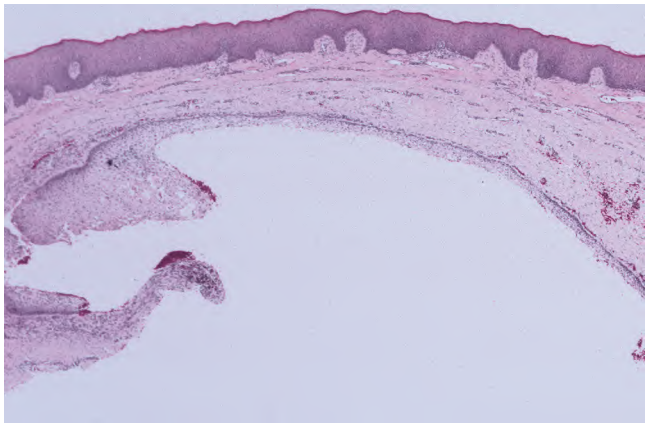
The **eruption cyst** is the soft tissue analogue of the dentigerous cyst. The cyst develops as a result of separation of the dental follicle from around the crown of an erupting tooth that is within the soft tissues overlying the alveolar bone.

Clinical Features

The eruption cyst appears as a soft, often translucent swelling in the gingival mucosa overlying the crown of an erupting deciduous or permanent tooth. Most examples are seen in children younger than age 10. Although the cyst may occur with any erupting tooth, the lesion is most commonly



• **Fig. 15-9 Eruption Cyst.** This soft gingival swelling contains considerable blood and can also be designated as an eruption hematoma.



• **Fig. 15-10 Eruption Cyst.** A cystic epithelial cavity can be seen below the mucosal surface.

associated with the deciduous mandibular central incisors, the first permanent molars, and the deciduous maxillary incisors. Surface trauma may result in a considerable amount of blood in the cystic fluid, which imparts a blue to purple-brown color. Such lesions sometimes are referred to as **eruption hematomas** (Fig. 15-9).

Histopathologic Features

Intact eruption cysts seldom are submitted to the oral and maxillofacial pathology laboratory, and most examples consist of the excised roof of the cyst, which has been removed to facilitate tooth eruption. These show surface oral epithelium on the superior aspect. The underlying lamina propria shows a variable inflammatory cell infiltrate. The deep portion of the specimen, which represents the roof of the cyst, shows a thin layer of nonkeratinizing squamous epithelium (Fig. 15-10).

Treatment and Prognosis

Treatment may not be required because the cyst usually ruptures spontaneously, permitting the tooth to erupt. If

this does not occur, then simple excision of the roof of the cyst generally permits speedy eruption of the tooth.

PRIMORDIAL CYST

The concept and meaning of the term **primordial cyst** often have been controversial and confusing. In the older classification of cysts used in the United States, the primordial cyst was considered to originate from cystic degeneration of the enamel organ epithelium before the development of dental hard tissue. Therefore, the primordial cyst would occur in place of a tooth.

In the mid-1950s, oral and maxillofacial pathologists in Europe introduced the term **odontogenic keratocyst (OKC)** to denote a cyst with specific histopathologic features and clinical behavior, which was believed to arise from the dental lamina (i.e., the dental primordium). Subsequently, this concept was widely accepted, and the terms *odontogenic keratocyst* and *primordial cyst* were used synonymously. The 1972 WHO classification used the designation *primordial cyst* as the preferred term for this lesion. The 1992 WHO classification, however, listed *odontogenic keratocyst* as the preferred designation.

Almost all examples of so-called primordial cysts (i.e., a cyst that develops in the place of a tooth) microscopically will be OKCs (Fig. 15-11). Whether there could be such a radiographic presentation that is not microscopically an OKC is still unsettled. If such a lesion exists, then it must be exceedingly rare.

ODONTOGENIC KERATOCYST (KERATOCYSTIC ODONTOGENIC TUMOR)

The **odontogenic keratocyst (OKC)** is a distinctive form of developmental odontogenic cyst that deserves special consideration because of its specific histopathologic features and clinical behavior. There is general agreement that the OKC arises from cell rests of the dental lamina. This cyst shows a different growth mechanism and biologic behavior from the more common dentigerous cyst and radicular cyst. Most authors believe that dentigerous and radicular cysts continue to enlarge as a result of increased osmotic pressure within the lumen of the cyst. This mechanism does not appear to hold true for OKCs, and their growth may be related to genetic factors inherent in the epithelium itself or enzymatic activity in the fibrous wall.

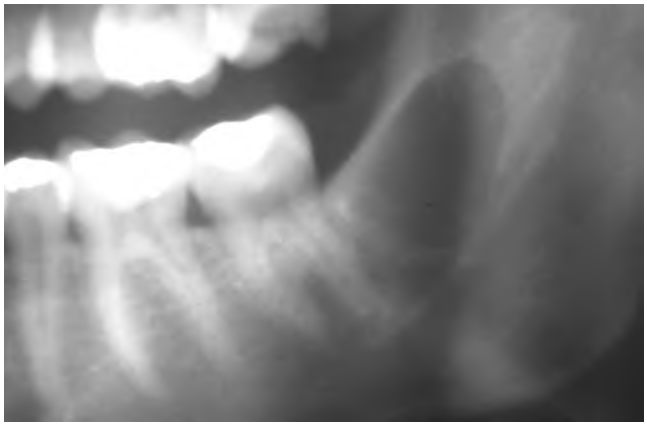


Fig. 15-11 Primordial Cyst. This patient gave no history of extraction of the third molar. A cyst is located in the third molar area. The cyst was excised, and histopathologic examination revealed an odontogenic keratocyst (OKC).

Several investigators have suggested that the OKC be regarded as a benign cystic neoplasm rather than a cyst, and in the latest WHO monograph on head and neck tumors, this lesion has been given the name **keratocystic odontogenic tumor (KCOT).** The arguments to support this change in nomenclature largely rely on studies that have shown certain molecular genetic alterations that are also present in some neoplasms. When compared to other odontogenic cysts, the OKC shows significantly greater expression of proliferating cell nuclear antigen (PCNA) and Ki-67, especially in the suprabasilar layer. Almost 30% of sporadic OKCs and over 85% of OKCs associated with the nevoid basal cell carcinoma syndrome show mutations of PTCH1, an important molecule in the Hedgehog signalling pathway. Also, genetic analyses have demonstrated loss of heterozygosity for various other tumor suppressor genes *(p16, p53, MCC, TSLC1, LATS2,* and *FHIT)* in many OKCs.

Whether such molecular findings warrant reclassification of the OKC as a neoplasm (KCOT) remains a hotly debated topic in oral pathology circles. The authors currently favor retaining "odontogenic keratocyst" as the primary term for this lesion, although both terms will be found in the literature and should be considered synonymous. Regardless of which term is preferred, these lesions are significant for three reasons:

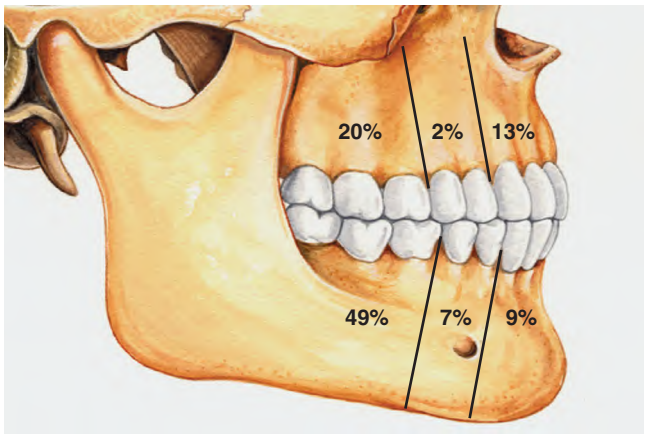
1. Greater growth potential than most other odontogenic cysts
2. Higher recurrence rate
3. Possible association with the nevoid basal cell carcinoma syndrome

Although there are wide variations in the reported frequency of OKCs compared with that of other types of odontogenic cysts, most studies indicate that OKCs make up 3% to 11% of all odontogenic cysts.

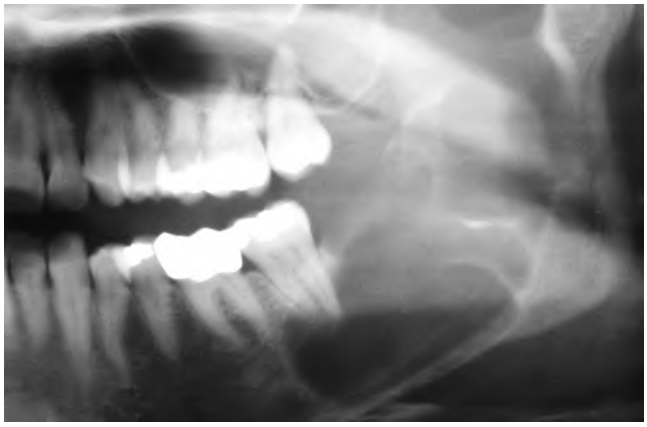
Clinical and Radiographic Features

OKCs may be found in patients who range in age from infancy to old age, but about 60% of all cases are diagnosed in people between 10 and 40 years of age. There is a slight male predilection. The mandible is involved in 60% to 80% of cases, with a marked tendency to involve the posterior body and ramus (Fig. 15-12).

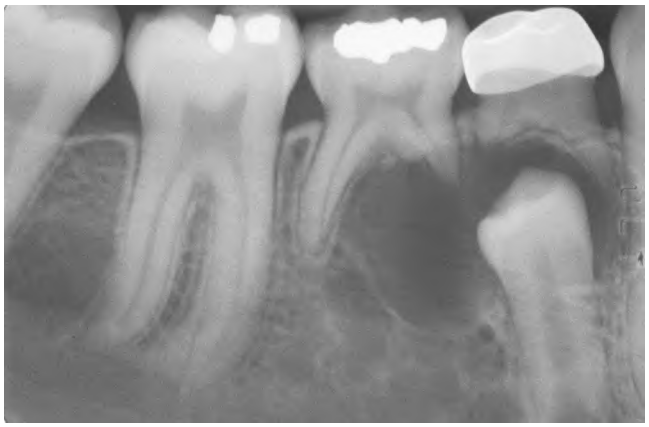
Small OKCs are usually asymptomatic and discovered only during the course of a radiographic examination.



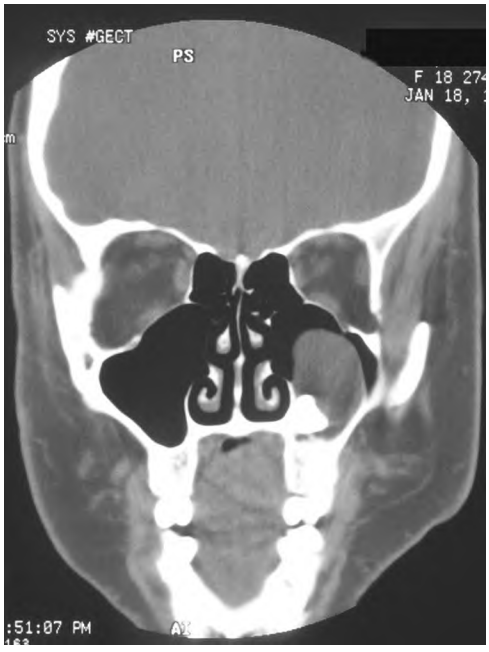
• **Fig. 15-12 Odontogenic Keratocyst (OKC).** Relative distribution of OKCs in the jaws.



• **Fig. 15-13 Odontogenic Keratocyst (OKC).** Large, multilocular cyst involving most of the ascending ramus. (Courtesy of Dr. S.C. Roddy.)



• **Fig. 15-14 Odontogenic Keratocyst (OKC).** This cyst involves the crown of an unerupted premolar. Radiographically, this lesion cannot be differentiated from a dentigerous cyst.



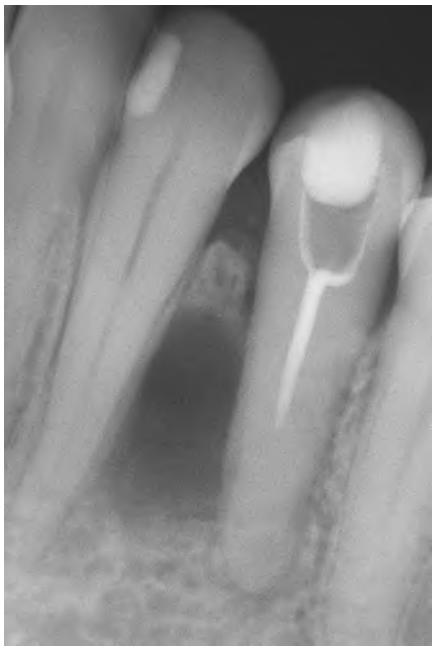
• **Fig. 15-15 Odontogenic Keratocyst (OKC).** Computed tomography (CT) scan showing a large cyst involving the crown of an unerupted maxillary third molar. The cyst largely fills the maxillary sinus. (Courtesy of Dr. E.B. Bass.)

Larger OKCs may be associated with pain, swelling, or drainage. Some extremely large cysts, however, may cause no symptoms.

OKCs tend to grow in an anteroposterior direction within the medullary cavity of the bone without causing obvious bone expansion. This feature may be useful in differential clinical and radiographic diagnosis because dentigerous and radicular cysts of comparable size are usually associated with bony expansion. Multiple OKCs may be present, and such patients should be evaluated for other manifestations of the **nevoid basal cell carcinoma (Gorlin) syndrome** (see page 640).

OKCs demonstrate a well-defined radiolucent area with smooth and often corticated margins. Large lesions, particularly in the posterior body and ramus of the mandible, may appear multilocular (Fig. 15-13). An unerupted tooth is involved in the lesion in 25% to 40% of cases; in such instances, the radiographic features suggest the diagnosis of dentigerous cyst (Figs. 15-14 and 15-15). In these cases, the cyst has presumably arisen from dental lamina rests near an unerupted tooth and has grown to envelop the unerupted tooth. Resorption of the roots of erupted teeth adjacent to OKCs is less common than that noted with dentigerous and radicular cysts.

The diagnosis of OKC is based on the histopathologic features. The radiographic findings, although often highly suggestive, are not diagnostic. The radiographic findings in an OKC may simulate those of a dentigerous cyst, a radicular cyst, a residual cyst, a lateral periodontal cyst (Fig. 15-16), or the so-called globulomaxillary cyst (which is no longer considered to be a true entity). OKCs of the anterior midline maxillary region can mimic nasopalatine duct cysts. For unknown reasons, this particular subset of keratocyst usually occurs in older individuals with a mean age of nearly 70 years. Rare examples of peripheral OKCs within the gingival soft tissues have been reported.

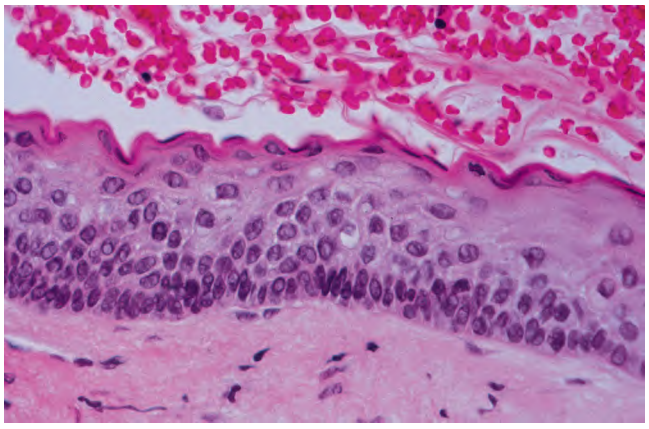


• **Fig. 15-16 Odontogenic Keratocyst (OKC).** This cyst cannot be radiographically differentiated from a lateral periodontal cyst. (Courtesy of Dr. Keith Lemmerman.)

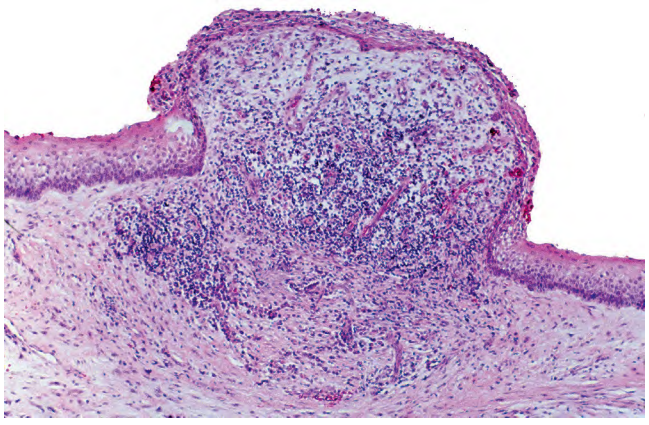
Histopathologic Features

The OKC typically shows a thin, friable wall, which is often difficult to enucleate from the bone in one piece. The cystic lumen may contain a clear liquid that is similar to a transudate of serum, or it may be filled with a cheesy material that, on microscopic examination, consists of keratinaceous debris. Microscopically, the thin fibrous wall is usually devoid of significant inflammation. The epithelial lining is composed of a uniform layer of stratified squamous epithelium, usually six to eight cells in thickness. The epithelium and connective tissue interface is usually flat, and rete ridge formation is inconspicuous. Detachment of portions of the cyst-lining epithelium from the fibrous wall is commonly observed. The luminal surface shows flattened parakeratotic epithelial cells, which exhibit a wavy or corrugated appearance (Fig. 15-17). On occasion, isolated foci of orthokeratin production may be found in addition to the parakeratin. The basal epithelial layer is composed of a palisaded layer of cuboidal or columnar epithelial cells, which are often hyperchromatic. Small satellite cysts, cords, or islands of odontogenic epithelium may be seen within the fibrous wall. These structures have been present in 7% to 26% of cases in various reported series. In rare instances, cartilage has been observed in the wall of an OKC.

In the presence of inflammatory changes, the typical features of the OKC may be altered. The parakeratinized luminal surface may disappear, and the epithelium may proliferate to form rete ridges with the loss of the characteristic palisaded basal layer (Fig. 15-18). When these changes involve most of the cyst lining, the diagnosis of OKC cannot be confirmed unless other sections show the typical features described earlier.



• **Fig. 15-17 Odontogenic Keratocyst (OKC).** The epithelial lining is 6 to 8 cells thick, with a hyperchromatic and palisaded basal cell layer. Note the corrugated parakeratotic surface.



• **Fig. 15-18 Odontogenic Keratocyst (OKC).** The characteristic microscopic features have been lost in the central area of this portion of the cystic lining because of the heavy chronic inflammatory cell infiltrate.

In the past, some investigators recognized a purely orthokeratotic variant of the OKC. However, these cysts do not demonstrate a hyperchromatic and palisaded basal cell layer, which is so characteristic of true OKCs. In addition, the clinical behavior of these orthokeratinized cysts differs markedly from that of the typical parakeratinized cysts described in this section. The authors believe that it is more logical to discuss these orthokeratinizing cysts separately (see following section).

Treatment and Prognosis

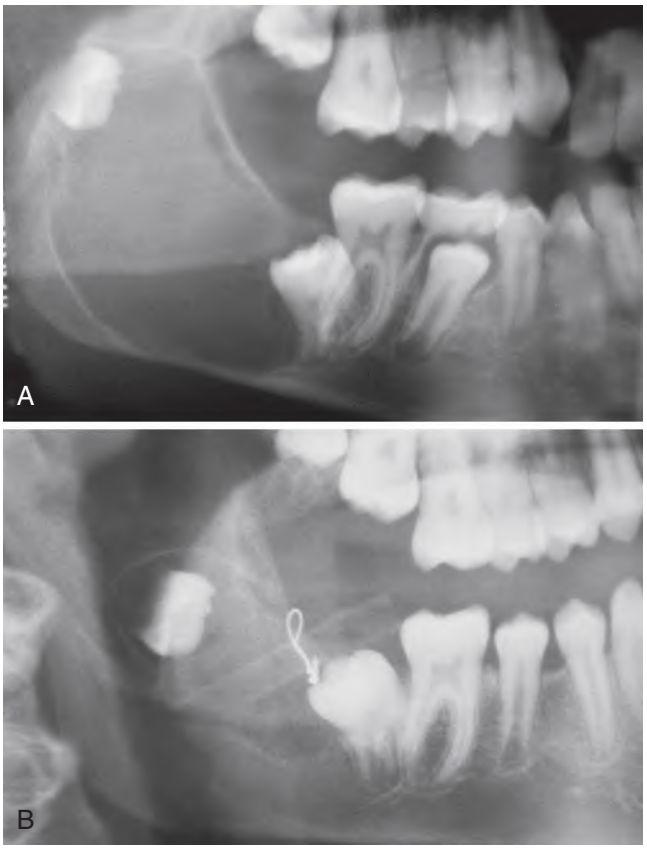
Although the presence of an OKC may be suspected on clinical or radiographic grounds, histopathologic confirmation is required for the diagnosis. Consequently, most OKCs are treated similarly to other odontogenic cysts—i.e., by enucleation and curettage. Complete removal of the cyst in one piece is often difficult because of the thin, friable nature of the cyst wall. In contrast to other odontogenic

cysts, OKCs often tend to recur after treatment. Whether this is due to fragments of the original cyst that were not removed at the time of the operation or a "new" cyst that has developed from dental lamina rests in the general area of the original cyst cannot be determined with certainty.

The reported frequency of recurrence in various studies ranges from 5% to 62%. This wide variation may be related to the total number of cases studied, the length of follow-up periods, and the inclusion or exclusion of orthokeratinized cysts in the study group. Several reports that include large numbers of cases indicate a recurrence rate of approximately 30%. Recurrence is encountered more often in mandibular OKCs, particularly those in the posterior body and ramus. Multiple recurrences are not unusual. Although many OKCs recur within 5 years of the original surgery, a significant number of recurrences may not be manifested until 10 or more years after the original surgical procedure. Long-term clinical and radiographic follow-up, therefore, is necessary.

Many surgeons recommend peripheral ostectomy of the bony cavity with a bone bur to reduce the frequency of recurrence. Others advocate chemical cauterization of the bony cavity with Carnoy's solution after cyst removal (although use of Carnoy's solution may not be permitted by some hospitals). Intraluminal injection of Carnoy's solution also has been used to free the cyst from the bony wall, thereby allowing easier removal with a lower recurrence rate. After cystotomy and incisional biopsy, some surgeons have treated large OKCs by insertion of a polyethylene drainage tube to allow decompression and subsequent reduction in size of the cystic cavity (Fig. 15-19). Such decompression treatment results in thickening of the cyst lining, allowing easier removal with an apparently lower recurrence rate.

Other than the tendency for recurrences, the overall prognosis for most OKCs is good. Occasionally, a locally aggressive OKC cannot be controlled without local resection and bone grafting. In extremely rare instances, keratocysts have been seen to extend up into the skull base region. A few examples of carcinoma arising in an OKC have been reported, but the propensity for an OKC to undergo malignant alteration is no greater and is possibly less than that for other types of odontogenic cysts. Patients with OKCs should be evaluated for manifestations of the nevoid basal cell carcinoma syndrome (see page 640), particularly if the patient is in the first or second decade of life or if multiple keratocysts are identified.



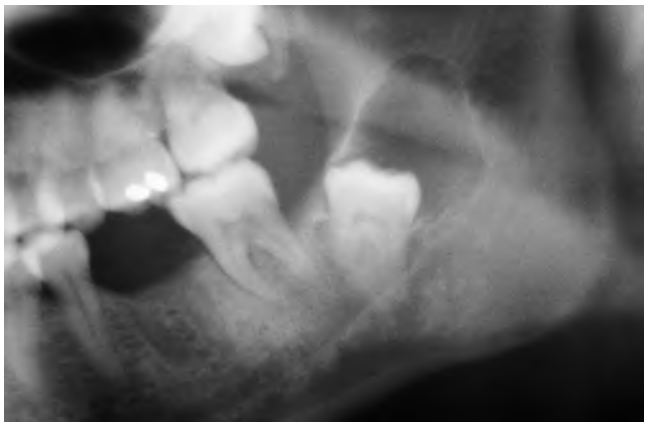
• **Fig. 15-19 Decompression of an Odontogenic Keratocyst (OKC). A,** Large unilocular radiolucency associated with the right mandibular third molar. **B,** Six months after insertion of a polyethylene drainage tube to allow decompression, the cyst has shrunk and the third molar has migrated downward and forward. (Courtesy of Dr. Tom Szakal.)

◆ ORTHOKERATINIZED ODONTOGENIC CYST

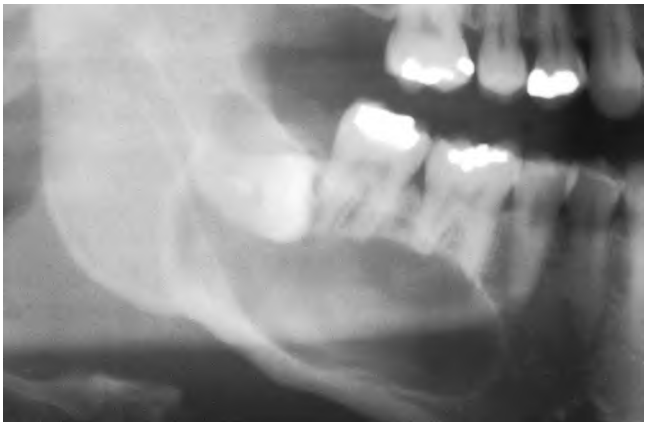
The designation **orthokeratinized odontogenic cyst** does not denote a specific clinical type of odontogenic cyst but refers only to an odontogenic cyst that microscopically has an orthokeratinized epithelial lining. Although such lesions were originally called the *orthokeratinized variant of odontogenic keratocyst,* it is generally accepted that they are clinicopathologically different from the more common parakeratinized odontogenic keratocyst (OKC) and should be placed into a different category. Orthokeratinized odontogenic cysts represent 7% to 17% of all keratinizing jaw cysts.

Clinical and Radiographic Features

Orthokeratinized odontogenic cysts occur predominantly in young adults and show over a 2:1 male-to-female ratio. The lesion occurs more frequently in the mandible than the maxilla (3:1 ratio), with a tendency to involve the posterior areas of the jaws. They have no clinical or radiographic features that differentiate them from other inflammatory or developmental odontogenic cysts. The lesion usually appears as a unilocular radiolucency, but occasional examples have been multilocular. About two-thirds of orthokeratinized odontogenic cysts are encountered in a lesion that appears clinically and radiographically to represent a dentigerous cyst; they most often involve an unerupted mandibular third molar tooth (Figs. 15-20 and 15-21). The size can vary from less than 1 cm to large lesions greater than 7 cm in diameter.



• **Fig. 15-20 Orthokeratinized Odontogenic Cyst.** Small unilocular radiolucency associated with the impacted mandibular left third molar. (Courtesy of Dr. Tom McDonald.)



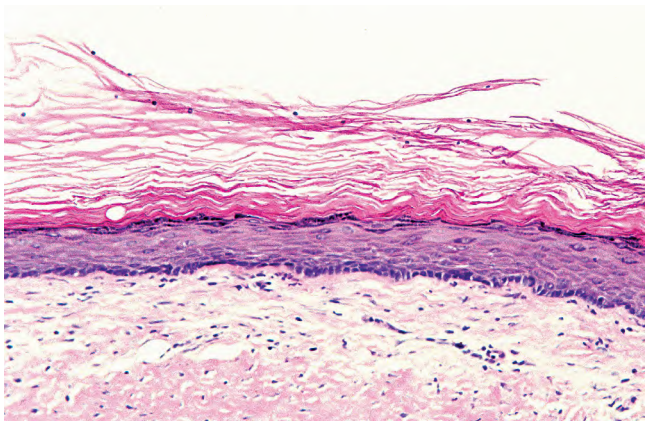
• **Fig. 15-21 Orthokeratinized Odontogenic Cyst.** A large cyst involving a horizontally impacted lower third molar. (Courtesy of Dr. Carroll Gallagher.)

Histopathologic Features

The cyst lining is composed of stratified squamous epithelium, which shows an orthokeratotic surface of varying thickness. Keratohyaline granules may be prominent in the superficial epithelial layer subjacent to the orthokeratin. The epithelial lining may be relatively thin, and a prominent palisaded basal layer, characteristic of the OKC, is not present (Fig. 15-22).

Treatment and Prognosis

Enucleation with curettage is the usual treatment for orthokeratinized odontogenic cysts. Recurrence has rarely been noted, and the reported frequency is around 2%, which is in marked contrast with the 30% or higher recurrence rate associated with OKCs. It has been suggested that cysts with an orthokeratinized surface may be at slightly greater risk for malignant transformation, but evidence for this is scant. Orthokeratinized odontogenic cysts typically are not associated with nevoid basal cell carcinoma syndrome.



• **Fig. 15-22 Orthokeratinized Odontogenic Cyst.** Microscopic features showing a thin epithelial lining. The basal epithelial layer does not demonstrate palisading. Keratohyaline granules are present, and a thick layer of orthokeratin is seen on the luminal surface.

◆ NEVOID BASAL CELL CARCINOMA SYNDROME (GORLIN SYNDROME)

Nevoid basal cell carcinoma syndrome (Gorlin syndrome) is an autosomal dominant inherited condition that exhibits high penetrance and variable expressivity. The syndrome is caused by mutations in **patched** *(PTCH),* a tumor suppressor gene that has been mapped to chromosome 9q22.3-q31. Approximately 35% to 50% of affected patients represent new mutations. One of the most common clinical features is development of OKCs, which can lead to early diagnosis. The prevalence of Gorlin syndrome is estimated to be anywhere from 1 in 19,000 to 1 in 256,000, depending on the population studied.

Clinical and Radiographic Features

There is great variability in the expressivity of nevoid basal cell carcinoma syndrome, and no single component is present in all patients. The most common and significant features are summarized in Box 15-2. The patient often has a characteristic facies, with frontal and temporoparietal bossing, which results in an increased cranial circumference (more than 60 cm in adults). The eyes may appear widely separated, and many patients have true mild ocular hypertelorism. Mild mandibular prognathism is also commonly present (Fig. 15-23).

Basal cell carcinomas of the skin are a major component of the syndrome. These tumors usually begin to appear at puberty or in the second and third decades of life, although they can develop in young children. The lesions may vary from flesh-colored papules to ulcerating plaques. They often appear on skin that is not exposed to sunlight, but they are most commonly located in the midface area (Fig. 15-24). The number of skin tumors may vary from only a few to many hundreds. Blacks with the syndrome tend to develop basal cell carcinomas less frequently than whites (40% versus 90%), and they have fewer of these lesions, probably because of protective skin pigmentation.

• BOX 15-2 Major Clinical Features of the Nevoid Basal Cell Carcinoma Syndrome

50% or Greater Frequency

- Multiple basal cell carcinomas
- Odontogenic keratocysts (OKCs)
- Epidermal cysts of the skin
- Palmar/plantar pits
- Calcified falx cerebri
- Enlarged head circumference
- Rib anomalies (splayed, fused, partially missing, and/or bifid)
- Mild ocular hypertelorism
- Spina bifida occulta of cervical or thoracic vertebrae

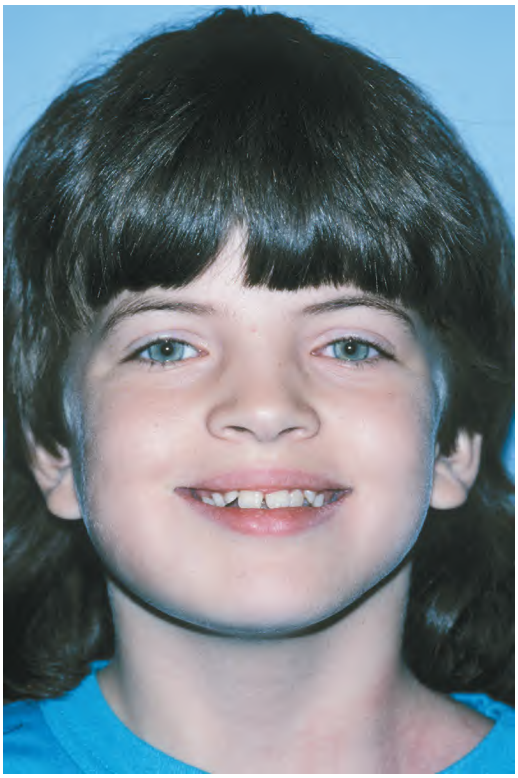
15% to 49% Frequency

- Calcified ovarian fibromas
- Short fourth metacarpals
- Kyphoscoliosis or other vertebral anomalies
- Pectus excavatum or carinatum
- Strabismus (exotropia)

Less than 15% Frequency (but Not Random)

- Medulloblastoma
- Meningioma
- Lymphomesenteric cysts
- Cardiac fibroma
- Fetal rhabdomyoma
- Marfanoid build
- Cleft lip and/or palate
- Hypogonadism in males
- Intellectual disability

From Gorlin RJ: Nevoid basal-cell carcinoma syndrome, *Medicine* 66:98-113, 1987.



• Fig. 15-23 Nevoid Basal Cell Carcinoma Syndrome. This 11-year-old girl shows hypertelorism and mandibular swelling. (Courtesy of Dr. Richard DeChamplain.)

• Fig. 15-24 Nevoid Basal Cell Carcinoma Syndrome. An ulcerating basal cell carcinoma is present on the upper face.

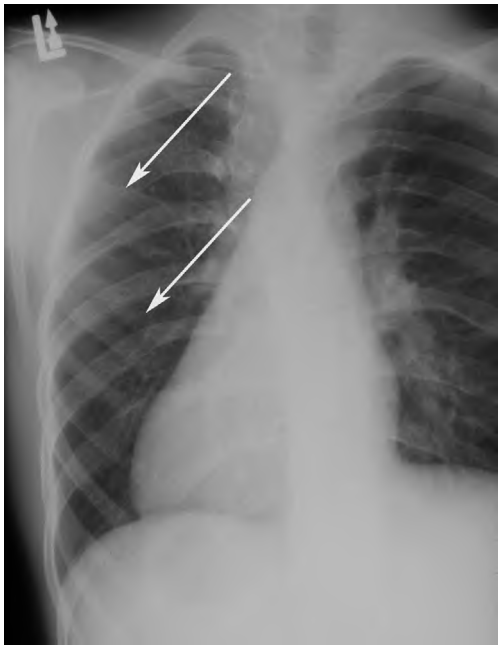
Palmar and plantar pits are present in about 65% to 85% of patients (Fig. 15-25). These punctate lesions represent a localized impairment of the maturation of basal epithelial cells, resulting in a focally depressed area as the result of a markedly thinned keratin layer. Basal cell carcinomas rarely may develop at the base of the pits.

Ovarian cysts and fibromas have been reported in 25% to 50% of women with this syndrome. A number of other tumors also have been reported to occur with lesser frequency. These include medulloblastoma within the first 2 years of life, meningioma, cardiac fibroma, and fetal rhabdomyoma.

Skeletal anomalies are present in 60% to 75% of patients with this syndrome. The most common anomaly is a bifid rib or splayed ribs (Fig. 15-26). This anomaly may involve several ribs and may be bilateral. Kyphoscoliosis has been observed in about 30% to 40% of patients, and a number of other anomalies, such as spina bifida occulta and shortened metacarpals, seem to occur with unusual frequency. A distinctive lamellar calcification of the falx cerebri, noted on an anteroposterior skull radiograph or computed tomography (CT) image, is a common finding and is present in most affected patients (Fig. 15-27).

Jaw cysts are one of the most constant features of the syndrome and are present in 90% of the patients. The cysts are OKCs, although there are some differences between the cysts in patients with nevoid basal cell carcinoma syndrome and in those with isolated OKCs. The cysts are frequently multiple; some patients have had as many as ten separate cysts. The patient's age when the first OKC is removed is significantly younger in those affected by this syndrome than in those with isolated OKCs. For most patients with this syndrome, their first OKC is removed before age 19. About one-third of patients with nevoid basal cell carcinoma syndrome have only a solitary cyst at the time of the

• **Fig. 15-25 Nevoid Basal Cell Carcinoma Syndrome.** Plantar pits.



• **Fig. 15-26 Nevoid Basal Cell Carcinoma Syndrome.** Chest film showing presence of bifid ribs *(arrows).*

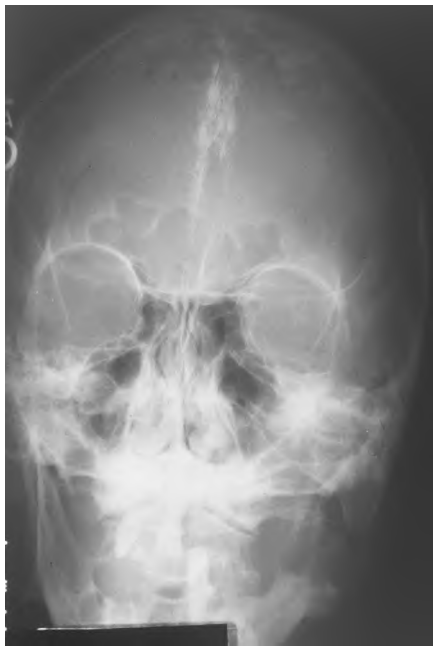
initial presentation, but in most cases additional cysts will develop over periods ranging from 1 to 20 years.

Radiographically, the cysts in patients with nevoid basal cell carcinoma syndrome do not differ significantly from isolated OKCs. The cysts in patients with this syndrome are often associated with the crowns of unerupted teeth; on radiographs they may mimic dentigerous cysts (Fig. 15-28).

Diagnostic criteria for the nevoid basal cell carcinoma syndrome are provided in Box 15-3.

Histopathologic Features

The cysts in the nevoid basal cell carcinoma syndrome histopathologically are invariably OKCs. The keratocysts in patients with this syndrome tend to have more satellite cysts, solid islands of epithelial proliferation, and



• **Fig. 15-27 Nevoid Basal Cell Carcinoma Syndrome.** Anteroposterior skull film showing calcification of the falx cerebri. (Courtesy of Dr. Ramesh Narang.)

odontogenic epithelial rests within the fibrous capsule than do isolated keratocysts (Fig. 15-29). Foci of calcification also appear to be more common. These features, however, are not diagnostic for nevoid basal cell carcinoma syndrome because they may be seen in isolated keratocysts. OKCs associated with this syndrome have been shown to demonstrate overexpression of p53 and cyclin D1 (bcl-1) oncoproteins when compared with nonsyndrome keratocysts.

The basal cell tumors of the skin cannot be distinguished from ordinary basal cell carcinomas. They exhibit a wide spectrum of histopathologic findings, from superficial basal cell lesions to aggressive, noduloulcerative basal cell carcinomas.

Treatment and Prognosis

Most of the anomalies in nevoid basal cell carcinoma syndrome are minor and usually not life threatening. The prognosis generally depends on the behavior of the skin tumors. In a few cases, aggressive basal cell carcinomas have caused the death of the patient as a result of tumor invasion of the brain or other vital structures (Figs. 15-30 and 15-31). Because the development of the basal cell carcinomas seems to be triggered by ultraviolet (UV) light exposure, patients should take appropriate precautions to avoid sunlight. For the same reason, radiation therapy should be avoided if at all possible. The jaw cysts are treated in the same manner as isolated OKCs, but in many patients additional cysts will continue to develop. Varying degrees of jaw deformity may result from the operations for multiple cysts. Infection of the cysts in patients with

• BOX 15-3 Diagnostic Criteria for the Nevoid Basal Cell Carcinoma Syndrome

A diagnosis can be made if the patient has:
1. Two major criteria
2. One major and two minor criteria
3. One major criterion and genetic confirmation

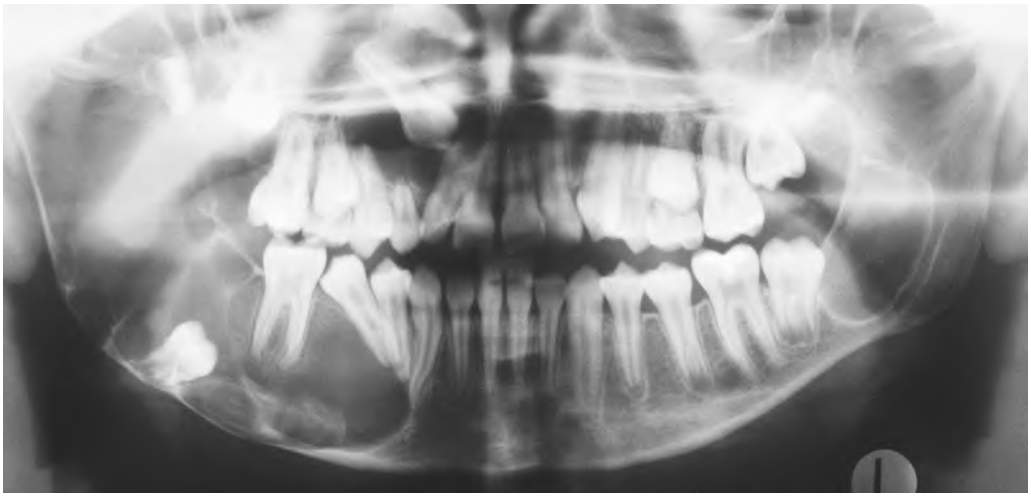
Major Criteria

1. Five or more basal cell carcinomas *or* one before the age of 30 years
2. Odontogenic keratocyst (OKC)
3. Lamellar calcification of the falx cerebri
4. Two or more palmar or plantar pits
5. First degree relative with the nevoid basal cell carcinoma syndrome

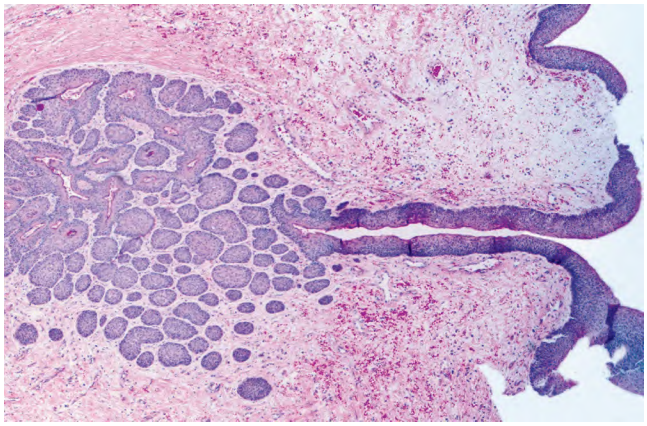
Minor Criteria

1. Macrocephaly
2. Congenital malformation: Cleft lip or palate, frontal bossing, coarse facial features, and/or hypertelorism
3. Preaxial or postaxial polydactyly
4. Rib or vertebral abnormalities: bifid, splayed, or extra ribs; bifid vertebrae
5. Ovarian or cardiac fibromas
6. Medulloblastoma*
7. Ocular anomalies: Cataract, coloboma, and/or microphthalmia
8. Lymphomesenteric or pleural cysts

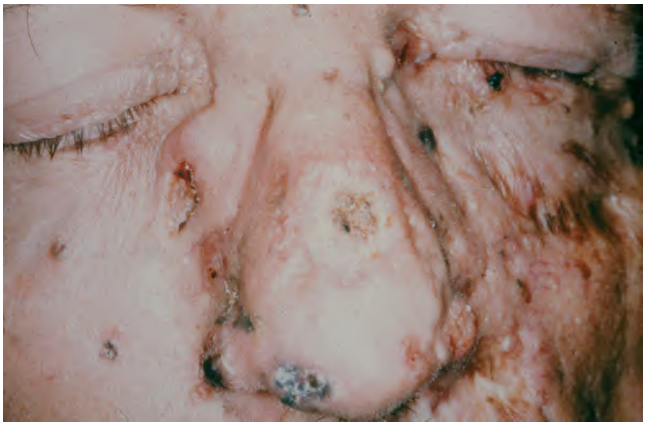
*In a recent consensus conference, it was suggested that medulloblastoma should be considered a major criterion.



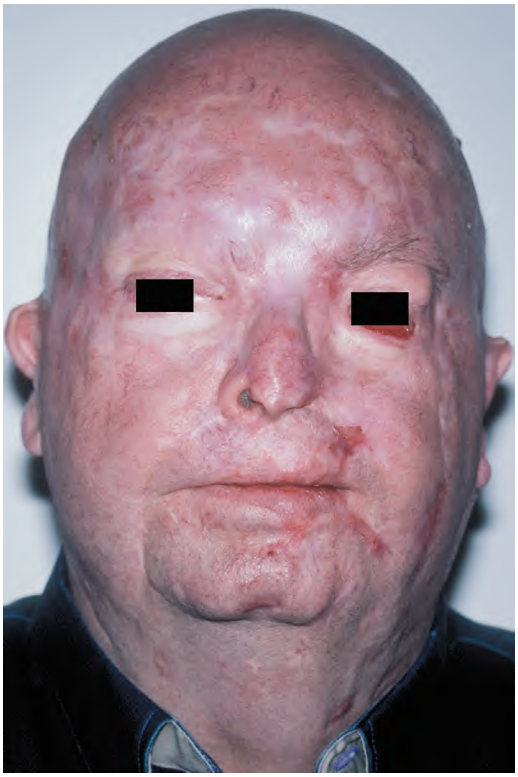
• **Fig. 15-28 Nevoid Basal Cell Carcinoma Syndrome.** Large cysts are present in the right and left mandibular molar regions, together with a smaller cyst involving the right maxillary canine in the same patient shown in Fig. 15-23. (Courtesy of Dr. Richard DeChamplain.)



• **Fig. 15-29 Nevoid Basal Cell Carcinoma Syndrome.** Odontogenic keratocyst (OKC) showing numerous odontogenic epithelial rests in the cyst wall.



• **Fig. 15-30 Nevoid Basal Cell Carcinoma Syndrome.** This 52-year-old man had more than 100 basal cell carcinomas removed from his face over a 30-year period. Several basal cell carcinomas are present in this photograph. The lesion at the inner canthus of the left eye was deeply invasive and was eventually fatal as a result of brain invasion.



• **Fig. 15-31 Nevoid Basal Cell Carcinoma Syndrome.** Facial deformity secondary to multiple surgical procedures to remove basal cell carcinomas.

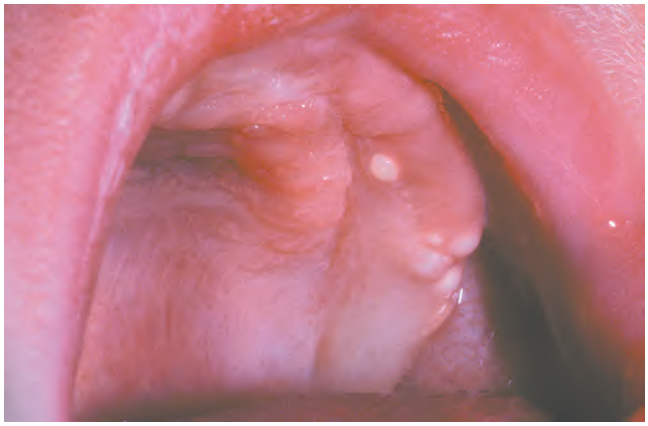
this syndrome is also relatively common. Some investigators have suggested that affected children should have magnetic resonance imaging (MRI) studies every 6 months until 7 years of age to monitor for the development of medulloblastoma. Genetic counseling is appropriate for affected individuals.

◆ GINGIVAL (ALVEOLAR) CYST OF THE NEWBORN

Gingival cysts of the newborn are small, superficial, keratin-filled cysts that are found on the alveolar mucosa of infants. These cysts arise from remnants of the dental lamina. They are common lesions, having been reported in up to half of all newborns. However, because they disappear spontaneously by rupture into the oral cavity, the lesions seldom are noticed or sampled for biopsy. Similar inclusion cysts (e.g., **Epstein's pearls** and **Bohn's nodules**) are also found in the midline of the palate or laterally on the hard and soft palate (see page 24).

Clinical Features

Gingival cysts of the newborn appear as small, usually multiple whitish papules on the mucosa overlying the alveolar processes of neonates (Fig. 15-32). The individual cysts are usually no more than 2 to 3 mm in diameter. The maxillary alveolus is more commonly involved than the mandibular.



• **Fig. 15-32 Gingival Cyst of the Newborn.** Multiple whitish papules on the alveolar ridge of a newborn infant.

Histopathologic Features

Examination of an intact gingival cyst of the newborn shows a thin, flattened epithelial lining with a parakeratotic luminal surface. The lumen contains keratinaceous debris.

Treatment and Prognosis

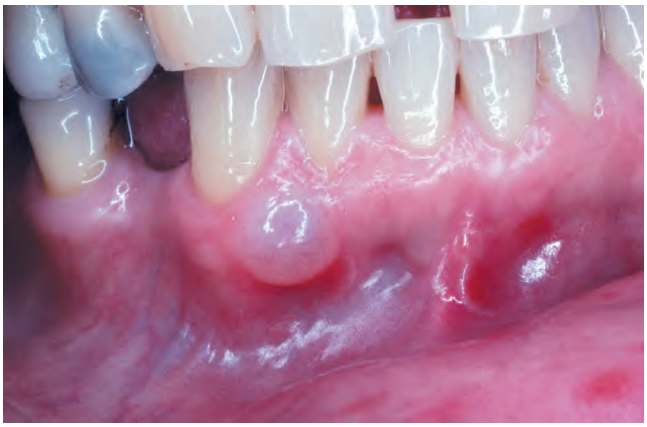
No treatment is indicated for gingival cysts of the newborn because the lesions spontaneously involute as a result of the rupture of the cysts and resultant contact with the oral mucosal surface. The lesions are rarely seen after 3 months of age.

◆ GINGIVAL CYST OF THE ADULT

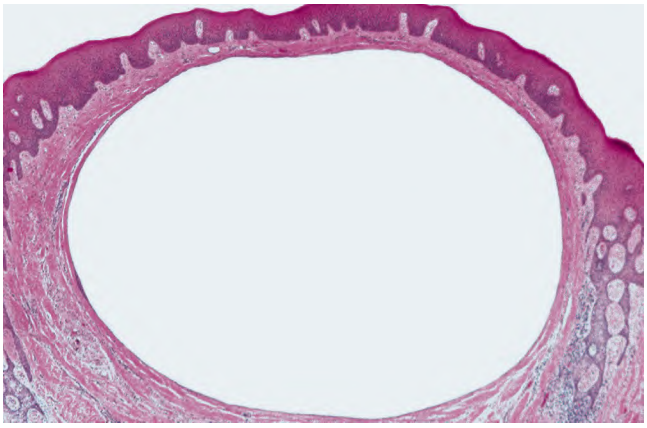
The **gingival cyst of the adult** is an uncommon lesion. It is considered to represent the soft tissue counterpart of the **lateral periodontal cyst** (see next topic), being derived from rests of the dental lamina (rests of Serres). The diagnosis of gingival cyst of the adult should be restricted to lesions with the same histopathologic features as those of the lateral periodontal cyst. On rare occasions, a cyst may develop in the gingiva at the site of a gingival graft; however, such lesions probably represent *epithelial inclusion cysts* that are a result of the surgical procedure.

Clinical Features

Like the lateral periodontal cyst, the gingival cyst of the adult shows a striking predilection to occur in the mandibular canine and premolar area (60% to 75% of cases). Gingival cysts of the adult are most commonly found in patients in the fifth and sixth decades of life. They are almost invariably located on the facial gingiva or alveolar mucosa. Maxillary gingival cysts are usually found in the incisor, canine, and premolar areas.



• **Fig. 15-33 Gingival Cyst of the Adult.** Tense, fluid-filled swelling on the facial gingiva.

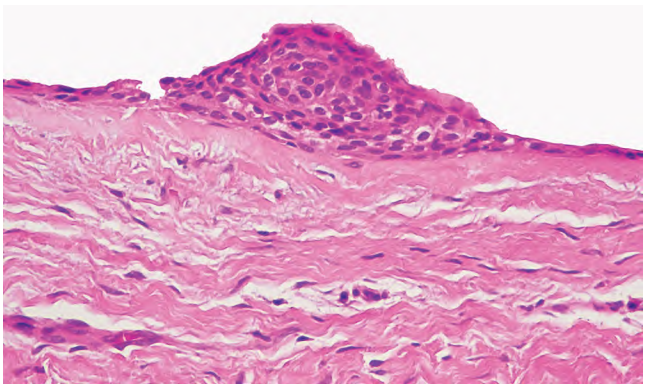


• **Fig. 15-34 Gingival Cyst of the Adult.** Low-power photomicrograph showing a thin-walled cyst in the gingival soft tissue.

Clinically, the cysts appear as painless, domelike swellings, usually less than 0.5 cm in diameter, although rarely they may be somewhat larger (Fig. 15-33). They are often bluish or blue-gray. In some instances, the cyst may cause a superficial "cupping out" of the alveolar bone, which is usually not detected on a radiograph but is apparent when the cyst is excised. If more bone is missing, one could argue that the lesion may be a lateral periodontal cyst that has eroded the cortical bone rather than a gingival cyst that originated in the mucosa.

Histopathologic Features

The histopathologic features of the gingival cyst of the adult are similar to those of the lateral periodontal cyst, consisting of a thin, flattened epithelial lining with or without focal plaques that contain clear cells (Figs. 15-34 and 15-35). Small nests of these glycogen-rich clear cells, which represent rests of the dental lamina, also may be seen in the surrounding connective tissue. Sometimes the cystic lining is so thin that it is easily mistaken for the endothelial lining of a dilated blood vessel.



• **Fig. 15-35 Gingival Cyst of the Adult.** High-power photomicrograph showing a plaquelike thickening of the epithelial lining.

Treatment and Prognosis

The gingival cyst of the adult responds well to simple surgical excision. The prognosis is excellent.

◆ LATERAL PERIODONTAL CYST (BOTRYOID ODONTOGENIC CYST)

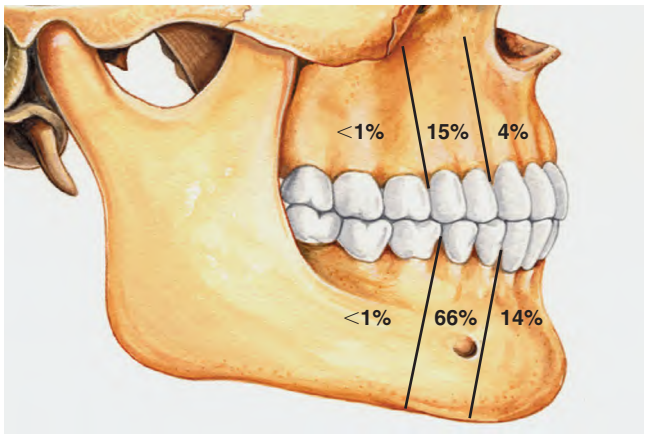
The **lateral periodontal cyst** is an uncommon type of developmental odontogenic cyst that typically occurs along the lateral root surface of a tooth. It is believed to arise from rests of the dental lamina, and it represents the intrabony counterpart of the gingival cyst of the adult. The lateral periodontal cyst accounts for less than 2% of all epithelium-lined jaw cysts.

In the past, the term *lateral periodontal cyst* was used to describe any cyst that developed along the lateral root surface, including lateral radicular cysts (see page 120) and OKCs (see page 636). However, the lateral periodontal cyst has distinctive clinical and microscopic features that distinguish it from other lesions that sometimes develop in the same location.

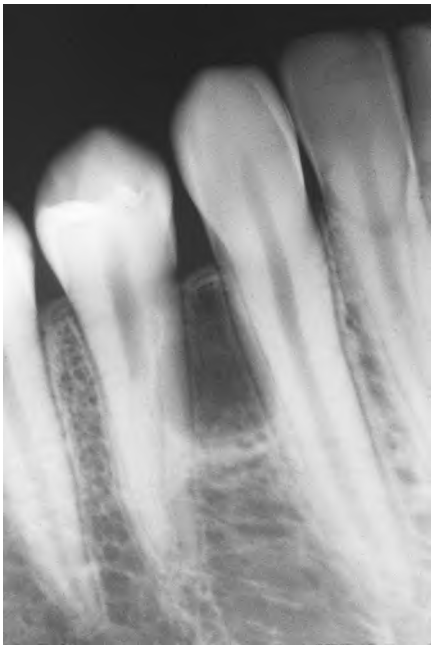
Clinical and Radiographic Features

The lateral periodontal cyst is most often an asymptomatic lesion that is detected only during a radiographic examination. It most frequently occurs in patients in the fifth through the seventh decades of life; rarely does it occur in someone younger than age 30. Around 75% to 80% of cases occur in the mandibular premolar-canine-lateral incisor area. Maxillary examples also usually involve this same tooth region (Fig. 15-36).

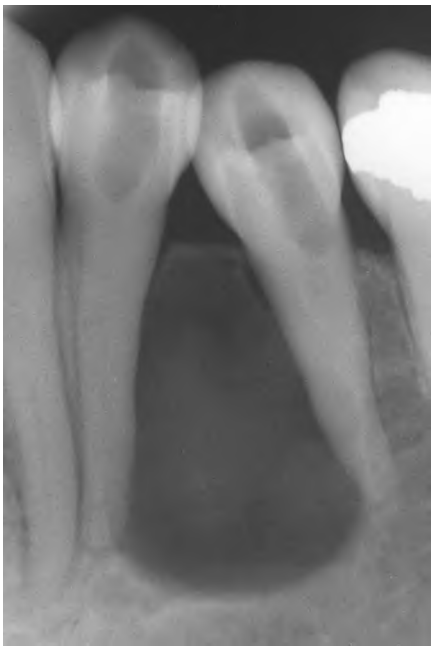
Radiographically, the cyst usually appears as a well-circumscribed radiolucent area located laterally to the root or roots of vital teeth. Most such cysts are less than 1.0 cm in greatest diameter (Figs. 15-37 and 15-38). In rare instances, multifocal lateral periodontal cysts have been described. In addition, some examples can develop in edentulous sites.



• **Fig. 15-36 Lateral Periodontal Cyst.** Relative distribution of lateral periodontal cysts in the jaws.



• **Fig. 15-37 Lateral Periodontal Cyst.** Radiolucent lesion between the roots of a vital mandibular canine and first premolar.



• **Fig. 15-38 Lateral Periodontal Cyst.** A larger lesion causing root divergence.

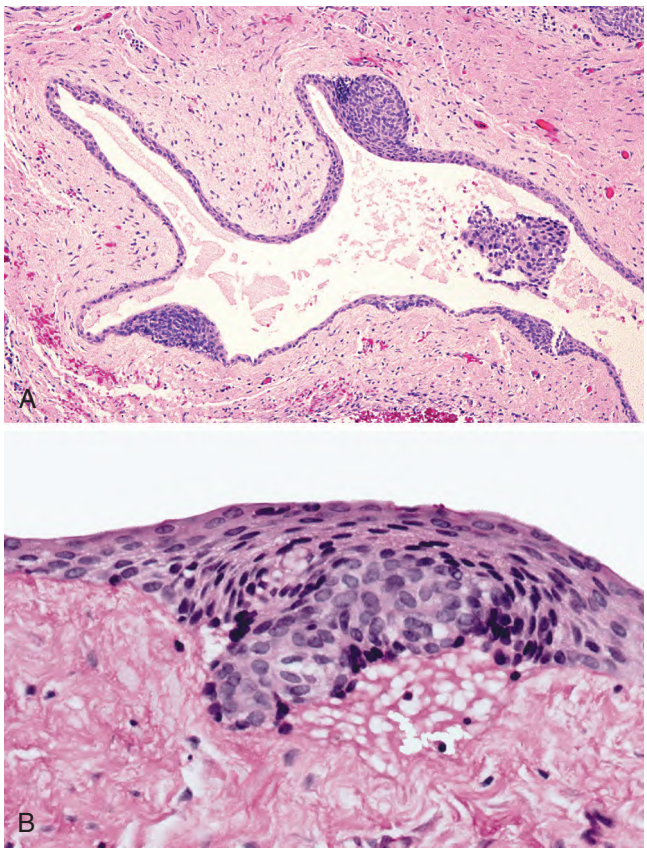
• **Fig. 15-39 Lateral Periodontal Cyst.** Gross specimen of a botryoid variant. Microscopically, this grapelike cluster revealed three separate cavities.

Occasionally, the lesion may have a polycystic appearance; such examples have been termed **botryoid odontogenic cysts.** Grossly and microscopically, they show a grapelike cluster of small individual cysts (Fig. 15-39). These lesions are generally considered to represent a variant of the lateral periodontal cyst, possibly the result of cystic degeneration and subsequent fusion of adjacent foci of dental lamina rests. The botryoid variant often shows a multilocular radiographic appearance, but it also may appear unilocular.

The radiographic features of the lateral periodontal cyst are not diagnostic; an OKC that develops between the roots of adjacent teeth may show identical radiographic findings. An inflammatory radicular cyst that occurs laterally to a root in relation to an accessory foramen or a cyst that arises from periodontal inflammation also may simulate a lateral periodontal cyst radiographically (see page 120). In one study of 46 cases of cystic lesions in the lateral periodontal region, only 13 met the histopathologic criteria for the lateral periodontal cyst; eight were OKCs, 20 were inflammatory cysts, and five were of undetermined origin.

Histopathologic Features

The lateral periodontal cyst has a thin, generally noninflamed, fibrous wall, with an epithelial lining that is only one to three cells thick in most areas. This epithelium usually consists of flattened squamous cells, but sometimes the cells are cuboidal in shape. Foci of glycogen-rich clear cells may be interspersed among the lining epithelial cells. Some cysts show focal nodular thickenings of the lining



• **Fig. 15-40 Lateral Periodontal Cyst. A,** This photomicrograph shows a thin epithelial lining with focal nodular thickenings. **B,** These thickenings often show a swirling appearance of the cells.

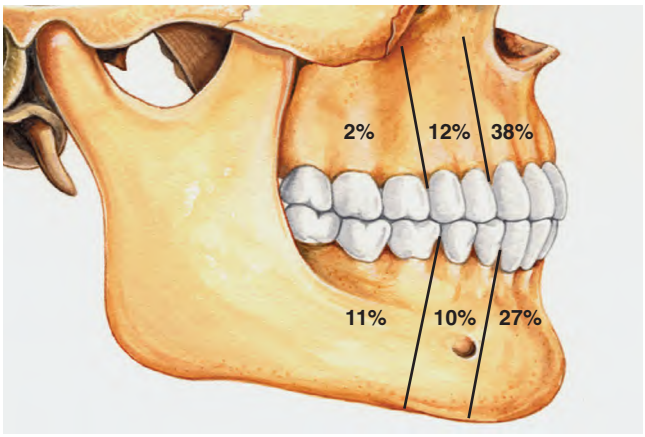
epithelium, which are composed chiefly of clear cells (Fig. 15-40). Clear cell epithelial rests sometimes are seen within the fibrous wall. Rarely, lateral periodontal cysts exhibit focal areas that histopathologically are suggestive of the glandular odontogenic cyst (see page 649).

Treatment and Prognosis

Conservative enucleation of the lateral periodontal cyst is the treatment of choice. Usually, this can be accomplished without damage to the adjacent teeth. Recurrence is unusual, although it has been reported with the botryoid variant, presumably because of its polycystic nature. An exceedingly rare case of squamous cell carcinoma, which apparently originated in a lateral periodontal cyst, also has been reported.

◆ CALCIFYING ODONTOGENIC CYST (CALCIFYING CYSTIC ODONTOGENIC TUMOR; GORLIN CYST; DENTINOGENIC GHOST CELL TUMOR; GHOST CELL ODONTOGENIC CARCINOMA)

First described in 1962 by Gorlin and associates, the **calcifying odontogenic cyst** is part of a spectrum of lesions



• **Fig. 15-41 Calcifying Odontogenic Cyst.** Relative distribution of calcifying odontogenic cysts in the jaws.

characterized by odontogenic epithelium containing "ghost cells," which then may undergo calcification. Although most examples grow in a cystic fashion, some lesions occur as solid tumorlike growths **(dentinogenic ghost cell tumor).** Therefore, in the current WHO classification system, these lesions have been categorized as odontogenic tumors under three categories (based on the cystic, solid, or malignant nature of the lesion):

1. Calcifying cystic odontogenic tumor
2. Dentinogenic ghost cell tumor
3. Ghost cell odontogenic carcinoma

The overwhelming majority of intraosseous ghost cell odontogenic lesions grow as cystic lesions, and less than 5% of cases can be classified as solid dentinogenic ghost cell tumors. Therefore, the authors still prefer to use the simpler designation "calcifying odontogenic cyst" for the cystic examples. Approximately one-third of peripheral lesions will be solid in nature, although these peripheral examples are not as aggressive as their intraosseous counterparts.

The calcifying odontogenic cyst may be associated with other recognized odontogenic tumors, most commonly **odontomas.** However, **adenomatoid odontogenic tumors** and **ameloblastomas** have also been associated with calcifying odontogenic cysts.

Clinical and Radiographic Features

Intraosseous calcifying odontogenic cysts occur with about equal frequency in the maxilla and mandible. About 65% of cases are found in the incisor and canine areas (Fig. 15-41). The mean age is 30 years, and most cases are diagnosed in the second to fourth decades of life. Calcifying odontogenic cysts that are associated with odontomas tend to occur in younger patients, with a mean age of 17 years.

The central calcifying odontogenic cyst is usually a unilocular, well-defined radiolucency, although the lesion occasionally may appear multilocular. Radiopaque structures within the lesion, either irregular calcifications or toothlike densities, are present in about one-third to one-half of cases (Fig. 15-42). In approximately one-third of cases, the radiolucent lesion is associated with an unerupted tooth, most

often a canine. Most calcifying odontogenic cysts are between 2.0 and 4.0 cm in greatest diameter, but lesions as large as 12.0 cm have been noted. Root resorption or divergence of adjacent teeth is seen with some frequency (Fig. 15-43).

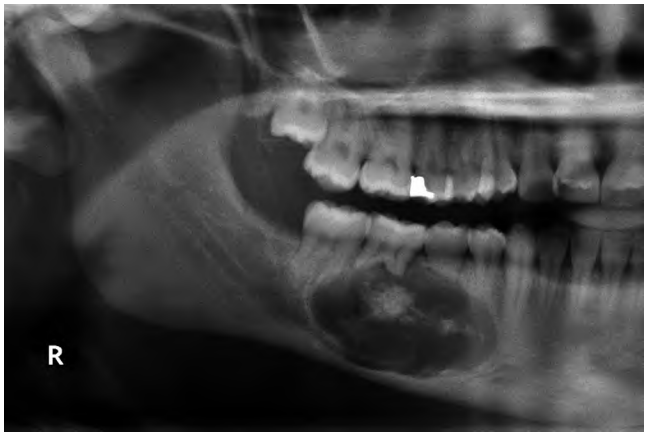
Extraosseous examples comprise from 5% to 17% of all cases, appearing as localized sessile or pedunculated gingival masses with no distinctive clinical features (Fig. 15-44). They can resemble common gingival fibromas, gingival cysts, or peripheral giant cell granulomas. Peripheral examples tend to occur later in life, with peak prevalence during the sixth to eighth decades.

Histopathologic Features

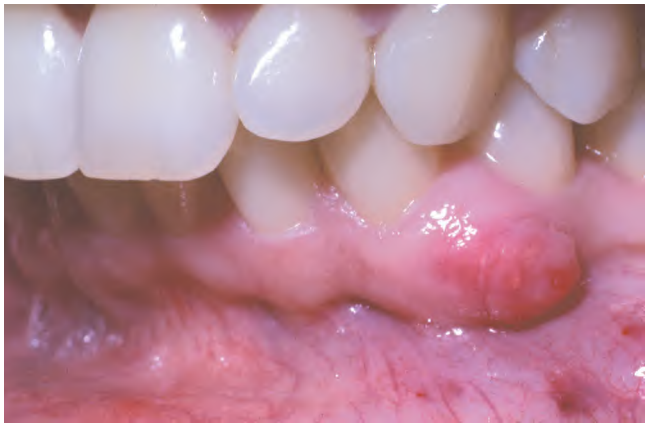
The calcifying odontogenic cyst most commonly occurs as a well-defined cystic lesion with a fibrous capsule and a lining of odontogenic epithelium of four to ten cells in thickness. The basal cells of the epithelial lining may be cuboidal or columnar and are similar to ameloblasts. The overlying layer of loosely arranged epithelium may resemble the stellate reticulum of an ameloblastoma.

The most characteristic histopathologic feature of the calcifying odontogenic cyst is the presence of variable numbers of "ghost cells" within the epithelial component. These eosinophilic ghost cells are altered epithelial cells that are characterized by the loss of nuclei with preservation of the basic cell outline (Fig. 15-45).

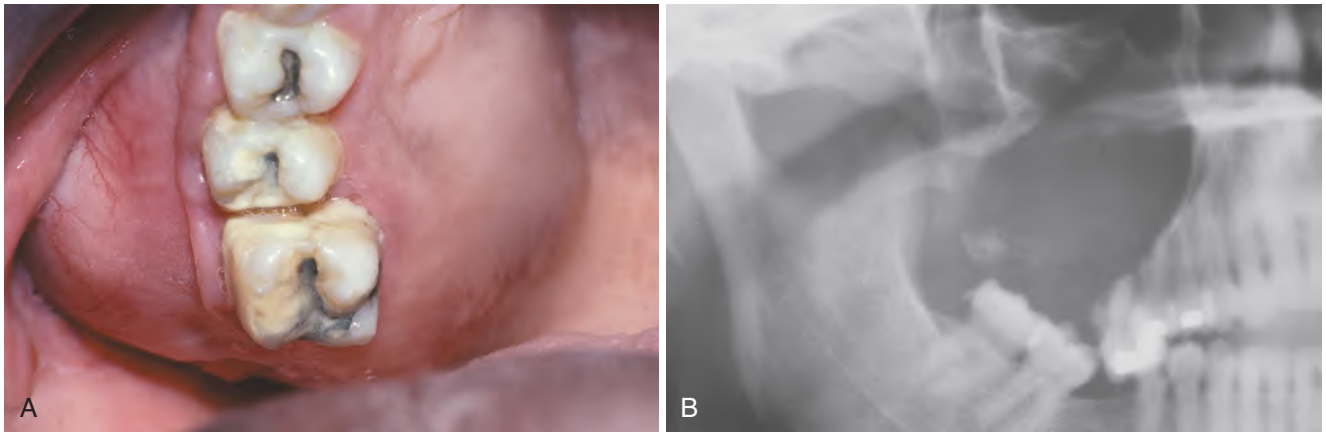
The nature of the ghost cell change is controversial. Some believe that this change represents coagulative necrosis or accumulation of enamel protein; others contend it is a form of normal or aberrant keratinization of odontogenic epithelium. Masses of ghost cells may fuse to form large sheets of amorphous, acellular material. Calcification within the ghost cells is common. This first appears as fine basophilic granules that may increase in size and number to form extensive masses of calcified material. Areas of an eosinophilic matrix material that are considered by some authors to represent dysplastic dentin (dentinoid) also may be present adjacent to the epithelial component. This is believed to be the result of an inductive effect by the



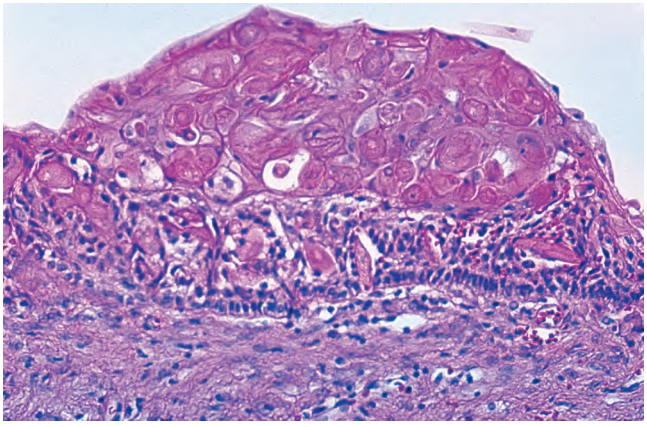
• **Fig. 15-42 Calcifying Odontogenic Cyst.** Well-circumscribed mixed radiolucent/radiopaque lesion in the right body of the mandible. (Courtesy of Dr. John Wright.)



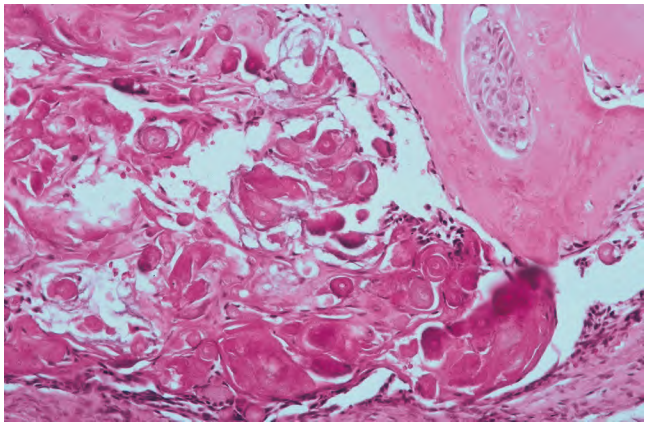
• **Fig. 15-44 Peripheral Calcifying Odontogenic Cyst.** Nodular mass of the mandibular facial gingiva.



• **Fig. 15-43 Calcifying Odontogenic Cyst. A,** Expansion of the posterior maxillary alveolus caused by a large calcifying odontogenic cyst. **B,** Panoramic radiograph of the same patient showing a large radiolucency in the posterior maxilla. A small calcified structure is seen in the lower portion of the cyst. (Courtesy of Dr. Tom Brock.)



• **Fig. 15-45 Calcifying Odontogenic Cyst.** The cyst lining shows ameloblastoma-like epithelial cells, with a columnar basal layer. Large eosinophilic ghost cells are present within the epithelial lining.



• **Fig. 15-46 Calcifying Odontogenic Cyst.** Eosinophilic dentinoid material is present adjacent to a sheet of ghost cells.

odontogenic epithelium on the adjacent mesenchymal tissue (Fig. 15-46).

Several variants of the cystic type of calcifying odontogenic cyst are seen. In some cases, the epithelial lining proliferates into the lumen so that the lumen is largely filled with masses of ghost cells and dystrophic calcifications. Multiple daughter cysts may be present within the fibrous wall, and a foreign body reaction to herniated ghost cells may be conspicuous.

In another variant, unifocal or multifocal epithelial proliferation of the cyst lining into the lumen may resemble ameloblastoma. These proliferations are intermixed with varying numbers of ghost cells. These epithelial proliferations superficially resemble, but do not meet, the strict histopathologic criteria for ameloblastoma.

About 20% of calcifying odontogenic cysts are associated with odontomas. This variant is usually a unicystic lesion that shows the features of a calcifying odontogenic cyst together with those of a small complex or compound odontoma.

Solid dentinogenic ghost cell tumors may occur intraosseously or extraosseously. The **extraosseous** forms appear to be more common. These show varying-sized islands of odontogenic epithelium in a fibrous stroma. The epithelial islands show peripheral palisaded columnar cells and central stellate reticulum, which resemble ameloblastoma. Nests of ghost cells, however, are present within the epithelium, and juxtaepithelial dentinoid is commonly present. These features differentiate this lesion from the peripheral ameloblastoma.

The rare **intraosseous** variant is a solid tumor that consists of ameloblastoma-like strands and islands of odontogenic epithelium in a mature fibrous connective tissue stroma. Variable numbers of ghost cells and juxtaepithelial dentinoid are present.

A small number of aggressive or malignant epithelial odontogenic ghost cell tumors **(ghost cell odontogenic carcinoma)** have been reported. These lesions have cellular pleomorphism and mitotic activity with invasion of the surrounding tissues.

Treatment and Prognosis

The prognosis for a patient with a calcifying odontogenic cyst is good; only a few recurrences after simple enucleation have been reported. Peripheral examples appear to have the same prognosis as a peripheral ameloblastoma, with a minimal chance of recurrence after simple surgical excision.

When a calcifying odontogenic cyst is associated with some other recognized odontogenic tumor, such as an ameloblastoma, the treatment and prognosis are likely to be the same as for the associated tumor. Although few cases have been reported, ghost cell odontogenic carcinomas appear to have an unpredictable behavior. Recurrences are common, and a few patients have died from either uncontrolled local disease or metastases. An overall 5-year survival rate of 73% has been calculated for reported cases.

◆ GLANDULAR ODONTOGENIC CYST (SIALO-ODONTOGENIC CYST)

The **glandular odontogenic cyst** is a rare type of developmental odontogenic cyst that can show aggressive behavior. Although it is generally accepted as being of odontogenic origin, it also shows glandular or salivary features that presumably are an indication of the pluripotentiality of odontogenic epithelium.

Clinical and Radiographic Features

The glandular odontogenic cyst occurs most commonly in middle-aged adults, with a mean age of 46 to 51 years at the time of diagnosis; rarely does it occur before the age of 20. Approximately 75% of reported cases have occurred in the mandible. The cyst has a strong predilection for the anterior region of the jaws, and many mandibular lesions will cross the midline.

The size of the cyst can vary from small lesions less than 1 cm in diameter to large destructive lesions that may involve most of the jaw. Small cysts may be asymptomatic; however, large cysts often produce clinical expansion, which sometimes can be associated with pain or paresthesia (Fig. 15-47).

Radiographically, the lesion presents as either a unilocular or multilocular radiolucency. The margins of the radiolucency are usually well defined with a corticated rim.

Histopathologic Features

The glandular odontogenic cyst is lined by squamous epithelium of varying thickness. The interface between the epithelium and the fibrous connective tissue wall is generally flat. The fibrous cyst wall is usually devoid of any inflammatory cell infiltrate. The superficial epithelial cells that line the cyst cavity tend to be cuboidal to columnar, resulting in an uneven hobnail and sometimes papillary surface (Fig. 15-48). The surface layer often includes mucin-producing goblet cells, occasionally with the presence of cilia. Glandular, ductlike spaces within the epithelial lining are another characteristic finding. These spaces are lined by cuboidal cells and often contain mucicarmine-positive fluid. In focal areas, the epithelial lining cells may form spherical nodules, similar to those seen in lateral periodontal cysts.

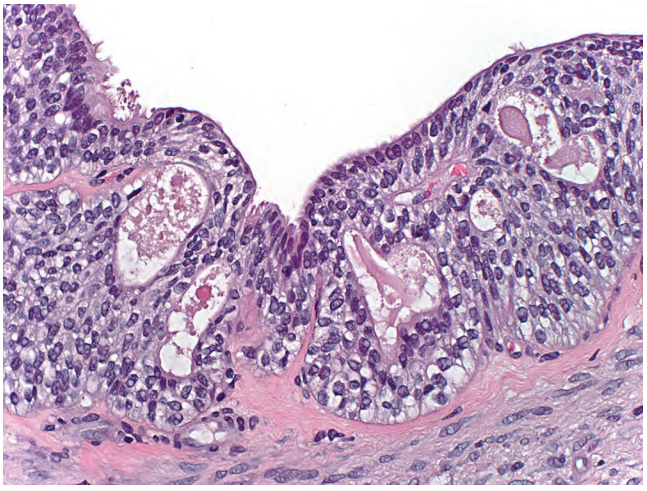
There is some histopathologic overlap between the features of the glandular odontogenic cyst and those of some intraosseous, low-grade, predominantly cystic mucoepidermoid carcinomas (see page 457). In selected microscopic fields, the microscopic features may be identical. Examination of multiple sections, however, usually permits the differentiation of these lesions. Also, glandular odontogenic cysts will not show *MAML2* gene rearrangements, which often are found in central mucoepidermoid carcinomas.

Treatment and Prognosis

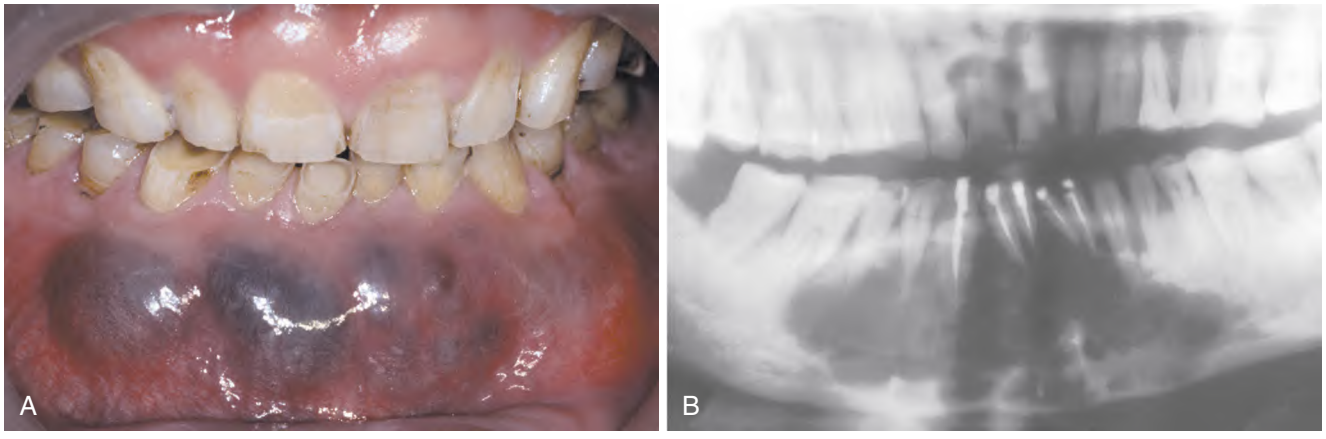
Most cases of glandular odontogenic cyst have been treated by enucleation or curettage. However, this cyst shows a propensity for recurrence, which is observed in approximately 30% of all cases. Recurrence appears to be more common among the lesions that present in a multilocular fashion. Because of its potentially aggressive nature and tendency for recurrence, some authors have advocated *en bloc* resection, particularly for multilocular lesions. Marsupialization and decompression may be attempted for larger lesions to promote shrinkage prior to surgery.

BUCCAL BIFURCATION CYST

The **buccal bifurcation cyst** is an uncommon inflammatory odontogenic cyst that characteristically develops on the buccal aspect of the mandibular first permanent molar, although some cases have involved the second molar. The pathogenesis of this cyst is uncertain. Some of these lesions have been associated with teeth that demonstrate buccal enamel extensions into the bifurcation area (see page 86). Such extensions may predispose these teeth to buccal pocket formation, which could then enlarge to form a cyst in



• **Fig. 15-48 Glandular Odontogenic Cyst.** The cyst is lined by stratified squamous epithelium that exhibits surface columnar cells with cilia. Numerous microcysts containing mucinous material are present.



• **Fig. 15-47 Glandular Odontogenic Cyst. A,** Expansile lesion of the anterior mandible. **B,** The panoramic radiograph shows a large multilocular radiolucency. (Courtesy of Dr. Cheng-Chung Lin.)

response to pericoronitis. It has been speculated that when the tooth erupts, an inflammatory response may occur in the surrounding follicular tissues that stimulates cyst formation.

The term **paradental cyst** sometimes has been used synonymously for the buccal bifurcation cyst. Such lesions typically occur distal or buccal of partially erupted mandibular third molars with a history of pericoronitis. The pathogenesis of the so-called paradental cyst also is uncertain. However, the distinction of paradental cysts from secondarily inflamed dentigerous cysts is difficult, if not impossible, in many instances (see page 632).

Clinical and Radiographic Features

The buccal bifurcation cyst typically occurs in children from 5 to 13 years of age. The patient has slight-to-moderate tenderness on the buccal aspect of the mandibular first or second molar, which may be in the process of erupting. The patient often notes associated clinical swelling and a foul-tasting discharge. Periodontal probing usually reveals pocket formation on the buccal aspect of the involved tooth. Around one-third of patients have been reported to have bilateral involvement of the first molars.

Radiographs typically show a well-circumscribed unilocular radiolucency involving the buccal bifurcation and root area of the involved tooth (Fig. 15-49). The average size of the lucent defect is 1.2 cm, but the lesion may be as large as 2.5 cm in diameter. An occlusal radiograph is most helpful in demonstrating the buccal location of the lesion. The root apices of the molar are characteristically tipped toward the lingual mandibular cortex (Fig. 15-50). Many cases are associated with proliferative periostitis (see page 134) of the overlying buccal cortex, which is characterized by a single or multiple layers of reactive bone formation.

Histopathologic Features

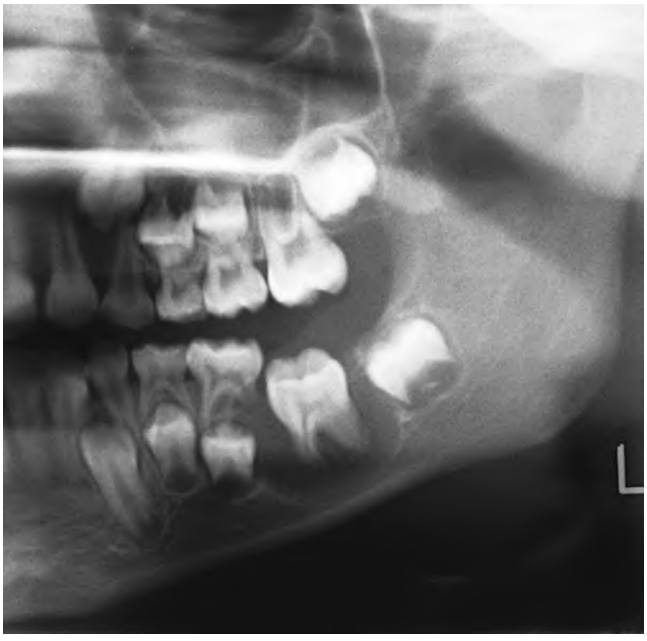
The microscopic features are nonspecific and show a cyst that is lined by nonkeratinizing stratified squamous epithelium with areas of hyperplasia. A prominent chronic inflammatory cell infiltrate is present in the surrounding connective tissue wall.

Treatment and Prognosis

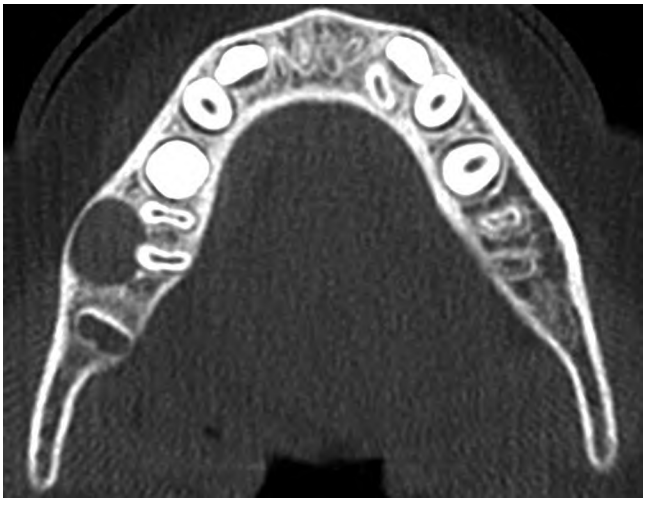
The buccal bifurcation cyst is usually treated by enucleation; extraction of the associated tooth is unnecessary. Within 1 year of surgery, there is usually complete healing with normalization of periodontal probing depths and radiographic evidence of bone fill. Several reports have described cases that resolved without surgery—either with no treatment at all or by daily irrigation of the buccal pocket with saline and hydrogen peroxide.

◆ CARCINOMA ARISING IN ODONTOGENIC CYSTS

Carcinoma arising within bone is a rare lesion that is essentially limited to the jaws. Because the putative source of the epithelium giving rise to the carcinoma is odontogenic, these intraosseous jaw carcinomas are collectively known as **odontogenic carcinomas.** Odontogenic carcinomas may arise in an ameloblastoma, rarely from other odontogenic tumors, *de novo* (without evidence of a preexisting lesion), or from the epithelial lining of odontogenic cysts. Some intraosseous mucoepidermoid carcinomas (see page 457) also may arise from mucous cells lining a dentigerous cyst.



• **Fig. 15-49 Buccal Bifurcation Cyst.** Well-circumscribed unilocular radiolucency superimposed on the roots of the mandibular first permanent molar. (Courtesy of Dr. Michael Pharoah.)



• **Fig. 15-50 Buccal Bifurcation Cyst.** Axial computed tomography (CT) image showing a circumscribed radiolucency buccal to the roots of the mandibular first molar. (Courtesy of Dr. Robert Clark.)

Most intraosseous carcinomas apparently arise in odontogenic cysts. Although infrequently documented in the literature, carcinomatous transformation of the lining of an odontogenic cyst may be more common than is generally appreciated. Several studies have shown that 1% to 2% of all oral cavity carcinomas seen in some oral and maxillofacial pathology services may originate from odontogenic cysts. The pathogenesis of carcinomas arising in odontogenic cysts is unknown. Occasionally, areas within the lining of odontogenic cysts histopathologically demonstrate varying degrees of epithelial dysplasia, and such changes likely give rise to the carcinoma.

Clinical and Radiographic Features

Although carcinomas arising in cysts may be seen in patients across a wide age range, they are encountered most often in older patients. The mean reported age is 60 years. This lesion is over twice as common in men as in women. Pain and swelling are the most common complaints. However, many patients have no symptoms, and the diagnosis of carcinoma is made only after microscopic examination of a presumed odontogenic cyst.

Radiographic findings may mimic those of any odontogenic cyst, although the margins of the radiolucent defect are usually irregular and ragged. CT scans of the lesion may demonstrate a destructive pattern that is not appreciated on viewing plain radiographs. A lesion considered to be a **residual periapical cyst** is apparently the most common type associated with carcinomatous transformation, although routine periapical cysts can also exhibit malignant change. These account for 60% of reported cases. In about 16% of cases, the carcinoma appeared to have arisen in a **dentigerous cyst** (Fig. 15-51). In one patient, the carcinoma was thought to originate from a **lateral periodontal cyst.**

A number of examples of carcinoma arising in an OKC also have been documented (Fig. 15-52). However, some reported examples do not appear to have arisen in true parakeratinized OKCs, but rather in **orthokeratinized odontogenic cysts.**

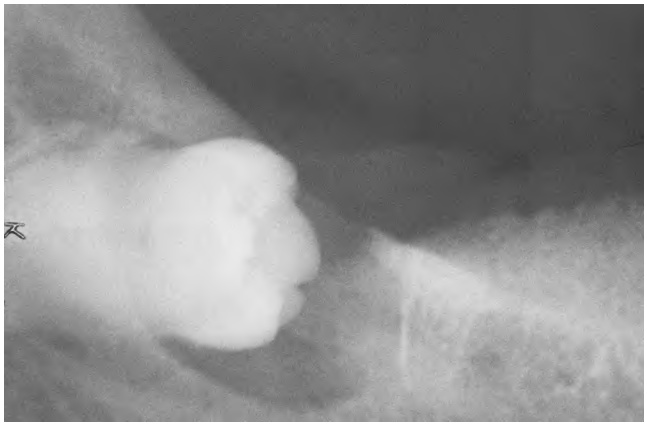
Histopathologic Features

Most carcinomas arising in cysts histopathologically have been **well-differentiated** or **moderately well-differentiated squamous cell carcinomas.** Sometimes it is possible to identify a transition from a normal-appearing cyst lining to invasive squamous cell carcinoma (Figs. 15-53 and 15-54).

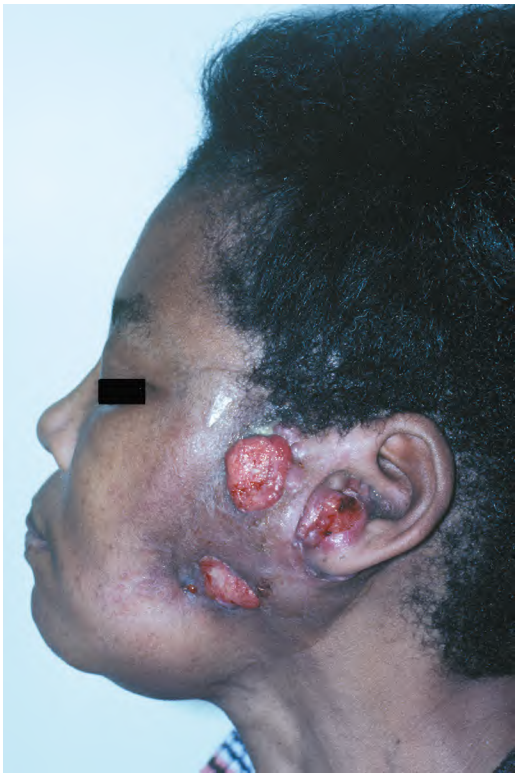
Treatment and Prognosis

The treatment of patients with carcinomas arising in cysts has varied from local block excision to radical resection, with or without radiation or adjunctive chemotherapy. The prognosis is difficult to evaluate because most reports consist of isolated cases. Metastases to regional lymph nodes have been demonstrated in a few cases. One review showed an overall 2-year survival rate of 62%, but the 5-year survival rate dropped to 38%.

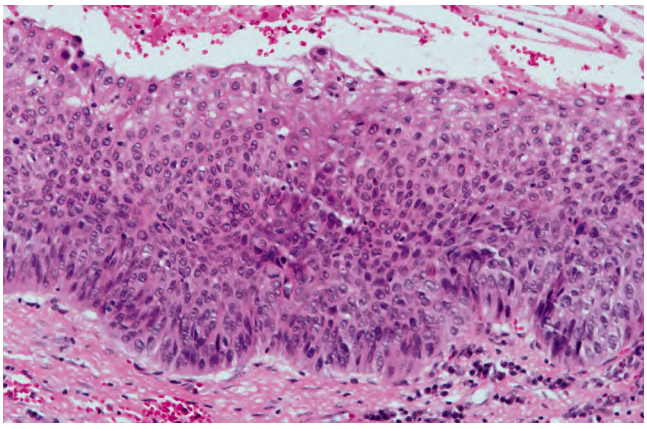
Before a given lesion can be accepted as an example of primary intraosseous carcinoma, the possibility that the tumor represents metastatic spread from an intraoral or extraoral site must be ruled out by appropriate studies.



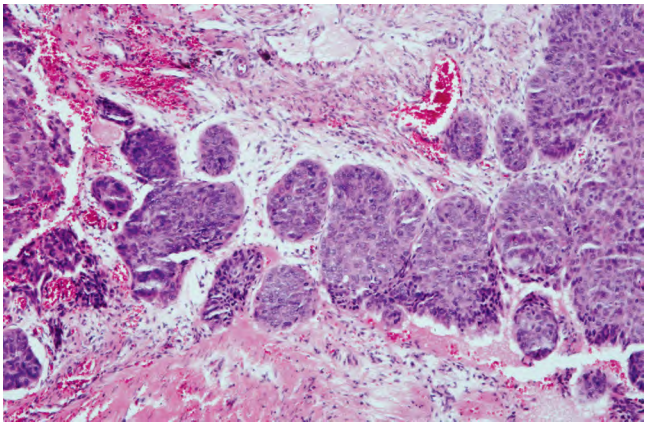
• **Fig. 15-51 Carcinoma Arising in a Dentigerous Cyst.** Radiolucent lesion surrounding the crown of an impacted third molar in a 56-year-old woman. This was clinically considered to be a dentigerous cyst. (Courtesy of Dr. Richard Ziegler.)



• **Fig. 15-52 Carcinoma Arising in a Cyst.** There is a massive carcinoma of the mandible, with extension into the parotid gland, the face, and the base of the brain. Nineteen years previously, a large odontogenic keratocyst (OKC) with areas of epithelial dysplasia had been removed from the ascending ramus. The patient had suffered multiple recurrences, with eventual change into invasive carcinoma.



• **Fig. 15-53 Carcinoma Arising in a Cyst.** High-power view of a dentigerous cyst from a 53-year-old man. The lining demonstrates full-thickness epithelial dysplasia.



• **Fig. 15-54 Carcinoma Arising in a Cyst.** Same case as Fig. 15-53 showing islands of invasive epithelial cells in the cyst wall.

ODONTOGENIC TUMORS

Odontogenic tumors comprise a complex group of lesions of diverse histopathologic types and clinical behavior. Some of these lesions are true neoplasms and may rarely exhibit malignant behavior. Others may represent tumorlike malformations (hamartomas).

Odontogenic tumors, like normal odontogenesis, demonstrate varying inductive interactions between odontogenic epithelium and odontogenic ectomesenchyme. This ectomesenchyme was formerly referred to as *mesenchyme* because it was thought to be derived from the mesodermal layer of the embryo. It is now accepted that this tissue differentiates from the ectodermal layer in the cephalic portion of the embryo. **Tumors of odontogenic epithelium** are composed only of odontogenic epithelium without any participation of odontogenic ectomesenchyme.

Other odontogenic neoplasms, sometimes referred to as **mixed odontogenic tumors,** are composed of odontogenic epithelium and ectomesenchymal elements. Dental hard tissue may or may not be formed in these lesions.

• BOX 15-4 Classification of Odontogenic Tumors

I. Tumors of odontogenic epithelium
  A. Ameloblastoma
    1. Malignant ameloblastoma
    2. Ameloblastic carcinoma
  B. Clear cell odontogenic carcinoma
  C. Adenomatoid odontogenic tumor
  D. Calcifying epithelial odontogenic tumor
  E. Squamous odontogenic tumor
II. Mixed odontogenic tumors
  A. Ameloblastic fibroma
  B. Ameloblastic fibro-odontoma
  C. Ameloblastic fibrosarcoma
  D. Odontoameloblastoma
  E. Compound odontoma
  F. Complex odontoma
III. Tumors of odontogenic ectomesenchyme
  A. Odontogenic fibroma
  B. Granular cell odontogenic tumor
  C. Odontogenic myxoma
  D. Cementoblastoma

A third group, **tumors of odontogenic ectomesenchyme,** is composed principally of ectomesenchymal elements. Although odontogenic epithelium may be included within these lesions, it does not appear to play any essential role in their pathogenesis.

Box 15-4 presents categories of odontogenic tumors modified from the 2005 WHO classification.

Because many of these lesions are quite rare, it is sometimes difficult to assess certain epidemiologic features accurately, as well as recommendations regarding treatment. It should be kept in mind that reports in the literature may be biased due to geopolitical/economic variations in submission of biopsies or the tendency of journal editors to publish reports of lesions that are unusual or aggressive.

TUMORS OF ODONTOGENIC EPITHELIUM

Epithelial odontogenic tumors are composed of odontogenic epithelium without participation of odontogenic ectomesenchyme. Several distinctly different tumors are included in the group; ameloblastoma is the most important and common of them.

◆ AMELOBLASTOMA

The **ameloblastoma** is the most common clinically significant odontogenic tumor. Its relative frequency equals the combined frequency of all other odontogenic tumors, excluding odontomas. Ameloblastomas are tumors of odontogenic epithelial origin. Theoretically, they may arise from rests of dental lamina, from a developing enamel organ, from the epithelial lining of an odontogenic cyst, or from the basal cells of the oral mucosa. Ameloblastomas are

slow-growing, locally invasive tumors that run a benign course in most cases. They typically have been described as having three different clinicoradiographic presentations, which deserve separate consideration because of potentially differing therapeutic considerations and prognosis:

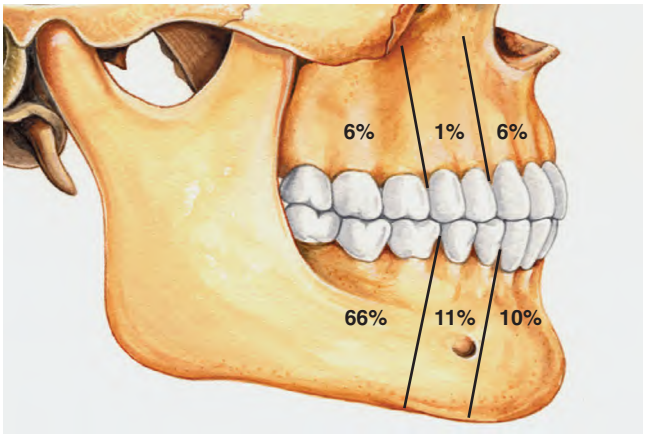
1. Conventional solid or multicystic (about 75% to 86% of all cases)
2. Unicystic (about 13% to 21% of all cases)
3. Peripheral (extraosseous) (about 1% to 4% of all cases)

CONVENTIONAL SOLID OR MULTICYSTIC INTRAOSSEOUS AMELOBLASTOMA

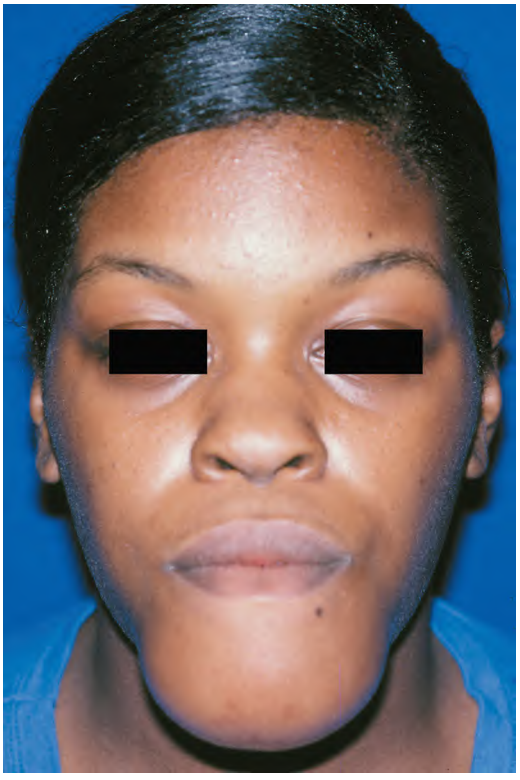
Clinical and Radiographic Features

Conventional solid or **multicystic intraosseous ameloblastoma** is encountered in patients across a wide age range. It is rare in children younger than age 10 and relatively uncommon in the 10- to 19-year-old group. The tumor shows an approximately equal prevalence in the third to seventh decades of life. There is no significant sex predilection. Some studies indicate a greater frequency in blacks; others show no racial predilection. About 80% to 85% of conventional ameloblastomas occur in the mandible, most often in the molar-ascending ramus area. About 15% to 20% of ameloblastomas occur in the maxilla, usually in the posterior regions (Fig. 15-55). The tumor is often asymptomatic, and smaller lesions are detected only during a radiographic examination. A painless swelling or expansion of the jaw is the usual clinical presentation (Figs. 15-56 and 15-57). If untreated, then the lesion may grow slowly to massive or grotesque proportions (Fig. 15-58). Pain and paresthesia are uncommon, even with large tumors.

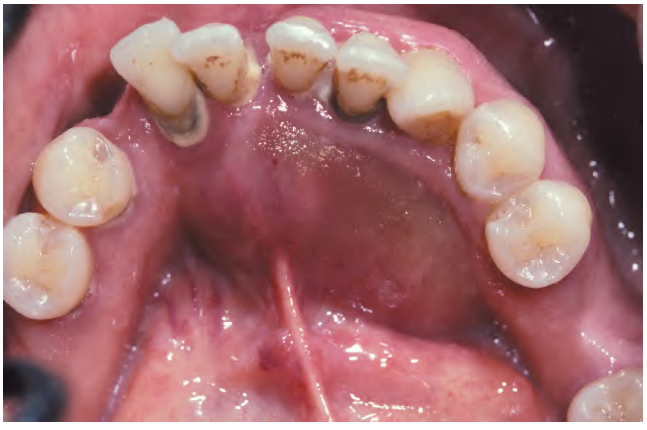
The most typical radiographic feature is that of a multilocular radiolucent lesion, although one large international study suggested that a unilocular presentation was just as likely. Multilocular lesions are described as having a "soap bubble" appearance (when the radiolucent loculations are large) or as being "honeycombed" (when the loculations are small) (Figs. 15-59 to 15-61). Buccal and lingual cortical expansion is frequently present. Resorption of the roots of teeth adjacent to the tumor is common. In many cases an unerupted tooth, most often a mandibular third molar, is associated with the radiolucent defect. Solid ameloblastomas may radiographically appear as unilocular radiolucent defects, which may resemble almost any type of cystic lesion (Fig. 15-62). The margins of these radiolucent lesions, however, often show irregular scalloping. Although the radiographic features, particularly of the typical multilocular defect, may be highly suggestive of ameloblastoma, a



• **Fig. 15-55 Ameloblastoma.** Relative distribution of ameloblastomas in the jaws.



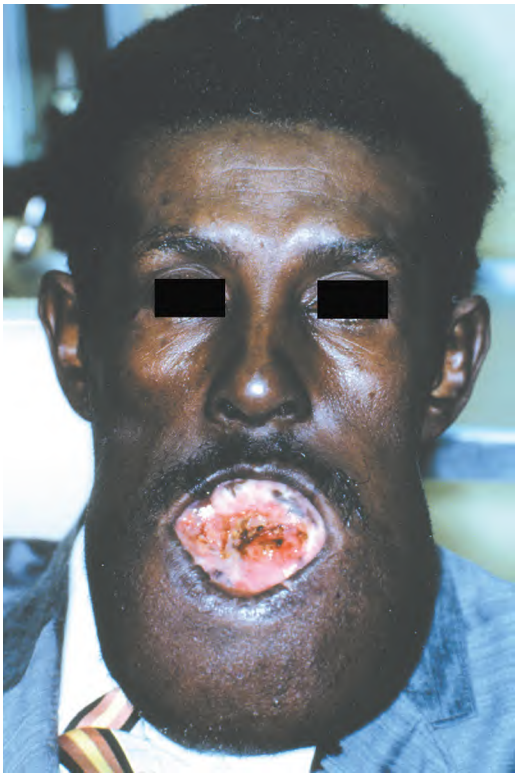
• **Fig. 15-56 Ameloblastoma.** Large expansile mass of the anterior mandible. (Courtesy of Dr. Michael Tabor.)



• **Fig. 15-57 Ameloblastoma.** Prominent expansion of the lingual alveolus caused by a large ameloblastoma of the mandibular symphysis.

variety of odontogenic and nonodontogenic lesions may show similar radiographic features (see Appendix).

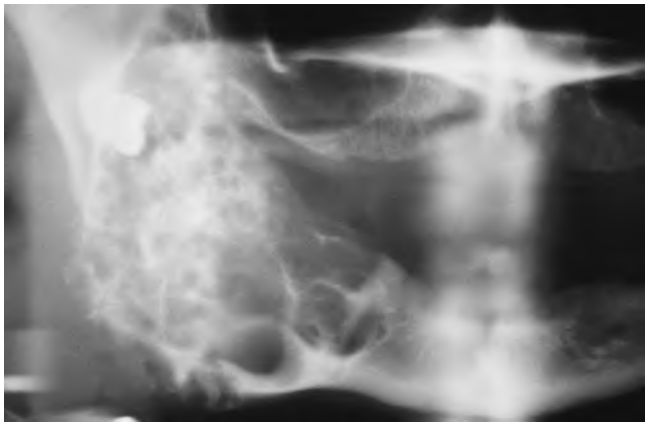
One form of ameloblastoma that does not have these characteristic features is the desmoplastic ameloblastoma, a variant that Eversole and colleagues documented initially in the literature in 1984. The desmoplastic ameloblastoma has a marked predilection to occur in the anterior regions of the jaws, with equal distribution between the mandible and the maxilla. Radiographically, this type may not suggest the diagnosis of ameloblastoma; the majority of these tumors resemble a fibro-osseous lesion because of their mixed radiolucent and radiopaque appearance (Fig. 15-63). This mixed radiographic appearance is due to osseous metaplasia within the dense fibrous septa that characterize the lesion, not because the tumor itself is producing a mineralized product.



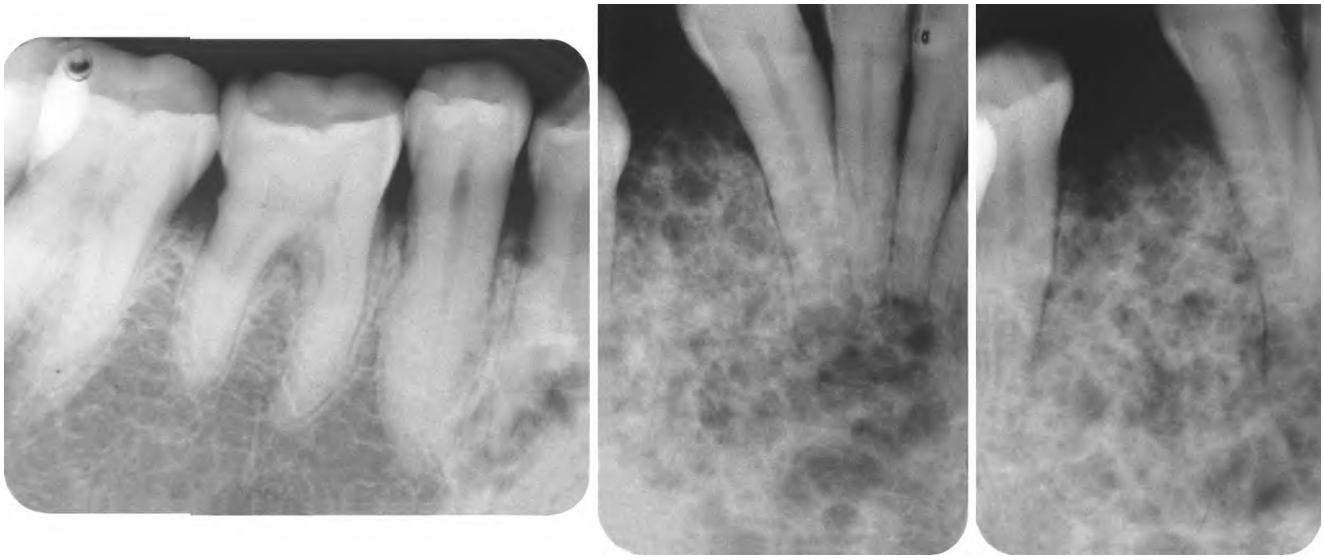
• **Fig. 15-58 Ameloblastoma.** Massive tumor of the anterior mandible. (Courtesy of Dr. Ronald Baughman.)

Histopathologic Features

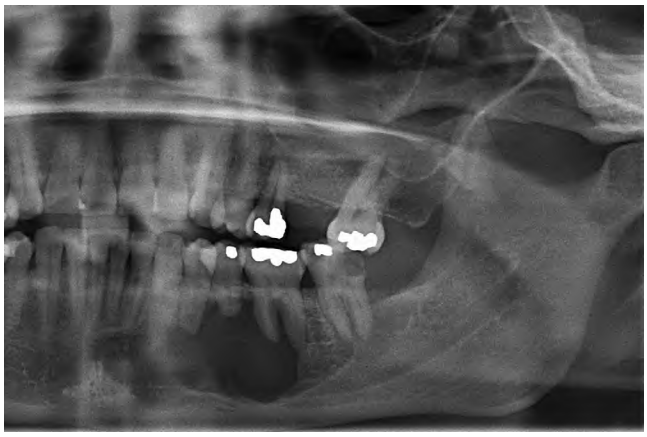
Conventional solid or multicystic intraosseous ameloblastomas show a remarkable tendency to undergo cystic change; grossly, most tumors have varying combinations of cystic and solid features. The cysts may be seen only at the microscopic level or may be present as multiple large cysts that include most of the tumor. Several microscopic subtypes of



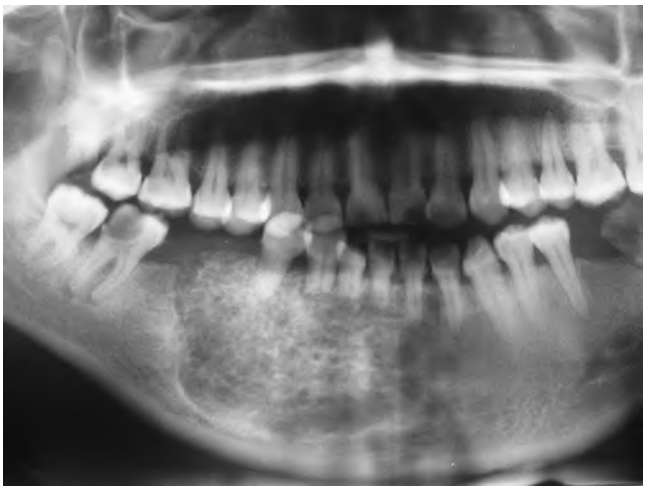
• **Fig. 15-59 Ameloblastoma.** Large multilocular lesion involving the mandibular angle and ascending ramus. The large loculations show the "soap bubble" appearance. An unerupted third molar has been displaced high into the ramus.



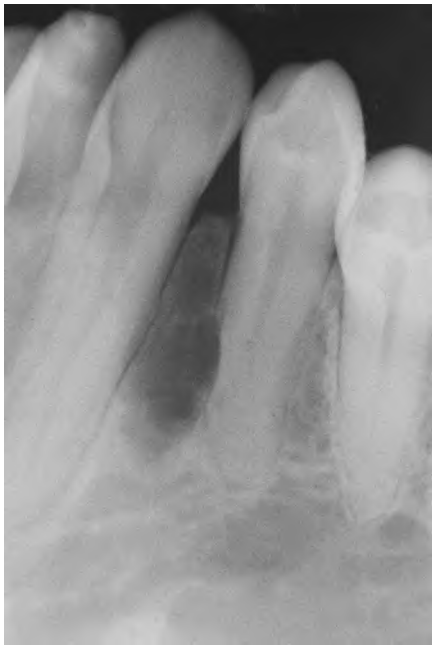
• **Fig. 15-60 Ameloblastoma.** Periapical films showing the "honeycombed" appearance. (Courtesy of Dr. John Hann.)



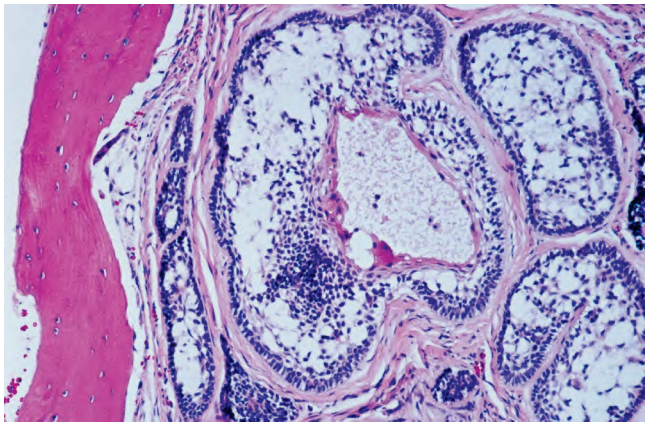
• **Fig. 15-61 Ameloblastoma.** Destructive radiolucent lesion with root resorption of the associated posterior teeth. (Courtesy of Dr. Louis Beto.)



• **Fig. 15-63 Desmoplastic Ameloblastoma.** Large mixed radiolucent and radiopaque lesion of the anterior and right body of the mandible. (Courtesy of Dr. Román Carlos.)



• **Fig. 15-62 Ameloblastoma.** This small unilocular radiolucency lesion could easily be mistaken for a lateral periodontal cyst. (Courtesy of Dr. Tony Traynham.)



• **Fig. 15-64 Ameloblastoma (Follicular Pattern).** Multiple islands of odontogenic epithelium demonstrating peripheral columnar differentiation with reverse polarization. The central zones resemble stellate reticulum and exhibit foci of cystic degeneration.

conventional ameloblastoma are recognized, but these microscopic patterns generally have little bearing on the behavior of the tumor. Large tumors often show a combination of microscopic patterns.

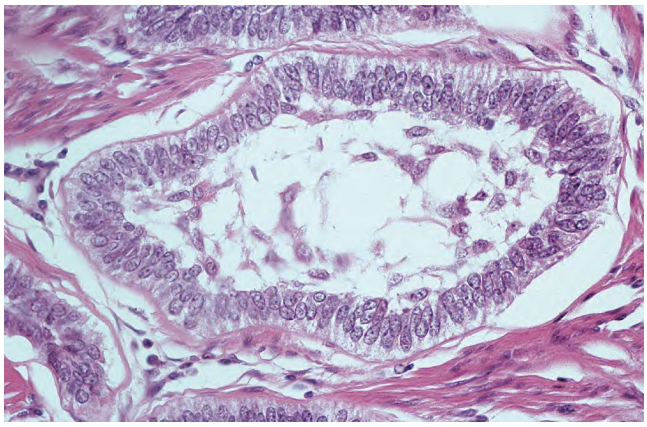
The **follicular** and **plexiform** patterns are the most common. Less common histopathologic patterns include the **acanthomatous, granular cell, desmoplastic,** and **basal cell** types.

Follicular Pattern

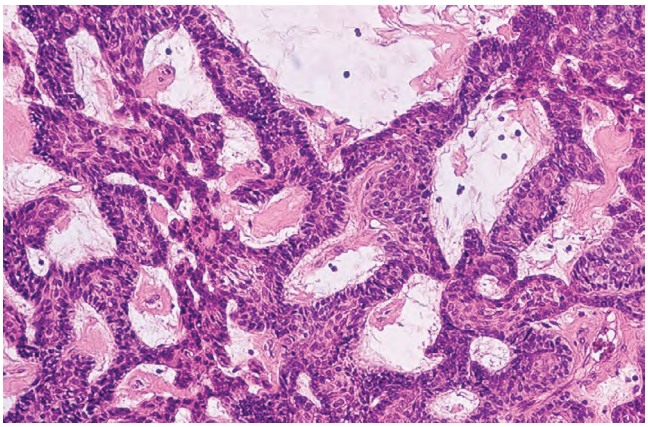
The follicular histopathologic pattern is the most common and recognizable. Islands of epithelium resemble enamel organ epithelium in a mature fibrous connective tissue stroma. The epithelial nests consist of a core of loosely arranged angular cells resembling the stellate reticulum of an enamel organ. A single layer of tall columnar ameloblast-like cells surrounds this central core. The nuclei of these cells are located at the opposite pole to the basement membrane **(reversed polarity).** In other areas, the peripheral cells may be more cuboidal and resemble basal cells. Cyst formation is common and may vary from microcysts, which form within the epithelial islands, to large macroscopic cysts, which may be several centimeters in diameter (Figs. 15-64 and 15-65). If an incisional biopsy is taken from such an area, an inappropriate diagnosis of "unicystic ameloblastoma" may be rendered by the pathologist.

Plexiform Pattern

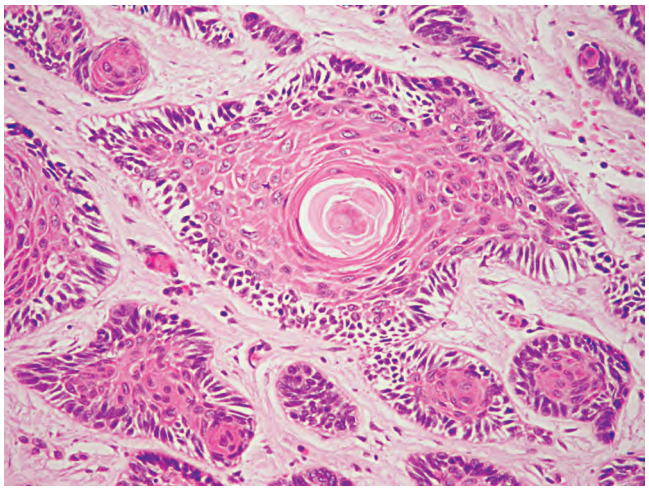
The plexiform type of ameloblastoma consists of long, anastomosing cords or larger sheets of odontogenic epithelium. The cords or sheets of epithelium are bounded by columnar or cuboidal ameloblast-like cells surrounding more loosely



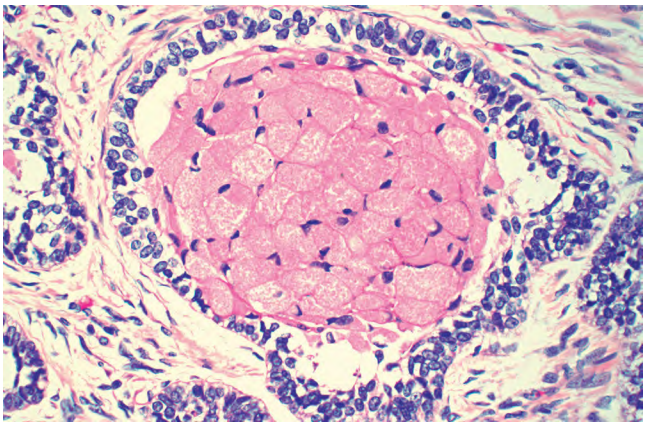
• **Fig. 15-65 Ameloblastoma (Follicular Pattern).** This high-power photomicrograph highlights the peripheral columnar cells exhibiting reverse polarization.



• **Fig. 15-66 Ameloblastoma (Plexiform Pattern).** Anastomosing cords of odontogenic epithelium.



• **Fig. 15-67 Ameloblastoma (Acanthomatous Pattern).** Islands of ameloblastoma demonstrating central squamous differentiation.



• **Fig. 15-68 Ameloblastoma (Granular Cell Variant).** Tumor island exhibiting central cells with prominent granular cytoplasm.

arranged epithelial cells. The supporting stroma tends to be loosely arranged and vascular. Cyst formation is relatively uncommon in this variety. When it occurs, it is more often associated with stromal degeneration rather than cystic change within the epithelium (Fig. 15-66).

Acanthomatous Pattern

When extensive squamous metaplasia, often associated with keratin formation, occurs in the central portions of the epithelial islands of a follicular ameloblastoma, the term **acanthomatous ameloblastoma** is sometimes applied. This change does not indicate a more aggressive course for the lesion; histopathologically, however, such a lesion may be confused with squamous cell carcinoma or squamous odontogenic tumor (Fig. 15-67).

Granular Cell Pattern

Ameloblastomas may sometimes show transformation of groups of lesional epithelial cells to granular cells. These cells have abundant cytoplasm filled with eosinophilic granules that resemble lysosomes ultrastructurally and histochemically. Although originally considered to represent an aging or degenerative change in long-standing lesions, this variant has been seen in young patients. When this granular cell change is extensive in an ameloblastoma, the designation of **granular cell ameloblastoma** is appropriate (Fig. 15-68).

Desmoplastic Pattern

This type of ameloblastoma contains small islands and cords of odontogenic epithelium in a densely collagenized stroma. Immunohistochemical studies have shown increased production of the cytokine known as *transforming growth factor-β (TGF-β)* in association with this lesion, suggesting that this may be responsible for the desmoplasia. Peripheral columnar ameloblast-like cells are inconspicuous about the epithelial islands (Fig. 15-69).

Basal Cell Pattern

The basal cell variant of ameloblastoma is the least common type. These lesions are composed of nests of uniform basaloid cells, and they histopathologically are very similar to

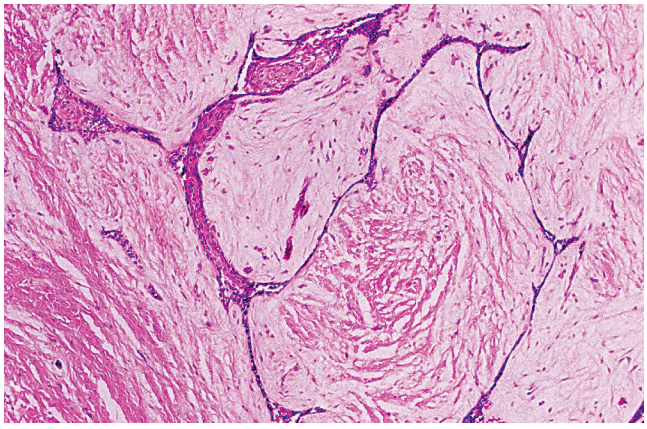
basal cell carcinoma of the skin. No stellate reticulum is present in the central portions of the nests. The peripheral cells about the nests tend to be cuboidal rather than columnar (Fig. 15-70).

Treatment and Prognosis

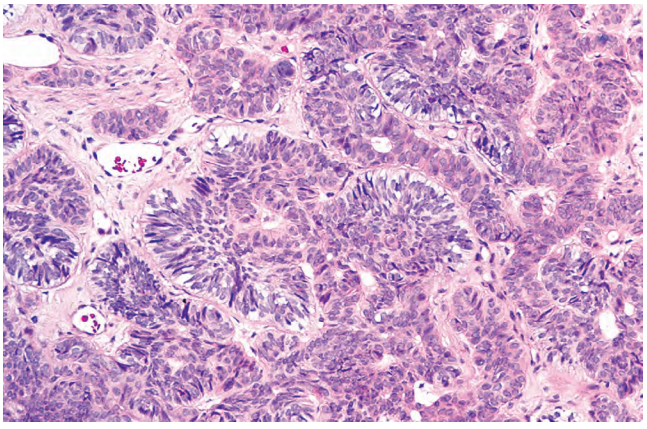
Patients with conventional solid or multicystic intraosseous ameloblastomas have been treated by a variety of means. These range from simple enucleation and curettage to *en bloc* resection (Fig. 15-71). The optimal method of treatment has been the subject of controversy for many years. The conventional ameloblastoma tends to infiltrate between intact cancellous bone trabeculae at the periphery of the lesion before bone resorption becomes radiographically evident. Therefore, the actual margin of the tumor often extends beyond its apparent radiographic or clinical margin. Attempts to remove the tumor by curettage often leave small islands of tumor within the bone, which later manifest as recurrences. Recurrence rates of 50% to 90% have been reported in various studies after curettage. Recurrence often takes many years to become clinically manifest, and 5-year disease-free periods do not indicate a cure.

Marginal resection is the most widely used treatment, but recurrence rates of up to 15% have been reported after marginal or block resection. Some surgeons advocate a more conservative approach to treatment by planning surgery after careful evaluation of CT scans of the tumor. Removal of the tumor, followed by peripheral ostectomy, often reduces the need for extensive reconstructive surgery. Some tumors may not be amenable to this approach because of their size or growth pattern.

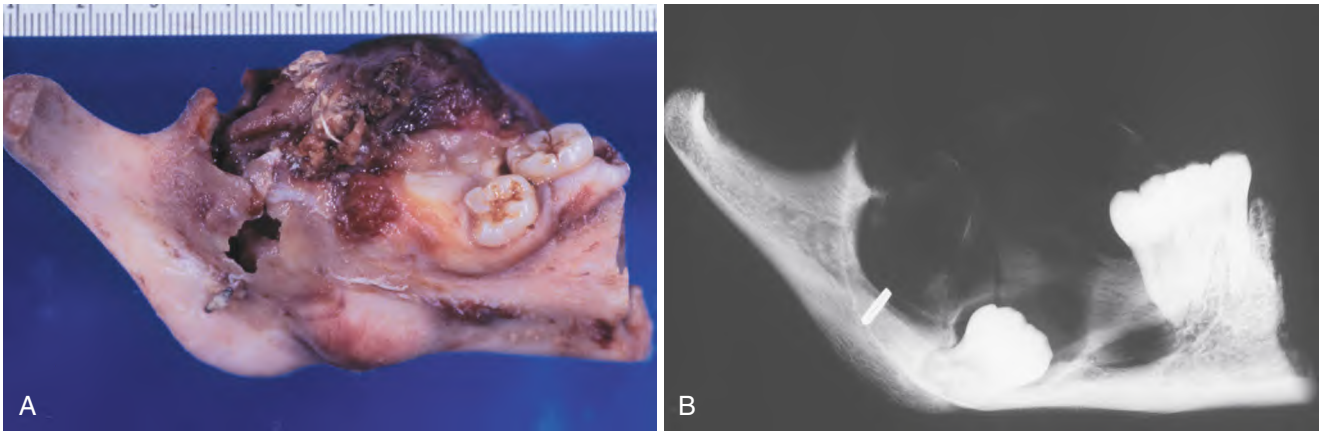
Other surgeons advocate that the margin of the resection should be at least 1.0 to 2.0 cm past the radiographic limits of the tumor. Ameloblastomas of the posterior maxilla are particularly dangerous because of the difficulty of obtaining an adequate surgical margin around the tumor. Orbital invasion by maxillary ameloblastomas occasionally has been described. Although some studies suggest that the ameloblastoma may be radiosensitive, radiation therapy has seldom been used as a treatment modality because of the intraosseous location of the tumor and the potential for



• **Fig. 15-69 Ameloblastoma (Desmoplastic Variant).** Thin cords of ameloblastic epithelium within a dense fibrous connective tissue stroma.



• **Fig. 15-70 Ameloblastoma (Basal Cell Variant).** Islands of hyperchromatic basaloid cells with peripheral palisading.



• **Fig. 15-71 Ameloblastoma. A,** Gross photograph of a mandibular resection specimen. **B,** The radiograph of the specimen shows a large radiolucent defect associated with an inferiorly displaced third molar. (Courtesy of Dr. Mary Richardson.)

secondary radiation-induced malignancy developing in a relatively young patient population.

The conventional ameloblastoma is a persistent, infiltrative neoplasm that very seldom may kill the patient by progressive spread to involve vital structures. Most of these tumors, however, are not life-threatening lesions. Rarely, an ameloblastoma exhibits frank malignant behavior. These are discussed separately.

UNICYSTIC AMELOBLASTOMA

The **unicystic ameloblastoma** has for several decades been given separate consideration based on its clinical, radiographic, and pathologic features. Although its response to treatment in reports from the 1970s and 1980s suggested that this lesion might behave in a less aggressive fashion, recent reports have disputed this concept. Unicystic ameloblastomas account for 10% to 46% of all intraosseous ameloblastomas in various studies. Whether the unicystic ameloblastoma originates *de novo* as a neoplasm or whether it is the result of neoplastic transformation of nonneoplastic cyst epithelium has been long debated. Both mechanisms probably occur, but proof of which is involved in an individual patient is virtually impossible to obtain.

Clinical and Radiographic Features

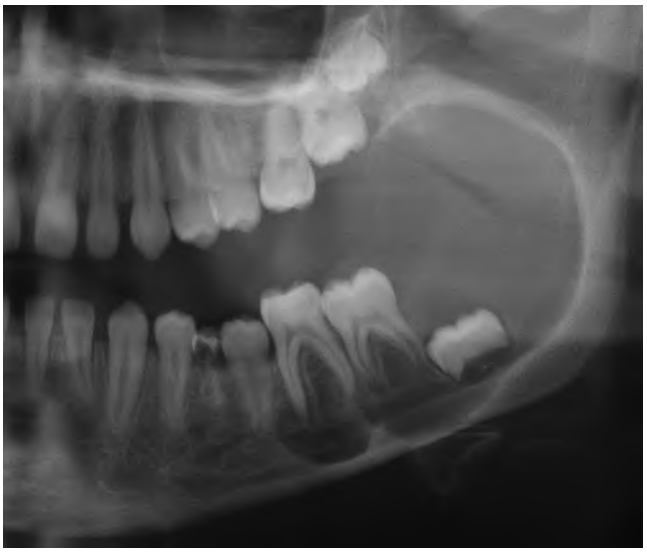
Unicystic ameloblastomas are seen most often in younger patients, with about 50% of all such tumors diagnosed during the second decade of life. The average age in one large series was 23 years. More than 90% of unicystic ameloblastomas are found in the mandible, usually in the posterior regions. The lesion is often asymptomatic, although large lesions may cause a painless swelling of the jaws.

In many patients, this lesion typically appears as a circumscribed radiolucency that surrounds the crown of an unerupted mandibular third molar (Figs. 15-72 and 15-73), clinically resembling a dentigerous cyst. Other tumors simply appear as sharply defined radiolucent areas and are usually considered to be a primordial, radicular, or residual cyst, depending on the relationship of the lesion to teeth in the area. In some instances, the radiolucent area may have scalloped margins but is still a unicystic ameloblastoma. Whether a unicystic ameloblastoma can have a truly multilocular radiographic presentation is arguable.

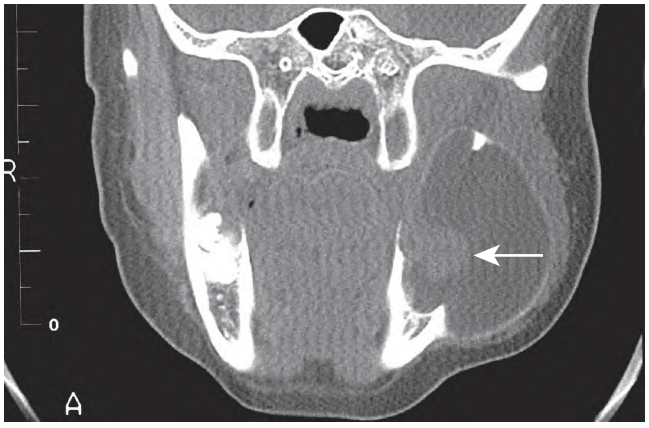
The surgical findings may also suggest that the lesion in question is a cyst, and the diagnosis of ameloblastoma is made only after microscopic study of the specimen.

Histopathologic Features

Three histopathologic variants of unicystic ameloblastoma have been described. In the first type **(luminal unicystic ameloblastoma),** the tumor is confined to the luminal surface of the cyst. The lesion consists of a fibrous cyst wall with a lining composed totally or partially of ameloblastic epithelium. The lining demonstrates a basal layer of columnar or cuboidal cells with hyperchromatic nuclei that show reverse polarity and basilar cytoplasmic vacuolization (Fig. 15-74). The upper epithelial cells are loosely cohesive and resemble stellate reticulum. This finding does not seem to be related to inflammatory edema.

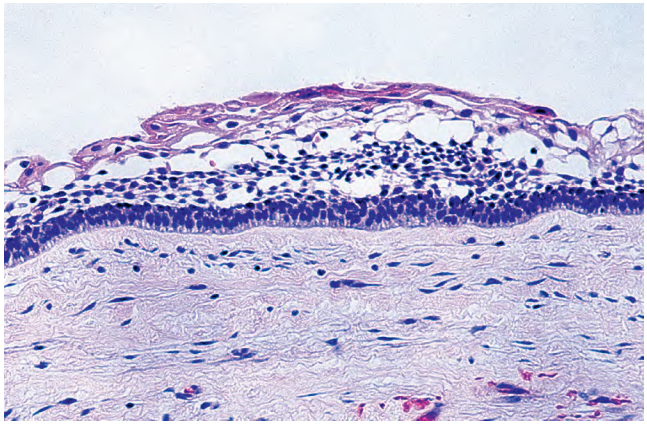


• **Fig. 15-72 Unicystic Ameloblastoma.** A large radiolucency associated with the crown of the developing mandibular third molar. (Courtesy of Dr. Antonia Kolokythas.)

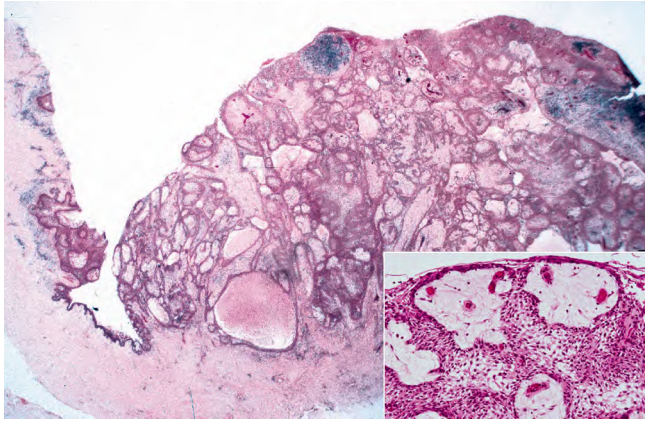


• **Fig. 15-73 Unicystic Ameloblastoma (Intraluminal Plexiform Type).** Coronal computed tomography (CT) image that shows a large cystic lesion with an intraluminal mass arising from the cyst wall *(arrow).*

In the second microscopic variant, one or more nodules of ameloblastoma project from the cystic lining into the lumen of the cyst. This type is called an **intraluminal unicystic ameloblastoma.** These nodules may be relatively small or largely fill the cystic lumen. In some cases, the nodule of tumor that projects into the lumen demonstrates an edematous, plexiform pattern that resembles the plexiform pattern seen in conventional ameloblastomas (Fig. 15-75). These lesions are sometimes referred to as **plexiform unicystic ameloblastomas.** The intraluminal cellular proliferation does not always meet the strict histopathologic



• **Fig. 15-74 Unicystic Ameloblastoma (Luminal Type).** The cyst is lined by ameloblastic epithelium showing a hyperchromatic, polarized basal layer. The overlying epithelial cells are loosely cohesive and resemble stellate reticulum.



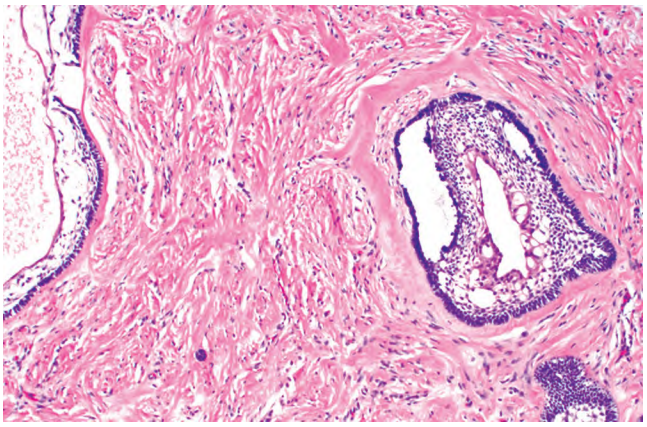
• **Fig. 15-75 Unicystic Ameloblastoma (Intraluminal Plexiform Type).** Photomicrograph of an intraluminal mass arising from the cyst wall. The *inset* shows the intraluminal mass at higher magnification.

criteria for ameloblastoma, and this may be secondary to inflammation that nearly always accompanies this pattern. Typical ameloblastoma, however, may be found in other, less inflamed parts of the specimen.

In the third variant, known as **mural unicystic ameloblastoma,** the fibrous wall of the cyst is infiltrated by typical follicular or plexiform ameloblastoma. The extent and depth of the ameloblastic infiltration may vary considerably. With any presumed unicystic ameloblastoma, multiple sections through many levels of the specimen are necessary to rule out the possibility of mural invasion of tumor cells (Fig. 15-76).

Treatment and Prognosis

The clinical and radiographic findings in most cases of unicystic ameloblastoma suggest that the lesion is an odontogenic cyst. These tumors are usually treated as cysts by enucleation. The diagnosis of ameloblastoma is made only after microscopic examination of the presumed cyst. If the ameloblastic elements are confined to the lumen of the cyst



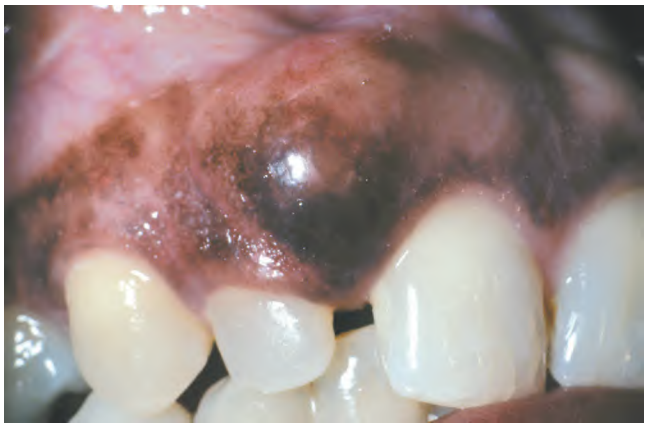
• **Fig. 15-76 Unicystic Ameloblastoma (Mural Type).** The epithelial lining of the cystic component can be seen on the left edge of the photomicrograph. Islands of follicular ameloblastoma are infiltrating into the fibrous connective tissue wall on the right.

with or without intraluminal tumor extension, then the cyst enucleation has probably been adequate treatment. The patient, however, should be kept under long-term follow-up. If the specimen shows extension of the tumor into the fibrous cyst wall for any appreciable distance, then subsequent management of the patient is more controversial. Some surgeons believe that local resection of the area is indicated as a prophylactic measure; others prefer to keep the patient under close radiographic observation and delay further treatment until there is evidence of recurrence.

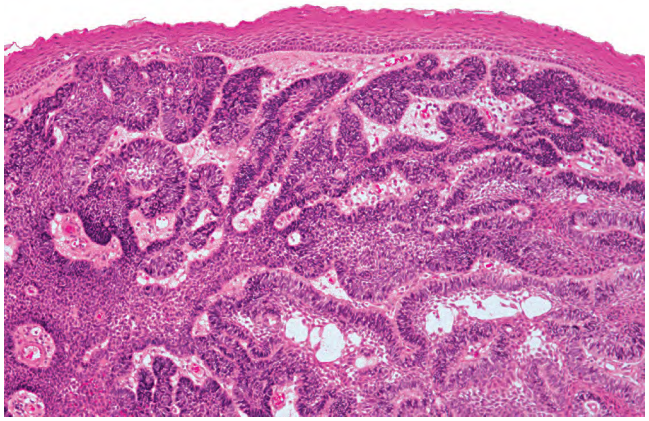
Recurrence rates of 10% to 20% were described after enucleation and curettage of unicystic ameloblastomas in many of the earlier series of cases. This range is considerably less than the 50% to 90% recurrence rates noted after curettage of conventional solid and multicystic intraosseous ameloblastomas. A systematic review of the literature before 2005 determined that 30% of these lesions recurred after enucleation, and a recent single-center study showed an identical recurrence rate of 60% after enucleation for both solid and unicystic ameloblastoma. These findings suggest that this lesion may not be as innocuous as previously thought. Alternatively, it is possible that some of those tumors that are designated as "unicystic" may, in fact, have a more characteristic invasive component that has not been detected histopathologically because it is essentially impossible to examine these lesions in every 360-degree plane of section.

PERIPHERAL (EXTRAOSSEOUS) AMELOBLASTOMA

The **peripheral ameloblastoma** is uncommon and accounts for about 1% to 4% of all ameloblastomas. This tumor probably arises from rests of dental lamina beneath the oral mucosa or from the basal epithelial cells of the surface epithelium. Histopathologically, these lesions have the same features as the intraosseous form of the tumor.



• **Fig. 15-77 Peripheral Ameloblastoma.** Sessile gingival mass. (Courtesy of Dr. Dean K. White.)



• **Fig. 15-78 Peripheral Ameloblastoma.** Interconnecting cords of ameloblastic epithelium filling the lamina propria.

Clinical Features

The peripheral ameloblastoma is usually a painless, nonulcerated sessile or pedunculated gingival or alveolar mucosal lesion. The clinical features are non-specific, and most lesions are clinically considered to represent a fibroma or pyogenic granuloma. Most examples are smaller than 1.5 cm, but larger lesions have been reported (Fig. 15-77). The tumor has been found in patients across a wide age range, but most are seen in middle-aged persons, with an average reported age of 52 years.

Peripheral ameloblastomas are most commonly found on the posterior gingival and alveolar mucosa, and they are somewhat more common in mandibular than in maxillary areas. In some cases, the superficial alveolar bone becomes slightly eroded, but significant bone involvement does not occur. A few examples of a microscopically identical lesion have been reported in the buccal mucosa at some distance from the alveolar or gingival soft tissues.

Histopathologic Features

Peripheral ameloblastomas have islands of ameloblastic epithelium that occupy the lamina propria underneath the surface epithelium (Fig. 15-78). The proliferating epithelium may show any of the features described for the intraosseous ameloblastoma; plexiform or follicular patterns are the most common. Connection of the tumor with the basal layer of the surface epithelium is seen in about 50% of cases. This may represent origin of the tumor from the basal layer of the epithelium in some cases, but in other instances the tumor could develop in the gingival connective tissue and merge with the surface epithelium.

Basal cell carcinomas of the gingival mucosa have been reported, but most of these would be designated best as peripheral ameloblastomas. A **peripheral odontogenic fibroma** may be confused microscopically with a peripheral ameloblastoma, particularly if a prominent epithelial component is present in the former. The presence of dysplastic dentin or cementum-like elements in the peripheral odontogenic fibroma and the lack of peripheral columnar epithelial cells showing reverse polarity of their nuclei should serve to distinguish the two lesions.

Treatment and Prognosis

Unlike the intraosseous ameloblastoma, the peripheral ameloblastoma shows an innocuous clinical behavior. Patients respond well to local surgical excision. Although local recurrence has been noted in 15% to 20% of cases, further local excision almost always results in a cure. Several examples of malignant change in a peripheral ameloblastoma have been reported, but this is rare.

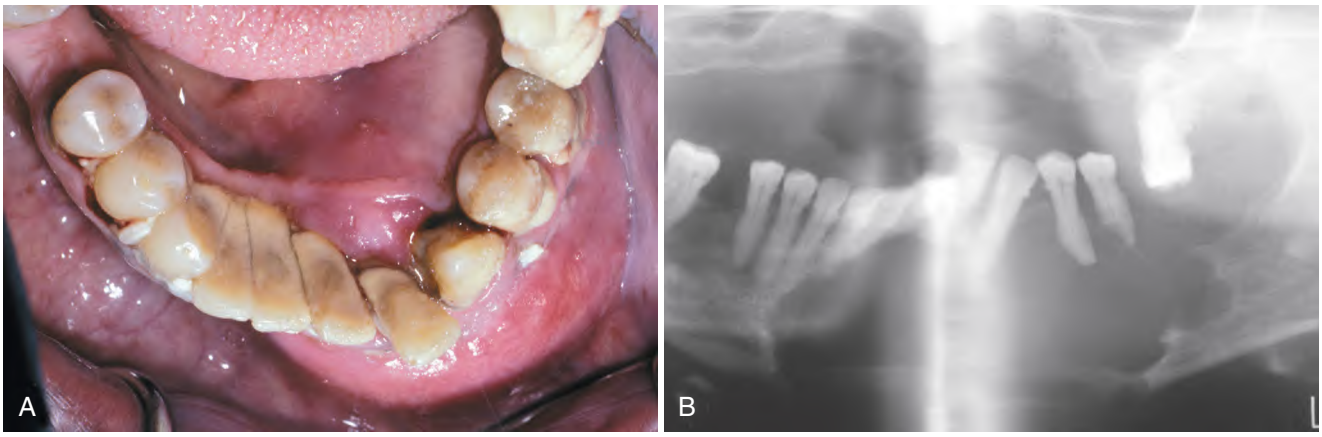
◆ MALIGNANT AMELOBLASTOMA AND AMELOBLASTIC CARCINOMA

Rarely, an ameloblastoma exhibits frank malignant behavior with development of metastases. The frequency of malignant behavior in ameloblastomas is difficult to determine but probably occurs in far less than 1% of all ameloblastomas.

The terminology for these lesions is somewhat confusing, but should not be considered controversial. The term *malignant ameloblastoma* is used for a tumor that shows the histopathologic features of ameloblastoma, both in the primary tumor and in the metastatic deposits. This is a very rare neoplasm, with fewer than 30 well-documented cases described in the literature. The term *ameloblastic carcinoma* should be reserved for an ameloblastoma that has cytologic features of malignancy in the primary tumor, in a recurrence, or in any metastatic deposit. This is also a rare condition, although approximately 200 cases have been reported. These lesions may follow a markedly aggressive local course, but metastases do not necessarily occur.

Clinical and Radiographic Features

Malignant ameloblastomas have been observed in patients who range in age from 6 to 61 years (mean age, 30 years),



• **Fig. 15-79 Ameloblastic Carcinoma. A,** Rapidly growing tumor showing prominent labial expansion of the mandible in the incisor and premolar area. **B,** The panoramic radiograph shows irregular destruction of the mandible. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Hamilton, 1999, BC Decker.)

and no sex predilection is seen. For patients with documented metastases, the interval between the initial treatment of the ameloblastoma and first evidence of metastasis varies from 3 to 45 years. In nearly one-third of cases, metastases do not become apparent until 10 years after treatment of the primary tumor. Ameloblastic carcinomas, in contrast, tend to develop later in life, with the mean age at diagnosis typically being in the sixth decade of life. Men are affected twice as frequently as women.

Metastases from ameloblastomas are found most often in the lungs. These have sometimes been regarded as aspiration or implant metastases. However, the peripheral location of some of these lung metastases suggests that they must have occurred by blood or lymphatic routes rather than aspiration.

Cervical lymph nodes are the second most common site for metastasis of an ameloblastoma. Spread to vertebrae, other bones, and viscera has also occasionally been confirmed.

The radiographic findings of malignant ameloblastomas may be essentially the same as those in typical nonmetastasizing ameloblastomas. Ameloblastic carcinomas are often more aggressive lesions, with ill-defined margins and cortical destruction (Fig. 15-79).

Histopathologic Features

With malignant ameloblastomas, the primary jaw tumor and the metastatic deposits show no microscopic features that differ from those of ameloblastomas with a completely benign local course. With ameloblastic carcinomas, the metastatic deposit or primary tumor shows the microscopic pattern of ameloblastoma in addition to cytologic features of malignancy. These include an increased nuclear-to-cytoplasmic ratio, nuclear hyperchromatism, and the presence of mitoses (Fig. 15-80). Necrosis in tumor islands and areas of dystrophic calcification may also be present.

Treatment and Prognosis

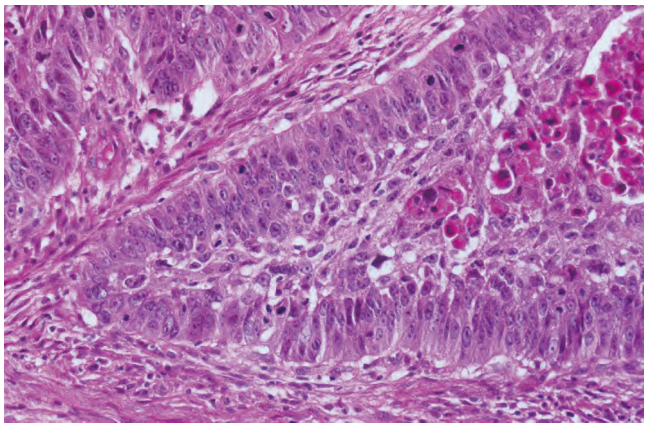
The prognosis of patients with malignant ameloblastomas appears to be poor, but the paucity of documented cases with long-term follow-up does not permit accurate assumptions to be made. About 50% of the patients with documented metastases and long-term follow-up have died of their disease. Lesions designated as *ameloblastic carcinoma* have demonstrated a uniformly aggressive clinical course, with perforation of the cortical plates of the jaw and extension of the tumor into adjacent soft tissues.

◆ CLEAR CELL ODONTOGENIC CARCINOMA (CLEAR CELL ODONTOGENIC TUMOR)

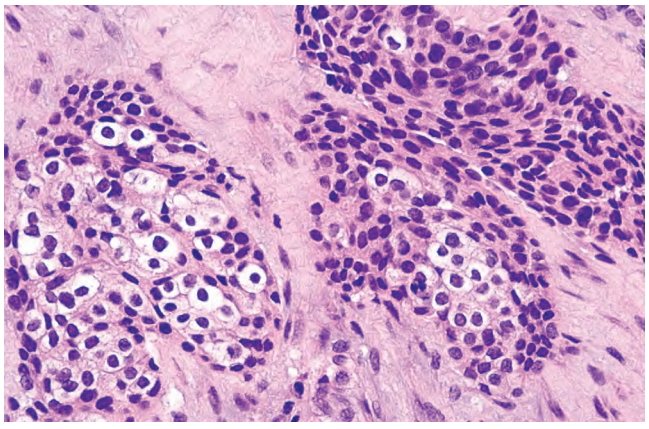
Clear cell odontogenic carcinoma is a rare jaw tumor that was first described in 1985. To date, approximately 80 examples have been documented. The tumor appears to be of odontogenic origin, but its histogenesis is uncertain. Histochemical and ultrastructural studies have suggested that the clear cells, which are the prominent feature of this neoplasm, may have similarities to glycogen-rich presecretory ameloblasts. Recent molecular studies, however, have identified rearrangements of the *EWSR1* gene in clear cell odontogenic carcinoma. This genetic alteration can be found in a variety of tumors, but it is often seen in hyalinizing clear cell carcinoma, a rare salivary gland malignancy. Consequently some authors have postulated that perhaps some clear cell odontogenic carcinomas may represent an intraosseous variant of hyalinizing clear cell carcinoma.

Clinical and Radiographic Features

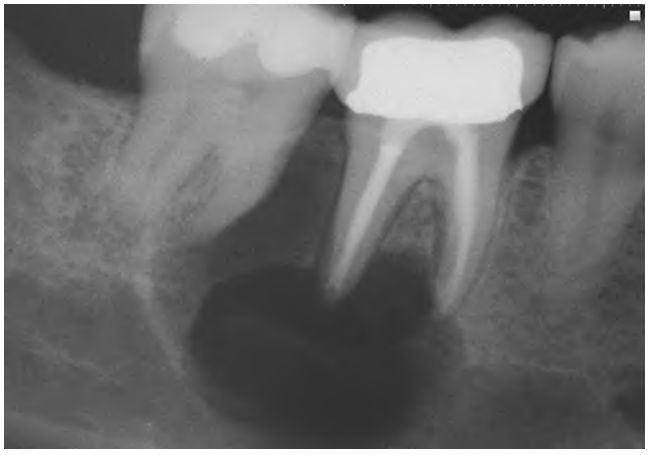
The clear cell odontogenic carcinoma exhibits a variable clinical pattern. A wide age range (from 14 to 89 years of age) has been described, but most cases are diagnosed in



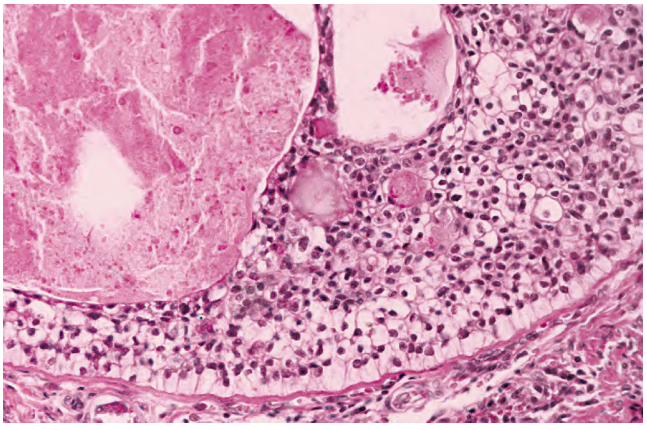
• **Fig. 15-80 Ameloblastic Carcinoma.** Ameloblastic epithelium demonstrating hyperchromatism, pleomorphism, and numerous mitotic figures.



• **Fig. 15-82 Clear Cell Odontogenic Carcinoma.** Hyperchromatic epithelial nests including clusters of cells with abundant clear cytoplasm.



• **Fig. 15-81 Clear Cell Odontogenic Carcinoma.** A radiolucent defect at the apex of the mandibular first molar. (Courtesy of Dr. John Werther.)



• **Fig. 15-83 Clear Cell Odontogenic Carcinoma.** Tumor island demonstrating cells with a clear cytoplasm. Note the peripheral columnar differentiation.

patients older than age 50. Nearly 80% of the lesions develop in the mandible. Some patients complain of pain or lower lip paresthesia, and bony swelling may be present. Other patients are relatively symptom free. Approximately 60% of patients will have evidence of soft tissue involvement by the tumor at the time of diagnosis because the lesion perforates bone.

Radiographically, the lesions appear as unilocular or multilocular radiolucencies. The margins of the radiolucency are often somewhat ill-defined or irregular (Fig. 15-81).

Histopathologic Features

Three histopathologic patterns have been described for clear cell odontogenic carcinoma. The biphasic pattern consists of varying-sized nests of epithelial cells, with a clear or faintly eosinophilic cytoplasm admixed with more eosinophilic polygonal epithelial cells (Fig. 15-82). The second pattern is more monophasic, characterized by only clear cells that are arranged in nests and cords. Thin strands of hyalinized connective tissue often separate the clear cell nests. The third pattern has a resemblance to ameloblastoma in that the peripheral cells of the clear cell islands may infrequently demonstrate palisading (Fig. 15-83). Often the lesional cells do not exhibit a significant degree of nuclear or cytologic pleomorphism. Furthermore, mitoses are generally sparse and necrosis is not a prominent feature. The clear cells contain small amounts of glycogen, but mucin stains are negative. In some cases, islands more typical of ameloblastoma are interspersed among the other tumor elements.

Hyalinizing clear cell carcinoma resembles clear cell odontogenic carcinoma, and although the salivary gland tumor develops in the soft tissues, for those lesions that have significant bone destruction, it may be difficult to identify the site of origin. Clear cell odontogenic carcinoma also may be difficult to distinguish from intraosseous mucoepidermoid carcinoma with a prominent clear cell component, although the negative mucin stains are consistent with the former. Amyloid stains would confirm the diagnosis of clear cell variant of the calcifying epithelial odontogenic tumor, because amyloid would not be present in clear cell

odontogenic tumor. A metastatic clear cell neoplasm, such as a renal cell carcinoma, clear cell breast carcinoma, or clear cell melanoma, may also need to be ruled out before the diagnosis of clear cell odontogenic carcinoma can be established.

Treatment and Prognosis

Clear cell odontogenic carcinomas largely demonstrate an aggressive clinical course, with invasion of contiguous structures and a significant tendency to recur, particularly if the initial treatment is enucleation or curettage. Most patients require fairly radical surgery. Metastatic involvement of regional lymph nodes has been documented in 20% to 25% of these patients, and pulmonary metastases have been described as well.

◆ ADENOMATOID ODONTOGENIC TUMOR

The **adenomatoid odontogenic tumor** represents 2% to 7% of all odontogenic tumors, and more than 750 examples have been reported in the literature. Although this lesion was formerly considered to be a variant of the ameloblastoma and was designated as "adenoameloblastoma," its clinical features and biologic behavior indicate that it is a separate entity. Postulated histogenetic sources of the tumor cells have included enamel organ epithelium, reduced enamel epithelium, and rests of Malassez; however, some investigators recently have suggested that the lesion arises from remnants of dental lamina associated with the gubernacular cord.

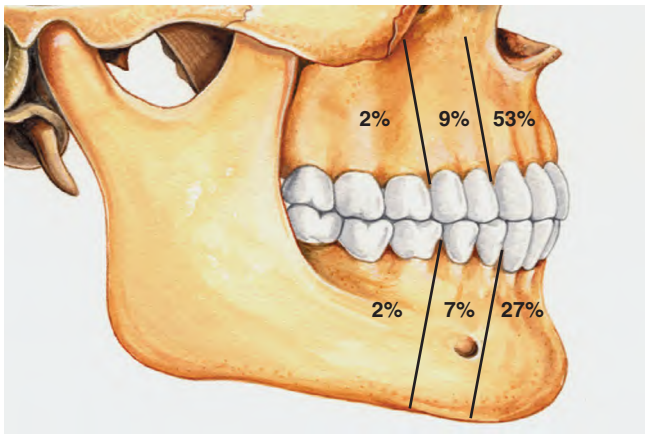
Clinical and Radiographic Features

Adenomatoid odontogenic tumors are largely limited to younger patients, and two-thirds of all cases are diagnosed when patients are 10 to 19 years of age. This tumor is definitely uncommon in a patient older than age 30. It has a striking tendency to occur in the anterior portions of the jaws and is found twice as often in the maxilla as in the mandible (Fig. 15-84). Females are affected about twice as often as males.

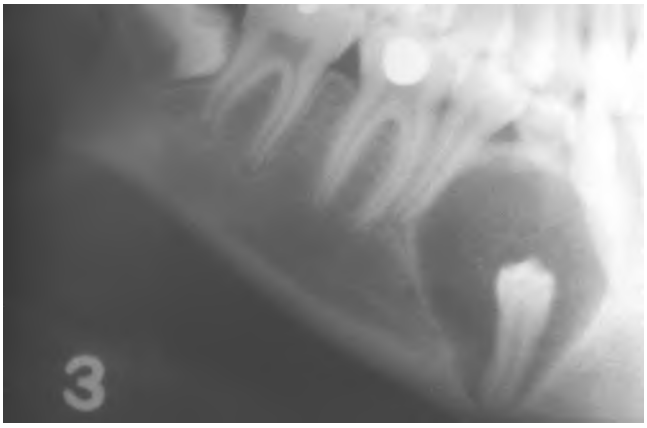
Most adenomatoid odontogenic tumors are relatively small. They seldom exceed 3 cm in greatest diameter, although a few large lesions have been reported. Peripheral (extraosseous) forms of the tumor are also encountered but are rare. These usually appear as small, sessile masses on the facial gingiva of the maxilla. Clinically, these lesions cannot be differentiated from the common gingival fibrous lesions.

Adenomatoid odontogenic tumors are frequently asymptomatic and are discovered during the course of a routine radiographic examination or when films are made to determine why a tooth has not erupted. Larger lesions cause a painless expansion of the bone.

In about 75% of cases, the tumor appears as a circumscribed, unilocular radiolucency that involves the crown of an unerupted tooth, most often a canine. This follicular type of adenomatoid odontogenic tumor may be impossible to differentiate radiographically from the more common dentigerous cyst. The radiolucency associated with the follicular type of adenomatoid odontogenic tumor sometimes extends apically along the root past the cementoenamel junction. This feature may help to distinguish an adenomatoid odontogenic tumor from a dentigerous cyst (Fig. 15-85).



• **Fig. 15-84 Adenomatoid Odontogenic Tumor.** Relative distribution of adenomatoid odontogenic tumor in the jaws.



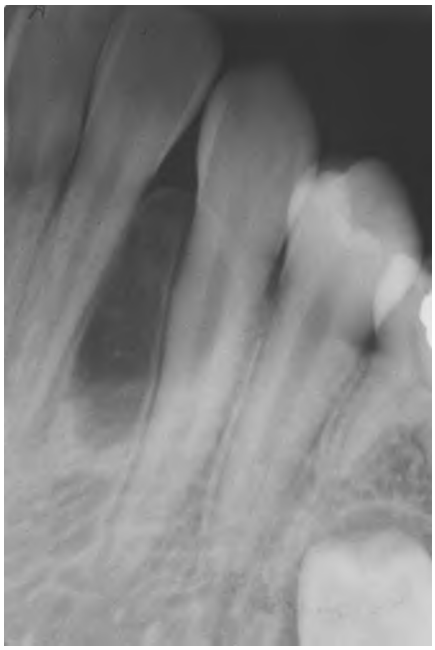
• **Fig. 15-85 Adenomatoid Odontogenic Tumor.** Radiolucent lesion involving an unerupted mandibular first premolar. In contrast to the usual dentigerous cyst, the radiolucency extends almost to the apex of the tooth. (Courtesy of Dr. Tony Traynham.)

Less often the adenomatoid odontogenic tumor is a well-delineated unilocular radiolucency that is not related to an unerupted tooth, but rather is located between the roots of erupted teeth (extrafollicular type) (Fig. 15-86).

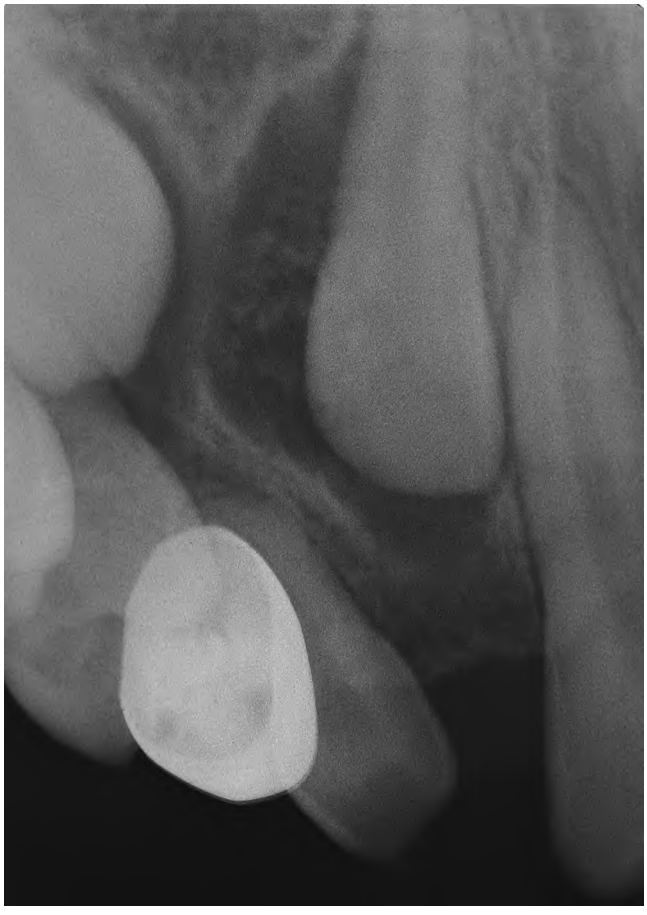
The lesion may appear completely radiolucent; often, however, it contains fine (snowflake) calcifications (Fig. 15-87). This feature may be helpful in differentiating the adenomatoid odontogenic tumor from a dentigerous cyst.

Histopathologic Features

The adenomatoid odontogenic tumor is a well-defined lesion that is usually surrounded by a thick, fibrous capsule.



• **Fig. 15-86 Adenomatoid Odontogenic Tumor.** A small radiolucency is present between the roots of the lateral incisor and canine. (Courtesy of Dr. Ramesh Narang.)



• **Fig. 15-87 Adenomatoid Odontogenic Tumor.** Well-defined pericoronal radiolucency enveloping the maxillary right lateral incisor in a 14-year-old male. Note the subtle snowflake-like calcifications within the lesion. (Courtesy of Dr. Jason Barker.)

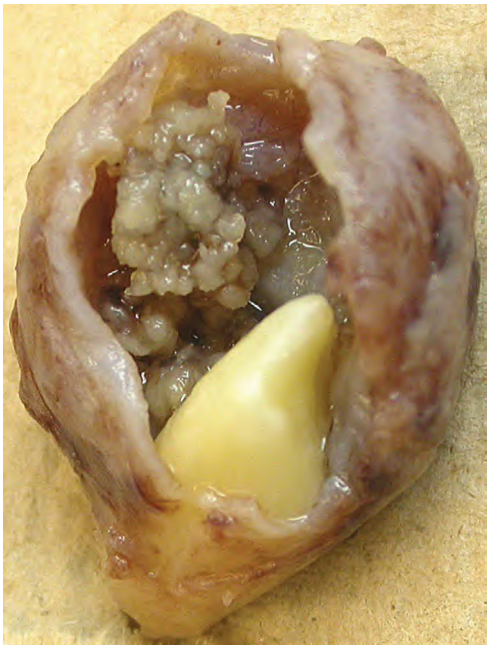
When the lesion is bisected, the central portion of the tumor may be essentially solid or may show varying degrees of cystic change (Fig. 15-88).

Microscopically, the tumor is composed of spindle-shaped epithelial cells that form sheets, strands, or whorled masses of cells in a scant fibrous stroma. The epithelial cells may form rosettelike structures about a central space, which may be empty or contain small amounts of eosinophilic material. This material may stain for amyloid.

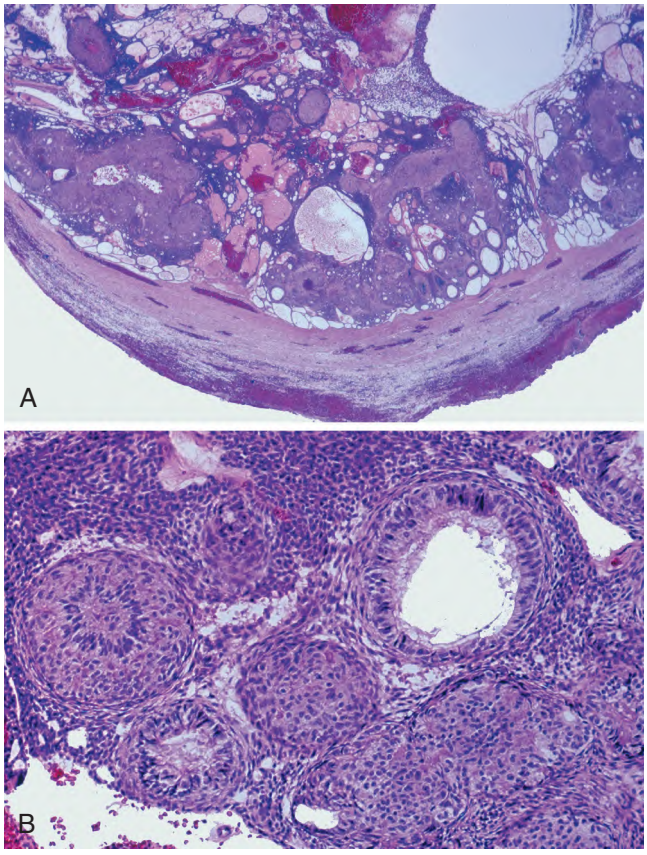
The tubular or ductlike structures, which are the characteristic feature of the adenomatoid odontogenic tumor, may be prominent, scanty, or even absent in a given lesion. These consist of a central space surrounded by a layer of columnar or cuboidal epithelial cells. The nuclei of these cells tend to be polarized away from the central space. The mechanism of formation of these tubular structures is not entirely clear but is likely the result of the secretory activity of the tumor cells, which appear to be preameloblasts. In any event, these structures are not true ducts, and no glandular elements are present in the tumor (Fig. 15-89).

Small foci of calcification may also be scattered throughout the tumor. These have been interpreted as abortive enamel formation. Some adenomatoid odontogenic tumors contain larger areas of matrix material or calcification. This material has been interpreted as dentinoid or cementum. Some lesions also have another pattern, particularly at the periphery of the tumor adjacent to the capsule. This consists of narrow, often anastomosing cords of epithelium in an eosinophilic, loosely arranged matrix.

The histopathologic features of this lesion are distinctive and should not be confused with any other odontogenic



• **Fig. 15-88 Adenomatoid Odontogenic Tumor.** A well-circumscribed cystlike mass can be seen enveloping the crown of a maxillary cuspid. Note the intraluminal vegetations, which represent nodular tumor growth.



• **Fig. 15-89 Adenomatoid Odontogenic Tumor. A,** Low-power view demonstrating a thick capsule surrounding the tumor. **B,** Higher magnification showing the ductlike epithelial structures. The nuclei of the columnar cells are polarized away from the central spaces.

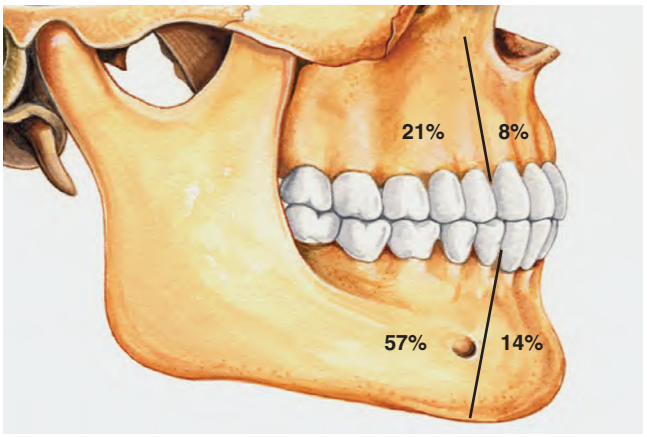
tumor. Interestingly, some adenomatoid odontogenic tumors have been described with focal areas that resemble calcifying epithelial odontogenic tumor, odontoma, or calcifying odontogenic cyst. These lesions appear to behave as a routine adenomatoid odontogenic tumor, however. The chief problem relates to mistaking this tumor for an ameloblastoma by a pathologist who is not familiar with this lesion. This error can lead to unnecessary radical surgery.

Treatment and Prognosis

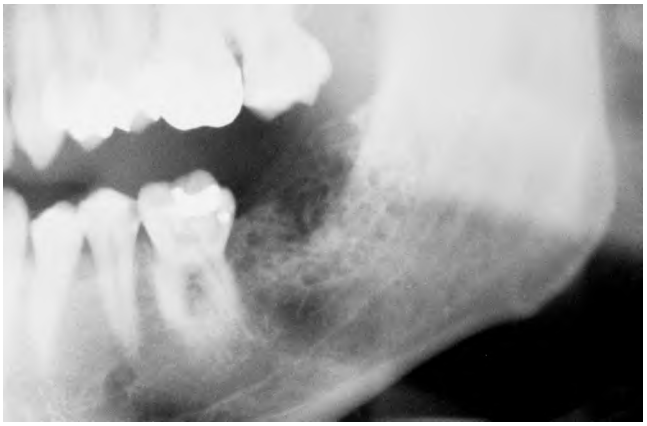
The adenomatoid odontogenic tumor is completely benign; because of its capsule, it enucleates easily from the bone. Aggressive behavior has not been documented, and recurrence after enucleation seldom, if ever, occurs.

◆ CALCIFYING EPITHELIAL ODONTOGENIC TUMOR (PINDBORG TUMOR)

The **calcifying epithelial odontogenic tumor,** also widely known as the **Pindborg tumor,** is an uncommon lesion that accounts for less than 1% of all odontogenic tumors. Approximately 200 cases have been reported to date.



• **Fig. 15-90 Calcifying Epithelial Odontogenic Tumor.** Relative distribution of calcifying epithelial odontogenic tumor in the jaws.



• **Fig. 15-91 Calcifying Epithelial Odontogenic Tumor.** Honeycombed multilocular radiolucency containing fine calcifications.

Although the tumor is clearly of odontogenic origin, its histogenesis is uncertain. The tumor cells bear a close morphologic resemblance to the cells of the stratum intermedium of the enamel organ; however, some investigators have recently suggested that the tumor arises from dental lamina remnants based on its anatomic distribution in the jaws. Mutations of the *PTCH1* gene have been identified in one small series of this neoplasm. This gene is characteristically associated with nevoid basal cell carcinoma syndrome (see page 640), but the calcifying epithelial odontogenic tumor is not a component of that condition.

Clinical and Radiographic Features

Although the calcifying epithelial odontogenic tumor has been found in patients across a wide age range and in many parts of the jaw, it is most often encountered in patients between 30 and 50 years of age. There is no sex predilection. About two-thirds of all reported cases have been found in the mandible, most often in the posterior areas (Fig. 15-90). A painless, slow-growing swelling is the most common presenting sign.

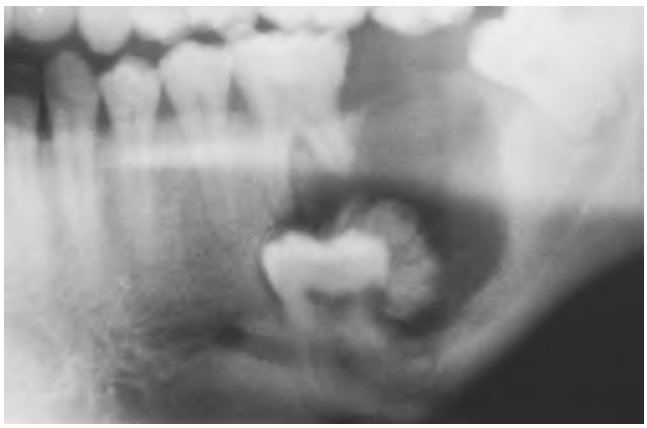
Radiographically, the tumor exhibits either a unilocular or a multilocular radiolucent defect (Fig. 15-91), with the

unilocular pattern encountered more commonly in the maxilla. The margins of the lytic defect are often scalloped and usually relatively well defined. However, approximately 20% of cases have an ill-defined periphery, and an additional 20% exhibit a corticated border. The tumor is frequently associated with an impacted tooth, most often a mandibular molar. The lesion may be entirely radiolucent, but calcified structures of varying size and density are commonly seen. Although some authors have suggested that these are often most prominent around the crown of the impacted tooth (Fig. 15-92), a review of the literature identified this feature in only 12% of published cases with adequate radiographic documentation. Similarly, the description of a "driven-snow" pattern of the calcifications appears to be much less common than previously believed.

A few cases of peripheral (extraosseous) calcifying epithelial odontogenic tumor have been reported. These appear as nonspecific, sessile gingival masses, most often on the anterior gingiva. Some of these have been associated with cupped-out erosion of the underlying bone.

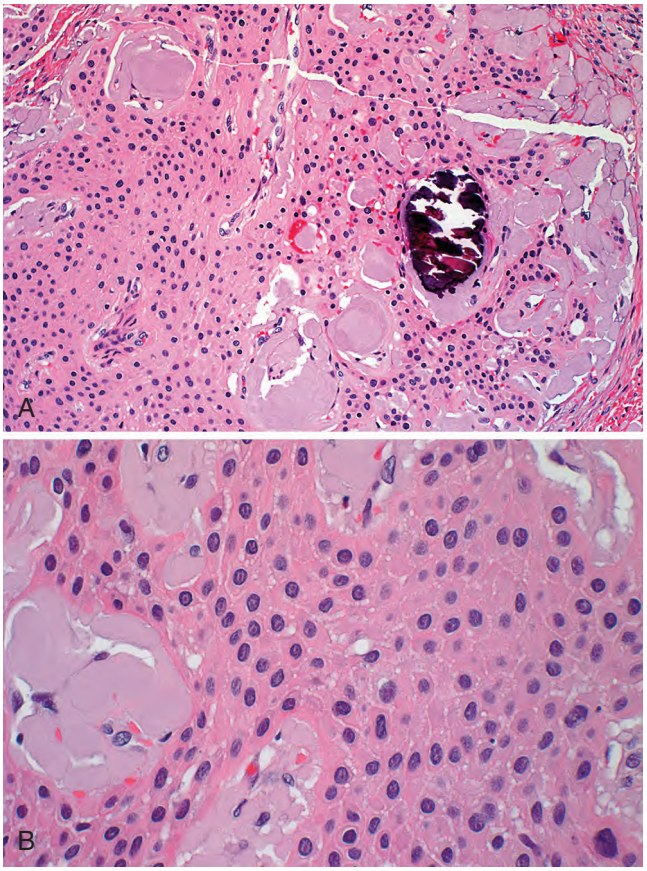
Histopathologic Features

The calcifying epithelial odontogenic tumor has discrete islands, strands, or sheets of polyhedral epithelial cells in a fibrous stroma (Fig. 15-93). The cellular outlines of the epithelial cells are distinct, and intercellular bridges may be noted. The nuclei show considerable variation, and giant nuclei may be seen. Some tumors show considerable nuclear pleomorphism, but this feature is not considered to indicate malignancy. Large areas of amorphous, eosinophilic, hyalinized (amyloid-like) extracellular material are also often present. The tumor islands frequently enclose masses of this hyaline material, resulting in a cribriform appearance. Calcifications, which are a distinctive feature of the tumor, develop within the amyloid-like material and form concentric rings *(Liesegang ring calcifications)* (Fig. 15-94). These tend to fuse and form large, complex masses.

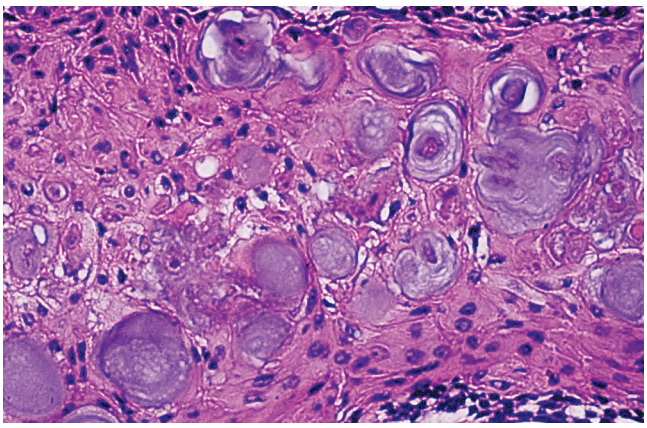


• **Fig. 15-92 Calcifying Epithelial Odontogenic Tumor.** Prominent calcification around the crown of an impacted second molar that is involved in the tumor. (Courtesy of Dr. Harold Peacock.)

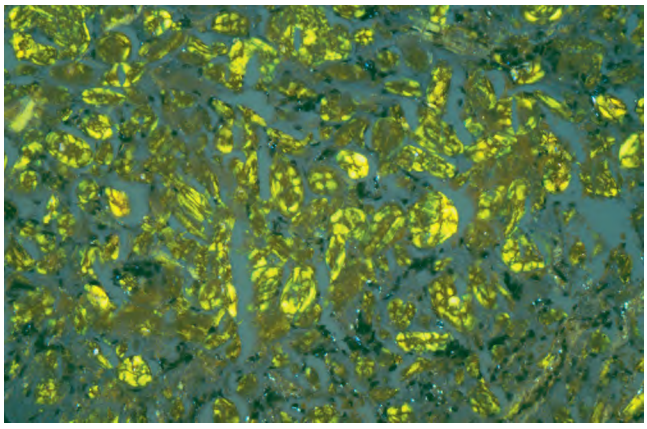
Several microscopic variations may be encountered. Some tumors consist of large sheets of epithelial cells with minimal production of amyloid-like material and calcifications. Others show large diffuse masses of amyloid-like material that contain only small nests or islands of epithelium. A clear cell variant has been described, in which clear cells constitute a significant portion of the epithelial



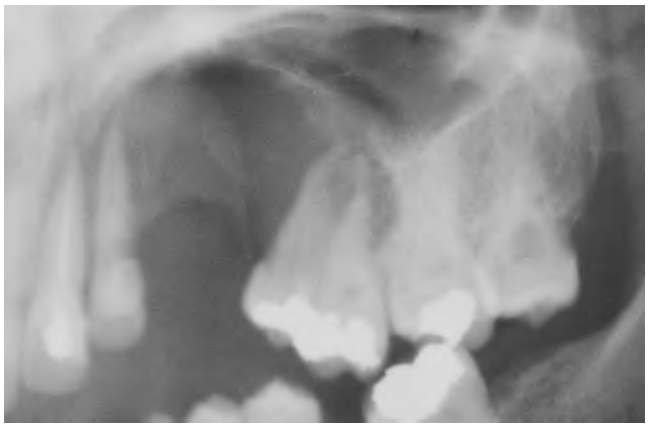
• **Fig. 15-93 Calcifying Epithelial Odontogenic Tumor. A,** Sheets of epithelial tumor cells that surround pools of amorphous, eosinophilic amyloid with focal calcification. **B,** Higher-power view showing polyhedral cells with eosinophilic cytoplasm and intercellular bridging. Adjacent amyloid deposits can be seen.



• **Fig. 15-94 Calcifying Epithelial Odontogenic Tumor.** Multiple concentric Liesegang ring calcifications.



• **Fig. 15-95 Calcifying Epithelial Odontogenic Tumor.** With Congo red staining, the pools of amyloid exhibit an apple-green birefringence when viewed with polarized light.



• **Fig. 15-96 Squamous Odontogenic Tumor.** Lucent defect extending along the roots of the lateral incisor and first premolar teeth. (Courtesy of Dr. Ed McGaha.)

component, and this tumor also has been reported to have a cystic growth pattern.

The amyloid-like material in the Pindborg tumor has been extensively investigated by histochemical, immunohistochemical, and biochemical methods, as well as by electron microscopy. The material generally stains as amyloid (i.e., positive staining results with Congo red). After Congo red staining, the amyloid will exhibit apple-green birefringence when viewed with polarized light (Fig. 15-95). Investigators have identified this material as a unique protein that is produced by this tumor, as well as by the normal odontogenic apparatus and other odontogenic neoplasms. Both the protein structure and the DNA sequence of the responsible gene have been described, and this material has been designated as odontogenic ameloblast-associated protein (ODAM).

Treatment and Prognosis

Although it was originally believed that the calcifying epithelial odontogenic tumor had about the same biologic behavior as the ameloblastoma, accumulating experience indicates that it tends to be less aggressive. Conservative local resection to include a narrow rim of surrounding bone appears to be the treatment of choice, although lesions in the posterior maxilla should probably be treated more aggressively. A recurrence rate of about 15% has been reported; tumors treated by curettage have the highest frequency of recurrence. The overall prognosis appears good, although rare examples of malignant or borderline malignant calcifying epithelial odontogenic tumor have been reported, with documented metastasis to regional lymph nodes and lung.

◆ SQUAMOUS ODONTOGENIC TUMOR

Squamous odontogenic tumor is a rare benign odontogenic neoplasm that was first described in 1975 and is now recognized as a distinct entity. Approximately 50 examples have been reported to date. Most of these have been located within bone, although a few peripheral examples have been described. Before 1975, this lesion was probably believed to represent an atypical acanthomatous ameloblastoma or even a squamous cell carcinoma. The squamous odontogenic tumor may arise from neoplastic transformation of dental lamina rests or perhaps the epithelial rests of Malassez. In some cases, the tumor appears to originate within the periodontal ligament that is associated with the lateral root surface of an erupted tooth.

Clinical and Radiographic Features

Squamous odontogenic tumors have been found in patients whose ages ranged from 8 to 74 years (average age, 38). They are randomly distributed throughout the alveolar processes of the maxilla and mandible, with no site of predilection. A few patients have had multiple squamous odontogenic tumors that involved several quadrants of the mouth; one family with three affected siblings who each had multiple lesions has been reported. There is no apparent sex predilection. A painless or mildly painful gingival swelling, often associated with mobility of the associated teeth, is the most common complaint. About 25% of reported patients have had no symptoms, and their lesions were detected during a radiographic examination.

The radiographic findings are not specific or diagnostic and consist of a triangular radiolucent defect lateral to the root or roots of the teeth (Fig. 15-96). In some instances, this suggests vertical periodontal bone loss. The radiolucent area may be somewhat ill defined or may show a well-defined, corticated margin. Most examples are relatively small lesions that seldom exceed 1.5 cm in greatest diameter.

Histopathologic Features

The microscopic findings of squamous odontogenic tumor are distinctive and consist of varying-shaped islands of bland-appearing squamous epithelium in a mature fibrous connective tissue stroma. The peripheral cells of the

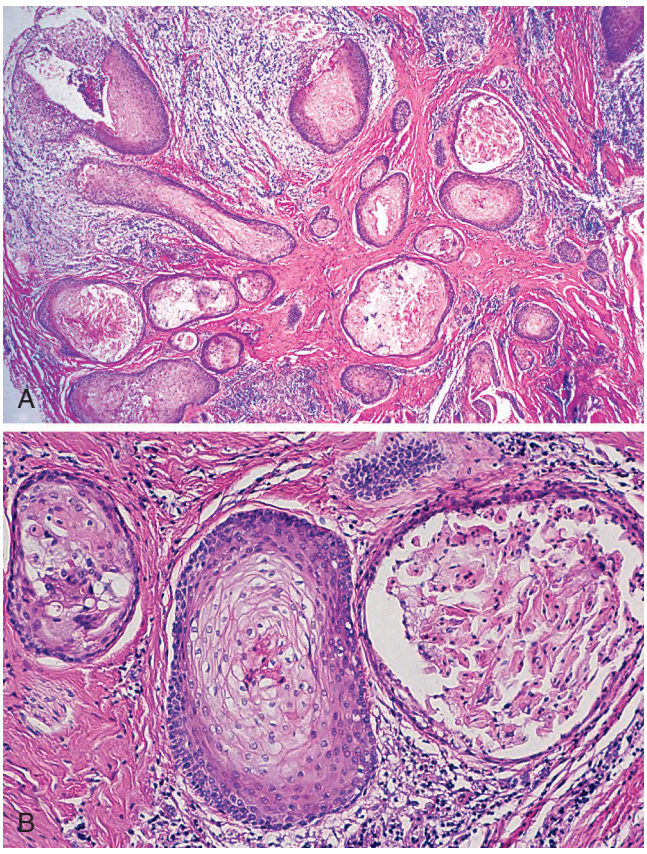
epithelial islands do not show the characteristic polarization seen in ameloblastomas (Fig. 15-97). Vacuolization and individual cell keratinization within the epithelial islands are common features. Small microcysts are sometimes observed within the epithelial islands. Laminated calcified bodies and globular eosinophilic structures, which do not stain for amyloid, are present within the epithelium in some cases. The former probably represents dystrophic calcifications; the nature of the latter is unknown.

Islands of epithelium that closely resemble those of the squamous odontogenic tumor have been observed within the fibrous walls of dentigerous and radicular cysts. These have been designated as *squamous odontogenic tumorlike proliferations* in odontogenic cysts. These islands do not appear to have any significance relative to the behavior of the cyst, and evaluation of the clinical, radiographic, and histopathologic features should permit differentiation from a squamous odontogenic tumor.

In published reports, some squamous odontogenic tumors have been misdiagnosed initially as ameloblastomas, resulting in unnecessary radical surgery.

Treatment and Prognosis

Conservative local excision or curettage appears to be effective for patients with squamous odontogenic tumors, and most reported cases have not recurred after local excision. A few instances of recurrence have been reported, but these have responded well to further local excision. Maxillary squamous odontogenic tumors may be somewhat more aggressive than mandibular lesions, with a greater tendency to invade adjacent structures. This may be because of the porous, spongy nature of the maxillary bone. The multicentric lesions have typically exhibited a less aggressive, almost hamartomatous behavior when compared with solitary lesions. A well-documented example of apparent malignant transformation of squamous odontogenic tumor has been reported.



• **Fig. 15-97 Squamous Odontogenic Tumor. A,** Low-power photomicrograph showing islands of bland-appearing squamous epithelium in a fibrous stroma. **B,** Higher-power photomicrograph showing bland appearance of the epithelium with microcyst formation.

MIXED ODONTOGENIC TUMORS

The group of mixed odontogenic tumors, composed of proliferating odontogenic epithelium in a cellular ectomesenchyme resembling the dental papilla, poses problems in classification. Some of these lesions show varying degrees of inductive effect by the epithelium on the mesenchyme, leading to the formation of varying amounts of enamel and dentin. Some of these lesions (the common odontomas) are clearly nonneoplastic developmental anomalies; others appear to be true neoplasms. The nature of others is uncertain.

In some instances, the histopathologic findings alone cannot distinguish between the neoplastic lesions and the developmental anomalies. Clinical and radiographic features often are of considerable assistance in making this distinction.

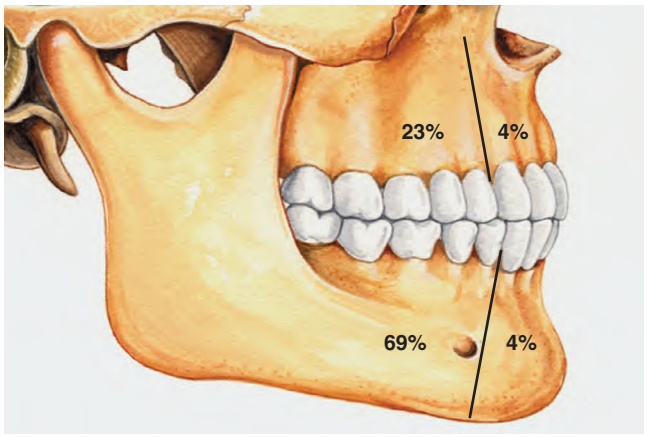
◆ AMELOBLASTIC FIBROMA

The **ameloblastic fibroma** is considered to be a true mixed tumor in which the epithelial and mesenchymal tissues are both neoplastic. It is an uncommon tumor, but the data regarding its frequency are difficult to evaluate because (particularly in earlier reports) some lesions that were diagnosed as ameloblastic fibroma may actually have represented the early developing stage of an odontoma.

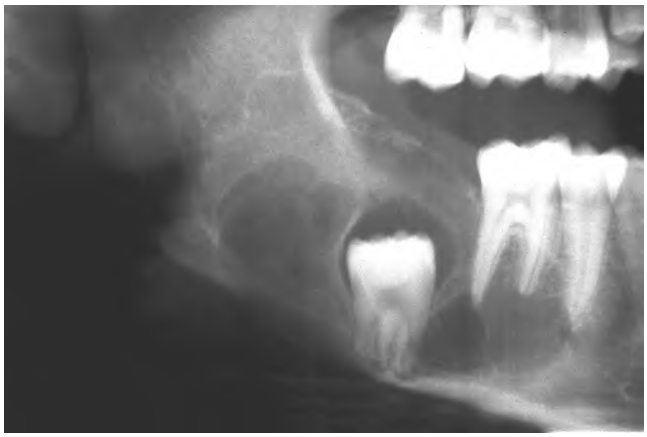
Clinical and Radiographic Features

Ameloblastic fibromas tend to occur in younger patients; most lesions are diagnosed in the first two decades of life. This lesion, however, is occasionally encountered in middle-aged patients. The tumor is slightly more common in males than in females. Small ameloblastic fibromas are asymptomatic; larger tumors are associated with swelling of the jaws. The posterior mandible is the most common site; about 70% of all cases are located in this area (Fig. 15-98). Convincing examples of this tumor arising within the gingival soft tissue have been described, but this appears to represent a rare phenomenon.

Radiographically, either a unilocular or multilocular radiolucent lesion is seen, with the smaller lesions tending to be unilocular. The radiographic margins tend to be well defined, and they may be corticated. An unerupted tooth



• **Fig. 15-98 Ameloblastic Fibroma.** Relative distribution of ameloblastic fibroma in the jaws.

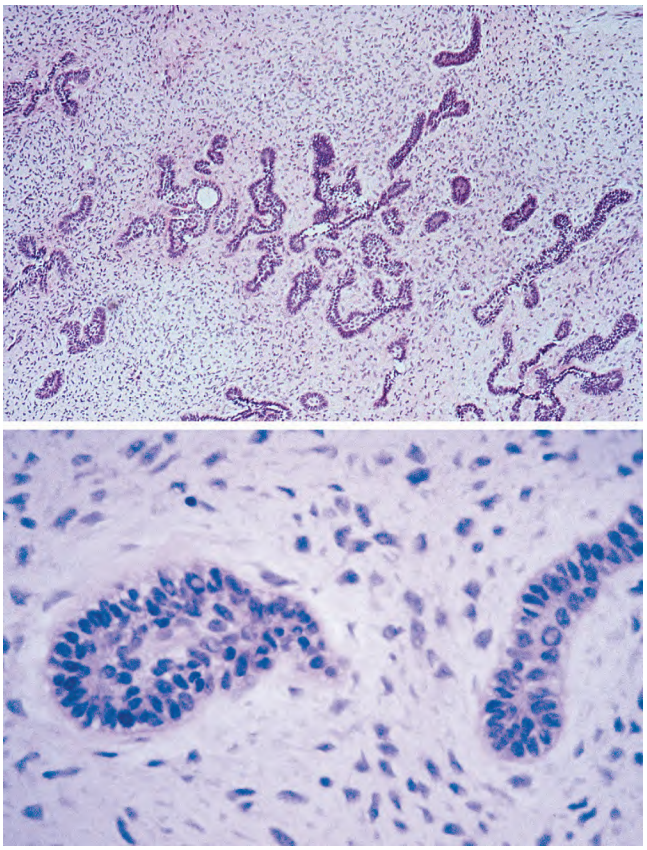


• **Fig. 15-99 Ameloblastic Fibroma.** Multilocular radiolucent defect associated with an unerupted second molar. (Courtesy of Dr. Mark Chishom.)

is associated with the lesion in about 75% of cases (Fig. 15-99). The ameloblastic fibroma may grow to a large size, and cases that involve a considerable portion of the body and ascending ramus of the mandible have been reported.

Histopathologic Features

The ameloblastic fibroma appears as a solid, soft tissue mass with a smooth outer surface. A definite capsule may or may not be present. Microscopically, the tumor is composed of a cell-rich mesenchymal tissue resembling the primitive dental papilla admixed with proliferating odontogenic epithelium. The latter may have one of two patterns, both of which are usually present in any given case. The most common epithelial pattern consists of long, narrow cords of odontogenic epithelium, often in an anastomosing arrangement. These cords are usually only two cells in thickness and are composed of cuboidal or columnar cells (Fig. 15-100). In the other pattern, the epithelial cells form small, discrete islands that resemble the follicular stage of the developing enamel organ. These show peripheral columnar



• **Fig. 15-100 Ameloblastic Fibroma. A,** Long, narrow cords of odontogenic epithelium supported by richly cellular, primitive connective tissue. **B,** Basophilic epithelial islands with peripheral nuclear palisading.

cells, which surround a mass of loosely arranged epithelial cells that resemble stellate reticulum. In contrast to the follicular type of ameloblastoma, these follicular islands in the ameloblastic fibroma seldom demonstrate microcyst formation.

The mesenchymal portion of the ameloblastic fibroma consists of plump stellate and ovoid cells in a loose matrix, which closely resembles the developing dental papilla. Collagen formation is generally inconspicuous. Juxtaepithelial hyalinization of the mesenchymal portion of the tumor is sometimes seen, and occasionally diffuse areas of hyalinized acellular lesional tissue are evident.

A few examples of ameloblastic fibroma occurring in conjunction with calcifying odontogenic cyst also have been reported.

Treatment and Prognosis

The proper management of ameloblastic fibroma has been an ongoing topic of debate. Although initially it was believed that the ameloblastic fibroma was an innocuous lesion that seldom recurred after simple local excision or curettage, subsequent reports seemed to indicate a substantial risk of recurrence after conservative therapy. The highest recurrence rate (43.5%) was recorded in a series of cases from

the Armed Forces Institute of Pathology, and it could be argued that this was a biased sample of larger lesions that were inherently more difficult to manage. In other series of cases, from 0% to 18% of ameloblastic fibromas were reported to recur after conservative removal and an adequate follow-up period. Based on these data, recent recommendations have emphasized conservative initial therapy for ameloblastic fibroma. More aggressive surgical excision should probably be reserved for recurrent lesions. Approximately 35% of the cases of the rare ameloblastic fibrosarcoma develop in the setting of a recurrent ameloblastic fibroma.

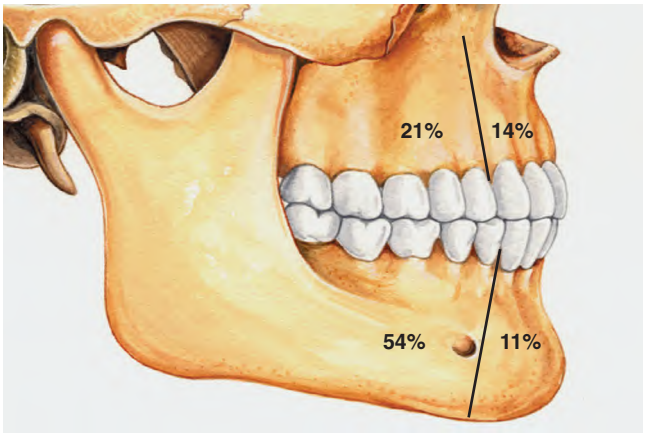
◆ AMELOBLASTIC FIBRO-ODONTOMA

The **ameloblastic fibro-odontoma** is defined as a tumor with the general features of an ameloblastic fibroma but that also contains enamel and dentin. Some investigators believe that the ameloblastic fibro-odontoma is only a stage in the development of an odontoma and do not consider it to be a separate entity. Certainly the histopathologic features of a developing odontoma may overlap somewhat with ameloblastic fibro-odontoma. There are well-documented examples, however, of this tumor exhibiting progressive growth and causing considerable deformity and bone destruction. Such lesions appear to be true neoplasms. However, distinguishing between a developing odontoma and an ameloblastic fibro-odontoma may be difficult based on histopathologic grounds alone.

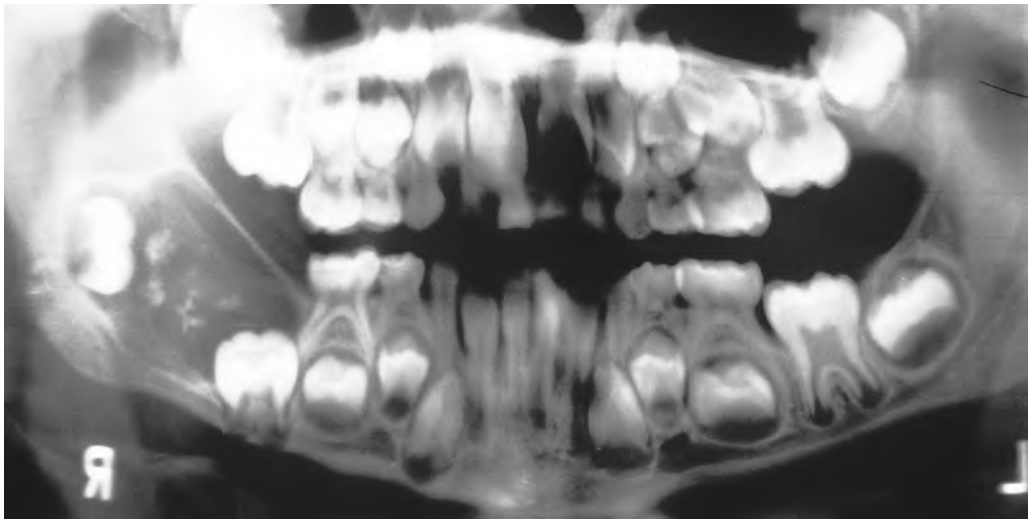
Clinical and Radiographic Features

The ameloblastic fibro-odontoma is usually seen in children with an average age of 10 years. It is rarely encountered in adults. Like the **ameloblastic fibroma,** ameloblastic fibro-odontomas occur more frequently in the posterior regions of the jaws, and the majority involves the mandible (Fig. 15-101). Males are affected somewhat more often than females, with a 3:2 ratio noted in the literature. The lesion is commonly asymptomatic and is discovered when radiographs are taken to determine the reason for failure of a tooth to erupt. Large examples may be associated with a painless swelling of the affected bone.

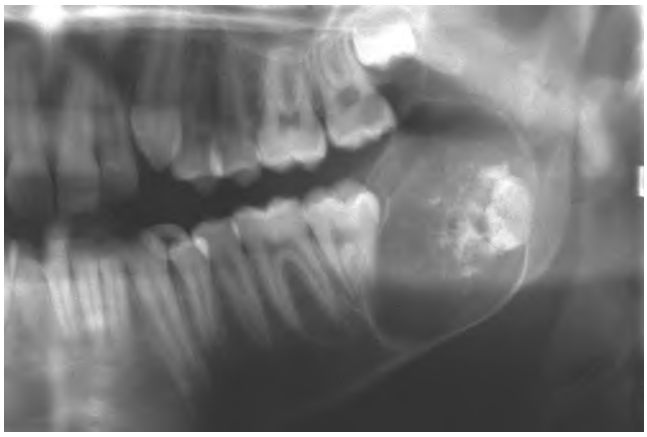
Radiographically, the tumor shows a well-circumscribed unilocular or, infrequently, multilocular radiolucent defect that contains a variable amount of calcified material with the radiodensity of tooth structure. The calcified material within the lesion may appear as multiple, small radiopacities or as a solid conglomerate mass (Fig. 15-102). In most instances, an unerupted tooth is present at the margin of the lesion, or the crown of the unerupted tooth may be included within the defect. Approximately 5% of ameloblastic fibro-odontomas contain only a minimal amount of calcifying enamel and dentin matrix and appear



• **Fig. 15-101 Ameloblastic Fibro-Odontoma.** Relative distribution of ameloblastic fibro-odontoma in the jaws.



• **Fig. 15-102 Ameloblastic Fibro-Odontoma.** Radiolucent defect in the ramus containing small calcifications having the radiodensity of tooth structure.



• **Fig. 15-103 Ameloblastic Fibro-Odontoma.** Unilocular radiolucent defect displacing the developing mandibular third molar posteriorly. Flecks of mineralized material are present in the radiolucent defect. (Courtesy of Dr. Dominic Adornato.)

radiographically as radiolucent lesions (Fig. 15-103). These cannot be differentiated from the wide variety of unilocular radiolucencies that may involve the jaws. At the other extreme, some ameloblastic fibro-odontomas appear as largely calcified masses with only a narrow rim of radiolucency about the periphery of the lesion.

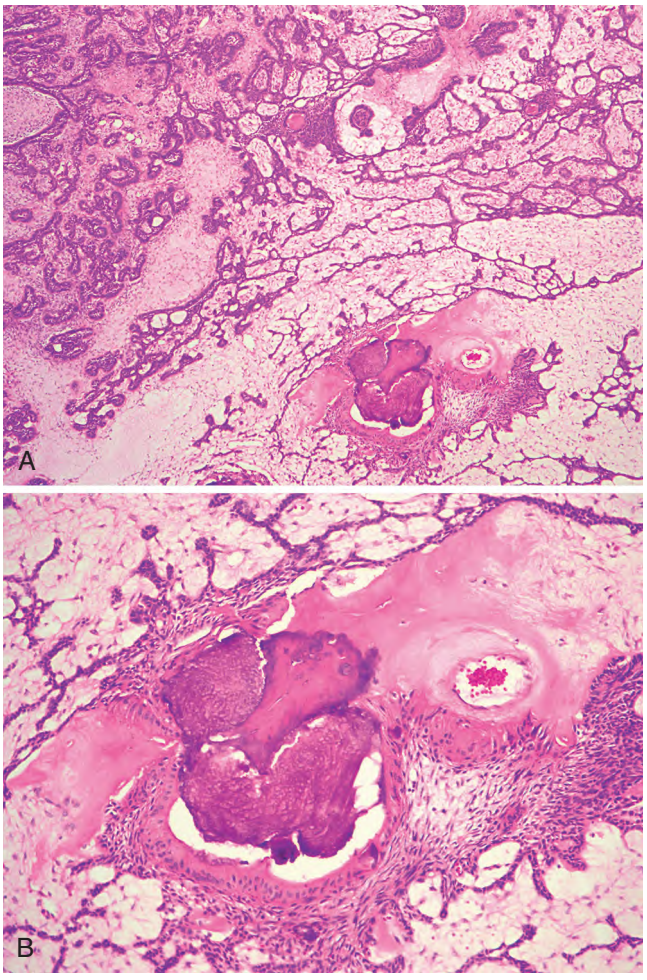
Histopathologic Features

The soft tissue component of the ameloblastic fibro-odontoma is microscopically identical to the **ameloblastic fibroma** and has narrow cords and small islands of odontogenic epithelium in a loose primitive-appearing connective tissue that resembles the dental papilla. The calcifying element consists of foci of enamel and dentin matrix formation in close relationship to the epithelial structures (Fig. 15-104). The more calcified lesions show mature dental structures in the form of rudimentary small teeth or conglomerate masses of enamel and dentin. Some researchers have designated a similar tumor in which the calcifying component consists only of dentin matrix and dentinoid material as **ameloblastic fibro-dentinoma.** It is questionable whether this lesion represents a separate entity, and it is probably best considered as only a variant of the ameloblastic fibro-odontoma.

Treatment and Prognosis

A patient with an ameloblastic fibro-odontoma is generally treated by conservative curettage, and the lesion usually separates easily from its bony bed. The tumor is well circumscribed and does not invade the surrounding bone.

The prognosis is excellent, and the recurrence rate after conservative removal is estimated to be about 7%. Development of an ameloblastic fibrosarcoma after curettage of an ameloblastic fibro-odontoma has been reported, but this is exceedingly rare.



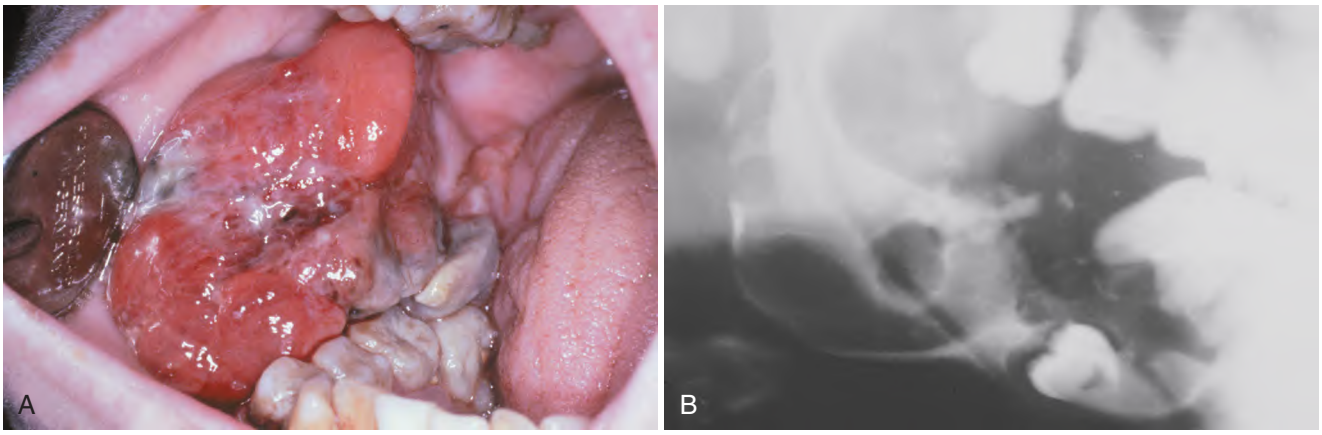
• **Fig. 15-104 Ameloblastic Fibro-Odontoma. A,** The soft tissue component of the tumor is indistinguishable from an ameloblastic fibroma. **B,** Formation of disorganized tooth structure can be seen.

◆ AMELOBLASTIC FIBROSARCOMA (AMELOBLASTIC SARCOMA)

The rare **ameloblastic fibrosarcoma** is considered to be the malignant counterpart of the ameloblastic fibroma, and approximately 70 cases have been documented in the literature. Interestingly, in most cases, only the mesenchymal portion of the lesion shows features of malignancy; the epithelial component remains rather bland. These tumors may apparently arise *de novo;* however, in at least one-third of known cases, the malignant lesion represents a recurrence of a tumor previously diagnosed as an ameloblastic fibroma or an ameloblastic fibro-odontoma.

Clinical and Radiographic Features

Ameloblastic fibrosarcomas occur about 1.5 times as often in males as in females. The lesion tends to occur in younger patients (mean reported age, 27.5 years). Although either the maxilla or the mandible may be involved, about 80% of cases have occurred in the mandible. Pain and swelling associated with rapid clinical growth are the common complaints.



• **Fig. 15-105 Ameloblastic Fibrosarcoma. A,** A 21-year-old woman complained of facial asymmetry and recent increase in size of a mandibular mass that had been present for some years. **B,** Radiograph of the same patient. Note the lytic destruction of the posterior mandible. (Courtesy of Dr. Sam McKenna.)

Radiographically, the ameloblastic fibrosarcoma shows an ill-defined destructive radiolucent lesion that suggests a malignant process (Fig. 15-105).

Histopathologic Features

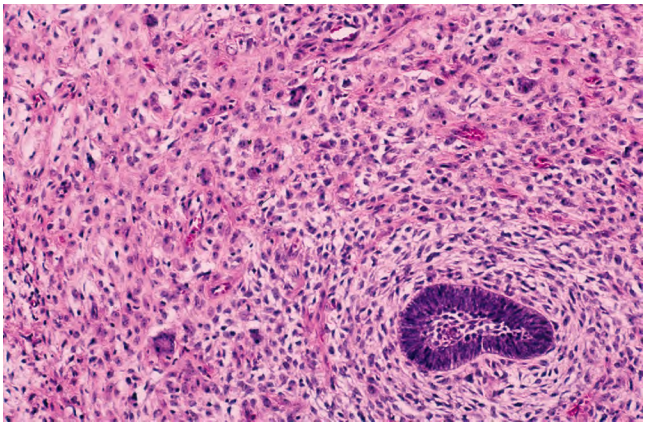
Ameloblastic fibrosarcomas contain an epithelial component similar to that seen in the ameloblastic fibroma, although it is frequently less prominent. The epithelial component appears histopathologically benign and does not demonstrate any cytologic atypia. The mesenchymal portion of the tumor, however, is highly cellular and shows hyperchromatic and often bizarre pleomorphic cells (Fig. 15-106). Mitoses are usually prominent. In some cases with multiple recurrences, the epithelial component becomes progressively less conspicuous so that the tumor eventually shows only a poorly differentiated fibrosarcoma.

In a few instances, dysplastic dentin or small amounts of enamel may be formed. Some have called such lesions **ameloblastic dentinosarcomas** or **ameloblastic fibro-odontosarcomas.** This additional subclassification, however, appears unnecessary. Another rare event that actually may be overrepresented in the literature is concurrent malignant transformation of both the epithelial and mesenchymal elements of an ameloblastic fibroma, resulting in an **ameloblastic carcinosarcoma.**

Treatment and Prognosis

Once the diagnosis of ameloblastic fibrosarcoma has been confirmed, radical surgical excision appears to be the treatment of choice. Curettage or local excision is usually followed by rapid local recurrence. The tumor is locally aggressive and infiltrates adjacent bone and soft tissues.

The long-term prognosis is difficult to ascertain because of the few reported cases with adequate follow-up, with the best estimates suggesting that 20% of these patients will succumb to their tumor. Most deaths have resulted from uncontrolled local disease, and metastatic tumor has been documented in only four of 54 evaluable cases.



• **Fig. 15-106 Ameloblastic Fibrosarcoma.** The cellular mesenchymal tissue shows hyperchromatism and atypical cells. A small island of ameloblastic epithelium is present.

◆ ODONTOAMELOBLASTOMA

The **odontoameloblastoma** is an extremely rare odontogenic tumor that contains an ameloblastomatous component and odontoma-like elements. Fewer than 20 cases have been reported with sufficient documentation to support this diagnosis. This tumor was formerly called *ameloblastic odontoma* and was confused with the more common (though still relatively rare) lesion currently designated as **ameloblastic fibro-odontoma.** Because the clinical behavior of these two tumors is quite different, they should be distinguished from one another. This neoplasm is also frequently confused with an odontoma that is in its early stages of development.

Clinical and Radiographic Features

Because of the rarity of odontoameloblastomas, little reliable information is available. The lesion appears to occur more often in younger patients, and either jaw can be affected. Pain, delayed eruption of teeth, and expansion of the affected bone may be noted.

Radiographically, the tumor shows a radiolucent, destructive process that contains calcified structures. These have the radiodensity of tooth structure and may resemble miniature teeth or occur as larger masses of calcified material similar to a complex odontoma.

Histopathologic Features

The histopathologic features of the odontoameloblastoma are complex. The proliferating epithelial portion of the tumor has features of an **ameloblastoma,** most often of the plexiform or follicular pattern. The ameloblastic component is intermingled with immature or more mature dental tissue in the form of developing rudimentary teeth, which is similar to the appearance of a **compound odontoma,** or conglomerate masses of enamel, dentin, and cementum, as seen in a **complex odontoma.**

Treatment and Prognosis

Multiple recurrences of odontoameloblastomas have been reported after local curettage, and it appears that this tumor has the same biologic potential as the ameloblastoma. It is probably wise to treat a patient with this lesion in the same manner as one with an ameloblastoma. However, there are no valid data on the long-term prognosis.

◆ ODONTOMA

Odontomas are the most common types of odontogenic tumors. Their prevalence exceeds that of all other odontogenic tumors combined. Odontomas are considered to be developmental anomalies **(hamartomas),** rather than true neoplasms. When fully developed, odontomas consist chiefly of enamel and dentin, with variable amounts of pulp and cementum. In their earlier developmental stages, varying amounts of proliferating odontogenic epithelium and mesenchyme are present.

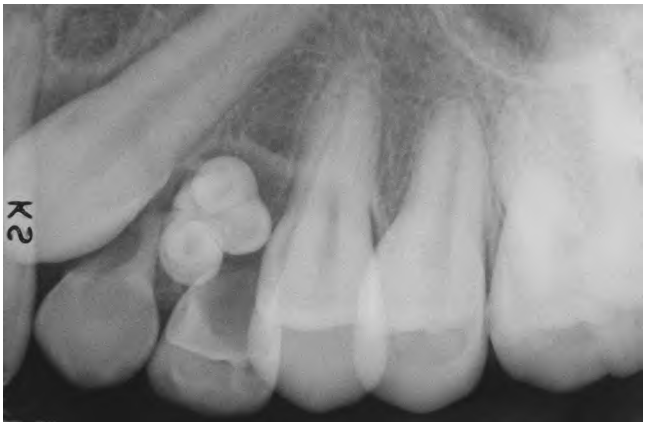
Odontomas are further subdivided into compound and complex types. The **compound odontoma** is composed of multiple, small toothlike structures. The **complex odontoma** consists of a conglomerate mass of enamel and dentin, which bears no anatomic resemblance to a tooth. In most series, compound odontomas are more frequently diagnosed than complex, and it is possible that some compound odontomas are not submitted for microscopic examination because the clinician is comfortable with the clinical and radiographic diagnosis. Occasionally, an odontoma may show both compound and complex features.

Clinical and Radiographic Features

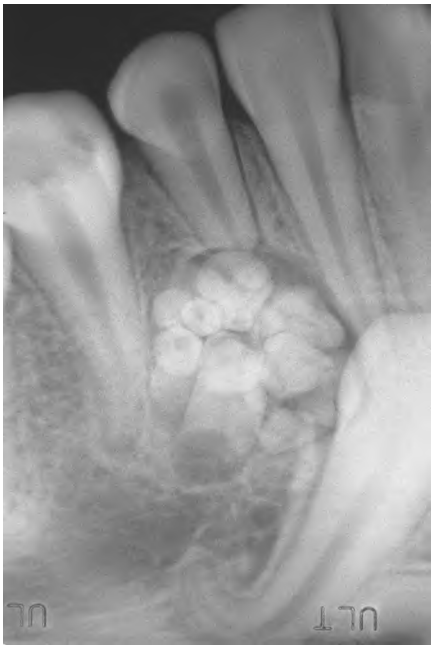
Most odontomas are detected during the first two decades of life, and the mean age at the time of diagnosis is 14 years. The majority of these lesions are completely asymptomatic, being discovered on a routine radiographic examination or when films are taken to determine the reason for failure of a tooth to erupt. Odontomas are typically relatively small and seldom exceed the size of a tooth in the area where they are located. However, large odontomas up to 6 cm or more in diameter are occasionally seen. These large odontomas can cause expansion of the jaw.

Odontomas occur somewhat more frequently in the maxilla than in the mandible. Although compound and complex odontomas may be found in any site, the compound type is more often seen in the anterior maxilla; complex odontomas occur more often in the molar regions of either jaw. Occasionally, an odontoma will develop completely within the gingival soft tissues.

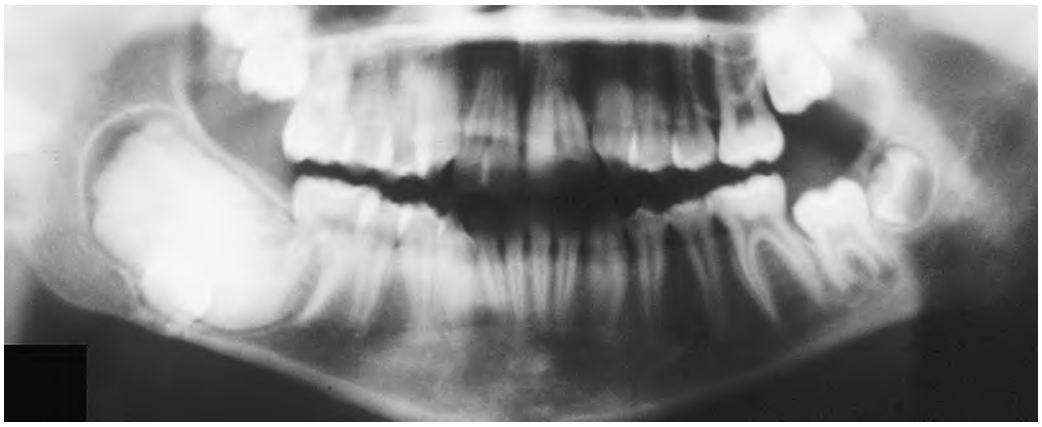
Radiographically, the **compound odontoma** appears as a collection of toothlike structures of varying size and shape surrounded by a narrow radiolucent zone (Figs. 15-107 and 15-108). The **complex odontoma** appears as a calcified



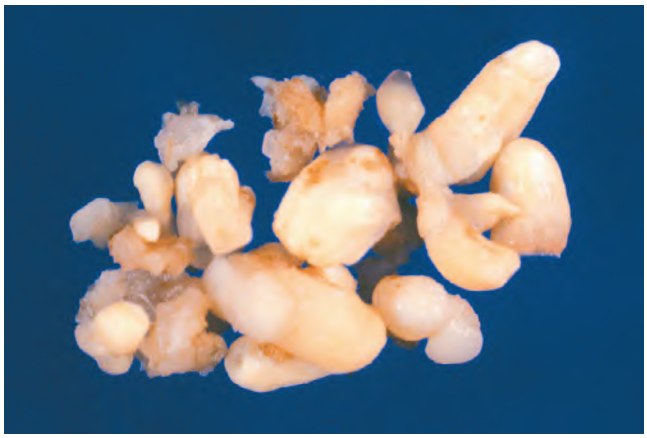
• **Fig. 15-107 Compound Odontoma.** A small cluster of toothlike structures is preventing the eruption of the maxillary canine. (Courtesy of Dr. Robert J. Powers.)



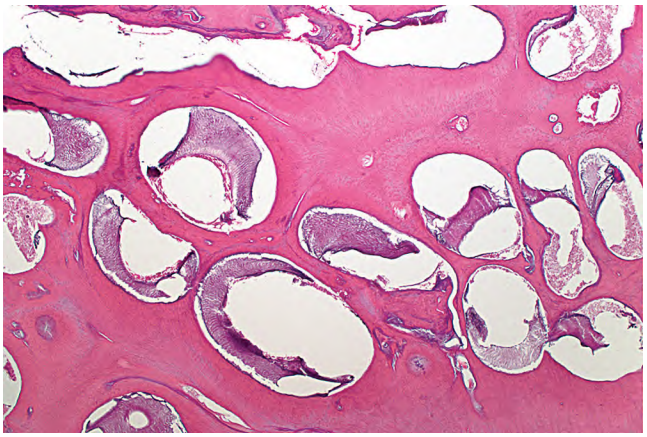
• **Fig. 15-108 Compound Odontoma.** Multiple toothlets preventing the eruption of the mandibular cuspid. (Courtesy of Dr. Brent Bernard.)



• **Fig. 15-109 Complex Odontoma.** A large radiopaque mass is overlying the crown of the mandibular right second molar, which has been displaced to the inferior border of the mandible.



• **Fig. 15-110 Compound Odontoma.** Surgical specimen consisting of more than 20 malformed toothlike structures.



• **Fig. 15-111 Complex Odontoma.** This decalcified section shows a disorganized mass of dentin intermixed with small pools of enamel matrix.

mass with the radiodensity of tooth structure, which is also surrounded by a narrow radiolucent rim. An unerupted tooth is frequently associated with the odontoma, and the odontoma prevents eruption of the tooth (Fig. 15-109). Some small odontomas are present between the roots of erupted teeth and are not associated with disturbance in eruption. The radiographic findings are usually diagnostic, and the compound odontoma is seldom confused with any other lesion. A developing odontoma may show little evidence of calcification and appear as a circumscribed radiolucent lesion. A complex odontoma, however, may be radiographically confused with an osteoma or some other highly calcified bone lesion.

Histopathologic Features

The compound odontoma consists of multiple structures resembling small, single-rooted teeth, contained in a loose fibrous matrix (Fig. 15-110). The mature enamel caps of the toothlike structures are lost during decalcification for preparation of the microscopic section, but varying amounts of enamel matrix are often present. Pulp tissue may be seen in the coronal and root portions of the toothlike structures. In patients with developing odontomas, structures that resemble tooth germs are present.

Complex odontomas consist largely of mature tubular dentin. This dentin encloses clefts or hollow circular structures that contained the mature enamel that was removed during decalcification. The spaces may contain small amounts of enamel matrix or immature enamel (Fig. 15-111). Small islands of eosinophilic-staining epithelial ghost cells are present in about 20% of complex odontomas. These may represent remnants of odontogenic epithelium that have undergone keratinization and cell death from the local anoxia. A thin layer of cementum is often present about the periphery of the mass. Occasionally, a dentigerous cyst may arise from the epithelial lining of the fibrous capsule of a complex odontoma.

Treatment and Prognosis

Odontomas are treated by simple local excision, and the prognosis is excellent.

TUMORS OF ODONTOGENIC ECTOMESENCHYME

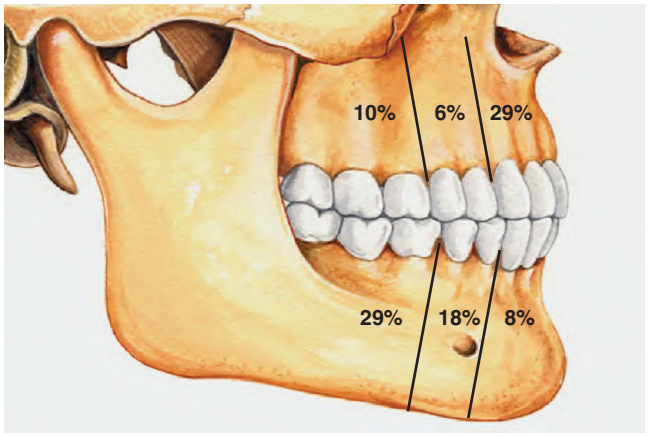
CENTRAL ODONTOGENIC FIBROMA

The **central odontogenic fibroma** is an uncommon and somewhat controversial lesion. Approximately 100 examples have been reported. Formerly, some oral and maxillofacial pathologists designated solid fibrous masses that were almost always associated with the crown of an unerupted tooth as *odontogenic fibromas.* Most oral and maxillofacial pathologists today consider such lesions to represent only hyperplastic dental follicles, and these should not be considered to be neoplasms.

Clinical and Radiographic Features

Odontogenic fibromas have been reported in patients whose ages ranged from 4 to 80 years (mean age, 40 years). Of those cases reported in the literature, a 1.8:1.0 female-to-male ratio has been noted, indicating a strong female predilection. The maxilla and mandible are affected nearly equally, with most maxillary lesions located anterior to the first molar tooth (Fig. 15-112). In the mandible, however, about half of the tumors are located posterior to the first molar. One-third of odontogenic fibromas are associated with an unerupted tooth. Smaller odontogenic fibromas are usually completely asymptomatic; larger lesions may be associated with localized bony expansion or loosening of teeth. Interestingly, the palatal mucosa that overlies the tumor occasionally may exhibit a defect or groove.

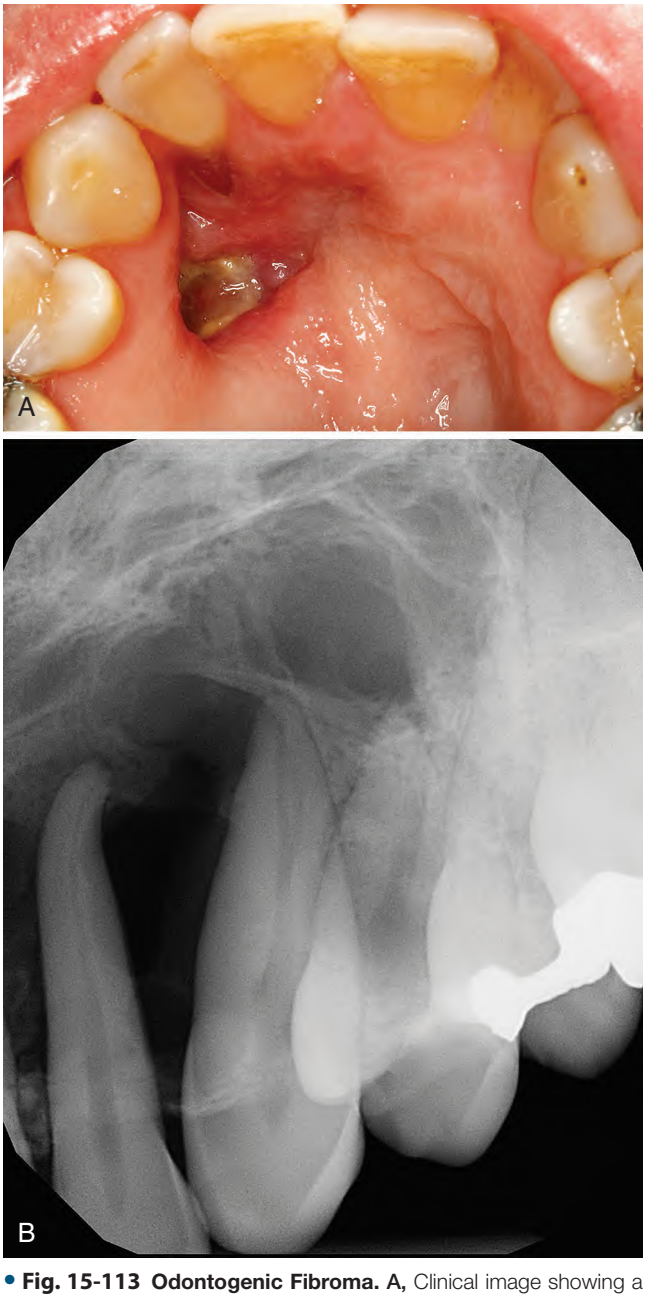
Radiographically, smaller odontogenic fibromas tend to be well-defined, unilocular, radiolucent lesions often associated with the periradicular area of erupted teeth (Fig. 15-113). Larger lesions tend to be multilocular radiolucencies. Many lesions have a corticated border. Root resorption of associated teeth is common, and lesions located between the teeth often cause root divergence. Approximately 12% of central odontogenic fibromas will exhibit radiopaque flecks within the lesion.



• **Fig. 15-112 Odontogenic Fibroma.** Relative distribution of odontogenic fibroma in the jaws.

Histopathologic Features

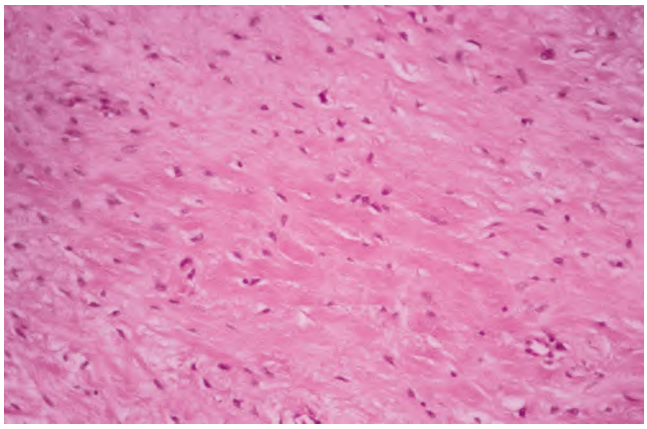
Lesions reported as central odontogenic fibroma have shown considerable histopathologic diversity; this has led some authors to describe two separate types, although this concept has been questioned. The World Health Organization (WHO) recognizes an epithelium-poor variant of central



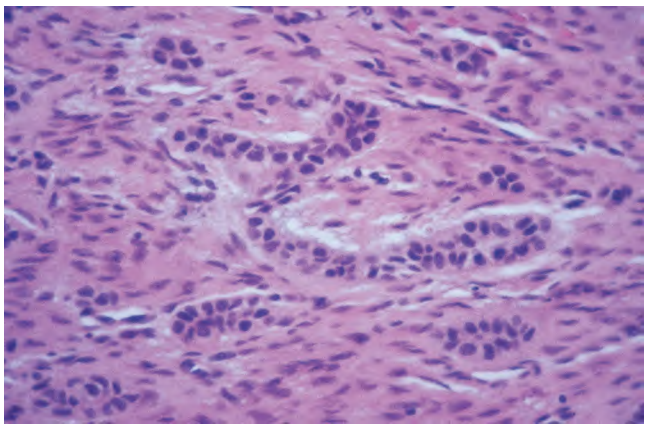
• **Fig. 15-113 Odontogenic Fibroma. A,** Clinical image showing a groove or defect in the palatal mucosa, a feature that has been described with maxillary lesions. **B,** Radiograph of this patient, depicting a multilocular radiolucency of the anterior maxilla. (Courtesy of Dr. Greg Adams.)

odontogenic fibroma (so-called **simple odontogenic fibroma**) and an epithelium-rich variant (so-called **WHO odontogenic fibroma**). The simple type of odontogenic fibroma is composed of stellate fibroblasts, often arranged in a whorled pattern with fine collagen fibrils and considerable ground substance (Fig. 15-114). Small foci of odontogenic epithelial rests should be present according to the WHO definition. Spindle cell collagenous lesions that do not have epithelial rests may represent other entities, such as desmoplastic fibroma, myofibroma, or neurofibroma. Occasional foci of dystrophic calcification may be seen.

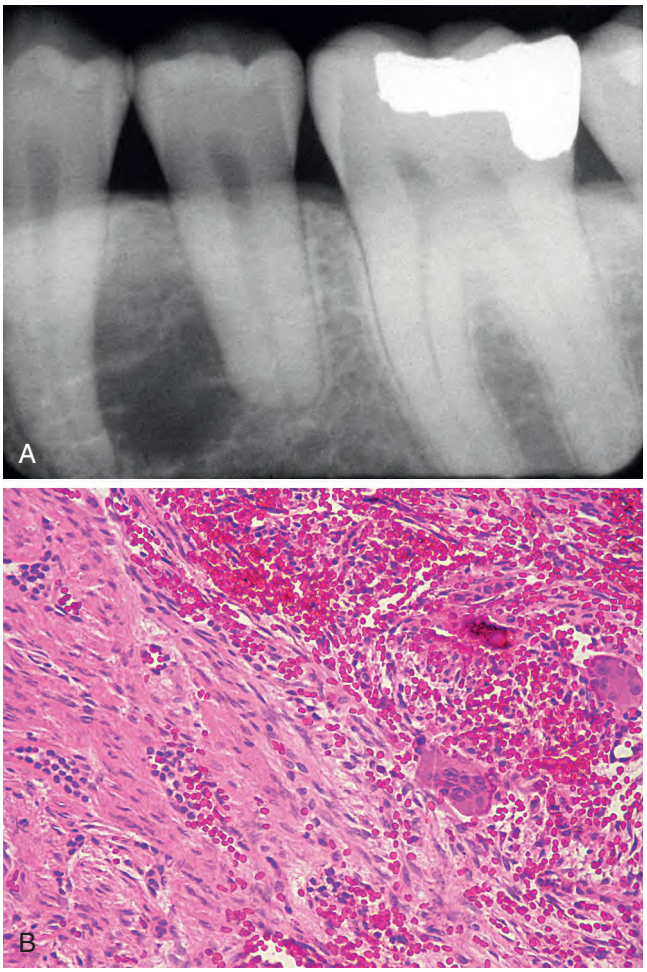
The epithelium-rich odontogenic fibroma has a more complex pattern, which often consists of a fairly cellular fibrous connective tissue with collagen fibers arranged in interlacing bundles. Odontogenic epithelium in the form of long strands or isolated nests is present throughout the lesion and may be a prominent component (Fig. 15-115). The fibrous component may vary from myxoid to densely hyalinized. Calcifications composed of cementum-like material or dentinoid are present in some cases. Focal deposits of odontogenic ameloblast-associated protein (ODAM), which represent a form of amyloid, have been described in a few central odontogenic fibromas, and the possibility that some of these lesions may represent calcifying epithelial odontogenic tumors cannot be excluded. Approximately 20 examples of central odontogenic fibroma associated with a **giant cell granuloma**–like component have been reported since 1992 (Fig. 15-116). It seems unlikely that this process represents a "collision" tumor with synchronous occurrence of an odontogenic fibroma and a giant cell granuloma. Several of these lesions have recurred, and the recurrences typically exhibit both components. Whether the odontogenic fibroma somehow induced a giant cell response in these patients, a giant cell granuloma triggered formation of an odontogenic fibroma, or whether this is a distinct biphasic lesion remains to be clarified.



• **Fig. 15-114 Odontogenic Fibroma (Simple Type).** Scattered fibroblasts within a collagenous background. No epithelial rests were found on multiple sections from this tumor.



• **Fig. 15-115 Odontogenic Fibroma (World Health Organization [WHO] Type).** A cellular fibroblastic lesion containing narrow cords of odontogenic epithelium.



• **Fig. 15-116 Odontogenic Fibroma (WHO Type) with Associated Giant Cell Granuloma. A,** Unilocular radiolucency between the left mandibular bicuspids. **B,** Microscopic examination reveals two distinct patterns. On the left, one can see cords of odontogenic epithelium within a fibrous background, consistent with odontogenic fibroma (WHO type). Typical features of central giant cell granuloma are present on the right side of the field.

Treatment and Prognosis

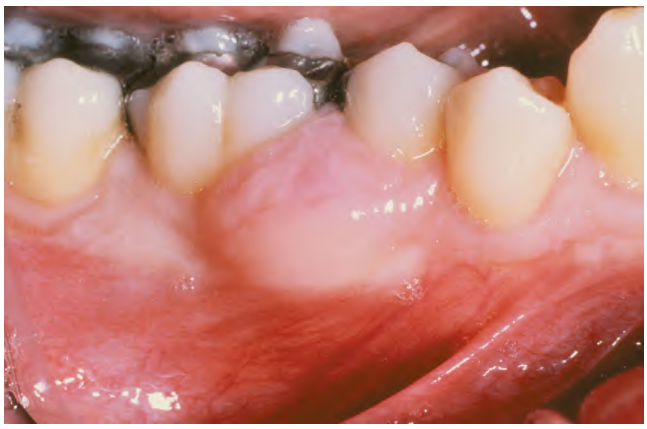
Odontogenic fibromas are usually treated by enucleation and vigorous curettage. Although the tumor does not have a definite capsule, it appears to have a limited growth potential, particularly in the anterior regions of the jaws. A few recurrences have been documented, but the prognosis is very good.

◆ PERIPHERAL ODONTOGENIC FIBROMA

The relatively uncommon **peripheral odontogenic fibroma** is considered to represent the soft tissue counterpart of the **central (intraosseous) odontogenic fibroma.** In the past, some authors have designated clinically and histopathologically similar lesions as **odontogenic epithelial hamartoma** or as **peripheral fibroameloblastic dentinoma.** It is likely that all of these terms refer to the same lesion, and peripheral odontogenic fibroma seems to be the most appropriate designation. A few series of this lesion have been reported in the past three decades, bringing the total number of cases in the literature to over 375.

Clinical and Radiographic Features

The peripheral odontogenic fibroma appears as a firm, slow-growing, and usually sessile gingival mass covered by normal-appearing mucosa (Fig. 15-117). Rarely, multifocal or diffuse lesions have been described. Clinically, the peripheral odontogenic fibroma cannot be distinguished from the much more common fibrous gingival lesions (see Chapter 12). The lesion is most often encountered on the facial gingiva of the mandible. Most lesions are between 0.5 and 1.5 cm in diameter, and they infrequently cause displacement of the teeth. Peripheral odontogenic fibromas have been recorded in patients across a wide age range, with most identified from the second to the fourth decades of life.



• **Fig. 15-117 Peripheral Odontogenic Fibroma.** This sessile gingival mass cannot be clinically distinguished from the common peripheral ossifying fibroma. (Courtesy of Dr. Jerry Stovall.)

Radiographic studies demonstrate a soft tissue mass, which in some cases has shown areas of calcification. The lesion typically does not involve the underlying bone, although occasionally a "cupped out" appearance has been noted.

Histopathologic Features

The peripheral odontogenic fibroma shows similar histopathologic features to the central odontogenic fibroma (WHO type). The tumor consists of interwoven fascicles of cellular fibrous connective tissue, which may be interspersed with areas of less cellular, myxoid connective tissue. A granular cell change has been rarely identified in the connective tissue component, and giant cell granuloma–like areas have been described in a few lesions. Islands or strands of odontogenic epithelium are scattered throughout the connective tissue. These may be prominent or scarce. The epithelial cells may show vacuolization. Dysplastic dentin, amorphous ovoid cementum-like calcifications, and trabeculae of osteoid may also be present.

Treatment and Prognosis

The peripheral odontogenic fibroma is treated by local surgical excision, and the prognosis is good. Recurrence of this lesion has been documented, however, so the patient and clinician should be aware of this possibility.

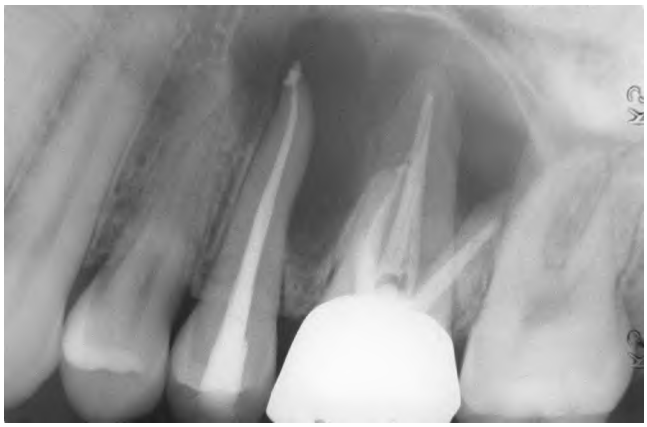
◆ GRANULAR CELL ODONTOGENIC TUMOR (GRANULAR CELL ODONTOGENIC FIBROMA)

The rare **granular cell odontogenic tumor** was initially reported as "granular cell ameloblastic fibroma." Subsequently, it was designated as **granular cell odontogenic fibroma,** but the noncommittal term **granular cell odontogenic tumor** is probably more appropriate, given the controversial nature of the lesion. Approximately 30 cases of this unusual tumor have been reported.

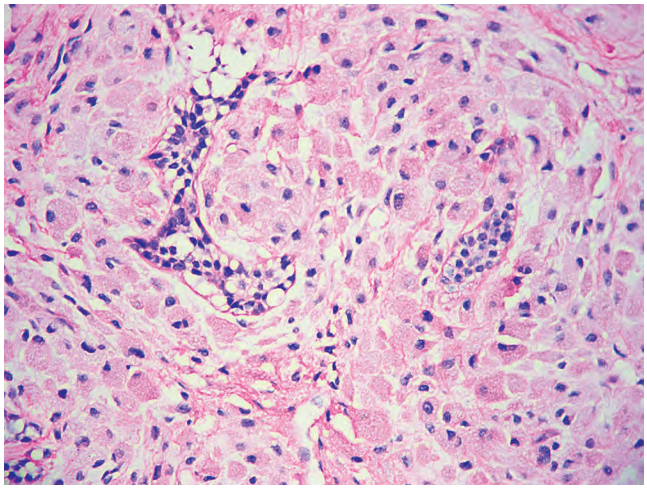
Clinical and Radiographic Features

Patients with granular cell odontogenic tumors have all been adults at the time of diagnosis, with more than half being older than 40 years of age. More than 70% of the cases have developed in women. The tumor occurs primarily in the mandible and most often in the premolar and molar region. Some lesions are completely asymptomatic; others present as a painless, localized expansion of the affected area. A few cases of granular cell odontogenic tumor have been described in the gingival soft tissues as well.

Radiographically, the lesion appears as a well-demarcated radiolucency, which may be unilocular or multilocular and occasionally shows small calcifications (Fig. 15-118).



• **Fig. 15-118 Granular Cell Odontogenic Tumor.** Radiolucent lesion involving the apical area of endodontically treated maxillary teeth. (Courtesy of Dr. Steve Ferry.)

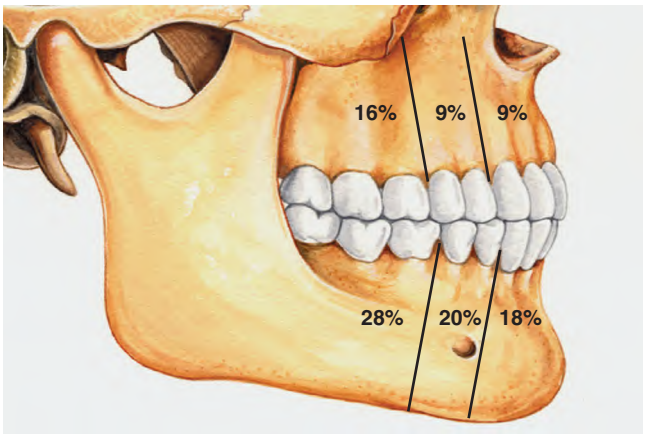


• **Fig. 15-119 Granular Cell Odontogenic Tumor.** Sheet of large granular mesenchymal cells with small nests of odontogenic epithelium.

Histopathologic Features

The granular cell odontogenic tumor is composed of large eosinophilic granular cells, which closely resemble the granular cells seen in the soft tissue granular cell tumor (see page 502) or the granular cells seen in the granular cell variant of the ameloblastoma (see page 657). Narrow cords or small islands of odontogenic epithelium are scattered among the granular cells (Fig. 15-119). Small cementum-like or dystrophic calcifications associated with the granular cells have been seen in some lesions.

The nature of the granular cells is controversial. Ultrastructural studies reveal the features of mesenchymal cells, and bodies consistent with lysosomal structures have been identified within the lesional cell cytoplasm. Immunohistochemically, the granular cells in the granular cell odontogenic tumor do not react with antibodies directed against S-100 protein, in contrast to the positive S-100 reactivity of the granular cell tumor.



• **Fig. 15-120 Odontogenic Myxoma.** Relative distribution of odontogenic myxoma in the jaws.

Treatment and Prognosis

The granular cell odontogenic fibroma appears to be completely benign in the overwhelming majority of instances and responds well to curettage. Only one recurrence has been documented, and a solitary example of a malignant central granular cell odontogenic fibroma has been reported.

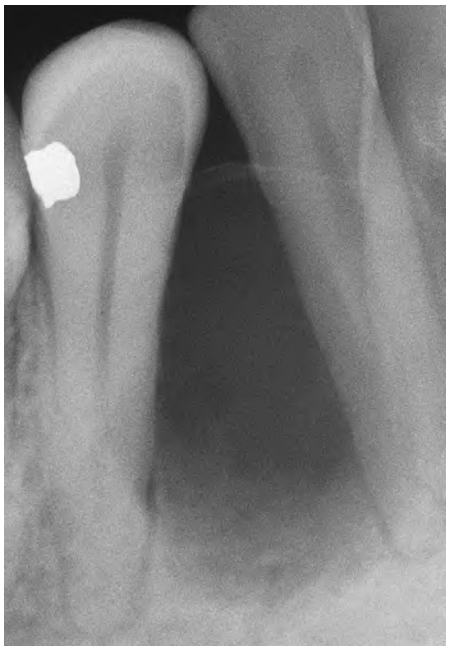
◆ ODONTOGENIC MYXOMA

Myxomas of the jaws are believed to arise from odontogenic ectomesenchyme. They bear a close microscopic resemblance to the mesenchymal portion of a developing tooth. Formerly, some investigators made a distinction between **odontogenic myxomas** (derived from odontogenic mesenchyme) and **osteogenic myxomas** (presumably derived from primitive bone tissue). However, most authorities in orthopedic pathologic practice do not accept that myxomas occur in the extragnathic skeleton, and all myxomas of the jaws are currently considered to be of odontogenic origin.

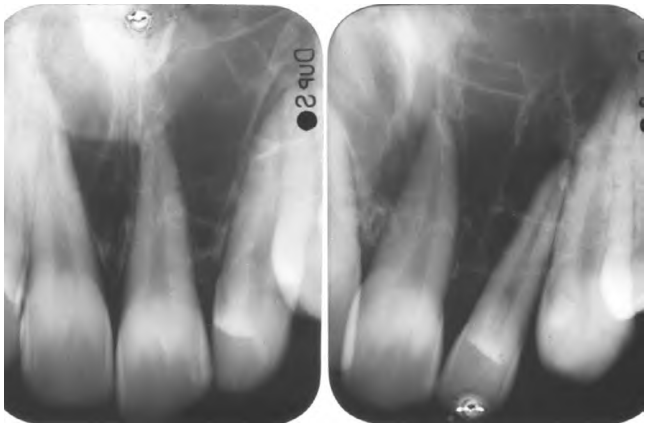
Clinical and Radiographic Features

Myxomas are predominantly found in young adults but may occur across a wide age group. The average age for patients with myxomas is 25 to 30 years. There is no sex predilection. The tumor may be found in almost any area of the jaws, and the mandible is involved more commonly than the maxilla (Fig. 15-120). Smaller lesions may be asymptomatic and are discovered only during a radiographic examination. Larger lesions are often associated with a painless expansion of the involved bone. In some instances, clinical growth of the tumor may be rapid; this is probably related to the accumulation of myxoid ground substance in the tumor.

Radiographically, the myxoma appears as a unilocular or multilocular radiolucency that may displace or cause resorption of teeth in the area of the tumor (Fig. 15-121). The margins of the radiolucency are often irregular or scalloped. The radiolucent defect may contain thin, wispy trabeculae



• **Fig. 15-121 Odontogenic Myxoma.** Unilocular radiolucency between the right mandibular lateral incisor and cuspid.

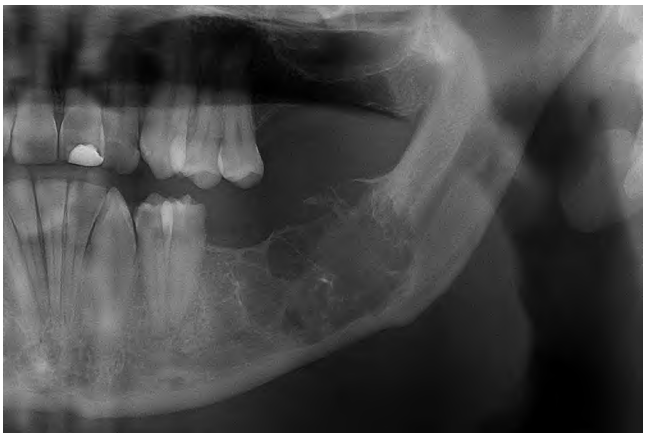


• **Fig. 15-122 Odontogenic Myxoma.** Radiolucent lesion of anterior maxilla showing fine residual bone trabeculae arranged at right angles to one another ("stepladder" pattern).

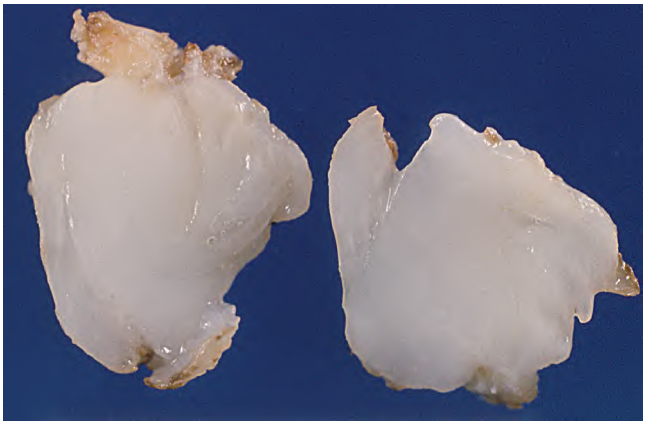
of residual bone, which are often arranged at right angles to one another (Fig. 15-122). Large myxomas of the mandible may show a "soap bubble" radiolucent pattern, which is indistinguishable from that seen in ameloblastomas (Fig. 15-123).

Histopathologic Features

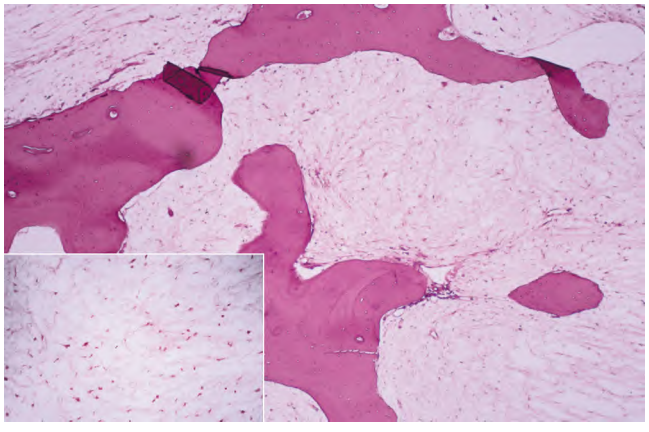
At the time of surgery or gross examination of the specimen, the gelatinous, loose structure of the myxoma is obvious (Fig. 15-124). Microscopically, the tumor is composed of haphazardly arranged stellate, spindle-shaped, and round cells in an abundant, loose myxoid stroma that contains only a few collagen fibrils (Fig. 15-125). Histochemical



• **Fig. 15-123 Odontogenic Myxoma.** Multilocular expansile radiolucency of the posterior mandible. (Courtesy of Dr. Steve Anderson.)



• **Fig. 15-124 Odontogenic Myxoma.** Gross specimen of case shown in Fig. 15-121, demonstrating a white gelatinous mass.



• **Fig. 15-125 Odontogenic Myxoma.** A loose, myxomatous tumor can be seen filling the marrow spaces between the bony trabeculae. The *inset* shows stellate-shaped cells and fine collagen fibrils.

study shows that the ground substance is composed of glycosaminoglycans, chiefly hyaluronic acid and chondroitin sulfate. Immunohistochemically, the myxoma cells show diffuse immunoreactivity with antibodies directed against vimentin, with focal reactivity for muscle-specific actin.

Small islands of inactive-appearing odontogenic epithelial rests may be scattered throughout the myxoid ground substance. These epithelial rests are not required for the diagnosis and are not obvious in most cases. In some patients, the tumor may have a greater tendency to form collagen fibers; such lesions are sometimes designated as **fibromyxomas** or **myxofibromas.** There is no evidence that the more collagenized variants deserve separate consideration, although some investigators have suggested that these may represent part of a spectrum that includes the central odontogenic fibroma at the other endpoint. Myxomas may rarely exhibit cementum-like calcifications.

A myxoma may be microscopically confused with other myxoid jaw neoplasms, such as the rare chondromyxoid fibroma (see page 611) or the myxoid neurofibroma (see page 494). Chondromyxoid fibroma should have areas of cartilaginous differentiation, whereas myxoid neurofibromas tend to have areas in which lesional cells are arranged in vague fascicles, as well as scattered cells that are positive for antibodies directed against S-100 protein. Myxoid change in an enlarged dental follicle or the dental papilla of a developing tooth may be microscopically similar to a myxoma. Evaluation of the clinical and radiographic features, however, prevents overdiagnosis of these lesions as myxomas.

Treatment and Prognosis

Small myxomas are generally treated by curettage, but careful periodic reevaluation is necessary for at least 5 years. For larger lesions, more extensive resection may be required because myxomas are not encapsulated and tend to infiltrate the surrounding bone. Complete removal of a large tumor by curettage is often difficult to accomplish, and lesions of the posterior maxilla, in particular, should be treated more aggressively in most instances. Recurrence rates from various studies average approximately 25%. In spite of local recurrences, the overall prognosis is good, and metastases do not occur.

In rare cases the myxoma microscopically shows marked cellularity and cellular atypism. Some have designated these lesions as *myxosarcomas* or *malignant odontogenic myxoma.* They appear to have a more aggressive local course than do the usual myxomas. Death because of involvement of vital structures by the tumor has been described, but distant metastases have not been reported.

◆ CEMENTOBLASTOMA ("TRUE CEMENTOMA")

Many oral and maxillofacial pathologists consider the **cementoblastoma** to represent an odontogenic tumor. However, other pathologists have pointed out that the histopathologic features of cementoblastomas of the jaws are identical to those of a bone tumor, osteoblastoma, seen both in the jaws and extragnathic skeleton. Cementoblastomas are discussed in Chapter 14 (see page 610).

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16 Dermatologic Diseases

ECTODERMAL DYSPLASIA

Ectodermal dysplasia represents a group of inherited conditions in which two or more ectodermally derived anatomic structures fail to develop. Thus depending on the type of ectodermal dysplasia, hypoplasia or aplasia of tissues (e.g., skin, hair, nails, teeth, and sweat glands) may be seen. The various types of this disorder may be inherited in any one of several genetic patterns, including autosomal dominant, autosomal recessive, and X-linked patterns. Even though by some accounts almost 200 different subtypes of ectodermal dysplasia can be defined, these disorders are considered to be relatively rare, with an estimated frequency of seven cases occurring in every 10,000 births. For fewer than 20% of these conditions, the specific genetic mutations and their chromosomal locations have been identified. Systematically classifying these conditions can be challenging because of their wide-ranging clinical features; however, some investigators have suggested that a classification scheme based on the molecular genetic alteration associated with each type might be appropriate. Thus groups of ectodermal dysplasia syndromes could be categorized as being caused by mutations in genes encoding cell-cell signals, genes encoding adhesion molecules, or genes regulating transcription.

Clinical Features

Perhaps the best known of the ectodermal dysplasia syndromes is **hypohidrotic ectodermal dysplasia**. In most instances, this disorder seems to show an X-linked inheritance pattern, with the gene mapping to Xq12-q13.1; therefore, a male predominance is usually seen. However, a few families have been identified that show autosomal recessive or autosomal dominant patterns of inheritance.

Affected individuals typically display heat intolerance because of a reduced number of eccrine sweat glands. Sometimes the diagnosis is made during infancy because the baby appears to have a fever of undetermined origin; however, the infant simply cannot regulate body temperature appropriately because of the decreased number of sweat glands. Uncommonly, death results from the markedly elevated body temperature, although this generally happens only when the condition is not identified. Sometimes, as a diagnostic aid, a special impression can be made of the patient's fingertips and then examined microscopically to count the density of the sweat glands. Such findings should be interpreted in conjunction with appropriate age-matched controls.

Other signs of this disorder include fine, sparse hair, including a reduced density of eyebrow and eyelash hair (Fig. 16-1). The periocular skin may show a fine wrinkling with hyperpigmentation (Fig. 16-2), and midface hypoplasia is frequently observed, often resulting in protuberant lips. Because the salivary glands are ectodermally derived, these glands may be hypoplastic or absent, and patients may exhibit varying degrees of xerostomia. The nails may also appear dystrophic and brittle.

The teeth are usually markedly reduced in number **(oligodontia** or **hypodontia),** and their crown shapes are characteristically abnormal (Fig. 16-3). The incisor crowns usually appear tapered, conical, or pointed, and the molar crowns are reduced in diameter. Complete lack of tooth development **(anodontia)** has also been reported, but this appears to be uncommon.

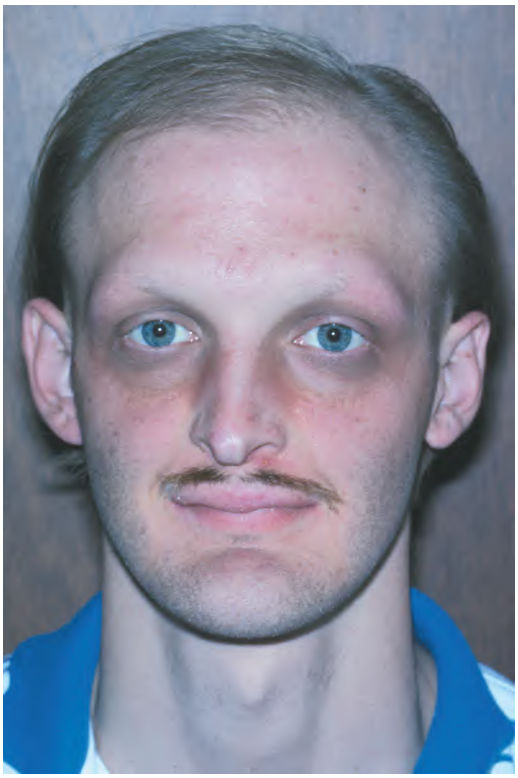
Female patients may show partial expression of the abnormal gene; that is, their teeth may be reduced in number or may have mild structural changes. This incomplete presentation can be explained by the **Lyon hypothesis,** with half of the female patient's X chromosomes expressing the normal gene, and the other half expressing the defective gene.

Histopathologic Features

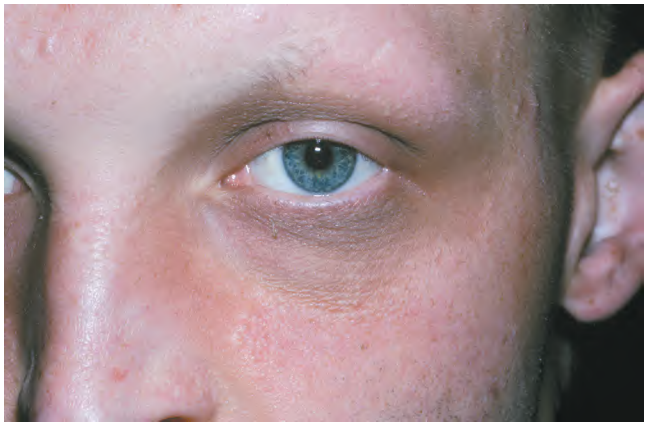
Histopathologic examination of the skin from a patient with hypohidrotic ectodermal dysplasia shows a decreased number of sweat glands and hair follicles. The adnexal structures that are present are hypoplastic and malformed.

Treatment and Prognosis

Management of hypohidrotic ectodermal dysplasia warrants genetic counseling for the parents and the patient. The dental problems are best managed by prosthetic replacement of the dentition with complete dentures, overdentures, or fixed appliances, depending on the number and location of the remaining teeth. With careful site selection,



• **Fig. 16-1 Ectodermal Dysplasia.** The sparse hair, periocular hyperpigmentation, and mild midfacial hypoplasia are characteristic features evident in this affected patient.

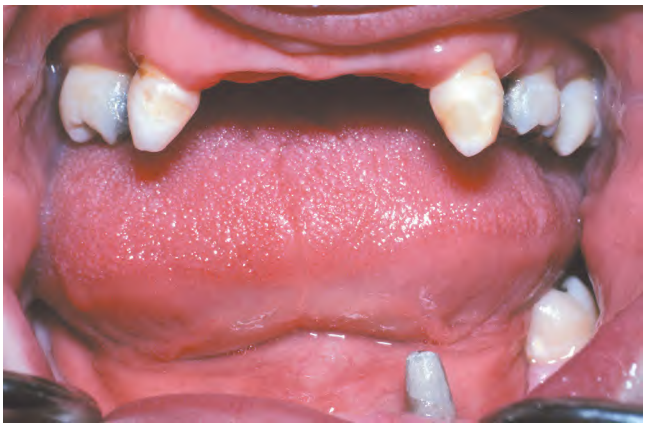


• **Fig. 16-2 Ectodermal Dysplasia.** Closer view of the same patient depicted in Fig. 16-1. Fine periocular wrinkling, as well as sparse eyelash and eyebrow hair, can be observed.

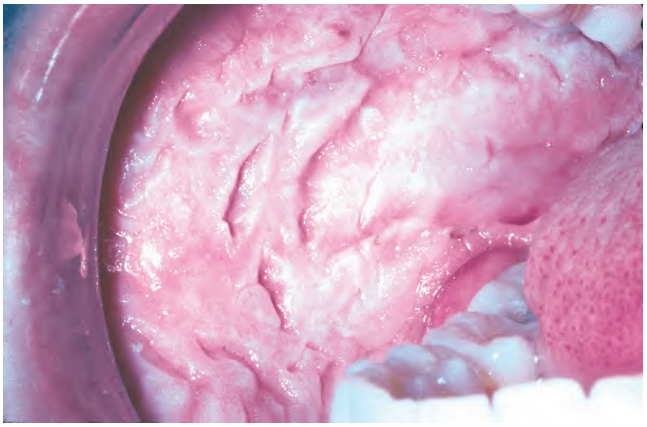
endosseous dental implants may be considered for facilitating prosthetic management of patients older than 6 years of age.

◆ WHITE SPONGE NEVUS (CANNON DISEASE; FAMILIAL WHITE FOLDED DYSPLASIA)

White sponge nevus is a relatively rare genodermatosis (a genetically determined skin disorder) that is inherited as an autosomal dominant trait displaying a high degree of penetrance and variable expressivity. This condition is due to a defect in the normal keratinization of the oral mucosa. In the 30-member family of keratin filaments, the pair of keratins known as *keratin 4* and *keratin 13* is specifically expressed in the spinous cell layer of mucosal epithelium. Mutations in either of these keratin genes have been shown to be responsible for the clinical manifestations of white sponge nevus.



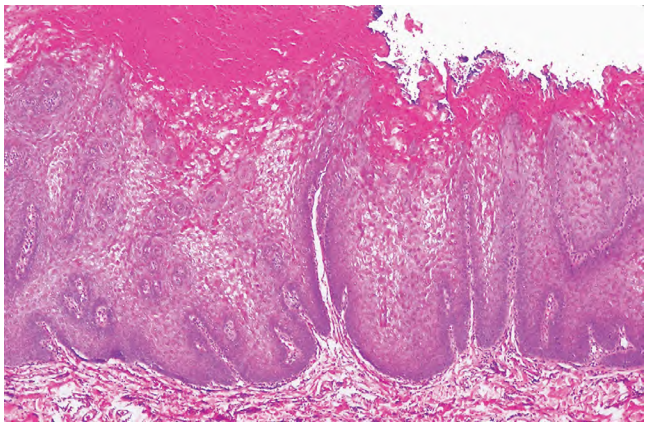
• **Fig. 16-3 Ectodermal Dysplasia.** Oligodontia and conical crown forms are typical oral manifestations. (Courtesy of Dr. Charles Hook and Dr. Bob Gellin.)



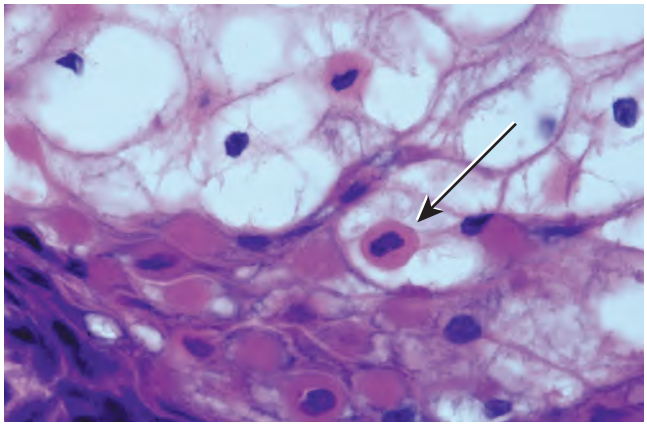
• **Fig. 16-4 White Sponge Nevus.** Diffuse, thickened white plaques of the buccal mucosa.

Clinical Features

The lesions of white sponge nevus usually appear at birth or in early childhood, but sometimes the condition develops during adolescence. Symmetrical, thickened, white, corrugated or velvety, diffuse plaques affect the buccal mucosa bilaterally in most instances (Fig. 16-4). Other common intraoral sites of involvement include the ventral tongue, labial mucosa, soft palate, alveolar mucosa, and floor of the mouth, although the extent of involvement can vary from patient to patient. Extraoral mucosal sites, such as the nasal, esophageal, laryngeal, and anogenital



• **Fig. 16-5 White Sponge Nevus.** This low-power photomicrograph shows prominent hyperparakeratosis, marked thickening (acanthosis), and vacuolation of the spinous cell layer.



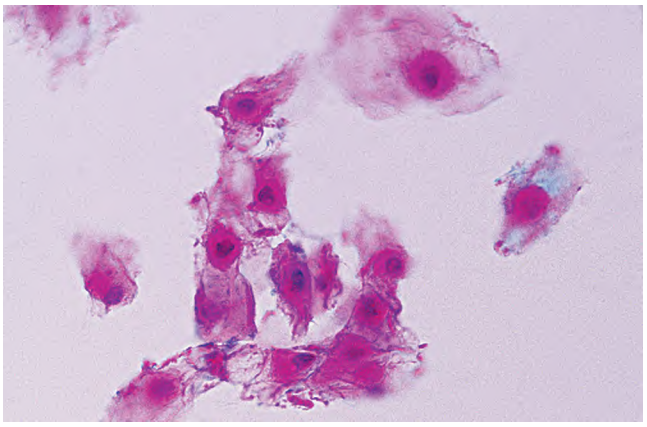
• **Fig. 16-6 White Sponge Nevus.** This high-power photomicrograph shows vacuolation of the cytoplasm of the cells of the spinous layer, with no evidence of epithelial atypia. Perinuclear condensation of keratin tonofilaments can also be observed in some cells.

mucosa, appear to be less commonly affected. Patients are usually asymptomatic.

Histopathologic Features

The microscopic features of white sponge nevus are characteristic but not necessarily pathognomonic. Prominent hyperparakeratosis and marked acanthosis with clearing of the cytoplasm of the cells in the spinous layer are common features (Figs. 16-5 and 16-6); however, similar microscopic findings may be associated with leukoedema and hereditary benign intraepithelial dyskeratosis (HBID). In some instances, an eosinophilic condensation is noted in the perinuclear region of the cells in the superficial layers of the epithelium, a feature that is unique to white sponge nevus. Ultrastructurally, this condensed material can be identified as tangled masses of keratin tonofilaments.

Exfoliative cytologic studies may provide more definitive diagnostic information. A cytologic preparation stained with the Papanicolaou method often shows the eosinophilic perinuclear condensation of the epithelial cell cytoplasm to a greater extent than does the histopathologic section (Fig. 16-7).



• **Fig. 16-7 White Sponge Nevus.** This high-power photomicrograph of a Papanicolaou-stained cytologic preparation shows the pathognomonic perinuclear condensation of keratin tonofilaments.

Treatment and Prognosis

Because this is a benign condition, no treatment is necessary. The prognosis is good.

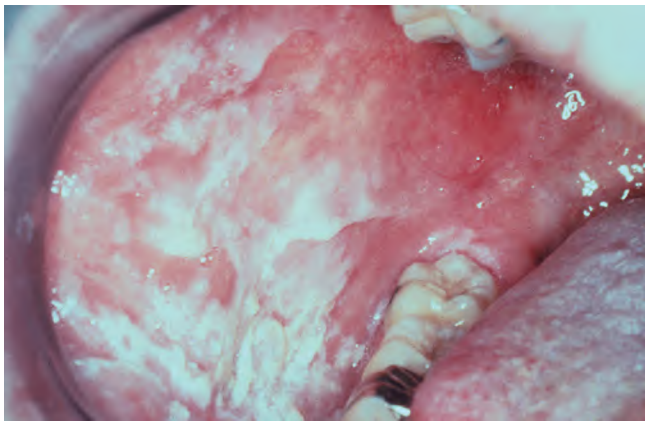
◆ HEREDITARY BENIGN INTRAEPITHELIAL DYSKERATOSIS (WITKOP-VON SALLMANN SYNDROME)

Hereditary benign intraepithelial dyskeratosis (HBID) is a rare autosomal dominant genodermatosis primarily affecting descendants of a triracial isolate (Native American, black, and white) of people who originally lived in North Carolina. Examples of HBID have sporadically been reported from other areas of the United States because of migration of affected individuals, and descriptions of affected patients with no apparent connection to North Carolina have also appeared in the literature.

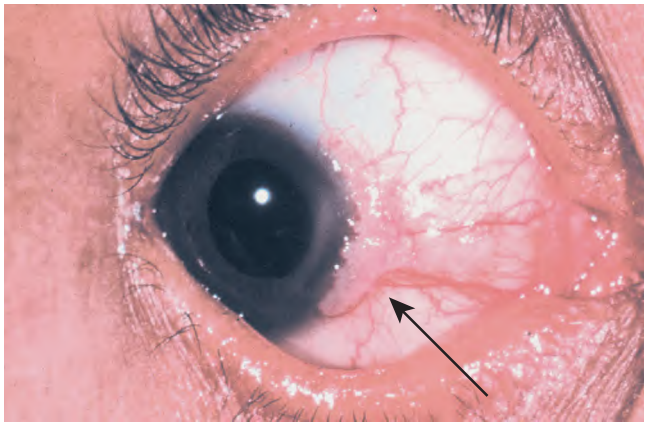
Clinical Features

The lesions of HBID usually develop during childhood, in most instances affecting the oral and conjunctival mucosa. The oral lesions are similar to those of white sponge nevus, with both conditions showing thick, corrugated white plaques involving the buccal and labial mucosa (Fig. 16-8). Milder cases may exhibit the opalescent appearance of leukoedema. Other oral mucosal sites, such as the floor of the mouth and lateral tongue, may also be affected. These oral lesions may exhibit a superimposed candidal infection as well.

The most interesting feature of HBID is the ocular lesions, which begin to develop very early in life. These



• **Fig. 16-8 Hereditary Benign Intraepithelial Dyskeratosis (HBID).** Oral lesions appear as corrugated white plaques of the buccal mucosa. (Courtesy of Dr. John McDonald.)

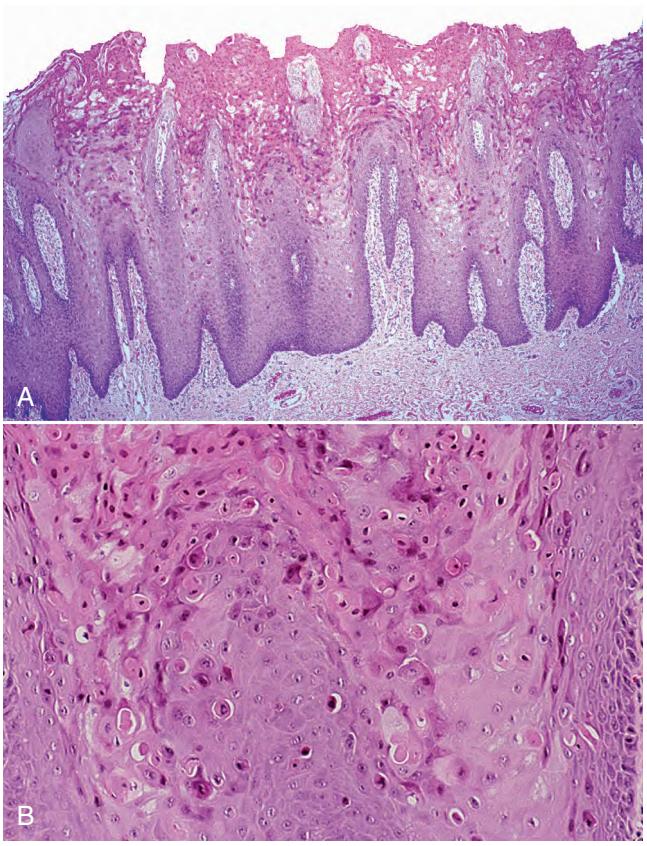


• **Fig. 16-9 Hereditary Benign Intraepithelial Dyskeratosis (HBID).** Ocular lesions appear as gelatinous plaques *(arrow)* of the bulbar conjunctivae. (Courtesy of Dr. Carl Witkop.)

appear as thick, opaque, gelatinous plaques affecting the bulbar conjunctiva adjacent to the cornea (Fig. 16-9) and sometimes involving the cornea itself. When the lesions are active, patients may experience tearing, photophobia, and itching of the eyes. In many patients, the plaques are most prominent in the spring and tend to regress during the summer or autumn. Sometimes blindness may result from the induction of vascularity of the cornea secondary to the shedding process.

Histopathologic Features

The histopathologic features of HBID include prominent parakeratin production in addition to marked acanthosis. A peculiar dyskeratotic process, similar to that of Darier disease, is scattered throughout the upper spinous layer of the surface oral epithelium (Fig. 16-10). With this dyskeratotic process, an epithelial cell appears to be surrounded or engulfed by an adjacent epithelial cell, resulting in the so-called *cell-within-a-cell* phenomenon.



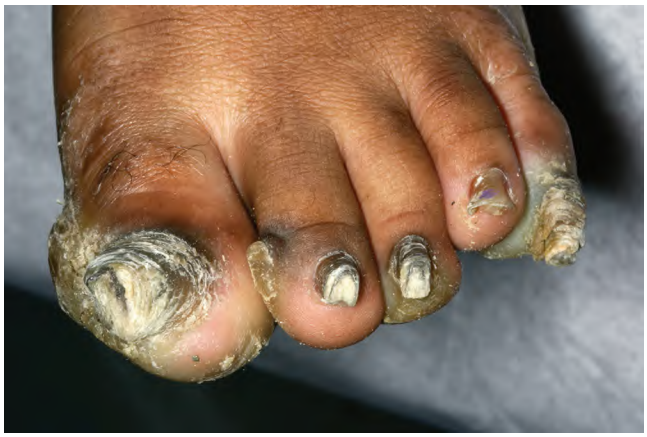
• **Fig. 16-10 Hereditary Benign Intraepithelial Dyskeratosis (HBID). A,** Medium-power photomicrograph exhibiting hyperparakeratosis, acanthosis, and dyskeratosis. **B,** Higher magnification showing dyskeratotic cells.

Treatment and Prognosis

Because HBID is a benign condition, no treatment is generally required or indicated for the oral lesions. If superimposed candidiasis develops, then an antifungal medication can be used. Patients with symptomatic ocular lesions should be referred to an ophthalmologist. Typically, the plaques that obscure vision must be surgically excised. This procedure, however, is recognized as a temporary measure because the lesions often recur.

◆ PACHYONYCHIA CONGENITA (JADASSOHN-LEWANDOWSKY TYPE; JACKSON-LAWLER TYPE)

Pachyonychia congenita is a group of rare genodermatoses that are usually inherited as an autosomal dominant trait. Mutations of genes that encode for keratin 6a, 6b, 16, or 17 are responsible for this condition, with different phenotypic expressions depending on the particular mutation. The nails, especially the toenails, are dramatically affected in most patients. Oral lesions are seen most frequently in patients who have mutation of the keratin 6a (*KRT6A*) gene, but can be found in a reduced percentage of the other



• **Fig. 16-11 Pachyonychia Congenita.** The nails often have a tubular configuration due to keratin accumulation beneath the nailbed.

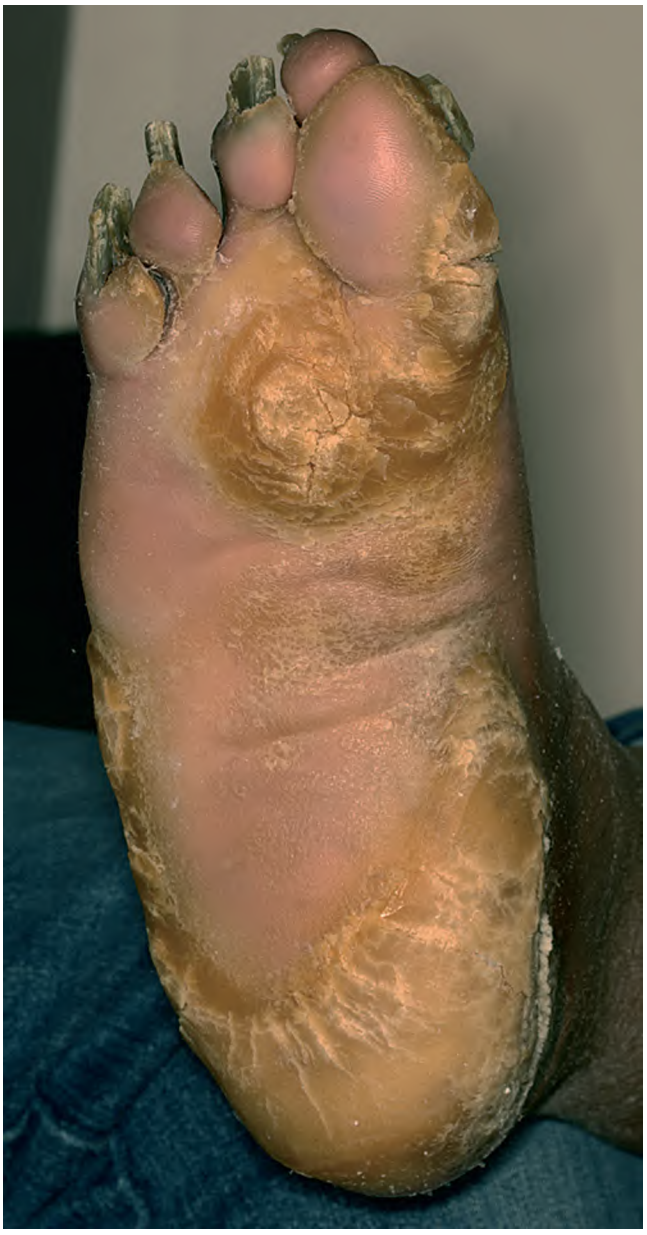
keratin mutations. Throughout the world, approximately 5000 to 10,000 people are thought to have this condition. Historically, pachyonychia congenita has been divided into the Jadassohn-Lewandowsky type (pachyonychia congenita, type 1) and the Jackson-Lawler type (pachyonychia congenita, type 2). It may be more appropriate, however, to categorize this group of disorders based on the specific keratin mutation that affects a particular patient.

Clinical Features

Virtually all patients with pachyonychia congenita exhibit characteristic nail changes, either at birth or in the early neonatal period. The free margins of the nails are lifted up because of an accumulation of keratinaceous material in the nail beds. This results in a pinched, tubular configuration (Fig. 16-11). Ultimately, nail loss may occur.

Other skin changes that may occur include marked hyperkeratosis of the palmar and plantar surfaces, producing thick, callous-like lesions (Fig. 16-12). Hyperhidrosis of the palms and soles is also commonly present. The rest of the skin shows punctate papules, representing an abnormal accumulation of keratin in the hair follicles. One disabling feature of the syndrome is severe pain with walking, which is believed to be due to the formation of blisters beneath the thick calluses on the soles of the feet. Fissuring of the thickened plantar calluses can also occur and cause pain upon walking.

The oral lesions seen in pachyonychia congenita consist of thickened white plaques that involve the lateral margins and dorsal surface of the tongue. Other oral mucosal regions that are frequently exposed to mild trauma, such as the palate, buccal mucosa, and alveolar mucosa, may also be affected (Fig. 16-13). Neonatal teeth are seen in a majority of patients with mutations of the keratin 17 gene, but only one-third of these individuals have oral white lesions. Hoarseness and dyspnea have been described in some patients as a result of laryngeal mucosal involvement.



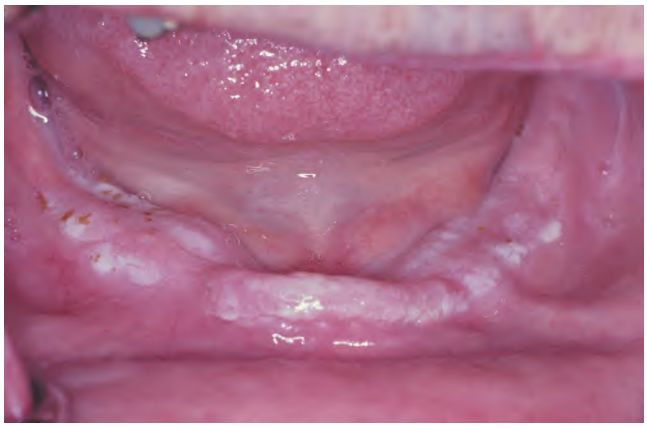
• **Fig. 16-12 Pachyonychia Congenita.** The soles of the feet of affected patients typically show marked callus-like thickenings.

Histopathologic Features

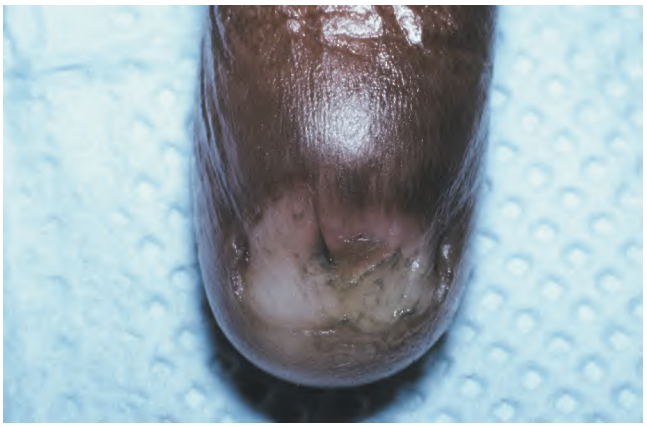
Microscopic examination of lesional oral mucosa shows marked hyperparakeratosis and acanthosis with perinuclear clearing of the epithelial cells.

Treatment and Prognosis

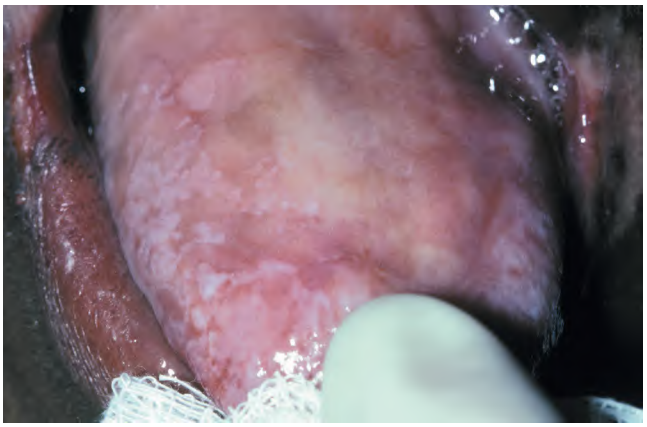
Because the oral lesions of pachyonychia congenita show no apparent tendency for malignant transformation, no treatment is required. The nails are often lost or may need to be surgically removed because of the deformity. In addition, the keratin accumulation on the palms and soles can be quite uncomfortable and distressing to many of the affected individuals. Most patients have to pay continuous attention



• **Fig. 16-13 Pachyonychia Congenita.** Although tongue lesions are more common in patients with pachyonychia congenita, other oral mucosal sites exposed to minor trauma, such as the alveolar mucosa, may develop thickened white patches. (Courtesy of Dr. John Lenox.)



• **Fig. 16-14 Dyskeratosis Congenita.** Dysplastic nail changes.



• **Fig. 16-15 Dyskeratosis Congenita.** Atrophy and hyperkeratosis of the dorsal tongue mucosa are visible.

to removal of the excess keratin, and issues related to quality of life often arise. Oral retinoids may be of some benefit for select patients, but the dosage has to be carefully monitored in order to minimize medication side effects. Patients should receive genetic counseling, as an aid in family planning. Chorionic villus sampling can be used to identify the various keratin mutations associated with these disorders, thereby allowing prenatal diagnosis.

◆ DYSKERATOSIS CONGENITA (COLE-ENGMAN SYNDROME; ZINSSER-COLE-ENGMAN SYNDROME)

Dyskeratosis congenita is a rare genodermatosis that is usually inherited as an X-linked recessive trait, resulting in a striking male predilection. Autosomal dominant and autosomal recessive forms, although less common, have been reported. Mutations in the *DKC1* gene initially were determined to cause the X-linked form of dyskeratosis congenita. The mutated gene appears to disrupt the normal maintenance of telomerase, an enzyme that is critical in determining normal cellular longevity. Subsequently, mutations of six other genes responsible for telomere maintenance have been identified for the other inheritance patterns of dyskeratosis congenita. The clinician should be aware of the condition because the oral lesions may undergo malignant transformation, and patients are susceptible to aplastic anemia.

Clinical Features

Dyskeratosis congenita usually becomes evident during the first 10 years of life. A reticular pattern of skin hyperpigmentation develops, affecting the face, neck, and upper chest. In addition, abnormal, dysplastic changes of the nails are evident at this time (Fig. 16-14).

Intraorally, the tongue and buccal mucosa develop bullae; these are followed by erosions and, eventually, leukoplakic lesions (Fig. 16-15). The leukoplakic lesions are considered to be premalignant, and approximately one-third of them become malignant in a 10- to 30-year period. The actual rate of transformation may be higher, but this may not be appreciated because of the shortened life span of these patients. Rapidly progressive periodontal disease has been reported sporadically.

Thrombocytopenia is usually the first hematologic problem that develops, typically during the second decade of life, followed by anemia. Ultimately, aplastic anemia develops in approximately 80% of these patients (see page 541). Mild to moderate intellectual disability may also be present. Generally, the autosomal recessive and X-linked recessive forms show a more severe pattern of disease expression.

Histopathologic Features

Biopsy specimens of the early oral mucosal lesions show hyperorthokeratosis with epithelial atrophy. As the lesions progress, epithelial dysplasia develops until frank squamous cell carcinoma evolves.

Treatment and Prognosis

The discomfort of the oral lesions is managed symptomatically, and careful periodic oral mucosal examinations are performed to check for evidence of malignant transformation. Routine medical evaluation is warranted to monitor the patient for the development of aplastic anemia. Certain anabolic steroids have been shown to increase telomerase activity, and treatment with these drugs may result in temporary improvement in the hematologic status. Bone marrow failure ultimately ensues, however. Selected patients may be considered for allogeneic hematopoietic stem cell transplantation once the aplastic anemia is identified.

As a result of these potentially life-threatening complications, the prognosis is guarded. The average life span for the more severely affected patients is 32 years of age. The parents and the patient should receive genetic counseling.

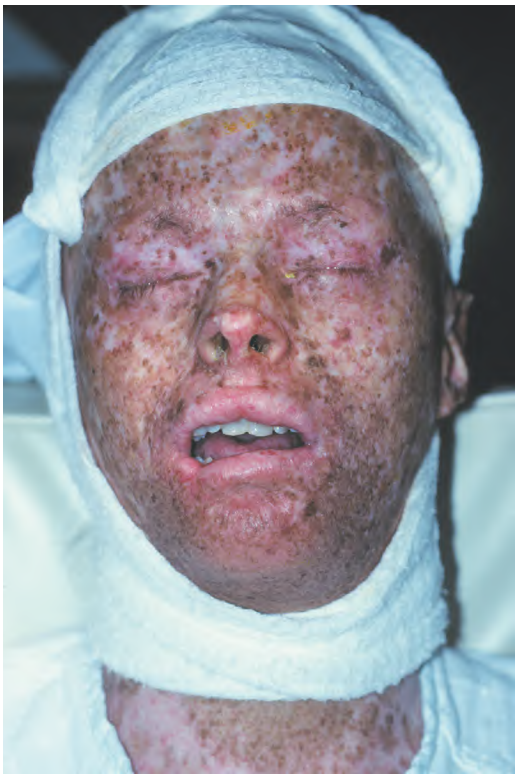
◆ XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is a rare genodermatosis in which numerous cutaneous malignancies develop at a very early age. The prevalence of the condition in the United States is estimated to be 1 in 250,000 to 500,000. The condition is inherited as an autosomal recessive trait and is caused by one of several defects in the excision repair and/or postreplication repair mechanism of DNA. As a result of the inability of the epithelial cells to repair ultraviolet (UV) light-induced damage, mutations in the epithelial cells occur, leading to the development of nonmelanoma skin cancer at a rate 10,000 times what would normally be expected in people younger than 20 years of age.

Clinical Features

During the first few years of life, patients affected by xeroderma pigmentosum show a markedly increased tendency to sunburn. Skin changes, such as atrophy, freckled pigmentation, and patchy depigmentation, soon follow (Fig. 16-16). In early childhood, **actinic keratoses** begin developing, a process that normally does not take place before 40 years of age. These lesions quickly progress to **squamous cell carcinoma,** with **basal cell carcinoma** also appearing; consequently, in most patients a nonmelanoma skin cancer develops during the first decade of life. Melanoma develops in about 5% of patients with xeroderma pigmentosum, but it evolves at a slightly later time. As a consequence of sun exposure, the head and neck region is the site most frequently affected by these cutaneous malignancies. Neurologic degenerative changes occur in 20% to 30% of affected patients and include subnormal intelligence, ataxia, sensorineural deafness, and impaired eyesight. The precise cause for the neurologic problems is currently unclear.

Oral manifestations, which often occur before 20 years of age, include development of **squamous cell carcinoma** of the lower lip and the tip of the tongue. This latter site is most unusual for oral cancer, and its involvement is again undoubtedly related to the increased sun exposure, however minimal, which this area receives in contrast to the rest of the oral mucosa.



• **Fig. 16-16 Xeroderma Pigmentosum.** The atrophic changes and pigmentation disturbances shown are characteristic of xeroderma pigmentosum.

The diagnosis of xeroderma pigmentosum is usually made when the patient is evaluated for the cutaneous lesions, because it is highly unusual for a very young person to have skin cancer. Because xeroderma pigmentosum is an autosomal recessive trait, a family history of the disorder is not likely to be present, but the possibility of a consanguineous relationship of the affected child's parents should be investigated.

Histopathologic Features

The histopathologic features of xeroderma pigmentosum are relatively nonspecific, in that the cutaneous premalignant lesions and malignancies that occur are microscopically indistinguishable from those observed in unaffected patients.

Treatment and Prognosis

Treatment of xeroderma pigmentosum is challenging because in most instances significant sun damage has already occurred by the time of diagnosis. Patients are advised to avoid sunlight and unfiltered fluorescent light and to wear appropriate protective clothing and sunscreens if they cannot avoid sun exposure. Before receiving dental treatment, a calibrated UV light meter should be used to

evaluate the amount of UV light being emitted from various sources in the dental office, such as the examination light, the radiograph view box, computer screens in the area, fiber-optic lights, or lights that are used for curing composite restorations. Some authors have suggested that any reading greater than 0 nm/cm^2 would be unacceptable. A dermatologist should evaluate the patient every 3 months to monitor the development of cutaneous lesions.

Topical chemotherapeutic agents (e.g., 5-fluorouracil) may be used to treat actinic keratoses. Nonmelanoma skin cancers should be excised conservatively, preferably with microscopically controlled excision (Mohs surgery) to preserve as much normal tissue as possible. Patients should also receive genetic counseling, because a high number of consanguineous marriages have been reported in some series.

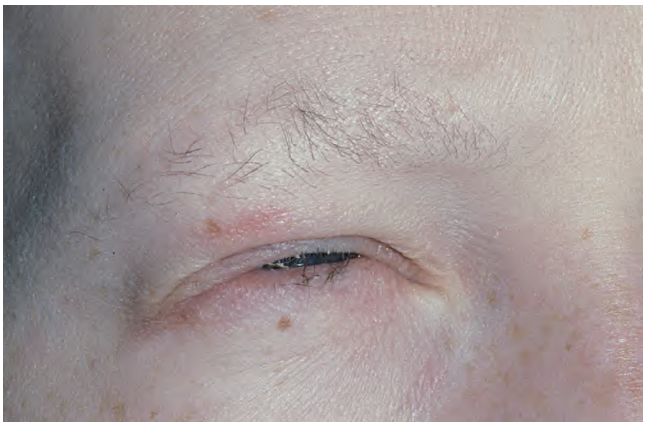
The prognosis is still poor. Most patients die 30 years earlier than the normal population, either directly from cutaneous malignancy or from complications associated with the treatment of the cancer. The outlook is much better if patients adhere to a strict program of life-long UV light avoidance, but this can be difficult to achieve.

◆ HEREDITARY MUCOEPITHELIAL DYSPLASIA

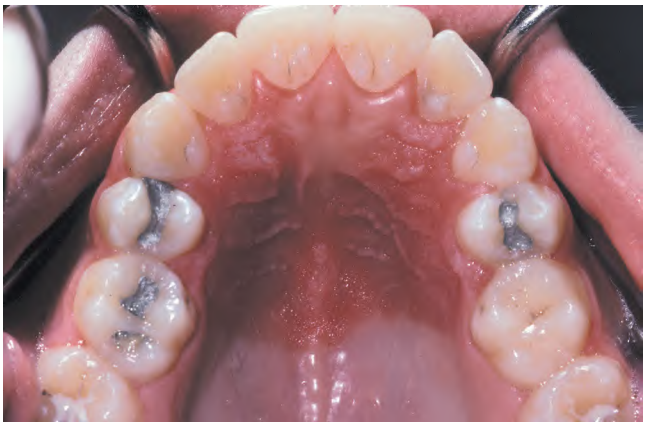
Hereditary mucoepithelial dysplasia is a rare disorder that may occur sporadically or may be inherited as an autosomal dominant trait. Approximately 30 cases have been reported, although affected patients may not be recognized due to the rarity of condition. For reasons that are not entirely understood, the mucosal epithelial cells do not develop in a normal fashion, and for this reason the designation of *dysplasia* has been given. However, in this situation, no increased risk of malignant transformation is seen. When a cervical exfoliative cytologic preparation (Pap smear) is done, the epithelial cells that are harvested may be interpreted as appearing cytologically unusual or atypical; in the past, some female patients have been advised to undergo hysterectomy because of this misinterpretation. Consequently, accurate identification of this disorder is extremely important for these patients.

Clinical Features

Hereditary mucoepithelial dysplasia is characterized by both cutaneous and mucosal abnormalities. Patients typically have sparse, coarse hair with nonscarring alopecia. Eyelashes and eyebrows are generally affected (Fig. 16-17). Severe photophobia develops at an early age, and most of these patients will have evidence of cataracts beginning in childhood or early adult life. Corneal vascularization, keratitis secondary to corneal erosions, cataracts, and nystagmus are also commonly described. As would be expected, vision is usually markedly impaired for these patients. Other skin manifestations include a prominent perineal rash that appears during infancy, as well as a widespread rough, dry texture because of follicular keratosis.



• **Fig. 16-17 Hereditary Mucoepithelial Dysplasia.** Sparse hair is noted on the eyebrows and eyelashes.



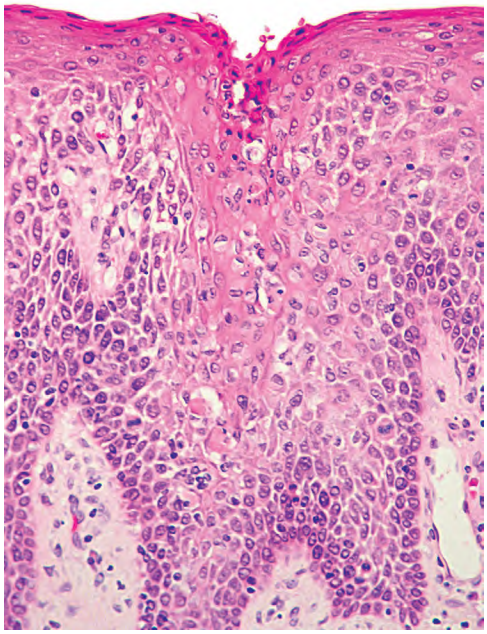
• **Fig. 16-18 Hereditary Mucoepithelial Dysplasia.** Marked erythema of the anterior hard palate.

Pulmonary complications related to mucoepithelial dysplasia can range in severity, presumably because of the degree of gene expression. In one family, cavitary bullae were reported to form within the lung parenchyma, and these led to recurrent bouts of pneumonia, often resulting in life-threatening complications.

The oral manifestations of hereditary mucoepithelial dysplasia are usually quite striking, appearing as demarcated fiery-red erythema of the hard palate (Fig. 16-18), with generally less involvement of the attached gingivae and tongue mucosa. These mucosal alterations are typically asymptomatic, despite their remarkable clinical appearance. The nasal, conjunctival, vaginal, cervical, urethral, and bladder mucosa may have the same unusual erythematous features.

Histopathologic Features

Biopsies of the mucosal lesions of hereditary mucoepithelial dysplasia show epithelium with minimal keratinization and a disorganized maturation pattern. The squamous epithelial cells may have a relatively high nuclear/cytoplasmic ratio,



• **Fig. 16-19 Hereditary Mucoepithelial Dysplasia.** Disorganized epithelium exhibiting scattered intracytoplasmic vacuoles.

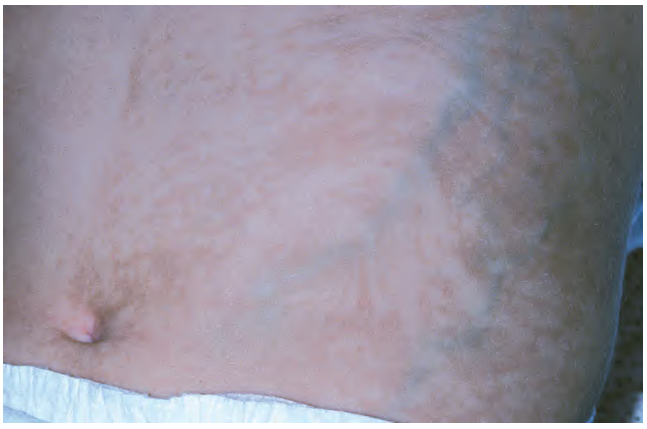
but significant nuclear or cellular pleomorphism is not observed. Cytoplasmic vacuoles have been described and may appear as grayish inclusions (Fig. 16-19). These vacuoles also may be observed in exfoliative cytology samples. Ultrastructurally, the lesional cells have been described as having reduced numbers of desmosomes and internalized gap junctions.

Treatment and Prognosis

Given the genetic nature of this disease, supportive care and genetic counseling are typically offered. Affected patients should be monitored for development of pulmonary disease.

◆ INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER SYNDROME)

Incontinentia pigmenti is a relatively rare inherited disorder, with approximately 800 cases reported worldwide. It typically evolves in several stages, primarily affecting the skin, eyes, and central nervous system (CNS), as well as oral structures. There is a marked female predilection, with a 37 : 1 female-to-male ratio reported. The condition is inherited as an X-linked dominant trait, with the single unpaired gene on the X chromosome being lethal for most males. The mutated gene responsible for producing the phenotypic features of incontinentia pigmenti maps to the Xq28 locus, where the genetic information related to *nuclear factor-κB essential modulator (NEMO)* is found. Of the few males who survive, a small percentage have Klinefelter syndrome (XXY karyotype), whereas the rest usually show mosaicism for the *NEMO* gene, suggesting a postzygotic mutation.



• **Fig. 16-20 Incontinentia Pigmenti.** Swirling pattern of pigmentation on the abdomen of an infant.

Clinical Features

The clinical manifestations of incontinentia pigmenti usually begin in the first few weeks of infancy. There are four classic stages associated with the cutaneous lesions:

1. Vesicular stage: Vesiculobullous lesions appear on the skin of the trunk and limbs. Spontaneous resolution occurs within 4 months.
2. Verrucous stage: Verrucous cutaneous plaques develop, affecting the limbs. These clear by 6 months of age, evolving into the third stage.
3. Hyperpigmentation stage: Macular, brown skin lesions appear, characterized by a strange swirling pattern (Fig. 16-20), although these tend to fade around the time of puberty.
4. Atrophy and depigmentation stage: Atrophy and depigmentation of the skin ultimately occur. Considerable overlap among these stages can occur at times, however.

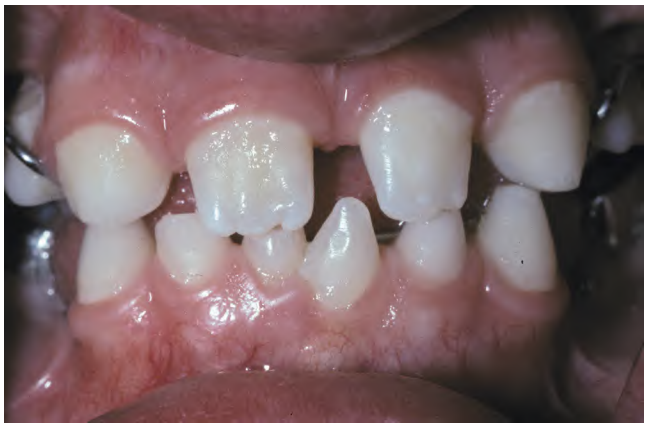
CNS abnormalities occur in approximately 30% of affected patients. The most common problems are intellectual disability, seizure disorders, and motor difficulties. Ocular problems (e.g., strabismus, nystagmus, cataracts, retinal vascular abnormalities, and optic nerve atrophy) may also be identified in nearly 35% of these patients.

The oral manifestations of incontinentia pigmenti, noted in 70% to 95% of the cases, include **oligodontia (hypodontia),** delayed eruption, and hypoplasia of the teeth (Fig. 16-21). The teeth are small and cone shaped; both the primary and permanent dentitions are affected.

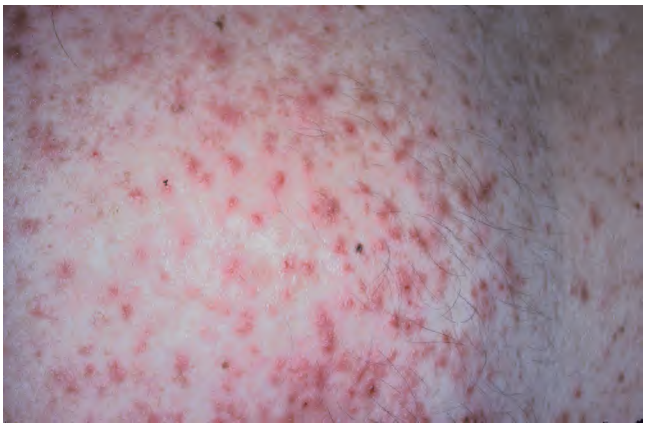
Histopathologic Features

The microscopic findings in incontinentia pigmenti vary, depending on when a biopsy of the skin lesions is performed.

In the initial vesicular stage, intraepithelial clefts filled with eosinophils are observed. During the verrucous stage, hyperkeratosis, acanthosis, and papillomatosis are noted. The hyperpigmentation stage shows numerous melanin-containing macrophages (melanin incontinence) in the



• **Fig. 16-21 Incontinentia Pigmenti.** Hypodontia and conical teeth.



• **Fig. 16-22 Darier Disease.** Erythematous cutaneous papules on the chest.

subepithelial connective tissue, the feature from which the disorder derives its name.

Treatment and Prognosis

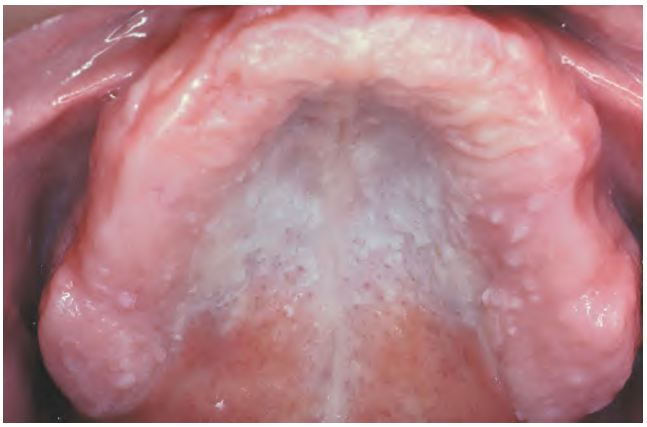
Treatment of incontinentia pigmenti is directed toward the various abnormalities. Dental management includes appropriate prosthodontic and restorative care, although this is sometimes difficult if CNS problems are severe. Prenatal genetic testing can be performed, but currently this is not widely available.

◆ DARIER DISEASE (KERATOSIS FOLLICULARIS; DYSKERATOSIS FOLLICULARIS; DARIER-WHITE DISEASE)

Darier disease is an uncommon genodermatosis with rather striking skin involvement and relatively subtle oral mucosal lesions. The condition is inherited as an autosomal dominant trait, having a high degree of penetrance and variable expressivity. A lack of cohesion among the surface epithelial cells characterizes this disease, and mutation of a gene (identified as *ATP2A2*) that encodes an intracellular calcium pump (SERCA2—sarco/endoplasmic reticulum Ca^{2+}-ATPase isoform 2) has been identified as the cause for abnormal desmosomal organization in the affected epithelial cells. Estimates of the prevalence of Darier disease in Northern European populations range from 1 in 36,000 to 1 in 100,000.

Clinical Features

Patients with Darier disease have numerous erythematous, often pruritic, papules on the skin of the trunk and the scalp that develop during the first or second decade of life (Fig. 16-22). An accumulation of keratin, producing a rough texture, may be seen in association with the lesions, and a foul odor may be present as a result of bacterial degradation of the keratin. The process generally becomes worse during the summer months, either because of sensitivity of some patients to UV light or because increased heat results in sweating, which induces more epithelial clefting. The palms and soles often exhibit pits and keratoses. The nails show longitudinal lines, ridges, or painful splits.

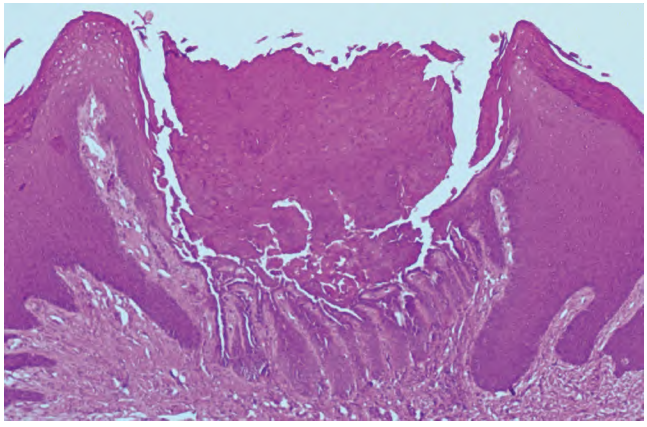


• **Fig. 16-23 Darier Disease.** The oral mucosa may show multiple white papules. (Courtesy of Dr. George Blozis.)

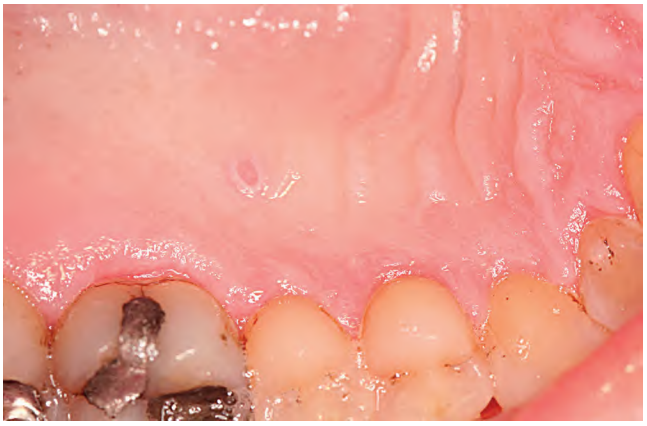
The oral lesions are typically asymptomatic and are discovered on routine examination. The frequency of occurrence of oral lesions ranges from 15% to 50%. They consist of multiple, normal-colored or white, flat-topped papules that, if numerous enough to be confluent, result in a cobblestone mucosal appearance (Fig. 16-23). These lesions affect the hard palate and alveolar mucosa primarily, although the buccal mucosa or tongue may be occasionally involved. If the palatal lesions are prominent, then the condition may resemble inflammatory papillary hyperplasia or nicotine stomatitis. Some patients with this condition also experience recurrent obstructive parotid swelling secondary to duct abnormalities.

Histopathologic Features

Microscopic examination of the cutaneous or mucosal lesions shows a dyskeratotic process characterized by a



• **Fig. 16-24 Darier Disease.** Low-power photomicrograph showing a thick keratin plug, intraepithelial clefting, and elongated rete ridges.



• **Fig. 16-25 Warty Dyskeratoma.** Umbilicated papule on the hard palate. (Courtesy of Dr. Greg Adams.)

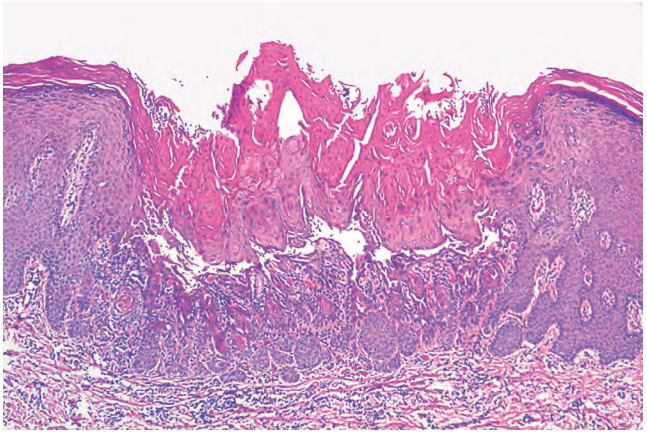
central keratin plug that overlies epithelium exhibiting a suprabasilar cleft (Fig. 16-24). This intraepithelial clefting phenomenon, also known as **acantholysis,** is not unique to Darier disease and may be seen in conditions, such as pemphigus vulgaris (see page 712). In addition, the epithelial rete ridges associated with the lesions appear narrow, elongated, and "test tube"–shaped. Closer inspection of the epithelium reveals varying numbers of two types of dyskeratotic cells, called ***corps ronds*** (round bodies) or **grains** (because they resemble cereal grains).

Treatment and Prognosis

Treatment of Darier disease depends on the severity of involvement. Photosensitive patients should use a sunscreen, and all patients should minimize unnecessary exposure to hot environments. For relatively mild cases, keratolytic agents or emollients may be the only treatment required. For more severely affected patients, systemic retinoids are often beneficial, but the side effects of such medications are often quite bothersome to the patient and can be significant; therefore, the physician should carefully monitor their use. Although the condition is not premalignant or otherwise life threatening, genetic counseling is appropriate.

◆ WARTY DYSKERATOMA (ISOLATED DARIER DISEASE; ISOLATED DYSKERATOSIS FOLLICULARIS; FOCAL ACANTHOLYTIC DYSKERATOSIS; FOLLICULAR DYSKERATOMA)

The **warty dyskeratoma** is a distinctly uncommon solitary lesion that can occur on skin or oral mucosa. It is histopathologically identical to Darier disease. For this reason the lesion has been termed **isolated Darier disease.** The lesion is not otherwise related to Darier disease, however, and its cause remains unknown.



• **Fig. 16-26 Warty Dyskeratoma.** Well-circumscribed invagination filled with a thick parakeratin plug. There is hyperplasia of the basilar cells with a suprabasilar cleft.

Clinical Features

The cutaneous warty dyskeratoma typically appears as a solitary, asymptomatic, umbilicated papule on the skin of the head or neck of an older adult. The intraoral lesion also develops in patients older than age 40, and a slight male predilection has been identified. The intraoral warty dyskeratoma appears as a pink or white, umbilicated papule located on the keratinized mucosa, especially the hard palate and the alveolar ridge (Fig. 16-25). A warty or roughened surface is noted in some lesions. Most warty dyskeratomas are smaller than 0.5 cm in diameter.

Histopathologic Features

Histopathologically, the warty dyskeratoma appears very similar to **keratosis follicularis.** Both conditions display dyskeratosis, basilar hyperplasia, and a suprabasilar cleft (Fig. 16-26). The warty dyskeratoma is a solitary lesion, however, and the formation of *corps ronds* and grains is not a prominent feature.

Treatment and Prognosis

Treatment of the warty dyskeratoma consists of conservative excision. The prognosis is excellent; these lesions have not been reported to recur, and they have no apparent malignant potential. Careful histopathologic evaluation of the tissue should be performed, because some epithelial dysplasias may show a marked lack of cellular cohesiveness, resulting in a similar acantholytic appearance microscopically.

◆ PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome is a relatively rare but well-recognized condition, having a prevalence of approximately 1 in 50,000 to 200,000 births. It is characterized by freckle-like lesions of the hands, perioral skin, and oral mucosa, in conjunction with intestinal polyposis and predisposition for affected patients to develop cancer. The syndrome is generally inherited as an autosomal dominant trait, although as many as 35% of cases represent new mutations. Mutation of the tumor suppressor gene, *STK11* (also known as *LKB1*) is responsible for most cases of Peutz-Jeghers syndrome. This gene, which encodes for a serine/threonine kinase, is located on chromosome 19p13.3.

Clinical Features

The skin lesions of Peutz-Jeghers syndrome usually develop early in childhood and involve the periorificial areas (e.g., mouth, nose, anus, and genital region). The skin of the extremities is affected in about 50% of patients (Fig. 16-27). The lesions resemble freckles, but they do not wax and wane with sun exposure, as do true freckles.

The intestinal polyps, generally considered to be hamartomatous growths, are scattered throughout the mucus-producing areas of the gastrointestinal tract. The jejunum and ileum are most commonly affected. Patients often have problems with intestinal obstruction because of intussusception ("telescoping" of a proximal segment of the bowel into a distal portion), a problem that usually becomes evident during the third decade of life. Most of these episodes are self-correcting, but surgical intervention is sometimes necessary to prevent ischemic necrosis of the bowel, with subsequent peritonitis. Gastrointestinal adenocarcinoma develops in a significant percentage of affected patients, although the polyps themselves do not appear to be premalignant. In one large series of cases, 9% of the patients had developed gastrointestinal malignancy by 40 years of age and 33% by 60 years of age. This compares to 0.1% and 1.0%, respectively, in the general population. Other tumors affecting the pancreas, male and female genital tract, breast, and ovary may also develop. In women, the risk of developing breast cancer approaches 50% by 60 years of age. The increased frequency of malignancy in these patients overall is estimated to be approximately 10 to 18 times greater than normal.

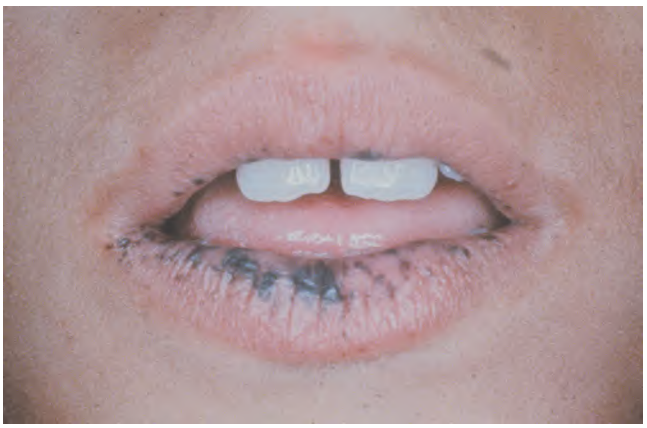
The oral lesions essentially represent an extension of the perioral freckling. These 1- to 4-mm brown to blue-gray macules primarily affect the vermilion zone, the labial and buccal mucosa, and the tongue; they are seen in more than 90% of these patients (Fig. 16-28). The number of lesions and the extent of involvement can vary markedly from patient to patient. Some degree of fading of the pigmented lesions may be noted during adolescence.

Histopathologic Features

The gastrointestinal polyps of Peutz-Jeghers syndrome histopathologically represent benign overgrowths of intestinal glandular epithelium supported by a core of smooth muscle. Epithelial atypia is not usually a prominent feature, unlike the polyps of Gardner syndrome (see page 606).

Microscopic evaluation of the pigmented cutaneous lesions shows slight acanthosis of the epithelium with elongation of the rete ridges. No apparent increase in melanocyte number is detected by electron microscopy, but the dendritic processes of the melanocytes are elongated. Furthermore, the melanin pigment appears to be retained in

• **Fig. 16-27 Peutz-Jeghers Syndrome.** Cutaneous lesions appear as brown, macular, freckle-like areas, often concentrated around the mouth or on the hands. (Courtesy of Dr. Ahmed Uthman.)



• **Fig. 16-28 Peutz-Jeghers Syndrome.** Oral manifestations include multiple, dark, freckle-like lesions of the lips. (Courtesy of Dr. Ahmed Uthman.)

the melanocytes rather than being transferred to adjacent keratinocytes.

Treatment and Prognosis

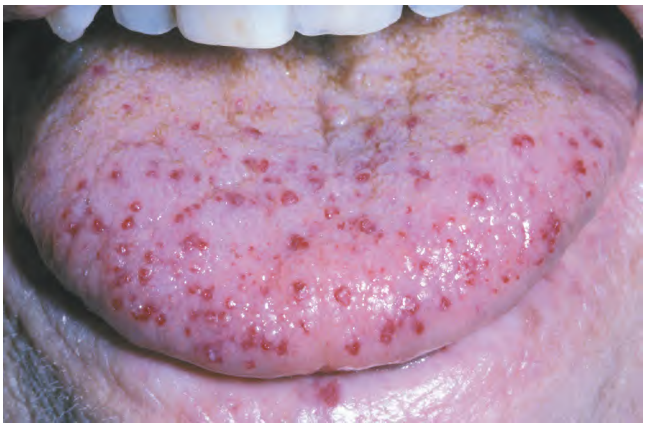
Patients with Peutz-Jeghers syndrome should be monitored for development of intussusception or tumor formation. Genetic counseling is also appropriate.

◆ HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER-WEBER-RENDU SYNDROME)

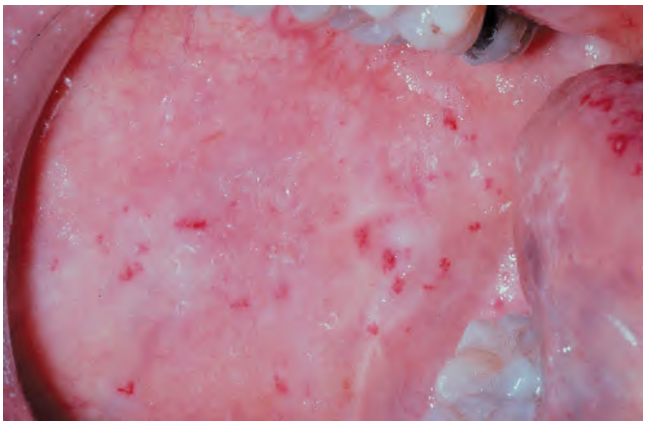
Hereditary hemorrhagic telangiectasia (HHT) is an uncommon mucocutaneous disorder that is inherited as an autosomal dominant trait, and epidemiologic studies suggest a prevalence that ranges from 1 in 5,000 to 18,000 people, depending on the geographic region. Mutation of either one of two different genes at two separate loci is responsible for the condition. HHT1 is caused by a mutation of the *endoglin (ENG)* gene on chromosome 9, whereas mutation of *activin receptor-like kinase-1 (ALK1; ACVRL1),* a gene located on chromosome 12, produces HHT2. The proteins produced by these genes may play a role in blood vessel wall integrity. With both types of HHT, numerous vascular hamartomas develop, affecting the skin and mucosa; however, other vascular problems, such as arteriovenous fistulas, may also be seen. Patients affected with HHT1 tend to have more pulmonary and cerebral involvement, whereas those with HHT2 generally have a later onset of their telangiectasias and a greater degree of hepatic involvement. A much less common mutation, involving the *MADH4* gene, has also been identified, and these patients exhibit an overlap syndrome characterized by HHT and juvenile polyposis. The polyps involve both the upper and lower gastrointestinal tract, and these patients have an increased risk for developing colorectal carcinoma at an early age. The clinician should be familiar with HHT because the oral lesions are often the most dramatic and most easily identified component of this syndrome.

Clinical Features

Patients with HHT are often diagnosed initially because of frequent episodes of epistaxis. On further examination, the nasal and oropharyngeal mucosae exhibit numerous scattered red papules, 1 to 2 mm in size, which blanch when diascopy is used. This blanching indicates that the red color is due to blood contained within blood vessels (in this case, small collections of dilated capillaries **[telangiectasias]** that are close to the surface of the mucosa). These telangiectatic vessels are most frequently found on the vermilion zone of the lips, tongue, and buccal mucosa, although any oral mucosal site may be affected (Figs. 16-29 and 16-30). With aging, the telangiectasias tend to become more numerous and slightly larger.



• **Fig. 16-29 Hereditary Hemorrhagic Telangiectasia (HHT).** The tongue of this patient shows multiple red papules, which represent superficial collections of dilated capillary spaces.

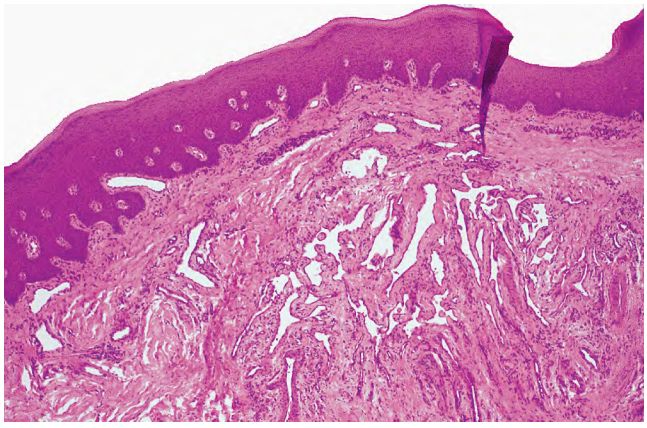


• **Fig. 16-30 Hereditary Hemorrhagic Telangiectasia (HHT).** Red macules similar to the tongue lesions are observed on the buccal mucosa.

In many patients, telangiectasias are seen on the hands and feet. The lesions are often distributed throughout the gastrointestinal mucosa, the genitourinary mucosa, and the conjunctival mucosa. The gastrointestinal telangiectasias have a tendency to rupture, which may cause significant blood loss. Chronic iron-deficiency anemia is often a problem for such individuals. Significantly, arteriovenous fistulas may develop in the lungs (15% to 45% of HHT patients), liver (30%), or brain (10% to 20%). The pulmonary arteriovenous malformations seem to predispose these patients to the development of brain abscesses due to right-to-left shunting of bacteria that might be introduced into the bloodstream. In at least one instance, periodontal vascular malformations were felt to be the cause of septic pulmonary emboli that resolved only after several teeth with periodontal abscesses were extracted.

A diagnosis of HHT can be made if a patient has three of the following four criteria:

1. Recurrent spontaneous epistaxis
2. Telangiectasias of the mucosa and skin
3. Arteriovenous malformation involving the lungs, liver, or CNS
4. Family history of HHT



• **Fig. 16-31 Hereditary Hemorrhagic Telangiectasia (HHT).** This low-power photomicrograph shows multiple dilated vascular spaces located immediately subjacent to the epithelium.

In some instances, CREST syndrome (**C**alcinosis cutis, **R**aynaud phenomenon, **E**sophageal dysfunction, **S**clerodactyly, and **T**elangiectasia) (see page 747) must be considered in the differential diagnosis. In these cases, serologic studies for anticentromere autoantibodies often help to distinguish between the two conditions because these antibodies typically would be present only in CREST syndrome.

Histopathologic Features

If one of the telangiectasias is submitted for biopsy, the microscopic features essentially show a superficially located collection of thin-walled vascular spaces that contain erythrocytes (Fig. 16-31).

Treatment and Prognosis

For mild cases of HHT, no treatment may be required. Moderate cases may be managed by selective cryosurgery or electrocautery of the most bothersome of the telangiectatic vessels. Laser ablation of the telangiectatic lesions has also been used, although this approach appears to be most successful for patients with mild to moderate disease. More severely affected patients, particularly those troubled by repeated episodes of epistaxis, may require a surgical procedure of the nasal septum (septal dermoplasty). The involved nasal mucosa is removed and replaced by a skin graft; however, some long-term follow-up studies suggest that the grafts eventually become revascularized, resulting in recurrence of the problem. Nasal closure is another surgical technique that has been performed for patients with severe epistaxis in whom other methods have failed.

Combined progesterone and estrogen therapy may benefit some patients, but because of the potentially serious side effects, this should be limited to the most severely affected individuals. Bevacizumab, an antibody directed against vascular endothelial growth factor, has shown some promise in controlling epistaxis, but this is a costly medication. Iron replacement therapy is indicated for the iron-deficient patient, and occasionally blood transfusions may be necessary to compensate for blood loss.

From a dental standpoint, some authors recommend the use of prophylactic antibiotics before dental procedures that might cause bacteremia in patients with HHT and evidence of a pulmonary arteriovenous malformation. For patients with a history of HHT, such antibiotics are advocated until a pulmonary arteriovenous malformation is ruled out because of the 1% prevalence of brain abscesses in affected individuals. Researchers believe that antibiotic coverage, similar to that for endocarditis prophylaxis, may prevent this serious complication. Patients with a history of HHT should be screened for arteriovenous malformations, which can be eliminated by embolization or other vasodestructive techniques using interventional radiologic methods. The decision to treat such a lesion often depends on the anatomic site and the severity of the malformation.

The prognosis is generally good, although a 1% to 2% mortality rate is reported from complications related to blood loss. For patients with brain abscesses, the mortality rate can range up to 10%, even with early diagnosis and appropriate therapy.

◆ EHLERS-DANLOS SYNDROMES

The **Ehlers-Danlos syndromes,** a group of inherited connective tissue disorders, are relatively heterogeneous. At least ten types have been described over the years, but recent clinical and molecular evidence suggests that seven categories of this disease may be more appropriate. The patient exhibits problems that are usually attributed to the production of abnormal collagen, the protein that is the main structural component of the connective tissue. Because the production of collagen necessitates many biochemical steps that are controlled by several genes, the potential exists for any one of these genes to mutate, producing selective defects in collagen synthesis. The various forms of abnormal collagen result in many overlapping clinical features for each of the types of the Ehlers-Danlos syndrome (Table 16-1). This discussion concentrates on the most common and significant forms of this group of conditions.

Typical clinical findings include hypermobility of the joints, easy bruisability, and marked elasticity of the skin. Some affected individuals have worked in circus sideshows as the "rubber" man and the "contortionist" as a result of their pronounced joint mobility and ability to stretch the skin.

Clinical Features

The pattern of inheritance and the clinical manifestations vary with the type of Ehlers-Danlos syndrome being examined. About 80% of patients have the **classical type** in either the **mild** or **severe** form. Classical Ehlers-Danlos syndrome is inherited as an autosomal dominant trait, and defects of type I collagen have been reported in some families, whereas problems with type V collagen have been

TABLE 16-1 Ehlers-Danlos Syndromes

Type	Clinical Features	Inheritance	Defect
Classical (severe)	Hyperextensible skin, easy bruising, hypermobile joints, papyraceous scarring of skin	AD	Collagen type V mutations
Classical (mild)	Less severe classical manifestations	AD	Collagen type V mutations
Hypermobility	Soft skin, no scarring, marked joint hyperextensibility	AD	Not known
Vascular	Severe bruising; risk for arterial, bowel, and uterine rupture	AD	Collagen type III mutations
Kyphoscoliosis	Ocular globe fragility, hyperextensible skin, hypermobile joints, scoliosis	AR	Lysyl hydroxylase point mutations
Arthrochalasis	Congenital hip dislocation, joint hypermobility, normal scarring, mandibular hypoplasia	AD	Collagen type I mutations
Dermatosparaxis	Severe skin fragility, sagging skin	AR	Procollagen peptidase deficiency
Other (includes X-linked, periodontal, and fibronectin types)	X-linked and periodontal similar to mild classic type; fibronectin has platelet defect	XLR, AD, AR	Not known; possible collagen type I and III defect; possible defect in fibronectin

AD, Autosomal dominant; *AR*, autosomal recessive; *XLR,* X-linked recessive.

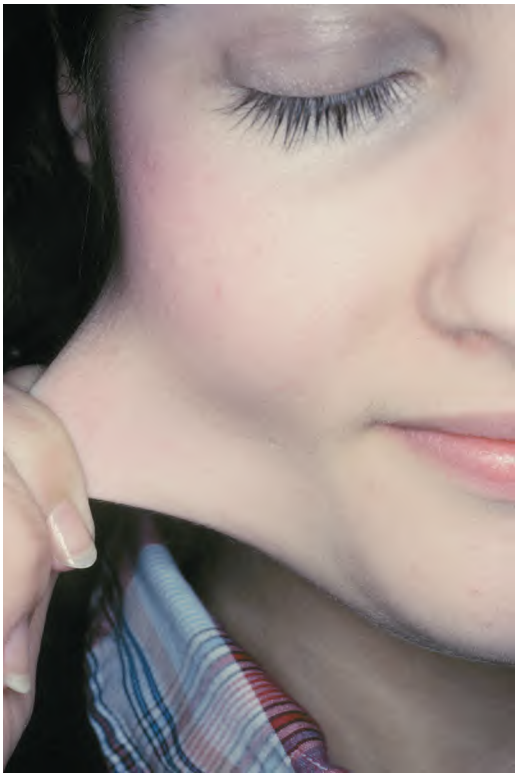
identified in others, suggesting genetic heterogeneity. Hyperelasticity of the skin (Fig. 16-32) and cutaneous fragility can be observed. An unusual healing response that often occurs with relatively minor injury to the skin is termed **papyraceous scarring** because it resembles crumpled cigarette paper (Fig. 16-33).

Patients with the **hypermobility type** of Ehlers-Danlos syndrome exhibit remarkable joint hypermobility but no evidence of unusual scarring.

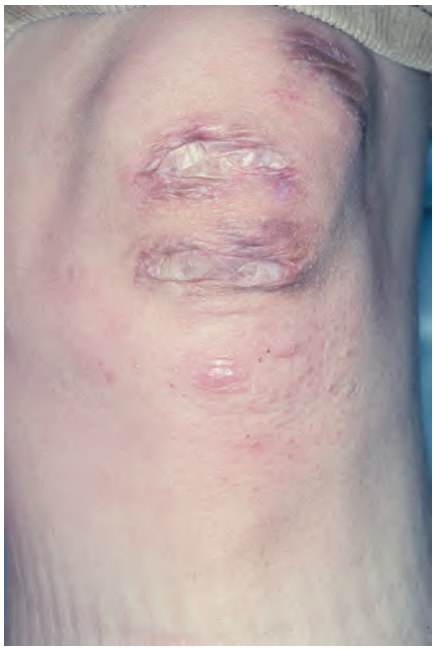
The **vascular type** of Ehlers-Danlos used to be known as the **ecchymotic** type because of the extensive bruising that occurs with everyday trauma. Defects in type III collagen have been identified in this disorder. This form is inherited in an autosomal dominant pattern, and a young patient may be mistaken for a victim of child abuse. The life expectancy of these patients is often greatly reduced because of the tendency for aortic aneurysm formation and rupture.

One rare form of Ehlers-Danlos syndrome (type VIII) has dental manifestations as a hallmark feature, with patients showing marked periodontal disease activity at a relatively early age. Although these patients may have overlapping features with either the classical or vascular forms of the disease, studies of five affected families in Sweden have suggested that this form of Ehlers-Danlos syndrome is linked to a specific mutation of a gene that has been mapped to chromosome 12p13.

The oral manifestations of Ehlers-Danlos syndrome include the ability of 50% of these patients to touch the tip of their nose with their tongue **(Gorlin sign),** a feat that



• **Fig. 16-32 Ehlers-Danlos Syndrome.** The hyperelasticity of the skin is evident in this patient affected by the mild form of classical Ehlers-Danlos syndrome.



• **Fig. 16-33 Ehlers-Danlos Syndrome.** Scarring that resembles crumpled cigarette paper (papyraceous scarring) is associated with minimal trauma in patients with Ehlers-Danlos syndromes. These lesions involve the skin of the knee.

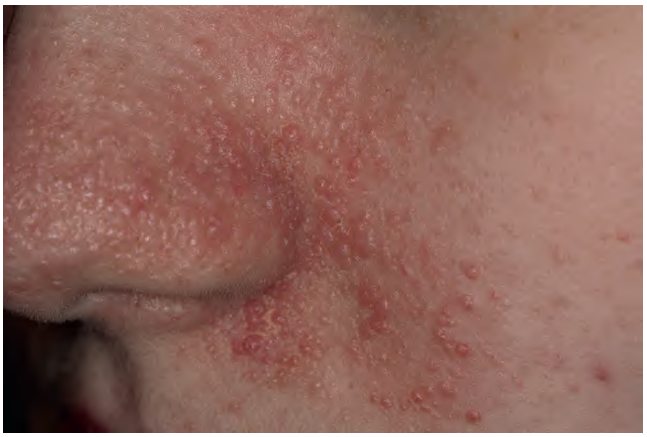
can be achieved by less than 10% of the general population. Some authors have noted easy bruising and bleeding during minor manipulations of the oral mucosa; others state that oral mucosal friability is present. A tendency for recurrent subluxation of the temporomandibular joint (TMJ) and the development of other TMJ disorders has also been reported.

Most patients with Ehlers-Danlos syndrome have normal teeth. A variety of dental abnormalities have been described, however, including malformed, stunted tooth roots, large pulp stones, and hypoplastic enamel. Although most of these findings have not been consistently correlated with any particular type of the syndrome, pulp stones seem to occur more commonly in patients affected by classical Ehlers-Danlos syndrome.

Treatment and Prognosis

The prognosis for the patient with Ehlers-Danlos syndrome depends on the type. Some forms, such as the vascular type, can be very serious, with sudden death occurring from rupture of the aorta secondary to the weakened, abnormal collagen that constitutes the vessel wall. The mild classical type is generally compatible with a normal life span, although affected women may have problems with placental tearing and hemorrhage during gestation.

Accurate diagnosis is important because it affects the prognosis heavily. Similarly, because the various types of this syndrome show a variety of inheritance patterns, an accurate diagnosis is required so that appropriate genetic counseling can be provided.



• **Fig. 16-34 Tuberous Sclerosis.** Patients typically have multiple papular facial lesions that microscopically are angiofibromas.

◆ TUBEROUS SCLEROSIS (EPILOIA; BOURNEVILLE-PRINGLE SYNDROME)

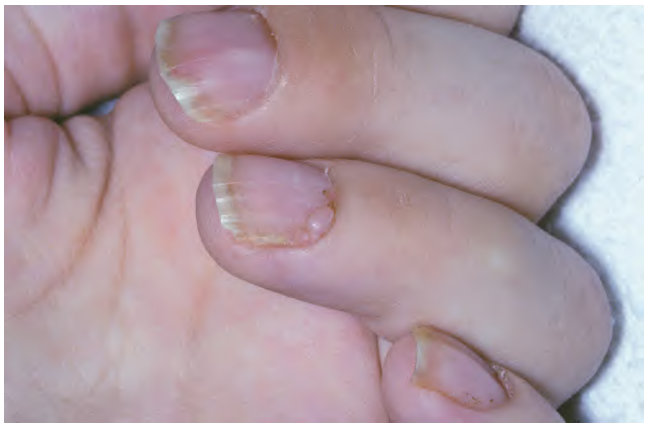
Tuberous sclerosis is an uncommon syndrome that is classically characterized by intellectual disability, seizure disorders, and angiofibromas of the skin. The condition is often inherited as an autosomal dominant trait, but two-thirds of the cases are sporadic and appear to represent new mutations. These mutations involve either one of two genes: *TSC1* (found on chromosome 9) or, more commonly, *TSC2* (found on chromosome 16). Both of these gene products are believed to contribute to the same intracellular biochemical pathway that seems to have a tumor suppressor function. The multiple hamartomatous growths that are seen in this disorder are thought to arise from disruption of the normal tumor suppressor function of these genes. Tuberous sclerosis has a wide range of clinical severity, although patients who have the *TSC2* mutation have a more severe expression of the disease than patients who have the *TSC1* mutation. Milder forms of tuberous sclerosis may be difficult to diagnose.

The prevalence is at least 1 in 10,000 in the general population, although in some long-term care facilities tuberous sclerosis accounts for as high as 1% of the intellectually disabled patients. Nevertheless, average intelligence is present in over half of tuberous sclerosis patients.

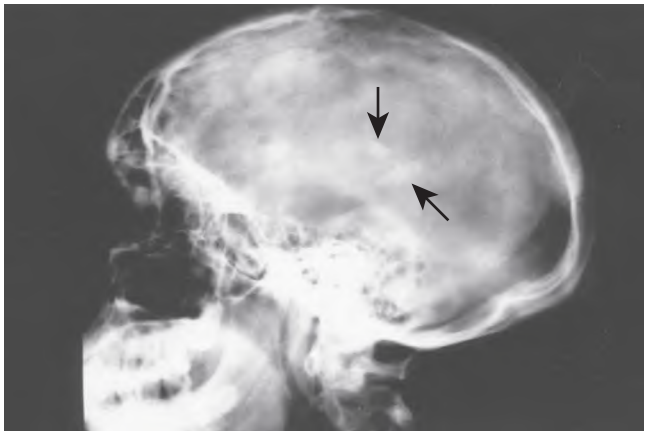
Clinical Features

Several clinical features characterize tuberous sclerosis. The first of these, **facial angiofibromas,** used to be called *adenoma sebaceum.* Because these lesions are neither adenomas nor sebaceous, the use of that term should be discontinued. Facial angiofibromas appear as multiple, smooth-surfaced papules and occur primarily in the nasolabial fold area (Fig. 16-34). Similar lesions, called *ungual* or *periungual fibromas,* are seen around or under the margins of the nails (Fig. 16-35).

Two other characteristic skin lesions are connective tissue hamartomas called **shagreen patches** and ovoid areas of



• **Fig. 16-35 Tuberous Sclerosis.** Examination of the fingers often shows periungual fibromas.

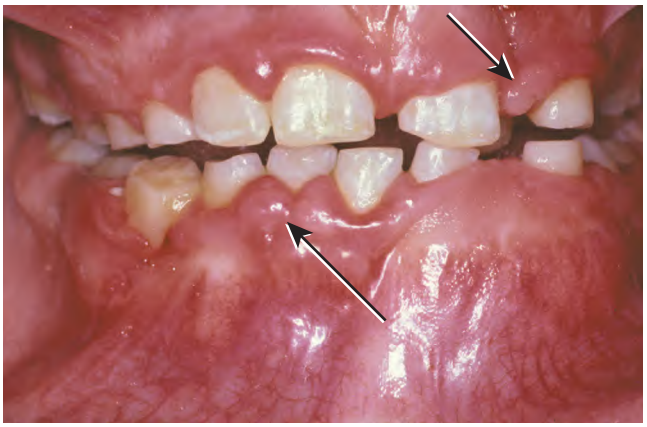


• **Fig. 16-36 Tuberous Sclerosis.** Patchy calcifications *(arrows)* associated with intracranial hamartoma formation are seen on this lateral skull radiograph. (Courtesy of Dr. Reg Munden.)

hypopigmentation called **ash-leaf spots.** Even though approximately 5% of the general population may have an ash-leaf spot, studies have reported that 90% to 98% of children with tuberous sclerosis display these lesions. The shagreen patches, so named because of their resemblance to sharkskin-derived shagreen cloth, affect the skin of the trunk. The ash-leaf spots may appear on any cutaneous surface and may be best visualized using UV (Wood's lamp) illumination.

CNS manifestations include seizure disorders in 70% to 80% of affected patients and intellectual disability in approximately 30%. In addition, hamartomatous proliferations in the CNS develop into the potato-like growths ("tubers") seen at autopsy, from which the term *tuberous sclerosis* is derived (Fig. 16-36). The tuberous hamartomas can best be visualized using T2-weighted magnetic resonance imaging (MRI) and are present in 80% to 95% of these patients. Also, approximately 10% of tuberous sclerosis patients will develop a type of benign brain tumor known as *subependymal giant cell astrocytoma.*

A relatively rare tumor of the heart muscle, called **cardiac rhabdomyoma,** is also typically associated with this syndrome. This lesion, which probably represents a hamartoma rather than a true neoplasm, occurs in approximately 30% to 50% of affected patients and is typically identified in early childhood. Problems with myocardial function may develop as a result of this process, but many of these tumors undergo spontaneous regression.



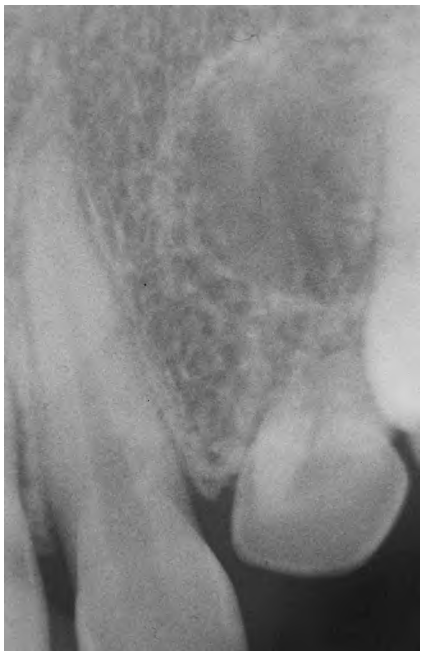
• **Fig. 16-37 Tuberous Sclerosis.** Patients often exhibit gingival hyperplasia, which may be secondary to phenytoin medications used to control seizures in some cases. Fibrous papules of the gingiva *(arrows)* may also be present.

Another hamartomatous type of growth related to this disorder is the **angiomyolipoma.** This is a benign neoplasm composed of vascular smooth muscle and adipose tissue and occurs primarily in the kidney, typically bilaterally. Even though the angiomyolipoma is benign, the tumors are often associated with large dilated blood vessels, and significant clinical problems can arise if these vessels rupture spontaneously.

Oral manifestations of tuberous sclerosis include developmental enamel pitting on the facial aspect of the anterior permanent dentition in 50% to 100% of patients. These pits are more readily appreciated after applying a dental plaque–disclosing solution to the teeth. Multiple fibrous papules affect 11% to 56% of patients. The fibrous papules are seen predominantly on the anterior gingival mucosa (Fig. 16-37), although the lips, buccal mucosa, palate, and tongue may be involved. Diffuse fibrous gingival enlargement is reported in affected patients—even those who are not taking phenytoin; however, most cases of gingival hyperplasia in these individuals are probably related to medication taken to control seizures. Some patients with tuberous sclerosis may also exhibit radiolucencies of the jaws that represent dense fibrous connective tissue proliferations (Fig. 16-38).

The diagnosis of tuberous sclerosis can be based on finding at least two of the following major features:

- Facial angiofibromas
- Ungual or periungual fibromas
- Hypomelanotic macules (three or more)
- Shagreen patch
- CNS hamartomas
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma



• **Fig. 16-38 Tuberous Sclerosis.** Periapical radiograph exhibiting a well-defined radiolucency apical to the maxillary left lateral incisor. Biopsy revealed an intraosseous fibrous proliferation.

- Renal angiomyolipoma
- Multiple retinal nodular hamartomas

The presence of one major and two minor features may also confirm the diagnosis. The minor features include the following:

- Multiple, randomly distributed enamel pits
- Gingival fibromas
- Bone "cysts" (actually fibrous proliferations)
- Multiple renal cysts
- Hamartomatous rectal polyps

Histopathologic Features

Microscopic examination of the fibrous papules of the oral mucosa or the enlarged gingivae shows a nonspecific fibrous hyperplasia. Similarly, the radiolucent jaw lesions consist of dense fibrous connective tissue that resembles desmoplastic fibroma or the simple type of central odontogenic fibroma. The angiofibroma of the skin is a benign aggregation of delicate fibrous connective tissue characterized by plump, uniformly spaced fibroblasts with numerous interspersed thin-walled vascular channels.

Treatment and Prognosis

For patients with tuberous sclerosis, most of the treatment is directed toward the management of the seizure disorder with anticonvulsant agents. Periodic MRI of the head may be done to screen for intracranial lesions, whereas ultrasound evaluation is performed for evaluation of kidney involvement. Intellectually disabled patients may have problems with oral hygiene procedures, and poor oral hygiene contributes to phenytoin-induced gingival hyperplasia. Recent studies examining medications (such as, everolimus) that block the metabolic pathway that causes tuberous sclerosis have shown significant shrinkage of several tumor types associated with this disorder, including renal angiomyolipoma, facial angiofibroma, and subependymal giant cell astrocytoma. Patients affected by tuberous sclerosis have a slightly reduced life span compared with the general population, with death usually related to CNS or kidney disease. Genetic counseling is also appropriate for affected patients, and genetic testing is available for both *TSC1* and *TSC2* mutations if prenatal or preimplantation family planning is desired.

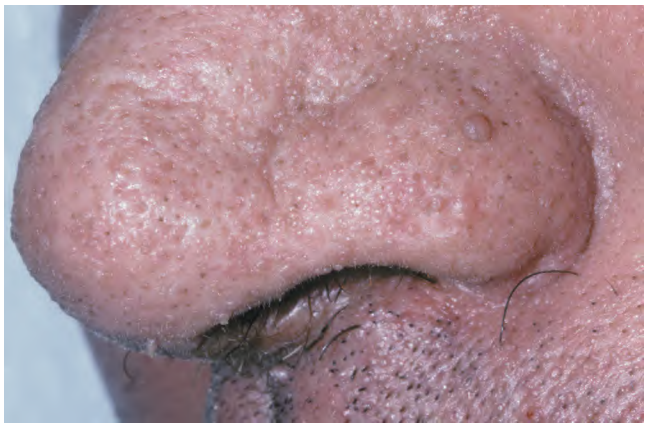
◆ MULTIPLE HAMARTOMA SYNDROME (COWDEN SYNDROME; *PTEN* HAMARTOMA-TUMOR SYNDROME)

Multiple hamartoma syndrome is a rare condition that has important implications for the affected patient, because malignancies, in addition to the benign hamartomatous growths, develop in a high percentage of these individuals. Usually, the syndrome is inherited as an autosomal dominant trait showing a high degree of penetrance and a range of expressivity. The gene responsible for this disorder has been mapped to chromosome 10, and a mutation of the *phosphatase and tensin homolog deleted on chromosome 10 (PTEN)* gene has been implicated in its pathogenesis. The estimated prevalence of this condition is approximately 1 in 200,000, and more than 300 affected patients have been described in the literature. In recent years, overlapping clinical features of multiple hamartoma syndrome with **Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome,** and **Proteus-like syndrome** have been noted, and all of these disorders have demonstrated mutations of the *PTEN* gene.

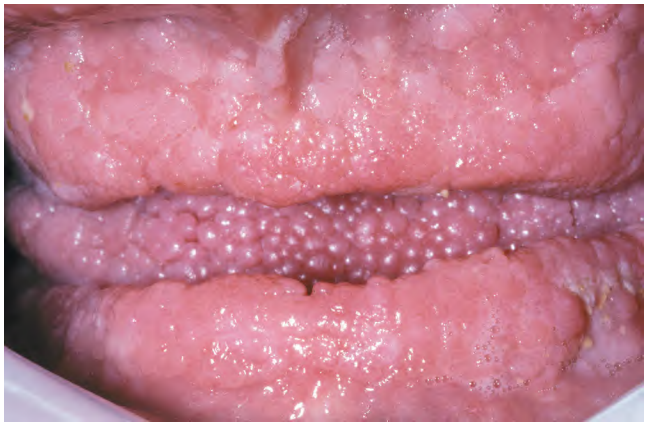
Clinical Features

Cutaneous manifestations are present in almost all patients with multiple hamartoma syndrome, usually developing during the second decade of life. The majority of the skin lesions appear as multiple, small (less than 1 mm) papules, primarily on the facial skin, especially around the mouth, nose, and ears (Fig. 16-39). Microscopically, most of these papules represent hair follicle hamartomas called **trichilemmomas.** Other commonly noted skin lesions are **acral keratosis,** a warty-appearing growth that develops on the dorsal surface of the hand, and **palmoplantar keratosis,** a prominent callus-like lesion on the palms or soles. Cutaneous **hemangiomas, neuromas, xanthomas,** and **lipomas** have also been described.

Other problems can appear in these patients as well. Thyroid disease usually appears as either a goiter or a thyroid adenoma, but papillary or follicular adenocarcinoma may develop. In one large series, thyroid malignancy was



• **Fig. 16-39 Multiple Hamartoma Syndrome.** These tiny cutaneous facial papules represent hair follicle hamartomas (trichilemmomas).



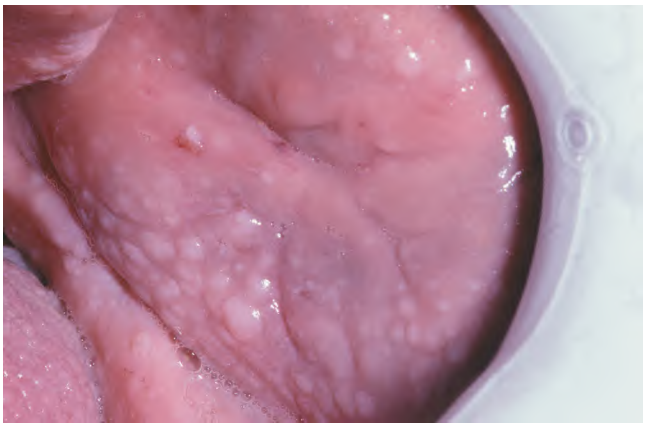
• **Fig. 16-40 Multiple Hamartoma Syndrome.** Multiple, irregular fibroepithelial papules involve the tongue *(center)* and alveolar ridge mucosa.

identified in 14% of patients with this condition. In women, fibrocystic disease of the breast is frequently observed. Unfortunately, breast cancer occurs with a relatively high frequency (25% to 50%) in these patients. The mean age at diagnosis of breast malignancy is 40 years, which is much younger than usual. In the gastrointestinal tract, multiple benign hamartomatous polyps may be present. In addition, several types of benign and malignant tumors of the female genitourinary tract occur more often than in the normal population.

The oral lesions vary in severity from patient to patient and usually consist of multiple papules affecting the gingivae, dorsal tongue, and buccal mucosa (Figs. 16-40 and 16-41). These lesions have been reported in more than 80% of affected patients and generally produce no symptoms. Other possible oral findings include a high-arched palate, periodontitis, and extensive dental caries, although it is unclear whether the latter two conditions are significantly related to the syndrome.

Histopathologic Features

The histopathologic features of the oral lesions are rather nonspecific, essentially representing fibroepithelial hyperplasia. Other lesions associated with this syndrome have their own characteristic histopathologic findings, depending on the hamartomatous or neoplastic tissue origin.



• **Fig. 16-41 Multiple Hamartoma Syndrome.** Multiple papules on the left buccal mucosa.

Diagnosis

The diagnosis can be based on the finding of two of the following three pathognomonic signs:

1. Multiple facial trichilemmomas
2. Multiple oral papules
3. Acral keratoses

A variety of other major and minor diagnostic criteria, as well as a positive family history, are also helpful in confirming the diagnosis. Genetic testing for mutations of the *PTEN* gene are clinically available, but 20% of patients who otherwise have characteristic multiple hamartoma syndrome will not demonstrate a genetic abnormality; therefore, a negative test does not necessarily preclude the diagnosis of multiple hamartoma syndrome.

Treatment and Prognosis

Treatment of multiple hamartoma syndrome is controversial. Although most of the tumors that develop are benign, the prevalence of malignancy is higher than in the general population; therefore, annual physical examinations should be performed that focus specifically on anatomic sites of increased tumor prevalence, particularly breast, uterus, and thyroid. Some investigators recommend bilateral prophylactic mastectomies as early as the third decade of life for female patients because of the associated increased risk of breast cancer.

◆ EPIDERMOLYSIS BULLOSA

The term **epidermolysis bullosa** describes a heterogeneous group of inherited blistering mucocutaneous disorders. Each has a specific defect in the attachment mechanisms of the epithelial cells, either to each other or to the underlying connective tissue. Recent advances in the understanding of

the clinical features, epidemiology, immunofluorescence mapping, and molecular genetic abnormalities of these conditions have led to the identification of approximately 34 different forms. Depending on the defective mechanism of cellular cohesion, there are four broad categories:

1. Simplex
2. Junctional
3. Dystrophic
4. Kindler syndrome

Each category consists of several forms of the disorder. A variety of inheritance patterns may be seen, depending on the particular form. The degree of severity can range from relatively mild, annoying forms, such as the **simplex** types, through a spectrum that includes severe, fatal disease. For example, many cases of **junctional** epidermolysis bullosa result in death at birth because of the significant sloughing of the skin during passage through the birth canal. Specific mutations in the genes encoding keratin 5 and keratin 14 have been identified as being responsible for most of the **simplex** types, whereas mutations in the genetic codes of laminin-332, type XVII collagen, or $\alpha 6\beta 4$ integrin have been documented for the **junctional** types. Most of the **dystrophic** types are caused by mutations in the genes responsible for type VII collagen production, with over 300 distinctly different mutations identified to date. **Kindler syndrome** is the most recently characterized pattern of this group of disorders, and mutations of the gene that encodes for a hemidesmosomal attachment protein, kindlin-1, are responsible for this rare condition.

A few representative examples of the types of epidermolysis bullosa are summarized in Table 16-2. Because oral lesions are most commonly observed in the dystrophic forms, this discussion centers on these forms. Dental abnormalities, such as anodontia, enamel hypoplasia, pitting of the enamel, neonatal teeth, severe periodontitis, and severe dental caries, have been variably associated with several of the different types of epidermolysis bullosa, although studies have suggested that the prevalence of dental abnormalities is significantly increased only with the **junctional** type. A disorder termed **epidermolysis bullosa acquisita** is mentioned because of the similarity of its name; however, this is an unrelated condition, having an autoimmune (rather than a genetic) origin (see page 721).

Clinical Features

Dominant Dystrophic Types

The **dystrophic** forms of epidermolysis bullosa that are inherited in an autosomal dominant fashion are not usually life threatening, although they may certainly be disfiguring and pose many problems. The initial lesions are vesicles or bullae, which are seen early in life and develop on areas exposed to low-grade, chronic trauma, such as the knuckles or knees (Fig. 16-42). The bullae rupture, resulting in erosions or ulcerations that ultimately heal with scarring. In the process, appendages such as fingernails may be lost.

The oral manifestations are typically mild, with some gingival erythema and tenderness. Gingival recession and reduction in the depth of the buccal vestibule may be observed (Fig. 16-43).

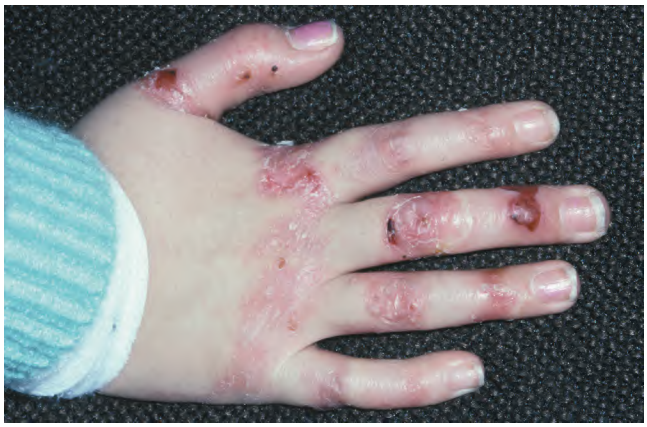
Recessive Dystrophic Types

Generalized recessive dystrophic epidermolysis bullosa represents one of the more debilitating forms of the disease. Vesicles and bullae form with even minor trauma. Secondary infections are often a problem because of the large surface areas that may be involved. If the patient manages

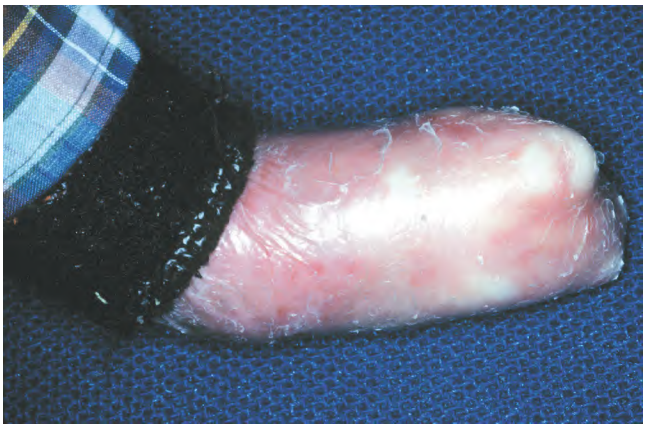
TABLE 16-2 Examples of Epidermolysis Bullosa

Form	Inheritance	Clinical Features	Defect
EB simplex	AD	Blistering of the hands and feet; mucosal involvement uncommon; blisters heal without scarring; prognosis usually good	Keratin gene defects
Junctional EB, generalized gravis variant	AR	Severe blistering at birth; granulation tissue around the mouth; oral erosions common; pitted enamel hypoplasia; often fatal (previously called *EB letalis*)	Defects of hemidesmosomes
Dominant, dystrophic EB, Pasini type	AD	Generalized blistering, white papules	Defect in type VII collagen
Dominant, dystrophic EB, Cockayne-Touraine type	AD	Extremities primarily affected	Defect in type VII collagen
Recessive, dystrophic EB, generalized gravis type	AR	Severe mucosal involvement; mittenlike scarring; deformities of hands and feet; patients usually do not survive past early adulthood	Defect in type VII collagen
Recessive, dystrophic EB, inverse type	AR	Involvement of groin and axilla; severe oral and esophageal lesions	Defect in type VII collagen

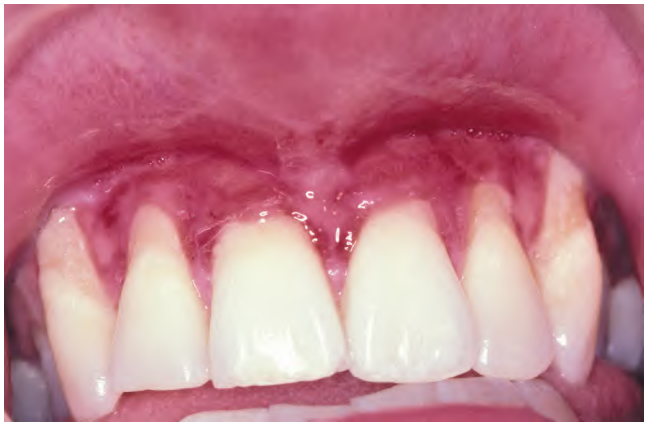
EB, Epidermolysis bullosa; *AD*, autosomal dominant; *AR*, autosomal recessive.



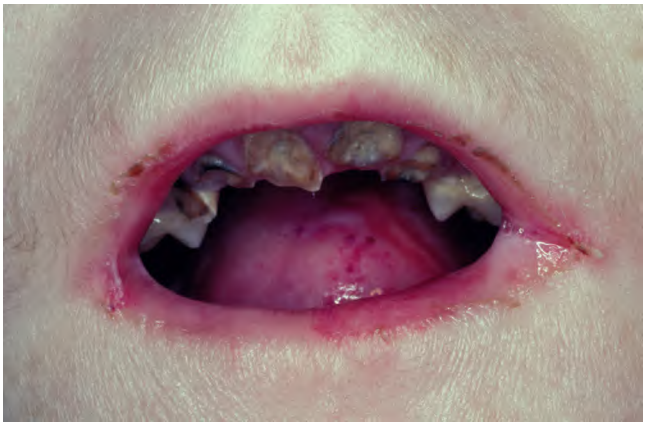
• **Fig. 16-42 Epidermolysis Bullosa.** A young girl, affected by the dominant dystrophic form of epidermolysis bullosa, shows the characteristic hemorrhagic bullae, scarring, and erosion associated with minimal trauma to the hands.



• **Fig. 16-44 Epidermolysis Bullosa.** A 19-year-old man, affected by recessive dystrophic epidermolysis bullosa, shows the typical mittenlike deformity of the hand caused by scarring of the tissue after damage associated with normal activity.



• **Fig. 16-43 Epidermolysis Bullosa.** A teenaged boy, affected by dominant dystrophic epidermolysis bullosa, shows a reduced depth of the labial vestibule caused by repeated mucosal tearing and healing with scarring.



• **Fig. 16-45 Epidermolysis Bullosa.** Same patient as depicted in Fig. 16-44. Microstomia has been caused by repeated trauma and healing with scarring. Note the severe dental caries activity associated with a soft cariogenic diet.

to survive into the second decade, then hand function is often greatly diminished because of the repeated episodes of cutaneous breakdown and healing with scarring, resulting in fusion of the fingers into a mittenlike deformity (Fig. 16-44).

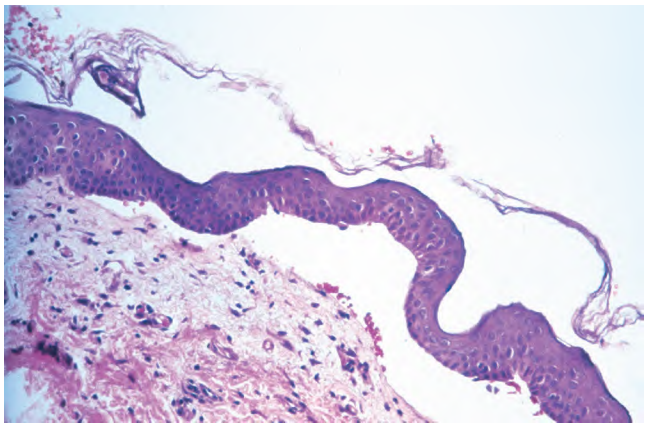
The oral problems are no less severe. Bulla and vesicle formation is induced by virtually any food having some degree of texture. Even with a soft diet, the repeated cycles of scarring often result in microstomia (Fig. 16-45) and ankyloglossia. Similar mucosal injury and scarring may cause severe stricture of the esophagus. Because a soft diet is usually highly cariogenic, carious destruction of the dentition at an early age is common.

Histopathologic Features

The histopathologic features of epidermolysis bullosa vary with the type being examined. The **simplex** form shows intraepithelial clefting by light microscopy. **Junctional, dystrophic,** and **Kindler** forms show subepithelial clefting (Fig. 16-46). Electron microscopic examination reveals clefting at the level of the lamina lucida of the basement membrane in the **junctional** forms and below the lamina densa of the basement membrane in the **dystrophic** forms. In contrast, the **Kindler** form shows clefting just below the basal cell layer, at its interface with the lamina lucida. Immunohistochemical evaluation of perilesional tissue is now typically used to identify specific defects to classify and subtype the condition further. Molecular genetic analysis may also be helpful for confirming the diagnosis in some instances.

Treatment and Prognosis

Treatment of epidermolysis bullosa varies with the type. For milder cases, no treatment other than local wound care may be needed. Sterile drainage of larger blisters and the use of topical antibiotics are often indicated in these situations. For the more severe cases, intensive management with oral antibiotics may be necessary if cellulitis develops; despite



• **Fig. 16-46 Epidermolysis Bullosa.** Complete separation of the epithelium from the connective tissue is seen in this photomicrograph of a tissue section obtained from a patient affected by a junctional form of epidermolysis bullosa.

intensive medical care, some patients die as a result of infectious complications.

The "mitten" deformity of the hands, seen in recessive dystrophic epidermolysis bullosa, can be corrected with plastic surgery, but the problem usually recurs after a period of time, and surgical intervention is required every 2 years on average. With esophageal involvement, dysphagia may be a significant problem, resulting in malnutrition and weight loss. Placement of a gastrostomy tube may be necessary at times. Patients with the recessive dystrophic forms are also predisposed to development of **cutaneous squamous cell carcinoma.** This malignancy often develops in areas of chronic ulceration during the second through third decades of life and represents a significant cause of death for these patients. Infrequently, the lingual mucosa of affected patients has been reported to undergo malignant transformation as well.

Management of the oral manifestations also depends on the type of the disease. For patients who are susceptible to mucosal bulla formation, dental manipulation should be kept to a minimum. To achieve this, topical 1% neutral sodium fluoride solution should be administered daily to prevent dental caries. A soft diet that is as noncariogenic as possible, as well as atraumatic oral hygiene procedures, should be encouraged. Maintaining adequate nutrition for affected patients is critical to ensure optimal wound healing. Endosseous dental implants, followed by fixed dental prostheses, have been successfully placed in some patients with recessive dystrophic epidermolysis bullosa.

If dental restorative care is required, the lips should be lubricated to minimize trauma. Injections for local anesthesia can usually be accomplished by depositing the anesthetic slowly and deeply within the tissues. For extensive dental care, endotracheal anesthesia may be performed without significant problems in most cases.

Unfortunately, because of the genetic nature of these diseases, no cure exists. Genetic counseling of affected families is indicated. Both prenatal diagnosis and preimplantation diagnosis are available as adjuncts to family planning.

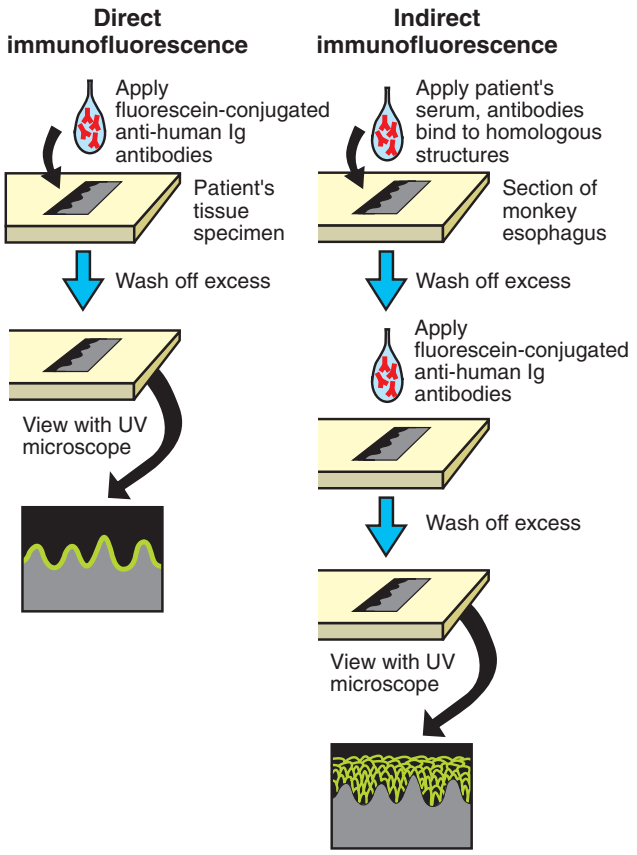
IMMUNE-MEDIATED DISEASES AND THEIR EVALUATION

Several conditions discussed in this chapter are the result of inappropriate production of antibodies by the patient (autoantibodies). These autoantibodies are directed against various constituents of the molecular apparatus that hold epithelial cells together or that bind the surface epithelium to the underlying connective tissue. The ensuing damage produced by the interaction of these autoantibodies with the host tissue is seen clinically as a disease process, often termed an **immunobullous** disease. Because each disease is characterized by production of specific types of autoantibodies, identification of the antibodies and the tissues against which they are targeted is important diagnostically. The two techniques that are widely used to investigate the immunobullous diseases are 1) direct immunofluorescence and 2) indirect immunofluorescence studies. Following is a brief overview of how they work.

Direct immunofluorescence is used to detect autoantibodies that are bound to the patient's tissue. Before testing can take place, several procedures must occur. Inoculating human immunoglobulins into a goat creates antibodies directed against these human immunoglobulins. The antibodies raised in response to the human immunoglobulins are harvested from the animal and tagged with fluorescein, a dye that glows when viewed with UV light. As illustrated on the left side of Fig. 16-47, a frozen section of the patient's tissue is placed on a slide, and this is incubated with fluorescein-conjugated goat antihuman antibodies. These antibodies bind to the tissue at any site where human immunoglobulin is present. The excess antibody suspension is washed off, and the section is then viewed with a microscope having a UV light source.

With indirect immunofluorescence studies, the patient is being evaluated for presence of antibodies that are circulating in the blood. As shown on the right side of Fig. 16-47, a frozen section of tissue that is similar to human oral mucosa (e.g., Old World monkey esophagus) is placed on a slide and incubated with the patient's serum. If there are autoantibodies directed against epithelial attachment structures in the patient's serum, then they will attach to the homologous structures on the monkey esophagus. The excess serum is washed off, and fluorescein-conjugated goat antihuman antibody is incubated with the section. The excess is washed off, and the section is examined with UV light to detect the presence of autoantibodies that might have been in the serum.

Examples of the molecular sites of attack of the autoantibodies are seen diagrammatically in Fig. 16-48. Each site is distinctive for a particular disease; however, the complexities of the epithelial attachment mechanisms are still being elucidated, and more precise mapping may be possible in the future. A summary of the clinical, microscopic, and



• **Fig. 16-47 Immunofluorescence Techniques.** Comparison of the techniques for direct and indirect immunofluorescence. The left side depicts the direct immunofluorescent findings in cicatricial pemphigoid, a disease that has autoantibodies directed toward the basement zone. The right side shows the indirect immunofluorescent findings for pemphigus vulgaris, a disease that has autoantibodies directed toward the intercellular areas between the spinous cells of the epithelium. *Ig,* Immunoglobulin; *UV,* ultraviolet.

immunopathologic features of the more important immune-mediated mucocutaneous diseases is found in Table 16-3.

◆ PEMPHIGUS

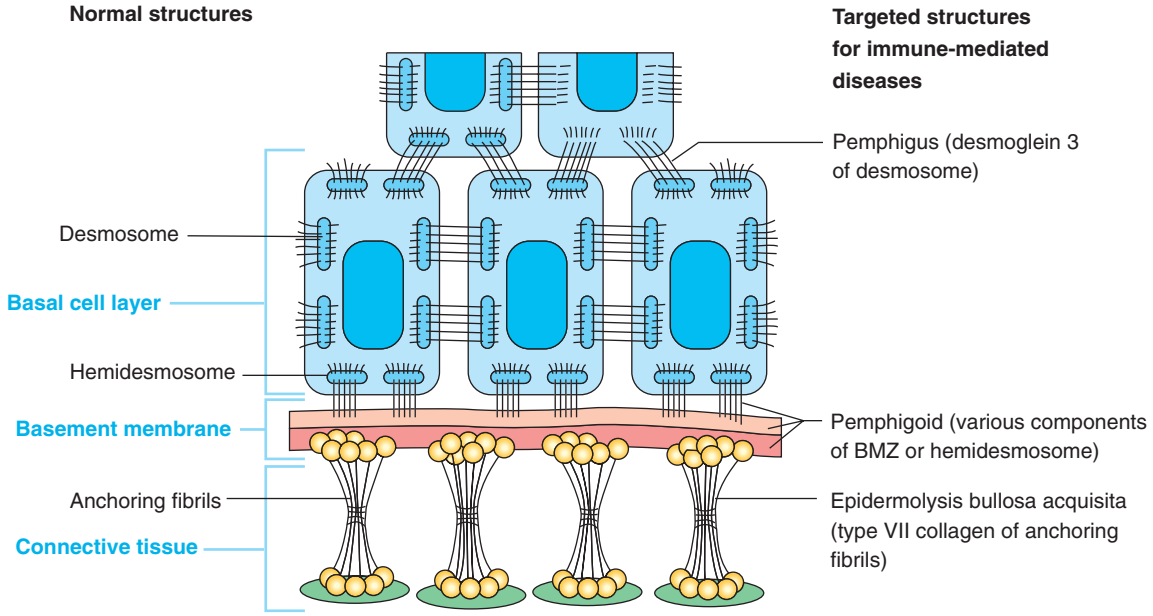
The condition known as **pemphigus** represents four related diseases of an autoimmune origin:

1. Pemphigus vulgaris
2. Pemphigus vegetans
3. Pemphigus erythematosus
4. Pemphigus foliaceus

Only the first two of these affect the oral mucosa, and the discussion is limited to **pemphigus vulgaris. Pemphigus vegetans** is rare; most authorities now feel it represents simply a variant of pemphigus vulgaris.

Pemphigus vulgaris is the most common of these disorders *(vulgaris* is Latin for *common).* Even so, it is not seen very often. The estimated incidence is one to five cases per million people diagnosed each year in the general population. Nevertheless, pemphigus vulgaris is an important condition because, if untreated, it often results in the patient's death. Furthermore, the oral lesions are often the first sign of the disease, and they are the most difficult to resolve with therapy. This has prompted the description of the oral lesions as "the first to show, and the last to go."

The blistering that typifies this disease is due to an abnormal production, for unknown reasons, of autoantibodies that are directed against the epidermal cell surface glycoproteins, desmoglein 3 and desmoglein 1. These desmogleins are components of **desmosomes** (structures that bond epithelial cells to each other), and the autoantibodies attach to these desmosomal components, effectively inhibiting the molecular interaction that is responsible for adherence. As



• **Fig. 16-48 Epithelial Attachment Apparatus.** Schematic diagram demonstrating targeted structures in several immune-mediated diseases. *BMZ,* Basement membrane zone.

TABLE 16-3 Chronic Vesiculoulcerative Diseases

Condition	Mean Age	Sex Predilection	Clinical Features	Histopathologic Features	Direct Immunofluorescence	Indirect Immunofluorescence
Pemphigus vulgaris	Fourth to sixth decade	Equal	Vesicles, erosions, and ulcerations on any oral mucosal or skin surface	Intraepithelial clefting	Positive intercellular	Positive
Paraneoplastic pemphigus	Sixth to seventh decade	Equal	Vesicles, erosions, and ulcerations on any mucosal or skin surface	Subepithelial and intraepithelial clefting	Positive, intercellular and basement membrane zone	Positive (rat bladder)
Mucous membrane pemphigoid	Sixth to seventh decade	Female	Primarily mucosal lesions	Subepithelial clefting	Positive, basement membrane zone	Negative
Bullous pemphigoid	Seventh to eighth decade	Equal	Primarily skin lesions	Subepithelial clefting	Positive, basement membrane zone	Positive
Erythema multiforme	Third to fourth decade	Male	Skin and mucosa involved; target lesions on skin	Subepithelial edema and perivascular inflammations	Nondiagnostic	Negative
Lichen planus	Fifth to sixth decade	Female	Oral and/or skin lesions; may or may not be erosive	Hyperkeratosis, saw-toothed rete ridges, bandlike infiltrate of lymphocytes	Fibrinogen, basement membrane zone	Negative

a result of this immunologic attack on the desmosomes, a split develops within the epithelium, causing a blister to form. Desmoglein 3 is preferentially expressed in the parabasal region of the epidermis and oral epithelium, whereas desmoglein 1 is found primarily in the superficial portion of the epidermis, with minimal expression in oral epithelium. Patients who have developed autoantibodies directed against desmoglein 3, with or without desmoglein 1, will histopathologically show intraepithelial clefting just above the basal layer, and clinically oral mucosal blisters of pemphigus vulgaris will form. Patients who develop autoantibodies directed against only desmoglein 1 will histopathologically show superficial intraepithelial clefting of the epidermis, but oral mucosa will not be affected. Clinically, the fine scaly red lesions of pemphigus foliaceus or pemphigus erythematosus will be evident.

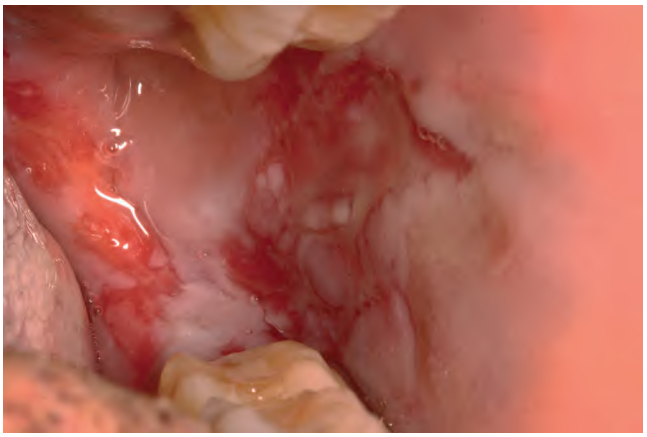
Occasionally, a pemphigus-like oral and cutaneous eruption may occur in patients taking certain medications (e.g., penicillamine, angiotensin-converting enzyme [ACE] inhibitors, nonsteroidal antiinflammatory drugs [NSAIDs]) or in patients with malignancy, especially lymphoreticular malignancies (so-called **paraneoplastic pemphigus**) (see page 716). Similarly, a variety of other conditions may produce chronic vesiculoulcerative or erosive lesions of the oral mucosa, and these often need to be considered in the differential diagnosis (see Table 16-3). In addition, a rare genetic condition termed **chronic benign familial pemphigus** or **Hailey-Hailey disease** may have erosive cutaneous lesions, but oral involvement in that process appears to be uncommon.

Clinical Features

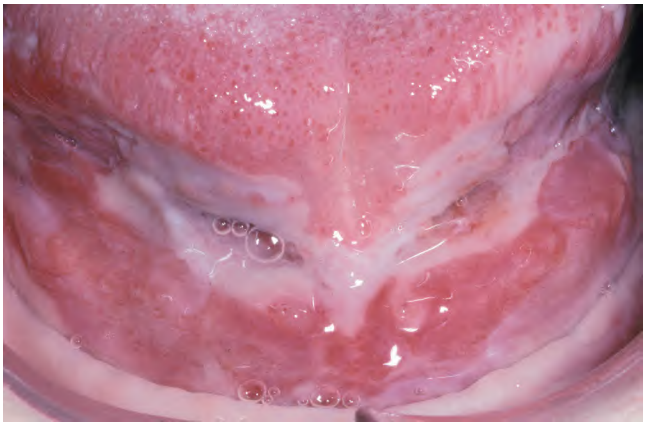
The initial manifestations of pemphigus vulgaris often involve the oral mucosa, typically in adults. The average age at diagnosis is 50 years, although rare cases may be seen in childhood. No sex predilection is observed, and the condition seems to be more common in persons of Mediterranean, South Asian, or Jewish heritage.

Patients usually complain of oral soreness, and examination shows superficial, ragged erosions and ulcerations distributed haphazardly on the oral mucosa (Figs. 16-49 to 16-52). Such lesions may affect virtually any oral mucosal location, although the palate, labial mucosa, buccal mucosa, ventral tongue, and gingivae are often involved. Patients rarely report vesicle or bulla formation intraorally, and such lesions can seldom be identified by the examining clinician, probably because of early rupture of the thin, friable roof of the blisters. More than 50% of the patients have oral mucosal lesions before the onset of cutaneous lesions, sometimes by as much as 1 year or more. Eventually, however, nearly all patients have intraoral involvement. The skin lesions appear as flaccid vesicles and bullae (Fig. 16-53) that rupture quickly, usually within hours to a few days, leaving an erythematous, denuded surface. Infrequently ocular involvement may be seen, usually appearing as bilateral conjunctivitis. Unlike cicatricial pemphigoid, the ocular lesions of pemphigus typically do not cause scarring and symblepharon formation (see page 719).

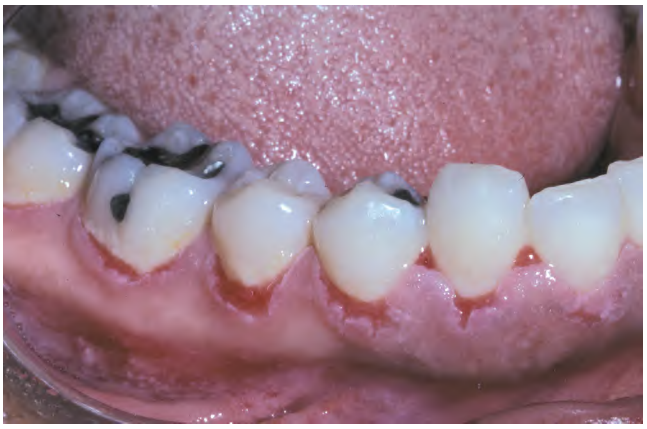
Without proper treatment, the oral and cutaneous lesions tend to persist and progressively involve more surface area. A characteristic feature of pemphigus vulgaris is that a bulla can be induced on normal-appearing skin if



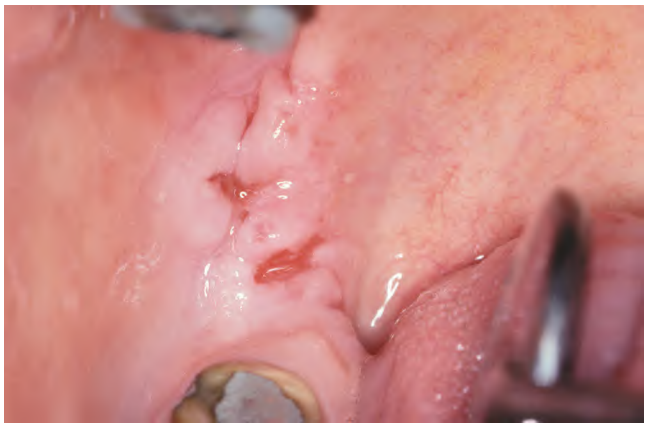
• **Fig. 16-49 Pemphigus Vulgaris.** Multiple erosions of the left buccal mucosa and soft palate.



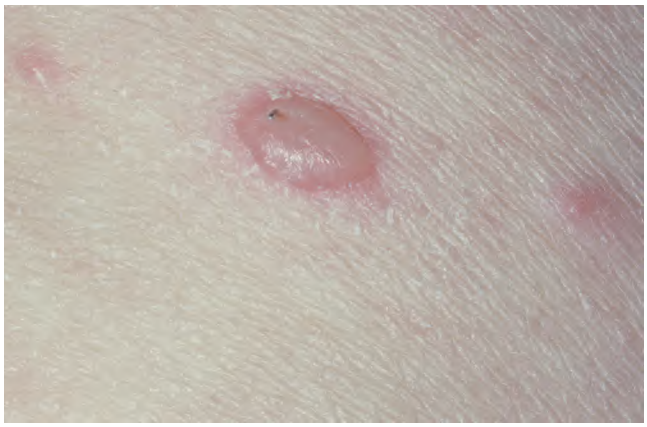
• **Fig. 16-50 Pemphigus Vulgaris.** Large, irregularly shaped ulcerations involving the floor of the mouth and ventral tongue.



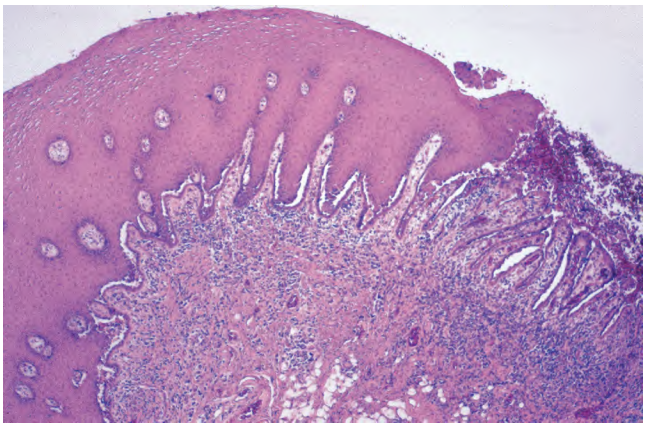
• **Fig. 16-51 Pemphigus Vulgaris.** Multiple erosions affecting the marginal gingiva.



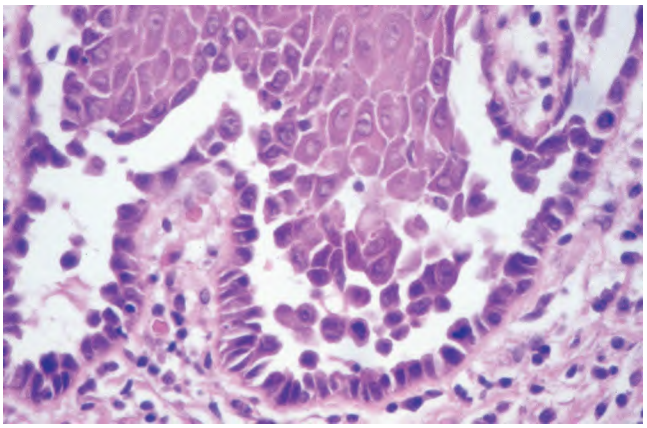
• **Fig. 16-52 Pemphigus Vulgaris.** The patient, with a known diagnosis of pemphigus vulgaris, had been treated with immunosuppressive therapy. The oral erosions shown here were the only persistent manifestation of her disease.



• **Fig. 16-53 Pemphigus Vulgaris.** This flaccid cutaneous bulla is characteristic of skin involvement.



• **Fig. 16-54 Pemphigus Vulgaris.** Low-power photomicrograph of perilesional mucosa affected by pemphigus vulgaris. An intraepithelial cleft is located just above the basal cell layer.



• **Fig. 16-55 Pemphigus Vulgaris.** High-power photomicrograph showing rounded, acantholytic epithelial cells sitting within the intraepithelial cleft.

firm lateral pressure is exerted. This is called a **positive Nikolsky sign.**

Histopathologic Features

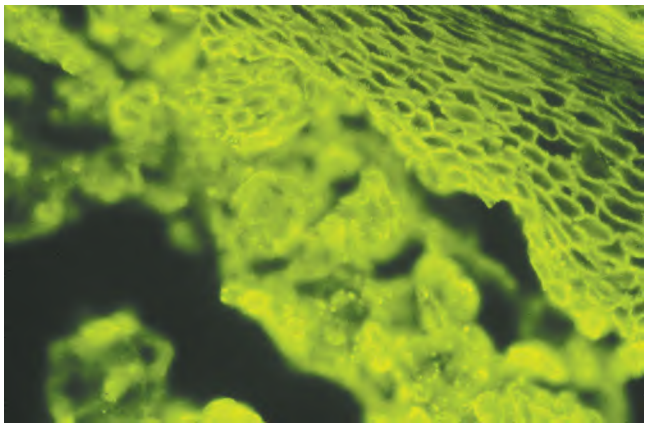
Biopsy specimens of perilesional tissue show characteristic intraepithelial separation, which occurs just above the basal cell layer of the epithelium (Fig. 16-54). Sometimes the entire superficial layers of the epithelium are stripped away, leaving only the basal cells, which have been described as resembling a "row of tombstones." The cells of the spinous layer of the surface epithelium typically appear to fall apart, a feature that has been termed **acantholysis,** and the loose cells tend to assume a rounded shape (Fig. 16-55). This feature of pemphigus vulgaris can be used in making a diagnosis based on the identification of these rounded cells **(Tzanck cells)** in an exfoliative cytologic preparation. A mild-to-moderate chronic inflammatory cell infiltrate is usually seen in the underlying connective tissue.

The diagnosis of pemphigus vulgaris should be confirmed by direct immunofluorescence examination of fresh perilesional tissue or tissue submitted in Michel's solution. With this procedure, antibodies (usually IgG or IgM) and complement components (usually C3) can be demonstrated in the intercellular spaces between the epithelial cells (Fig. 16-56) in almost all patients with this disease. Indirect immunofluorescence is also typically positive in 80% to 90% of cases, demonstrating the presence of circulating autoantibodies in the patient's serum. Enzyme-linked immunosorbent assays (ELISAs) have been developed to detect circulating autoantibodies as well.

It is critical that perilesional tissue be obtained for both light microscopy and direct immunofluorescence to maximize the probability of a diagnostic sample. If ulcerated mucosa is submitted for testing, then the results are often inconclusive because of either a lack of an intact interface between the epithelium and connective tissue or a great deal of nonspecific inflammation.

Treatment and Prognosis

A diagnosis of pemphigus vulgaris should be made as early in its course as possible because control is generally easier to achieve. Pemphigus is a systemic disease; therefore,



• **Fig. 16-56 Pemphigus Vulgaris.** Photomicrograph depicting the direct immunofluorescence pattern of pemphigus vulgaris. Immunoreactants are deposited in the intercellular areas between the surface epithelial cells, resulting in a "chicken wire" pattern.

treatment consists primarily of systemic corticosteroids (usually prednisone), often in combination with other immunosuppressive drugs (so-called steroid-sparing agents), such as mycophenolate mofetil or azathioprine. Although some clinicians have advocated the use of topical corticosteroids in the management of oral lesions, the observed improvement is undoubtedly because of the absorption of the topical agents, resulting in a greater systemic dose. The potential side effects associated with the long-term use of systemic corticosteroids are significant and include the following:

- Diabetes mellitus
- Adrenal suppression
- Weight gain
- Osteoporosis
- Peptic ulcers
- Severe mood swings
- Increased susceptibility to a wide range of infections

Ideally, a physician with expertise in immunosuppressive therapy should manage the patient. The most common approach is to use relatively high doses of systemic corticosteroids initially to clear the lesions, and then attempt to maintain the patient on as low a dose of corticosteroids as is necessary to control the condition. Often the clinician can monitor the success of therapy by measuring the titers of circulating autoantibodies using indirect immunofluorescence, because disease activity frequently correlates with the abnormal antibody levels. The use of rituximab, a monoclonal antibody that targets B-lymphocytes, represents another promising approach to managing this disease, as it targets the cells responsible for producing the autoantibodies that cause pemphigus.

Pemphigus may undergo complete resolution, although remissions and exacerbations are common. One study suggested that up to 75% of patients will have disease resolution after 10 years of treatment, although most centers report a remission rate of approximately 30%.

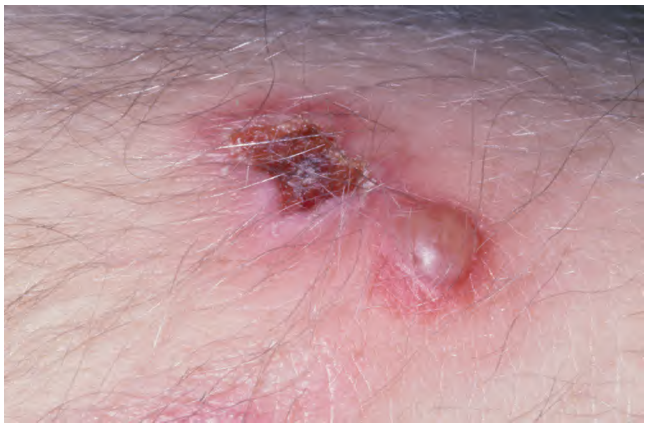
Before the development of corticosteroid therapy, as many as 60% to 90% of these patients died, primarily as a result of infections and electrolyte imbalances. Even today, the mortality rate associated with pemphigus vulgaris is in the range of 5% to 10%, usually because of the complications of long-term systemic corticosteroid use.

◆ PARANEOPLASTIC PEMPHIGUS (NEOPLASIA-INDUCED PEMPHIGUS; PARANEOPLASTIC AUTOIMMUNE MULTIORGAN SYNDROME)

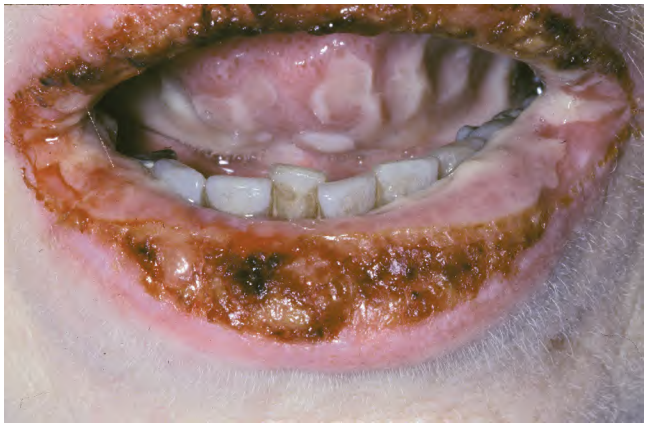
Paraneoplastic pemphigus is a rare vesiculobullous disorder that affects patients who have a neoplasm, usually **lymphoma** or **chronic lymphocytic leukemia.** Approximately 250 cases have been documented. Although the precise pathogenetic mechanisms are unknown, some evidence suggests abnormal levels of the cytokine, interleukin-6 (IL-6), could be produced by host lymphocytes in response to the patient's tumor. IL-6 may then be responsible for stimulating the abnormal production of antibodies directed against antigens associated with the desmosomal complex and the basement membrane zone of the epithelium. In addition to a variety of different antibodies that attack these epithelial adherence structures, some investigators have described cutaneous and mucosal damage that appears to be mediated by cytotoxic T lymphocytes in some cases of paraneoplastic pemphigus. As a result of this multifaceted immunologic attack, the disease manifests in an array of clinical features, histopathologic findings, and immunopathologic findings that may be perplexing if the clinician is unfamiliar with this condition.

Clinical Features

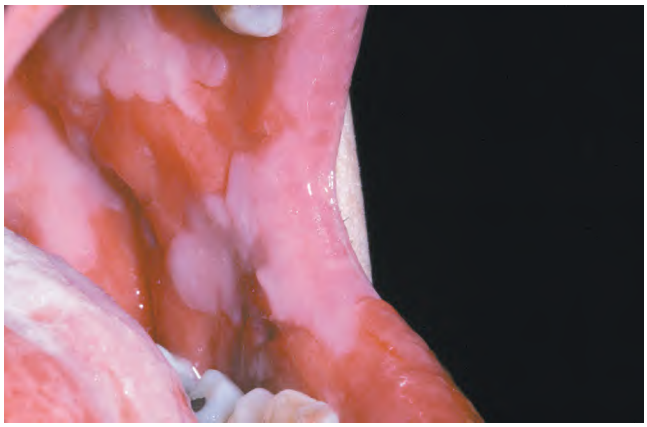
Patients typically have a history of a malignant lymphoreticular neoplasm, or less commonly, a benign lymphoproliferative disorder such as angiofollicular lymph node hyperplasia (Castleman disease). In approximately one-third of reported cases, paraneoplastic pemphigus developed before a neoplasm was identified, thus signaling the presence of a tumor. The neoplastic disease may or may not be under control at the time of onset of the paraneoplastic condition. Signs and symptoms of paraneoplastic pemphigus usually begin suddenly and may appear polymorphous. In some instances, multiple vesiculobullous lesions affect the skin (Fig. 16-57) and oral mucosa. Palmar or plantar bullae may be evident, a feature that is uncommon in pemphigus vulgaris. For other patients, skin lesions can appear more papular and pruritic, similar to cutaneous lichen planus. The lips often show hemorrhagic crusting similar to that of erythema multiforme (Fig. 16-58). Oral mucosal involvement is an early, consistent feature of paraneoplastic pemphigus, and patients develop multiple areas of erythema and diffuse, irregular ulceration (Fig. 16-59), affecting virtually any oral mucosal surface. If the lesions remain



• **Fig. 16-57 Paraneoplastic Pemphigus.** The bulla and crusted ulcerations on this patient's arm are representative of the polymorphous cutaneous lesions.



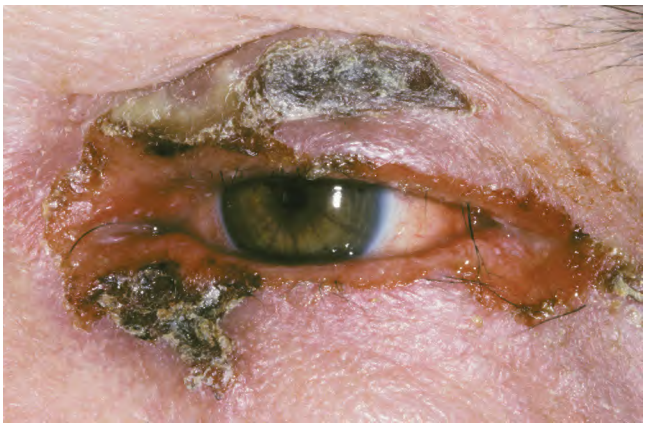
• **Fig. 16-58 Paraneoplastic Pemphigus.** Crusted, hemorrhagic lip lesions may be mistaken for erythema multiforme or herpes simplex infection.



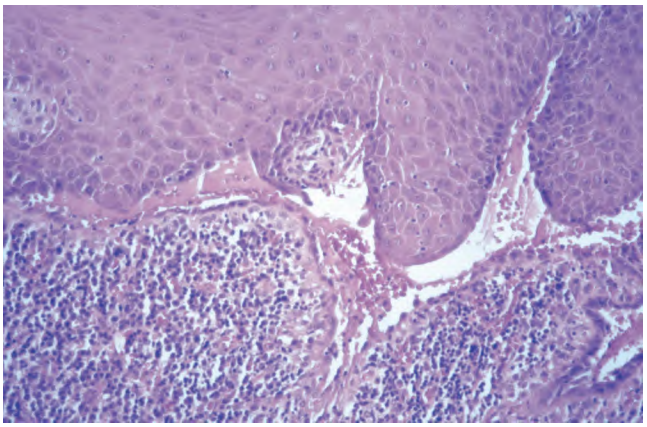
• **Fig. 16-59 Paraneoplastic Pemphigus.** These diffuse oral ulcerations are quite painful.

untreated, then they persist and worsen. Some patients may develop only oropharyngeal lesions, without cutaneous involvement.

Other mucosal surfaces are also commonly affected, with 70% of patients having involvement of the conjunctival mucosa. In this area, a cicatrizing (scarring) conjunctivitis develops, similar to that seen with cicatricial pemphigoid (Fig. 16-60). The anogenital, nasopharyngeal, esophageal, and respiratory tract mucosa may also be involved. Involvement of the bronchiolar mucosa is particularly significant because the lining epithelium sloughs and occludes the bronchiolar lumina and the alveoli of the lung, resulting in a condition known as **bronchiolitis obliterans.**



• **Fig. 16-60 Paraneoplastic Pemphigus.** Ocular involvement.



• **Fig. 16-61 Paraneoplastic Pemphigus.** This medium-power photomicrograph shows both intraepithelial and subepithelial clefting.

Histopathologic Features

The features of paraneoplastic pemphigus on light microscopic examination may be as diverse as the clinical features. In most cases, a lichenoid mucositis is seen, usually with subepithelial clefting (like pemphigoid) or intraepithelial clefting (like pemphigus) (Fig. 16-61).

Direct immunofluorescence studies may show a weakly positive deposition of immunoreactants (IgG and complement) in the intercellular zones of the epithelium and/or a linear deposition of immunoreactants at the basement membrane zone. Although antibodies directed against desmoglein 1 and 3, as well as the bullous pemphigoid antigens are often produced, antibodies directed against the plakin family of desmosomal components are more commonly identified and are more specific for paraneoplastic

pemphigus. ELISA or immunoblotting techniques are used to confirm the presence of antibodies directed against periplakin or envoplakin specifically. If these tests are not available, then indirect immunofluorescence can be conducted using a transitional type of epithelium (e.g., rat urinary bladder mucosa) as the substrate due to its rich expression of plakins. This technique shows a fairly specific pattern of antibody localization to the intercellular areas of the epithelium. Examples of paraneoplastic pemphigus that show only a lichenoid reaction with no demonstrable autoantibody production have infrequently been described.

Treatment and Prognosis

Paraneoplastic pemphigus is often a very serious condition with a high morbidity and mortality rate, with some series having a mortality rate of 90%. For the infrequent cases associated with a benign lymphoproliferative condition, surgical removal of the tumor may result in regression of the paraneoplastic pemphigus. For those cases associated with malignancy, treatment usually consists of systemic prednisone combined with cyclosporine. Cyclophosphamide, another immunosuppressive agent, may be added to this regimen, although other immunosuppressive and immune-modulating drugs are also being evaluated. As with pemphigus vulgaris, the skin lesions usually respond more quickly to treatment than the oral lesions. Unfortunately, although the immunosuppressive therapy often manages to control the autoimmune disease, this immunosuppression often seems to trigger a reactivation of the malignant neoplasm. Thus a high mortality rate is seen, with patients succumbing to complications of the vesiculobullous lesions, complications of immune suppressive therapy, respiratory failure due to bronchiolitis obliterans, or progression of malignant disease. Occasionally, long-term survivors are reported, but these seem to be in the minority. As more of these patients are identified, therapeutic strategies can be better evaluated and modified for optimal care in the future.

◆ MUCOUS MEMBRANE PEMPHIGOID (CICATRICIAL PEMPHIGOID; BENIGN MUCOUS MEMBRANE PEMPHIGOID)

Evidence has accumulated to suggest that **mucous membrane pemphigoid** represents a group of chronic, blistering, mucocutaneous autoimmune diseases in which tissue-bound autoantibodies are directed against one or more components of the basement membrane. As such, this condition has a heterogeneous origin, with autoantibodies being produced against any one of a variety of basement membrane components, all of which produce similar clinical manifestations. The precise prevalence is unknown, but most authors believe that it is at least twice as common as pemphigus vulgaris.

The term **pemphigoid** is used because clinically it often appears similar (the meaning of the *-oid* suffix) to **pemphigus.** The prognosis and microscopic features of pemphigoid, however, are very different.

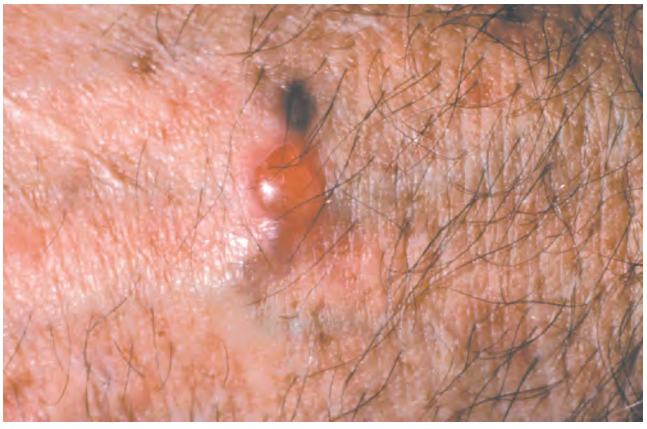
Although a variety of terms have been used over the decades to designate this condition, a group of experts from both medicine and dentistry met in 1999 and came to an agreement that **mucous membrane pemphigoid** would be the most appropriate name for the disease. **Cicatricial pemphigoid,** another commonly used name for this process, is derived from the word **cicatrix,** meaning *scar.* When the conjunctival mucosa is affected, the scarring that results is the most significant aspect of this disorder because it invariably results in blindness unless the condition is recognized and treated. Interestingly, the oral lesions seldom exhibit this tendency for scar formation.

Clinical Features

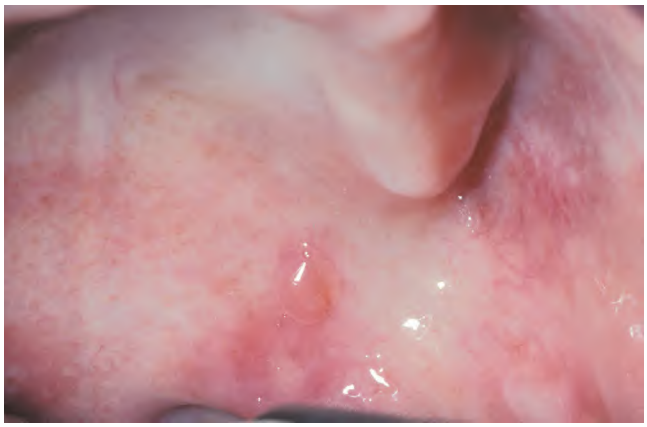
Mucous membrane pemphigoid usually affects older adults, with an average age of 50 to 60 years at the onset of disease. Females are affected more frequently than males by a 2:1 ratio. Oral lesions are seen in most patients, but other sites, such as conjunctival, nasal, esophageal, laryngeal, and vaginal mucosa, as well as the skin (Fig. 16-62), may be involved.

The oral lesions of pemphigoid begin as either vesicles or bullae that may occasionally be identified clinically (Fig. 16-63). In contrast, patients with pemphigus rarely display such blisters. The most likely explanation for this difference is that the pemphigoid blister forms in a subepithelial location, producing a thicker, stronger roof than the intraepithelial, acantholytic pemphigus blister. Eventually, the oral blisters rupture, leaving large, superficial, ulcerated, and denuded areas of mucosa (Fig. 16-64). The ulcerated lesions are usually painful and persist for weeks to months if untreated.

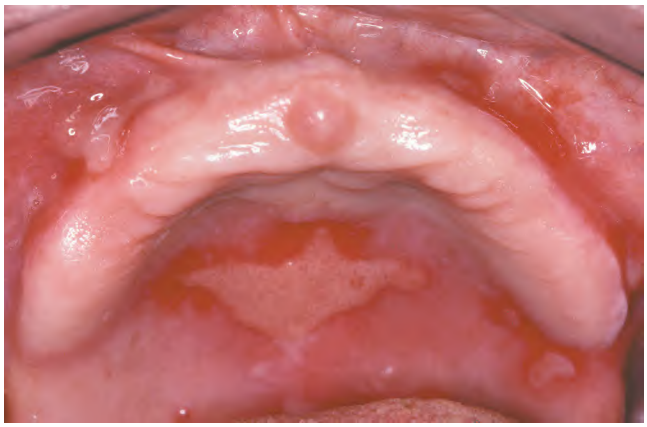
Often this process is seen diffusely throughout the mouth, but it may be limited to certain areas, especially the gingiva (Fig. 16-65). Gingival involvement produces a clinical reaction pattern termed **desquamative gingivitis**



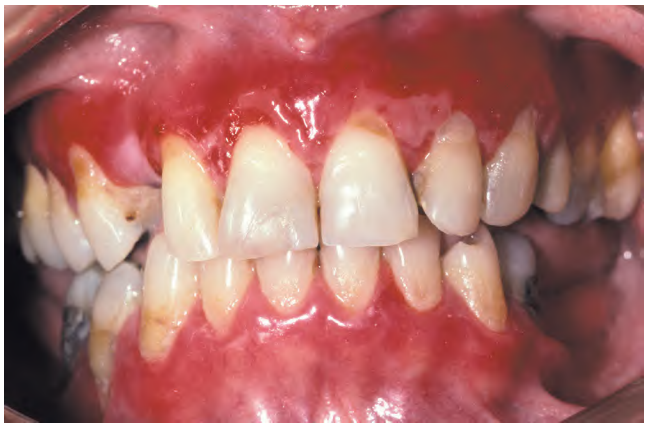
• **Fig. 16-62 Mucous Membrane Pemphigoid.** Although cutaneous lesions are not common, tense bullae such as these may develop on the skin of 20% of affected patients. (Courtesy of Dr. Charles Camisa.)



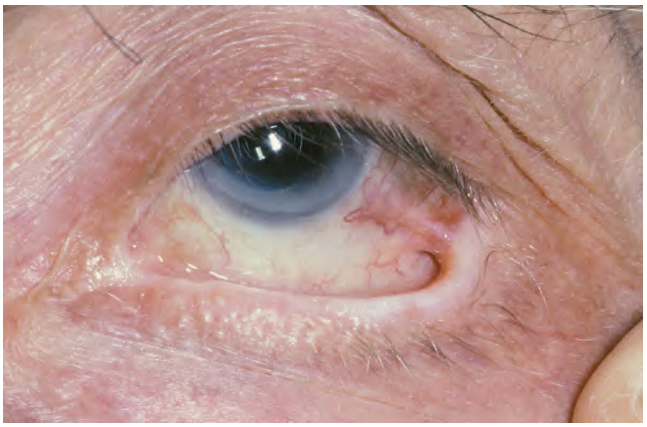
• **Fig. 16-63 Mucous Membrane Pemphigoid.** One or more intraoral vesicles, as seen on the soft palate, may be detected in patients with cicatricial pemphigoid. Usually, ulcerations of the oral mucosa are also present.



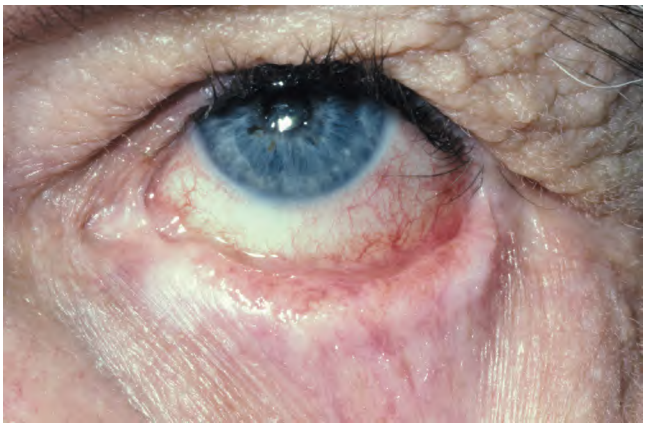
• **Fig. 16-64 Mucous Membrane Pemphigoid.** Large, irregular oral ulcerations characterize the lesions after the initial bullae rupture.



• **Fig. 16-65 Mucous Membrane Pemphigoid.** Often the gingival tissues are the only affected site, resulting in a clinical pattern known as *desquamative gingivitis.* Such a pattern may also be seen with lichen planus and pemphigus vulgaris.



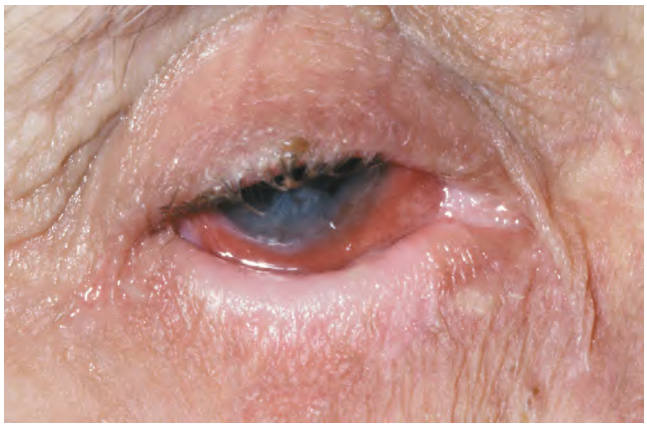
• **Fig. 16-66 Mucous Membrane Pemphigoid.** Although the earliest ocular changes are difficult to identify, patients with ocular involvement may show adhesions (symblepharons) between the bulbar and palpebral conjunctivae before severe ocular damage occurs.



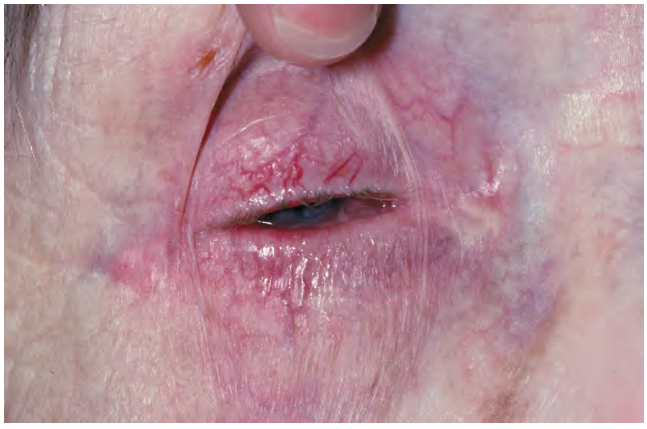
• **Fig. 16-67 Mucous Membrane Pemphigoid.** The disease has caused the upper eyelid of this patient to turn inward (entropion), resulting in the eyelashes rubbing against the eye itself (trichiasis). Also note the obliteration of the lower fornix of the eye.

(see page 148). This pattern may also be seen in other conditions, such as **erosive lichen planus** or, much less frequently, **pemphigus vulgaris.**

The most significant complication of mucous membrane pemphigoid, however, is ocular involvement. Although exact figures are not available, up to 25% of patients with oral lesions may eventually develop ocular disease. One eye may be affected before the other. The earliest change is subconjunctival fibrosis, which usually can be detected by an ophthalmologist using slit-lamp microscopic examination. As the disease progresses, the conjunctiva becomes inflamed and eroded. Attempts at healing lead to scarring between the bulbar (lining the globe of the eye) and palpebral (lining the inner surface of the eyelid) conjunctivae. Adhesions called **symblepharons** result (Fig. 16-66). Without treatment the inflammatory changes become more severe, although conjunctival vesicle formation is rarely seen (Fig. 16-67). Scarring can ultimately cause the eyelids to



• **Fig. 16-68 Mucous Membrane Pemphigoid.** A patient with ocular involvement shows severe conjunctival inflammation. An ophthalmologist removed the lower eyelashes because of trichiasis associated with entropion.

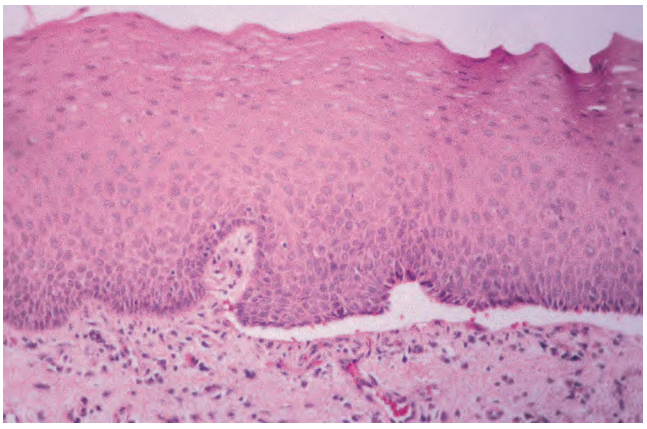


• **Fig. 16-69 Mucous Membrane Pemphigoid.** In this patient, the ocular involvement has resulted in nearly complete scarring between the conjunctival mucosa and the eyelids themselves, producing blindness.

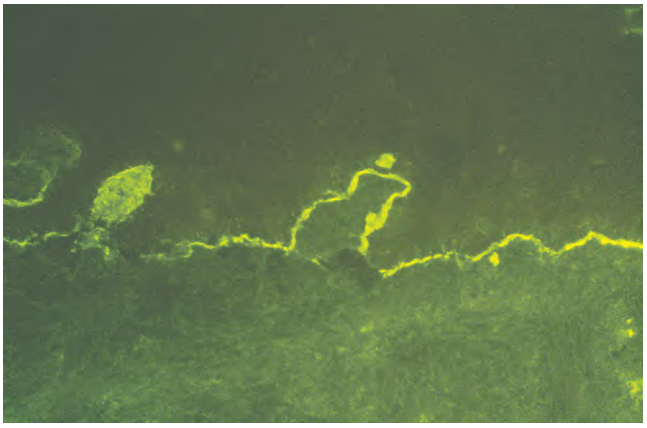
turn inward **(entropion).** This causes the eyelashes to rub against the cornea and globe **(trichiasis)** (Fig. 16-68). The scarring closes off the openings of the lacrimal glands as well, and with the loss of tears, the eye becomes extremely dry. The cornea then produces keratin as a protective mechanism; however, keratin is an opaque material, and blindness ensues. End-stage ocular involvement may also be characterized by adhesions between the upper and lower eyelids themselves (Fig. 16-69).

Other mucosal sites may also be involved and cause considerable difficulty for the patient. In females, the vaginal mucosal lesions may cause considerable pain during attempts at intercourse **(dyspareunia).**

Laryngeal lesions, which are fairly uncommon, may be especially significant because of the possibility of airway obstruction by the bullae that are formed. Patients who experience a sudden change in vocalization or who have difficulty breathing should undergo examination with laryngoscopy.



• **Fig. 16-70 Mucous Membrane Pemphigoid.** Medium-power photomicrograph of perilesional tissue shows characteristic subepithelial clefting.



• **Fig. 16-71 Mucous Membrane Pemphigoid.** Direct immunofluorescence studies show a deposition of immunoreactants at the basement membrane zone of the epithelium. (Courtesy of Dr. Ronald Grimwood.)

Histopathologic Features

Biopsy of perilesional mucosa shows a split between the surface epithelium and the underlying connective tissue in the region of the basement membrane (Fig. 16-70). A mild chronic inflammatory cell infiltrate is present in the superficial submucosa.

Direct immunofluorescence studies of perilesional mucosa show a continuous linear band of immunoreactants at the basement membrane zone in nearly 90% of affected patients (Fig. 16-71). The immune deposits consist primarily of IgG and C3, although IgA and IgM may also be identified. One study has suggested that, when IgG and IgA deposits are found in the same patient, the disease may be more severe. All of these immunoreactants may play a role in the pathogenesis of the subepithelial vesicle formation by weakening the attachment of the basement membrane through a variety of mechanisms, including complement activation with recruitment of inflammatory cells, particularly neutrophils.

Indirect immunofluorescence is positive in only 5% to 25% of these patients, indicating a relatively consistent lack of readily detectable circulating autoantibodies. One type of mucous membrane pemphigoid produces low levels of circulating autoantibodies to epiligrin (laminin-5), a component of the basement membrane. Antiepiligrin mucous membrane pemphigoid seems to have more widespread involvement, affecting oral, nasal, ocular, and laryngeal mucosa, compared with other forms of mucous membrane pemphigoid. In contrast, another group of investigators has shown that pemphigoid patients with only oral mucosal involvement have circulating autoantibodies to α6 integrin, a component of the hemidesmosome.

For an accurate diagnosis, perilesional tissue—rather than the ulcerated lesion itself—should be obtained. Often the epithelium in the area of the lesion is so loosely attached that it strips off as the clinician attempts to perform the biopsy. Such tissue is not usually adequate for diagnostic purposes because the interface between the epithelium and connective tissue is no longer intact (although some investigators have shown positive immunofluorescence with this tissue).

Other relatively rare conditions can mimic pemphigoid histopathologically. These include **linear IgA bullous dermatosis, angina bullosa hemorrhagica,** and **epidermolysis bullosa acquisita.**

Linear IgA Bullous Dermatosis

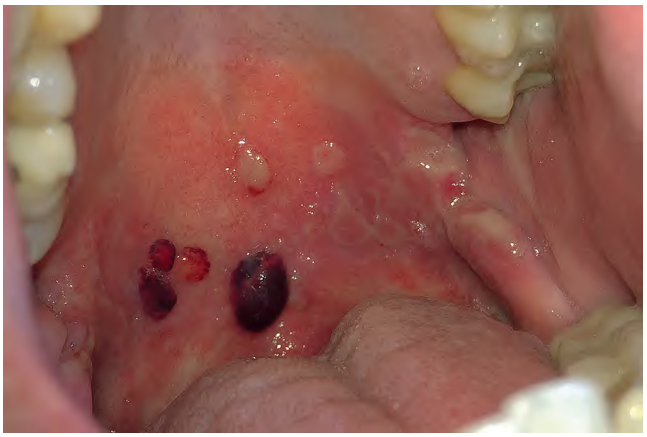
Linear IgA bullous dermatosis, as the name indicates, is characterized by the linear deposition of only IgA along the basement membrane zone. Even though some cases of mucous membrane pemphigoid may have IgA antibodies, linear IgA bullous dermatosis predominantly affects the skin and, therefore, can usually be distinguished from mucous membrane pemphigoid on a clinical basis.

Angina Bullosa Hemorrhagica

Angina bullosa hemorrhagica is a rare, poorly characterized oral mucosal disorder that exhibits variably painful, blood-filled vesicles or bullae, usually affecting the soft palate of middle-aged or older adults (Fig. 16-72). The blisters typically rupture spontaneously and heal without scarring. A subepithelial cleft is noted microscopically. No hematologic or immunopathologic abnormalities have been detected, and although the cause is unknown, many patients have a history of trauma or corticosteroid inhaler use.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita is an immunologically mediated condition characterized by autoantibodies directed against type VII collagen, the principal component of the anchoring fibrils. The anchoring fibrils play an important role in bonding the epithelium to the underlying connective tissue. As a result, their immunologic destruction leads to the formation of bullous lesions of the skin and mucosa with minimal trauma. The disease was named epidermolysis bullosa acquisita ("acquisita" means "acquired") because of its clinical resemblance to the inherited condition, dystrophic epidermolysis bullosa. Unlike the inherited disorder, epidermolysis bullosa acquisita typically affects middle-aged or older adults.



• **Fig. 16-72 Angina Bullosa Hemorrhagica.** Hemorrhagic blisters on the soft palate in a patient who regularly used a corticosteroid inhaler. (Courtesy of Dr. Peter Lyu.)

Oral lesions are present in nearly 50% of the cases, although such lesions are uncommon in the absence of cutaneous lesions. To distinguish epidermolysis bullosa acquisita from other immunobullous diseases with subepithelial clefting, a special technique is performed. A sample of the patient's perilesional skin is incubated in a concentrated salt solution; this causes the epithelium to separate from the connective tissue, forming an artificially induced bulla. Immunohistochemical evaluation shows deposition of IgG autoantibodies on the floor (connective tissue side) of the bulla where type VII collagen resides. This finding is in contrast to that of most forms of mucous membrane pemphigoid, in which the autoantibodies are usually localized to the roof of the induced blister.

Treatment and Prognosis

Once the diagnosis of mucous membrane pemphigoid has been established by light microscopy and direct immunofluorescence, the patient should be referred to an ophthalmologist who is familiar with the ocular lesions of this condition for a baseline examination of the conjunctivae. This should be done whether or not the patient is experiencing ocular complaints. In addition, if the patient is experiencing symptoms at other anatomic sites, then the appropriate specialist should be consulted.

Because this condition is characterized by heterogeneous pathogenetic mechanisms, it is not surprising that treatments advocated over the years have been varied. In fact, there is no single good therapy for every patient; treatment must be individualized, depending on lesional distribution, disease activity, and therapeutic response. Perhaps as the

various forms of pemphigoid are better defined immunopathologically, more specific, directed therapy can be devised.

Topical Agents

If only oral lesions are present, sometimes the disease can be controlled with application of one of the more potent topical corticosteroids to the lesions several times each day. Once control is achieved, the applications can be discontinued, although the lesions are certain to flare up again. Sometimes alternate-day application prevents such exacerbations of disease activity.

Patients with only gingival lesions often benefit from good oral hygiene measures, which can help to decrease the severity of the lesions and reduce the amount of topical corticosteroids required. As an additional aid in treating gingival lesions, a flexible mouth guard may be fabricated to use as a carrier for the corticosteroid medication.

Systemic Agents

If topical corticosteroids are unsuccessful, systemic treatments are available. Dapsone, which is a sulfa drug derivative, can be used to treat patients with mild-to-moderate involvement by mucous membrane pemphigoid. Systemic treatment with dapsone typically has fewer serious side effects when compared to systemic corticosteroid therapy, for example.

Some centers report good results with dapsone, but others observe that a minority of patients respond adequately. Contraindications to its use include glucose-6-phosphate dehydrogenase deficiency or allergy to sulfa drugs.

Another alternative systemic therapy that may be used for patients with less severe disease is tetracycline or minocycline and niacinamide (nicotinamide). Systemic daily divided doses of 0.5 to 2.0 g of each drug have been reported (in open-label trials) to be effective in controlling mucous membrane pemphigoid. Double-blind, placebo-controlled studies on larger groups of patients should be done to confirm this form of therapy, however.

For more severely affected patients with mucous membrane pemphigoid, corticosteroids plus other immunosuppressive/immune modulating agents, (such as, rituximab, mycophenolate mofetil, or cyclophosphamide) may be used. This type of aggressive treatment is often indicated in the presence of advancing ocular disease, but it must be realized that many of these patients are older and may have preexisting medical conditions that may preclude aggressive immune suppression. Some studies have suggested that treatment with intravenous (IV) human immunoglobulin (which is very expensive) may be more effective in managing ocular lesions of pemphigoid than systemic corticosteroid therapy. Attempts at surgical correction of any symblepharons that might have formed must be done when the disease is under control or quiescent; otherwise, the manipulation often induces an acute flare of the ocular lesions.

BULLOUS PEMPHIGOID

Bullous pemphigoid is the most common of the autoimmune blistering conditions, occurring at an estimated rate of ten cases per million population per year. The disease is characterized by the production of autoantibodies directed against components of the basement membrane. In many respects, bullous pemphigoid resembles **mucous membrane pemphigoid,** but most investigators note that there are enough differences to consider these diseases as distinct but related entities. One significant difference is that the clinical course in patients with bullous pemphigoid is usually characterized by periods of remission followed by relapse, whereas the course in patients with mucous membrane pemphigoid is usually protracted and progressive.

Clinical Features

Bullous pemphigoid typically develops in older people; most patients are between 75 and 80 years of age. No sex or racial predilection is generally reported, although one group of investigators noted that men are overrepresented in this disease by a 2:1 margin when one corrects for the skewing of the aging population toward the female gender. Pruritus is often an early symptom. This is followed by the development of multiple, tense bullae on either normal or erythematous skin (Fig. 16-73). These lesions eventually rupture after several days, causing a superficial crust to form. Eventually, healing takes place without scarring.

Oral mucosal involvement is uncommon, with approximately 10% to 20% of patients being affected. The oral lesions, like the skin lesions, begin as bullae, but they tend to rupture sooner, probably as a result of the constant low-grade trauma to which the oral mucosa is subjected. Large, shallow ulcerations with smooth, distinct margins are present after the bullae rupture (Fig. 16-74).

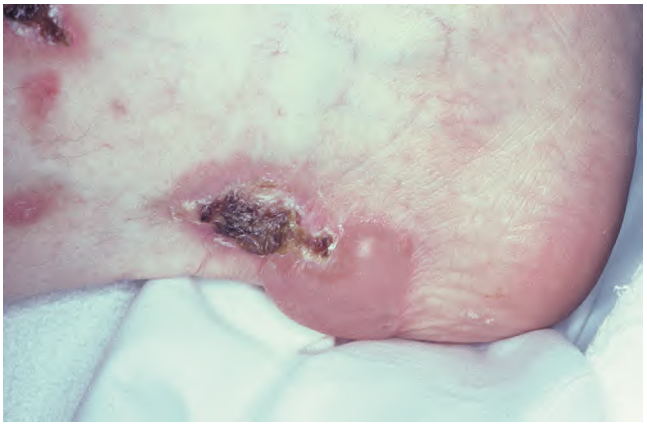
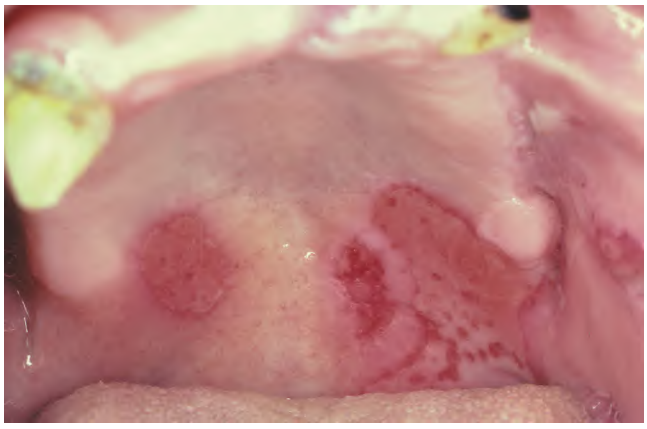


Fig. 16-73 Bullous Pemphigoid. Cutaneous vesiculobullous lesions of the heel. The bullae eventually rupture, leaving hemorrhagic crusted areas.



• **Fig. 16-74 Bullous Pemphigoid.** These oral lesions appear as large, shallow ulcerations involving the soft palate.

Histopathologic Features

Microscopic examination of tissue obtained from the perilesional margin of a bulla shows separation of the epithelium from the connective tissue at the basement membrane zone, resulting in a subepithelial separation. Modest numbers of both acute and chronic inflammatory cells are typically seen in the lesional area, and the presence of eosinophils within the bulla itself is characteristic.

Direct immunofluorescence studies show a continuous linear band of immunoreactants, usually IgG and C3, localized to the basement membrane zone in 90% to 100% of affected patients. These antibodies bind to proteins associated with **hemidesmosomes,** structures that bind the basal cell layer of the epithelium to the basement membrane and the underlying connective tissue. These proteins have been designated as **bullous pemphigoid antigens (BP180 and BP230),** and immunoelectron microscopy has demonstrated the localization of BP180 to the upper portion of the lamina lucida of the basement membrane.

In addition to the tissue-bound autoantibodies, 50% to 90% of the patients also have circulating autoantibodies in the serum, producing an indirect immunofluorescent pattern that is identical to that of the direct immunofluorescence. Unlike pemphigus vulgaris, the antibody titers seen in bullous pemphigoid do not appear to correlate with disease activity. The antibodies alone do not appear to be capable of inducing bullae in this disease. Instead, binding of the antibodies to the basement membrane initiates the complement cascade, which in turn results in degranulation of mast cells, with recruitment of neutrophils and eosinophils to the area. The damage to the basement membrane is thought to be mediated by elastases and matrix metalloproteinases released by these inflammatory cells.

Treatment and Prognosis

Treatment of patients with mild or localized bullous pemphigoid consists of application of one of the stronger topical corticosteroid preparations. Management of the patient with moderate-to-severe, widespread bullous pemphigoid consists of systemic immunosuppressive therapy. Moderate daily doses of systemic prednisone usually control the condition, after which alternate-day therapy may be given to reduce the risk of corticosteroid complications. If the lesions do not respond to prednisone alone, then another immunosuppressive agent (such as, azathioprine, methotrexate, or mycophenolate mofetil) may be added to the regimen. Dapsone, a sulfa derivative, may be used as an alternative therapeutic agent, and tetracycline and niacinamide therapy is reported to be effective for some patients. The more severe, resistant cases require prednisone combined with cyclophosphamide; however, this regimen has the potential for significant side effects.

The prognosis is generally good with respect to control of the skin lesions, with many patients experiencing remission. Recent reports based on a relatively large series of bullous pemphigoid patients have suggested that problems frequently develop due to the immunosuppressive therapy used in this older adult population. Mortality rates that are three times that of an age- and sex-matched control population may be seen, with approximately 20% of patients expiring 1 year after diagnosis.

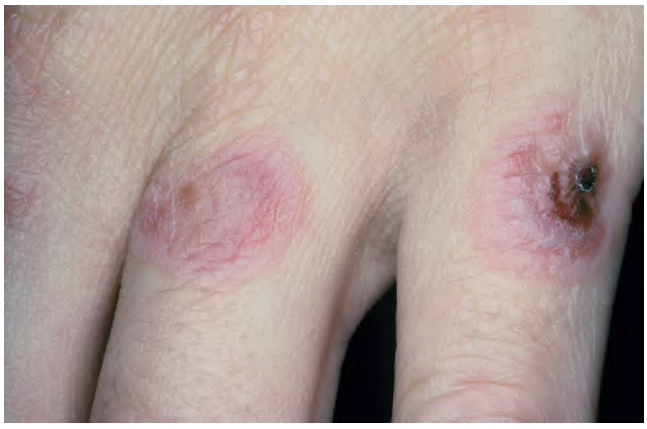
◆ ERYTHEMA MULTIFORME

Erythema multiforme is a blistering, ulcerative mucocutaneous condition of uncertain etiopathogenesis. This is probably an immunologically mediated process, although the cause is poorly understood. In about 50% of the cases, the clinician can identify an apparent precipitating cause, usually a preceding infection, such as **herpes simplex** or ***Mycoplasma pneumoniae,*** or less commonly, exposure to any one of a variety of drugs and medications, particularly antibiotics or analgesics. These agents may trigger the immunologic derangement that produces the disease. Sophisticated techniques in molecular biology have demonstrated the presence of herpes simplex DNA in patients with recurrent erythema multiforme, thus supporting the concept of an immunologic precipitating event. Interestingly, direct and indirect immunofluorescence studies are nonspecific and are not really very useful diagnostically except to rule out other vesiculobullous diseases.

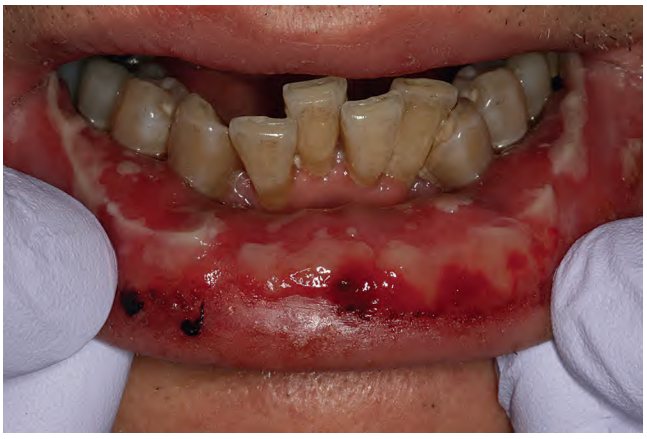
For many years it was thought that erythema multiforme exhibited a spectrum of severity, ranging from **erythema multiforme minor** through **erythema multiforme major** (traditionally thought to be synonymous with **Stevens-Johnson syndrome**) and **toxic epidermal necrolysis (Lyell disease).** Most authorities currently feel that erythema multiforme minor and major may represent a distinctly different process from the latter two conditions. Therefore, Stevens-Johnson syndrome and toxic epidermal necrolysis will be discussed separately in the next section.

Clinical Features

Erythema multiforme typically has an acute onset and usually affects young adults in their 20s or 30s, with a slight



• **Fig. 16-75 Erythema Multiforme.** The concentric erythematous pattern of the cutaneous lesions on the fingers resembles a target or bull's-eye.



• **Fig. 16-76 Erythema Multiforme.** Focal hemorrhagic crusting of the lips is seen in conjunction with diffuse shallow ulcerations and erosions involving this patient's mandibular labial mucosa.

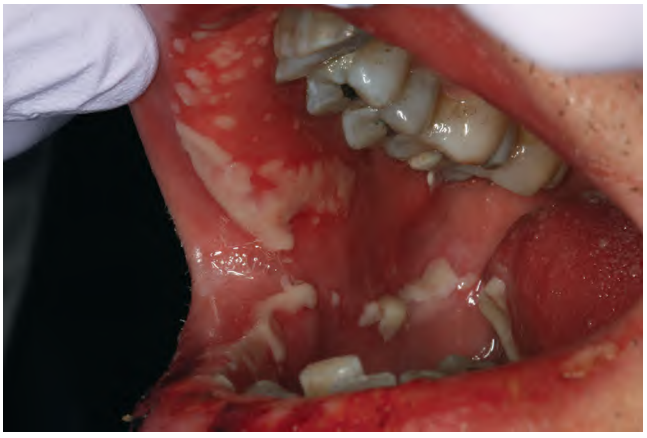
female predilection in current series of cases. Prodromal symptoms are often present and include fever, malaise, headache, cough, and sore throat, occurring approximately 1 week before onset. The condition may show varying degrees of severity in affected patients. Milder cases, known as **erythema multiforme minor,** usually begin with the development of slightly elevated, round, dusky-red patches on the skin of the extremities. These lesions may have a variety of appearances, however *(multiforme* means *many forms).* Some of these skin lesions develop features that are highly characteristic for the disease. These lesions appear as concentric circular erythematous rings resembling a target or bull's-eye **(target lesions)** (Fig. 16-75). In more severe cases, these may evolve into bullae with necrotic centers.

The oral cavity is the most frequently involved mucosal site, although the conjunctival, genitourinary, and respiratory mucosa also may be affected. Involvement of extraoral mucosal areas is usually associated with the more severe form of this condition, erythema multiforme major.

The frequency of oral involvement is difficult to determine and is reported to range from 25% to 70%. Discrepancies in the prevalence may be due to referral patterns or degree of scrutiny of the oral mucosa. The oral lesions begin as erythematous patches that undergo epithelial necrosis and evolve into large, shallow erosions and ulcerations with irregular borders (Fig. 16-76). Hemorrhagic crusting of the vermilion zone of the lips is common (Fig. 16-77). These oral lesions, like the skin lesions, emerge quickly and are uncomfortable. Sometimes patients are dehydrated because they are unable to ingest liquids as a result of mouth pain. The ulcerations often have a diffuse distribution. The lips, labial mucosa, buccal mucosa, tongue, floor of the mouth, and soft palate are the most common sites of involvement. Usually, the gingivae and hard palate are relatively spared.

Erythema Multiforme Major

A diagnosis of *erythema multiforme major* can be made if two or more mucosal sites are affected in conjunction with widespread skin lesions. In most cases the oral mucosa is involved in addition to either the ocular (Fig. 16-78) or genital mucosae. With severe ocular involvement, scarring (symblepharon formation) may occur, similar to that in cicatricial pemphigoid (see page 719).



• **Fig. 16-77 Erythema Multiforme.** Same patient as Figure 16-76. Diffuse shallow ulcerations of varying sizes are noted on the right buccal mucosa. The patient had finished a course of sulfamethoxazole and trimethoprim for a urinary tract infection a few days before the onset of the lesions.

Histopathologic Features

Histopathologic examination of the perilesional mucosa in erythema multiforme reveals a pattern that is characteristic but not pathognomonic. Subepithelial or intraepithelial vesiculation may be seen in association with necrotic basal keratinocytes (Fig. 16-79). A mixed inflammatory infiltrate is present, consisting of lymphocytes, neutrophils, and often eosinophils. Sometimes these cells are arranged in a perivascular orientation (Fig. 16-80). Because the immunopathologic features are also nonspecific, the diagnosis is often based on the clinical presentation and the exclusion of other vesiculobullous disorders.

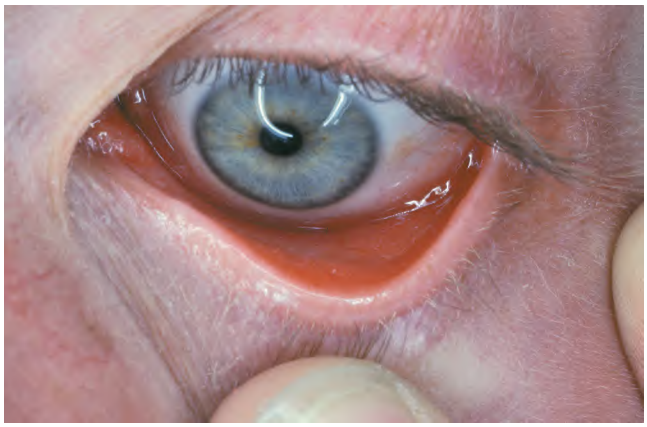


Fig. 16-78 Erythema Multiforme Major. While involvement of other mucosal surfaces is more frequently seen with Stevens-Johnson syndrome, this patient's condition was preceded by oral herpetic infection. This finding, combined with his cutaneous manifestations, resulted in a diagnosis of erythema multiforme major, in this case causing the severe conjunctivitis depicted in this photograph.

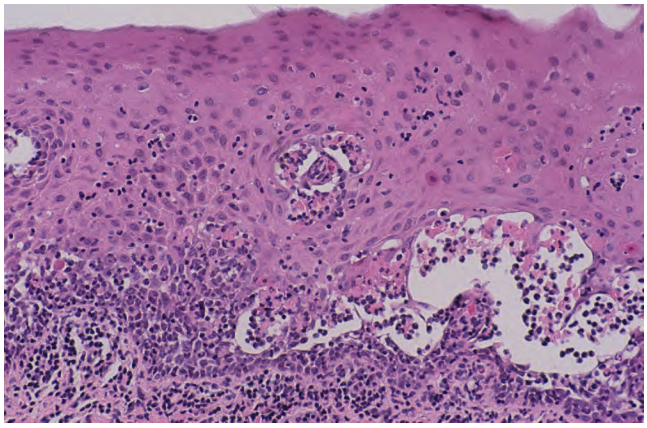


Fig. 16-79 Erythema Multiforme. This medium-power photomicrograph shows inflammation and intraepithelial vesicle formation in the basilar portion of the epithelium. Numerous necrotic and apoptotic eosinophilic keratinocytes are present in the blister area.

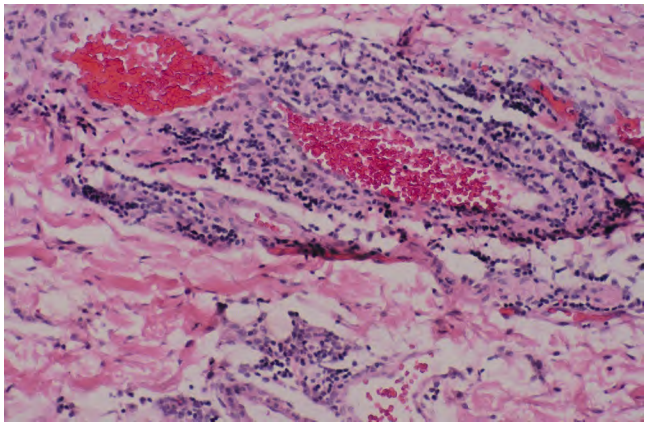


Fig. 16-80 Erythema Multiforme. This medium-power photomicrograph shows the perivascular inflammatory infiltrate, typically seen in erythema multiforme.

Treatment and Prognosis

Management of erythema multiforme, in many respects, remains controversial. In the past, the use of systemic or topical corticosteroids was often advocated, especially in the early stages of the disease. Although there is little good clinical evidence from controlled trials that such treatment is beneficial, this treatment is typically used at most centers. If a causative drug is identified or suspected, then it should be discontinued immediately.

If the patient is dehydrated as a result of an inability to eat because of oral pain, then IV rehydration may be necessary along with topical anesthetic agents to decrease discomfort.

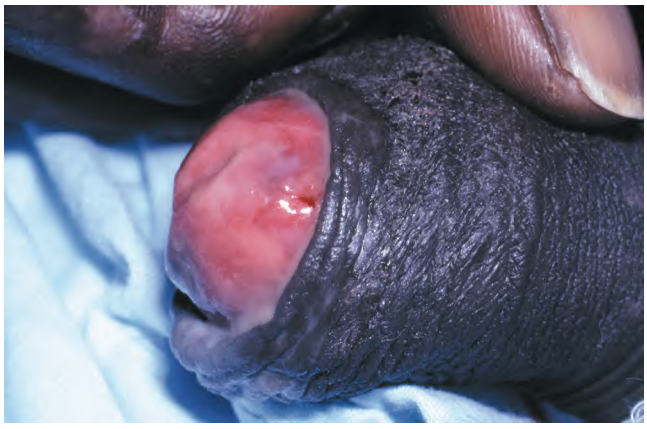
Even though the disease is self-limiting, usually lasting 2 to 6 weeks, about 20% of patients experience recurrent episodes, usually in the spring and autumn. If recurrent episodes of erythema multiforme are a problem, then an initiating factor, such as recurrent herpesvirus infection or drug exposure, should be sought. If disease is triggered by herpes simplex, then continuous oral acyclovir or valacyclovir therapy can prevent recurrences. Very infrequently patients may have continuous lesions of erythema multiforme. In most cases erythema multiforme is not life-threatening except in its most severe form.

◆ STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

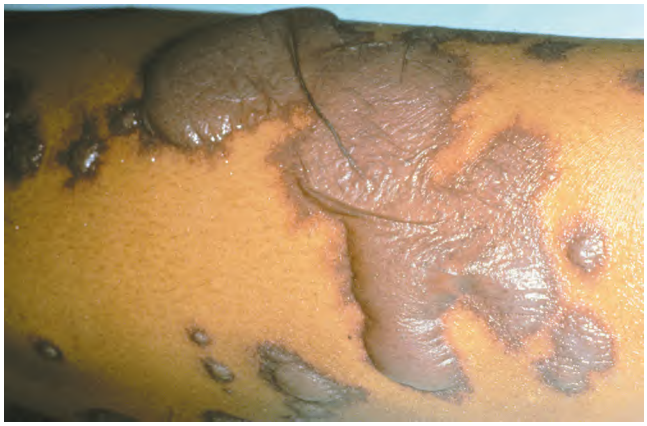
In the past, many dermatologists considered Stevens-Johnson syndrome and toxic epidermal necrolysis to represent the most severe end of the erythema multiforme spectrum. As careful documentation of the clinical features of these uncommon diseases was compiled, it became evident that there were subtle, but distinct, differences between these two conditions. Although the inciting event in erythema multiforme is usually a herpesvirus infection, Stevens-Johnson syndrome and toxic epidermal necrolysis are almost always triggered by drug exposure, with more than 200 different medications having been implicated. Recent studies have shown that the damage to the epithelium is due to increased apoptosis of the epithelial cells, and several mechanisms have been postulated to account for this phenomenon.

Clinical Features

The difference between Stevens-Johnson syndrome and toxic epidermal necrolysis is the degree of skin involvement, with Stevens-Johnson syndrome having less than 10% of the body surface affected by lesions, and toxic epidermal necrolysis having more than 30% involvement. These severe blistering diseases are rare. Stevens-Johnson syndrome occurs at an average rate of one to seven cases per million population per year, whereas toxic epidermal necrolysis occurs at a rate of about one case per million per year. In



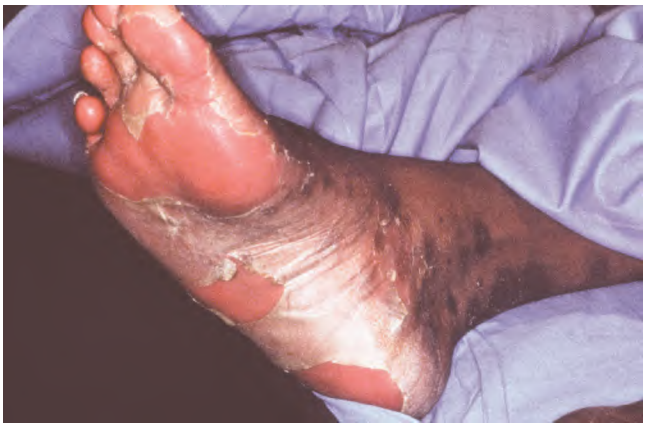
• **Fig. 16-81 Stevens-Johnson Syndrome.** Genital ulcerations, demonstrated in this patient by the involvement of the glans penis, may be a component of Stevens-Johnson syndrome, which tends to be more severe than erythema multiforme major.



• **Fig. 16-82 Toxic Epidermal Necrolysis.** This serious mucocutaneous disorder is characterized by diffuse bullous skin lesions. (Courtesy of Dr. Peter Larsen.)

contrast to Stevens-Johnson syndrome, which is usually seen in younger patients, toxic epidermal necrolysis tends to occur in people over 60 years of age. A female predilection is observed.

These patients usually have flu-like prodromal signs and symptoms, including fever, malaise, sore throat, headache, and loss of appetite. Within a few days, skin lesions begin to develop, but unlike erythema multiforme, the cutaneous lesions of Stevens-Johnson syndrome and toxic epidermal necrolysis initially appear on the trunk, presenting as erythematous macules (completely flat). Within 1 to 14 days, however, sloughing of the skin and flaccid bullae develop. Virtually all of these patients will have mucosal sites of involvement (Fig. 16-81), particularly the oral mucosa. Diffuse sloughing of a significant proportion of the skin and mucosal surfaces makes it appear as if the patient had been badly scalded (Figs. 16-82 and 16-83). If the patient survives, then the cutaneous process resolves in 3 to 5 weeks; however, oral lesions may take longer to heal, and significant residual ocular damage is evident in half of the patients.



• **Fig. 16-83 Toxic Epidermal Necrolysis.** The desquamation of the skin of the foot is characteristic of the diffuse sloughing cutaneous lesions. (Courtesy of Dr. Peter Larsen.)

Histopathologic Features

Biopsy of a developing bulla of Stevens-Johnson syndrome or toxic epidermal necrolysis typically shows a subepithelial blister that is characterized by degenerating, necrotic basal keratinocytes. The underlying connective tissue usually supports a rather sparse population of chronic inflammatory cells.

Treatment and Prognosis

One of the most important aspects in managing patients with Stevens-Johnson syndrome and toxic epidermal necrolysis is identifying and immediately discontinuing any drug that might be initiating the condition. Because the lesions of toxic epidermal necrolysis are analogous to those suffered by burn patients, management of these patients in the burn unit of the hospital is recommended. Corticosteroids should be avoided in the management of toxic epidermal necrolysis because some investigators have found that such drugs may be detrimental. IV administration of pooled human immunoglobulins has been shown in several open-label trials to produce remarkable resolution of toxic epidermal necrolysis, presumably because of blockade of Fas ligand, which is believed to play a role in inducing epithelial cell apoptosis. The mortality rate in patients with toxic epidermal necrolysis historically has been approximately 25% to 30%; the rate in those with Stevens-Johnson syndrome is 1% to 5%.

◆ ERYTHEMA MIGRANS (GEOGRAPHIC TONGUE; BENIGN MIGRATORY GLOSSITIS; WANDERING RASH OF THE TONGUE; ERYTHEMA AREATA MIGRANS; STOMATITIS AREATA MIGRANS)

Erythema migrans is a common benign condition that primarily affects the tongue. It is often detected on routine

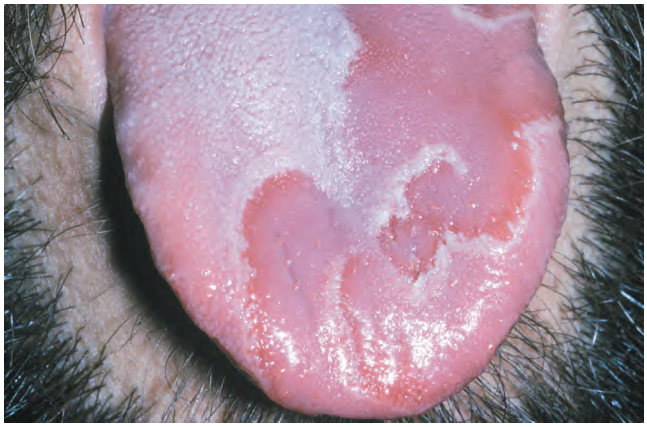
examination of the oral mucosa. The lesion occurs in 1% to 3% of the population. Some epidemiologic studies have shown that females are affected more frequently than males by a 2:1 ratio, whereas other series do not identify a gender predilection. Patients occasionally may consult a health care professional if they happen to notice the unusual appearance of their tongue or if the lingual mucosa becomes sensitive to hot or spicy foods as a result of the process.

Even though erythema migrans has been documented for many years, the etiopathogenesis is still unknown. Some investigators have suggested that erythema migrans occurs with increased frequency in atopic individuals; however, one large epidemiologic study in the United States found no statistically significant association between erythema migrans and a variety of conditions that had previously been postulated either to cause or influence this process. Erythema migrans was not seen as frequently in cigarette smokers, while there seemed to be no significant differences in frequency related to age, sex, oral contraceptive use, presence of allergies, diabetes mellitus, or psychological or dermatologic conditions. A similar study in Turkey essentially agreed with these findings, with the exception of an association with a history of allergy or atopy.

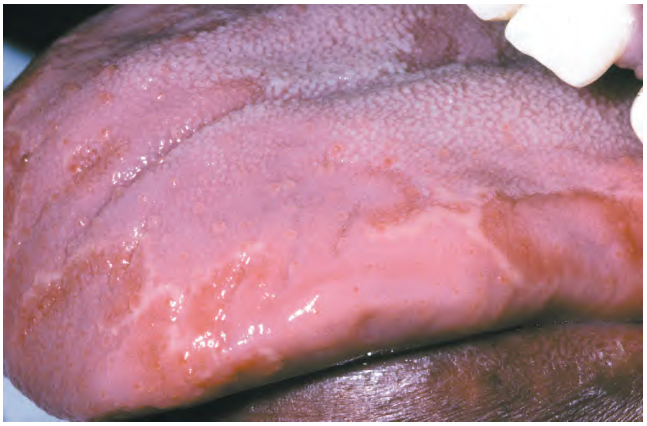
Clinical Features

The characteristic lesions of erythema migrans are seen on the anterior two-thirds of the dorsal tongue mucosa. They appear as multiple, well-demarcated zones of erythema (Figs. 16-84 and 16-85), concentrated at the tip and lateral borders of the tongue. This erythema is due to atrophy of the filiform papillae, and these atrophic areas are typically surrounded at least partially by a slightly elevated, yellow-white, serpentine or scalloped border (Fig. 16-86). The patient who is aware of the process is often able to describe the lesions as appearing quickly in one area, healing within a few days or weeks, and then developing in a very different area. Frequently, the lesion begins as a small white patch, which then develops a central erythematous atrophic zone and enlarges centrifugally. Approximately one-third of patients with **fissured tongue** (see page 11) are affected with erythema migrans as well. Some patients may have only a solitary lesion, but this is uncommon. The lesions are usually asymptomatic, although a burning sensation or sensitivity to hot or spicy foods may be noted when the lesions are active. Only rarely is the burning sensation more constant and severe.

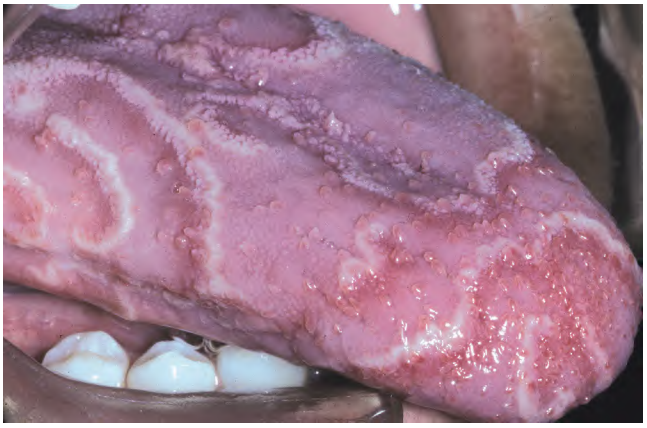
Very infrequently, erythema migrans may occur on oral mucosal sites other than the tongue. In these instances, the tongue is almost always affected; however, other lesions develop on the buccal mucosa, on the labial mucosa, and (less frequently) on the soft palate or floor of the mouth (Figs. 16-87 and 16-88). These lesions typically produce no symptoms and can be identified by a yellow-white serpentine or scalloped border that surrounds an erythematous zone. These features should prevent confusion with such conditions as candidiasis or erythroplakia.



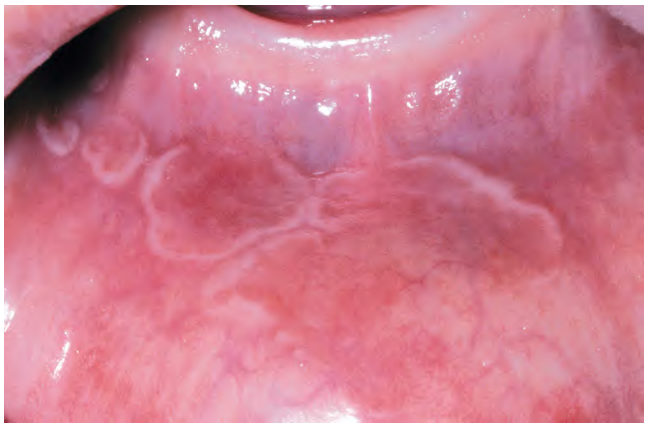
• **Fig. 16-84 Erythema Migrans.** The erythematous, well-demarcated areas of papillary atrophy are characteristic of erythema migrans affecting the tongue (benign migratory glossitis). Note the asymmetrical distribution and the tendency to involve the lateral aspects of the tongue.



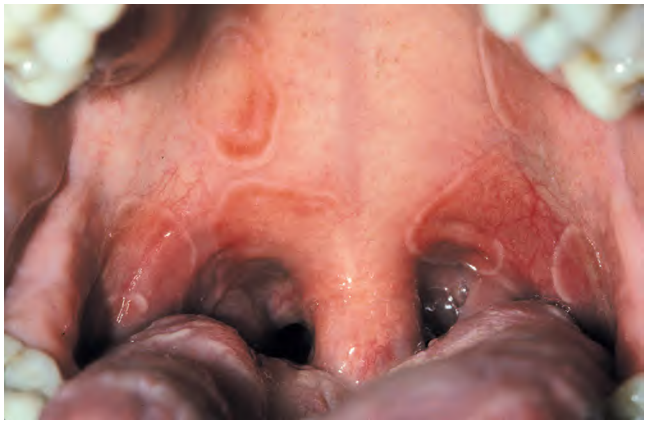
• **Fig. 16-85 Erythema Migrans.** Lingual mucosa of a different patient than the one in Fig. 16-84. The lateral distribution of the lesions is shown.



• **Fig. 16-86 Erythema Migrans.** Striking involvement of the dorsal and lateral surfaces of the tongue.



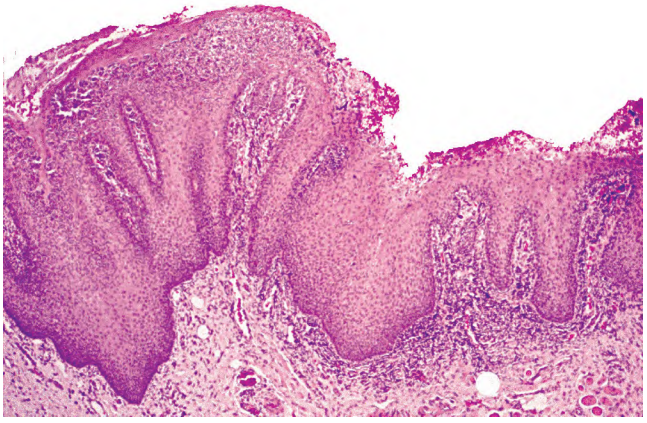
• **Fig. 16-87 Erythema Migrans.** Lesions of the lower labial mucosa.



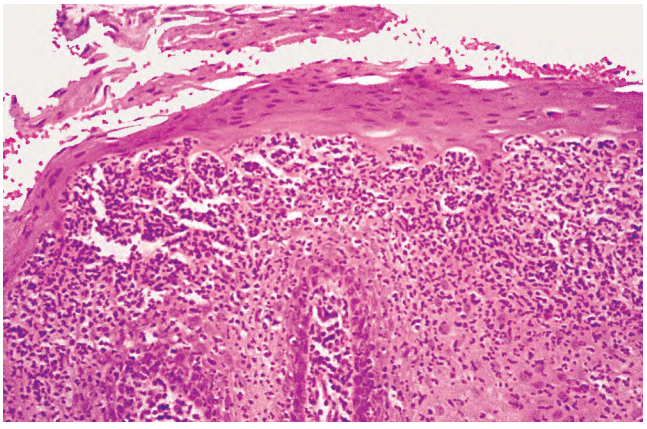
• **Fig. 16-88 Erythema Migrans.** These palatal lesions show well-demarcated erythematous areas surrounded by a white border, similar to the process involving the tongue.

Histopathologic Features

If a biopsy specimen of the peripheral region of erythema migrans is examined, a characteristic histopathologic pattern is observed. Hyperparakeratosis, spongiosis, acanthosis, and elongation of the epithelial rete ridges are seen (Fig. 16-89). In addition, collections of neutrophils **(Munro abscesses)** are observed within the epithelium (Fig. 16-90); lymphocytes and neutrophils involve the lamina propria. The intense neutrophilic infiltrate may be responsible for the destruction of the superficial portion of the epithelium, thus producing an atrophic, reddened mucosa as the lesion progresses. Because these histopathologic features are reminiscent of **psoriasis,** this is called a **psoriasiform mucositis.** Despite the apparent lack of association between dermatologic conditions and erythema migrans in some reports, at least one case-control study of psoriatic patients showed that erythema migrans occurred at a rate of about 10%; only 2.5% of an age-matched and sex-matched population were affected. A Brazilian study determined that both patients with psoriasis and those with benign migratory glossitis were more likely to have the same human leukocyte antigen (HLA) group, namely HLA-Cw6. Whether these findings mean that erythema migrans represents oral psoriasis or that patients with psoriasis are just more susceptible to erythema migrans is open to debate.



• **Fig. 16-89 Erythema Migrans.** This low-power photomicrograph shows the elongation of the rete ridges with parakeratosis and neutrophilic infiltration. Such features are also common in psoriasis, which explains why this is known as a *psoriasiform mucositis.*



• **Fig. 16-90 Erythema Migrans.** This medium-power photomicrograph shows collections of neutrophils in the superficial spinous layer of the epithelium.

Treatment and Prognosis

Generally no treatment is indicated for patients with erythema migrans. Reassuring the patient that the condition is completely benign is often all that is necessary. Infrequently, patients may complain of tenderness or a burning sensation that is so severe that it disrupts their lifestyle. In such cases, topical corticosteroids, such as fluocinonide or betamethasone gel, may provide relief when applied as a thin film several times a day to the lesional areas.

◆ REACTIVE ARTHRITIS (REITER SYNDROME)

Reactive arthritis represents a group of uncommon diseases that most likely have an immunologically mediated cause.

Current evidence suggests that these disorders may be triggered by any one of several infectious agents in a genetically susceptible person. In some instances, the arthritis will be accompanied by mucocutaneous findings, including oral lesions. A classic triad of signs has been described:

1. Nongonococcal urethritis
2. Arthritis
3. Conjunctivitis

However, most patients do not exhibit all three of these signs. Although reactive arthritis with a mucocutaneous component is also known as **Reiter syndrome,** some authors have advocated removing the *Reiter* eponym because of Hans Reiter's Nazi criminal activities during World War II, and he was not the first to describe this syndrome.

It is interesting that reactive arthritis has been reported with some frequency in patients infected with the human immunodeficiency virus (HIV).

Clinical Features

Reactive arthritis is particularly prevalent in young adult men. In some series, a male-to-female ratio of up to 9:1 has been reported. The majority (60% to 80%) of these patients are positive for HLA-B27, a haplotype present in only 10% of the population. The syndrome usually develops 1 to 4 weeks after an episode of dysentery or venereal disease; in fact, two French physicians published a description of this entity affecting four postdysenteric soldiers 1 week before Reiter's paper appeared.

Urethritis is often the first sign and is seen in both affected males and females. Females may also have inflammation of the uterine cervix. Conjunctivitis usually appears concurrently with the urethritis, and after several days, arthritis ensues. The arthritis usually affects the joints of the lower extremities, although TMJ involvement has been identified in one-third of these patients, typically as erosion of the condylar head. Skin lesions often take the form of a characteristic lesion of the glans penis **(balanitis circinata).** These lesions develop in about 20% to 30% of patients with reactive arthritis, and they appear as well-circumscribed erythematous erosions with a scalloped, whitish linear boundary.

The oral lesions, which occur in slightly less than 20% of patients with this disorder, are described in various ways. Some reports mention painless erythematous papules distributed on the buccal mucosa and palate; other reports describe shallow, painless ulcers that affect the tongue, buccal mucosa, palate, and gingiva. Some authors have even implied that **geographic tongue** may be a component of reactive arthritis, probably because geographic tongue bears a superficial resemblance to the lesions of balanitis circinata.

The American Rheumatism Association has defined reactive arthritis based on the clinical findings of a peripheral arthritis that lasts longer than 1 month in conjunction with urethritis, cervicitis, or both.

Histopathologic Features

The histopathologic findings of the cutaneous lesions in patients with reactive arthritis are frequently similar to those found in patients with **psoriasis,** particularly with respect to the presence of microabscesses within the superficial layers of the surface epithelium. Other features in common with psoriasis include hyperparakeratosis with elongated, thin rete ridges.

Treatment and Prognosis

Some patients with reactive arthritis experience spontaneous resolution of their disease after 3 to 12 months, but many others have chronic symptoms that may wax and wane. Treatment may not be necessary for the milder cases. NSAIDs are initially used for managing arthritis, and sulfasalazine may be helpful in resolving cases that do not respond. Immunosuppressive or immune modulating agents, including corticosteroids, azathioprine, etanercept, and methotrexate, are reserved for the most resistant cases if they are not associated with HIV infection.

Physical therapy probably helps to reduce joint fibrosis associated with arthritis. About 15% to 20% of patients with this disorder have severe disability, usually from arthritis.

◆ LICHEN PLANUS

Lichen planus is a relatively common, chronic dermatologic disease that often affects the oral mucosa. The strange name of the condition was provided by the British physician Erasmus Wilson, who first described it in 1869. Lichens are primitive plants composed of symbiotic algae and fungi. The term *planus* is Latin for *flat.* Wilson probably thought that the skin lesions looked similar enough to the lichens growing on rocks to merit this designation. Even though the term *lichen planus* suggests a flat, fungal condition, current evidence indicates that this is an immunologically mediated mucocutaneous disorder.

A variety of medications may induce lesions that can appear clinically very similar to the idiopathic form of the condition; however, the term **lichenoid mucositis** (or **lichenoid dermatitis,** depending on the site involved) is probably a better name for the drug-related alterations (see page 317). Similarly, foreign material that becomes inadvertently embedded in the gingiva may elicit a host response that is termed **lichenoid foreign body gingivitis** (see page 146). Reports of hepatitis C infection associated with oral lichen planus occasionally have appeared in the literature, usually from the Mediterranean countries, but this does not appear to be a significant association in the United States or Great Britain. More recent, carefully controlled epidemiologic studies do not appear to support an association of oral lichen planus with hepatitis C. However, genetic influences presumably may have an effect on the expression of lichen planus in select populations.

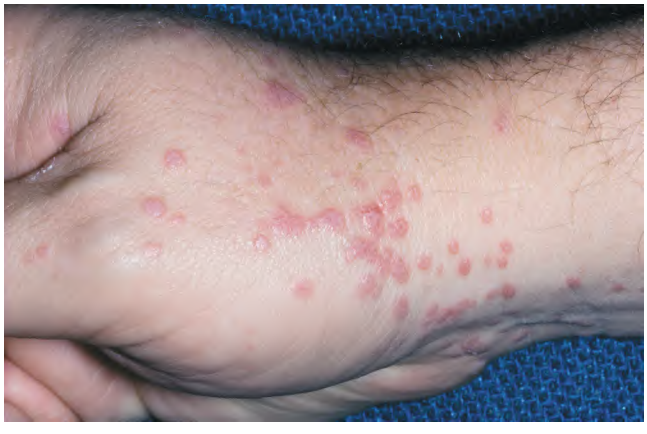
The relationship of stress or anxiety to the development of lichen planus is controversial, and most cited cases appear to be anecdotal or lack appropriate controls. Those studies that have applied psychologic questionnaires often find increased levels of anxiety in these patients; however, many patients who have been told that they have lichen planus are aware that anxiety has been linked to the disorder. Whether this awareness may influence the manner in which they answer the psychologic questionnaires could be debated. In one study that used psychologic questionnaires to attempt to resolve this question, patients with oral lichen planus had no greater degree of stress in their lives than did age-matched and sex-matched control patients. It might be that stress has no bearing on the pathogenesis of lichen planus; however, an alternative explanation might be that those patients who have lichen planus simply respond in this fashion to levels of stress that do not induce lesions in other people.

Clinical Features

Most patients with lichen planus are middle-aged adults. It is rare for children to be affected. Women predominate in most series of cases, usually by a 3:2 ratio over men. Approximately 1% of the population may have cutaneous lichen planus. The prevalence of oral lichen planus is between 0.1% and 2.2%.

The skin lesions of lichen planus have been classically described as purple, pruritic, polygonal papules (Fig. 16-91). These usually affect the flexor surfaces of the extremities. Excoriations may not be visible, despite the fact that the lesions itch, because it hurts the patient when he or she scratches them.

Careful examination of the surface of the skin papules reveals a fine, lacelike network of white lines **(Wickham striae)** (Fig. 16-92). Other sites of extraoral involvement include the glans penis, the vulvar mucosa, and the nails. Essentially there are two forms of oral lesions: reticular and erosive.

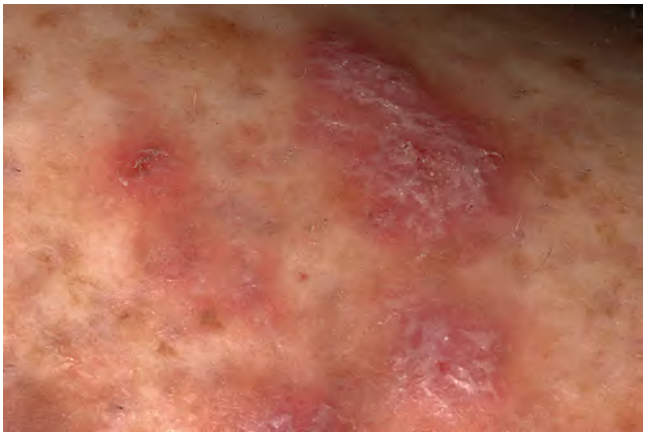


• **Fig. 16-91 Lichen Planus.** The cutaneous lesions on the wrist appear as purple, polygonal papules.

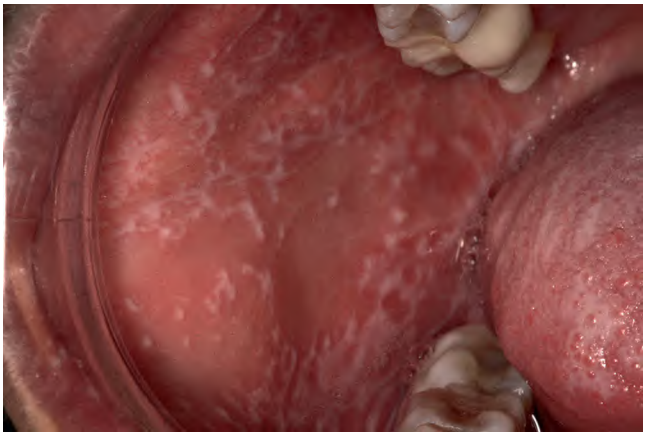
Reticular Lichen Planus

Reticular lichen planus is much more common than the erosive form, but the erosive form predominates in several studies. This is probably because of referral bias (because the erosive form is symptomatic and, therefore, the patient is more likely to be referred to an academic center for evaluation). The reticular form usually causes no symptoms and involves the posterior buccal mucosa bilaterally (Fig. 16-93). Post-inflammatory melanosis occasionally accompanies the reticular striae, particularly in persons of color (Fig. 16-94). Other oral mucosal surfaces may also be involved concurrently, such as the lateral and dorsal tongue, the gingivae, the palate, and vermilion border (Fig. 16-95).

Reticular lichen planus is thus named because of its characteristic pattern of interlacing white lines (also referred to as *Wickham striae*); however, the white lesions may appear as papules in some instances. These lesions are typically not static but wax and wane over weeks or months (Fig. 16-96). The reticular pattern may not be as evident in some sites,



• **Fig. 16-92 Lichen Planus.** Closer view of a skin lesion of lichen planus. Careful examination shows a network of fine white lines (Wickham striae) on the surface of the papules.



• **Fig. 16-93 Lichen Planus.** The interlacing white lines and papules are typical of reticular lichen planus involving the buccal mucosa, the most common site of oral involvement.

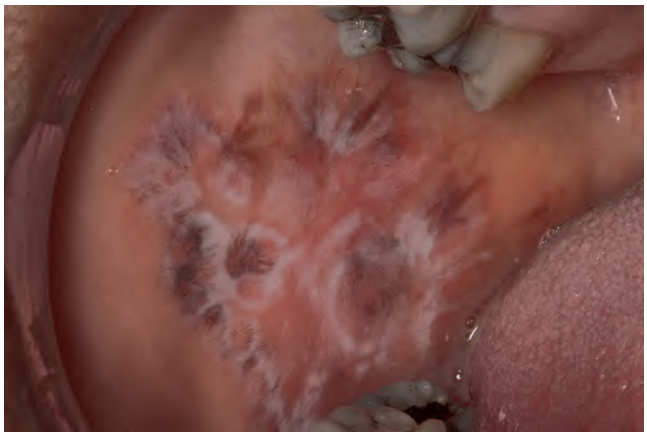


Fig. 16-94 Lichen Planus. In persons of color who develop lichen planus, it is not unusual to see patchy areas of reactive (benign) melanosis develop in the lesions, presumably due to stimulation of the melanocytes in this area by the inflammatory cells that cause this condition.

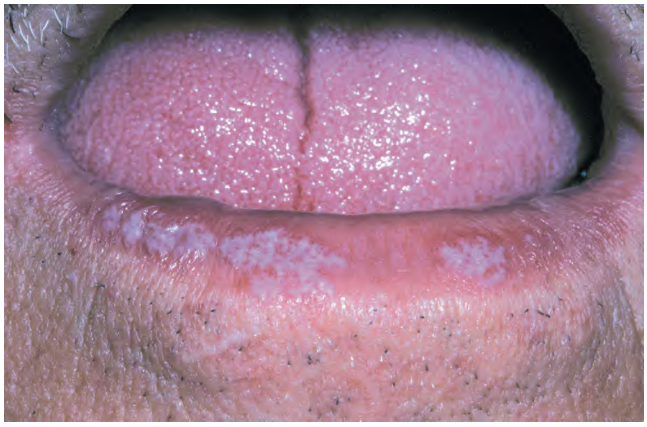


Fig. 16-95 Lichen Planus. Reticular lesions of the lower lip vermilion.

such as the dorsal tongue, where the lesions appear more as keratotic plaques with atrophy of the papillae (Fig. 16-97). In addition, superficial mucoceles may develop within, or adjacent to, mucosal areas that are involved by lichen planus.

Erosive Lichen Planus

Erosive lichen planus, although not as common as the reticular form, is more significant for the patient because the lesions are usually symptomatic. Clinically, there are atrophic, erythematous areas with central ulceration of varying degrees. The periphery of the atrophic regions is usually bordered by fine, white radiating striae (Figs. 16-98 and 16-99). Sometimes the atrophy and ulceration are confined to the gingival mucosa, producing the reaction pattern called **desquamative gingivitis** (see page 148) (Fig. 16-100). In such cases, biopsy specimens should be obtained for light microscopic and immunofluorescent studies of perilesional tissue, because mucous membrane pemphigoid (see page 718) and pemphigus vulgaris (see page 712) may appear in a similar fashion.

If the erosive component is severe, epithelial separation from the underlying connective tissue may occur. This results in the relatively rare presentation of **bullous lichen planus.**

Histopathologic Features

The histopathologic features of lichen planus are characteristic but may not be specific, because other conditions, such as **lichenoid drug reaction, lichenoid amalgam reaction, oral graft-versus-host disease (GVHD), lupus erythematosus (LE), chronic ulcerative stomatitis,** and **oral mucosal cinnamon reaction** may also show a similar histopathologic pattern. Varying degrees of orthokeratosis and parakeratosis may be present on the surface of the epithelium, depending on whether the biopsy specimen is taken from an erosive or reticular lesion.

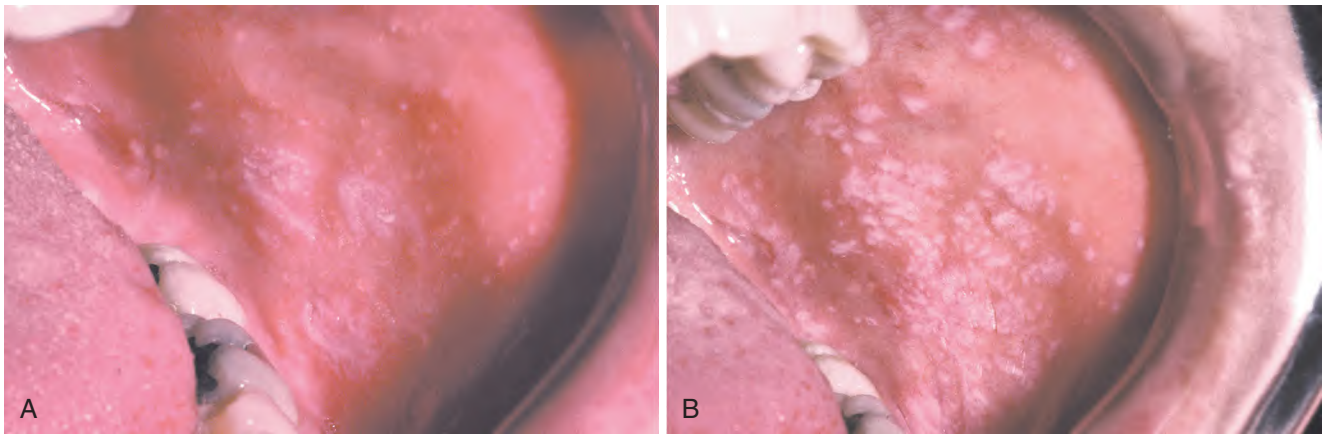


Fig. 16-96 Lichen Planus. A, A middle-aged woman with mild reticular lichen planus of the left buccal mucosa. **B,** Same patient 2 weeks later, showing exacerbation of the lesions. Such waxing and waning is characteristic of lichen planus.

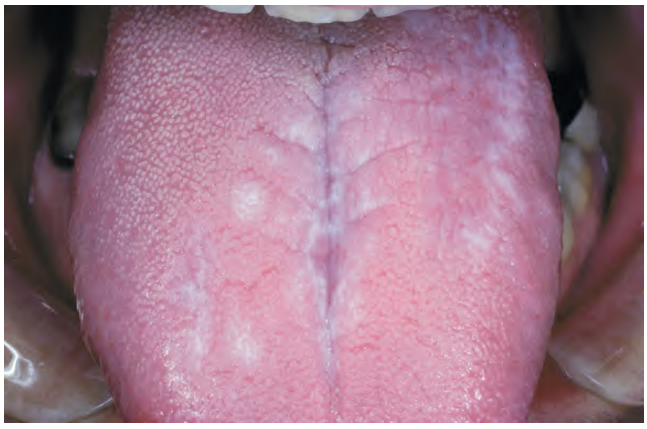


Fig. 16-97 Lichen Planus. With involvement of the dorsal tongue by reticular lichen planus, the characteristic interlacing striae seen in the buccal mucosal lesions are usually not present. Instead, smooth white plaques are typically observed replacing the normal papillary surface of the tongue.

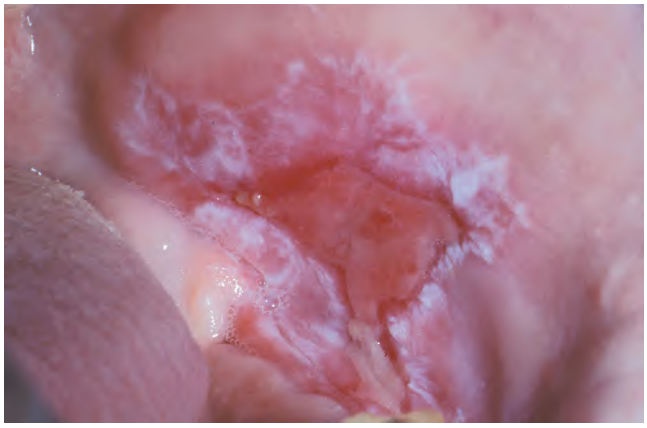


Fig. 16-98 Lichen Planus. Ulceration of the buccal mucosa shows peripheral radiating keratotic striae, characteristic of oral erosive lichen planus.

The thickness of the spinous layer can also vary. The rete ridges may be absent or hyperplastic, but they classically have a pointed or "saw-toothed" shape (Fig. 16-101).

Destruction of the basal cell layer of the epithelium **(hydropic degeneration)** is also evident. This is accompanied by an intense, bandlike infiltrate of predominantly T lymphocytes immediately subjacent to the epithelium (Fig. 16-102). Degenerating keratinocytes may be seen in the area of the epithelium and connective tissue interface and have been termed **colloid, cytoid, hyaline,** or **Civatte bodies.** No significant degree of epithelial atypia is expected in oral lichen planus, although lesions having a superimposed candidal infection may appear worrisome. These should be reevaluated histopathologically after the candidal infection is treated. On occasion, the chronic inflammatory host response to the atypical cells of **epithelial dysplasia** can appear virtually indistinguishable histopathologically from lichen planus, particularly in milder cases of epithelial dysplasia. Such ambiguity may contribute to the controversy related to the malignant transformation potential of lichen planus.

The immunopathologic features of lichen planus are nonspecific. Most lesions show the deposition of a shaggy band of fibrinogen at the basement membrane zone.

Diagnosis

The diagnosis of **reticular lichen planus** can often be made based on the clinical findings alone. The interlacing white striae appearing bilaterally on the posterior buccal mucosa are virtually pathognomonic. Difficulties in diagnosis may arise if candidiasis is superimposed on the lesions because the organism may alter the characteristic reticular pattern of the lichen planus (Fig. 16-103).

Erosive lichen planus is sometimes more challenging to diagnose (based on clinical features alone) than the reticular form. If the typical radiating white striae and erythematous,

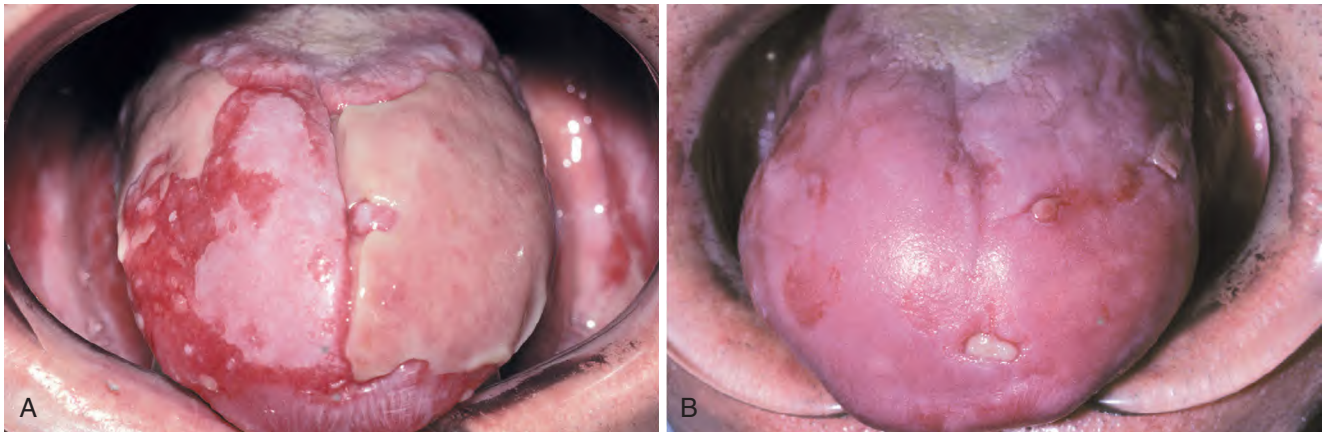
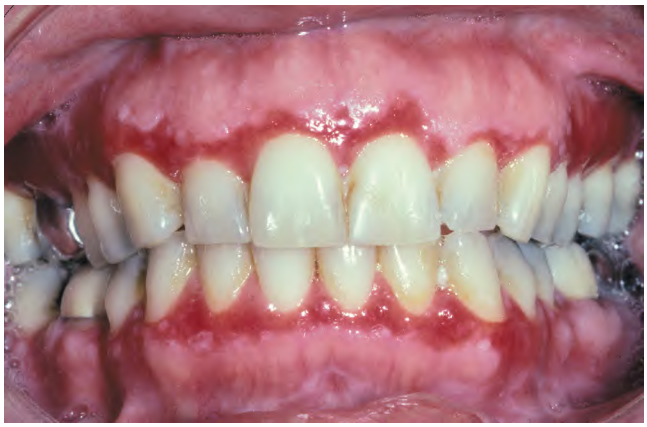


Fig. 16-99 Lichen Planus. A, The dorsal surface of the tongue shows extensive ulceration caused by erosive lichen planus. Note the fine white streaks at the periphery of the ulcerations. **B,** Same patient after systemic corticosteroid therapy. Much of the mucosa has reepithelialized, with only focal ulcerations remaining.



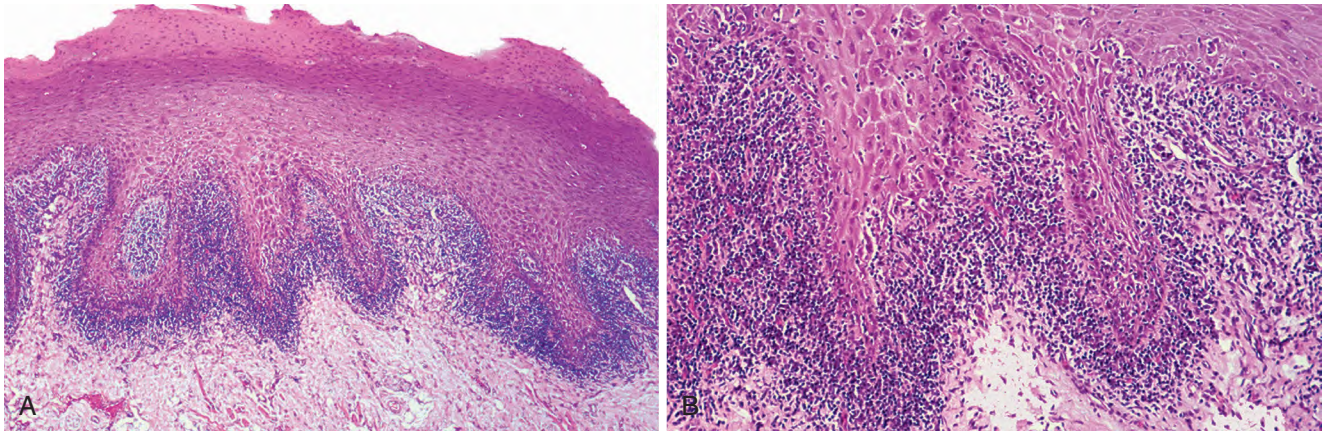
• **Fig. 16-100 Lichen Planus.** Erosive lichen planus often appears as a desquamative gingivitis, producing gingival erythema and tenderness.

atrophic mucosa are present at the periphery of well-demarcated ulcerations on the posterior buccal mucosa bilaterally, then the diagnosis can sometimes be rendered without the support of histopathologic findings. However, a biopsy, often with direct immunofluorescence studies, may be necessary to rule out other ulcerative or erosive diseases, such as lupus erythematosus or chronic ulcerative stomatitis.

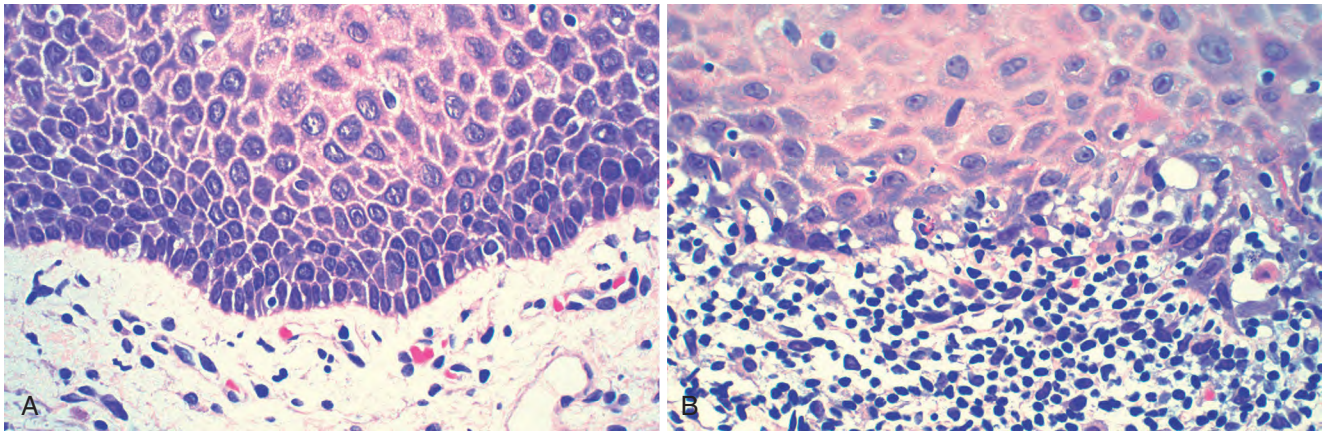
Specimens of isolated erosive lichenoid lesions, particularly those of the soft palate, the lateral and ventral tongue, or the floor of the mouth, should be obtained for biopsy to rule out premalignant changes or malignancy. Another condition that may mimic an isolated lesion of lichen planus, both clinically and histopathologically, is a **lichenoid reaction to dental amalgam** (see page 324).

Treatment and Prognosis

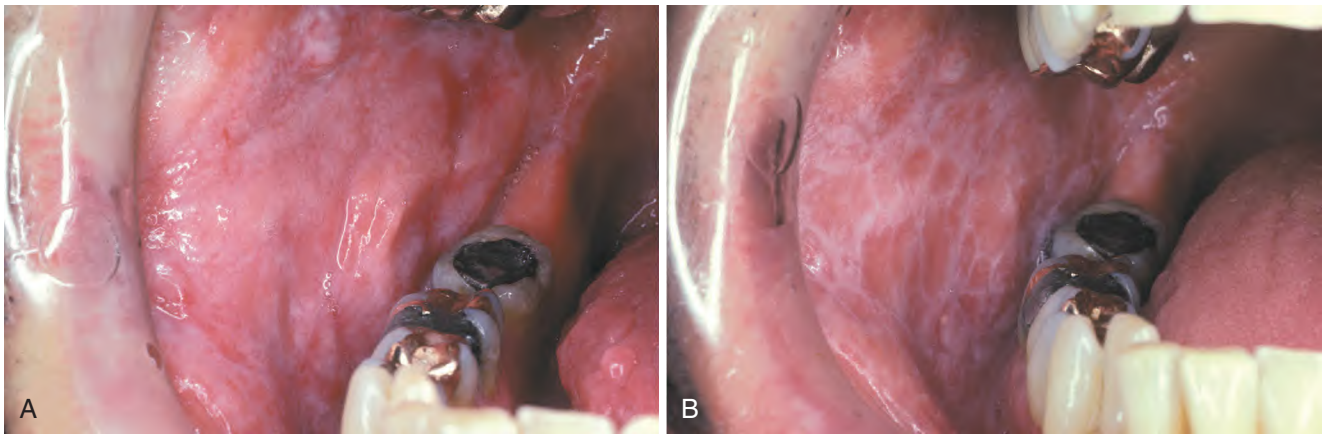
Reticular lichen planus typically produces no symptoms, and no treatment is needed. Occasionally, affected patients



• **Fig. 16-101 Lichen Planus. A,** This low-power photomicrograph of an oral lesion shows hyperkeratosis, saw-toothed rete ridges, and a bandlike infiltrate of lymphocytes immediately subjacent to the epithelium. **B,** Higher-power view showing migration of lymphocytes into the lower epithelium with interface degeneration of the basal cell layer.



• **Fig. 16-102 Lichen Planus. A,** High-power photomicrograph of normal epithelium showing an intact basal cell layer and no inflammation. **B,** High-power photomicrograph of lichen planus showing degeneration of the basal epithelial layer and an intense lymphocytic infiltrate in the superficial lamina propria.



• **Fig. 16-103 Lichen Planus. A,** These relatively nondescript white lesions affected the buccal mucosa of a patient who had complained of a burning sensation. Histopathologic evaluation of the lesion showed a lichenoid mucositis with superimposed candidiasis. **B,** Same patient 2 weeks after antifungal therapy. Once the mucosal reaction to the candidal organism was eliminated, the characteristic white striae of reticular lichen planus were identified.

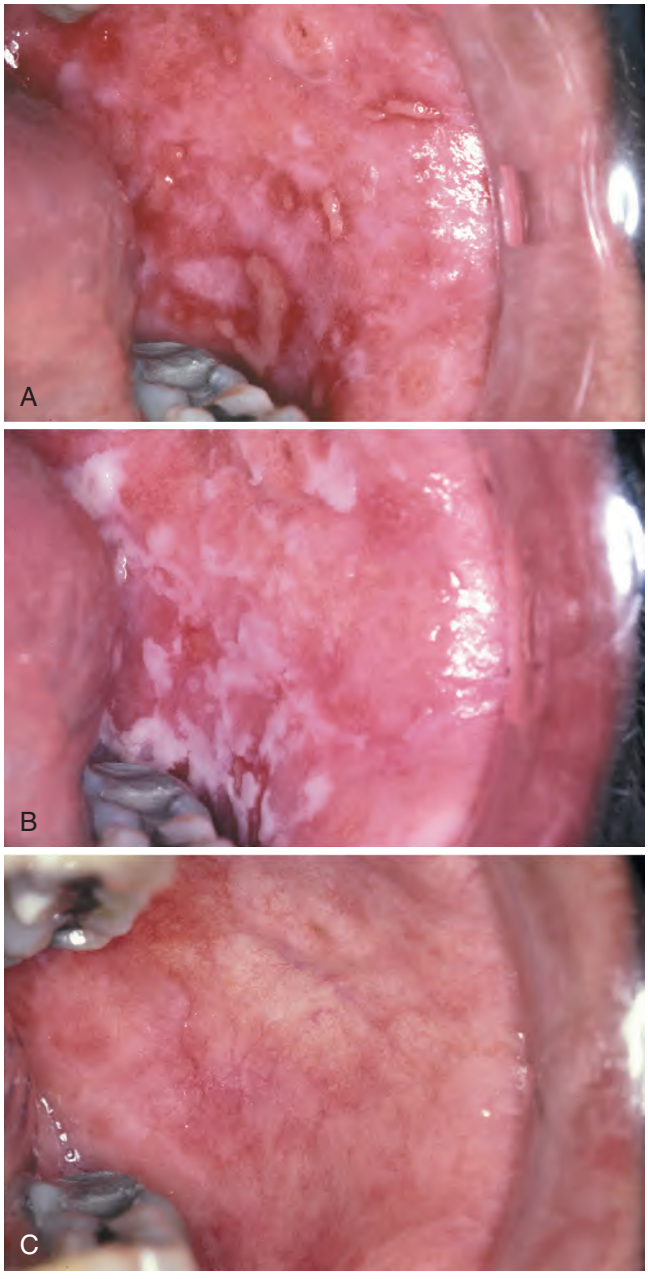
may have superimposed candidiasis, in which case they may complain of a burning sensation of the oral mucosa. Antifungal therapy is necessary in such a case. Some investigators recommend annual reevaluation of the reticular lesions of oral lichen planus.

Erosive lichen planus is often bothersome because of the open sores in the mouth. Because it is an immunologically mediated condition, corticosteroids are recommended. The lesions respond to systemic corticosteroids, but such drastic therapy is usually not necessary. One of the stronger topical corticosteroids (e.g., fluocinonide, betamethasone, or clobetasol gel) applied as a thin film several times per day to the most symptomatic areas is usually sufficient to induce healing within 1 or 2 weeks. The patient should be warned that the condition will undoubtedly flare up again, in which case the corticosteroids should be reapplied. In addition, the possibility of iatrogenic candidiasis associated with corticosteroid use should be monitored (Fig. 16-104). Some investigators have recommended compounding corticosteroid ointments with an adhesive methylcellulose base, but patient compliance may be reduced because this material is difficult to apply. Although the use of agents (such as, topical retinoids, tacrolimus, mycophenolate mofetil, or cyclosporine) has occasionally been advocated for recalcitrant cases of erosive lichen planus, reports of their efficacy have usually been limited to small series of cases or have been contradictory. Furthermore, their side effects can be significant, and in the case of tacrolimus or cyclosporine, the cost of the drug may be prohibitive. Some investigators suggest that patients with oral erosive lichen planus be evaluated every 3 to 6 months, particularly if the lesions are not typical.

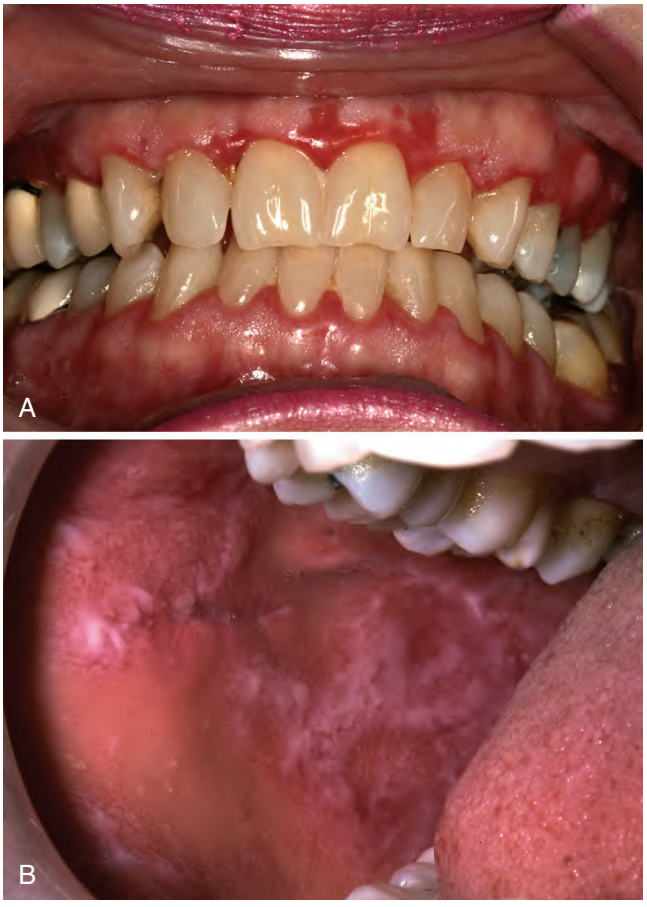
The question of the malignant potential of lichen planus, particularly the erosive form, is yet to be resolved. Most cases of reported malignant transformation are rather poorly documented. Some of these reported cases may not have been true lichen planus, but rather they may have actually been dysplastic leukoplakias with a secondary lichenoid inflammatory infiltrate that mimicked lichen planus ("lichenoid dysplasia"). In addition, the argument can be made that because both lichen planus and squamous cell carcinoma are not rare, some people may have both problems simultaneously, and the two processes may be unrelated to one another. Conversely, some investigators say that the atrophic epithelium of lichen planus may be more susceptible to the action of carcinogens, resulting in an increased risk of malignant transformation. Two studies have examined the molecular characteristics of classic reticular lichen planus, comparing the loss of heterozygosity at purported tumor suppressor gene loci in these lesions with that of varying grades of oral epithelial dysplasia, squamous cell carcinoma, normal oral mucosa, and oral reactive lesions. The molecular profile of oral lichen planus more closely resembled that of normal or reactive oral mucosa, a finding that provides less support for the concept of lichen planus being precancerous. Another study evaluated the malignant transformation rate of typical oral lichen planus compared with oral "lichenoid" lesions. The lichenoid lesions had some features of lichen planus, but were not completely representative, either clinically or histopathologically, of that disease. These investigators found that there was no transformation of characteristic lichen planus, although several of the "lichenoid" lesions developed into squamous cell carcinoma. Additional prospective clinical studies with strict clinical and histopathologic criteria for the definition of oral lichen planus will need to be performed to resolve this question. If the potential for malignant transformation exists, then it appears to be small. Most of the reported cases have been confined to patients with either the erosive or so-called plaque-type form of lichen planus.

◆ CHRONIC ULCERATIVE STOMATITIS

Chronic ulcerative stomatitis is another immune-mediated disorder that affects the oral mucosa. This condition was



• **Fig. 16-104 Lichen Planus. A,** This patient was diagnosed with erosive lichen planus affecting the buccal mucosa and was treated with topical corticosteroids. **B,** Same patient 2 weeks later. The creamy-white plaques of pseudomembranous candidiasis have developed as a result of the corticosteroid therapy. **C,** Same patient after antifungal therapy. At this point, he was asymptomatic.



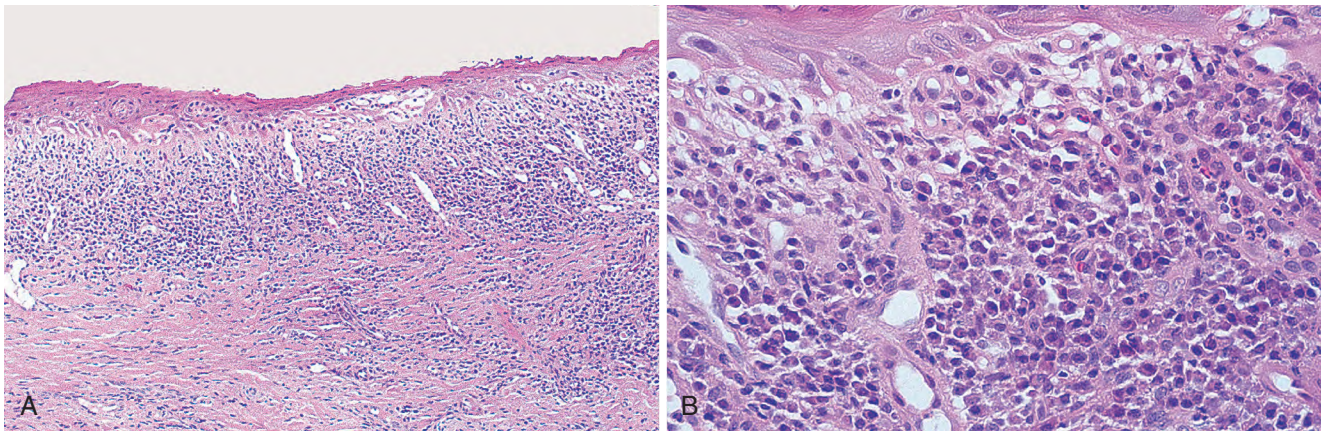
• **Fig. 16-105 Chronic Ulcerative Stomatitis. A,** Gingival lesions having a "desquamative gingivitis" presentation, requiring biopsy with direct immunofluorescence studies for diagnosis. **B,** Buccal mucosal involvement. The lesions appear somewhat lichenoid, although classic Wickham striae are not evident.

initially described in 1989, and slightly more than 40 cases have been reported. Although the precise pathogenetic mechanisms are unknown, these patients develop autoantibodies against a 70-kD nuclear protein, ΔNp63α, an isoform of p63, and *in vitro* studies suggest that these antibodies play a role in development of this disease by interrupting the normal maintenance of the epithelium/connective tissue interface.

The prevalence of this disease may be more common than is realized. Because of its clinical similarity to erosive lichen planus, it is possible that only a clinical diagnosis is made when an affected patient is encountered, and a biopsy is not performed. Even if a biopsy is done, the tissue is often submitted for routine light microscopy alone, and the direct immunofluorescence studies that are required for its diagnosis are not ordered. Distinction from lichen planus should be made because chronic ulcerative stomatitis typically does not respond as well to corticosteroid therapy, and just as is the case with lupus erythematosus (LE), chronic ulcerative stomatitis often can be effectively treated using antimalarial drugs.

Clinical Features

Chronic ulcerative stomatitis usually affects adult women, and the mean age at diagnosis is late in the sixth decade of life. The condition may appear as desquamative gingivitis, although ulcerations or erosions of the tongue or buccal mucosa are also quite common (Fig. 16-105). The ulcers are generally surrounded by patchy zones of erythema and streaky keratosis that somewhat resemble lichen planus, although classic striae formation is not evident. The ulcers



• **Fig. 16-106 Chronic Ulcerative Stomatitis. A,** Low-power photomicrograph showing epithelial atrophy with a heavy chronic inflammatory cell infiltrate in the superficial lamina propria. **B,** High-power photomicrograph showing interface degeneration of the basilar epithelium in association with the inflammation. Unlike lichen planus, this infiltrate includes numerous plasma cells, as well as lymphocytes.

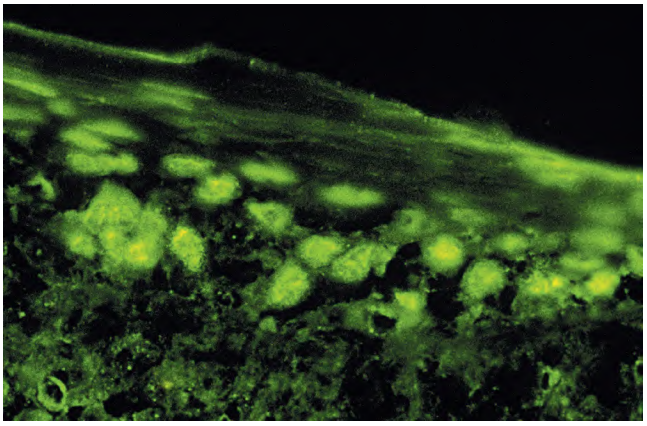
heal without scarring and often migrate around the oral mucosa. As is typical with most immune-mediated conditions, the severity of the oral lesions tends to wax and wane. Fewer than 20% of affected patients will develop concurrent lichenoid skin lesions.

Histopathologic Features

Although the histopathologic features of chronic ulcerative stomatitis are similar to those of lichen planus, the epithelium is generally more atrophic and the inflammatory infiltrate usually contains significant numbers of plasma cells in addition to lymphocytes (Fig. 16-106). Artifactual epithelial separation from the underlying connective tissue is not unusual.

Diagnosis

The diagnosis of chronic ulcerative stomatitis is essentially based on its characteristic immunopathologic pattern. Although it may not be economically feasible to do immunologic testing on every case of lichen planus, this procedure should be considered for erosive lichenoid lesions that do not have a characteristic appearance or distribution, as well as for erosive lesions that do not respond to topical corticosteroid therapy. With direct immunofluorescence studies, autoantibodies (usually IgG) that are directed against the nuclei of stratified squamous epithelial cells in the basal and parabasal regions of the epithelium are detected (Fig. 16-107). Indirect immunofluorescence studies are also positive for these stratified epithelium-specific antinuclear antibodies (ANAs), and some investigators believe that confirmation of the diagnosis is necessary using serum for indirect immunofluorescence evaluation. An ELISA test has been developed, and if it becomes commercially available, this should make screening for this condition much more cost-effective. Other immune-mediated conditions (e.g., systemic sclerosis and LE) may show ANA deposition with direct immunofluorescence; however, nuclei throughout the entire thickness of the epithelium are positive with those diseases.



• **Fig. 16-107 Chronic Ulcerative Stomatitis.** Direct immunofluorescence studies show presence of IgG in the basal and parabasal epithelial nuclei.

Treatment and Prognosis

Unlike the lichen planus lesions of erosive lichen planus, the lesions associated with chronic ulcerative stomatitis may not respond as well to topical or systemic corticosteroid therapy. If the lesions are not adequately controlled with corticosteroids, then management with hydroxychloroquine, an antimalarial drug, should be considered. Hydroxychloroquine therapy, however, requires both periodic ophthalmologic evaluation to monitor for drug-related retinopathy and periodic hematologic evaluation.

◆ GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) occurs mainly in recipients of allogeneic bone marrow transplantation, a procedure

performed on approximately 8000 patients in the United States each year. Such transplants are performed at major medical centers to treat life-threatening diseases of the blood or bone marrow, such as leukemia, lymphoma, multiple myeloma, aplastic anemia, thalassemia, sickle cell anemia, or disseminated metastatic disease. Cytotoxic drugs, radiation, or both may be used to destroy the malignant cells, but in the process the normal hematopoietic cells of the patient are destroyed. To provide the patient with an immune system, an HLA-matched donor must be found. The donor supplies hematopoietic stem cells obtained from bone marrow, peripheral blood, or umbilical cord blood. These stem cells are transfused into the patient, whose own hematopoietic and immune cells have been destroyed. The transfused hematopoietic cells make their way to the recipient's bone marrow and begin to reestablish normal function.

Unfortunately, the HLA match is not always exact, and despite the use of immunomodulating and immunosuppressive drugs (such as, cyclosporine, methotrexate, and prednisone), the engrafted cells often recognize that they are not in their native environment. When this happens, these cells start attacking what they perceive as a foreign body. The result of this attack is GVHD, and it can be quite devastating to the patient.

In recent years, oncologists have taken advantage of this type of immunologic attack when treating leukemia patients, and often a beneficial "graft-versus-leukemia" effect is seen when the donor cells interpret the leukemic cells as being foreign. For older patients, who tend to have more significant side effects with traditional bone marrow transplantation, the concept of a "mini-allograft" has been developed. Not all of the patient's white blood cells (WBCs) are destroyed in this procedure, which is also known as *nonmyeloablative allogenic hematopoietic cell transplantation,* to allow the donor cells to mount a more aggressive assault on the patient's leukemic cells.

Autologous stem cell transplantation has also become an increasingly popular method of treatment for some of these life-threatening diseases. Because these cells are derived from the patient, there is no risk of GVHD in this setting.

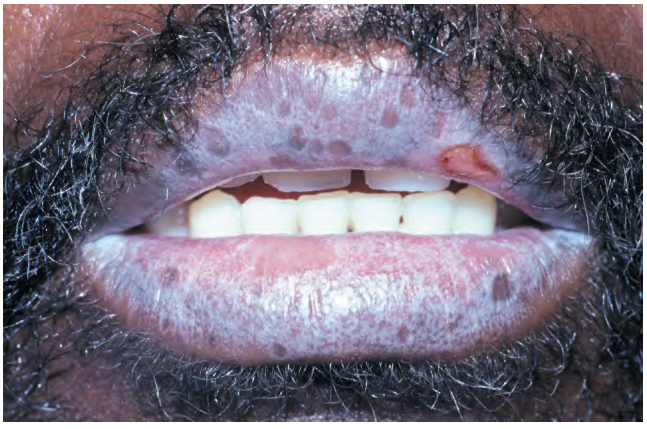
Clinical Features

The systemic signs of GVHD are varied, depending on the organ system involved and whether the problem is acute or chronic. The severity of GVHD depends on several factors, with milder disease seen in patients who have a better histocompatibility match, are younger, have received cord blood, and are female.

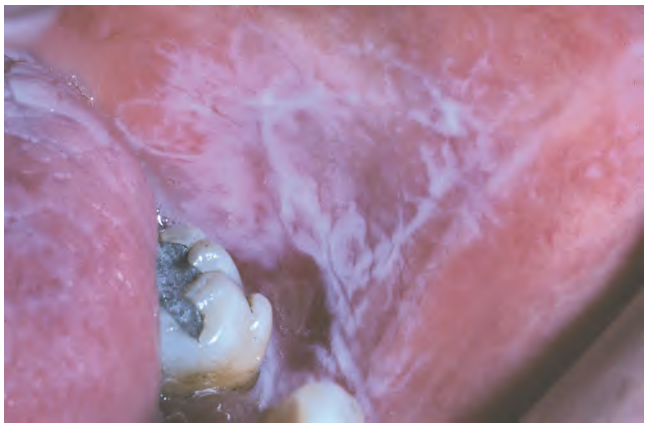
Acute GVHD is typically observed within the first few weeks after bone marrow transplantation. Although acute GVHD has arbitrarily been defined as occurring within 100 days after the procedure, most investigators make this diagnosis based on the clinical features rather than a specific time point. The disease affects about 50% of bone marrow transplant patients. The skin lesions that develop may range from a mild rash to a diffuse severe sloughing that resembles toxic epidermal necrolysis (see page 725). These signs may be accompanied by diarrhea, nausea, vomiting, abdominal pain, and liver dysfunction.

Chronic GVHD may represent a continuation of a previously diagnosed case of acute GVHD, or it may develop later than 100 days after bone marrow transplantation, sometimes not appearing for several years after the procedure. Chronic GVHD can be expected to develop in 30% to 70% of bone marrow transplant recipients, and it often mimics any one of a variety of autoimmune conditions, such as systemic lupus erythematosus (SLE), Sjögren syndrome, or primary biliary cirrhosis. Skin involvement, which is the most common manifestation, may resemble lichen planus or even systemic sclerosis.

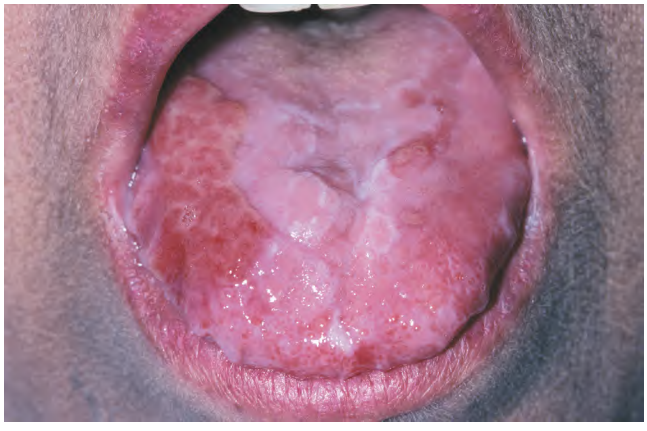
The oral mucosal manifestations of GVHD can also vary, depending on the duration and severity of the attack and the targeted oral tissues. Of patients with acute GVHD, 33% to 75% will have oral involvement; of patients with chronic GVHD, 80% or more will have oral lesions. Sometimes the oral lesions of GVHD are the only sign of the disorder. In most patients with oral GVHD, there is a fine, reticular network of white striae that resembles oral lichen planus, although a more diffuse pattern of pinpoint white papules has also been described (Figs. 16-108 to 16-110). The tongue, the labial mucosa, and the buccal mucosa are the oral mucosal sites most frequently involved. Patients often complain of a burning sensation of the oral mucosa, and care must be taken not to overlook possible candidiasis. Atrophy of the oral mucosa may be present, and this can contribute to the mucosal discomfort. Ulcerations that are related to the chemotherapeutic conditioning and neutropenic state of the patient often develop during the first 2 weeks after bone marrow transplantation. Ulcers that persist longer than 2 weeks may represent acute GVHD, and these should be differentiated from intraoral herpesvirus infection or bacterial infection. Bone marrow transplant patients have a small but increased risk for the development of both oral



• **Fig. 16-108 Graft-Versus-Host Disease (GVHD).** Confluent, interlacing white linear lesions of the vermilion zone superficially resemble oral lichen planus.



• **Fig. 16-109 Graft-Versus-Host Disease (GVHD).** Lichenoid lesions of the left buccal mucosa.



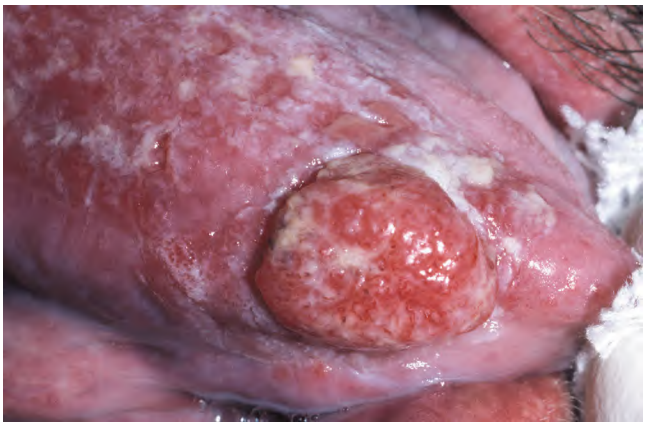
• **Fig. 16-110 Graft-Versus-Host Disease (GVHD).** Involvement of the tongue showing erosions and ulcerations that resemble erosive lichen planus.

and cutaneous epithelial dysplasia and squamous cell carcinoma. Demarcated white or red plaques of the oral mucosa that do not have the characteristic lichenoid features should be biopsied to rule out preneoplastic or neoplastic changes (Fig. 16-111).

Xerostomia is also a common complaint. If the patient is not taking drugs that dry the mouth, it is likely that the immunologic response is destroying the salivary gland tissue. Other evidence of salivary gland involvement includes the development of small superficial mucoceles, particularly on the soft palate.

Histopathologic Features

The histopathologic features of GVHD resemble those of oral lichen planus to a certain degree. Both lesions display hyperorthokeratosis, short and pointed rete ridges, and degeneration of the basal cell layer. The inflammatory response in GVHD is usually not as intense as in lichen planus. With advanced cases, an abnormal deposition of collagen is present, similar to the pattern in systemic sclerosis. Minor salivary gland tissue usually shows periductal



• **Fig. 16-111 Squamous Cell Carcinoma Arising in Graft-Versus-Host Disease (GVHD).** Erythematous, ulcerated mass arising on the lateral border of the tongue. Note the surrounding mucosal erosions, which represent GVHD.

inflammation in the early stages, with gradual acinar destruction and extensive periductal fibrosis appearing later.

Diagnosis

The diagnosis of GVHD may be difficult because of the varied clinical manifestations. Such a diagnosis is of great clinical significance to the patient because complications of the condition and its treatment may be lethal. Although the diagnosis of GVHD is based on the clinical and histopathologic findings, each patient may have a different constellation of signs and symptoms. Oral lesions appear to have value as a highly predictive index of the presence of GVHD.

Treatment and Prognosis

The primary strategy for dealing with GVHD is to reduce or prevent its occurrence. Careful tissue histocompatibility matching is performed, and the patient is given prophylactic therapy with immunomodulatory and immunosuppressive agents, such as prednisone in combination with either cyclosporine or tacrolimus. If GVHD develops, then the doses of these drugs may be increased or similar pharmacologic agents, such as mycophenolate mofetil, or azathioprine, may be added. The drug thalidomide has shown some promise for cases of chronic GVHD that have been resistant to standard therapy.

Topical corticosteroids may facilitate the healing of focal oral ulcerations associated with GVHD, and some reports have suggested that topical tacrolimus may be useful in managing ulcers that are resistant to corticosteroids. Topical anesthetic agents are administered to provide patient comfort while the lesions are present, although narcotic analgesics may be required in some cases. The use of **p**soralen and **u**ltra**v**iolet **A** (PUVA) therapy also has been shown to improve the cutaneous and oral lesions of patients with

the lichenoid form of GVHD. If significant xerostomia is present in a dentulous patient, then topical fluorides should be used daily to prevent xerostomia-related caries. If significant amounts of salivary acinar tissue remain, then treatment with pilocarpine hydrochloride or cevimeline hydrochloride may improve the salivary flow. Current recommendations are to evaluate the oral status of patients before bone marrow transplantation and eliminate any potential sources of infection. Interestingly, one study showed no differences in posttransplant infections or survival between a group of patients who received dental treatment before their transplant and a group who did not.

In general, some degree of GVHD is expected in most allogeneic bone marrow transplant recipients. The prognosis depends on the extent to which the condition progresses and whether or not it can be controlled. The significance of this complication is reflected in the survival of more than 70% of patients with relatively mild GVHD at 6 years posttransplant, compared with approximately 15% of patients with severe GVHD.

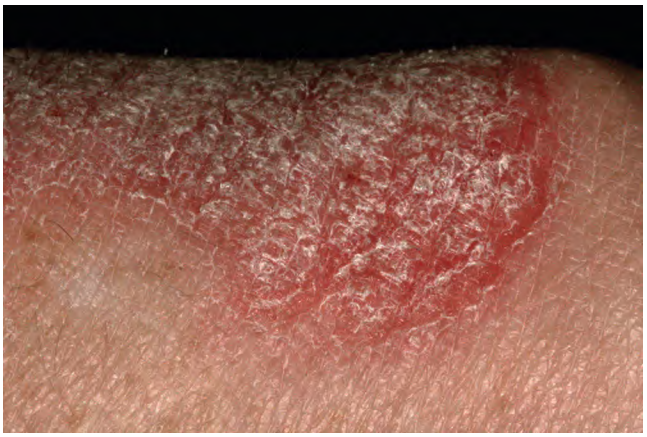
PSORIASIS

Psoriasis is a common chronic skin disease affecting approximately 2% of people in the United States. According to some estimates, roughly 6 million people in this country have psoriasis, and up to 250,000 new cases are diagnosed each year.

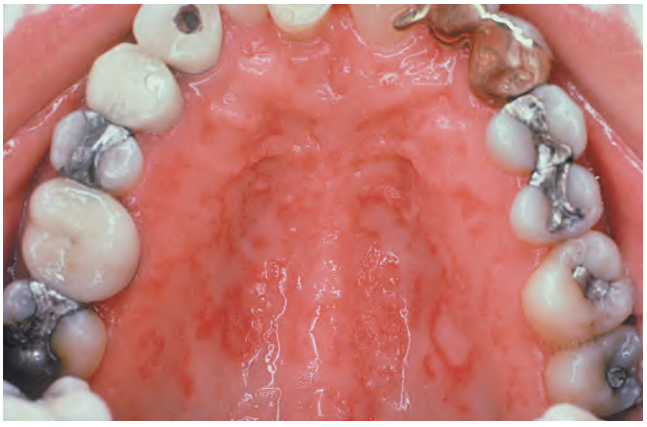
Psoriasis is characterized by an increased proliferative activity of the cutaneous keratinocytes. Recent advances in cell kinetics, immunology, and molecular biology have increased the understanding of the etiopathogenesis of the keratinocyte proliferation in this disorder. Although the triggering agent has yet to be identified, activated T lymphocytes appear to orchestrate a complex scenario that includes abnormal production of cytokines, adhesion molecules, chemotactic polypeptides, and growth factors. Genetic factors also seem to play a role, because as many as one-third of these patients have affected relatives. Currently nine different genetic loci have been identified that may be related to the development of psoriasis. If one twin in a set of identical twins has psoriasis, there is a 35% to 72% chance that the other twin will have it. This suggests that genetic factors are not entirely responsible for the condition, and that one or more unidentified environmental agents must influence its pathogenesis.

Clinical Features

Psoriasis often has its onset during the second or third decade of life and tends to persist for years, with periods of exacerbation and quiescence. Patients frequently report that the lesions improve during the summer and worsen during the winter, an observation that may be related to lesional exposure to UV light. The lesions are typically symmetrically distributed in certain favored locations, such as the scalp, elbows, and knees. The classic description is a well-demarcated, erythematous plaque with a silvery scale on its surface (Fig. 16-112). The lesions are often asymptomatic, but it is not unusual for a patient to complain of itching—in fact, the term *psoriasis* is derived from the Greek word for itching. An unfortunate complication affecting approximately 11% of these patients is **psoriatic arthritis,** which may involve the TMJ.

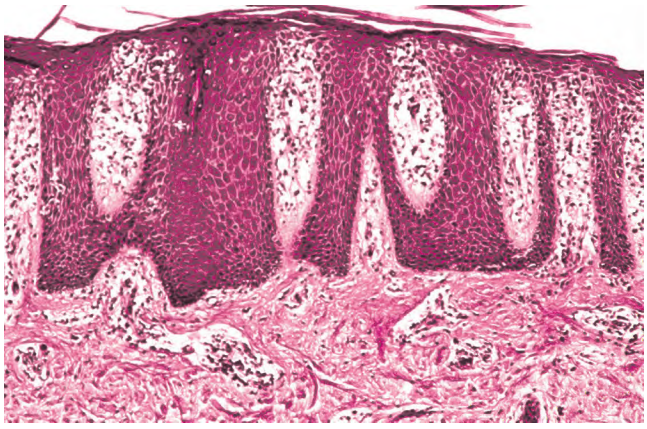


• **Fig. 16-112 Psoriasis.** Characteristic cutaneous lesion, characterized by an erythematous plaque surmounted by silvery keratotic scales.



• **Fig. 16-113 Psoriasis.** This is an example of relatively rare involvement of the oral mucosa by psoriasis. The erythematous linear patches tended to flare with the patient's cutaneous lesions. (Courtesy of Dr. George Blozis.)

Oral lesions may occur in patients with psoriasis, but they are distinctly uncommon. Because descriptions of these lesions have ranged from white plaques to red plaques to ulcerations, it is difficult to determine the true nature of intraoral psoriasis (Fig. 16-113). To render a diagnosis of intraoral psoriasis, some investigators say that the activity of the oral lesions should parallel that of the cutaneous lesions. Some authors refer to **erythema migrans** (see page 726) as *intraoral psoriasis,* and the prevalence of erythema migrans in psoriatic patients appears to be slightly greater than that seen in the rest of the population. It is difficult, however, to prove a direct correlation of that common mucosal alteration with psoriasis.



• **Fig. 16-114 Psoriasis.** Low-power photomicrograph showing elongation of the rete ridges, hyperkeratosis, and inflammation of the papillary dermis.

Histopathologic Features

Microscopically, psoriasis has a characteristic pattern. The surface epithelium shows marked parakeratin production, and the epithelial rete ridges are elongated (Fig. 16-114). The connective tissue papillae, which contain dilated capillaries, approach close to the epithelial surface, and a perivascular chronic inflammatory cell infiltrate is present. In addition, collections of neutrophils **(Munro abscesses),** are seen within the parakeratin layer.

With respect to oral lesions, good correlation with skin disease activity should be seen in addition to the characteristic histopathologic features, because other intraoral lesions, such as erythema migrans and oral mucosal cinnamon reaction (see page 322), exhibit a psoriasiform microscopic appearance.

Treatment and Prognosis

The treatment of psoriasis depends on the severity of the disease activity. For mild lesions, no treatment may be necessary.

For moderate involvement, topical corticosteroids are commonly prescribed in the United States. Coal tar derivatives and keratolytic agents also may be used. Other topical drugs that have proven effective include vitamin D_3 analogues (calcipotriene, calcipotriol, and calcitriol), and tazarotene, a retinoid (vitamin A) compound. Newer topical biologic agents include the calcineurin inhibitors, tacrolimus and pimecrolimus, although these are usually reserved for recalcitrant lesions. Exposure to UV radiation may also be helpful for mild to moderate disease.

For severe cases, **p**soralen and **u**ltra**v**iolet **A** (PUVA) therapy or ultraviolet B (UVB) therapy may be needed. Methotrexate or cyclosporine may also be used as systemic treatments for severe disease; however, these drugs have significant side effects. Newer systemic biologic agents that target specific disease-related components include infliximab, adalimumab, and etanercept (directed against tumor necrosis factor-alpha [TNF-α]); alefacept (directed against T-cell receptors); or ustekinumab (directed against IL-12 and IL-23).

Although the mortality rate is not increased in patients with psoriasis, the condition often persists for years despite therapy. A recent 30-year prospective study has shown a definite increase in the risk for cutaneous squamous cell carcinoma in psoriasis patients who have received over 350 life-time PUVA treatments, but those who received fewer than 150 had a very modest increase. Interestingly, the risk for development of basal cell carcinoma did not seem to be significantly elevated.

◆ LUPUS ERYTHEMATOSUS

Lupus erythematosus (LE) is a classic example of an immunologically mediated condition, and is the most common of the so-called collagen vascular or connective tissue diseases in the United States, with more than 1.5 million people affected. It may exhibit any one of several clinicopathologic forms.

Systemic lupus erythematosus (SLE) is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of the humoral limb (B lymphocytes) of the immune system in conjunction with abnormal function of the T lymphocytes. Although genetic factors probably play a role in the pathogenesis of SLE, the precise cause is unknown. Undoubtedly, interplay between genetic and environmental factors occurs, for if SLE develops in one monozygotic (identical) twin, then the other twin has a 24% chance of having SLE as well. In contrast, if one dizygotic (fraternal) twin has SLE, then the other twin has only a 2% chance of being affected.

Chronic cutaneous lupus erythematosus (CCLE) may represent a different, but related, process. It primarily affects the skin and oral mucosa, and the prognosis is good.

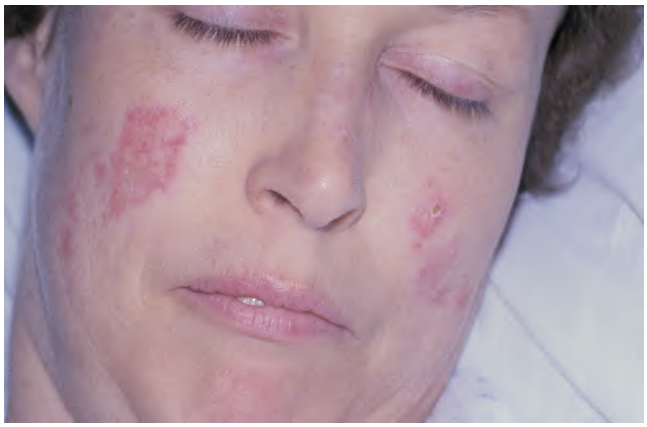
Subacute cutaneous lupus erythematosus (SCLE) is a third form of the disease, which has clinical features intermediate between those of SLE and CCLE.

Clinical Features

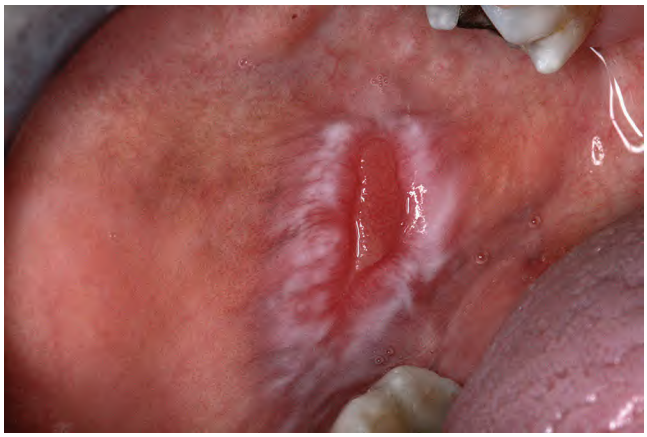
Systemic Lupus Erythematosus

SLE can be a very difficult disease to diagnose in its early stages because it often appears in a nonspecific, vague fashion, frequently with periods of remission or disease inactivity. Women are affected nearly 8 to 10 times more frequently than men. The average age at diagnosis is 31 years. Common findings include fever, weight loss, arthritis, fatigue, and general malaise. In 40% to 50% of affected patients, a characteristic rash, having the pattern of a butterfly, develops over the malar area and nose (Fig. 16-115), typically sparing the nasolabial folds. Sunlight often makes the lesions worse.

The kidneys are affected in approximately 40% to 50% of SLE patients. This complication may ultimately lead to kidney failure; thus it is typically the most significant aspect of the disease.



• **Fig. 16-115 Systemic Lupus Erythematosus (SLE).** The erythematous patches seen in the malar regions are a characteristic sign.

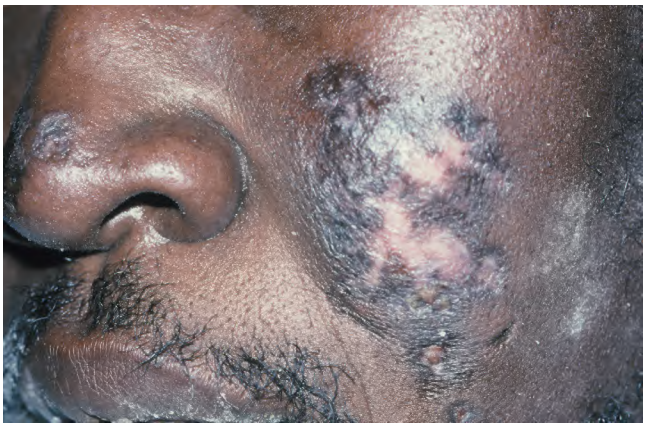


• **Fig. 16-116 Systemic Lupus Erythematosus (SLE).** This ulceration of the buccal mucosa exhibits fine radiating white striae at its periphery, clinically appearing similar to erosive lichen planus.

Cardiac involvement is also common, with pericarditis being the most frequent complication. At autopsy nearly 50% of SLE patients display warty vegetations affecting the heart valves **(Libman-Sacks endocarditis).** Its significance is debatable, although some patients may develop superimposed subacute bacterial endocarditis on these otherwise sterile outgrowths of fibrinoid material and connective tissue cells.

Oral lesions of SLE develop in 5% to 25% of these patients, although some studies indicate prevalence as high as 40%. The lesions usually affect the palate, buccal mucosa, and gingivae. Sometimes they appear as lichenoid areas, but they may also look nonspecific or even somewhat granulomatous (Fig. 16-116). Involvement of the vermilion zone of the lower lip **(lupus cheilitis)** is sometimes seen. Varying degrees of ulceration, pain, erythema, and hyperkeratosis may be present. Other oral complaints such as xerostomia, stomatodynia, candidiasis, periodontal disease, and dysgeusia have been described, but the direct association of these problems with SLE remains to be proven.

Confirming the diagnosis of SLE can often be difficult, particularly in the early stages. Criteria for making the diagnosis of SLE have been established by the American Rheumatism Association, and these include both clinical and laboratory findings (Table 16-4).



• **Fig. 16-117 Chronic Cutaneous Lupus Erythematosus (CCLE).** The skin lesions are characterized by scaling, atrophy, and pigmentary disturbances, which are most evident on sun-exposed skin.

Chronic Cutaneous Lupus Erythematosus

Patients with CCLE usually have few or no systemic signs or symptoms, with lesions being limited to skin or mucosal surfaces. The skin lesions of CCLE most commonly present as **discoid lupus erythematosus.** They begin as scaly, erythematous patches that are frequently distributed on sun-exposed skin, especially in the head and neck area (Fig. 16-117). Patients may indicate that the lesions are exacerbated by sun exposure. With time, the lesions may heal spontaneously in one area, only to appear in another area. The healing process usually results in cutaneous atrophy with scarring and hypopigmentation or hyperpigmentation of the resolving lesion. Conjunctival involvement by CCLE has rarely been reported to cause cicatrizing conjunctivitis, clinically similar to mucous membrane pemphigoid.

In most cases the oral manifestations of CCLE essentially appear clinically identical to the lesions of erosive lichen planus. Unlike the oral lesions of lichen planus, however, the oral lesions of CCLE seldom occur in the absence of skin lesions. An ulcerated or atrophic, erythematous central zone, surrounded by white, fine, radiating striae, characterizes the oral lesion of CCLE (Figs. 16-118 and 16-119). Sometimes the erythematous, atrophic central region of a lesion may show a fine stippling of white dots. As with erosive lichen planus, the ulcerative and atrophic oral lesions of CCLE may be painful, especially when exposed to acidic or salty foods.

Subacute Cutaneous Lupus Erythematosus

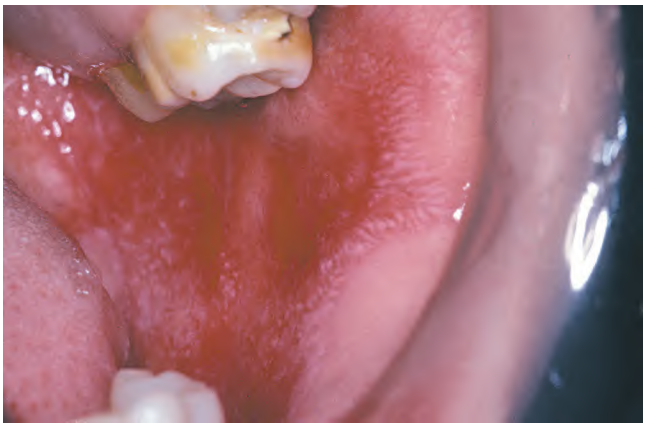
Patients with SCLE have clinical manifestations intermediate between those of SLE and CCLE. The skin lesions are the most prominent feature of this variation. They are characterized by photosensitivity and are, therefore, generally present in sun-exposed areas. These lesions do not show the induration and scarring seen with the skin lesions of CCLE.

TABLE 16-4 Prevalence of Clinical and Laboratory Manifestations of Systemic Lupus Erythematosus

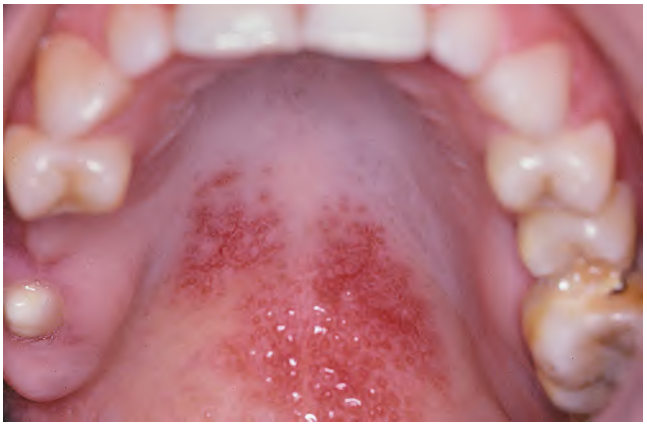
Findings	Affected Patients (%)
Systemic Signs and Symptoms: Fatigue, Malaise, Fever, Anorexia, Weight Loss	**95%**
MUSCULOSKELETAL SYMPTOMS	**95%**
Arthralgia/myalgia	95%
Nonerosive polyarthritis	60%
CUTANEOUS SIGNS	**80%**
Photosensitivity	70%
Malar rash	50%
Oral ulcers	40%
Discoid rash	20%
HEMATOLOGIC SIGNS	**85%**
Anemia (chronic disease)	70%
Leukopenia (<4000/μL)	65%
Lymphopenia (<1500/μL)	50%
Thrombocytopenia (<100,000/μL)	15%
Hemolytic anemia	10%
NEUROLOGIC SIGNS AND SYMPTOMS	**60%**
Cognitive disorder	50%
Headache	25%
Seizures	20%
CARDIOPULMONARY SIGNS	**60%**
Pleurisy, pericarditis, effusions	30%-50%
Myocarditis, endocarditis	10%
RENAL SIGNS	**30%-50%**
Proteinuria > 500 mg/24 hours, cellular casts	30%-50%
Nephrotic syndrome	25%
End-stage renal disease	5%-10%

Adapted from Hahn BH: Systemic lupus erythematosus. In Longo DL, Fauci AS, Kasper DL, et al, editors: *Harrison's principles of internal medicine,* ed 18, New York, 2012, McGraw-Hill, pp 2724-2735. Reproduced with permission of The McGraw-Hill Companies.

Oral lesions similar to those of CCLE have been described in this variant of lupus as well. Usually, the renal or neurologic abnormalities associated with SLE are not present, although most patients will have arthritis or musculoskeletal problems. SCLE may be triggered by any one of a variety of medications (see page 317).



• **Fig. 16-118 Chronic Cutaneous Lupus Erythematosus (CCLE).** Radiating keratotic striae surround erythematous zones of the buccal mucosa. These features are similar to those of erosive lichen planus.



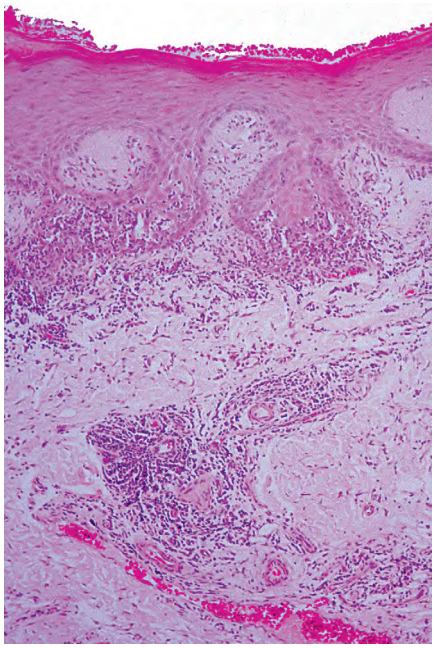
• **Fig. 16-119 Chronic Cutaneous Lupus Erythematosus (CCLE).** Oral involvement may also include relatively nondescript erythematous patches, such as this one in the palate.

Histopathologic Features

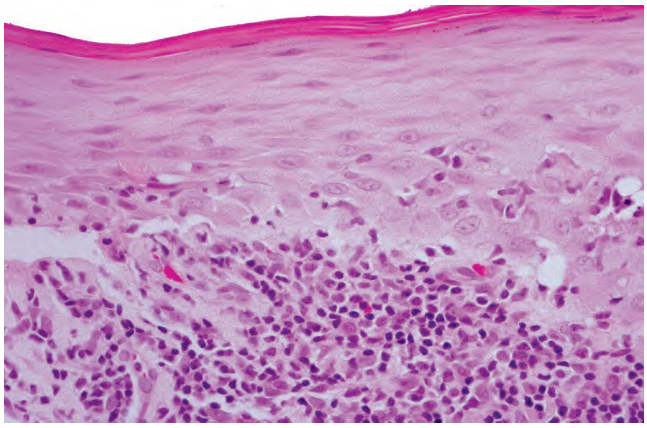
The histopathologic features of the skin and oral lesions of the various forms of LE show some features in common but are different enough to warrant separate discussions.

The skin lesions of CCLE are characterized by hyperkeratosis, often displaying keratin packed into the openings of hair follicles ("follicular plugging"). In all forms of LE, degeneration of the basal cell layer is frequently observed, and the underlying connective tissue supports patchy to dense aggregates of chronic inflammatory cells (Figs. 16-120 and 16-121). In the deeper connective tissue, the inflammatory infiltrate often surrounds the small blood vessels.

The oral lesions demonstrate hyperkeratosis, alternating atrophy and thickening of the spinous cell layer, degeneration of the basal cell layer, and subepithelial lymphocytic infiltration. These features may also be seen in oral lichen planus; however, the two conditions can usually be distinguished by the presence in LE of patchy deposits of a periodic acid-Schiff (PAS)-positive material in the basement membrane zone, subepithelial edema (sometimes to the point of vesicle formation), and a more diffuse, deep



• **Fig. 16-120 Lupus Erythematosus (LE).** Low-power photomicrograph showing hyperparakeratosis with interface mucositis and perivascular inflammation.



• **Fig. 16-121 Lupus Erythematosus (LE).** High-power photomicrograph of the interface mucositis.

inflammatory infiltrate, often in a perivascular orientation. Some authorities, however, feel that differentiating lichen planus from LE is best done by direct immunofluorescence studies or histopathologic examination of the cutaneous lesions.

Diagnosis

In addition to the clinical and microscopic features, a number of additional immunologic studies may be helpful in making the diagnosis of LE.

Direct immunofluorescence testing of lesional tissue shows deposition of one or more immunoreactants (usually IgM, IgG, or C3) in a shaggy or granular band at the basement membrane zone. In addition, direct immunofluorescence testing of clinically normal skin of SLE patients often shows a similar deposition of IgG, IgM, or complement components. This finding is known as a **positive lupus band test.** Although a positive lupus band test is consistent with the diagnosis of LE, it is now known that other conditions, such as rheumatoid arthritis, Sjögren syndrome, and systemic sclerosis, may also have similar positive findings. Furthermore, some patients with LE may not have a positive lupus band test; therefore, this study must always be interpreted in the context of other clinical signs.

Evaluation of serum obtained from a patient with SLE shows various immunologic abnormalities. Approximately 95% of these patients have antibodies directed against multiple nuclear antigens (i.e., antinuclear antibodies [ANAs]). Although this is a nonspecific finding that may be seen in other autoimmune diseases, as well as in otherwise healthy older individuals, it is nevertheless useful as a screening study. Furthermore, if results are negative on multiple occasions, then the diagnosis of SLE should probably be doubted. Antibodies directed against double-stranded DNA are noted in 70% of patients with SLE, and these are more specific for the disease. Another 30% of patients show antibodies directed against Sm, a protein that is complexed with small nuclear RNA. This finding is very specific for SLE.

A summary of selected immunologic findings in LE is shown in Table 16-5.

Treatment and Prognosis

Patients with SLE should avoid excessive exposure to sunlight because UV light may precipitate disease activity. Mild active disease may be effectively managed using NSAIDs combined with antimalarial drugs, such as hydroxychloroquine. For more severe, acute episodes that involve arthritis, pericarditis, thrombocytopenia, or nephritis, systemic corticosteroids are generally indicated; these may be combined with other immunosuppressive and immunomodulating agents. If oral lesions are present, they typically respond to the systemic therapy.

As with SLE patients, patients with CCLE should avoid excessive sunlight exposure. Because most of the manifestations of CCLE are cutaneous, topical corticosteroids are often reasonably effective. Topical calcineurin inhibitors (tacrolimus or pimecrolimus) may also be used, although these medications are relatively expensive. For cases that are resistant to topical therapy, systemic antimalarial drugs, immunosuppressive drugs, immunomodulating drugs, or low-dose thalidomide may produce a response. Topical corticosteroids are also helpful in treating the oral lesions of CCLE.

The prognosis for the patient with SLE is variable. For patients undergoing treatment today, the 5-year survival rate is approximately 95%; however, by 20 years, the survival rate falls to 75%. Ultimately, the prognosis depends on which organs are affected and how frequently the disease is reactivated. The most common cause of death is renal failure; however, chronic immunosuppression also predisposes these patients to increased mortality because of

TABLE 16-5 Selected Abnormal Immunologic Findings in Lupus Erythematosus

Findings	Frequency	Significance
Direct immunofluorescence, lesional skin	CCLE: 90% SLE: 95%	May help distinguish among the various types of LE
Direct immunofluorescence, normal skin	CCLE: 0% SLE: 25%-60%	Lupus band test
Antinuclear antibodies (ANAs)	CCLE: 0%-10% SLE: 95%	Very sensitive for SLE, but not very specific; not useful for CCLE diagnosis
Antidouble-stranded DNA antibodies	CCLE: 0% SLE: 70%-80%	Specific for SLE; may indicate disease activity or kidney involvement
Anti-Sm antibodies	CCLE: 0% SLE: 10%-30%	Specific for SLE

CCLE, Chronic cutaneous lupus erythematosus; *SLE,* systemic lupus erythematosus; *LE,* lupus erythematosus.

infection and development of malignancy. For reasons that are poorly understood, the prognosis is worse for men than for women. In addition, blacks tend to fare more poorly than whites.

The prognosis for patients with CCLE is considerably better than that for patients with SLE, although transformation to SLE may be seen in approximately 5% of CCLE patients. Usually, CCLE remains confined to the skin, but it may persist and be quite a nuisance. For about 50% of CCLE patients, the problem eventually resolves after several years.

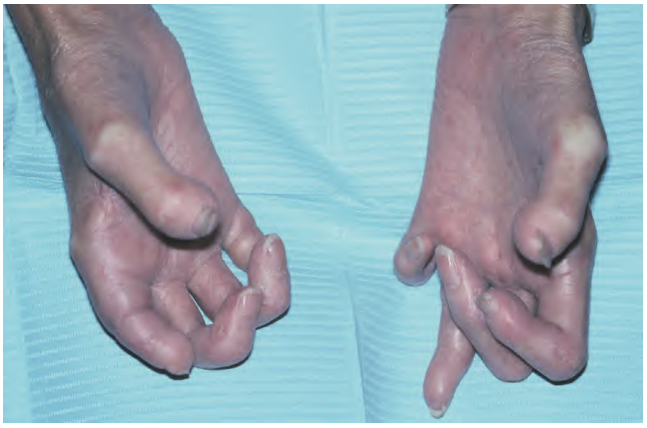
◆ SYSTEMIC SCLEROSIS (PROGRESSIVE SYSTEMIC SCLEROSIS; SCLERODERMA; HIDE-BOUND DISEASE)

Systemic sclerosis is a relatively rare condition that probably has an immunologically mediated pathogenesis involving abnormal interactions among vascular tissue, connective tissue, and immune cells in genetically predisposed individuals. For reasons that are not understood, dense collagen is deposited in the tissues of the body in extraordinary amounts. Although its most dramatic effects are seen in association with the skin, the disease is often quite serious, with most organs of the body affected.

Clinical and Radiographic Features

Systemic sclerosis affects approximately 10 to 20 persons per million population each year. Women have the condition three to five times more frequently than do men. Most patients are adults. The onset of the disease is generally insidious, with the cutaneous changes often responsible for bringing the problem to the patient's attention.

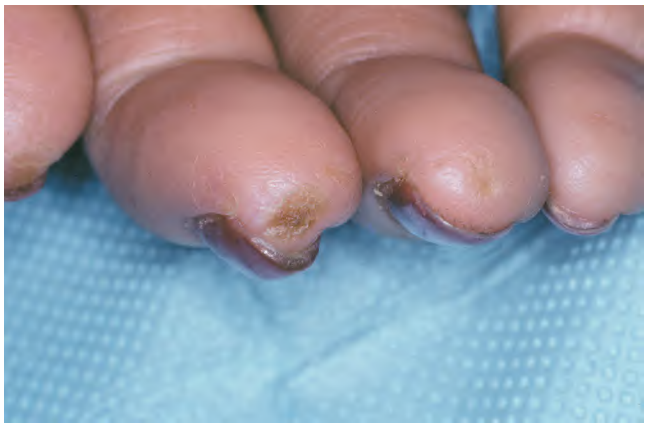
Often one of the first signs of the disease is **Raynaud phenomenon**, a vasoconstrictive event triggered by emotional distress or exposure to cold. Raynaud phenomenon



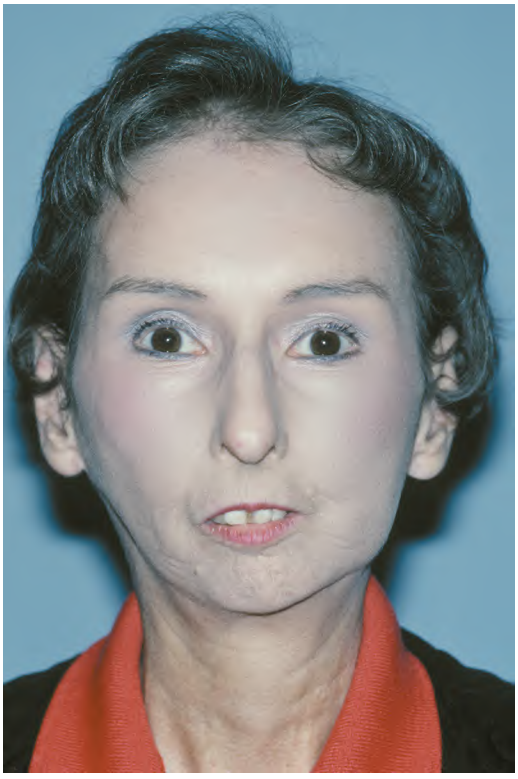
• **Fig. 16-122 Systemic Sclerosis.** The tense, shiny appearance of the skin is evident. Note that the fingers are fixed in a clawlike position, with some showing shortening as a result of acro-osteolysis.

(see CREST syndrome, on page 747) is not specific for systemic sclerosis, however, because it may be present in other immunologically mediated diseases and in otherwise healthy people. Resorption of the terminal phalanges **(acro-osteolysis)** and flexion contractures produce shortened, clawlike fingers (Fig. 16-122). The vascular events and the abnormal collagen deposition contribute to the production of ulcerations on the fingertips (Fig. 16-123).

The skin develops a diffuse, hard texture (*sclero* = hard; *derma* = skin), and its surface is usually smooth. Involvement of the facial skin by subcutaneous collagen deposition results in the characteristic smooth, taut, masklike facies (Fig. 16-124). Similarly, the nasal alae become atrophied, resulting in a pinched appearance to the nose, called a *mouse facies.* When the skin changes are confined to the hands, face, feet, and lower portions of the limbs, the designation of *limited cutaneous systemic sclerosis* is applied. If these changes progress rapidly to involve the skin of the trunk and the proximal limbs, or if the changes begin in these areas, then the process is termed *diffuse cutaneous*



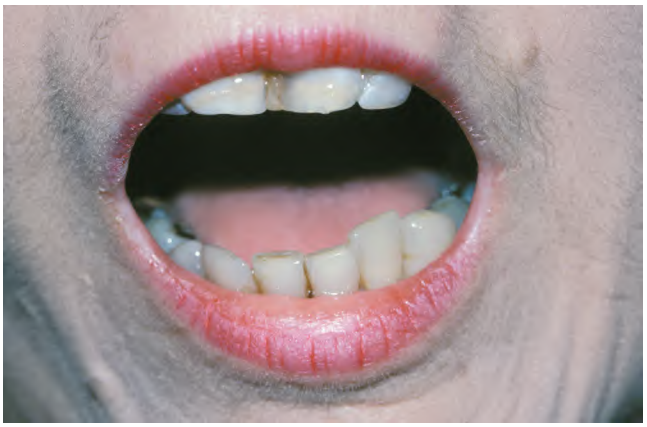
• **Fig. 16-123 Systemic Sclerosis.** Ulcerations of the fingertips.



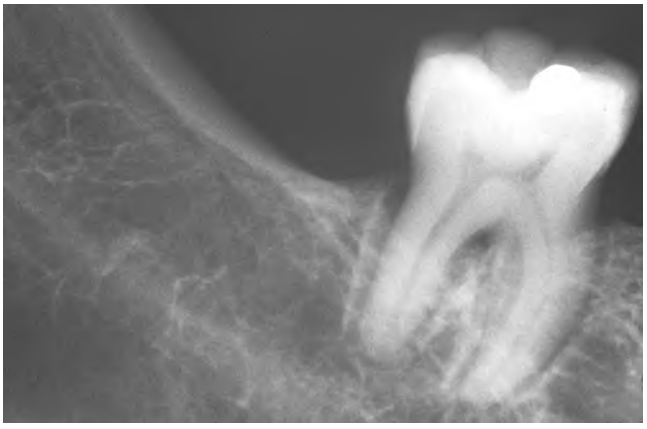
• **Fig. 16-124 Systemic Sclerosis.** The involvement of the facial skin with abnormal collagen deposition produces a masklike facies. Note the loss of the alae of the nose.

systemic sclerosis. These two presentations seem to have different prognoses.

Involvement of other organs may be subtle at first, but the results are more serious. Fibrosis of the lungs, heart, kidneys, and gastrointestinal tract are seen primarily in patients with diffuse cutaneous systemic sclerosis, and the abnormal collagen deposition leads to organ failure, typically within the first 3 years after the diagnosis is made. Pulmonary fibrosis is particularly significant, leading to pulmonary hypertension and heart failure, a primary cause of death for these patients. Patients with limited cutaneous systemic sclerosis tend to develop pulmonary hypertension later than those with a diffuse presentation.



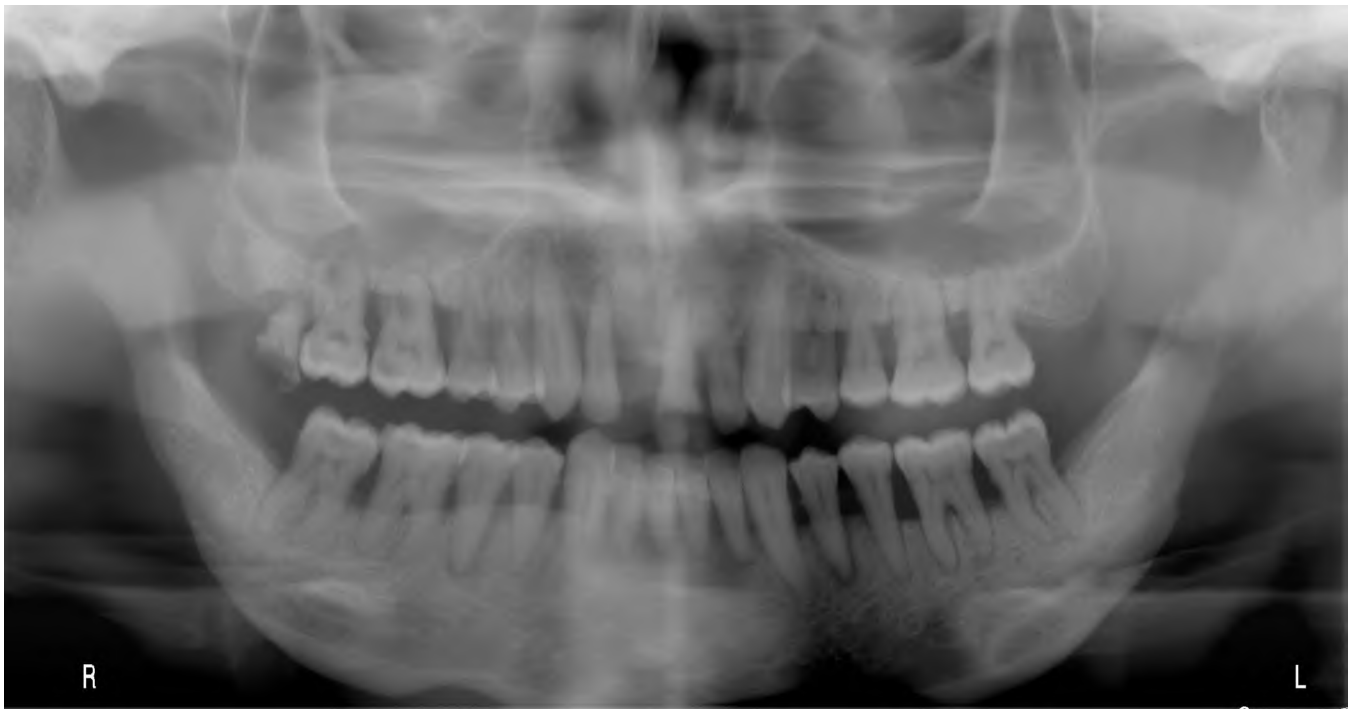
• **Fig. 16-125 Systemic Sclerosis.** Same patient as depicted in Fig. 16-124. Because of the associated microstomia, this is the patient's maximal opening.



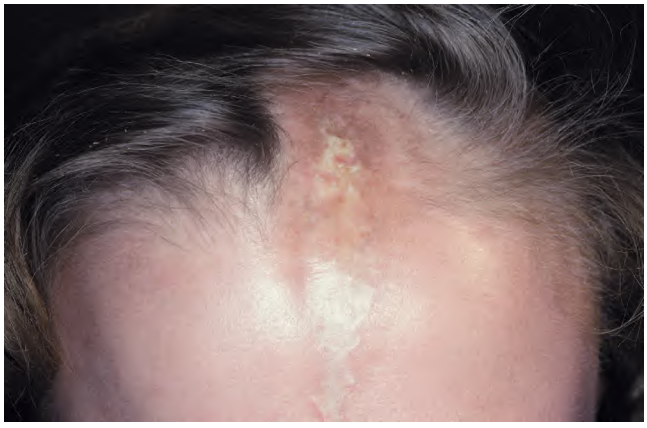
• **Fig. 16-126 Systemic Sclerosis.** Diffuse widening of the periodontal ligament space is often identified on evaluation of periapical radiographs.

The oral manifestations occur in varying degrees. **Microstomia** often develops as a result of collagen deposition in the perioral tissues. This causes a limitation of opening the mouth in nearly 70% of these patients (Fig. 16-125). Characteristic furrows radiating from the mouth produce a "purse string" appearance. Loss of attached gingival mucosa and multiple areas of gingival recession may occur in some patients. Dysphagia often develops as a result of deposition of collagen in the lingual and esophageal submucosa, producing a firm, hypomobile (boardlike) tongue and an inelastic esophagus, thus hindering swallowing. Xerostomia is frequently identified in these patients, and the possibility of concurrent secondary Sjögren syndrome may require consideration.

On dental radiographs, diffuse widening of the periodontal ligament space is often present throughout the dentition. The extent of the widening may vary, with some examples being subtle and others quite dramatic (Fig. 16-126). Varying degrees of resorption of the posterior ramus of the mandible, the coronoid process, the chin, and the condyle may be detected on panoramic radiographs, affecting approximately 10% to 20% of patients (Fig. 16-127). In



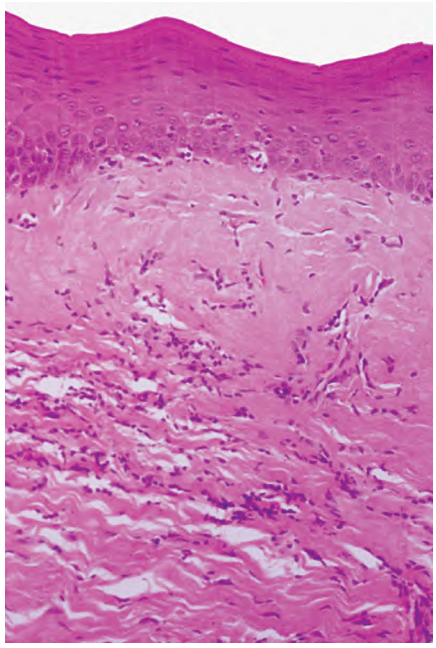
• **Fig. 16-127 Systemic Sclerosis.** Panoramic radiographic evaluation may show a characteristic resorption of the ramus, coronoid process, or condyle.



• **Fig. 16-128 Localized Scleroderma (Morphea).** The cutaneous alteration on the patient's forehead represents a limited form of scleroderma called *en coup de sabre,* because the lesion resembles a scar that might result from a cut with a sword.

theory, these areas are resorbed because of the increased pressure associated with the abnormal collagen production. Individual tooth resorption has also been reported to occur at a higher frequency in these patients.

A milder condition that resembles cutaneous systemic sclerosis has been called **localized scleroderma** or **morphea,** and it usually affects only a solitary patch of skin. Because these lesions often look like scars, the name *en coup de sabre* ("strike of the sword") is used to describe them (Fig. 16-128). This problem is primarily cosmetic and, unlike systemic sclerosis, it is rarely life threatening. For this reason, many authorities now feel that this disorder may be unrelated to systemic sclerosis.



• **Fig. 16-129 Systemic Sclerosis.** Medium-power photomicrograph of an oral biopsy specimen. Diffuse deposition of collagen is apparent throughout the lamina propria.

Histopathologic Features

Microscopic examination of tissue involved by systemic sclerosis shows diffuse deposition of dense collagen within and around the normal structures (Fig. 16-129). This abnormal collagen replaces and destroys the normal tissue, causing the loss of normal tissue function.

Diagnosis

During the early phases, it may be difficult to make a diagnosis of systemic sclerosis. Generally, the clinical signs of stiffened skin texture along with the development of Raynaud phenomenon are suggestive of the diagnosis. A skin biopsy may be supportive of the diagnosis if abundant collagen deposition is observed microscopically.

Laboratory studies may be helpful to the diagnostic process if anticentromere antibodies or anti-Scl 70 (topoisomerase I) is detected. Anti-topoisomerase I antibodies are seen more often with diffuse cutaneous systemic sclerosis and development of pulmonary fibrosis; anticentromere antibodies are usually associated with limited cutaneous systemic sclerosis (including **CREST syndrome**—see next topic), as well as development of pulmonary hypertension.

Treatment and Prognosis

The management of systemic sclerosis is difficult. Unfortunately, many of the recommended treatments have not been examined in controlled trials, and the natural waxing and waning course of the disease makes it difficult to assess the effectiveness of a given treatment in an open-label trial. Systemic medications, such as penicillamine, are prescribed in an attempt to inhibit collagen production. One double-blind study, however, showed no difference in measured patient outcomes with high-dose versus low-dose penicillamine, suggesting that perhaps this medication has limited efficacy. Surprisingly, corticosteroids are of little benefit, and some studies have suggested that their use may increase the risk of renal disease. Extracorporeal photochemotherapy has shown some beneficial effect on the skin lesions; however, no improvement of the pulmonary function tests is observed.

Other management strategies are directed at controlling symptoms. Such techniques as esophageal dilation are used, for example, to temporarily correct the esophageal dysfunction and dysphagia. Calcium channel blocking agents help to increase peripheral blood flow and lessen the symptoms of Raynaud phenomenon, but many patients can reduce episodes by keeping warm (especially their hands and feet) or by stopping cigarette smoking. Angiotensin-converting enzyme (ACE) inhibitors often effectively control hypertension if kidney involvement is prominent.

From a dental standpoint, problems may develop for patients who wear prostheses because of the microstomia and inelasticity of the mouth. Collapsible dental appliances with special hinges have been made to facilitate the insertion and removal of dentures. Microstomia and inelastic soft tissue also hamper the maintenance of good oral hygiene, and affected patients have a decreased ability to manipulate a toothbrush as a result of sclerotic changes in the fingers and hands. Surgical correction of open bite associated with condylar resorption has been described. Infrequently, the resorption of the mandible may become so great as to cause a pathologic fracture.

The prognosis is poor, although the outlook is better for patients with limited cutaneous involvement than for those with diffuse involvement. If the heart is affected, then the prognosis is particularly poor, but most patients die because of pulmonary involvement. Overall survival figures are difficult to calculate due to a variety of factors, including the rarity of the disease, the inherent variability of its natural course, and the variation in treatments provided at medical centers around the world. With current treatment regimens, it is estimated that 10-year survival rates for patients with limited cutaneous systemic sclerosis approach 75% to 80%, whereas survival drops to 55% to 60% for patients with diffuse cutaneous systemic sclerosis.

◆ CREST SYNDROME (ACROSCLEROSIS; LIMITED SCLERODERMA)

CREST syndrome is an uncommon condition that some authorities now believe represents a variant of limited cutaneous systemic sclerosis. The term *CREST* is an acronym for **C**alcinosis cutis, **R**aynaud phenomenon, **E**sophageal dysfunction, **S**clerodactyly, and **T**elangiectasia.

Clinical Features

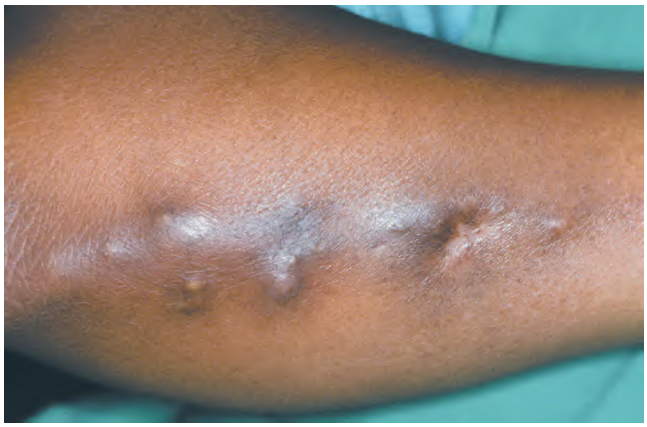
As with all types of systemic sclerosis, most patients with CREST syndrome are women in the sixth or seventh decade of life. The characteristic signs may not appear synchronously but instead may develop sequentially over a period of months to years.

Calcinosis cutis occurs in the form of movable, nontender, subcutaneous nodules, 0.5 to 2.0 cm in size, which are usually multiple (Fig. 16-130). Larger, more numerous or superficial calcifications may occasionally become bothersome and require removal.

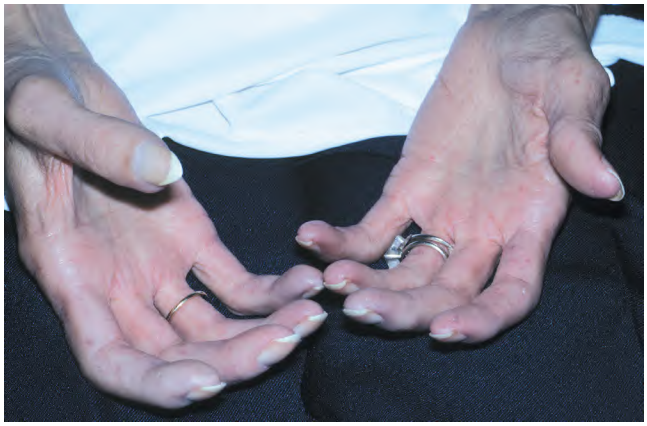
Raynaud phenomenon may be observed when a person's hands or feet are exposed to cold temperatures. The initial clinical sign is a dramatic blanching of the digits, which appear dead-white in color as a result of severe vasospasm. A few minutes later, the affected extremity takes on a bluish color because of venous stasis. After warming, increased blood flow results in a dusky-red hue with the return of hyperemic blood flow. This may be accompanied by varying degrees of throbbing pain.

Esophageal dysfunction, caused by abnormal collagen deposition in the esophageal submucosa, may not be noticeable in the early phases of CREST syndrome. Often the subtle initial signs of this problem must be demonstrated by barium swallow radiologic studies.

The **sclerodactyly** of CREST syndrome is rather remarkable. The fingers become stiff, and the skin takes on a smooth, shiny appearance. Often the fingers undergo permanent flexure, resulting in a characteristic "claw" deformity (Fig. 16-131). As with other forms of cutaneous systemic sclerosis, this change is due to abnormal deposition of collagen within the dermis in these areas.



• **Fig. 16-130 CREST Syndrome.** The subcutaneous nodules on this patient's arm represent deposition of calcium salts (calcinosis cutis). (Courtesy of Dr. Román Carlos.)



• **Fig. 16-131 CREST Syndrome.** Clawlike deformity affecting the hands (sclerodactyly).

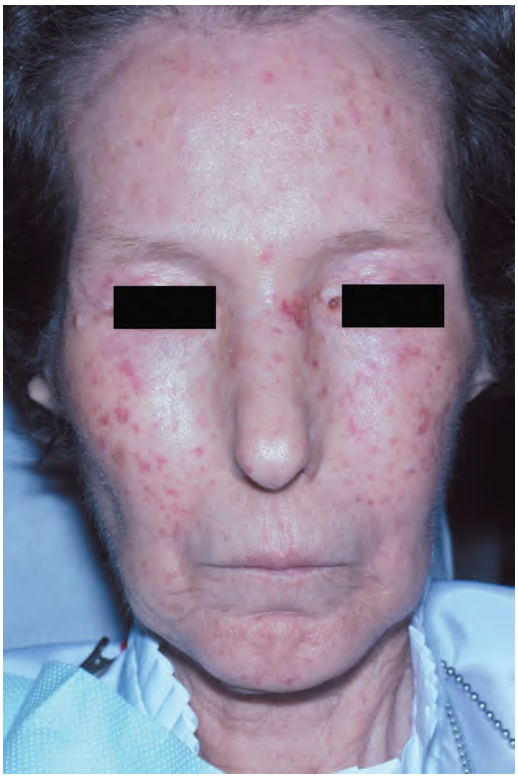
The **telangiectasias** in this syndrome are similar to those seen in hereditary hemorrhagic telangiectasia (HHT) (see page 702). As with that condition, significant bleeding from the superficial dilated capillaries may occur. The facial skin and the vermilion zone of the lips are commonly affected (Fig. 16-132).

Histopathologic Features

The histopathologic findings in CREST syndrome are similar, although milder, to those seen in systemic sclerosis. Superficial dilated capillaries are observed if a telangiectatic vessel is included in the biopsy specimen.

Diagnosis

Sometimes, HHT may be considered in the differential diagnosis if the history is unclear and the other signs of CREST syndrome are not yet evident. In these cases, laboratory studies directed at identifying anticentromere antibodies may be useful, because this test is relatively specific for CREST syndrome and other types of limited cutaneous systemic sclerosis.



• **Fig. 16-132 CREST Syndrome.** The patient shows numerous red facial macules representing telangiectatic blood vessels.

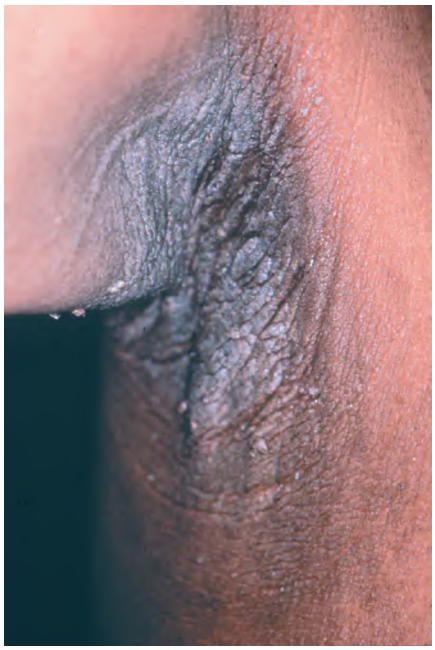
Treatment and Prognosis

The treatment of patients with CREST syndrome is essentially the same as that of those with systemic sclerosis. Because CREST syndrome usually is not as severe, the treatment does not have to be as aggressive. Although the prognosis for this condition is much better than that for systemic sclerosis, patients should be monitored for an increased risk of developing pulmonary hypertension or primary biliary cirrhosis, generally more than 10 years after the initial diagnosis.

◆ ACANTHOSIS NIGRICANS

Acanthosis nigricans is an acquired dermatologic problem characterized by the development of a velvety, brownish alteration of the skin. In some instances, this unusual condition develops in conjunction with a malignancy, usually gastrointestinal cancer, and is termed **malignant acanthosis nigricans.** The cutaneous lesion itself is benign, yet it is significant because it represents a cutaneous marker for internal malignancy. The cause of malignant acanthosis nigricans is unknown, although a cytokine-like peptide capable of affecting the epidermal cells may be produced by the malignancy.

Most cases, estimated to affect as many as 5% of adults, are not associated with a malignancy and are termed **benign acanthosis nigricans.** A clinically similar form, **pseudoacanthosis nigricans,** may occur in some obese people. Some



• **Fig. 16-133 Acanthosis Nigricans.** The lesions are characterized by numerous fine, almost velvety, confluent papules. The lesions most often affect the flexural areas, such as the axilla depicted in this photograph. (From Hall JM, Moreland A, Cox GJ, et al: Oral acanthosis nigricans: report of a case and comparison of oral and cutaneous pathology, *Am J Dermatopathol* 10:68-73, 1988.)

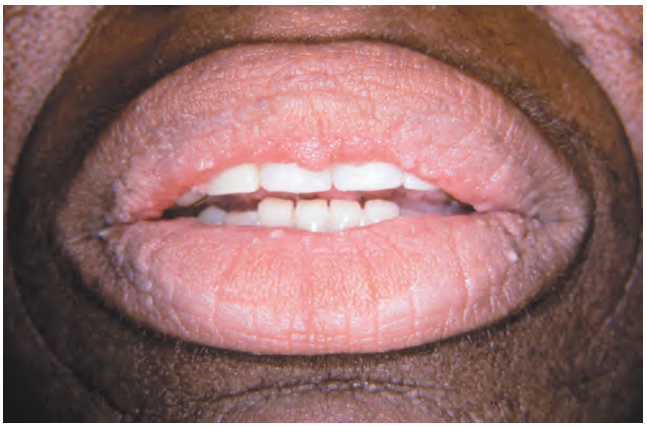
benign forms of acanthosis nigricans may be inherited or may occur in association with various endocrinopathies, such as diabetes mellitus, Addison disease, hypothyroidism, and acromegaly. Furthermore, benign acanthosis nigricans may occur with certain syndromes (e.g., Crouzon syndrome) or drug ingestion (e.g., oral contraceptives or corticosteroids). These forms of the condition are typically associated with resistance of the tissues to the effects of insulin, similar to the insulin resistance seen in non–insulin-dependent diabetes mellitus (NIDDM). Even though the affected individuals may not have overt diabetes mellitus, they often show increased levels of insulin or an abnormal response to exogenously administered insulin.

Clinical Features

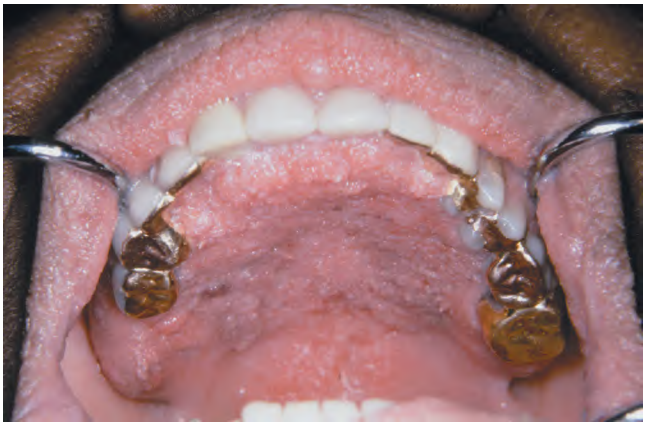
The malignant form of acanthosis nigricans develops in association with an internal malignancy, particularly adenocarcinoma of the gastrointestinal tract. Approximately 20% of the cases of malignant acanthosis nigricans are identified before the malignancy is found, but most appear at about the same time as discovery of the gastrointestinal tumor or thereafter.

Both forms of acanthosis nigricans affect the flexural areas of the skin predominantly, appearing as finely papillary, hyperkeratotic, brownish patches that are usually asymptomatic (Fig. 16-133). The texture of the lesions has been variably described as either velvety or leathery.

Oral lesions of acanthosis nigricans have also been reported and may occur in 25% to 50% of affected patients,



• **Fig. 16-134 Acanthosis Nigricans.** The vermilion zone of the lips is affected. (Courtesy of Dr. George Blozis.)



• **Fig. 16-135 Acanthosis Nigricans.** Same patient as depicted in Fig. 16-134. Note involvement of the palatal mucosa. (Courtesy of Dr. George Blozis.)

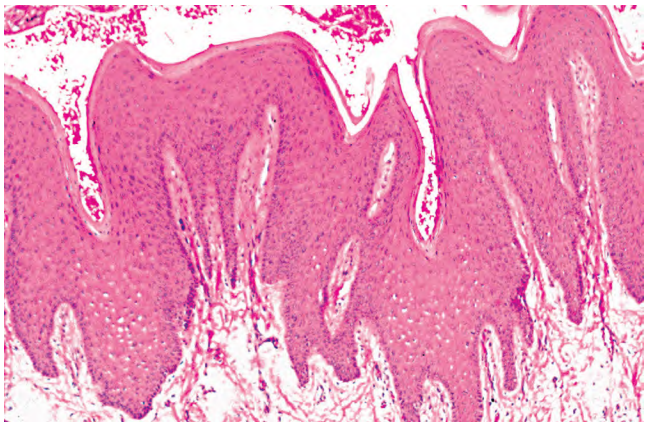
especially those with the malignant form. These lesions appear as diffuse, finely papillary areas of mucosal alteration that most often involve the tongue or lips, particularly the upper lip (Figs. 16-134 and 16-135). The buccal mucosa may also be affected. The brownish pigmentation associated with the cutaneous lesions is usually not seen in oral acanthosis nigricans.

Histopathologic Features

The histopathologic features of the various forms of acanthosis nigricans are essentially identical. The epidermis exhibits hyperorthokeratosis and papillomatosis. Usually, some degree of increased melanin deposition is noted, but the extent of acanthosis (thickening of the spinous layer) is really rather mild. The oral lesions have much more acanthosis, but show minimal increased melanin pigmentation (Fig. 16-136).

Treatment and Prognosis

Although acanthosis nigricans itself is a harmless process, the patient should be evaluated to ascertain which form of the



• **Fig. 16-136 Acanthosis Nigricans.** Medium-power photomicrograph of an oral lesion showing papillomatosis, mild hyperkeratosis, and acanthosis of the epithelium.

disease is present. Identification and treatment of the underlying malignancy obviously are important for patients with the malignant type; unfortunately, the prognosis for these individuals is very poor. Interestingly, malignant acanthosis nigricans may resolve when the cancer is treated. Keratolytic agents may improve the appearance of the benign forms.

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17 Oral Manifestations of Systemic Diseases

MUCOPOLYSACCHARIDOSIS

The **mucopolysaccharidoses** are a heterogeneous group of metabolic disorders that are usually inherited in an autosomal recessive fashion. These disorders are all characterized by the lack of any one of several normal enzymes needed to process the important intercellular substances known as *glycosaminoglycans.* These substances used to be known as *mucopolysaccharides,* thus the term *mucopolysaccharidosis.* Examples of glycosaminoglycans include the following:

- Heparan sulfate
- Dermatan sulfate
- Keratan sulfate
- Chondroitin sulfate

The type of mucopolysaccharidosis that is seen clinically depends on which of these substrates lacks its particular enzyme. The mucopolysaccharidoses as a group occur with a frequency of approximately 1 in 15,000 to 29,000 live births, although some types are much less common.

Clinical and Radiographic Features

The clinical features of the mucopolysaccharidoses vary, depending on the particular syndrome that is examined (Table 17-1). Furthermore, affected patients with a particular type of this disorder often exhibit a wide range of severity of involvement. Most types of mucopolysaccharidosis are associated with some degree of intellectual disability. Often the facial features of affected patients are somewhat coarse, with heavy brow ridges (Fig. 17-1), and there are other skeletal changes, such as stiff joints. Cloudy degeneration of the corneas, a problem that frequently leads to blindness, is seen in several forms of mucopolysaccharidosis.

The oral manifestations vary according to the particular type of mucopolysaccharidosis. Most types show some degree of macroglossia. Gingival hyperplasia may be present, particularly in the anterior regions, as a result of the drying and irritating effects of mouth breathing. The dental changes include thin enamel with pointed cusps on the posterior teeth, although this seems to be a feature unique to mucopolysaccharidosis type IVA. Other dental manifestations include numerous impacted teeth with prominent follicular spaces (Fig. 17-2), possibly caused by the accumulation of glycosaminoglycans in the follicular connective tissue. Some investigators have reported the occurrence of multiple impacted teeth that are congregated in a single large follicle, forming a rosette pattern radiographically.

Although the clinical findings may suggest that a patient is affected by one of the mucopolysaccharidoses, the diagnosis is confirmed by finding elevated levels of glycosaminoglycans in the urine, as well as deficiencies of the specific enzymes in the patient's leukocytes and fibroblasts.

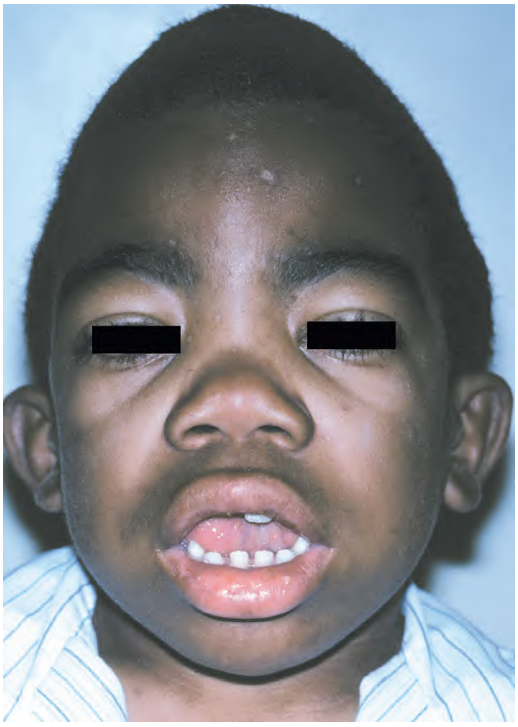
Treatment and Prognosis

No satisfactory systemic treatment of the mucopolysaccharidoses exists at this time. Several forms of mucopolysaccharidosis are associated with a markedly reduced life span and with intellectual disability. Attempts to improve the survival and quality of life of these patients using hematopoietic stem cell transplantation have met with some success. Unfortunately, not all aspects of the disease are corrected, and the complications associated with transplantation must be addressed. Such complications are associated with a 15% to 20% mortality rate. Enzyme replacement therapy currently is available for mucopolysaccharidosis types I, II, and VI. Initiation of the respective recombinant human enzymes—laronidase, idursulfase, and galsulfase—early in the patient's life appears to improve significantly many of the aspects of the disease, although complete resolution does not occur. Because of the rarity of these conditions and the expense of developing the treatments, the annual cost for such therapy can range from $176,000 for laronidase to $657,000 for idursulfase, which currently has the dubious distinction of being the most expensive prescription medication. Genetic counseling is indicated for the parents and siblings of a patient affected by one of the mucopolysaccharidosis syndromes. Prenatal diagnosis is available for family planning as well.

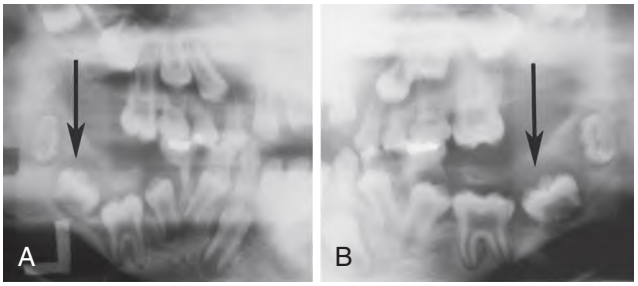
TABLE 17-1 Features of Selected Mucopolysaccharidosis Syndromes

Type	Eponym	Inheritance	Enzyme Deficiency	Stored Substrate	Clinical Features
I-H	Hurler	AR	α-L-Iduronidase	HS and DS	Appears in infancy; cloudy corneas, growth impairment, reduced intelligence, coronary artery disease; rarely live 10 years
I-S	Scheie	AR	α-L-Iduronidase	HS and DS	Onset in late childhood; cloudy corneas, normal intelligence, aortic regurgitation; survive to adulthood
II	Hunter	X-linked R	Iduronate-2-sulfatase	HS and DS	Appears at 1 to 2 years of age; clear corneas, reduced intelligence, growth impairment, stiff joints
III-A	Sanfilippo-A	AR	Heparan *N*-sulphatase	HS	Appears at 4 to 6 years of age; clear corneas, reduced intelligence, mild skeletal changes; death in adolescence
III-B	Sanfilippo-B	AR	α-*N*-acetylglucosaminidase	HS	Generally same as Sanfilippo-A
IV-A	Morquio-A	AR	Galactose-6-sulfatase	KS and CS	Appears at 1 to 2 years of age; cloudy corneas, normal intelligence, lax joints; may survive to middle age
IV-B	Morquio-B	AR	β-galactosidase	KS	Generally similar to Morquio-A
VI	Maroteaux-Lamy	AR	Arylsulphatase B	DS and CS	Appears at 2 to 6 years of age; cloudy corneas, normal intelligence, growth impairment, stiff joints; may survive to adulthood

AR, Autosomal recessive; *CS*, chondroitin sulfate; *DS*, dermatan sulfate; *HS*, heparan sulfate; *KS*, keratan sulfate; *R*, recessive



• **Fig. 17-1 Mucopolysaccharidosis.** This patient affected by Hunter syndrome exhibits the characteristic facial features of this disorder.



• **Fig. 17-2 Mucopolysaccharidosis.** Radiographic examination of the dentition of a child affected by Hunter syndrome typically shows radiolucencies *(arrows)* associated with the crowns of unerupted teeth.

Management of the dental problems of these patients is essentially no different from that of other patients. However, several factors may have to be taken into account:

- Degree of intellectual disability (if any)
- Presence or absence of a seizure disorder
- Degree of joint stiffening
- Extent of other related medical problems

Depending on which of these factors is present and the extent of involvement, dental care may warrant sedation, hospitalization, or general anesthesia of the patient for optimal results. General anesthesia and sedation may be challenging, however, because of excess amounts of pharyngeal

tissues that often produce a smaller than normal airway. In severely affected patients, general anesthesia probably should be considered only in life-threatening situations.

◆ LIPID RETICULOENDOTHELIOSES

The **lipid reticuloendothelioses** are a relatively rare group of inherited disorders. These include the following conditions:

- Gaucher disease
- Niemann-Pick disease
- Tay-Sachs disease

These conditions are seen with increased frequency in patients with Ashkenazi Jewish heritage. Affected patients lack certain enzymes necessary for processing specific lipids; this results in an accumulation of the lipids within a variety of cells. Because of this accumulation, it appeared that cells were attempting to store these substances; therefore, the term *storage disease* was commonly used for these disorders.

In **Gaucher disease** (the most common of the reticuloendothelioses), a lack of glucocerebrosidase results in the accumulation of glucosylceramide, particularly within the lysosomes of cells of the macrophage and monocyte lineage. Three types of Gaucher disease are now recognized: type 1 (nonneuronopathic) is seen primarily in the Ashkenazi Jewish population, and types 2 and 3 (neuronopathic) have a panethnic distribution.

Niemann-Pick disease is characterized by a deficiency of acid sphingomyelinase, resulting in the accumulation of sphingomyelin, also within the lysosomes of macrophages.

Tay-Sachs disease is caused by a lack of β-hexosaminidase A, which results in the accumulation of a ganglioside, principally within the lysosomes of neurons.

All these disorders are inherited as autosomal recessive traits. The genetic mutation known to cause Gaucher disease has been evaluated for the Ashkenazi Jewish population, and approximately 1 in 12 to 17 persons carry the defective gene. Most of the individuals identified as having the gene, however, were heterozygous and, therefore, asymptomatic.

Clinical and Radiographic Features

Gaucher Disease

The clinical features of Gaucher disease are generally the result of the effects of the abnormal storage of glucosylceramide. Macrophages laden with this glucocerebroside are typically rendered relatively nonfunctional, and they tend to accumulate within the liver, spleen, and bone marrow of the affected patient. Bone marrow accumulation displaces the normal hematopoietic cells and produces anemia and thrombocytopenia. In addition, these patients are susceptible to bone infarctions. The resulting bone pain is often the presenting complaint. Characteristic *Erlenmeyer flask* deformities of the long bones, particularly of the femur, are often identified. Accumulations of the macrophages in the spleen and liver result in visceral enlargement. Many affected patients show a significant degree of growth impairment. Neurologic deterioration occurs in patients with the less common types 2 and 3 Gaucher disease. Jaw lesions typically appear as ill-defined radiolucencies that usually affect the mandible, producing thinning of the cortical bone without causing devitalization of the teeth or significant resorption of the lamina dura. The walls of the mandibular canal may also be obliterated by the disease process. Decreased salivary flow has been documented for patients with Gaucher disease compared with an age- and sex-matched population, although this decrease may not be clinically important.

Niemann-Pick Disease

Niemann-Pick disease occurs as three different types, each associated with a different clinical expression and prognosis. Types A and B are caused by a deficiency of acid sphingomyelinase, whereas type C is primarily the result of mutations of either *NPC-1* or *NPC-2,* genes involved with cholesterol processing. Types A and C have **neuronopathic** features, characterized by psychomotor impairment, dementia, spasticity, and hepatosplenomegaly, with death occurring during the first or second decade of life. Type B patients normally survive into adulthood and exhibit **visceral signs,** primarily hepatosplenomegaly, and sometimes pulmonary involvement.

Tay-Sachs Disease

Tay-Sachs disease may have a wide clinical range because the condition is genetically heterogeneous. Some forms are mild, with patients surviving into adulthood. In the severe infantile form, however, rapidly progressive neuronal degeneration develops shortly after birth. Signs and symptoms include blindness, developmental impairment, and intractable seizures. Death usually occurs by 3 to 5 years of age.

Histopathologic Features

Histopathologic examination of an osseous lesion of Gaucher disease shows sheets of lipid-engorged macrophages (Gaucher cells) exhibiting abundant bluish cytoplasm, which has a fine texture resembling wrinkled silk. In Niemann-Pick disease, the characteristic cell seen on examination of a bone marrow aspirate is the "sea blue" histiocyte.

Treatment and Prognosis

Gaucher Disease

For patients with a mild expression of Gaucher disease, no treatment may be necessary. For more severe forms of Gaucher disease, enzyme replacement therapy with one of the macrophage-targeted glucocerebrosidases, including imiglucerase, velaglucerase alfa, and taliglucerase alfa, is used. All of these medications require intravenous (IV) infusion and are quite expensive, often costing more than $150,000 per year for treatment. After 9 to 12 months of therapy, patients exhibit improvement in the status of their anemia, a decrease in plasma glucocerebroside levels, and a

decrease in hepatosplenomegaly. Resolution of the radiographic bone changes takes place over a longer period. Children treated with this regimen may show significant gain in height. Unfortunately enzyme replacement therapy has shown minimal effect on the neuronopathic Gaucher disease types 2 and 3, primarily because the medication cannot cross the blood-brain barrier. Bone marrow transplantation has also been attempted; however, the problems inherent in graft-versus-host disease (GVHD) are still present with that form of therapy, and thus it is not recommended. A case-control study showed that adults with Gaucher disease have an increased risk for hematologic malignancies, particularly lymphoma and multiple myeloma. Genetic counseling should be provided to all affected patients.

Niemann-Pick and Tay-Sachs Disease

The neuronopathic forms of Niemann-Pick disease and the infantile form of Tay-Sachs disease are associated with a poor prognosis. Genetic counseling should be provided for affected families. Molecular markers of these disorders have been developed to identify carriers. Such identification allows earlier intervention in terms of counseling, and targeted population screening for the gene that causes Tay-Sachs disease has resulted in a marked decrease in affected patients during the past three decades.

◆ LIPOID PROTEINOSIS (HYALINOSIS CUTIS ET MUCOSAE; URBACH-WIETHE SYNDROME)

A rare condition, **lipoid proteinosis** is inherited as an autosomal recessive trait. It is characterized by the deposition of a waxy material in the dermis and submucosal connective tissue of affected patients. The earliest thorough description of lipoid proteinosis was by Urbach and Wiethe in 1929, and more than 300 patients, most being of European background, have been reported to date. Mutations of the *ECM1* gene, which encodes a glycoprotein known as *extracellular matrix protein 1,* have been identified as the cause for this condition.

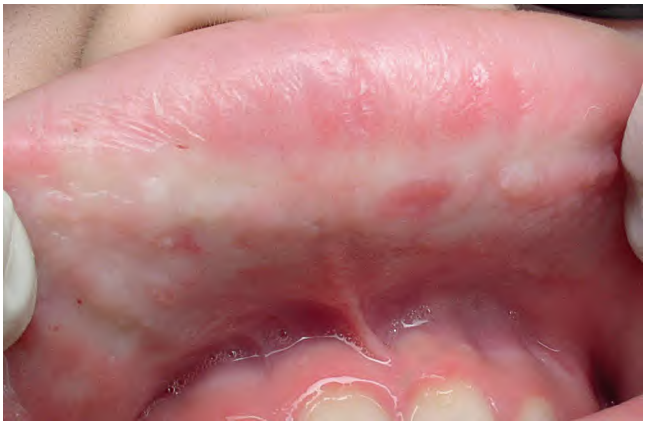
Clinical Features

The laryngeal mucosa and vocal cords are usually the sites that are initially affected by lipoid proteinosis. Therefore, the first sign of the disease may be one of the following:

- An inability of the infant to make a crying sound
- A hoarse cry in infancy
- The development of a hoarse voice during early childhood

The vocal cords become thickened as the accumulation of an amorphous material begins to affect the laryngeal mucosa. This infiltrative mucosal process may also involve the pharynx, esophagus, tonsils, vulva, and rectum. Skin lesions also develop early in life, appearing as thickened, yellowish, waxy papules; plaques; or nodules that often affect the face, particularly the lips and the margins of the eyelids (Fig. 17-3). Some lesions may begin as dark-crusted vesicles that heal as atrophic hyperpigmented patches.

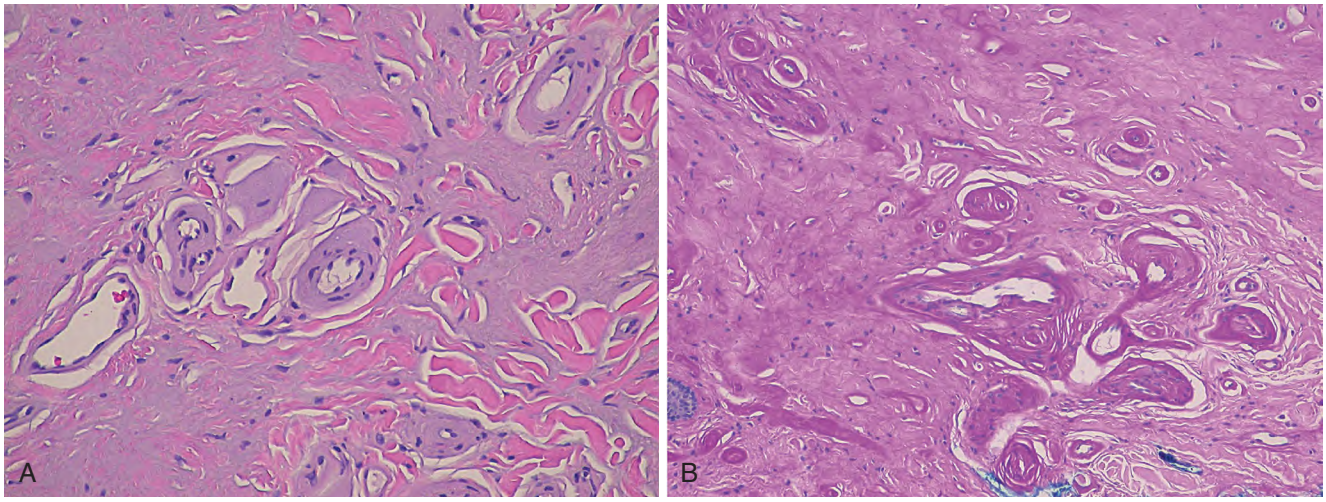
• **Fig. 17-3 Lipoid Proteinosis.** Thickened papules are present along the margin of the eyelid. (Courtesy of Dr. Maria Copete.)



• **Fig. 17-4 Lipoid Proteinosis.** The upper labial mucosa exhibits yellow-white, nodular thickening. (Courtesy of Dr. Maria Copete.)

Eventually, most patients exhibit a thickened, furrowed appearance of the skin. Other areas of the skin that may be involved include the neck, palms, axillae, elbows, scrotum, knees, and digits. In those areas subjected to chronic trauma, a hyperkeratotic, verrucous surface often develops. In addition to the cutaneous manifestations, symmetrical intracranial calcifications of the medial temporal lobes have been identified in approximately 70% of affected patients. These lesions are usually asymptomatic, although a few patients with such calcifications have been reported to have a seizure disorder.

The oral mucosal abnormalities typically become evident in the second decade of life. The tongue, labial mucosa, and buccal mucosa become nodular, diffusely enlarged, and thickened because of infiltration with waxy, yellow-white plaques and nodules (Fig. 17-4). The dorsal tongue papillae are eventually destroyed, and the tongue develops a smooth surface. The accumulation of the amorphous material within the tongue may result in its being bound to the floor of the mouth. Therefore, the patient may not be able to



• **Fig. 17-5 Lipoid Proteinosis. A,** This medium-power photomicrograph shows perivascular deposition of a lamellar, acellular material. **B,** The periodic acid-Schiff (PAS) method is used to stain and highlight the perivascular deposits. (Courtesy of Dr. Maria Copete.)

protrude the tongue. Gingival enlargement appears to be an infrequent finding.

Histopathologic Features

A biopsy specimen of an early lesion of lipoid proteinosis typically reveals the deposition of a lamellar material around the blood vessels, nerves, hair follicles, and sweat glands. This material stains positively with the periodic acid-Schiff (PAS) method and is not digested by diastase. The location of this material, its staining properties, and the presence of increased laminin, type IV collagen, and type V collagen suggest a basement membrane origin.

A biopsy specimen of a lesion in its later stages usually shows not only the lamellar material but also deposition of an amorphous substance within the dermal connective tissue (Fig. 17-5).

Treatment and Prognosis

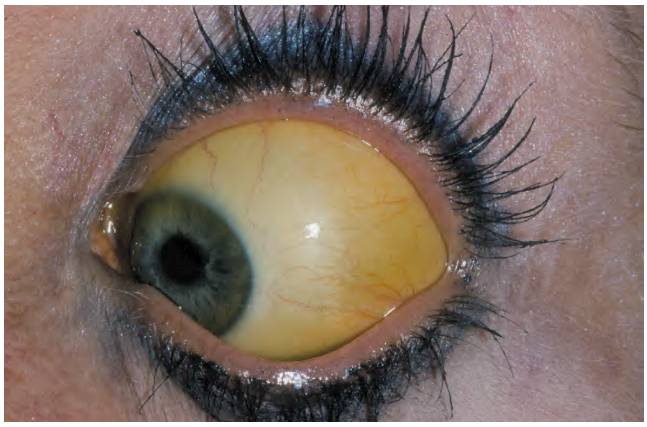
Generally, no specific treatment is available for lipoid proteinosis other than genetic counseling. In rare instances, the infiltration of the laryngeal mucosa may produce difficult breathing for some infants, in which case debulking of the mucosal lesions may be necessary. Most patients with lipoid proteinosis have a normal life span. Certainly, however, the vocal hoarseness and the appearance of the skin may influence the quality of life for affected patients. As is the case with several other hyperkeratotic genodermatoses, the rough, scaly skin lesions may respond to systemic retinoid therapy, but the deposits of abnormal material in the dermis and submucosa do not.

◆ JAUNDICE (ICTERUS)

Jaundice is a condition characterized by excess bilirubin in the bloodstream. The bilirubin accumulates in the tissues, which results in a yellowish discoloration of the skin and mucosa. To understand jaundice, it is important to know something about the metabolism of bilirubin. Most bilirubin is derived from the breakdown of hemoglobin, the oxygen-carrying pigment of erythrocytes. The average life span of an erythrocyte in the circulation is 120 days. After this time, it undergoes physiologic breakdown. The hemoglobin is degraded and processed by the cells of the reticuloendothelial system, and bilirubin is liberated into the bloodstream in an unconjugated state. In the liver, bilirubin is taken up by the hepatocytes and conjugated with glucuronic acid, which produces conjugated bilirubin, a soluble product that can be excreted in the bile.

There are numerous causes for increased serum levels of bilirubin; some are physiologic, and many are pathologic. Therefore, the presence of jaundice is not a specific sign and generally necessitates physical examination and laboratory studies to determine the precise cause. The basic disturbances associated with increased bilirubin levels include an increased production of bilirubin. This occurs when the red blood cells (RBCs) are being broken down at such a rapid rate that the liver cannot keep pace with processing. This breakdown is seen in such conditions as **autoimmune hemolytic anemia** or **sickle cell anemia.**

In addition, the liver may not be functioning correctly, resulting in decreased uptake of the bilirubin from the circulation or decreased conjugation of bilirubin in the liver cells. Jaundice is frequently present at birth as a result of the low level of activity of the enzyme system that conjugates bilirubin. Defects in this enzyme system may also be seen with certain inherited problems, one of the more common of which is **Gilbert syndrome.** This innocuous condition is often detected on routine examination, and it is estimated to affect up to 5% of people in the United States. Because most of these examples of jaundice occur with impaired processing of bilirubin, laboratory studies usually show unconjugated bilirubin in the serum.



• **Fig. 17-6 Jaundice.** The yellow color of the sclera represents a common finding.

The presence of conjugated bilirubinemia in jaundice can usually be explained by the reduced excretion of bilirubin into the bile ducts. This can be the result of swelling of the hepatocytes (resulting in an occlusion of the bile canaliculi) or hepatocyte necrosis, with disruption of the bile canaliculi and liberation of conjugated bilirubin. Thus liver function may be disturbed because of any one of a variety of infections (e.g., viruses) or toxins (e.g., alcohol). Occlusion of the bile duct from gallstones, stricture, or cancer can also force conjugated bilirubin into the bloodstream.

Clinical Features

The patient affected by jaundice exhibits a diffuse, uniform, yellowish discoloration of the skin and mucosa. The color varies in intensity, depending on the serum level of bilirubin and the anatomic site. Because elastin fibers have an affinity for bilirubin, tissues that have a high content of elastin, including the sclera, lingual frenum, and soft palate, are prominently affected. The sclera of the eye is often the first site at which the yellow color is noted (Fig. 17-6). The yellow discoloration caused by **hypercarotenemia** (resulting from excess ingestion of carotene, a vitamin-A precursor found in yellow vegetables and fruits) may be confused with jaundice, but the sclera is not involved in that condition.

Other signs and symptoms associated with jaundice vary with the underlying cause of the hyperbilirubinemia. For example, patients with viral hepatitis usually have a fever, abdominal pain, anorexia, and fatigue. The patient with jaundice typically requires a complete medical evaluation to determine the precise cause of the condition so that proper therapy can be instituted.

Treatment and Prognosis

The treatment and prognosis of the patient with jaundice vary with the cause. The jaundice that is commonly noted at birth often resolves spontaneously; however, if the infant is placed under special lights, then the clearing will occur more quickly because conjugation of the bilirubin molecule is triggered by exposure to blue light. If the episode of jaundice is due to significant liver damage, as may be seen with viral hepatitis B or hepatotoxic chemical injury, then the prognosis will vary, depending on the extent of liver damage. The prognosis for patients with jaundice secondary to liver damage associated with metastatic malignancy is poor.

◆ AMYLOIDOSIS

Amyloidosis represents a heterogeneous group of conditions characterized by the deposition of an extracellular proteinaceous substance called **amyloid.** Virchow coined the term *amyloid* in the middle of the nineteenth century because he believed it to be a starch-like material (*amyl* = starch; *oid* = resembling). We now understand that amyloid can be formed in a variety of settings, each with its own specific type of amyloid protein. Many of these amyloid proteins have been identified precisely with respect to their biochemical composition, and ideally an attempt should be made to categorize the type of amyloid specifically when this diagnosis is made. The various amyloid proteins are designated with an *A*, to indicate amyloid, followed by an abbreviation for the specific amyloid protein. For example, *AL* would identify amyloid composed of immunoglobulin light (L) chain molecules. Although amyloid may have several sources, all types of amyloid have the common feature of a β-pleated sheet molecular configuration, which can be seen with x-ray diffraction crystallographic analysis. Because of this similarity of molecular structure, the different types of amyloid have similar staining patterns with special stains.

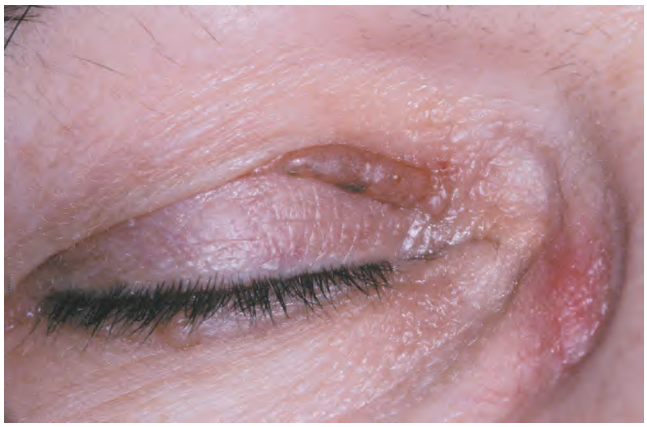
Amyloidosis can produce a variety of effects, depending on the organ of involvement and the extent to which the amyloid is deposited. With limited cutaneous forms of amyloidosis, virtually no effect on survival is seen. With some forms of systemic amyloidosis, however, death may occur within a few years of the diagnosis as a result of cardiac or renal failure. Furthermore, the presence of amyloid may be associated with other problems, such as multiple myeloma or chronic infections.

Clinical Features

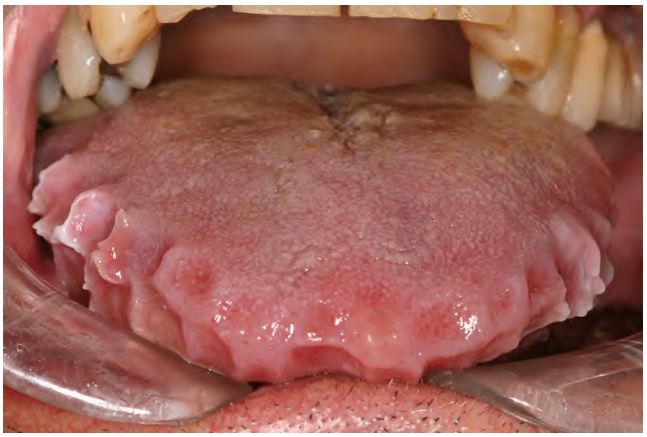
Several classifications of amyloidosis have been proposed in the past decade, each evolving as the knowledge of this unusual condition increases. None of the classifications is completely satisfactory, although in recent years, the biochemical makeup of these proteins has figured more prominently in most classifications. This discussion attempts to be as concise and direct as possible. Essentially, amyloidosis may be divided into **organ-limited** and **systemic** forms from a clinical standpoint.

Organ-Limited Amyloidosis

Although organ-limited amyloidosis may occur in a variety of organs, it has infrequently been reported in the oral soft



• **Fig. 17-7 Amyloidosis.** This patient exhibits a firm, waxy nodular lesion in the periocular region, a finding that is characteristic of this condition.



• **Fig. 17-8 Amyloidosis.** The patient exhibits an enlarged and crenated tongue. (Courtesy of Dr. Gregory Erena.)

tissues. An example of a limited form of amyloidosis is the amyloid nodule, which appears as a solitary, otherwise asymptomatic, submucosal deposit. Most of the organ-limited forms of amyloidosis consist of aggregates of immunoglobulin light chains, which in some cases are produced by a focal collection of monoclonal plasma cells. By definition, such amyloid deposits are not associated with any systemic alteration.

Systemic Amyloidosis

Systemic amyloidosis may occur in several forms:

- Primary
- Myeloma associated
- Secondary
- Hemodialysis associated
- Heredofamilial

Primary and Myeloma-Associated Amyloidosis

The primary and myeloma-associated forms of amyloidosis usually affect older adults (average age, 65 years), and a slight male predilection is present. These types of amyloidosis are caused by deposition of light chain molecules (thus the designation *AL*), with most cases being idiopathic, although approximately 15% to 20% are associated with multiple myeloma. The initial signs and symptoms may be nonspecific, often resulting in a delayed diagnosis. Fatigue, weight loss, paresthesia, hoarseness, edema, and orthostatic hypotension are among the first indications of this disease process. Eventually, carpal tunnel syndrome, mucocutaneous lesions, hepatomegaly, and macroglossia develop as a result of the deposition of the amyloid protein. The skin lesions appear as smooth-surfaced, firm, waxy papules and plaques. These most commonly affect the eyelid region (Fig. 17-7), the retroauricular region, the neck, and the lips. The lesions are often associated with petechiae and ecchymoses. Macroglossia has been reported in 10% to 40% of these patients and may appear as diffuse or nodular enlargement of the tongue (Fig. 17-8). Sometimes oral amyloid nodules show ulceration and submucosal hemorrhage overlying the lesions. Infrequently, patients may complain of dry eyes or dry mouth, which is secondary to amyloid infiltration and destruction of the lacrimal and salivary glands. When significant blood vessel infiltration has occurred, claudication of the jaw musculature may be noticed.

Secondary Amyloidosis

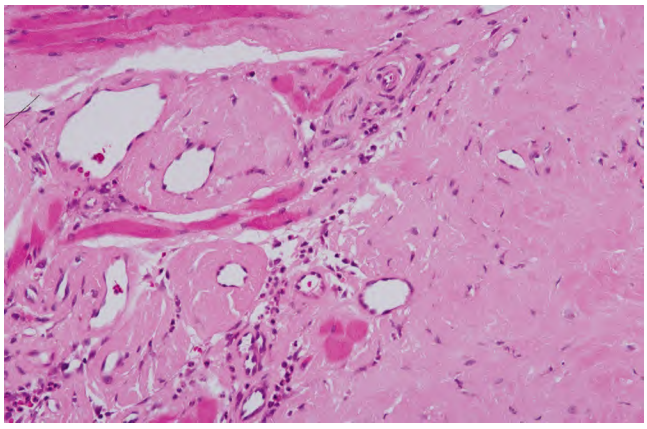
Secondary amyloidosis is so named because it characteristically develops as a result of a chronic inflammatory process, such as long-standing osteomyelitis, tuberculosis, or sarcoidosis. Cleavage fragments of a circulating acute-phase reactant protein appear to comprise this type of amyloidosis, which is thus designated *AA*. The heart is usually not affected as in other forms of amyloidosis. Liver, kidney, spleen, and adrenal involvement are typical, however. With the advent of modern antibiotic therapy, this form of amyloidosis has become much less common in the United States.

Hemodialysis-Associated Amyloidosis

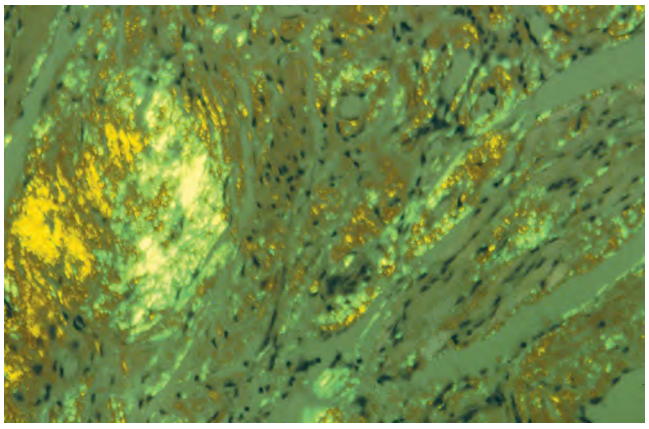
Patients who have undergone long-term renal dialysis also are susceptible to amyloidosis, although in this case the amyloid protein has been identified as β_2-microglobulin, and this type of amyloidosis is designated as $A\beta_2M$. β_2-Microglobulin is a normally occurring protein that usually is not removed by the dialysis procedure, and it accumulates in the plasma. Eventually, it forms deposits, particularly in the bones and joints. Often, carpal tunnel syndrome occurs, as well as cervical spine pain and dysfunction. Tongue involvement has been reported. This type of amyloidosis may become less of a problem in the future because of increased use of dialyzers with larger pores that permit removal of the large β_2-microglobulin molecule.

Heredofamilial Amyloidosis

Heredofamilial amyloidosis is an uncommon but significant form of the disease. Several kindred have been identified in Swedish, Portuguese, and Japanese populations, and most types are inherited as autosomal dominant traits. An



• **Fig. 17-9 Amyloidosis.** This medium-power photomicrograph shows the eosinophilic, acellular deposits that are characteristic of amyloid deposition.



• **Fig. 17-10 Amyloidosis.** High-power photomicrograph of a Congo red–stained section, demonstrating characteristic apple-green birefringence when viewed with polarized light. (Courtesy of Dr. John Kalmar.)

autosomal recessive form, known as *familial Mediterranean fever,* has also been described. Several of these conditions appear as polyneuropathies, although other manifestations, such as cardiomyopathy, cardiac arrhythmias, congestive heart failure, and renal failure, eventually develop as the amyloid deposition continues.

Histopathologic Features

Biopsy of rectal mucosa has classically been used to confirm a diagnosis of primary or myeloma-associated amyloidosis, with up to 80% of such biopsy specimens being positive. Aspiration biopsy of abdominal subcutaneous fat is a simpler procedure, however, and the sensitivity of this technique has been reported to range from 55% to 75%. Alternative tissue sources, however, are the gingiva and labial salivary glands. Histopathologic examination of gingival tissue that has been affected by amyloidosis shows extracellular deposition in the submucosal connective tissue of an amorphous, eosinophilic material, which may be arranged in a perivascular orientation or may be diffusely present throughout the tissue (Fig. 17-9). Relatively low sensitivity has been reported for gingival biopsies, whereas labial salivary gland tissue shows deposition of amyloid in a periductal or perivascular location in more than 80% of the cases.

If the amorphous eosinophilic material represents amyloid, it will be stained by the dye, Congo red, which has an affinity for the abnormal protein. In tissue sections stained with Congo red, the amyloid appears red. When the tissue that takes up the Congo red stain is viewed with polarized light, it exhibits an apple-green birefringence (Fig. 17-10). This Congo red staining method is considered to be the "gold standard" for identifying the presence of amyloid. Other techniques have been used, but these are less sensitive or specific. Microscopic sections stained with crystal violet reveal a characteristic metachromasia; this normally purple dye appears more reddish when it reacts with amyloid. Staining with thioflavine T, a fluorescent dye, also gives positive results if amyloid is present. Ultrastructurally, amyloid is seen as a collection of 7.5- to 10-nm diameter, nonbranching, linear fibrils.

Diagnosis

Once the histopathologic diagnosis of amyloidosis has been made, the patient must be evaluated medically to determine the type of amyloidosis that is present. This often entails a workup that includes serum immunoelectrophoresis to determine whether a monoclonal gammopathy exists so that multiple myeloma can be ruled out. Immunohistochemical studies are proving to be very useful in distinguishing the specific type of amyloid protein. Family history and physical examination findings are also important.

Treatment and Prognosis

In most instances, no effective therapy is available for amyloidosis. Surgical debulking of amyloid deposition in the tongue has met with limited success. Selected forms of amyloidosis may respond to treatment, or at least their progression may be slowed, depending on the underlying cause. In cases of secondary amyloidosis associated with an infectious agent, treatment of the infection and reduction of the inflammation often result in clinical improvement. Renal transplantation may arrest the progression of the bone lesions in hemodialysis-associated amyloidosis, but this procedure apparently does not reverse the process. Liver transplantation can improve the prognosis of several forms of inherited amyloidosis, particularly the transthyretin variant. Familial Mediterranean fever may respond to systemic colchicine therapy. Genetic counseling is also appropriate for patients affected by the inherited forms of amyloidosis. Treatment of primary amyloidosis (AL) with colchicine, prednisone, and melphalan appears to improve the prognosis of patients who do not have cardiac or renal involvement, although the outlook is guarded to poor in most instances. Most patients die of cardiac failure, arrhythmia, or renal disease within months to a few years after the diagnosis.

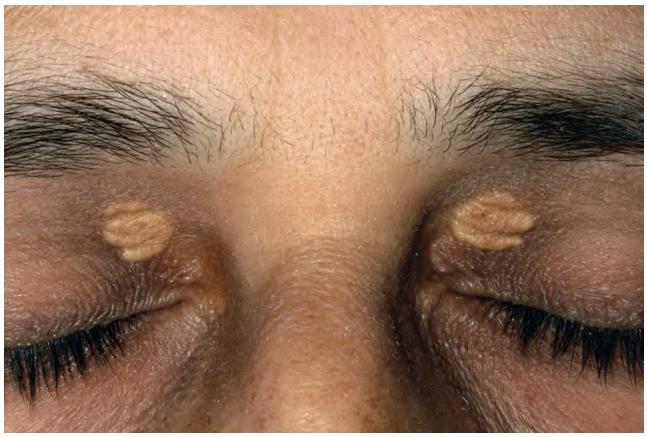


Fig. 17-11 Xanthelasma. These soft yellowish plaques on the medial aspect of the skin of the upper eyelid are characteristic of xanthelasma.

XANTHELASMA (XANTHELASMA PALPEBRARUM)

Xanthelasma is the most common of the cutaneous xanthomas, occurring in approximately 1% of the adult population. The condition is mentioned because these lesions appear somewhat similar to cutaneous amyloid deposits. In addition, the presence of xanthelasma has been related to an increased risk of atherosclerosis as well as elevated serum lipids.

Clinical Features

Xanthelasma is typically identified in middle-aged or older adults, presenting as one or more soft, yellowish plaques associated with the periocular skin (Fig. 17-11). The lesions tend to develop on the medial aspect of the upper eyelid. Their soft consistency and yellow color clinically should help distinguish xanthelasma from amyloid deposits.

Histopathologic Features

Biopsy of xanthelasma shows a collection of lipid-laden histiocytes in the superficial to mid-dermal connective tissue.

Treatment and Prognosis

Treatment of xanthelasma itself is not necessary and is generally considered a cosmetic procedure. If the patient has not been evaluated recently with respect to their cholesterol levels, referral to a primary care physician for serum lipid assessment would be prudent. The lesions can be surgically removed, although recurrence is not unusual, even if serum lipids are controlled.

VITAMIN DEFICIENCY

In the United States today, significant vitamin deficiencies are not common. Patients with malabsorption syndromes or eating disorders, persons who follow "fad diets," and alcoholics are the groups most commonly affected.

Vitamin A (retinol) is essential for the maintenance of vision, and it also plays a role in growth and tissue differentiation. Vitamin A can be obtained directly from dietary sources, such as organ meats (particularly liver), or the body can synthesize it from β-carotene, which is abundant in red and yellow vegetables.

Vitamin B_1 (thiamin) acts as a coenzyme for several metabolic reactions and is thought to maintain the proper functioning of neurons. Thiamin is found in many animal and vegetable food sources.

Vitamin B_2 (riboflavin) is necessary for cellular oxidation-reduction reactions. Foods that contain significant amounts of riboflavin include milk, green vegetables, lean meat, fish, legumes, and eggs.

Vitamin B_3 (niacin) acts as a coenzyme for oxidation-reduction reactions. Rich sources include food from animal sources, especially lean meat and liver, milk, eggs, whole grains, peanuts, yeast, and cereal bran or germ.

Vitamin B_6 (pyridoxine) serves as a cofactor associated with enzymes that participate in amino acid synthesis. It is found in many animal and vegetable food sources.

Vitamin C (ascorbic acid) is necessary for the proper synthesis of collagen. This vitamin is present in a wide variety of vegetables and fruits, although it is particularly abundant in citrus fruits.

Vitamin D, which is now considered to be a hormone, can be synthesized in adequate amounts within the epidermis if the skin is exposed to a moderate degree of sunlight. Most milk and processed cereal is fortified with vitamin D in the United States today, however. Appropriate levels of vitamin D and its active metabolites are necessary for calcium absorption from the gut.

Vitamin E (α-tocopherol) is a fat-soluble vitamin that is widely stored throughout the body. It probably functions as an antioxidant. Vegetable oils, meats, nuts, cereal grains, and fresh greens and vegetables are good sources of vitamin E.

Vitamin K is a fat-soluble vitamin found in a wide variety of green vegetables, as well as milk, butter, and liver; intestinal bacteria also produce it. This vitamin is necessary for the proper synthesis of various proteins, including the clotting factors II, VII, IX, and X.

Clinical Features

Vitamin A

A severe deficiency of vitamin A during infancy may result in blindness. The early changes associated with a lack of this vitamin later in life include an inability of the eye to adapt to reduced light conditions (i.e., night blindness). With more severe, prolonged deficiency, dryness of the skin and conjunctiva develop, and the ocular changes may progress to ulceration of the cornea, leading to blindness.

Thiamin

A deficiency of thiamin results in a condition called **beriberi,** a problem that is relatively uncommon in the Western

world except in alcoholics or other individuals who do not receive a balanced diet. Thiamin deficiency has also been documented in patients who have had gastric bypass surgery for weight control, presumably because an adequate amount of the vitamin is not obtained in the diet. The condition became prevalent in Southeast Asia when the practice of removing the outer husks of the rice grain by machine was introduced. Because these outer husks contained nearly all of the thiamin, people who subsisted on the "polished" rice became deficient in this vitamin. The disorder is manifested by cardiovascular problems (e.g., peripheral vasodilation, heart failure, and edema) and neurologic problems (including peripheral neuropathy and Wernicke encephalopathy). Patients with Wernicke encephalopathy experience vomiting, nystagmus, and progressive mental deterioration, which may lead to coma and death.

Riboflavin

A diet that is chronically deficient in riboflavin causes a number of oral alterations, including glossitis, angular cheilitis, sore throat, and swelling and erythema of the oral mucosa. A normocytic, normochromic anemia may be present, and seborrheic dermatitis may affect the skin.

Niacin

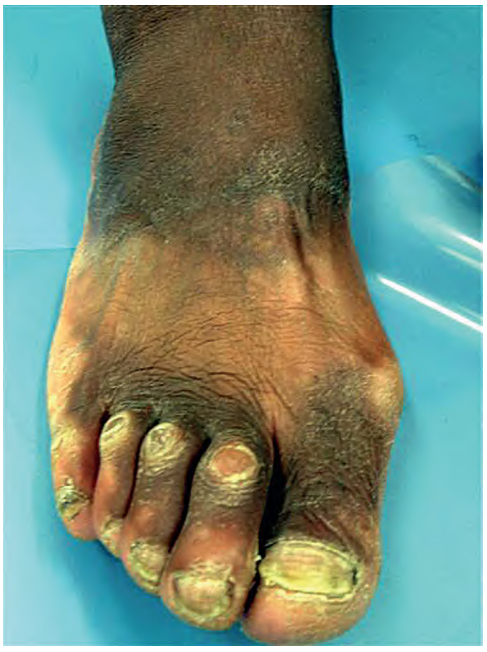
A deficiency of niacin causes a condition known as **pellagra,** a term derived from the Italian words *pelle agra,* meaning *rough skin.* This condition may occur in populations that use maize as a principal component of their diets, because corn is a poor source of niacin. Pellagra was once common in the southeastern United States and may still be seen in some parts of the world. The classic systemic signs and symptoms include the triad of dermatitis, dementia, and diarrhea. The dermatitis is distributed symmetrically; sun-exposed areas, such as the face, neck, and forearms, are affected most severely (Fig. 17-12). The oral manifestations have been described as stomatitis and glossitis, with the tongue appearing red, smooth, and raw. Without correction of the niacin deficiency, the disease may evolve and persist over a period of years, eventually leading to death.

Pyridoxine

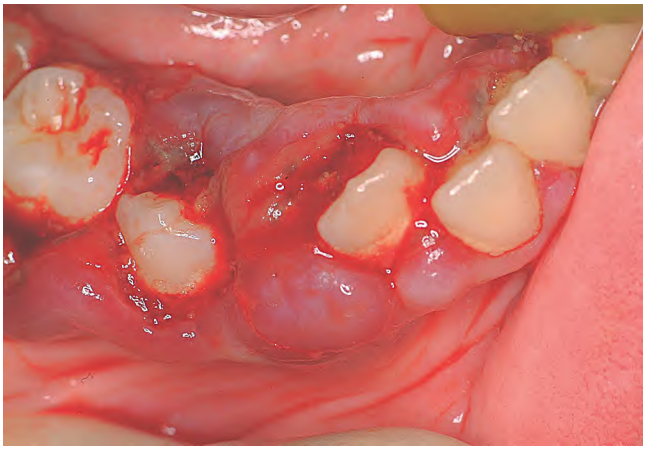
A deficiency of pyridoxine is unusual because of its widespread occurrence in a variety of foods. A number of drugs, such as the antituberculosis drug isoniazid, act as pyridoxine antagonists; therefore, patients who receive these medications may have a deficiency state. Because the vitamin plays a role in neuronal function, patients may show weakness, dizziness, or seizure disorders. Cheilitis and glossitis, reported in people with pellagra, are also reported in patients with pyridoxine deficiency.

Vitamin C

A deficiency of vitamin C is known as **scurvy,** and its occurrence in the United States is usually limited to people whose diets lack fresh fruits and vegetables. Commonly affected groups include inner-city infants (whose diets often consist entirely of milk) and older edentulous men, particularly those who live alone.



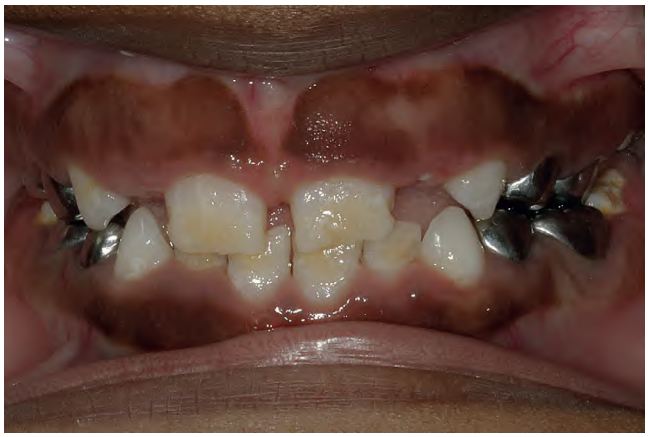
• **Fig. 17-12 Pellagra.** The skin on the foot is rough and hyperpigmented, except for a central band that was protected from sunlight by a sandal strap. (Courtesy of Dr. Sylvie Brener.)



• **Fig. 17-13 Scurvy.** Hemorrhagic gingival enlargement (scorbutic gingivitis) because of capillary fragility. (Courtesy of Dr. James Hargan.)

The clinical signs of scurvy are typically related to inadequate collagen synthesis. For example, weakened vascular walls may result in widespread petechial hemorrhage and ecchymosis. Similarly, wound healing is delayed, and recently healed wounds may break down. In childhood, painful subperiosteal hemorrhages may occur.

The oral manifestations are well documented and include generalized gingival swelling with spontaneous hemorrhage, ulceration, tooth mobility, and increased severity of periodontal infection and periodontal bone loss. The gingival lesions have been termed **scorbutic gingivitis** (Fig. 17-13). If untreated, scurvy may ultimately lead to death, often as a result of intracranial hemorrhage.



• **Fig. 17-14 Vitamin D Deficiency.** Hypocalcification of the teeth is seen in this child who had vitamin D deficiency related to a diet of breast milk exclusively and lack of adequate sunlight exposure. (Courtesy of Dr. Pamela McDonald.)

Vitamin D

A deficiency of vitamin D during infancy results in a condition called **rickets;** adults who are deficient in this vitamin develop **osteomalacia.** With the vitamin-D supplementation of milk and cereal, rickets is a relatively uncommon disease today in the United States. In past centuries, however, rickets was often seen, particularly in the temperate zones of the world, which often do not receive adequate sunlight to ensure physiologic levels of vitamin D. Even today in the United States, children who are dark-skinned and do not receive adequate sun exposure, as well as solely breast-fed infants, remain at risk for developing rickets. Nutritional rickets remains a problem in many developing countries, although the condition is thought to be associated more with calcium deficiency than vitamin-D deficiency.

Clinical manifestations of rickets include irritability, growth impairment, and prominence of the costochondral junctions *(rachitic rosary).* As the child ages and begins to put weight on the long bones of the legs, significant bowing results because of the poor mineralization of the skeleton. Vitamin-D deficiency occurring during the period of tooth development will result hypomineralization of the teeth (Fig. 17-14).

A similar pattern of poorly mineralized bone is seen in osteomalacia in adults. Bone normally undergoes continuous remodeling and turnover, and the osteoid that is produced during this process does not have sufficient calcium to mineralize completely. Thus a weak, fragile bone structure results. Patients affected by osteomalacia frequently complain of diffuse skeletal pain, and their bones are susceptible to fracture with relatively minor injury.

Vitamin E

A deficiency of vitamin E is rare and occurs primarily in children who suffer from chronic cholestatic liver disease. These patients have severe malabsorption of all fat-soluble vitamins, but particularly vitamin E. Multiple neurologic signs develop as a result of abnormalities in the central nervous system (CNS) and peripheral nervous system.

Vitamin K

A deficiency of vitamin K may be seen in patients with malabsorption syndromes or in those whose intestinal microflora has been eliminated by long-term, broad-spectrum antibiotic use. Oral anticoagulants in the dicumarol family also inhibit the normal enzymatic activity of vitamin K. A deficiency or inhibition of synthesis of vitamin K leads to a coagulopathy because of the inadequate synthesis of prothrombin and other clotting factors. Intraorally, this coagulopathy is most often manifested by gingival bleeding. If the coagulopathy is not corrected, death may result from uncontrolled systemic hemorrhage.

Treatment and Prognosis

Replacement therapy is indicated for vitamin deficiencies. However, such deficiencies are uncommon, except for the situations described earlier. In fact, vitamin excess is perhaps more likely to be encountered in the United States today because so many people self-medicate with unnecessary and potentially harmful vitamin supplements. For example, excess vitamin A may cause abdominal pain, vomiting, headache, joint pain, and exostoses, whereas excess vitamin C may induce the formation of additional kidney stones in individuals with a history of nephrolithiasis. Similarly, an increased prevalence of kidney stones can be seen with excess oral intake of vitamin D.

◆ IRON-DEFICIENCY ANEMIA

Iron-deficiency anemia is the most common cause of anemia in the United States and throughout the world. This form of anemia develops when the amount of iron available to the body cannot keep pace with the need for iron in the production of red blood cells (RBCs). This type of anemia develops under four conditions:

1. Excessive blood loss
2. Increased demand for RBCs
3. Decreased intake of iron
4. Decreased absorption of iron

It is estimated up to 11% of women of childbearing age in the United States are iron deficient as a result of the chronic blood loss associated with excessive menstrual flow **(menorrhagia).** Similarly, 2% of adult men are iron deficient because of chronic blood loss, usually associated with gastrointestinal disease, such as peptic ulcer disease, diverticulosis, hiatal hernia, or malignancy.

An increased demand for erythrocyte production occurs during childhood growth spurts and during pregnancy. A decreased intake of iron may be seen during infancy when the diet consists of relatively iron-poor foods, such as cereals and milk. Likewise, the diets of older people may be deficient if their dental condition prohibits them from eating the proper foods or if they cannot afford iron-rich foods,

such as meats and vegetables. In the developing world, intestinal parasites (especially hookworms) are a common cause of iron deficiency in children and pregnant women.

Decreased absorption is a much less common problem; however, it can be seen in patients who have had a complete gastrectomy or who have **celiac sprue,** a condition that results in severe chronic diarrhea because of sensitivity to the plant protein, gluten.

Clinical Features

Patients with iron-deficiency anemia that is severe enough to cause symptoms may complain of fatigue, easy tiring, palpitations, lightheadedness, and lack of energy. Oral manifestations include angular cheilitis and atrophic glossitis or generalized oral mucosal atrophy. The glossitis has been described as a diffuse or patchy atrophy of the dorsal tongue papillae, often accompanied by tenderness or a burning sensation. Such findings are also evident in oral candidiasis, and some investigators have suggested that iron deficiency predisposes the patient to candidal infection, which results in the changes seen at the corners of the mouth and on the tongue. Such lesions are rarely seen in the United States, perhaps because the anemia is usually detected relatively early before the oral mucosal changes have had a chance to develop.

Laboratory Findings

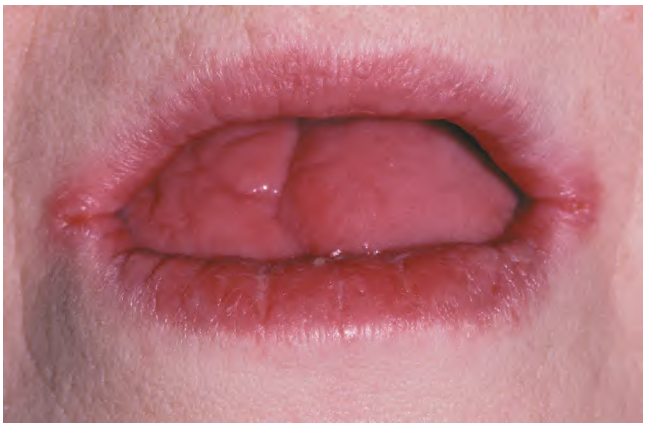
The diagnosis should be established by means of a complete blood count with RBC indices because many other conditions, such as hypothyroidism, other anemias, or chronic depression, may elicit similar systemic clinical complaints. The laboratory evaluation characteristically shows hypochromic microcytic RBCs, which may be reduced in numbers. Additional supporting evidence for iron deficiency includes the findings of low serum iron levels and ferritin concentration together with elevated total iron-binding capacity.

Treatment and Prognosis

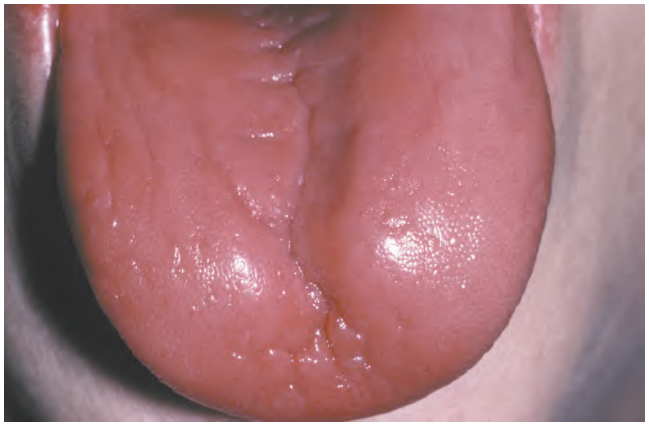
Therapy for most cases of iron-deficiency anemia consists of dietary iron supplementation by means of oral ferrous sulfate. For patients with malabsorption problems or severe anemia, parenteral iron may be given periodically. The response to therapy is usually prompt, with red cell parameters returning to normal within 1 to 2 months. The underlying cause of the anemia should be identified so that it may be addressed, if feasible.

◆ PLUMMER-VINSON SYNDROME (PATERSON-KELLY SYNDROME; SIDEROPENIC DYSPHAGIA)

Plummer-Vinson syndrome is a rare condition characterized by iron-deficiency anemia, seen in conjunction with glossitis and dysphagia. Its prevalence in developed countries has been declining, probably as a result of the improved nutritional status of the populations. The condition is significant in that it has been associated with a high frequency of both oral and esophageal squamous cell carcinoma; therefore, it is considered a premalignant process.



• **Fig. 17-15 Plummer-Vinson Syndrome.** Patients often show angular cheilitis.



• **Fig. 17-16 Plummer-Vinson Syndrome.** The diffuse papillary atrophy of the dorsal tongue is characteristic of the oral changes. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Philadelphia, 1999, Lippincott Williams & Wilkins.)

Clinical and Radiographic Features

Most reported patients with Plummer-Vinson syndrome have been women of Scandinavian or Northern European background, between 30 and 50 years of age. Patients typically complain of a burning sensation associated with the tongue and oral mucosa. Sometimes this discomfort is so severe that dentures cannot be worn. Angular cheilitis is often present and may be severe (Fig. 17-15). Marked atrophy of the lingual papillae, which produces a smooth, red appearance of the dorsal tongue, is seen clinically (Fig. 17-16).

Patients also frequently complain of difficulty in swallowing **(dysphagia)** or pain on swallowing. An evaluation

with endoscopy or esophageal barium contrast radiographic studies usually shows the presence of abnormal bands of tissue in the esophagus, called **esophageal webs.** Another sign is an alteration of the growth pattern of the nails, which results in a spoon-shaped configuration **(koilonychia).** The nails may also be brittle.

Symptoms of anemia may prompt patients with Plummer-Vinson syndrome to seek medical care. Fatigue, shortness of breath, and weakness are characteristic symptoms.

Laboratory Findings

Hematologic studies show a hypochromic microcytic anemia that is consistent with an iron-deficiency anemia.

Histopathologic Features

A biopsy specimen of involved mucosa from a patient with Plummer-Vinson syndrome typically shows epithelial atrophy with varying degrees of submucosal chronic inflammation. In advanced cases, evidence of epithelial atypia or dysplasia may be seen.

Treatment and Prognosis

Treatment of Plummer-Vinson syndrome is primarily directed at correcting the iron-deficiency anemia by means of dietary iron supplementation. This therapy usually resolves the anemia, relieves the glossodynia, and may reduce the severity of the esophageal symptoms. Occasionally, esophageal dilation is necessary to help improve the symptoms of dysphagia. Patients with Plummer-Vinson syndrome should be evaluated periodically for oral, hypopharyngeal, and esophageal cancer because a 5% to 50% prevalence of upper aerodigestive tract malignancy has been reported in affected persons.

◆ PERNICIOUS ANEMIA

Pernicious anemia is an uncommon condition that occurs with greatest frequency among older patients of Northern European heritage, although recent studies have identified the disease in black and Hispanic populations as well. Asian populations seem to be affected much less frequently. The disease is a megaloblastic anemia caused by poor absorption of cobalamin (vitamin B_{12}, extrinsic factor). Intrinsic factor, which is produced by the parietal cells of the stomach lining, is needed for vitamin-B_{12} absorption. Normally, when cobalamin is ingested, it binds to intrinsic factor in the duodenum. Because the lining cells of the intestine preferentially take up the cobalamin-intrinsic factor complex, significant amounts of the vitamin cannot be absorbed unless both components are present.

In the case of pernicious anemia, most patients lack intrinsic factor because of an autoimmune destruction of the parietal cells of the stomach; this results in decreased absorption of cobalamin. Antibodies directed against intrinsic factor are also found in the serum of these patients. Vitamin B_{12} deficiency may occur for other reasons, and although the resulting signs and symptoms may be identical to those of pernicious anemia, these should be considered as distinctly different deficiency disorders. For example, a decreased ability to absorb cobalamin may also occur after gastrointestinal bypass operations. In addition, because cobalamin is primarily derived from animal sources, some strict vegetarians (vegans) may develop vitamin B_{12} deficiency.

Because cobalamin is necessary for normal nucleic acid synthesis, anything that disrupts the absorption of the vitamin causes problems, especially for cells that are multiplying rapidly and, therefore, synthesizing large amounts of nucleic acids. The cells that are the most mitotically active are affected to the greatest degree, especially the hematopoietic cells and the gastrointestinal lining epithelial cells.

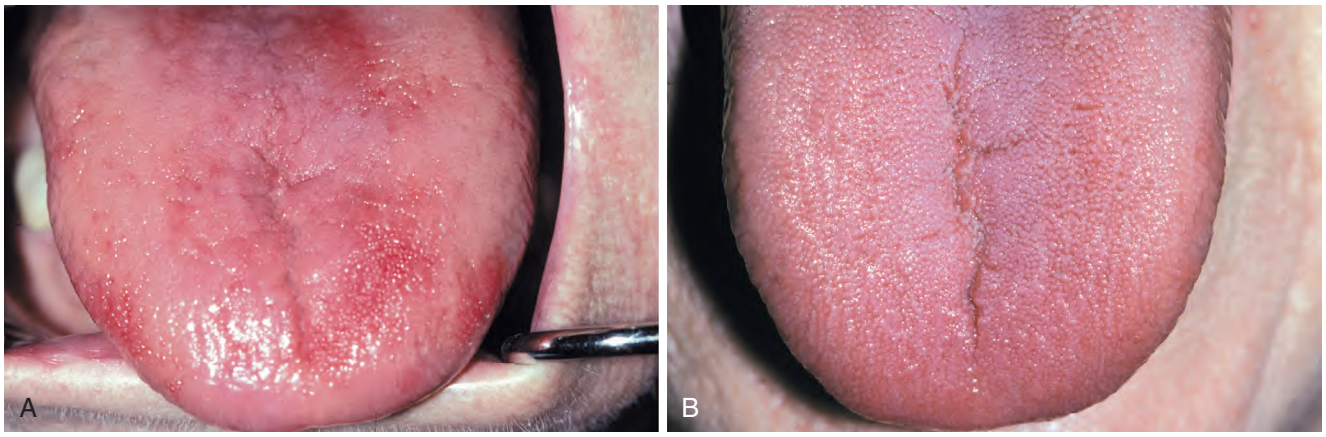
Clinical Features

With respect to systemic complaints, patients with pernicious anemia often report fatigue, weakness, shortness of breath, headache, and feeling faint. Such symptoms are associated with most anemias and probably reflect the reduced oxygen-carrying capacity of the blood. Vitamin B_{12} also functions to maintain myelin throughout the nervous system; therefore, with reduced levels of the vitamin, many patients report paresthesia, tingling, or numbness of the extremities. Difficulty in walking and diminished vibratory and positional sense may be present. Psychiatric symptoms of memory loss, irritability, depression, and dementia have also been described.

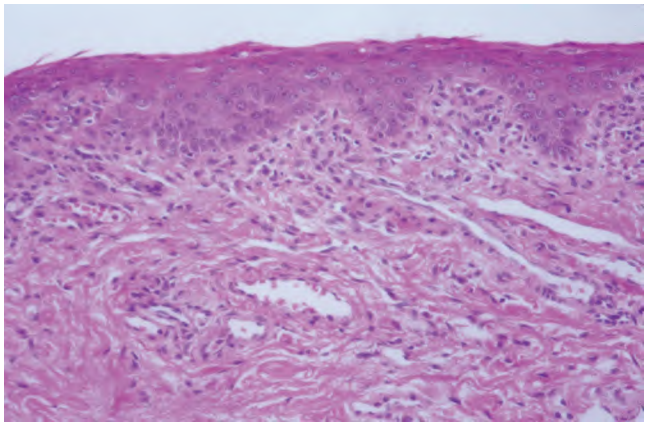
Oral symptoms often consist of a burning sensation of the tongue, lips, buccal mucosa, or other mucosal sites. Clinical examination may show focal patchy areas of oral mucosal erythema and atrophy (Fig. 17-17), or the process may be more diffuse, depending on the severity and duration of the condition. The tongue may be affected in as many as 50% to 60% of patients with pernicious anemia, but it may not show as much involvement as other areas of the oral mucosa in some instances. The atrophy and erythema may be easier to appreciate on the dorsal tongue than at other sites, however.

Histopathologic Features

Histopathologic examination of an erythematous portion of the oral mucosa shows marked epithelial atrophy with loss of rete ridges, an increased nuclear-to-cytoplasmic ratio of the surface epithelial cells, and prominent nucleoli (Fig. 17-18). This pattern can be misinterpreted as epithelial dysplasia at times, although the nuclei in pernicious anemia typically are pale staining and show peripheral chromatin clumping. A patchy diffuse chronic inflammatory cell infiltrate is usually noted in the underlying connective tissue.



• **Fig. 17-17 Pernicious Anemia. A,** The dorsal tongue shows erythema and atrophy. **B,** After therapy with vitamin B_{12}, the mucosal alteration resolved.



• **Fig. 17-18 Pernicious Anemia.** This medium-power photomicrograph shows epithelial atrophy and atypia with chronic inflammation of the underlying connective tissue. These features are characteristic of a megaloblastic anemia, such as pernicious anemia.

Laboratory Findings

Hematologic evaluation of vitamin B_{12} deficiency shows a macrocytic anemia and reduced serum cobalamin levels. The Schilling test for pernicious anemia has been used to determine the pathogenesis of the cobalamin deficiency by comparing absorption and excretion rates of radiolabeled cobalamin. However, this study is rather complicated to perform, and is now considered to be obsolete. The presence of serum antibodies directed against intrinsic factor is quite specific for pernicious anemia.

Treatment and Prognosis

Once the diagnosis of pernicious anemia is established, treatment traditionally has consisted of monthly intramuscular injections of cyanocobalamin. The condition responds rapidly once therapy is initiated, with reports of clearing of oral lesions within 5 days. High-dose oral cobalamin therapy has also been shown to be an equally effective treatment, however, with advantages being its cost-effectiveness and the elimination of painful injections. One recent systematic literature review has identified what appears to be an increased risk of gastric carcinoma, with pernicious anemia patients being seven times more likely to develop this tumor compared to the general population. Both vitamin B_{12} deficiency and folate deficiency will cause megaloblastic anemia, and it is important to distinguish between the two problems. Treatment of vitamin B_{12} deficiency with folate will resolve the anemia and the oral mucosal atrophy, but reduced myelin production will continue, resulting in further CNS damage.

◆ PITUITARY DWARFISM

Pituitary dwarfism is a relatively rare condition that results from either the diminished production of growth hormone by the anterior pituitary gland, abnormalities of the growth hormone molecule, or a reduced capacity of the tissues to respond to growth hormone. Affected patients are typically much shorter than normal, although their body proportions are generally appropriate.

Several conditions may cause short stature, and a careful evaluation of the patient must be performed to rule out other possible causes, such as the following:

1. Intrinsic defects in the patient's tissues (e.g., certain skeletal dysplasias, chromosomal abnormalities, and idiopathic short stature)
2. Alterations in the environment of the growing tissues (e.g., malnutrition, hypothyroidism, and diabetes mellitus)

If a lack of growth hormone is detected, the cause should be determined. Sometimes the fault lies with the pituitary gland itself (e.g., aplasia or hypoplasia). In other instances, the problem may be related to destruction of the pituitary or hypothalamus by tumors, therapeutic radiation, or infection.

If the hypothalamus is affected, a deficiency in growth hormone–releasing hormone, which is produced by the hypothalamus, results in a deficiency of growth hormone. Often deficiencies in other hormones, such as thyroid

hormone and cortisol, are also detected in patients with primary pituitary or hypothalamic disorders.

Some patients exhibit normal or even elevated levels of growth hormone, yet still show little evidence of growth. These individuals usually have inherited an autosomal recessive trait, resulting in abnormal and reduced growth hormone receptors on the patients' cells. Thus normal growth cannot proceed.

Clinical Features

Perhaps the most striking feature of pituitary dwarfism is the remarkably short stature of the affected patient. Sometimes this is not noticed until the early years of childhood, but a review of the patient's growth history should show a consistent pattern of failure to achieve the minimal height on the standard growth chart. Often the patient's height may be as much as three standard deviations below normal for a given age. Unlike the body proportions in many of the dysmorphic syndromes and skeletal dysplasias, the body proportions of patients affected by a lack of growth hormone are usually normal. One possible exception is the size of the skull, which is usually within normal limits. Because the facial skeleton does not keep pace with the skull, however, the face of an affected patient may appear smaller than it should be. Mental status is generally within normal limits.

The maxilla and mandible of affected patients are smaller than normal, and the teeth show a delayed pattern of eruption. The delay ranges from 1 to 3 years for teeth that normally erupt during the first decade of life and from 3 to 10 years for teeth that normally erupt in the second decade of life. Often the shedding of deciduous teeth is delayed by several years, and the development of the roots of the permanent teeth also appears to be delayed. A lack of development of the third molars seems to be a common finding. The size of the teeth is usually reduced in proportion to the other anatomic structures. One recent study suggested that growth hormone-deficient patients may exhibit more severe periodontal disease compared to a matched control population.

Laboratory Findings

Radioimmunoassay for human growth hormone shows levels that are markedly below normal.

Treatment and Prognosis

Replacement therapy with human growth hormone is the treatment of choice for patients with pituitary dwarfism if the disorder is detected before closure of the epiphyseal growth plates. In the past, growth hormone was extracted from cadaveric pituitary glands; today, genetically engineered human growth hormone is produced with recombinant DNA technology. For patients with a growth hormone deficiency caused by a hypothalamic defect, treatment with growth hormone–releasing hormone is appropriate. If patients are identified and treated at an early age, they can be expected to achieve a relatively normal height. The craniofacial bone structure also assumes a less childlike pattern. Evaluation of a series of patients who had been treated for long periods with growth hormone determined that up to half developed acromegalic features, including larger feet and a larger mandible. For patients who lack growth hormone receptors, no treatment is available.

◆ GIGANTISM

Gigantism is a rare condition caused by an increased production of growth hormone, usually related to a functional pituitary adenoma. The increased production of growth hormone takes place before closure of the epiphyseal plates, and the affected person grows at a much more rapid pace, becoming abnormally tall. Although the average height of the population of the United States has been gradually increasing during the past several decades, individuals who exceed the mean height by more than three standard deviations may be considered candidates for endocrinologic evaluation. Familial examples of gigantism have also been described.

Clinical and Radiographic Features

Patients with gigantism usually show markedly accelerated growth during childhood, irrespective of normal growth spurts. Radiographic evaluation of the skull often shows an enlarged sella as a result of the presence of a pituitary adenoma. The adenoma may result in hormonal deficiencies, such as hypothyroidism and hypoadrenocorticism, if the remaining normal pituitary gland tissue is compressed and destroyed. **McCune-Albright syndrome** (polyostotic fibrous dysplasia and *café au lait* pigmentation with associated endocrinologic disturbances) (see page 593) may account for as many as 20% of the cases of gigantism.

If the condition remains uncorrected for a prolonged period, extreme height (more than 7 feet tall) will be achieved, and enlargement of the facial soft tissues, the mandible, and the hands and feet will become apparent. These changes often resemble those seen in **acromegaly** (discussed later). Another oral finding is true generalized macrodontia.

Treatment and Prognosis

Appropriate management of gigantism involves the surgical removal of the functioning pituitary adenoma, usually by a transsphenoidal approach. Radiation therapy may also be used, as well as one of the somatostatin analogues and a growth hormone receptor antagonist (discussed in the next topic, **acromegaly**).

The life span of patients with gigantism is usually markedly reduced. Complications associated with hypertension, peripheral neuropathy, osteoporosis, and pulmonary disease contribute to increased morbidity and mortality.

◆ ACROMEGALY

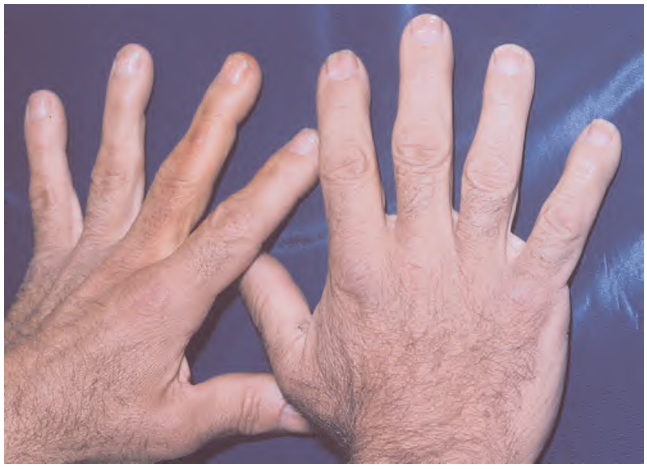
Acromegaly is an uncommon condition characterized by the excess production of growth hormone after closure of the epiphyseal plates in the affected patient. Usually, this increase in growth hormone is due to a functional pituitary adenoma. The incidence is estimated to be approximately three to five new cases diagnosed per million population per year. The prevalence is now believed to be between 40 and 130 affected patients per million.

Clinical and Radiographic Features

Because most patients with acromegaly have a pituitary adenoma, symptoms related directly to the space-occupying mass of the tumor may be present. These symptoms include headaches, visual disturbances, and other signs of a brain tumor. Sometimes pressure atrophy of the residual normal pituitary by the adenoma results in diminished production of other pituitary hormones and causes other indirect endocrine problems. The direct effects of increased levels of growth hormone include a variety of problems, such as hypertension, heart disease, hyperhidrosis, arthritis, and peripheral neuropathy.

Renewed growth in the small bones of the hands and feet (Fig. 17-19) and in the membranous bones of the skull and jaws is typically observed. Patients may complain of gloves, rings, or hats becoming "too small." The soft tissue is also often affected, producing a coarse facial appearance (Fig. 17-20). Hypertrophy of the soft palatal tissues may cause or accentuate sleep apnea. Because these signs and symptoms are slow to develop and are vague at the onset, an average time of 6 to 10 years elapses from the onset of symptoms to the diagnosis of disease. The average age at diagnosis is 42 years, and no sex predilection is seen.

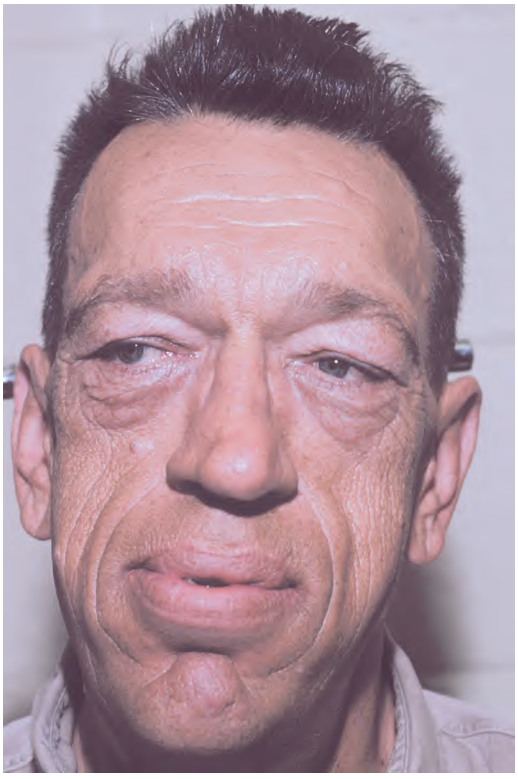
From a dental perspective, these patients have mandibular prognathism as a result of the increased growth of the mandible (Fig. 17-21), which may cause apertognathia (anterior open bite). Growth of the jaws also may cause spacing of the teeth, resulting in diastema formation. Soft tissue growth often produces uniform macroglossia in affected patients.



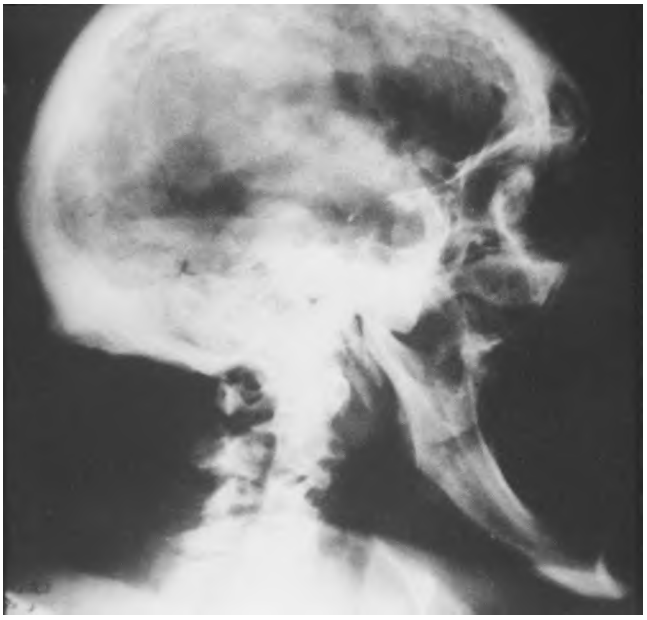
• **Fig. 17-19 Acromegaly.** Enlargement of the bones of the hands. (Courtesy of Dr. William Bruce.)

Laboratory Findings and Diagnosis

If acromegaly is suspected, measurement of serum growth hormone levels is done after giving the patient a measured



• **Fig. 17-20 Acromegaly.** This patient shows the typical coarse facial features. (Courtesy of Dr. William Bruce.)



• **Fig. 17-21 Acromegaly.** This lateral skull film shows the dramatic degree of mandibular enlargement that may occur.

quantity of glucose orally. Normally, this glucose challenge will reduce the production of growth hormone, but if the patient has acromegaly, growth hormone will not be suppressed. Usually magnetic resonance imaging (MRI) will identify the pituitary adenoma that is responsible for inappropriate growth hormone secretion.

Treatment and Prognosis

The treatment of a patient with acromegaly is typically directed at the removal of the pituitary tumor mass and the return of the growth hormone levels to normal. The most effective treatment with the least associated morbidity is surgical excision by a transsphenoidal approach. The prognosis for such a procedure is good, although a mortality rate of approximately 1% is still expected. The condition is usually controlled with this procedure, but patients with larger tumors and markedly elevated growth hormone levels are less likely to be controlled.

Radiation therapy may be used in some instances, but the return of the growth hormone levels to normal is not as rapid or as predictable as with surgery. Because some patients also experience hypopituitarism caused by radiation effects on the rest of the gland, some centers may offer radiation therapy as treatment only when surgery fails or is too risky. Pharmacotherapy with one of the somatostatin analogues (e.g., octreotide, lanreotide, and vapreotide) helps to control acromegaly if surgical treatment is unsuccessful or if surgery is contraindicated. A growth hormone receptor–blocking agent, pegvisomant, has also been developed and may be used in conjunction with one of the somatostatin analogues or by itself if the patient cannot tolerate the somatostatin analogue. Pegvisomant is injected daily and acts in the peripheral tissues to inhibit the action of growth hormone. These drugs are also used as an adjunct to radiation therapy during the prolonged period that is sometimes necessary for that treatment to take effect.

The prognosis for untreated patients is guarded, with an increased mortality rate compared with that of the general population. Hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, respiratory disease, and colon cancer are seen with increased frequency in acromegalic patients, and each of these contributes to the increased mortality rate. Although treatment of the patient with acromegaly helps to control many of the other complicating problems and improves the prognosis, the life span of these patients still is shortened, particularly for those with persistent elevated growth hormone levels, cardiomyopathy, or hypertension.

◆ HYPOTHYROIDISM (CRETINISM; MYXEDEMA)

Hypothyroidism is a condition that is characterized by decreased levels of thyroid hormone. When this decrease occurs during infancy, the resulting clinical problem is known as **cretinism.** If an adult has markedly decreased thyroid hormone levels for a prolonged period, then deposition of a glycosaminoglycan ground substance is seen in the subcutaneous tissues, producing a nonpitting edema. Some call this severe form of hypothyroidism **myxedema;** others use the terms *myxedema* and *hypothyroidism* interchangeably.

Hypothyroidism may be classified as either **primary** or **secondary.** In primary hypothyroidism, the thyroid gland itself is in some way abnormal; in secondary hypothyroidism, the pituitary gland does not produce an adequate amount of thyroid-stimulating hormone (TSH), which is necessary for the appropriate release of thyroid hormone. Secondary hypothyroidism, for example, often develops after radiation therapy for brain tumors, resulting in unavoidable radiation damage to the pituitary gland. Most cases, however, represent the primary form of the disease.

Screening for this disorder is routinely carried out at birth, and the prevalence of congenital hypothyroidism in North America is approximately 1 in 4000 births. Usually, this is due to hypoplasia or agenesis of the thyroid gland. In other areas of the world, hypothyroidism in infancy is usually due to a lack of dietary iodine. In adults, hypothyroidism is often caused by autoimmune destruction of the thyroid gland (known as **Hashimoto thyroiditis**) or iatrogenic factors, such as radioactive iodine therapy or surgery for the treatment of hyperthyroidism. Because thyroid hormone is necessary for normal cellular metabolism, many of the clinical signs and symptoms of hypothyroidism can be related to the decreased metabolic rate in these patients.

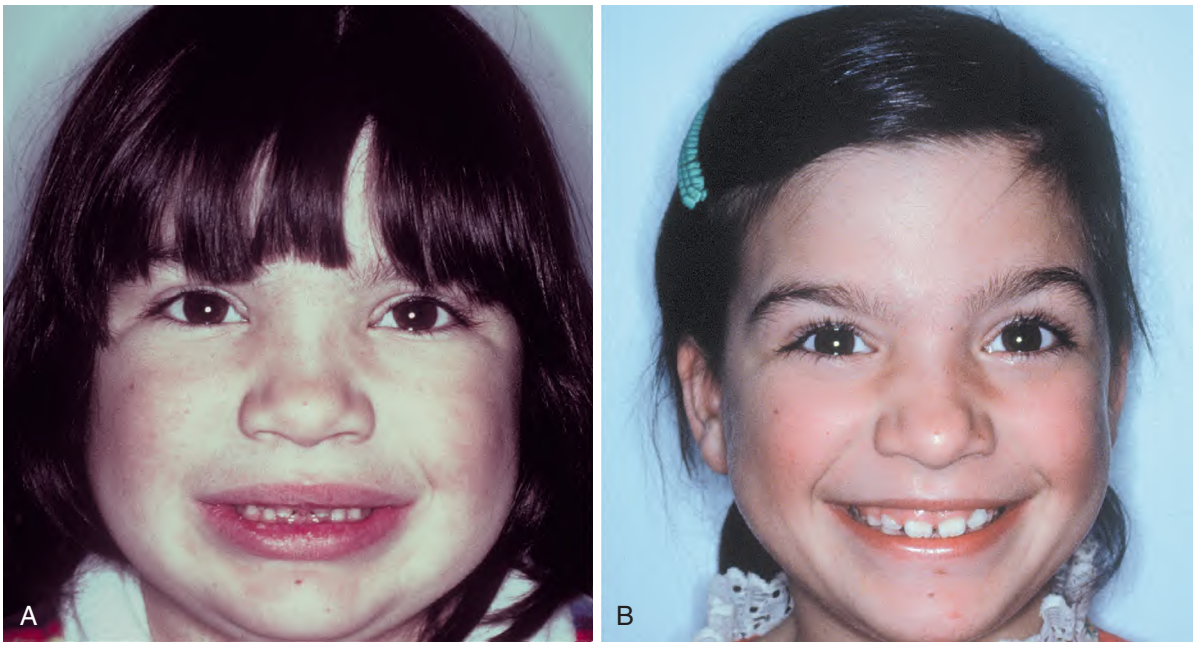
Clinical Features

The most common features of hypothyroidism include such signs and symptoms as lethargy, dry and coarse skin, swelling of the face (Fig. 17-22) and extremities, huskiness of the voice, constipation, weakness, and fatigue. The heart rate is usually slowed **(bradycardia).** Reduced body temperature **(hypothermia)** may be present, and the skin often feels cool and dry to the touch. In the infant, these signs may not be readily apparent, and the failure to grow normally may be the first indication of the disease.

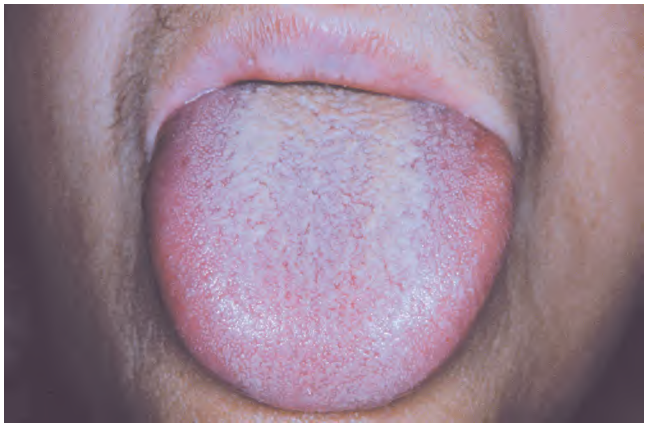
With respect to the oral findings, the lips may appear thickened because of the accumulation of glycosaminoglycans. Diffuse enlargement of the tongue occurs for the same reason (Fig. 17-23). If the condition develops during childhood, the teeth may fail to erupt, although tooth formation may not be impaired (Figs. 17-24 and 17-25).

Laboratory Findings

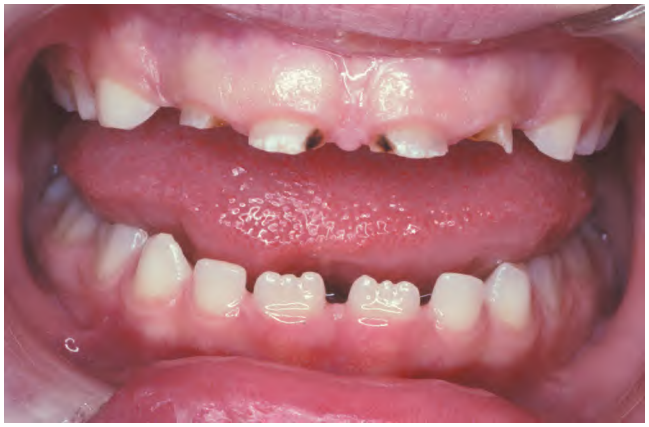
The diagnosis is made by assaying the free thyroxine (T_4) levels. If these levels are low, then TSH levels are measured to determine whether primary or secondary hypothyroidism is present. With primary thyroid disease, TSH levels are elevated. With secondary disease caused by pituitary dysfunction, TSH levels are normal or borderline.



• **Fig. 17-22 Hypothyroidism. A,** The facial appearance of this 9-year-old child is due to the accumulation of tissue edema secondary to severe hypothyroidism. **B,** Same patient after 1 year of thyroid hormone replacement therapy. Note the eruption of the maxillary permanent teeth.



• **Fig. 17-23 Hypothyroidism.** The enlarged tongue (macroglossia) is secondary to edema associated with adult hypothyroidism (myxedema). (Courtesy of Dr. George Blozis.)



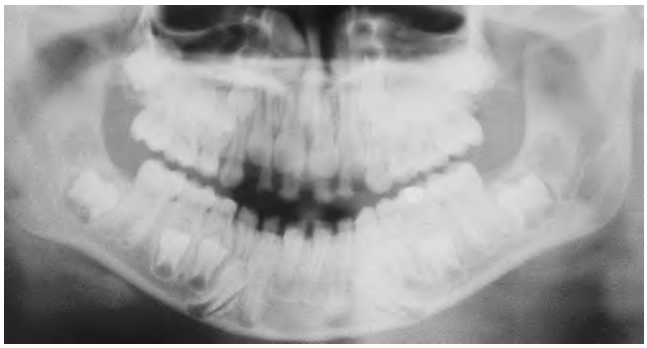
• **Fig. 17-24 Hypothyroidism.** Photograph of the same patient depicted in Fig. 17-22 before hormone replacement therapy. Note the retained deciduous teeth, for which the patient was initially referred.

Treatment and Prognosis

Thyroid replacement therapy, usually with levothyroxine, is indicated for confirmed cases of hypothyroidism. The prognosis is generally good for adult patients. If the condition is recognized within a reasonable time, the prognosis is also good for children. If the condition is not identified in a timely manner, however, permanent damage to the CNS may occur, resulting in intellectual disability. For affected children, thyroid hormone replacement therapy often results in a dramatic resolution of the condition (see Fig. 17-22).

◆ HYPERTHYROIDISM (THYROTOXICOSIS; GRAVES DISEASE)

Hyperthyroidism is a condition caused by excess production of thyroid hormone. This excess production results in a state of markedly increased metabolism in the affected patient. Most cases (60% to 90%) are due to **Graves disease**, a condition that was initially described in the early nineteenth century. It is thought to be triggered by autoantibodies that are directed against receptors for thyroid-stimulating hormone (TSH) on the surface of the thyroid cells. When the autoantibodies bind to these receptors, they seem to stimulate the thyroid cells to release inappropriate thyroid hormone.



• **Fig. 17-25 Hypothyroidism.** Panoramic radiograph of the same patient in Figs. 17-22 and 17-24. Note the unerupted, yet fully developed permanent dentition.

Other causes of hyperthyroidism include hyperplastic thyroid tissue and thyroid tumors, both benign and malignant, which secrete inappropriate thyroid hormone. Similarly, a pituitary adenoma may produce TSH, which can then stimulate the thyroid to secrete excess thyroid hormone.

Clinical Features

Graves disease is five to ten times more common in women than in men and is seen with some frequency. It affects almost 2% of the adult female population. Graves disease is most commonly diagnosed in patients during the third and fourth decades of life.

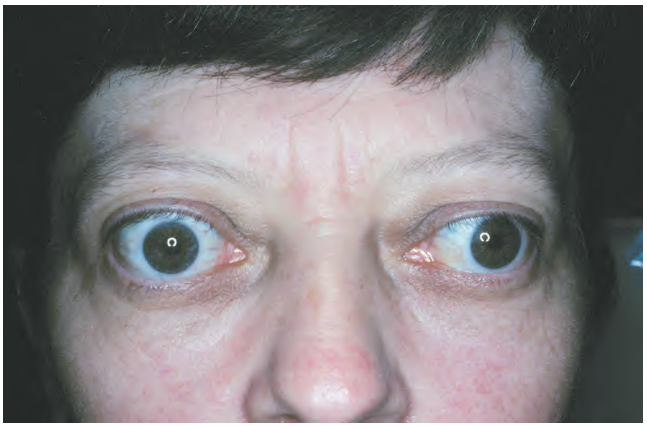
Most patients with Graves disease exhibit diffuse thyroid enlargement. Many of the signs and symptoms of hyperthyroidism can be attributed to an increased metabolic rate caused by the excess thyroid hormone. Patients usually complain about nervousness, heart palpitations, heat intolerance, emotional lability, and muscle weakness. The following are often noted during the clinical evaluation:

- Weight loss despite increased appetite
- Tachycardia
- Excessive perspiration
- Widened pulse pressure (increased systolic and decreased diastolic pressures)
- Warm, smooth skin
- Tremor

Ocular involvement, which develops in 20% to 40% of affected patients, is perhaps the most striking feature of this disease. In the early stages of hyperthyroidism, patients have a characteristic stare with eyelid retraction and lid lag. With some forms of Graves disease, protrusion of the eyes **(exophthalmos** or **proptosis)** develops (Fig. 17-26). This bulging of the eyes is due to an accumulation of glycosaminoglycans in the retro-orbital connective tissues.

Laboratory Findings

The diagnosis of hyperthyroidism is made by assaying free T_4 (thyroxine) and TSH levels in the serum. In affected patients, the T_4 levels should be elevated and the TSH concentration is typically depressed.



• **Fig. 17-26 Hyperthyroidism.** The prominent eyes are characteristic of the exophthalmos associated with Graves disease.

Histopathologic Features

Diffuse enlargement and hypercellularity of the thyroid gland are seen in patients with Graves disease, typically with hyperplastic thyroid epithelium and little apparent colloid production. Lymphocytic infiltration of the glandular parenchyma is also often noted.

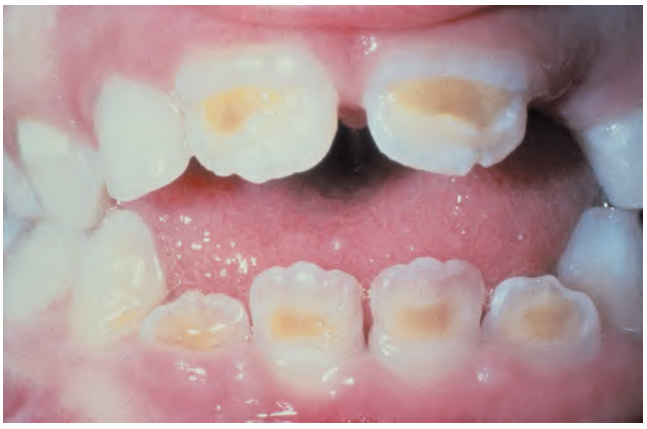
Treatment and Prognosis

In the United States, radioactive iodine (^{131}I) is the most commonly used form of therapy for adult patients with Graves disease. The thyroid gland normally takes up iodine from the bloodstream because this element is a critical component of thyroid hormone. When radioactive iodine is given to a patient with Graves disease, the thyroid gland quickly removes it from the bloodstream and sequesters the radioactive material within the glandular tissue. The radioactivity then destroys the hyperactive thyroid tissue, bringing the thyroid hormone levels back to normal. Most of the radiation is received during the first few weeks because the half-life of ^{131}I is short.

Other techniques include drug therapy with agents that block the normal use of iodine by the thyroid gland, and this form of therapy is initially favored in most European centers. The two drugs that have been widely prescribed in the United States are propylthiouracil (PTU) and methimazole. PTU has been associated with liver toxicity in some patients, and the US Food and Drug Administration has recommended that its use should be limited to specific circumstances, such as methimazole allergy or during the first trimester of pregnancy. Sometimes methimazole may be administered chronically in the hope that a remission may be induced. In addition, the thyroid gland, or a significant portion of it, may be removed surgically, thereby reducing thyroid hormone production. Methimazole is often given prior to either surgical removal of the thyroid or treatment with radioactive iodine in order to bring thyroid hormone levels into the normal range.

Drug therapy alone is often unsuccessful in controlling hyperthyroidism, and approximately half of patients treated in this way will relapse. Unfortunately, with radioactive iodine and surgery, the risk of hypothyroidism is relatively great, and thyroid hormone replacement therapy is often needed.

In a patient with uncontrolled hyperthyroidism, a definite risk exists with respect to an inappropriate release of large amounts of thyroid hormone at one time, resulting in a condition called a **thyroid storm.** A thyroid storm may be precipitated by infection, psychologic trauma, or stress. Clinically, patients may have delirium, convulsions, an elevated temperature (up to 106° F), and tachycardia (sometimes more than 140 beats/minute). Such individuals should be hospitalized immediately because the mortality rate associated with thyroid storm is approximately 20%. The clinician should be aware of the potential for this problem, and patients with hyperthyroidism should ideally have the condition under control before dental treatment.



• **Fig. 17-27 Hypoparathyroidism.** Enamel hypoplasia has affected the dentition of this patient, who had hypoparathyroidism while the teeth were forming.

◆ HYPOPARATHYROIDISM

Calcium levels in extracellular tissues are normally regulated by parathyroid hormone (PTH) (parathormone) in conjunction with vitamin D. If calcium levels drop below a certain point, then the release of PTH is stimulated. The hormone then acts directly on the kidney and the osteoblasts of the bone to restore the calcium to normal levels. In the kidney, calcium reabsorption is promoted, phosphate excretion is enhanced, and the production of vitamin D is stimulated, which increases the absorption of calcium from the gut. Osteoblasts are stimulated to produce a variety of cytokines that subsequently increase osteoclastic differentiation and metabolically activate the osteoclasts to resorb bone, thus liberating calcium.

If a reduced amount of PTH is produced, the relatively rare condition known as **hypoparathyroidism** results. Usually, hypoparathyroidism is due to inadvertent surgical removal of the parathyroid glands when the thyroid gland is excised for other reasons, but sometimes it is the result of autoimmune destruction of the parathyroid tissue. Rare syndromes, such as **DiGeorge syndrome** and the **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (endocrine-candidiasis syndrome, autoimmune polyglandular syndrome, type 1),** may be associated with hypoparathyroidism.

Clinical Features

With the loss of parathyroid function, the serum levels of calcium drop, resulting in hypocalcemia. Often the patient with chronic hypoparathyroidism adapts to the presence of hypocalcemia and is asymptomatic unless situations that further reduce the calcium levels are encountered. Such situations include metabolic alkalosis, as seen during hyperventilation, when a state of tetany may become evident.

Chvostek sign is an oral finding of significance, characterized by a twitching of the upper lip when the facial nerve is tapped just below the zygomatic process. A positive response suggests a latent degree of tetany. If the hypoparathyroidism develops early in life during odontogenesis, then a pitting enamel hypoplasia and failure of tooth eruption may occur (Fig. 17-27). The presence of persistent oral candidiasis in a young patient may signal the onset of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (see page 196). Hypoparathyroidism may be only one of several endocrine deficiencies associated with this condition.

Laboratory Findings

PTH can be measured by means of a radioimmunoassay. If serum PTH levels are decreased in conjunction with a decreased serum calcium concentration, elevated serum phosphate level, and normal renal function, then a diagnosis of hypoparathyroidism can be made.

Treatment and Prognosis

Patients with hypoparathyroidism are usually treated with oral doses of an active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol, vitamin D_3). Additional supplements of dietary calcium are also typically necessary to maintain the proper serum calcium levels. With this regimen, patients can often live a fairly normal life. Teriparatide, a recombinant form of the active component of human parathormone, has been developed but is not approved in the United States for management of hypoparathyroidism. Clinical trials have shown that, when given twice daily as subcutaneous injections, this drug may have promise as an alternative management strategy for hypoparathyroidism, although it is relatively expensive.

PSEUDOHYPOPARATHYROIDISM (ALBRIGHT HEREDITARY OSTEODYSTROPHY; ACRODYSOSTOSIS)

The rare condition known as **pseudohypoparathyroidism** represents at least two broad disorders in which normal parathyroid hormone (PTH) is present in adequate amounts but the biochemical pathways responsible for activating the target cells are not functioning properly. The clinical result is a patient who appears to have hypoparathyroidism.

In the case of pseudohypoparathyroidism type I, three subcategories have been defined. For type Ia, a molecular defect of a specific intracellular binding protein known as $G_s\alpha$ seems to prevent the formation of cyclic adenosine monophosphate (cAMP), a critical component in the activation of cell metabolism. Because other hormones also require binding with $G_s\alpha$ to carry out their functions, patients have multiple problems with other endocrine organs and functions. This condition is usually inherited as an autosomal dominant trait.

With respect to pseudohypoparathyroidism type Ib, the problem is thought to be caused by defective receptors for the PTH on the surface of the target cells (the proximal renal tubules). For this reason, no other endocrine tissues or functions are affected. An autosomal dominant mode of inheritance has been suggested for a few families affected by type Ib pseudohypoparathyroidism, but most cases are apparently sporadic. The mechanism of action for pseudohypoparathyroidism type Ic is less clear, but it may involve a defect in adenylate cyclase or a subtle $G_s\alpha$ alteration.

Pseudohypoparathyroidism type II is characterized by the induction of cAMP by PTH in the target cells; however, a functional response by the cells is not invoked. All of the reported cases of this form of the disease appear to be sporadic.

Clinical Features

Pseudohypoparathyroidism most commonly appears as type Ia disease. Patients affected by pseudohypoparathyroidism, either type Ia or Ic, have a characteristic array of features that includes mild intellectual disability, obesity, round face, short neck, and markedly short stature. Midfacial hypoplasia is also commonly observed. The metacarpals and metatarsals are usually shortened, and the fingers appear short and thick. Subcutaneous calcifications **(osteoma cutis)** may be identified in some patients. Other endocrine abnormalities that are typically encountered include hypogonadism and hypothyroidism.

Patients with type Ib and II disease clinically appear normal, aside from their symptoms of hypocalcemia.

Dental manifestations of pseudohypoparathyroidism include generalized enamel hypoplasia, widened pulp chambers with intrapulpal calcifications, oligodontia, delayed eruption, and blunting of the apices of the teeth. The pulpal calcifications are often described as "dagger" shaped.

The diagnosis of pseudohypoparathyroidism is made based on elevated serum levels of PTH seen concurrently with hypocalcemia, hyperphosphatemia, and otherwise normal renal function. More sophisticated studies are necessary to delineate the various subtypes.

Treatment and Prognosis

Pseudohypoparathyroidism is managed by the administration of vitamin D and calcium. The serum calcium levels and urinary calcium excretion are carefully monitored. Because of individual patient differences, the medication may need to be carefully adjusted; however, the prognosis is considered to be good.

HYPERPARATHYROIDISM

Excess production of parathyroid hormone (PTH) results in the condition known as **hyperparathyroidism.** PTH normally is produced by the parathyroid glands in response to a decrease in serum calcium levels.

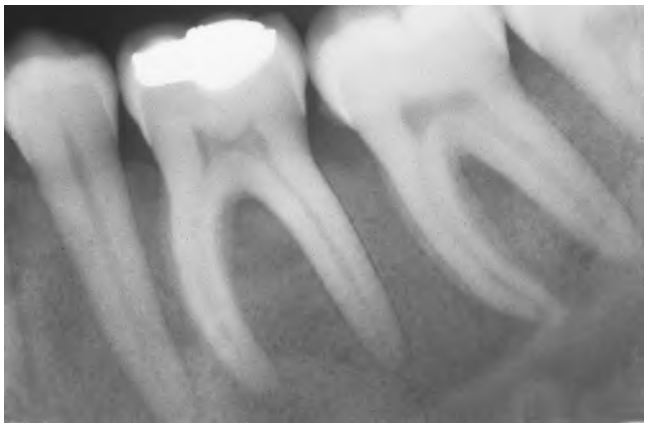
Primary hyperparathyroidism is the uncontrolled production of PTH, usually as a result of a parathyroid adenoma (80% to 90% of cases) or parathyroid hyperplasia (10% to 15% of cases). Rarely (approximately 1% of cases), a parathyroid carcinoma may be the cause of primary hyperparathyroidism. Infrequently this endocrine disturbance is caused by any one of several inherited syndromes, including **multiple endocrine neoplasia type 1** or **type 2a,** or **hyperparathyroidism–jaw tumor syndrome.** In the latter condition, affected patients develop multiple jaw lesions that histopathologically are consistent with central ossifying fibroma (see page 602). There also appears to be an increased risk for these patients to develop parathyroid carcinoma.

Secondary hyperparathyroidism develops when PTH is continuously produced in response to chronic low levels of serum calcium, a situation usually associated with chronic renal disease. The kidney processes vitamin D, which is necessary for calcium absorption from the gut. Therefore, in a patient with chronic renal disease, active vitamin D is not produced and less calcium is absorbed from the gut, resulting in lowered serum calcium levels.

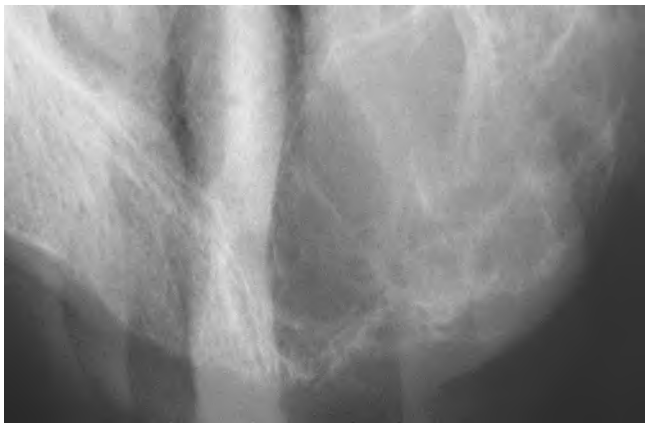
Clinical and Radiographic Features

Most patients with primary hyperparathyroidism are older than 60 years of age. Women have this condition two to four times more often than men do. In developed countries, the condition typically is identified on routine serologic testing, and the majority of patients are relatively asymptomatic.

Patients with the classic triad of signs and symptoms of hyperparathyroidism are described as having "stones, bones, and abdominal groans." Affected individuals are more likely to present with these signs and symptoms in economically less developed countries where serologic evaluation is not done on a routine basis.



• **Fig. 17-28 Hyperparathyroidism.** This periapical radiograph reveals the "ground glass" appearance of the trabeculae and loss of lamina dura in a patient with secondary hyperparathyroidism. (Courtesy of Dr. Randy Anderson.)

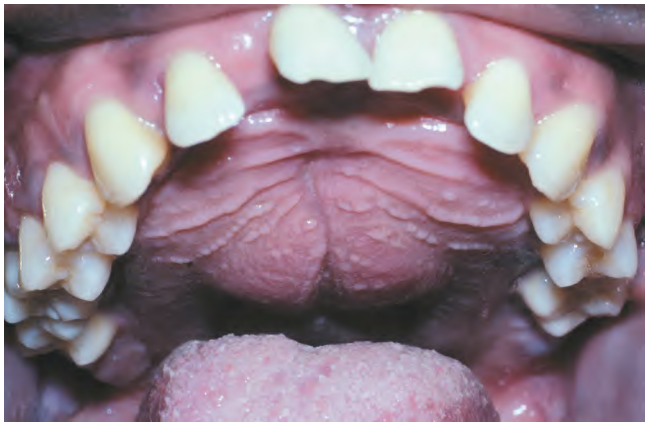


• **Fig. 17-29 Hyperparathyroidism.** This occlusal radiograph of the edentulous maxillary anterior region shows a multilocular radiolucency characteristic of a brown tumor of primary hyperparathyroidism. (Courtesy of Dr. Brian Blocher.)

"Stones" refers to the fact that these patients, particularly those with primary hyperparathyroidism, have a marked tendency to develop renal calculi (kidney stones, nephrolithiasis) because of the elevated serum calcium levels. Metastatic calcifications are also seen, frequently involving other soft tissues, such as blood vessel walls, subcutaneous soft tissues, the sclera, the dura, and the regions around the joints.

"Bones" refers to a variety of osseous changes that may occur in conjunction with hyperparathyroidism. One of the first clinical signs of this disease is seen radiographically as subperiosteal resorption of the phalanges of the index and middle fingers. Generalized loss of the lamina dura surrounding the roots of the teeth is also seen as an early manifestation of the condition (Fig. 17-28). Alterations in trabecular pattern characteristically develop next. A decrease in trabecular density and blurring of the normal trabecular pattern occur; often a "ground glass" appearance results.

With persistent disease, other osseous lesions develop, such as the so-called **brown tumor** of hyperparathyroidism. This lesion derives its name from the color of the tissue specimen, which is usually a dark red-brown because of the abundant hemorrhage and hemosiderin deposition within the tumor. These lesions appear radiographically as well-demarcated unilocular or multilocular radiolucencies (Fig. 17-29). They commonly affect the mandible, clavicles, ribs, and pelvis. They may be solitary but are often multiple, and long-standing lesions may produce significant cortical expansion. Typically, the other osseous changes are observable if brown tumors are present. The most severe skeletal manifestation of chronic hyperparathyroidism has been called **osteitis fibrosa cystica,** a condition that develops from the central degeneration and fibrosis of long-standing brown tumors. In patients with secondary hyperparathyroidism caused by end-stage renal disease **(renal osteodystrophy; chronic kidney disease—mineral and bone disorder),** striking enlargement of the jaws has been known



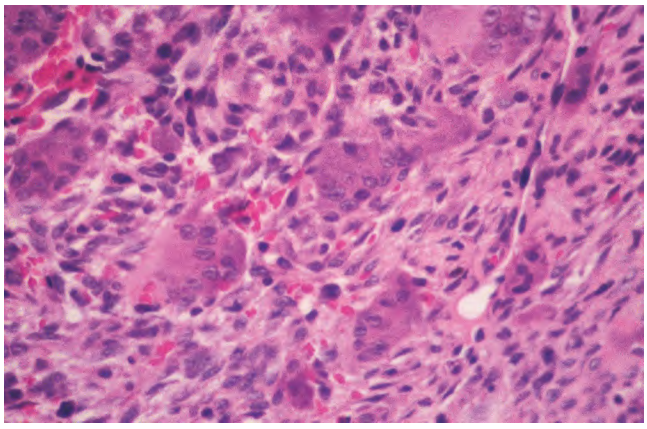
• **Fig. 17-30 Hyperparathyroidism.** Palatal enlargement is characteristic of the renal osteodystrophy associated with secondary hyperparathyroidism.

to occur (Fig. 17-30) and produce a "ground-glass" radiographic pattern (see Fig. 17-28).

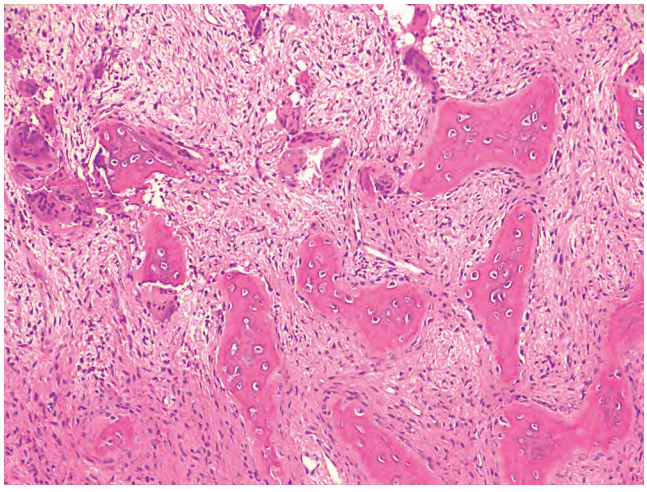
"Abdominal groans" refers to the tendency for the development of duodenal ulcers. In addition, changes in mental status are often seen, ranging from lethargy and weakness to confusion or dementia.

Histopathologic Features

The brown tumor of hyperparathyroidism is histopathologically identical to the **central giant cell granuloma** of the jaws, a benign tumorlike lesion that usually affects teenagers and young adults (see page 584). Both lesions are characterized by a proliferation of exceedingly vascular granulation tissue, which serves as a background for numerous multinucleated osteoclast-type giant cells (Fig. 17-31). Some lesions may also show a proliferative response characterized by a parallel arrangement of spicules of woven bone set in a cellular fibroblastic background with variable numbers of multinucleated giant cells (Fig. 17-32). This pattern is often



• **Fig. 17-31 Hyperparathyroidism.** This high-power photomicrograph of a brown tumor of hyperparathyroidism shows scattered multinucleated giant cells within a vascular and proliferative fibroblastic background.



• **Fig. 17-32 Hyperparathyroidism.** This medium-power photomicrograph shows trabeculae of cellular woven bone and clusters of multinucleated giant cells within a background of cellular fibrous connective tissue. These features are characteristic of tissue changes seen in renal osteodystrophy.

associated with secondary hyperparathyroidism related to chronic renal disease (renal osteodystrophy).

Treatment and Prognosis

In **primary hyperparathyroidism,** the hyperplastic parathyroid tissue or the functional tumor must be removed surgically to reduce PTH levels to normal. Localization of the parathyroid adenoma is often facilitated by a sestamibi scan, which is a nuclear medicine technique using a technetium 99-labeled small protein that is preferentially taken up by the tumor. Such tumors are frequently removed by a minimally invasive surgical technique, and intraoperative assessment of the adequacy of excision can be determined by noting a drop in parathormone levels within 10 minutes of removing the adenoma.

Secondary hyperparathyroidism may evolve to produce signs and symptoms related to renal calculi or renal osteodystrophy. Restriction of dietary phosphate, use of phosphate-binding agents, and pharmacologic treatment with an active vitamin D metabolite (e.g., calcitriol) and a calcimimetic agent, such as cinacalcet, may avert problems. Cinacalcet sensitizes the calcium receptors of the parathyroid cells to extracellular calcium, causing the cells to reduce their output of parathormone. Exposure to aluminum salts, which inhibit bone mineralization, should be eliminated also. Patients who do not respond to medical therapy may require parathyroidectomy. Renal transplantation may restore the normal physiologic processing of vitamin D, as well as phosphorus and calcium reabsorption and excretion; however, this does not occur in every case.

◆ HYPERCORTISOLISM (CUSHING SYNDROME)

Hypercortisolism is a clinical condition that results from a sustained increase in glucocorticoid levels. In most cases this increase is due to corticosteroid therapy that is prescribed for other medical purposes. The increase is less commonly caused by an endogenous source, such as production of adrenocorticotropic hormone (ACTH) by an adrenal tumor or pituitary adenoma. If a pituitary adenoma is responsible, then the term **Cushing disease** is applied. This condition is rather rare and usually affects young adult women.

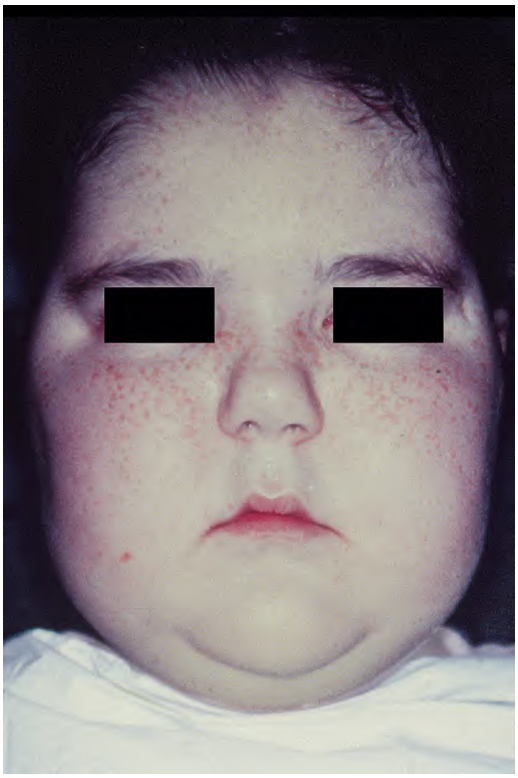
Clinical Features

The signs of Cushing syndrome usually develop slowly. The most consistent clinical observation is weight gain, particularly in the central areas of the body. The accumulation of fat in the dorsocervical spine region results in a "buffalo hump" appearance; fatty tissue deposition in the facial area results in the characteristic rounded facial appearance known as *moon facies* (Fig. 17-33). Other common findings include the following:

- Red-purple abdominal striae
- Hirsutism
- Poor healing
- Osteoporosis
- Hypertension
- Mood changes (particularly depression)
- Hyperglycemia with thirst and polyuria
- Muscle wasting with weakness

Diagnosis

If the patient has been receiving large amounts of corticosteroids (greater than the equivalent of 20 mg of prednisone) on a daily basis for several months, then the diagnosis is rather obvious, given the classic signs and symptoms described earlier. The diagnosis may be more difficult to establish in patients with a functioning adrenal cortical tumor or an ACTH-secreting pituitary adenoma. Evaluation of these patients should include the measurement of



• **Fig. 17-33 Cushing Syndrome.** The rounded facial features ("moon facies") of this patient are due to the abnormal deposition of fat, which is induced by excess corticosteroid hormone. (Courtesy of Dr. George Blozis.)

free cortisol in the urine and an assay of the effect of dexamethasone (a potent artificial corticosteroid) on the serum ACTH and cortisol levels. In an unaffected patient, the levels of free cortisol should be within normal limits, and the administration of an exogenous corticosteroid, such as dexamethasone, should suppress the normal level of ACTH, with a concomitant decrease in the cortisol levels. Because functioning tumors do not respond to normal feedback mechanisms, the anticipated decreases in ACTH and cortisol would not be seen in a patient with such a tumor.

Treatment and Prognosis

The clinician should be aware of the signs and symptoms of hypercortisolism to refer affected patients for appropriate endocrinologic evaluation and diagnosis. Once the diagnosis is established and the cause is determined to be an adrenal or pituitary tumor, surgical removal of the lesion is the treatment of choice. Radiation therapy also may be effective, particularly in younger patients. For patients with unresectable tumors, drugs that inhibit cortisol synthesis (such as, ketoconazole, metyrapone, or aminoglutethimide) may be used to help control the excess production of cortisol.

Most cases of hypercortisolism, however, are caused by systemic corticosteroid therapy that is given for a variety of immunologic reasons, including treatment of autoimmune diseases and allogeneic transplant recipients. Certain strategies, such as the use of corticosteroid-sparing agents or alternate-day therapy, may minimize the corticosteroid dose needed. The goal should be for patients to use the lowest dose possible to manage immunologic disease.

In normal situations, cortisol is critical to the function of the body, particularly in dealing with stress. As the hormone is metabolized and serum levels drop, feedback to the pituitary gland signals it to produce ACTH, which stimulates the adrenal gland to produce additional cortisol. Unfortunately, therapeutic corticosteroids suppress the production of ACTH by the pituitary gland to the extent that the pituitary gland may not be able to produce ACTH in response to stress, and an acute episode of hypoadrenocorticism *(addisonian crisis)* may be precipitated. Therefore, the clinician must be aware of the potential side effects of chronic high-dose corticosteroid use and must be able to adapt the treatment of the patient accordingly. For stressful dental and surgical procedures especially, it is often necessary to increase the corticosteroid dose because of the greater need of the body for cortisol. Consultation with the physician who is managing the corticosteroid therapy is advised to determine to what extent the dose should be adjusted.

◆ ADDISON DISEASE (HYPOADRENOCORTICISM)

Insufficient production of adrenal corticosteroid hormones caused by the destruction of the adrenal cortex results in the condition known as **Addison disease**, or **primary hypoadrenocorticism.** The incidence of new cases diagnosed in the Western hemisphere is approximately 4 per million population per year, while the prevalence is about 140 cases per million people. The causes are diverse and include the following:

- Autoimmune destruction (most common cause in Western societies)
- Infections (e.g., tuberculosis and deep fungal diseases, particularly in patients with acquired immunodeficiency syndrome [AIDS])
- Rarely, metastatic tumors, sarcoidosis, hemochromatosis, or amyloidosis

If the pituitary gland is not functioning properly, **secondary hypoadrenocorticism** may develop because of decreased production of ACTH, the hormone responsible for maintaining normal levels of serum cortisol.

Clinical Features

The clinical features of hypoadrenocorticism do not actually begin to appear until at least 90% of the glandular tissue has been destroyed. With gradual destruction of the adrenal cortex, an insidious onset of fatigue, irritability, depression, weakness, and hypotension is noted over a period of months. A generalized hyperpigmentation of the skin occurs, classically described as *bronzing*. The hyperpigmentation is

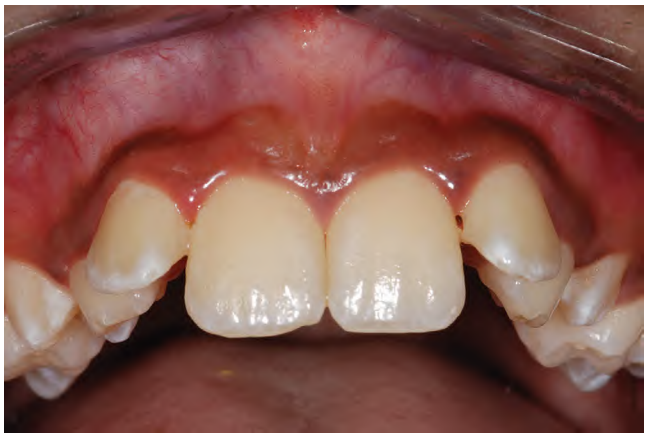


Fig. 17-34 Addison Disease. Diffuse pigmentation of the maxillary facial gingiva in a patient with Addison disease. (Courtesy of Dr. John Kalmar.)

generally more prominent on sun-exposed skin and over pressure points, such as the elbows and knees; it is caused by increased levels of beta-lipotropin or ACTH, each of which can stimulate melanocytes. The patient usually complains of gastrointestinal upset with anorexia, nausea, vomiting, diarrhea, weight loss, and a peculiar craving for salt, due to hyponatremia caused by lack of the mineralocorticoid, aldosterone. When hypoadrenocorticism is accompanied by hypoparathyroidism and mucocutaneous candidiasis, the possibility of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome should be considered (see page 196).

The oral manifestations include diffuse or patchy, brown, macular pigmentation of the oral mucosa caused by excess melanin production (Fig. 17-34). Often the oral mucosal changes are the first manifestation of the disease, with the skin hyperpigmentation occurring afterward. Sometimes the oral hypermelanosis may be difficult to distinguish from physiologic racial pigmentation, but a history of a recent onset of oral pigmentation should suggest the possibility of Addison disease.

Laboratory Findings

The diagnosis of hypoadrenocorticism is confirmed by a rapid ACTH stimulation test and measurement of serum cortisol levels and plasma ACTH levels. If serum cortisol levels are below 18 µg/dL, then the patient has adrenal insufficiency. In primary hypoadrenocorticism, the plasma ACTH levels are high (>100 ng/L). In secondary hypoadrenocorticism, the levels are normal (9 to 52 ng/L) or low, as would be expected because the condition results from decreased ACTH production by the pituitary gland.

Treatment and Prognosis

Addison disease is managed with replacement therapy, including both a glucocorticoid (such as, hydrocortisone) and mineralocorticoid (such as, fludrocortisone). The physiologic dose of glucocorticoid is considered to be approximately 30 to 45 mg of hydrocortisone or its equivalent per day, usually given in divided doses. Because the body's need for corticosteroid hormones increases during stressful events, the patient must take this into account and increase the dose accordingly. This adjustment is generally not required for dental procedures performed using local anesthesia and lasting less than 1 hour, but an increased dose may be necessary for certain dental and oral surgical procedures that are more lengthy or are done under general anesthesia.

Before the availability of corticosteroids, the prognosis for patients with hypoadrenocorticism was poor, with most patients surviving less than 2 years. Even today, if the condition is not recognized promptly, death may result in a relatively short period of time. With proper diagnosis and management, most patients with hypoadrenocorticism can expect to have a normal life span, although a recent population-based study suggested an increased mortality rate related to malignancy and cardiovascular disease.

DIABETES MELLITUS

Diabetes mellitus is a common disorder of carbohydrate metabolism that is thought to have several causes, although the basic problem is one of either decreased production of insulin or tissue resistance to the effects of insulin. The net result of this abnormal state is an increase in the blood glucose level **(hyperglycemia).**

Diabetes mellitus is usually divided into two presentations:

1. Type I—characterized by complete, or nearly complete, lack of insulin production
2. Type II—characterized by inadequate insulin production or resistance of target tissues to the effects of insulin

Type I diabetes mellitus was formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes, but these terms are not considered to be accurate. Type II diabetics often require insulin injections in order to manage their disease, and from 5% to 10% of type 1 diabetics develop their disease after 30 years of age. Patients with type 1 diabetes mellitus usually exhibit severe hyperglycemia and ketoacidosis without treatment, and they require exogenous insulin injections to survive.

Type II diabetes mellitus is sometimes more difficult to diagnose. It usually occurs in older, obese adults, but it may be seen in obese adolescents as well. For this reason, the term "adult-onset diabetes" was abandoned. Although hyperglycemia is present, ketoacidosis rarely develops. Furthermore, patients can produce some endogenous insulin. Certain patients may require insulin to help control their disease; the insulin injections, however, are usually not necessary for the patient's survival.

With respect to epidemiology, in the United States diabetes mellitus affects approximately 8% of the population, or 26 million people, although approximately 6 million of these cases remain undiagnosed. More than 1.5 million new cases are identified each year in the United States. Of these

affected patients, most have type II diabetes; only 5% to 10% have type I.

Diabetes is an important disease when we consider the many complications associated with it and the economic effect it has on society. One of the main complications of diabetes is **peripheral vascular disease,** a problem that results in kidney failure, as well as ischemia and gangrenous involvement of the limbs. By some estimates, 25% of all new cases of kidney failure occur in diabetic patients. Thus diabetes is the leading cause of kidney failure in the United States. Each year more than 50,000 amputations are performed for the gangrenous complications of diabetes. This disease is the leading cause of lower limb amputations in the United States. Retinal involvement often results in blindness; thus the leading cause of new cases of blindness in working-age adults in the United States is diabetes, with more than 12,000 people affected annually. Complications because of diabetes are estimated to contribute to the deaths of more than 200,000 Americans each year.

The cause of diabetes mellitus is essentially unknown, although most cases of type I diabetes appear to be caused by autoimmune destruction of the pancreatic islet cells, and this immunologic attack may be precipitated by a viral infection in a genetically susceptible individual. Type II diabetes does not appear to have an autoimmune cause, however, because no destruction of the islet cells is seen microscopically. Instead, genetic abnormalities have been detected in patients with certain types of type II diabetes, which may explain why the condition occurs so often in families. If one parent is affected by type II diabetes, then the chances of a child having the disorder is about 40%. Similarly, if one identical twin has type II diabetes, then the chances are 90% that the disease will also develop in the other twin.

Clinical Features

Although a complete review of the pathophysiology of diabetes mellitus is beyond the scope of this text, the clinical signs and symptoms of a patient with this disease are easier to understand with some basic knowledge of the process. The hormone insulin, produced by the beta cells of the pancreatic islets of Langerhans, is necessary for the uptake of glucose by the cells of the body. When insulin binds to its specific cell surface receptor, a resulting cascade of intracellular molecular events causes the recruitment of intracellular glucose-binding proteins, which facilitate the uptake of glucose by each cell.

Type I Diabetes Mellitus

Because patients with type I diabetes have a deficiency in the amount of insulin, the body's cells cannot absorb glucose and it remains in the blood. Normal blood glucose levels are between 70 and 120 mg/dL; in diabetic patients, these levels are often between 200 and 400 mg/dL. Above 300 mg/dL, the kidneys can no longer reabsorb the glucose; therefore, it spills over into the urine. Because glucose is the main source of energy for the body, and because none of this energy can be used because glucose cannot be absorbed, the patient feels tired and lethargic. The body begins to use other energy sources, such as fat and protein, resulting in the production of ketones as a by-product of those energy consumption pathways. The patient often loses weight, despite increased food intake **(polyphagia).** With the hyperglycemia, the osmolarity of the blood and urine increases. The increased osmolarity results in frequent urination **(polyuria)** and thirst, which leads to increased water intake **(polydipsia).** Clinically, most patients with type I diabetes are younger (average age at diagnosis being 14 years), and they have a thin body habitus.

Type II Diabetes Mellitus

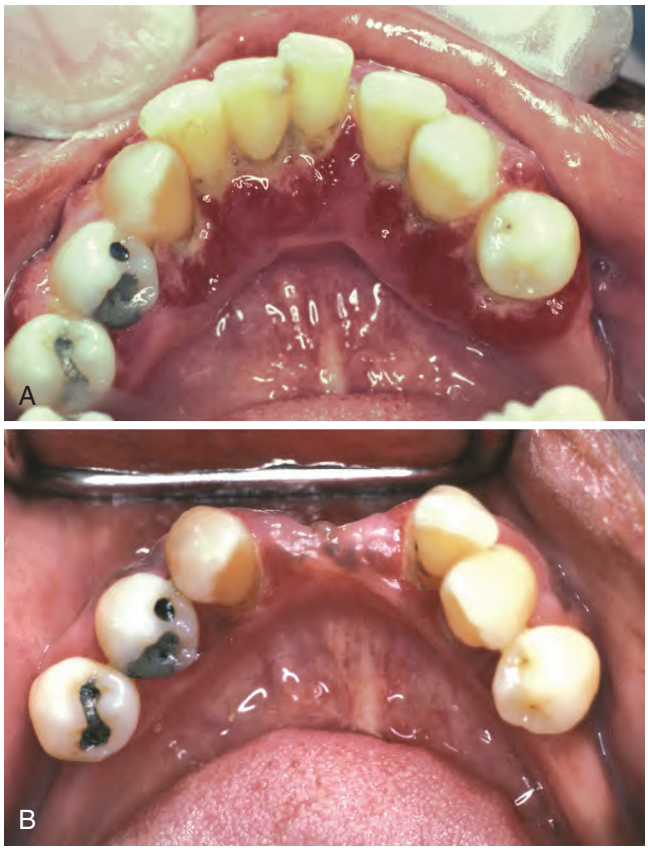
By contrast, patients with type II diabetes are usually older than 40 years of age at diagnosis, and 80% to 90% of them are obese. In this situation, it is thought that a decrease in the number of insulin receptors or abnormal post-binding molecular events related to glucose uptake results in glucose not being absorbed by the body's cells. Thus patients are said to show "insulin resistance" because serum insulin levels are usually within normal limits or even elevated. If the hyperglycemia is taken into account, however, the amount of circulating insulin is typically not as much as would be present in a normal person with a similar level of blood glucose. Therefore, many of these patients are described as having a relative lack of insulin.

The symptoms associated with type II diabetes are much more subtle in comparison to those seen with type I. The first sign of type II diabetes is often detected with routine hematologic examination rather than any specific patient complaint. Ketoacidosis is rarely seen in patients with type II diabetes. Nevertheless, many of the other complications of diabetes are still associated with this form of the disease.

Complications

Many complications of diabetes mellitus are directly related to the **microangiopathy** caused by the disease. The microangiopathy results in occlusion of the small blood vessels, producing peripheral vascular disease. The resultant decrease in tissue perfusion results in ischemia. The ischemia predisposes the patient to infection, particularly severe infections such as gangrene. Another contributing factor is the impairment of neutrophil function, particularly neutrophil chemotaxis.

Amputation of the lower extremity often is necessary because of the lack of tissue perfusion and the patient's inability to cope with infection. Similar vascular occlusion may affect the coronary arteries (which places the patient at risk for myocardial infarction) or the carotid arteries and their branches (predisposing the patient to cerebrovascular accident, or stroke). When microvascular occlusion affects the retinal vessels, blindness typically results. Kidney failure is the outcome of renal blood vessel involvement. If the ketoacidosis is not corrected in type I diabetes, the patient may lapse into a diabetic coma.



• **Fig. 17-35 Diabetes Mellitus. A,** This diffuse, erythematous enlargement of the gingival tissues developed in a diabetic patient who discontinued taking her insulin. **B,** The gingival tissues have greatly improved after reinstitution of regular insulin injections. Several incisors were extracted because of severe periodontal bone loss.

The oral manifestations of diabetes mellitus are generally limited to patients with type I diabetes. Problems include periodontal disease, which occurs more frequently and progresses more rapidly than in normal patients. Healing after surgery may be delayed, and the likelihood of infection is probably increased. Diffuse, nontender, bilateral enlargement of the parotid glands, called **diabetic sialadenosis** (see page 437), may be seen in patients with either form of diabetes. In uncontrolled or poorly controlled diabetic patients, a striking enlargement and erythema of the attached gingiva has been described (Fig. 17-35). In addition, these patients appear to be more susceptible to **oral candidiasis** in its various clinical forms (see page 191). Erythematous candidiasis, which appears as central papillary atrophy of the dorsal tongue papillae, is reported in up to 30% of these patients. **Mucormycosis** (see page 208) may occur in patients with poorly controlled type I diabetes. Some investigators have identified an increased prevalence of **benign migratory glossitis** (see page 726) in patients with type I diabetes; however, others have not been able to confirm this finding. **Xerostomia,** a subjective feeling of dryness of the oral mucosa, has been reported as a complaint in one-third of diabetic patients. Unfortunately, studies that attempt to confirm an actual decrease in salivary flow rate in diabetic patients have produced conflicting results. Some studies show a decrease in salivary flow; some, no difference from normal; and some, an increased salivary flow rate.

Treatment and Prognosis

For patients with type II diabetes, dietary modification coupled with exercise may be the only treatment necessary, with the goal being weight loss. The dietary and lifestyle changes may need to be coupled with one or more oral hypoglycemic agents. These drugs are designed to affect different pathophysiologic aspects of the disease. For example, secretagogues increase the insulin supply. These include the second-generation sulfonylurea medications, such as glipizide or glyburide. Metformin is a biguanide that increases glucose utilization and decreases insulin resistance and hepatic glucose production. Thiazolidinediones, such as rosiglitazone and pioglitazone, also reduce insulin resistance. Acarbose and miglitol are α-glucosidase inhibitors that reduce the absorption of glucose from the gastrointestinal tract by inhibiting enzymatic degradation of more complex sugars. If these modalities do not control the blood glucose levels, then treatment with insulin is necessary.

For patients with type I diabetes, injections of insulin are required to control blood glucose levels. Different types of insulin are marketed, each type having different degrees of duration and times of peak activity. Insulin was previously extracted primarily from beef and pork pancreata. In some patients, however, antibodies developed to this foreign protein and rendered the insulin useless. To overcome this problem, pharmaceutical companies have developed brands of insulin that have the molecular structure of human insulin. Laboratories produce this human insulin with genetically engineered bacteria using recombinant DNA technology.

The patient's schedule of insulin injections must be carefully structured and monitored to provide optimal control of blood glucose levels. This schedule is carefully formulated by the patient's physician and takes into account such factors as the patient's activity level and the severity of the insulin deficiency. It is imperative that adequate dietary carbohydrates be ingested after the administration of the insulin; otherwise, a condition known as **insulin shock** may occur. If carbohydrates are not consumed after an insulin injection, then the blood glucose levels may fall to dangerously low levels. The brain is virtually dependent on blood glucose as its energy source. If the blood glucose level drops below 40 mg/dL, the patient may go into shock. This condition can be treated by administration of sublingual dextrose paste, IV infusion of a dextrose solution, or injection of glucagon.

In summary, diabetes mellitus is a common, complex medical problem with many complications. The prognosis is guarded. Studies suggest that strict control of blood glucose levels results in a slowing of the development of the late complications of type I diabetes (e.g., blindness, kidney damage, and neuropathy) and reduces the frequency of

these complications. Health care practitioners should be aware of the problems these patients may have and should be prepared to deal with them. Consultation with the patient's physician may be necessary, particularly for patients with type I diabetes that show poor blood glucose control, have active infections, or require extensive oral surgical procedures.

◆ HYPOPHOSPHATASIA

Hypophosphatasia is a rare metabolic bone disease that is characterized by a deficiency of tissue-nonspecific alkaline phosphatase. Approximately 150 distinct mutations of the gene responsible for alkaline phosphatase production have been described. One of the first presenting signs of hypophosphatasia may be the premature loss of the primary teeth, presumably caused by a lack of cementum on the root surfaces. In the homozygous autosomal recessive form, there are rather severe manifestations, and many of these patients are identified in infancy. The milder forms of the disease are inherited in an autosomal dominant or recessive fashion, appearing in childhood or even adulthood, with variable degrees of expression. Generally, the younger the age of onset, the more severe the expression of the disease. The common factors in all types include the following:

- Reduced levels of the bone, liver, and kidney isozyme of alkaline phosphatase
- Increased levels of blood and urinary phosphoethanolamine
- Bone abnormalities that resemble rickets

Most authorities believe that the decreased alkaline phosphatase levels probably are responsible for the clinically observed abnormalities. Alkaline phosphatase is thought to play a role in the production of bone, but its precise mechanism of action is unknown.

Clinical and Radiographic Features

Six types of hypophosphatasia are now recognized, depending on the severity and the age of onset of the symptoms:

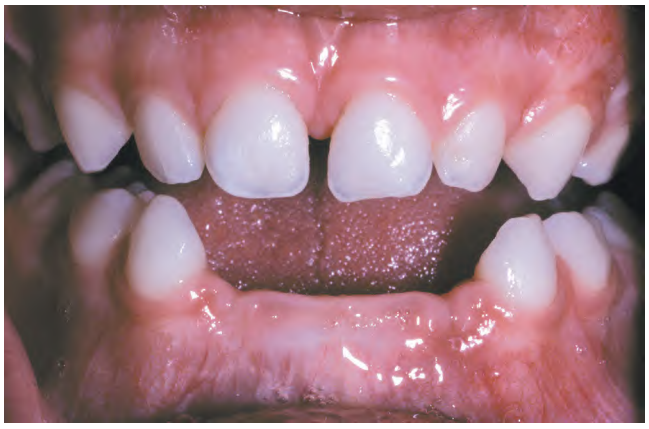
1. Perinatal lethal
2. Perinatal benign
3. Infantile
4. Childhood
5. Adult
6. Odontohypophosphatasia

Perinatal Lethal Hypophosphatasia

The **perinatal lethal** form has the most severe manifestations. It is usually diagnosed at birth, and the infant rarely survives for more than a few hours. Death is due to respiratory failure. Marked hypocalcification of the skeletal structures is observed.

Perinatal Benign Hypophosphatasia

The **perinatal benign** form of hypophosphatasia appears similar to the lethal form, but these infants have a clinical course similar to infantile hypophosphatasia. Some investigators have noted that skeletal calcification may be detected in some of these fetuses during the third trimester of pregnancy, in contrast to the lethal form.



• **Fig. 17-36 Hypophosphatasia.** Premature loss of the mandibular anterior teeth. (Courtesy of Dr. Jackie Banahan.)

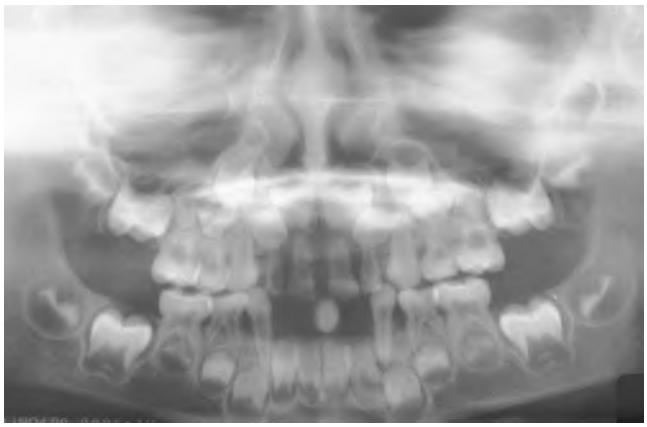
Infantile Hypophosphatasia

Babies affected by **infantile** hypophosphatasia may appear normal up to 6 months of age; after this time, they begin to show a failure to grow. Vomiting and hypotonia may develop as well. Skeletal malformations that suggest rickets are typically observed; these malformations include shortened, bowed limbs. Deformities of the ribs predispose these patients to pneumonia, and skull deformities cause increased intracranial pressure. Nephrocalcinosis and nephrolithiasis also produce problems for these infants. Radiographs show a markedly reduced degree of ossification with a preponderance of hypomineralized osteoid. If these infants survive, premature shedding of the deciduous teeth is often seen.

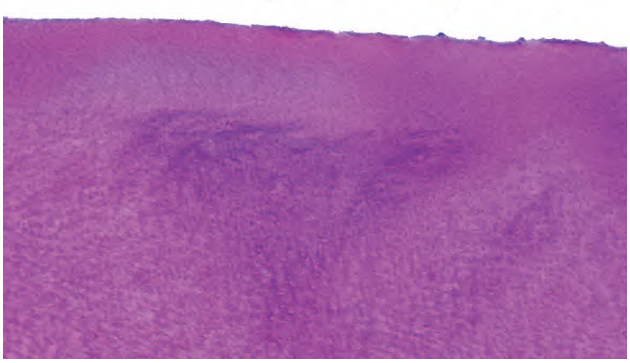
Childhood Hypophosphatasia

The **childhood** form is usually detected at a later age and has a wide range of clinical expression. One of the more consistent features is the premature loss of the primary teeth without evidence of a significant inflammatory response (Figs. 17-36 and 17-37). The deciduous incisor teeth are usually affected first and may be the only teeth involved. In some patients, this may be the only expression of the disease. The teeth may show enlarged pulp chambers in some instances, and a significant degree of alveolar bone loss may be seen. More severely affected patients may have open fontanelles with premature fusion of cranial sutures. This early fusion occasionally leads to increased intracranial pressure and subsequent brain damage. Affected patients typically have a short stature, bowed legs, and a waddling gait. The development of motor skills is often delayed.

Radiographically, the skull of more severely affected individuals may show uniformly spaced, poorly defined, small radiolucencies, a pattern that has been described as resembling "beaten copper." This appearance may be the result of



• **Fig. 17-37 Hypophosphatasia.** This panoramic radiograph shows the loss of the mandibular anterior teeth. (Courtesy of Dr. Jackie Banahan.)



• **Fig. 17-38 Hypophosphatasia.** This medium-power photomicrograph of an exfoliated tooth shows no cementum associated with the root surface.

areas of thinning of the inner cortical plate produced by the cerebral gyri.

Adult Hypophosphatasia

The **adult** form is typically mild. Patients often have a history of premature loss of their primary or permanent dentition, and many of these patients are edentulous. Stress fractures that involve the metatarsal bones of the feet may be a presenting sign of the condition, or an increased number of fractures associated with relatively minor trauma may alert the clinician to this disorder.

Odontohypophosphatasia

This form of hypophosphatasia is perhaps the most controversial. Affected patients present with premature loss of the incisor teeth as the only clinical sign of disease, although serologic studies will be consistent with hypophosphatasia. Some investigators have suggested that this may simply represent a mild expression of the disorder.

Diagnosis

The diagnosis of hypophosphatasia is based on the clinical manifestations and the finding of decreased levels of serum alkaline phosphatase and increased amounts of phosphoethanolamine in both the urine and the blood. Interestingly, as some patients grow older, serum alkaline phosphatase levels may approach normal.

Histopathologic Features

The histopathologic evaluation of bone sampled from a patient affected with the **infantile** form of hypophosphatasia shows abundant production of poorly mineralized osteoid. In the **childhood** or **adult** form, the bone may appear relatively normal or it may show an increased amount of woven bone, which is a less mature form of osseous tissue.

The histopathologic examination of either a primary or permanent tooth that has been exfoliated from an affected patient often shows an absence or a marked reduction of cementum that covers the root's surface (Fig. 17-38). This reduced amount of cementum is thought to predispose to tooth loss because of the inability of periodontal ligament fibers to attach to the tooth and to maintain it in its normal position.

Treatment and Prognosis

The treatment of hypophosphatasia is essentially symptomatic because the lack of alkaline phosphatase cannot be corrected. Attempts to treat this condition by infusing alkaline phosphatase have been unsuccessful, presumably because the enzyme functions within the cell rather than in the extracellular environment. Basically, fractures are treated with orthopedic surgery, followed by rehabilitation. Prosthetic appliances are indicated to replace missing teeth, but satisfactory results are not always possible because the alveolar bone is hypoplastic. In patients who are skeletally mature, dental implants have also been used successfully in managing the edentulous spaces. Because mutational analysis of DNA can identify carriers of the defective gene, patients and their parents should be provided with genetic counseling. As stated earlier, the prognosis varies with the onset of symptoms; the perinatal and infantile types are associated with a rather poor outcome. The childhood and adult forms are usually compatible with a normal life span.

◆ VITAMIN D–RESISTANT RICKETS (HEREDITARY HYPOPHOSPHATEMIA; FAMILIAL HYPOPHOSPHATEMIC RICKETS)

After the use of vitamin D to treat rickets became widespread, it was recognized that some individuals with clinical features characteristic of rickets did not seem to respond to therapeutic doses of the vitamin. For this reason, this condition in these patients was called **vitamin D–resistant rickets**. Most cases of this rare condition appear to be

inherited as an X-linked dominant trait; therefore, males are usually affected more severely than females, who presumably have attenuated features because of lyonization. In the United States, this condition occurs at a frequency of 1 in 20,000 births. In addition to the rachitic changes, these patients are also hypophosphatemic and show a decreased capacity for reabsorption of phosphate from the renal tubules. The disorder is caused by mutations in a zinc metalloproteinase gene known as *phosphate-regulating gene with endopeptidase activity on the X chromosome (PHEX)*. Although the precise mechanisms of action of this gene are unclear, it appears to play a role in vitamin D metabolism.

In contrast, patients affected by the rare autosomal recessive condition known as **vitamin D–dependent rickets** exhibit hypocalcification of the teeth, unlike those with vitamin D–resistant rickets. Otherwise, the two disorders have similar clinical features. Vitamin D–dependent rickets is caused by a lack of 1α-hydroxylase, the enzyme responsible for converting the relatively inactive vitamin D precursor, 25-hydroxycholecalciferol (calcifediol) to the active metabolite 1,25-dihydroxycholecalciferol (calcitriol) in the kidney. Therefore, these patients respond to replacement therapy with active vitamin D (calcitriol).

Clinical Features

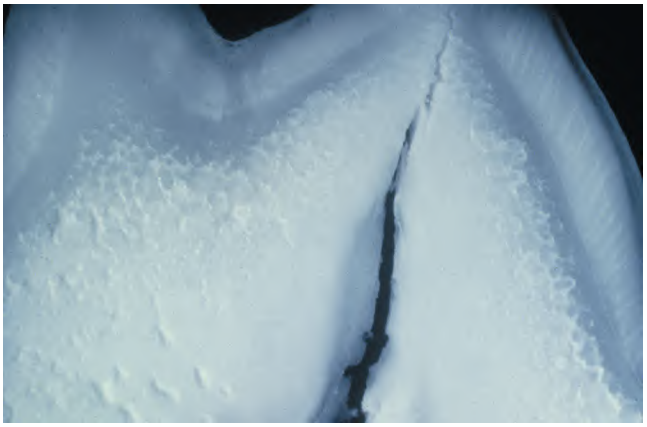
Patients with vitamin D–resistant rickets have a short stature. The upper body segment appears more normal, but the lower body segment is shortened. The lower limbs are generally shortened and bowed.

Laboratory investigation reveals hypophosphatemia with diminished renal reabsorption of phosphate and decreased intestinal absorption of calcium. This typically results in rachitic changes that are unresponsive to vitamin D (calciferol). With aging, ankylosis of the spine frequently develops.

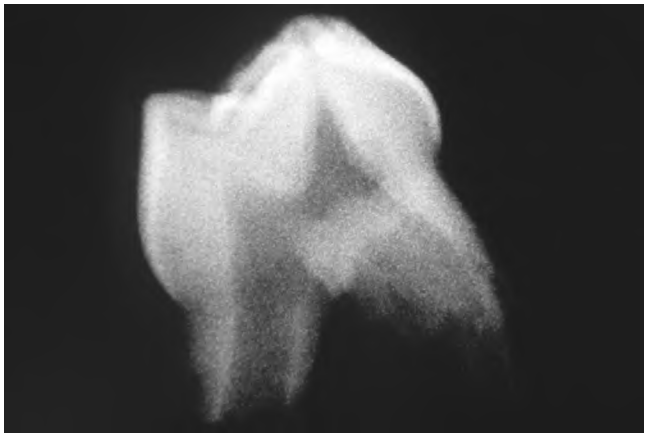
From a dental standpoint, the teeth have large pulp chambers, with pulp horns extending almost to the dentinoenamel junction (Figs. 17-39 and 17-40). In some cases the cuspal enamel may be worn down by attrition to the level of the pulp horn, causing pulpal exposure and pulp death. The exposure may be so small that the resulting periapical abscesses and gingival sinus tracts seem to affect what appear to be otherwise normal teeth (Fig. 17-41). Studies have also shown that microclefts may develop in the enamel, giving the oral microflora access to the dentinal tubules and subsequently to the pulp. One study examined a series of affected children and found that 25% of these patients had multiple abscesses involving the primary dentition. Affected adults also have an increased frequency of endodontic problems, with an average of approximately seven endodontically treated teeth per person in people over 40 years of age, compared to two endodontically treated teeth per person in a matched control group.

Histopathologic Features

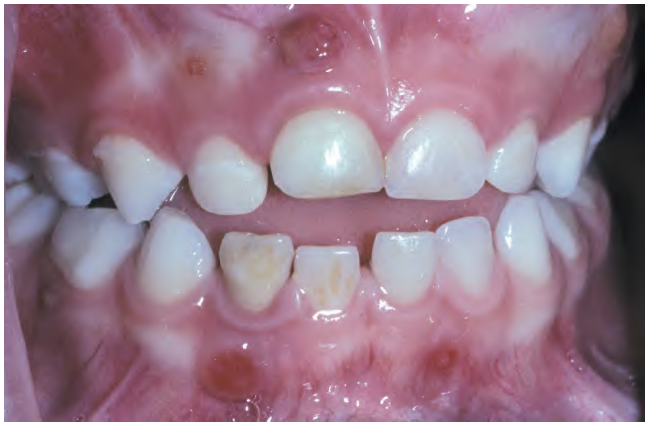
Microscopic examination of an erupted tooth from a patient with vitamin D–resistant rickets usually shows markedly



• **Fig. 17-40 Vitamin D–Resistant Rickets.** Ground section of the same tooth depicted in Fig. 17-39. A pulp horn extends to the dentinoenamel junction. (Courtesy of Dr. Carl Witkop.)



• **Fig. 17-39 Vitamin D–Resistant Rickets.** This radiograph of an extracted tooth shows a prominent pulp chamber with pulp horns extending out toward the dentinoenamel junction.



• **Fig. 17-41 Vitamin D–Resistant Rickets.** This patient exhibits multiple nonvital teeth with associated parulides. This arose in the absence of caries or trauma.

enlarged pulp horns. The dentin appears abnormal and is characterized by the deposition of globular dentin, which often exhibits clefting. The clefts may extend from the pulp chamber to the dentinoenamel junction. Microclefts are also seen within the enamel. The pulp frequently is nonvital, presumably because of the bacterial contamination associated with both the enamel and the dentinal clefts.

Treatment and Prognosis

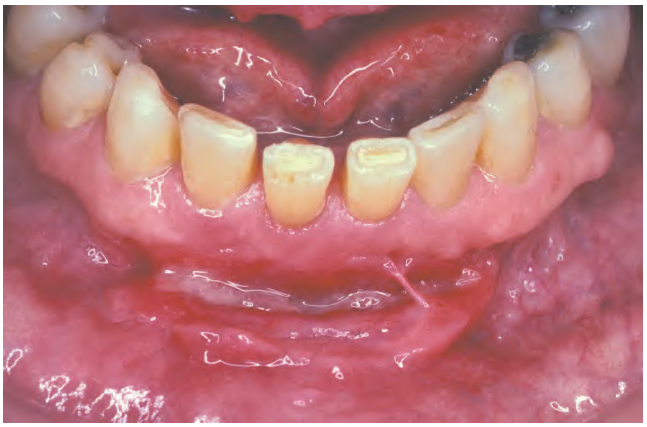
For a normal stature to develop, patients with vitamin D–resistant rickets usually need early treatment with calcitriol and multiple daily doses of phosphate. Endodontic therapy is necessary for the pulpally involved teeth. Initiating therapy in early childhood with a synthetic vitamin D compound (1α-hydroxycholecalciferol) appears to reduce dental problems in affected patients when compared with untreated historic controls. Interestingly, the radiographic dental abnormalities do not seem to be improved. Some investigators have suggested that application of the newer dental sealants may reduce the frequency of pulpal necrosis, but long-term follow-up studies will be necessary to confirm this. Although serum and urine calcium levels must be monitored carefully to prevent nephrocalcinosis with its potential for kidney damage, patients generally have a normal life span.

◆ CROHN DISEASE (REGIONAL ILEITIS; REGIONAL ENTERITIS)

Crohn disease is an inflammatory and probably an immunologically mediated condition of unknown cause that primarily affects the distal portion of the small bowel and the proximal colon. It is now well established that the manifestations of Crohn disease may be seen anywhere in the gastrointestinal tract, from the mouth to the anus. In addition, other extraintestinal sites of disease involvement (such as, the skin, eyes, and joints) have also been identified. The oral lesions are significant because they may precede the gastrointestinal lesions in as many as 30% of the cases that have both oral and gastrointestinal involvement. It is interesting that the prevalence of Crohn disease appears to be increasing, but the reasons for this increase have not been determined. Familial clustering of cases has suggested that genetic factors play a role in the pathogenesis of this disease.

Clinical Features

Most patients with Crohn disease are teenagers when the disease first becomes evident, although another diagnostic peak of disease activity occurs in patients more than 60 years of age. Gastrointestinal signs and symptoms usually include abdominal cramping and pain, nausea, and diarrhea, occasionally accompanied by fever. Weight loss and malnutrition may develop, which can lead to anemia, decreased growth, and short stature.

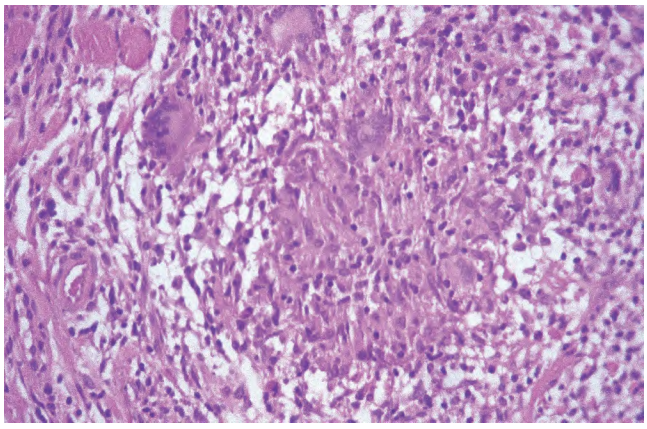


• **Fig. 17-42 Crohn Disease.** This patient has a linear ulceration of the mandibular vestibule. An adhesion between the alveolar and labial mucosae was caused by repeated ulceration and healing of the mucosa at this site.

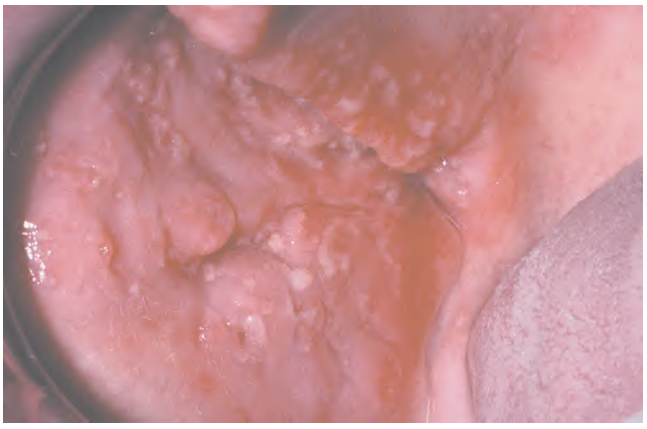
A wide range of oral lesions has been clinically reported in Crohn disease; however, many of the abnormalities described are relatively nonspecific and may be associated with other conditions that cause **orofacial granulomatosis** (see page 312). The more prominent findings include diffuse or nodular swelling of the oral and perioral tissues, a cobblestone appearance of the mucosa, and deep, granulomatous-appearing ulcers. The ulcers are often linear and develop in the buccal vestibule (Fig. 17-42). Patchy erythematous macules and plaques involving the attached and unattached gingivae have been termed *mucogingivitis* and may represent one of the more common lesions related to Crohn disease. Soft tissue swellings that resemble denture-related fibrous hyperplasia may be seen, as well as smaller mucosal tags. Another manifestation that has been reported is aphthous-like oral ulcerations, although the significance of this finding is uncertain because aphthous ulcerations are found rather frequently in the general population, including the same age group that is affected by Crohn disease. One large study showed no difference in the prevalence of aphthous ulcers in patients with Crohn disease compared with a control population. Less than 1% of patients with Crohn disease may develop diffuse stomatitis, with some cases apparently caused by *Staphylococcus aureus,* and others being nonspecific. In at least one instance, recurrent severe buccal space infections resulted in cutaneous salivary fistula formation. Infrequently, pyostomatitis vegetans (see next topic) has been associated with Crohn disease.

Histopathologic Features

Microscopic examination of lesional tissue obtained from the intestine or from the oral mucosa should show nonnecrotizing granulomatous inflammation within the submucosal connective tissue (Fig. 17-43). The severity of the granulomatous inflammation may vary tremendously from patient to patient and from various sites in the same patient. Therefore, a negative biopsy result at any one site and time



• **Fig. 17-43 Crohn Disease.** This medium-power photomicrograph of an oral lesion shows a nonnecrotizing granuloma in the submucosal connective tissue.



• **Fig. 17-44 Pyostomatitis Vegetans.** The characteristic lesions are seen on the buccal mucosa, appearing as yellow-white pustules.

may not necessarily rule out a diagnosis of Crohn disease. As with the clinical lesions, the histopathologic pattern is relatively nonspecific, resembling orofacial granulomatosis. Special stains should be performed to rule out the possibility of deep fungal infection, syphilis, or mycobacterial infection.

Treatment and Prognosis

Most patients with mild Crohn disease are initially treated medically with mesalamine (5-aminosalicylic acid) or sulfasalazine, a drug that is enzymatically broken down by bacteria in the colon to form sulfapyridine and 5-aminosalicylic acid. Some patients respond well to this medication, typically when it is combined with an antibiotic such as metronidazole. With moderate to severe involvement, systemic prednisone may be used and is often effective, particularly when combined with an immunosuppressive drug, such as azathioprine, methotrexate, or 6-mercaptopurine. For more severe or refractory cases of Crohn disease, one of the tumor necrosis factor-α inhibitors (such as, infliximab, adalimumab, or certolizumab pegol) may be used. Sometimes the disease cannot be maintained in remission by medical therapy, and complications develop that require surgical intervention. Complications may include bowel obstruction or fistula or abscess formation. If a significant segment of the terminal ileum has been removed surgically or is involved with the disease, then periodic injections of vitamin B_{12} may be necessary to prevent megaloblastic anemia secondary to the lack of ability to absorb the vitamin. Similar supplementation of magnesium, iron, the fat-soluble vitamins, and folate may also be required because of malabsorption. Cigarette smoking is known to exacerbate Crohn disease, and patients should be advised to stop this habit.

Oral lesions have been reported to clear with treatment of the gastrointestinal process in many cases. Occasionally persistent oral ulcerations will develop, and these may have to be treated with topical or intralesional corticosteroids. Systemic thalidomide and infliximab have been used successfully to manage refractory oral ulcers of Crohn disease.

◆ PYOSTOMATITIS VEGETANS

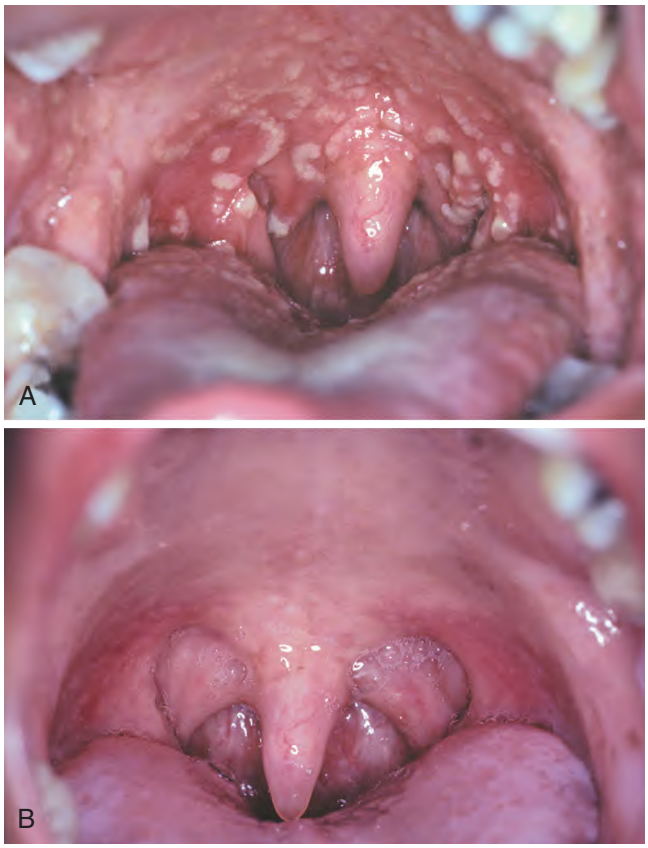
Pyostomatitis vegetans is a relatively rare condition that has a controversial history. It has been associated in the past with diseases such as pemphigus or pyodermatitis vegetans. Most investigators today, however, believe that pyostomatitis vegetans is an unusual oral expression of inflammatory bowel disease, particularly **ulcerative colitis** or **Crohn disease.** The pathogenesis of the condition, like that of inflammatory bowel disease, is poorly understood. A few patients with pyostomatitis vegetans have also been noted to have one of several concurrent liver abnormalities.

Clinical Features

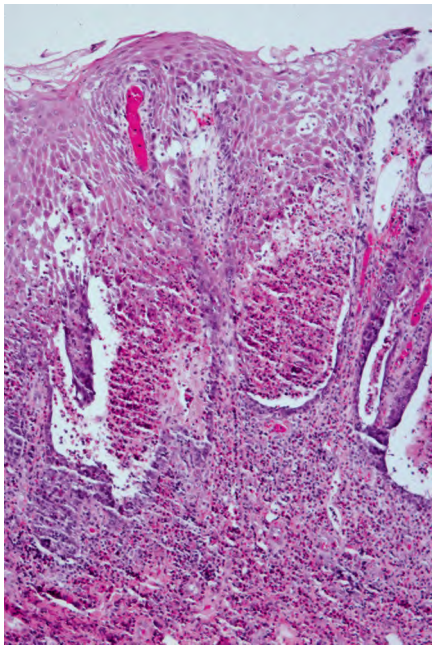
Patients with pyostomatitis vegetans exhibit characteristic yellowish, slightly elevated, linear, serpentine pustules set on an erythematous oral mucosa. The lesions primarily affect the buccal and labial mucosa, soft palate, and ventral tongue (Figs. 17-44 and 17-45). These lesions have been called "snail track" ulcerations, although in most instances the lesions are probably not truly ulcerated. Oral discomfort is variable but can be surprisingly minimal in some patients. This variation in symptoms may be related to the number of pustules that have ruptured to form ulcerations. The oral lesions may appear concurrently with the bowel symptoms, or they may precede the intestinal involvement.

Histopathologic Features

A biopsy specimen of an oral lesion of pyostomatitis vegetans usually shows marked edema, causing an acantholytic appearance of the involved epithelium. This may be the result of the accumulation of numerous eosinophils within the spinous layer, often forming intraepithelial abscesses (Fig. 17-46). Subepithelial eosinophilic abscesses have been



• **Fig. 17-45 Pyostomatitis Vegetans. A,** Characteristic "snail track" lesions involve the soft palate. **B,** Same patient after 5 days of prednisone therapy. (From Neville BW, Laden SA, Smith SE, et al: Pyostomatitis vegetans, *Am J Dermatopathol* 7:69-77, 1985.)



• **Fig. 17-46 Pyostomatitis Vegetans.** Medium-power photomicrograph showing intraepithelial abscesses composed of eosinophils.

reported in some instances. The underlying connective tissue usually supports a dense mixed infiltrate of inflammatory cells that consists of eosinophils, neutrophils, and lymphocytes. Perivascular inflammation may also be present.

Treatment and Prognosis

Usually, the intestinal signs and symptoms of inflammatory bowel disease are of most concern for patients with pyostomatitis vegetans. Medical management of the bowel disease with sulfasalazine or systemic corticosteroids also produces clearing of the oral lesions (see Fig. 17-45). Often the oral lesions clear within days after systemic corticosteroid therapy has begun, and they may recur if the medication is withdrawn. If the bowel symptoms are relatively mild, then the oral lesions have been reported to respond to topical therapy with some of the more potent corticosteroid preparations.

◆ UREMIC STOMATITIS

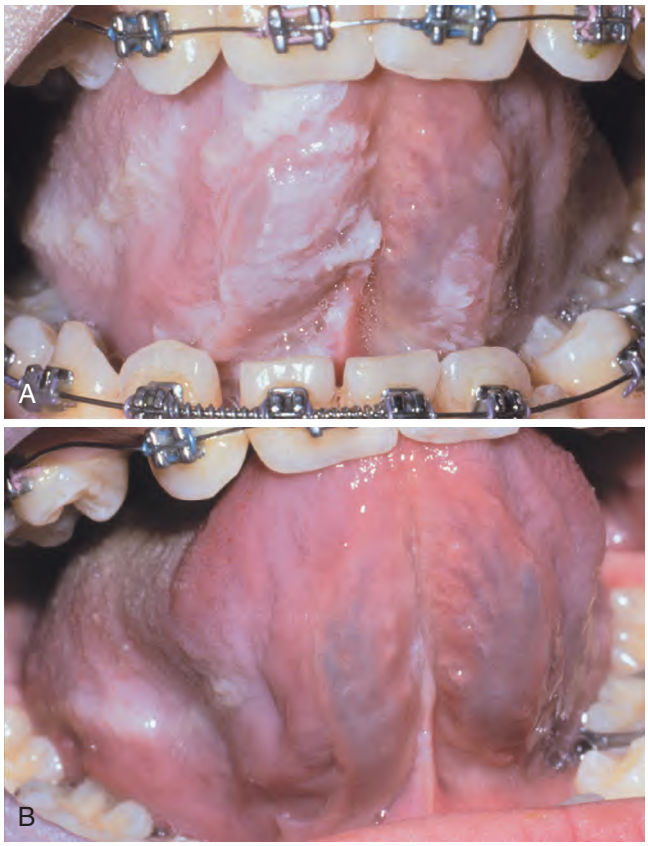
Patients who have either acute or chronic renal failure typically show markedly elevated levels of urea and other nitrogenous wastes in the bloodstream. **Uremic stomatitis** represents a relatively uncommon complication of renal failure. In two series that included 562 patients with renal failure, only eight examples of this oral mucosal condition were documented. Nevertheless, for the patients in whom uremic stomatitis develops, this can be a painful disorder. The cause of the oral lesions is unclear, but some investigators suggest that urease, an enzyme produced by the oral microflora, may degrade urea secreted in the saliva. This degradation results in the liberation of free ammonia, which presumably damages the oral mucosa.

Clinical Features

Most cases of uremic stomatitis have been reported in patients with acute renal failure. The onset may be abrupt, with white plaques distributed predominantly on the buccal mucosa, tongue, and floor of the mouth (Fig. 17-47). Patients may complain of unpleasant taste, oral pain, or a burning sensation with the lesions, and the clinician may detect an odor of ammonia or urine on the patient's breath. The clinical appearance occasionally has been known to mimic oral hairy leukoplakia.

Treatment and Prognosis

In some instances, uremic stomatitis may clear within a few days after renal dialysis, although such resolution may take place over 2 to 3 weeks. In other instances, treatment with a mildly acidic mouth rinse, such as diluted hydrogen peroxide, seems to clear the oral lesions. For control of pain while the lesions heal, patients may be given palliative therapy with ice chips or a topical anesthetic, such as viscous lidocaine or dyclonine hydrochloride. Although renal failure itself is life threatening, at least one example of a uremic



• **Fig. 17-47 Uremic Stomatitis. A,** Ragged white plaques affect the ventral tongue and floor of the mouth. **B,** Same patient after renal dialysis. (From Ross WF, Salisbury PL: Uremic stomatitis associated with undiagnosed renal failure, *Gen Dent* 42:410-412, 1994.)

plaque that presumably caused a patient's death has been recorded. This event was thought to have been caused by the dislodging of the plaque with subsequent obstruction of the patient's airway.

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18 Facial Pain and Neuromuscular Diseases

REVISED BY THERESA S. GONZALES

◆ BELL PALSY (IDIOPATHIC SEVENTH NERVE PARALYSIS; IDIOPATHIC FACIAL PARALYSIS)

Bell palsy is an acute weakness or paralysis of the facial nerve without an identifiable cause. Although the etiology is uncertain, evidence suggests that the condition may be related to either a herpes virus infection (herpes simplex or varicella-zoster) or a cell-mediated autoimmune reaction resulting in demyelination of the nerve. A variety of factors may increase the risk for developing Bell palsy, including:

- Pregnancy (especially third trimester)
- Preeclampsia
- Diabetes
- Hypertension
- Obesity
- Upper respiratory infections

Depending on the population studied, the annual incidence of Bell palsy ranges from 11.5 to 53.3 per 100,000 persons. The lifetime risk for developing this condition is 1 in 60. Although Bell palsy is the most common cause of facial paresis or paralysis, it is a diagnosis of exclusion that should be reserved for idiopathic cases of sudden onset. Other specific conditions may cause facial nerve paralysis, including neoplasms, sarcoidosis, orofacial granulomatosis (Melkersson-Rosenthal syndrome), Lyme disease, congenital malformations, inappropriate administration of local anesthesia, trauma, and postsurgical damage.

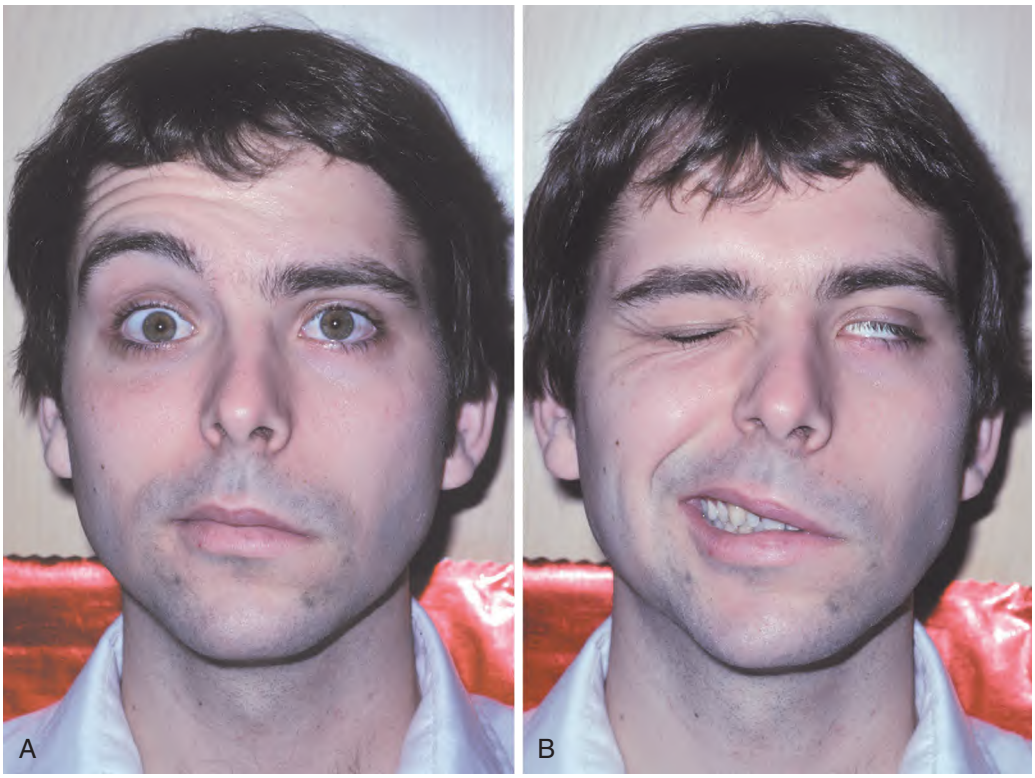
Clinical Features

Bell palsy can occur at any age, but it develops most frequently in young and middle-aged adults. The condition is characterized by an abrupt loss of muscular control on one side of the face, imparting a rigid masklike appearance and resulting in the inability to smile, to close the eye, to wink, or to raise the eyebrow (Fig. 18-1). The paralysis may take several hours to become complete, but patients frequently awaken in the morning with a full-fledged case. The corner of the mouth often droops, causing saliva to drool onto the skin. Speech becomes slurred and taste may be abnormal. Because the eyelid cannot close, conjunctival dryness or ulceration may occur. A few patients will experience prodromal pain on the affected side before the onset of paralysis.

Infrequently, bilateral involvement is seen. However, rapid onset of bilateral facial weakness should alert the clinician to the possibility of other diseases, such as **Guillain-Barré syndrome** or a form of sarcoidosis known as *uveoparotid fever* (see Heerfordt syndrome, page 310). If multiple cranial nerve deficits accompany facial nerve paralysis, then central nervous system (CNS) infectious diseases and basilar skull tumors must be considered in the differential diagnosis. If the patient has symptoms of vertigo or tinnitus, then a diagnosis of Ramsay Hunt syndrome must be suspected (see page 228).

Treatment and Prognosis

Bell palsy is a self-limiting condition, and most patients will recover over a 3 to 4 month period. Without treatment, complete facial nerve function will be restored in nearly three-quarters of patients with complete paralysis and in over 90% of patients with partial paralysis. However, as many as 20% to 30% of patients will not recover completely. The most consistently effective treatment is systemic corticosteroid therapy, which has been shown to improve recovery rates by 12.8% to 15%. A 10-day tapering course of prednisone is often prescribed, beginning at a dosage of 60 mg per day. Antiviral therapy (acyclovir, famciclovir, or valacyclovir) may be associated with a modest improvement in recovery, when given in combination with corticosteroids. However, antiviral therapy alone is not recommended.



• **Fig. 18-1 Bell Palsy.** Paralysis of the facial muscles on the patient's left side. **A,** Patient is trying to raise the eyebrows. **B,** Patient is attempting to close the eyes and smile. (Courtesy of Dr. Bruce B. Brehm.)

Surgical decompression of the facial nerve has been attempted in select cases, but evidence for the effectiveness of this approach is lacking. Eye protection is critical for patients with impaired eye closure. Topical ocular antibiotics and artificial tears may be required to prevent corneal ulceration, and the eyelid may have to be taped shut.

◆ FREY SYNDROME (AURICULOTEMPORAL SYNDROME; GUSTATORY SWEATING AND FLUSHING)

Named for Polish neurologist Łucja Frey, **Frey syndrome** is characterized by facial flushing and sweating along the distribution of the auriculotemporal nerve. These signs occur in response to gustatory stimuli, and the syndrome results from injury to the nerve.

The auriculotemporal nerve, in addition to supplying sensory fibers to the preauricular and temporal regions, carries parasympathetic fibers to the parotid gland and sympathetic vasomotor and sudomotor (sweat stimulating) fibers to the preauricular skin. After parotid abscess, trauma, mandibular surgery, or parotidectomy, the parasympathetic nerve fibers may be severed. In their attempt to reestablish innervation, these fibers occasionally become misdirected and regenerate along the sympathetic nerve pathways, establishing communication with the sympathetic nerve fibers of sweat glands and blood vessels of the facial skin. The most widely accepted mechanism of Frey syndrome is aberrant neuronal regeneration. Subsequent to these aberrant neural connections, when salivation is stimulated, local sweat glands are activated inadvertently and the patient's cheek becomes flushed and moist.

More than 40% of patients with parotidectomies will develop clinically evident Frey syndrome as a complication of surgery, although a much higher frequency (70% to 100%) can be documented if objective testing is performed (Minor starch-iodine test). The condition is rare in infancy but has been seen after forceps delivery. Neonatal cases typically do not occur until the child begins to eat solid foods, at which time it may be interpreted as an allergy. Interestingly, more than one-third of diabetics with neuropathy will experience bilateral gustatory sweating of the face and neck, especially those who also have severe kidney damage.

Related phenomena may accompany an operation or injury to the submandibular gland **(chorda tympani syndrome)** or the facial nerve proximal to the geniculate ganglion **(gustatory lacrimation syndrome, "crocodile tears").** The chin and submental skin demonstrate sweating and flushing in the former. Chewing food in the latter syndrome produces abundant tear formation.

Clinical Features

The presenting signs and symptoms of Frey syndrome include sweating, flushing, warmth, and occasionally pain

• **Fig. 18-2 Frey Syndrome.** This patient received an injury to her auriculotemporal nerve during orthognathic surgery 3 years earlier. Notice the region of sweating detected during mastication by a color change of the starch in the Minor starch-iodine test.

in the preauricular and temporal regions during chewing. Within 2 months to 2 years (average, 9 months) after the nerve injury, the sweating and flushing reactions commence and become steadily more severe for several months, remaining constant thereafter. When flushing occurs, the local skin temperature may be raised as much as 2° C. This may occur without sweating, especially in females. Pain, when present, is usually mild, and hypesthesia (hypoesthesia) or hyperesthesia are common features.

To detect sweating, a Minor starch-iodine test may be used. A 1% iodine solution is painted on the affected area of the skin. This solution is allowed to dry, and the area is then coated with a layer of starch. When the patient is given something to eat, the moisture of the sweat that is produced will mix with the iodine on the skin. This allows the iodine to react with the starch and produce a blue color (Fig. 18-2). Iodine-sublimated paper, which changes color when wet, also can be used, and thermography or surface thermometers will document the temperature changes of the skin.

Treatment and Prognosis

Most cases are mild enough that treatment is not required. Moreover, approximately 5% of adult patients and almost all affected infants experience spontaneous resolution of the syndrome.

If treatment is desired, intracutaneous injections of botulinum toxin A can provide long-term relief, although injections may need to be repeated. Topically applied anticholinergic medications, such as scopolamine and glycopyrrolate, also have been used for short-term control. Surgical management, such as insertion of various tissue barriers or tympanic neurectomy, rarely is indicated or required. The initial risk for developing Frey syndrome is greatly diminished by positioning a musculofascial flap or allograft between the gland and the overlying skin of the cheek at the time of parotidectomy.

HEAD AND NECK PAIN

Pain is a universal experience, and our understanding of pain and pain management has increased significantly over the past 30 years. For the most part, pain is a protective mechanism that alerts the organism to the possibility of harm. As pain is the primary motivation for the majority of health care encounters in our culture, it is prudent to consider pain in a broader context prior to discussing specific pain entities common to the head and neck region. Customarily pain is divided in acute and chronic forms, with acute pain management having the most predictable clinical outcomes. Estimates suggest that between 17% to 26% of the general population experience orofacial pain, and for 7% to 12% that pain presentation will become chronic. The majority of acute pain presentations in dental practice are associated with the teeth and their supporting structures, and dentists usually diagnose and treat these conditions with relative ease. Inflammatory conditions of the pulp and periodontium are managed so successfully that patients commonly seek dental services for any and all pains occurring in the head and neck region.

The diagnosis and management of non-odontogenic head and neck pain presents a challenge to even the most skilled diagnosticians. The complexity of the neural and vascular networks of the orofacial region contributes to the diagnostic difficulties. Ultimately pain fibers from this region travel to the spinal nucleus caudalis of the trigeminal nerve in a process known as *trigeminal convergence.* This convergence often makes it virtually impossible for patients to distinguish the site of their pain from the source of their pain in a reliable fashion. For this reason, it is important that health care providers have a working knowledge of the myriad of diagnostic possibilities for those patients presenting with chronic orofacial pain. Although it is well beyond the scope of this chapter to discuss each of these entities, differential considerations related to chronic orofacial pain are summarized in Box 18-1. In general, if the pain is thought to be of non-dental origin, then a comprehensive pain evaluation, complete with diagnostic anesthesia and appropriate laboratory testing, is warranted.

◆ TRIGEMINAL NEURALGIA (TIC DOULOUREUX; TIC)

The head and neck region is a common site for neuralgias (pain extending along the course of a nerve). Because facial neuralgias produce pain that often mimics pain of dental origin, the dental profession is frequently called on to rule out odontogenic or inflammatory causes. **Trigeminal neuralgia,** the most serious and the most common of the facial neuralgias, is characterized by an extremely severe electric shocklike or lancinating (i.e., sharp, jabbing) pain limited to one or more branches of the trigeminal nerve. In the majority of cases the pain is located in the maxillary (V2)

• BOX 18-1 Disorders Associated with Chronic Orofacial Pain

Temporomandibular Joint Disorders

Joint pain
- Arthralgia
- Arthritis

Joint disorders
- Disc-condyle complex disorder
- Hypomobility disorders
  - Adhesions
  - Ankylosis
- Hypermobility disorders
  - Subluxation
  - Luxation

Joint diseases
- Degenerative joint disease
- Condylysis
- Osteochondritis dissecans
- Osteonecrosis
- Synovial chondromatosis

Congenital/developmental disorders of the condyle
- Aplasia
- Hypoplasia
- Hyperplasia

Masticatory Muscle Disorders

Muscle pain limited to the orofacial region
- Myalgia
- Myositis

Masticatory muscle pain attributed to systemic/central disorders
- Fibromyalgia
- Centrally mediated myalgia

Primary Headache Disorders

Migraine headache
Tension-type headache (TTH)
Trigeminal autonomic cephalalgias (TACS)
- Cluster headache
- Paroxysmal hemicrania
- Short-lasting unilateral neuralgia headache attacks with conjunctival injection and tearing (SUNCT)

Other primary headaches
- Primary exertional headache
- Primary thunderclap headache
- Hypnic headache
- Hemicrania continua

Neuropathic Pain Disorders

Trigeminal neuralgia
Pretrigeminal neuralgia
Glossopharyngeal neuralgia
Nervus intermedius neuralgia
Superior laryngeal neuralgia
Occipital neuralgia
Painful ophthalmoplegia
Idiopathic (trigeminal) neuropathic pain
Postherpetic (trigeminal) neuralgia
Anesthesia dolorosa
Central post-stroke pain
Complex regional pain syndrome
Burning mouth syndrome

Cervical Pain Disorders

Cervicalgia
Sprain and strain of cervical spine
Cervical osteoarthritis
Radiculopathy
Spasmodic torticollis
Cervicogenic headache
Neck-tongue syndrome
Eagle syndrome

Systemic Causes of Orofacial Pain

Diabetes mellitus
Lyme disease
Multiple sclerosis
Connective tissue diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis (RA)
- Sjögren syndrome
- Systemic sclerosis

Giant cell arteritis
Primary malignancies

Modified from de Leeuw R, Klasser GD, editors: *Orofacial pain—guidelines for assessment, diagnosis and management,* ed 5, Chicago, 2013, Quintessence Publishing.

or the mandibular (V3) distribution of the nerve. The significance of this disorder is underscored by the fact that it has one of the highest suicide rates of any disease and is regarded as one of the most painful afflictions known.

Classical trigeminal neuralgia has no definite etiology, although it is often thought to be related to compression of the trigeminal nerve by aging blood vessels, which renders the nerve susceptible to localized demyelination. *Secondary* or *symptomatic* trigeminal neuralgia may develop in patients with **multiple sclerosis,** or occur secondary to compression of the nerve by tumors or arteriovenous malformations.

In the United States, the reported incidence of trigeminal neuralgia is 4 to 5 cases per 100,000 population annually. However, recent studies from Europe have reported much higher incidence rates of 26.8 to 28.9 per 100,000. From 2% to 4% of cases occur in patients with multiple sclerosis; conversely, approximately 2% to 4% of patients with multiple sclerosis will develop trigeminal neuralgia.

Clinical Features

Trigeminal neuralgia characteristically affects individuals older than 50 years of age, although it can develop at any age, including young children. Women are affected more often than men by a ratio of 1.5:1. One or more branches of the trigeminal nerve may be involved, but the ophthalmic division is affected alone in only 4% of cases. Bilateral involvement is unusual and may suggest the possibility of

underlying multiple sclerosis. Trigeminal neuralgia associated with multiple sclerosis also tends to develop at a younger age.

In the early stages, the pain of trigeminal neuralgia may be rather mild and is often described by the patient as a twinge, dull ache, or burning sensation. This clinical presentation may be attributed erroneously to disorders of the teeth, jaws, and paranasal sinuses, leading to inappropriate treatment. With time, the attacks occur at more frequent intervals and the pain becomes increasingly intense, sometimes being described as feeling like "an electric shock," "a bolt of lightning," or "being stabbed by an ice pick." Patients often clutch at the face and experience spasmodic contractions of the facial muscles during attacks, a feature that long ago led to the use of the term *tic douloureux* (i.e., painful jerking) for this disease.

For most patients, the pain will be provoked by stimulation of a specific trigger zone along the distribution of the trigeminal nerve, often in the nasolabial fold or intraoral region. Sudden onset of pain will occur following mild stimulation of this trigger area, such as:

- Washing the face
- Shaving
- Eating
- Brushing one's teeth
- Being exposed to a breeze

Each painful episode typically lasts for no longer than 2 minutes, followed by a refractory period in which stimulation of the trigger zone will not elicit another attack. This refractory period can be useful, clinically, in distinguishing trigeminal neuralgia from stimulus-provoked odontogenic pain.

Specific and strict criteria must be met for an accurate diagnosis (Box 18-2). If the pain pattern does not meet these criteria, then a different diagnosis should be considered. When these criteria are partially fulfilled, alternative terms such as *atypical trigeminal neuralgia, persistent idiopathic facial pain*, and *atypical facial neuralgia* are applied. Another distinguishing feature of trigeminal neuralgia is that objective signs of sensory loss cannot be demonstrated on physical examination. The presence of objective facial sensory loss, facial weakness, or ataxia should raise the distinct possibility of a CNS tumor.

Treatment and Prognosis

There have been rare reports of spontaneous permanent remissions of trigeminal neuralgia. However, more often than not, this disease is characterized by a protracted clinical course with increasing frequency and severity of exacerbations. The initial treatment for trigeminal neuralgia is pharmacological, with carbamazepine (an anticonvulsant) being the first drug of choice. Approximately 80% of patients will respond favorably to this medication, and an unequivocal response to carbamazepine can be used as a diagnostic test for this disease. Other anticonvulsant medications (phenytoin, oxcarbazepine, gabapentin, lamotrigine, and topiramate) also have been used, either alone or in combination with baclofen—a skeletal muscle relaxant. These drugs, unfortunately, often have significant side effects and may not be tolerated for long by the patient. Also, the effectiveness of anticonvulsants in controlling pain often decreases over time. Interestingly, opioid medications are typically ineffective in managing the pain of trigeminal neuralgia.

If medical management fails, a variety of surgical treatments may be considered (Box 18-3). Suboccipital microvascular decompression of the trigeminal nerve root is an invasive, but nondestructive, technique that attempts to alleviate the presumed cause of most cases of classical trigeminal neuralgia—i.e., compression of the nerve by adjacent blood vessels. This is a major neurosurgical procedure that is associated with a mortality rate of 0.2% to 1.2%. However, 65% to 73% of patients will be pain free 10 years or longer after surgery. Potential long-term complications include facial numbness and ipsilateral hearing loss.

Less invasive surgical techniques are aimed at destroying affected portions of the trigeminal nerve. These procedures include radiofrequency rhizotomy of the affected branch of the trigeminal nerve, percutaneous retrogasserian glycerol rhizotomy, balloon microcompression of the gasserian

• BOX 18-2 Necessary Criteria for a Diagnosis of Trigeminal Neuralgia

- The onset of a pain "attack" is abrupt, often initiated by a light touch to a specific and constant trigger point.
- The pain is extreme, paroxysmal, and lancinating.
- The duration of a single pain "spasm" is less than 2 minutes, although the overall attack may consist of numerous repeating spasms of short duration.
- For several minutes after an attack (the "refractory period"), touching the trigger point usually cannot induce additional attacks.
- The pain must be limited to the known distribution of one or more branches of the trigeminal nerve with no motor deficit in the affected area.
- The pain is dramatically diminished, at least initially, with the use of carbamazepine.
- Spontaneous remissions occur, often lasting more than 6 months, especially during the early phase of the disease.

• BOX 18-3 Neurosurgical Therapies for Trigeminal Neuralgia

- Repositioning of blood vessels impinging on trigeminal nerve (microvascular decompression)
- Injection of caustic material near nerves leaving or entering the gasserian ganglion (glycerol rhizotomy)
- Removal of skull base bony irregularities impinging on trigeminal nerve (decompression)
- Balloon microcompression of the gasserian ganglion
- Selective destruction of the sensory fibers of the nerve by crushing or by the application of heat (percutaneous radiofrequency rhizotomy)
- Severing the trigeminal sensory roots (neurectomy)

ganglion, and stereotactic radiosurgery (Gamma Knife). Short-term pain relief from these methods ranges from 60% to 79% at 2 years. However, repeated surgical procedures often become necessary, and techniques that deliberately damage neural tissues leave the patient with a sensory deficit. After surgery, up to 8% of patients develop distorted sensations of the facial skin **(facial dysesthesia)** or a combination of anesthesia and spontaneous pain **(anesthesia dolorosa).** Anesthesia dolorosa is a dreaded form of central pain that can occur after any neurosurgical procedure that causes a variable amount of sensory loss, but this complication occurs more commonly with procedures that totally denervate a region.

◆ GLOSSOPHARYNGEAL NEURALGIA (VAGOGLOSSOPHARYNGEAL NEURALGIA)

Neuralgia of the ninth cranial nerve, **glossopharyngeal neuralgia,** is similar to trigeminal neuralgia (see previous topic) except in the anatomic location of the pain. In glossopharyngeal neuralgia, the pain is centered on the tonsil and the ear. The pain often radiates from the throat to the ear because of the involvement of the tympanic branch of the glossopharyngeal nerve. Some unfortunate individuals have a combination of glossopharyngeal neuralgia and trigeminal neuralgia.

Glossopharyngeal neuralgia is rare, representing only 0.2% to 1.3% of facial pain syndromes. The pain also may affect sensory areas supplied by the pharyngeal and auricular branches of the vagus nerve. As with trigeminal neuralgia, two subtypes of glossopharyngeal neuralgia are recognized: *classical* and *symptomatic (secondary).* Classical glossopharyngeal is unassociated with any underlying disorder and often is attributed to arterial compression of the nerve as it courses through the subarachnoid space to the jugular foramen. Symptomatic glossopharyngeal neuralgia occurs secondary to compression of the nerve by a specific lesion, such as intracranial or cranial base tumors, oropharyngeal tumors, pagetic bone, or calcified stylohyoid ligament (Eagle syndrome; see page 21). Unlike trigeminal neuralgia, it is uncommon for glossopharyngeal neuralgia to be associated with multiple sclerosis.

Clinical Features

Glossopharyngeal neuralgia usually occurs in middle-aged and older adults. There is no sex predilection, and only rarely is there bilateral involvement. The paroxysmal pain may be felt in the ear **(tympanic plexus neuralgia),** infraauricular area, tonsil, base of the tongue, posterior mandible, or lateral wall of the pharynx; however, the patient often has difficulty localizing the pain in the oropharynx.

The episodic pain in this unilateral neuralgia is sharp, lancinating (jabbing), and extremely intense. Attacks have an abrupt onset and a short duration (seconds to minutes). The pain typically radiates upward from the oropharynx to the ipsilateral ear. Talking, chewing, swallowing, yawning, or touching a blunt instrument to the tonsil on the affected side may precipitate the pain, but a definite trigger zone is not easily identified. Because the pain is related to jaw movement, it may be confused with the pain of **temporomandibular joint dysfunction.**

Patients frequently point to the neck immediately below the angle of the mandible as the site of greatest pain, but trigger points are not found on the external skin, except within the ear canal. Excessive vagal effects will occur in approximately 10% of patients, resulting in syncope, hypotension, seizures, bradycardia, or cardiac arrest **(vagoglossopharyngeal neuralgia).**

Treatment and Prognosis

As in trigeminal neuralgia, glossopharyngeal neuralgia is subject to unpredictable remissions and recurrences. It is not unusual during the early stages for remissions to last 6 months or more. Painful episodes are of varying severity but generally become more severe and more frequent with time.

Many patients will experience pain relief when a topical anesthetic agent is applied to the tonsil and pharynx on the side of the pain. Because this relief lasts only 60 to 90 minutes, it is used more as a diagnostic tool and emergency measure than a long-term treatment. Repeated applications to a trigger point for 2 or 3 days may extend the pain-free episode enough to allow the patient to obtain much needed rest and nutrition.

For most patients with classical glossopharyngeal neuralgia, the first line of therapy is pharmacological. Anticonvulsants medications (such as, carbamazepine, oxcarbazepine, baclofen, phenytoin, and lamotrigine) may relieve the neuralgic pain for a long period, but no therapy is considered to be uniformly effective. For individuals with vagoglossopharyngeal neuralgia, atropine can be used to prevent the related cardiac phenomena. If a patient with glossopharyngeal neuralgia fails drug therapy, then surgical options should be considered. The preferred neurosurgical treatments are microvascular decompression or surgical sectioning of the glossopharyngeal nerve and the upper two rootlets of the vagus nerve. Other possible procedures include radiofrequency nerve ablation, balloon compression, and stereotactic radiosurgery (Gamma Knife ablation). If the pain is secondary to another condition (e.g., tumor or Eagle syndrome), then management of the underlying lesion must be addressed.

◆ GIANT CELL ARTERITIS (TEMPORAL ARTERITIS; GRANULOMATOUS ARTERITIS)

Giant cell arteritis is an immune-mediated vasculitis that affects medium-sized and larger arteries, leading to vascular

occlusion and ischemia. Because the superficial temporal artery is the most commonly affected site, the condition also is known as **temporal arteritis.** Although giant cell arteritis most often affects head and neck vessels, it is considered to be a systemic condition that can affect multiple vessels, including the aorta and its proximal branches. Although the exact cause is uncertain, there appears to be a strong genetic predisposition, with a higher frequency of disease in patients who express certain human leukocyte antigen (HLA) types, such as HLA-DR4. Because geographic and seasonal variations have been observed, an infectious etiology or trigger also has been suggested.

Giant cell arteritis occurs primarily in older individuals; the condition demonstrates an annual incidence rate of 15 to 25 per 100,000 population past the age of 50 years, with an increased incidence associated with advancing age. The disease shows a predilection for individuals of Scandinavian and northern European descent.

Clinical Features

Women are affected by giant cell arteritis more than twice as often as men, and patients are rarely younger than 50 years of age at the time of diagnosis (average age, 70 years). The disease most frequently involves the temporal artery, presenting with symptoms of severe headache and scalp tenderness. A highly characteristic feature is jaw claudication, which is described as cramping pain of the masseter and temporalis muscles that increases with usage (chewing or talking) but is relieved by rest. The superficial temporal artery is exquisitely sensitive to palpation and eventually appears erythematous, swollen, tortuous, or sometimes ulcerated. Rare examples of unilateral or bilateral tongue necrosis secondary to lingual artery involvement also have been described.

The most significant complication in the head and neck region is vision loss, which usually is due to vasculitis of the posterior ciliary artery and ischemic optic neuropathy. Ocular involvement has been reported in anywhere from 14% to 70% of patients, often resulting in partial or total loss of vision in one or both eyes. Permanent loss of vision occurs in 15% of patients. Visual disturbances often are an early manifestation of giant cell arteritis, sometimes occurring before the onset of other symptoms.

Systemic signs and symptoms include fever, malaise, fatigue, anorexia, and weight loss. Many patients develop **polymyalgia rheumatica,** which is characterized by aching pain and morning stiffness in the neck, shoulders, and pelvic girdle. Giant cell arteritis will affect the aorta and other large vessels in at least 50% of cases, although such involvement often is asymptomatic. On occasion, however, undetected aortic inflammation may be associated with aortic aneurysm and rupture. Rare manifestations include cerebrovascular accidents and cardiac infarction. Vasculitis of the extremities can lead to limb claudication and ischemic changes.

Histopathologic and Laboratory Features

The diagnosis of giant cell arteritis usually is confirmed by biopsy of the temporal artery. Microscopic changes tend to be segmental and can be missed if the specimen is too small. At least 1 cm of the affected vessel must, therefore, be examined for proper evaluation.

The disease is characterized by chronic inflammation of the tunica intima and tunica media of the involved artery, with narrowing of the lumen from edema and proliferation of the tunica intima. Necrosis of the smooth muscle and elastic lamina is frequent. A variable number of multinucleated giant cells are mixed with macrophages and lymphocytes. Thrombosis or complete occlusion of the lumen is not unusual.

Clinical laboratory features often include an elevated erythrocyte sedimentation rate, increased C-reactive protein levels, and an elevated platelet count.

Treatment and Prognosis

Because of the risk for sudden and permanent loss of vision, prompt treatment of giant cell arteritis is critical. The disease typically responds well to high-dose systemic corticosteroid therapy, and symptoms often subside within a few days. However, many cases are chronic and require treatment for years. Methotrexate or azathioprine sometimes will be added for their steroid-sparing effects.

◆ BURNING MOUTH DISORDER (STOMATOPYROSIS; STOMATODYNIA; GLOSSOPYROSIS; GLOSSODYNIA; BURNING TONGUE SYNDROME; BURNING MOUTH SYNDROME)

Burning mouth disorder (BMD) is a confounding pain condition that is generally considered neuropathic in nature with both peripheral and central components. Because dysgeusia (altered taste) and xerostomia frequently accompany the onset of burning sensation, this condition was previously referred to as *burning mouth syndrome.* Whether the presence of these additional clinical findings actually constitute a syndrome is a matter of much debate and, therefore, it is probably more appropriate to designate this condition as a disorder rather than a syndrome. Interestingly, more than two-thirds of patients with BMD report dysgeusia and these patients characteristically describe this alteration as a "metallic taste." Although there is considerable debate in the pain community regarding the pathophysiology of BMD, current research suggests that primary BMD is related to problems with both taste and sensory nerves. BMD may result from hyperactivity of the sensory component of the trigeminal system and loss of central inhibition secondary to damage to the chorda tympani or from a disturbance in the balance between the gustatory and sensory systems.

• BOX 18-4 Local and Systemic Factors Reportedly Associated with Burning Mouth Disorder

Local Factors

Xerostomia
Chronic mouth breathing
Chronic tongue thrust habit
Chronic mechanical trauma
Referred pain from teeth or tonsils
Trigeminal neuralgia
Atypical facial pain or neuralgia
Angioedema (angioneurotic edema)
Oral candidiasis
Temporomandibular dysfunction
Oral submucous fibrosis
Fusospirochetal infection
Contact stomatitis (allergy)
Trauma to lingual nerve

Systemic Factors

Vitamin B deficiency
- Vitamin B_1 or B_2 deficiency
- Pernicious anemia (B_{12})
- Pellagra (niacin deficiency)
- Folic acid deficiency

Diabetes mellitus
Chronic gastritis or regurgitation
Chronic gastric hypoacidity
Hypothyroidism
Mercurialism
Estrogen deficiency
Anxiety, stress, and depression
Parkinson disease
Acquired immunodeficiency syndrome (AIDS)

BMD is consistently described by the patient as a burning sensation of the oral mucosa. When this pain occurs in the absence of both clinical and laboratory findings, the condition is classified as primary or idiopathic BMD. Secondary BMD is reserved for those clinical presentations which are associated with underling local or systemic factors. Although the tongue is most commonly affected **(glossopyrosis),** other mucosal surfaces also may be symptomatic **(stomatopyrosis).** The anterior hard palate and the mucosal aspect of the lower lip are frequently involved.

Various local and systemic factors have been postulated to cause this condition (Box 18-4), but none have been proven. The disorder has been reported to be strongly associated with depression and anxiety states, but the relationship of the clinical presentation to the development of psychologic distress is unknown.

Burning tongue syndrome affects 0.7% to 15% of adults to some degree (12.2% of postmenopausal women). Asians and Native Americans have a considerably higher risk than whites or blacks, and there is increasing prevalence with advancing age, especially after 55 years of age. This disorder is one of the most common non-dental orofacial pains encountered in the clinical practice.

Clinical Features

Women are four to seven times more likely to present with burning tongue syndrome than men. The syndrome is rare before the age of 30 years (40 years for men), and the onset in women usually occurs within 3 to 12 years after menopause.

Typically, this disorder has an abrupt onset, although it may be quite gradual. The dorsum of the tongue develops a burning sensation, usually strongest in the anterior two-thirds. Occasionally, patients will describe an irritated or raw feeling that can be exacerbated by spicy or acidic foods. Mucosal changes are seldom visible, although some patients will show diminished numbers and size of filiform papillae, and individuals who habitually rub the tongue against the teeth often have erythematous and edematous papillae on the tip of the tongue. If the dorsum is significantly erythematous and smooth, an underlying systemic or local infectious process, such as anemia or erythematous candidiasis, should be suspected.

Further questioning often confirms that other oral sites are affected similarly, especially the anterior hard palate and the lips. There is seldom a significant decrease in stimulated salivary output in tests, despite the frequent patient complaint of xerostomia. Salivary levels of various proteins, immunoglobulins, and phosphates may be elevated, and there may be a decreased salivary pH or buffering capacity.

One frequently described pattern is that of mild discomfort on awakening, with increasing intensity throughout the day. Other affected patients describe a waxing and waning pattern that occurs over several days or weeks. Usually the condition does not interfere with sleep. A persistently altered (salty, bitter) or diminished taste may accompany the burning sensation. Contact with hot food or liquid often intensifies the symptoms. A minority describe a constant degree of discomfort. Most individuals with burning tongue disorder report that their symptoms flare in the presence of increased personal stressors as is typical with many chronic pain conditions.

As with other chronic discomforts, affected patients frequently demonstrate psychologic dysfunction, usually depression, anxiety, or irritability. The dysfunction often disappears, however, with resolution of the burning or painful tongue condition, and there is no correlation between duration and intensity of the burning sensation and the amount of psychologic dysfunction.

Treatment and Prognosis

If an underlying systemic or local cause can be identified and corrected, the burning symptoms should predictably disappear. Almost two-thirds of patients with idiopathic disease show at least some improvement of their symptoms with pharmacologic therapies including: anxiolytics, antioxidants, antidepressants and/or anticonvulsants alone or in combination. Evidence from randomized controlled trials suggests that a clinical trial of clonazepam should be

deployed as a first line therapy in patients with BMD. The use of topical or systemically administered clonazepam in conjunction with the antioxidant alpha lipoic acid (600 mg) has shown promise in the management of BMD. However, some studies have failed to confirm the effectiveness of alpha lipoic acid alone over placebo. Cognitive behavioral therapy alone or in combination with the evidence-based pharmacologic management described above may be particularly useful in those patients with significant underlying psychological factors.

The long-term prognosis for BMD is variable. It is reported that one-third to one-half of patients experience a spontaneous or gradual remission months or years after the onset of symptoms. However, other patients may be refractory to therapeutic interventions and continue to experience symptoms throughout the rest of their lives. Even though the condition is chronic and may not always respond to therapy, patients should be reassured that BMD is benign and not indicative of a more ominous disease.

◆ DYSGEUSIA AND HYPOGEUSIA (PHANTOM TASTE; DISTORTED TASTE)

Dysgeusia is defined as a persistent abnormal taste and this condition was mentioned briefly in the previous section on burning mouth disorder. However, dysgeusia occurs independently of this association and merits additional discussion here. Interestingly, the majority of purported taste disorders are in fact disorders of smell, and deficiencies in one or both of these senses has a potentially significant impact on the patient's quality of life. Dysgeusia is considerably less common than simple deficiencies in smell **(hyposmia, anosmia)** and taste **(hypogeusia, ageusia)** perception, which are found in approximately 2 million American adults. Dysgeusia is less tolerated than hypogeusia or hyposmia, explaining why it accounts for more than one-third of patients in chemosensory centers. In general, both taste and smell discriminatory capability decreases with advancing age.

Most cases of dysgeusia are produced by or associated with an underlying systemic disorder or by radiation therapy to the head and neck region (Box 18-5). Trauma, tumors, or inflammation of the peripheral nerves of the gustatory system usually produce transient hypogeusia rather than dysgeusia. In contrast, relatively common upper respiratory tract infections produce a temporary and mild dysgeusia in almost one-third of cases, although they seldom produce hypogeusia. CNS neoplasms predominantly produce dysgeusia, not hypogeusia or ageusia, and taste hallucinations are fairly common during migraine headaches, Bell palsy, or herpes zoster of the geniculate ganglion. Ischemia and infarction of the brainstem can lead to ageusia of only half of the tongue **(hemiageusia)** on the same side as the brainstem lesion.

The perception of a particular taste depends on its concentration in a liquid environment; hence, persons with severe dry mouth may suffer from both hypogeusia and dysgeusia. In addition, more than 200 drugs are known to produce taste disturbances (Table 18-1). Even without medication-induced alterations, 40% of persons with clinical depression complain of dysgeusia. Dysgeusia is also a relatively common complaint (second only to drug-induced alopecia) in patients undergoing chemotherapy with standard chemotherapeutic regimens. This is particularly disconcerting as it may lead to food aversion and subsequent

• BOX 18-5 Local and Systemic Factors Associated with Altered Taste Sensations (Dysgeusia) or Diminished Taste Sensations (Hypogeusia)

Local Factors

Oral candidiasis
Oral trichomoniasis
Desquamative gingivitis
Oral galvanism
Periodontitis or gingivitis
Chlorhexidine rinse
Oral lichen planus
Xerostomia

Systemic Factors

Vitamin A deficiency
Vitamin B_{12} deficiency
Zinc deficiency
Iron deficiency
Nutritional overdose (zinc, vitamin A, or pyridoxine)
Food sensitivity or allergy
Sjögren syndrome
Chorda tympani nerve damage
Anorexia, cachexia, or bulimia
Severe vomiting during pregnancy
Liver dysfunction
Crohn disease
Cystic fibrosis
Familial dysautonomia
Addison disease
Turner syndrome
Alcoholism
Medications (200 types)
Psychosis or depression
Pesticide ingestion
Lead, copper, or mercury poisoning
Temporal arteritis
Brainstem ischemia or infarction
Migraine headaches
Temporal lobe central nervous system (CNS) tumor
Nerve trauma, gustatory nerves
Herpes zoster, geniculate ganglion
Upper respiratory tract infection
Chronic gastritis or regurgitation
Bell palsy
Radiation therapy to head and neck

TABLE 18-1 Examples of Pharmaceutical Agents That May Be Associated with Altered Taste

Pharmaceutical Action	Examples
Anticoagulant	Phenindione
Antihistamine	Chlorpheniramine maleate
Antihypertensive or diuretic	Captopril, diazoxide, and ethacrynic acid
Antimicrobial	Amphotericin B, ampicillin, griseofulvin, idoxuridine, lincomycin, metronidazole, streptomycin, tetracycline, and tyrothricin
Antineoplastic or immunosuppressant	Doxorubicin, methotrexate, vincristine, azathioprine, and carmustine
Antiparkinsonian agent	Baclofen, chlormezanone, and levodopa
Antipsychotic or anticonvulsant	Carbamazepine, lithium, and phenytoin
Antirheumatic	Allopurinol, colchicine, gold, levamisole, penicillamine, and phenylbutazone
Antiseptic	Hexetidine and chlorhexidine
Antithyroid agent	Carbimazole, methimazole, and thiouracil
Hypoglycemic	Glipizide and phenformin
Opiate	Codeine and morphine
Sympathomimetic	Amphetamines and phenmetrazine
Vasodilator	Oxyfedrine and bamifylline

weight loss, which contributes to treatment delays in this patient cohort. The clinician should be especially diligent in assessing local, intraoral causes of dysgeusia, such as periodontal or dental abscess, oral candidiasis, and routine gingivitis or periodontitis.

Clinical Features

In contrast to hypogeusia, dysgeusia is discerned promptly and distressingly by affected individuals. The clinician must be certain that the patient's alteration is, in fact, a taste disorder rather than an olfactory one, because 75% of "flavor" information (e.g., taste, aroma, texture, temperature, and irritating properties) is derived from smell. Abnormal taste function should be verified through formal taste testing by using standard tastants that are representative of each of the four primary taste qualities (i.e., sweet, sour, salty, and bitter) in a nonodorous solution. Additional electrical and chemical analysis of taste bud function is frequently required. Because this is outside the scope of most general practices, patients are typically referred to a *taste and smell center.*

Affected patients may describe their altered taste as one of the primary ones, but many describe the new taste as metallic, foul, or rancid. The latter two are more likely to be associated with aberrant odor perception **(parosmia)** than with dysgeusia. The altered taste may require a stimulus, such as certain foods or liquids, in which case the taste is said to be distorted. If no stimulus is required, then the dysgeusia is classified as a *phantom taste.*

Treatment and Prognosis

If an underlying disease or process is identified and treated successfully, the taste function should return to normal. For idiopathic cases there is no effective pharmacologic therapy. Dysgeusia in particular tends to affect lifestyles and interpersonal relationships significantly, perhaps leading to depression, anxiety, or nutritional deficiencies from altered eating habits. Fortunately, two-thirds of dysgeusia patients experience spontaneous resolution (average duration, 10 months). Idiopathic hypogeusia is less of a problem for the patient, but slowly tends to become worse over time. Fortunately, spontaneous resolution is still a possibility for idiopathic hypogeusia.

◆ OSTEOARTHRITIS (DEGENERATIVE ARTHRITIS; DEGENERATIVE JOINT DISEASE)

Osteoarthritis is a common degenerative and destructive alteration of the joints that until recently was considered to be the inevitable result of simple wear and tear on aging anatomic structures. Osteoarthritis is thought by some to be unavoidable; almost everyone older than 50 years of age is affected to some extent, and it is almost universal after age 65. However, the condition is now known to have a strong inflammatory component as well—especially in small joints, such as the temporomandibular joint (TMJ).

Patients with osteoarthritis of the TMJ tend to be younger than those with disease affecting the large weight-bearing joints. In addition, osteoarthritis of the TMJ may not be clinically apparent, although it has been noted microscopically in 40% of older adults and radiographically in 14%. The disease accounts for approximately 10% of patients evaluated for TMJ pain.

Presumably, with advancing age, there is slower and less complete replacement of chondroblasts and chondrocytes in joint cartilage. The cartilage matrix (fibrocartilage in the case of the TMJ) turns over less rapidly, forcing available fibers to work longer and become susceptible to fatigue. The matrix also holds less water, becoming desiccated and brittle, in part because underlying marrow blood flow diminishes, providing poor nutrition. With continued joint use, the surface fibers break down and portions of the hyaline or fibrocartilage are destroyed, often breaking away to expose underlying bone. The exposed bone then undergoes a dual process of degenerative destruction and proliferation.

Clinical and Radiographic Features

Osteoarthritis usually involves multiple joints, typically the large weight-bearing joints. The disease is characterized by a gradually intensifying deep ache and pain, usually worse in the evening than in the morning. Some degree of morning joint stiffness and stiffness after inactivity is present in 80% of cases. The affected joint may become swollen and warm to the touch, rarely with erythema of the overlying skin. Degenerative changes occur in areas of greatest impact, and the joint may become so deformed that it limits motion. Crepitation (i.e., crackling noise during motion) is a late sign of the disease and is, therefore, associated with more pronounced damage.

These changes are seen also when the TMJ is affected, except that patients seldom experience stiffness of the TMJ. In addition, the muscles of mastication frequently exhibit tenderness because of the constant strain of "muscle guarding" (i.e., attempting to keep the painful joint immobile).

Radiographically, joints affected by osteoarthritis demonstrate mild changes early in the course of the disease. However, as the disease progresses, the radiographic presentation becomes more characteristic of arthritic joints in general with some combination of the following: erosion of the cortical outline, narrowing or obliteration of the joint space, surface irregularities and protuberances **(exostoses, osteophytes)**, flattening of the articular surface, osteosclerosis and osteolysis of bone beneath the cartilage, radiolucent **subchondral cysts,** and ossification within the synovial membrane **(ossicles).** More sensitive diagnostic techniques, such as computed tomography (CT) scanning arthrography, magnetic resonance imaging (MRI), and arthroscopy, reveal the same features but in much more detail; hence, they are able to identify earlier changes. With arthroscopy, 90% of the joints will show evidence of synovitis, usually before cartilage surface changes are radiographically demonstrable.

Histopathologic Features

The articulating surface of a joint affected by osteoarthritis has a diminished number of chondrocytes, is roughened, and contains variable numbers of vertical clefts; in older cases the clefts extend to the underlying bone. The surface is proliferative in some areas and degenerative in others. The bone beneath the cartilage shows a loss of osteocytes, minimal osteoblastic or osteoclastic activity, fatty degeneration or necrosis of the marrow, marrow fibrosis, infiltration by chronic inflammatory cells, and perhaps the formation of a large degenerative space beneath the articular cartilage **(subchondral cyst).** Inflammation and thickening of the synovial membrane is seen, sometimes with the formation of metaplastic bone **(ossicles)** or hyaline cartilage granules **(chondral bodies),** which may number in the hundreds within a single joint. The synovial joint fluid typically contains inflammatory and degradation molecules, the levels of which have prognostic significance.

The TMJ is unique because of its fibrocartilage covering and its meniscus. The disk may be centrally destroyed, and there is little vertical clefting of the articular surface. All other features of TMJ osteoarthritis, however, are similar to those noted in other joints.

Treatment and Prognosis

The treatment of osteoarthritis is usually palliative and consists of analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) for the symptoms. Occlusal adjustment and occlusal splints may reduce TMJ symptoms by relieving the pressure on the joint surfaces, and orofacial physiotherapy and hot or cold packs may be helpful to relax involved muscles. Arthroscopic lavage provides short-term pain relief in many cases, and low-dose doxycycline (collagenase inhibitor, anti-matrix metalloproteinase) has been shown to reduce symptoms. Glucosamine and chondroitin sulfate, common therapies for large joint arthritis, have shown some success in TMJ osteoarthritis patients.

Aggressive therapy might not be indicated for this disease except in its most severe form. A 30-year follow-up investigation found radiographic evidence of continued joint destruction, but the clinical signs and symptoms were no more severe than they had been initially. In general, surgical management of TMJ osteoarthritis is not recommended unless all conservative, nonsurgical means have failed and the patient's symptoms warrant an escalation of therapy. Arthrocentesis has shown some promising results in those patients refractory to conservative treatment protocols. Arthroplasty and joint replacement often are required for severely involved heavy weight–bearing joints and are used occasionally in the TMJ.

◆ RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, autoimmune disorder characterized by nonsuppurative inflammatory

destruction of synovium and subsequent destruction of the affected joints. Like most autoimmune diseases, the clinical course of RA is protean and protracted and the etiology is unknown. Investigators hypothesize that it may result from a cross-reaction of antibodies generated against hemolytic streptococci or other microorganisms or from an antibody attack against bacterial cell walls or viral capsule fragments deposited within the synovium. Some examples show a familial pattern, and more than twenty genes have been studied to determine their contribution to the development of RA. The human leukocyte antigen (HLA) locus DRβ1 has long been identified as the most significant genetic association for the development of RA. In 2003, gene peptidylarginine deiminase type 4 *(PADI4)* was identified as a second risk factor for RA, and since that time, several additional genes have been implicated. Environmental factors also have been shown to contribute to the development of RA in susceptible individuals.

This disease affects 2.0% to 2.5% of people in the United States to at least some degree, and approximately 200,000 new cases are diagnosed yearly. The temporomandibular joint (TMJ) eventually becomes involved in 50% to 75% of patients, although the involvement is usually so mild as to be clinically insignificant. RA demonstrates both intra-articular and extra-articular features. Systemic manifestations are relatively common in RA and include: vasculitis, interstitial lung diseases, cardiovascular diseases, anemia, osteoporosis, and ocular involvement (scleritis, keratoconjunctivitis, and uveitis).

In contrast to osteoarthritis (see previous topic), RA begins as an attack against the periarticular structures, such as the synovial membrane **(synovitis).** A reactive macrophage-laden fibroblastic proliferation **(pannus)** from the synovium creeps onto the joint surface. This releases collagenases and other proteases, which destroy the cartilage and underlying bone. Attempted remodeling by the damaged bone results in a characteristic deformation of the joint.

Clinical and Radiographic Features

RA affects women three times more frequently than men, although the condition in men usually is diagnosed at a somewhat younger age (25 to 35 years) than in women (35 to 45 years). The onset and course of the disease are extremely variable. For many patients, only one or two joints become involved and significant pain or limitation of motion never develops. In others, the disease rapidly progresses to debilitating **polyarthralgia.**

Typically, the signs and symptoms become more severe over time and include swelling, stiffness, pain, joint deformity, and disability, with possible fibrous or bony fusion of opposing articular surfaces **(ankylosis).** Periods of remission often are interspersed with periods of exacerbation. Symmetric polyarticular involvement of the small joints of the hands and feet almost always is present, but it is not unusual for knees and elbows to be affected. The hands often display a classic ulnar deviation with swan neck deformities of the fingers. The hip joint, the joint most often affected by osteoarthritis, is the joint least affected by RA. Twenty percent of patients have firm, partially movable, nontender **rheumatoid nodules** beneath the skin near the affected joint. These are considered pathognomonic for the disease.

Joints involved with RA have a characteristic "anvil" shape, with an irregular flattening of the central articular surface and a splaying of the lateral bone. Unlike the situation in osteoarthritis, narrowing of the joint space is seldom seen, except when ankylosis has occurred.

The TMJ is clinically affected to some degree in more than 40% of persons with RA. When present, TMJ involvement is usually bilateral and occurs late in the clinical course of the disease. The signs and symptoms are seldom as severe as in other joints and include stiffness, crepitation, pain or ache, tenderness, or limitation of mouth opening. Swelling is less obvious than with other joints.

Frequently, the pain of TMJ RA is not related to motion but rather to pressure on the joint. Clenching the teeth on one side produces pain of the contralateral joint. Similarly, subluxation or ankylosis is less frequent in the TMJs than in other joints, but gross destruction of the condylar heads may be so severe that a progressive class II malocclusion and anterior open bite develop. Permanent TMJ subluxation has been reported.

Radiographically, involved TMJs demonstrate a flattened condylar head with irregular surface features, an irregular temporal fossa surface, perhaps with remodeling of the fossa itself, and anterior displacement of the condyle. Several diagnostic techniques are available besides routine TMJ radiographs. CT scans, scanning arthrography, and arthroscopy are excellent tools for assessing TMJ damage. Thermography is used commonly in Europe to detect early disease. Ultrasonography is valuable for larger joints but has been used little in TMJ disease. Nuclear medicine scans that use scintigraphy have, in recent years, been largely replaced by MRI scans.

Laboratory Values

Anti-citrullinated protein antibodies (ACPAs) have been identified as specific serological markers of RA. The presence of these antibodies leads to the formation of immune complexes and subsequent inflammation of the type seen in RA. Additionally 80% of patients with RA exhibit significant elevations of rheumatoid factor (RF), an autoantibody thought to be directed toward an altered host IgG antibody that is no longer recognized by the body as "self." In addition, antinuclear antibodies (ANAs) can be detected in about 50% of the patients with RA, although it is not diagnostically specific because it also may be associated with other autoimmune diseases. During active phases of the disease, almost all patients have an elevated erythrocyte sedimentation rate (90%) and this test, although not highly

specific for RA, can be used to monitor the clinical course of the disease. In addition, some affected patients have mild anemia (25%).

Histopathologic Features

Needle biopsy is the most popular technique for obtaining diagnostic synovial material, but aspiration and analysis of synovial fluid from the affected joint frequently are undertaken to rule out other forms of arthritis. These techniques are seldom used for TMJ involvement.

Microscopically, early cases of RA demonstrate hyperplasia of the synovial lining cells with deeper portions of the membrane showing hyperemia, edema, and infiltration by lymphocytes, macrophages, and occasional neutrophils. Older lesions show continued, often pronounced synovial proliferation and edema, with cholesterol crystals and fewer inflammatory cells. Typically, the membrane protrudes into the joint space as villi or fingerlike projections. These projections occasionally undergo necrosis, producing **rice bodies**—small whitish villi fragments composed of cellular debris admixed with fibrin and collagen. When the TMJ is severely involved, the meniscus is typically perforated or replaced completely by fibrous scar.

The rheumatoid nodule is represented by a moderately well-demarcated area of amorphous, eosinophilic necrosis surrounded by a thick layer of mononuclear cells. The mononuclear cells closest to the amorphous center are typically large and palisaded.

Treatment and Prognosis

No cure exists for RA, and current treatments strive only to suppress the process as much as possible. The treatment for RA is lifelong and consists primarily of patient education, physical therapy, exercise, and medications. The various therapies that are used are largely empirical and aimed at nonspecific suppression of the inflammatory or immunologic process in an effort to attenuate not only the symptoms but also the progressive damage to articular structures. Drug therapy in early and mild cases consists of NSAIDs, perhaps aided by occasional corticosteroid injections into the joint. The latter injections are used sparingly, however, because frequent use is associated with additional degenerative changes and fibrous ankylosis.

Second-line medications often are required, and the wide variability in responses to these drugs typically results in an extended course of constantly changing doses and agents in an effort to achieve optimal relief. Systemic glucocorticoid therapy has been shown to be effective in providing symptomatic relief for patients with RA. A number of agents appear to have the capacity to modify the course of RA, and these medications are referred to as *disease-modifying antirheumatic drugs.* Agents such as gold injections, D-penicillamine, sulfasalazine, the antimalarials, and methotrexate are included in this group. Patients report clinical improvement with the use of these medications; they also demonstrate an improvement in serologic evidence of disease activity with reductions in C-reactive protein, erythrocyte sedimentation rate, and RF. Emerging evidence indicates that the early and aggressive use of disease-modifying antirheumatic drugs may actually retard the development of bone erosions and potentially facilitate healing of existing lesions. However, toxicity is a problem with all of these agents, and at present, no one drug has demonstrated a consistent advantage over the others. Methotrexate, a folic acid antagonist, is the most frequently used first-line agent in the disease-modifying group. The literature suggests that patients who fail or who have shown a suboptimal response to disease-modulating therapy might benefit from tumor necrosis factor-alpha (TNF-α) neutralizing agents (e.g., etanercept and infliximab), used alone or in combination with standard disease-modulation algorithms.

Immunosuppressive drugs (such as, azathioprine, cyclosporine, and cyclophosphamide) appear to be no more effective in the management of RA than the previously mentioned disease-modulating antirheumatic drugs, and the side effect profile of immunosuppressive therapy includes increased risk for serious infections and potential predisposition to the development of malignant neoplasms. Therefore, immunosuppressive therapy should be reserved for those patients who have failed all other efforts at disease modulation.

Severely damaged joints may require surgical replacement, with the goals of therapy being attenuation of pain and reduction of disability. Total joint replacement of the hips, knees, and shoulders are reported to have the highest satisfaction rates associated with surgical management of these patients.

◆ TEMPOROMANDIBULAR DISORDERS

Temporomandibular disorders (**TMDs**) are broadly defined by the American Association for Dental Research as "a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joints (TMJs), the masticatory muscles, and all associated tissues." Pain in the preauricular area is the most frequent clinical presentation for this group of disorders and the TMDs are the leading contributor to non-dental orofacial pain. Painful TMDs are generally myogenous (muscle) or arthrogenous (joint) in nature. Estimates suggest that 5% to 12% of the general population experience one or more episodes of preauricular pain, but only about one-third of these individuals develop symptoms that are significant enough to warrant medical attention. Multicenter studies have shown that TMD is not an isolated facial pain and that TMDs have underlying neurophysiologic mechanisms common to many chronic pain conditions.

Although the etiology of TMD is not known, it is generally agreed that a variety of conditions may reduce the organic physiologic adaptive capacity of the masticatory system and result in TMDs. The classification of TMDs (Box 18-6) remains a challenge due to our limited

• BOX 18-6 Classification of Temporomandibular Disorders

Muscular Disorders

- Hyperactivity, spasm, and trismus
- Inflammation (myositis)
- Trauma
- Myofascial pain and fibromyalgia
- Atrophy or hypertrophy

Arthrogenic Disorders

- Disc displacement (internal derangement)
- Hypomobility of the disc (adhesions or scars)
- Dislocation and subluxation
- Arthritis
- Infections
- Metabolic disease (gout, chondrocalcinosis)
- Capsulitis, synovitis
- Ankylosis (fibrous, bony)
- Fracture
- Condylar hyperplasia, hypoplasia, or aplasia
- Neoplasia

understanding of their etiology and the lack of universally accepted diagnostic criteria for the myriad of conditions presenting as TMDs. Many national and international subcommittees on chronic pain management are in continuous collaboration to define and refine diagnostic criteria in an effort to inform future scientific endeavor and improve patient outcomes. Our understanding of the TMDs has evolved as our understanding of the complex biopsychosocial nature of chronic pain has developed over the past five decades. These discoveries have led to the development of new diagnostic and treatment algorithms, not just for the orofacial pain patient cohort but also for the millions of chronic pain sufferers in general. Multicenter research efforts like the long-running clinical study, Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), attest to the idea that TMD is a complex multifactorial disease with genetic, physiological, and psychological implications.

Clinical and Radiographic Features

TMDs are seen primarily in young and middle-aged women, but they may affect any age and both sexes. Pain is primary motivation for seeking treatment, but limitations in jaw movement during functional excursions, and restricted joint movement with or without associated joint noises, are frequent complaints. The pain usually is localized to the preauricular area but may radiate to the temporal, frontal, or occipital areas. The pain may present as a headache **(cephalalgia),** a ringing in the ears **(tinnitus),** an earache **(otalgia),** a toothache **(odontalgia),** or any combination of these symptoms. The pain usually is associated with the surrounding musculature and soft tissue more than the TMJ itself. Muscle splinting can lead to involuntary CNS-induced muscular contractions **(myospasm),** or the muscle fibers themselves may become inflamed **(myositis).**

Myofascial trigger point pain is common in TMD, but it is seldom noted in other TMJ disorders. It is characterized by circumscribed regions, often referred to as taut bands within the muscle ("trigger points"), that elicit local or referred pain on palpation and may be a source of constant deep pain. In many instances, patients are aware only of the referred pain and not the trigger points themselves. The exact nature of the trigger points is not known, but they seem similar to small areas of myospasm and can, through their chronic nature, induce CNS excitatory effects. This hyperexcitability of the CNS produces the clinical findings of hyperalgesia (an exaggerated response to a painful stimulus) and allodynia (a painful response to a non-painful stimulus), which are characteristic of chronic pain conditions.

Non-arthritic inflammatory disorders of the TMJ are characterized by continuous deep pain or ache. The pain is evoked by palpation of the affected joint or by mandibular movement, especially chewing and clenching. Both TMJs may be involved, at the same time or at differing times.

Derangements of the condyle and meniscus complex are more often associated with dysfunction **(arthropathy)** than with joint pain **(arthralgia).** Articular disc displacements can occur in an anterior, posterior, and mediolateral direction and are characterized by a variety of joint noises and limitations in jaw opening. Laxity and elongation of the joint ligaments are thought to be major contributing factors to disc-condyle displacement disorders. Studies suggest that poor joint lubrication and osteoarthritis are implicated in the development of disc derangements. Disc-condyle disorders include both disc displacement with reduction and disc displacement without reduction. MRI of the TMJ complex reveals that up to 35% of asymptomatic individuals appear to have disc displacements.

Many systemic conditions are thought to contribute to the development of TMDs and must be included in the differential diagnosis of chronic orofacial pain. Inflammatory conditions of the musculoskeletal system and autoimmune-mediated connective tissue disorders (such as, lupus erythematosus, rheumatoid arthritis, and progressive systemic sclerosis) are frequently co-morbid with the TMDs.

There are many conventional and advanced imaging modalities for radiographic evaluation of the TMJ complex. The selection of imaging technique depends largely upon what type of information is needed from this adjunctive examination and how this information will affect patient management. Panoramic radiographs routinely are used as screening films for patients presenting with preauricular pain, and the interpretation of these films will influence the decision for the use of advanced imaging modalities. For TMD associated with internal joint damage or derangement, CT and MRI provide excellent diagnostic images of the TMJ. Transcranial and cephalometric radiographic images are still in use, but they have largely been replaced by tomography. Advances in CT, including cone beam computed tomography (CBCT), offer reduced radiation exposure and increased patient acceptance.

• BOX 18-7 Medications Used to Treat the Symptoms of Temporomandibular Disorders

- Aspirin
- Acetaminophen (with or without codeine)
- Other nonsteroidal antiinflammatory drugs (NSAIDs)
- Centrally acting muscle relaxants (methocarbamol and chlorzoxazone)
- Benzodiazepine derivatives (diazepam and chlordiazepoxide)
- Glucocorticoids (cortisone and prednisone)

Treatment and Prognosis

The natural clinical course of the TMDs is poorly understood and we cannot reliably determine which conditions will progress to more significant long term consequences. As many TMDs are transient and self-limiting, reversible and conservative therapies are encouraged. Conservative treatments include simple rest or immobilization of the joint, application of cold (usually reserved for acute injuries) or heat, occlusal splints and adjustment, and physical therapy. Various medications also have been used for TMD with some success (Box 18-7), although few TMD treatments have been examined in a blinded, controlled fashion. Long-term follow-up of large numbers of patients treated conservatively indicates that 85% to 90% experience significant or complete reduction of symptoms and that sustainable symptom reduction was achieved between 6 and 12 months after the initiation of therapy. Early conservative treatment not only provides greater patient satisfaction but also reduces the probability of developing a chronic condition. Because the clinical progression of the TMDs is not assured and owing to the demonstrated efficacy of reversible, conservative therapies, escalation of therapy should generally be avoided in all but the most extreme cases.

Surgical intervention may be required for severely affected joints, especially those with internal meniscal derangements, condylar dislocation or fracture, ankylosis, and degenerative or developmental deformities. Usually, TMD is treated conservatively for several years without improvement before surgery is attempted. Although surgery has frequently been used to treat a variety of painful conditions involving the TMJ, a review of the literature provides little objective evidence regarding the efficacy of most of these procedures. Therefore, the indications for surgery are limited. Of all patients sent to a specialist for TMD surgery, less than 1% actually undergoes surgery.

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19 Forensic Dentistry

EDWARD E. HERSCHAFT

Forensic dentistry, which is also referred to as *forensic odontology,* is the area of dentistry concerned with the correct management, examination, evaluation, and presentation of dental evidence in criminal or civil legal proceedings in the interest of justice. Thus the forensic dentist must be knowledgeable in both dentistry and law.

Classically, forensic dentistry can be considered a subspecialty of oral and maxillofacial pathology. This is analogous to the relationship in medicine between forensic pathology and pathology. The requirements of forensic dental field work, however, often demand an interdisciplinary knowledge of dental science. This has resulted in other dental specialists and general dentists joining oral and maxillofacial pathologists in providing legal authorities with dental expertise.

Regardless of background, forensic dentists assist legal authorities by preparing dental evidence in the following situations:

- Management and maintenance of dental records that comply with legal requirements to document all unique dental information—these data are the foundation on which dental identification of the patient is accomplished and potential malpractice litigation is reduced.
- Identification of human remains, through the comparison of antemortem and postmortem dental information, in cases that involve the death of an individual or multiple deaths in multiple fatality incident (MFI) situations. Collection and analysis of patterned marks (bite marks) in inanimate material or injured tissue that can be analyzed and potentially compared with a specific human or animal dentition.
- Recognition of the signs and symptoms of human abuse (including intimate partner violence [IPV], elder abuse, and child abuse) and the rights and responsibilities of the dental health care practitioner when reporting such abuse.
- Presentation of dental evidence as an expert witness in identification, bite mark, human abuse, malpractice, fraud, and personal injury cases.

RECORD MANAGEMENT

The dental record is a legal document, owned by the dentist or an incorporated dental practice, which contains all subjective and objective information about the patient. In the United States, the Privacy Rule governing the use of protected health information (PHI) is regulated under the federal Health Insurance Portability and Accountability Act (HIPAA) of 1996. Under this legislation the patient has the right to view original documents and obtain copies.

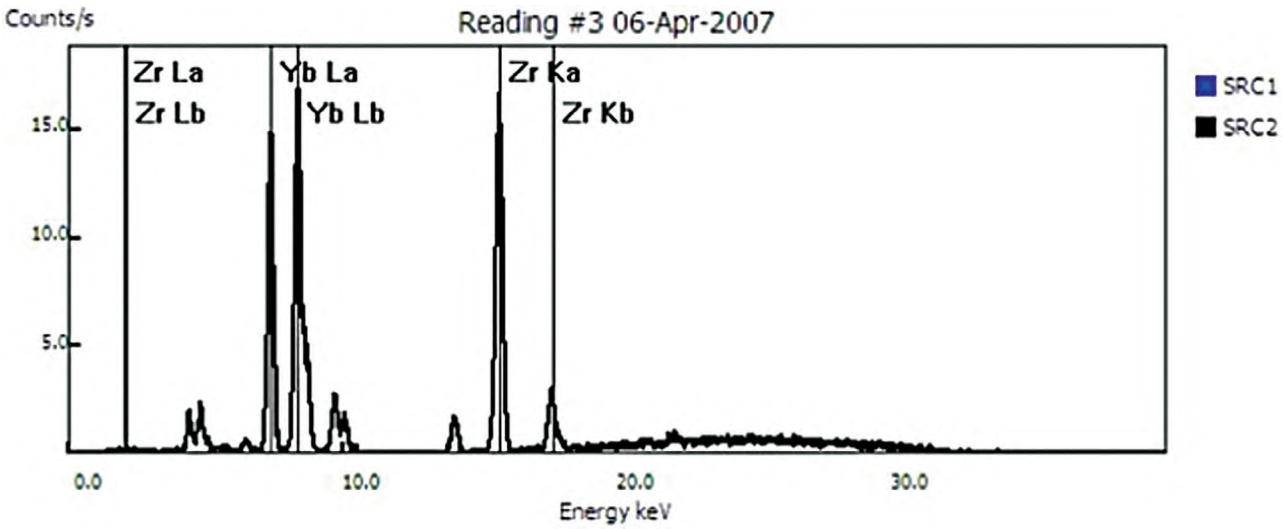
Despite the establishment of the Privacy Rule, the ability and necessity of forensic dentists, law enforcement personnel, medical examiners (MEs), and coroners to obtain released antemortem dental and medical records for forensic purposes without requiring consent of next-of-kin or a guardian was recognized and provided for in the HIPAA legislation—45 Code of Federal Regulations §164.512(g)(1).

Initially, demographic information is secured when the medical and dental history of the patient is obtained. Results of the physical examination of the dentition and supporting oral and paraoral structures are recorded.

In addition, the results of clinical laboratory tests, study casts, photographs, and radiographs become components of the record. With this database, the dentist can develop a thorough assessment of all of the patient's medical and dental problems. Subsequent documentation of this "problem list" facilitates the development of a plan of treatment and prognosis for the patient.

The treatment plan addresses the management of both systemic and oral problems. It can then be periodically revised and updated as problems resolve or as new ones develop. Supplemental material, such as dental laboratory authorizations, referral letters from other practitioners, statements of informed consent, written prescriptions, and insurance and financial statements, also is included and stored in the record.

The progress notes (i.e., daily log of actual treatment rendered) should contain information about restorative and



• **Fig. 19-1** The x-ray fluorescence (XRF) spectrum from a particle recovered from a cremation retort. The spectrum makes this a match for the restorative resin Four Seasons or Tetric Ceram (Ivoclar Vivadent, Amherst, NY). (Courtesy of Dr. Mary A. Bush and Peter J. Bush.)

therapeutic procedures provided. This information should include documentation of the specific brand of dental material used in restorative procedures. This concept has forensic import because each dental restorative product contains inorganic materials, trace elements, and fillers that are unique to that product and can be detected by **x-ray fluorescence (XRF)** technology even after incineration. The XRF trace element and major element analysis of dental remains may be useful as an adjunct to traditional evaluation of dental information in some forensic settings, including cremation and dismemberment cases (Fig. 19-1).

Unusual physiologic and psychological reactions and the patient's comments concerning therapy are entered in the record. Summaries of telephone conversations with patients, consultants, insurance company representatives, or legal authorities should be noted. All entries should be signed or initialed by recording personnel. Changes in the record should not be erased but corrected by a single line drawn through the incorrect material. This method permits the original entry to remain readable and removes any questions concerning fraudulent intent to alter recorded information.

By 2015 medical and dental records in the United States must be maintained in an electronic format and numerous commercial and individually designed computer software programs have been marketed to assist physicians, dentists, health care facilities, hospitals, and insurance companies in collecting and preserving the medical and dental information of patients. The obvious advantage of electronic medical, health, or dental record (EMR, EHR, and EDR) systems is facilitation of networking and exchange of records among the different formats ("interoperability") for routine professional consultation or use in forensic identification cases requiring medical and dental records for comparison.

However, the increased use of EHRs and EDRs has also created legal, financial, and ethical issues concerning patient privacy. Additionally, there may be a potential for insurance fraud associated with the computer enhancement of dental lesions or restorations on electronically generated dental radiographs.

The potential charge of insurance fraud associated with the enhancement of dental lesions or restorations on computer-generated or scanned **digital radiography (DR)** can be avoided if a clinician stores and maintains unaltered images. This is accomplished using programs with unchangeable, secure tagged block file extensions in their native file formats. When duplicates or copies are required, working images should be generated.

Computer-assisted management technology (e.g., WinID3 dental comparison software bridged with the Dexis DR program) has been an asset in expediting the comparison of antemortem and postmortem dental record information in recent MFI events, including the World Trade Center terrorist attack, the Indian Ocean tsunami disaster, and the Hurricane Katrina recovery effort. Additionally, software such as Adobe Photoshop and Mideo Systems CASEWORKSeis facilitates the superimposition of digitally scanned radiographs and photographs for comparison.

Whether preserved in written form or by using a computer database, the principles of record management describe a mechanism that ensures that dental information, which may be required to resolve a forensic problem, is properly maintained and retrievable. Additionally, records preserved in this manner are reliable evidentiary material if subpoenaed in peer review or malpractice litigation proceedings.

Time limits concerning how long records must be retained vary among the states. As a rule, states mandate that records be kept for 7 to 10 years. Federal legislation related to the problem of missing persons in the United States requires that records of pediatric dental patients be retained until the patient reaches the age of majority

(adulthood). Depending on the jurisdiction this can vary from 18 to 21 years of age.

The maintenance period for EHR and EDR patient data exceeds the duration of paper records and may vary from 20 to 100 years. Provisions for security and integrity of stored archival information in EHRs and EDRs must support ethical and legal principles regarding privacy because the technology used to input information will be unavailable to those who may need to examine this data in the future.

IDENTIFICATION

Legal situations often revolve around the establishment of a person's proper identity. Any death not certified by an individual's own physician must be referred to the medical examiner (ME) or coroner for review. However, cases requiring an **autopsy** to determine the time, cause, and manner of death represent a small percentage of cases. When required, these tasks are the responsibility of a coroner or ME. These officials are charged with the role of establishing identification; determining the cause, mechanism, and mode or manner of death; and issuing a death certificate. Besides identification of the decedent, these key issues of death investigation for the coroner or ME are defined according to the following:

- **Cause of death.** The disease, injury, or chemical or physical agent responsible for initiating the lethal sequence of events (e.g., myocardial infarction, cancer, bullet, knife, poison, ligature, lightning, and infectious agents)
- **Mechanism of death.** The pathologic process that results in death (e.g., congestive heart failure, cardiac arrhythmias, asphyxia, sepsis, exsanguination, renal failure, and hepatic failure)
- **Mode or manner of death.** According to the NASH classification, the mode or manner of death is considered to be **N**atural, **A**ccidental, **S**uicide, or **H**omicide. Natural deaths are caused exclusively by disease. Accidental deaths result from an environmental or human tragedy (e.g., lightning strike or vehicular incident).
- **Undetermined death.** Although the cause and mechanism of death may be resolved, the manner or mode may not be established because of decomposition, dismemberment, or postmortem destruction of the remains by insects or feral animals.

The coroner is an elected official and, depending on the laws of each state, does not necessarily have to be a physician or have advanced training in death investigation. An ME is an appointed official who is a pathologist specifically trained in forensic medicine. Many jurisdictions use forensic pathologists, and this trend has contributed to the professionalizing of a position increasingly involved with the interpretation of advanced scientific techniques requiring knowledge of toxicology, ballistics, pharmacology, and criminalistics, as well as pathology.

A death certificate, identifying the decedent, is required before probation of a will, release of life insurance claims, or resolution of other affairs associated with the settlement of an estate. Criminal cases involving homicide, suicide, and fraudulent misidentification may also require the expertise of forensic dentists and other forensic scientists trained in identification techniques. These professionals act as consultants to the coroner or ME and assist in this aspect of a death investigation.

Besides analysis of the dentition, the most common methods of identification include personal recognition, fingerprinting (friction ridge analysis), physical anthropologic examination of bones, and serologic and genetic (DNA) comparison techniques.

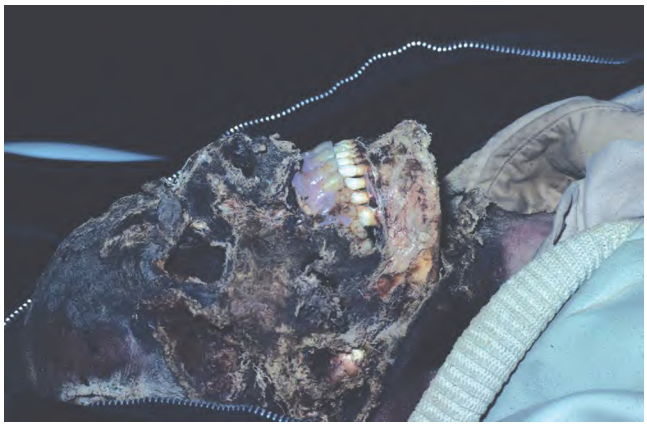
Additionally, the use of facial superimposition techniques (when the teeth are visible) and facial reconstruction techniques may also permit scientifically supported comparisons for identification. Each method has its advantages and disadvantages. However, all rely on the principle that identification is the positive correlation obtained by comparing known information about a suspect or victim with unique facts retrieved by physical examination of the suspect or victim.

Regardless of the method used to identify a decedent, the results of the antemortem and postmortem data comparison lead to one of the following four situations:

1. **Positive identification.** There is sufficient uniqueness among the comparable items in the antemortem and postmortem databases, and no major differences are observed.
2. **Presumptive (possible) identification.** There are commonalities among the comparable items in the antemortem and postmortem databases; however, enough information may be missing from either source to prevent the establishment of a positive identification.
3. **Insufficient identification evidence.** There is insufficient supportive evidence available to compare and arrive at a conclusion based on scientific principles.
4. **Exclusion of identification evidence.** Either explainable or unexplainable discrepancies exist among comparable items in the antemortem and postmortem databases. This results in inconsistencies that prevent the establishment of any identification. Exclusion may be just as important as a determination of positive identification.

Personal Recognition

Personal recognition is the least reliable method used to identify an individual. It is often based on the visual identification of a decedent by a family member, friend, or acquaintance. This process assesses artifactual material, such as clothing, jewelry, keys, wallet contents, luggage, other personal effects, scars, and tattoos to determine identification. Evidence in this type of identification can be accidentally or purposely exchanged between bodies. This can occur in MFI situations or when there is criminal intent to create a misidentification in cases of identity theft or alias associated with criminal activity.



• **Fig. 19-2** Unrecognizable partially decomposed human remains with a maxillary removable partial denture in place. Notice that the skin tissue of the neck that has been protected by the windbreaker jacket has not reached the stage of decomposition of the tissues of the exposed face. (Courtesy of Dr. Raymond D. Rawson.)

• **Fig. 19-3** A burn victim requiring identification by dental, DNA, or fingerprint methodology rather than personal recognition. (Courtesy of Dr. Raymond D. Rawson.)

Even when a body is viewed shortly after death, distraught relatives can inadvertently misidentify the decedent. After the occurrence of postmortem changes associated with soft tissue decomposition, insect and burn artifact, or dismemberment, this method of identification may be precluded (Figs. 19-2 and 19-3).

Fingerprinting

Anthropometry was the first "scientific" system police used to identify criminals. The French law enforcement officer, Alphonse Bertillon, developed this system in the latter part of the nineteenth century. The method was unreliable and flawed because it relied on biometric physical measurements of the head and body, individual markings including scars and tattoos, and other personal characteristics. Bertillon's anthropometry identification process was eventually replaced by analysis of the epidermal friction ridges of the fingers, palms, and feet commonly referred to as **fingerprinting.**

By the beginning of the twentieth century, forensic science had recognized that the ridge-like patterns on the fingertips and palms are unique for each person. These friction ridges are genetically determined, and not even homozygous twins have the same patterns of loops, arches, and whorls. A principal variation in the fingerprints of twins is that they appear as mirror images of each other. The morphometric variation in combinations of the loops, arches, and whorls permits a scientific comparison of fingerprint records with the friction ridges of an unidentified decedent.

Because the fingerprint pattern is inherited, it is a static characteristic and remains unchanged throughout life. This is an important advantage when one compares fingerprint identification with dental identification. The teeth and supporting structures have fluid characteristics. Dental patterns change as teeth erupt, exfoliate, decay, become restored, and, perhaps, are eventually extracted and replaced with implants or other prosthetic devices.

Unlike dental records, which are principally retained in private dental offices in the Americas and Western Europe, fingerprint information is maintained by governmental agencies. Several states retain records of non-criminals who work in sensitive occupations. In this regard, Nevada has a fingerprint database for employees in the gaming industry. The Criminal Justice Information Services (CJIS) Division of the Federal Bureau of Investigation (FBI) contains the largest biometric database in the world with approximately 130 million fingerprint records included in criminal, civil, and known and suspected terrorist formats.

Currently, these records are retained within the Integrated Automated Fingerprint Identification System (IAFIS). IAFIS permits input, matching, and retrieval of even a single fingerprint image for identification. Next Generation Identification (NGI) technology is being developed for the FBI to expand the morphometric information contained in IAFIS to include palm print, iris, and facial identification data.

The establishment of the CJIS Division's IAFIS files permits automated computer data entry and search capabilities for matching and retrieval of fingerprint images. This information is available for electronic exchange among law enforcement agencies for identification purposes. Included in the IAFIS database are criminal and civil ten-print fingerprint records, latent fingerprint services, and subject and criminal history search capabilities. Information from this fingerprint repository is shared with international legal agencies, such as Interpol and the Royal Canadian Mounted Police.

Fingerprint nomenclature is standardized in IAFIS, and all fingerprint experts use the same terminology worldwide. This advantage is not observed in dental identification, in which numerous charting and tooth-numbering systems are used. Because soft tissues decompose shortly after death, the friction ridge patterns within the epidermis may not be retrievable for fingerprint comparison. This is the principal disadvantage of fingerprint identification.

Physical Anthropologic Examination of Bones and Teeth

Forensic anthropologists and forensic dentists often work together to resolve problems associated with identification. Both disciplines are concerned with analysis of calcified structures of the body—bones and teeth. Historically, this anatomic material has assisted forensic anthropologists and dentists in determining the race, age, and sex of a person (Table 19-1). These characteristics have become less distinct in some populations as individuals from different cultures and races have intermarried and blended these genetically determined features in their offspring.

In addition to the study of osseous material and despite variations in crown and root development within the dentition, the teeth can be studied clinically, radiographically, histologically, and biochemically to determine the age of a living individual or decedent.

Forensically, this information is essential in casework involving the need to establish legal age of majority (adulthood), medicolegal age at death, clarification of the age of undocumented immigrants, age estimation of unidentified remains, and separation of comingled remains in a multiple fatality incident among others.

From fetal development to adolescence tooth maturation intervals are the principal method of dental age assessment. Lewis and Senn emphasize that dental age estimation of children becomes more accurate when teeth having less variance are used in these analyses and data derived from multiple teeth is considered. Additionally, studies have been performed to assess differences in crown and root formation and eruption sequences among children of both genders and various racial and ethnic populations.

As one approaches adulthood, age estimation acquired by analysis of the dentition can be supplemented with radiographic data obtained from the calcification centers of the hand and wrist, ribs, clavicles, and other bones to determine the precise age of a person younger than 20 years of age.

Biochemical laboratory procedures or assessment of dental post-formation changes are used to determine the age of adult individuals. Historically, dental post-formation changes of adult teeth included the study of their ground sections for variations in patterns of:

- Attrition
- Periodontal attachment
- Secondary dentin
- Cementum apposition
- Root resorption
- Transparency of root dentin

This approach, developed by Gustafson in 1947, has been modified to determine which of these factors are most significant—secondary dentin and transparency of root dentin. Additionally, these contemporary methods of dental post-formation analysis have been supplemented by those relying on the following techniques:

- Evaluation of the rate of racemization of levels of metabolically stable aspartic acid enantiomers in enamel and dentin to determine an exact age.
- Occlusal tooth wear which can provide reliable estimates of age to within 3 to 5 years. Often, anthropologic analysis is helpful in arriving at a presumptive identification based on these criteria.

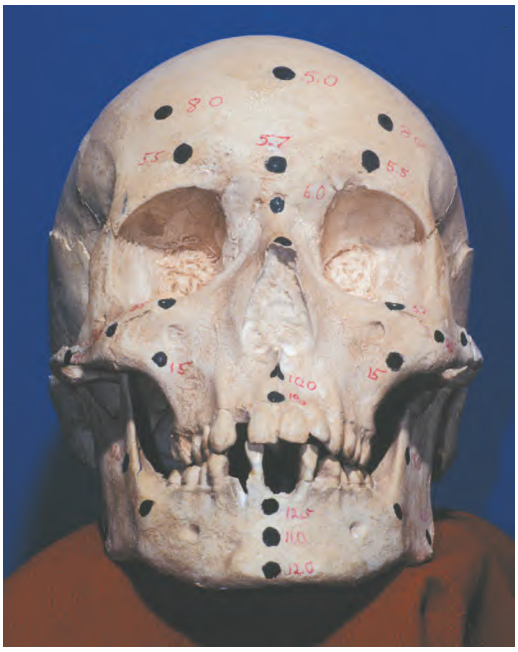
There are variations in the calcification and eruption patterns among various ethnic and cultural groups, and studies have been undertaken to delineate these differences further. After the third molars, long bones, and bones of the wrist and hand are completely developed, evaluation of biochemical components of the calcified structures and collagen is the most accurate method for determining chronologic age.

Methods that rely on an analysis of the rate of racemization of the stereoisomers of aspartic acid in enamel and dentin can be used to determine an accurate chronologic age. This is related to the fact that the change from the L-form of this amino acid to its mirror image D-form occurs over time. Thus the ratio of the L- to D-forms of

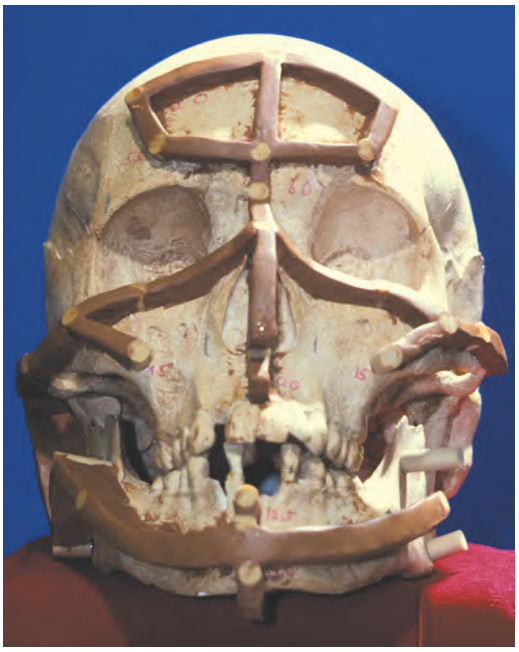
TABLE 19-1 Skeletal Anthropologic Variations Associated with Racial and Sexual Characteristics of the Skull

	Racial Characteristics		
	White	Black	Asian/Native American
Width	Narrow	Narrow	Broad
Height	High	Low	Intermediate
Profile	Straight	Prognathic	Intermediate
Orbit	Triangular/teardrop	Square	Circular
Nasal opening	Tapered	Wide	Rounded
Palate	Narrow	Wide	Intermediate

	Sexual Characteristics	
	Male	Female
Size	Large	Small
Glabellar (supraorbital) ridges	Pronounced	Not developed
Mastoid process	Large	Small
Occipital area	Pronounced muscle lines	Minimal muscle lines
Mandible	Larger, broader ramus	Smaller
Forehead	Steeper, slopes posteriorly	Rounded, more vertical



• **Fig. 19-4** Reconstruction of the facial soft tissue uses predetermined, standard anthropologic thickness measurements for specific points around the face. These measurements are based on variables that are related to racial and sexual characteristics. (Courtesy of Dr. Cleve Smith.)



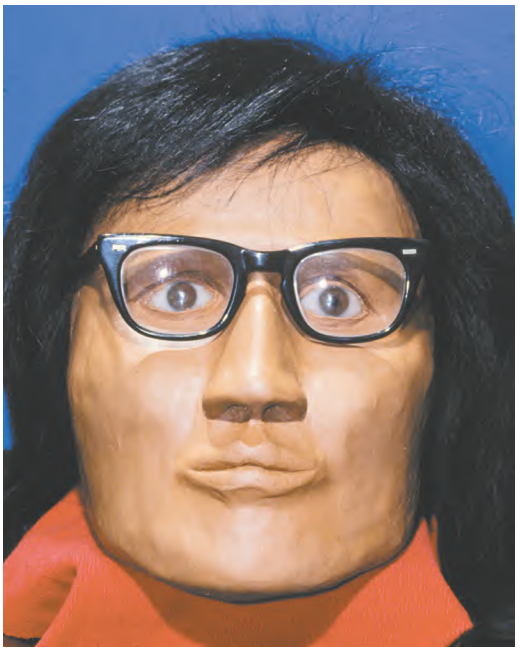
• **Fig. 19-5** The soft tissue thickness points can be connected with sculpting clay or digitized on a computer screen. The ultimate result of these techniques is a re-creation of the contour of the soft tissue features that permits a visual identification. (Courtesy of Dr. Cleve Smith.)

aspartic acid in the dentition is directly related to the age of the individual. Often, anthropologic and dental age analysis is helpful in arriving at a presumptive identification based on the criteria noted previously.

Positive identification may be achievable when the skull and facial bones are used as a foundation to reconstruct the facial soft tissues (Figs. 19-4 to 19-6). Three-dimensional (3D) computer images, computed tomography (CT) images, and radiographs have even been used in the replication of the face of Europe's oldest mummified human, a male dubbed Ötzi, whose 5300-year-old remains were removed from glacial ice in the Ötztal Alps on the Austrian-Italian border.

With knowledge of the anatomic relationships between the skull and face, antemortem facial photographs or radiographs can be superimposed for comparison with the skull of an unknown. Video superimposition with two television cameras and an electronic mixing device has been used successfully to overlay a photograph of a human face on an image of a skull for identification. The development of computer software programs capable of superimposition has further facilitated the process.

The anterior dentition of the skull can be overlaid and compared with a smiling antemortem photograph. The shapes and positions of the individual teeth and their relationships to each other have been considered distinctive enough features on which to base identification, as have certain significant cranial and facial landmarks, including the orbits, nasal openings, malar eminence, and chin. Prosthetic joint replacements, intraosseous and dental implants,



• **Fig. 19-6** The width of the mouth is related to the interpupillary distance. The length and shape of the nose are determined by the relationship between the inferior and superior nasal spines. If known, then the addition of a specific hairstyle, eyeglasses, and eye color can further individualize a facial reconstruction. (Courtesy of Dr. Cleve Smith.)

and radiographic signs of prior bone fracture are other anthropologic findings that can be used to facilitate identification.

Additionally, prosthetic devices, implanted defibrillators and pacemakers, and osseous implants are designated with individual identification code numbers provided by their manufacturers. These codes can be visualized in the various devices and are useful in identifying individuals in cremation and dismemberment scenarios when the teeth and fingerprints are not available for evaluation.

Serologic and Genetic (DNA) Comparison

Every individual is unique by virtue of his or her chromosomal DNA—a polymer structured as a double helix and composed of four different nucleotides. The polymorphic sequencing of these nucleotides along the two strands of the DNA molecule accounts for the genetic diversity of all living things. This "ultimate identification material" was first used forensically to obtain a conviction in a criminal case in 1986, and DNA comparison has since become an accepted forensic method to resolve problems of identification.

Before 1986, comparison of antigenic markers found on red blood cells (RBCs) and in body fluids of secretors of these markers among the human population was traditionally used as a means of exculpatory (exclusionary) evidence. Because the ABH antigenic surface markers of RBCs are not discriminatory, this type of evidence was primarily used to exclude a suspect or victim when negative comparative results were achieved. Positive comparisons were justified only to place the suspect or victim in a population of individuals having similar serologic antigens.

Although DNA has become the principal biologic substance used to effect a positive identification, antigenic surface markers A, B, and H of the ABO blood group system, as well as various components of the rhesus (Rh) and Lewis systems, continue to be accepted for medicolegal comparison. The ability to secrete the ABH antigens in saliva and other body fluids is genetically determined, and more than 80% of individuals are secretors. With appropriate laboratory tests, even dried samples of fluid and blood can be analyzed for these markers.

DNA found in human cells is composed of chromosomal and mitochondrial DNA (mtDNA). Two copies of chromosomal DNA are incorporated into the nuclei of a person's cells by DNA provided from both parents. However, hundreds of copies of mtDNA are contained in the cytoplasm of these cells. This DNA is only maternally transferred and can be isolated from cells without nuclei, such as RBCs. Unlike nuclear DNA, mtDNA is single stranded and circular. Because there is no mixing of sequence types from generation to generation in maternally transferred mtDNA, it can be compared with that of distant maternal relatives to effect identification when other reference sources are unavailable.

Restriction fragment length polymorphism (RFLP) and polymerase chain reaction (PCR) analyses are the principal laboratory techniques used to compare and evaluate fragments of DNA material from a suspect or victim's biologic forensic specimens (e.g., semen, vaginal fluid, teeth, soft tissues, and saliva). Both are extremely accurate, precise, and reproducible; these methods are used when the conditions of the sample DNA presented dictate the need for their respective advantages.

RFLP methods result in splitting source DNA into thousands of fragments using "biologic scissors" known as *restriction enzymes.* Fragment size varies among individuals related to the variable number of tandem repeats (VNTR) of base pairs. These short segments of DNA contain a number of repeat units that differ among individuals. After gel separation of the fragments and transfer to a nylon mesh, specific DNA fragments are identified using oligonucleotides labeled with radioisotopes. Analysis of a series of different VNTR loci permits generation of an individual DNA profile.

A match of four or more VNTR loci is consistent with a positive match between DNA evidence gathered from suspect, victim, or crime scene evidence. The RFLP method requires large amounts of high molecular weight DNA, a major disadvantage. Small DNA samples (< 100 ng) or degraded evidence in which the DNA has become denatured because of extreme heat or pH variation requires an analytic method other than RFLP.

The evaluation of minute quantities of DNA or DNA that has undergone degradation can be accomplished with the highly sensitive PCR test. Using this laboratory technique, smaller VNTR loci of a specific DNA sequence can be amplified into enough copies for sufficient analysis. Because of its high degree of sensitivity, PCR analysis has been used to evaluate small amounts of DNA from a suspect's clothing left at the scene of a crime, as well as from bone fragments from the Vietnam War. DNA amplification of microsatellite loci (referred to as *STRs*) and minisatellite loci (or *LTRs*) using PCR, is referred to as *AmpFLP analysis.*

The hard and soft tissues of the oral cavity and saliva are often good sources for DNA material. However, if the teeth or other hard structures of the mouth are to be used for the collection of DNA evidence, then the identification value of these structures should be considered (beyond their ability to yield a harvest DNA). A tooth or jaw fragment capriciously destroyed can result in the loss of valuable radiographic and anatomic sources for eventual dental identification. Besides the obvious source of DNA from human tissues, the forensic dentist often considers the evaluation of chewed gum, cigarette remains, licked envelopes, stamps, or similar inanimate objects as potential sources for DNA evidence using PCR analysis described previously.

Regardless of the surface from which DNA evidence may be harvested, the two-swab protocol developed by Dr. David Sweet and others at the Bureau of Legal Dentistry, University of British Columbia is the recovery method of choice:

- A sterile cotton swab is moistened with distilled water and rolled over the surface of the skin or object using moderate pressure and circular motion.

- This swab is air dried.
- A second *dry* cotton swab is rolled over the *same* surface of the skin or object using moderate pressure and circular motion *to absorb all moisture left by the first swab.*
- This swab is also air dried.
- Both swabs are placed in properly labeled storage containers and submitted to the laboratory for frozen storage at −20° C (−4° F).

Control samples may be collected from whole blood, autopsy tissue samples or oral buccal swabs from a living individual.

Passage of the DNA Identification Act of 1994 and the establishment of the FBI's National DNA Index System (NDIS) in 1998 have facilitated the exchange and comparison of DNA profiles among federal, state, and local crime laboratories in the United States. This is accomplished electronically through the FBI Laboratory's Combined DNA Index System (CODIS). Through the CODIS computer program's forensic and offender indexes, biologic evidence from crime scenes can be linked to DNA profiles of individuals convicted of sex offenses and other felonies. As of March 2007, the total number of DNA profiles contained in the CODIS databases was more than 4.5 million. More than 47,000 successful comparisons ("hits") were made among cases in which the CODIS system was activated. This represents a 98% success rate linking DNA from a crime scene with similar material from the convicted offender profiles.

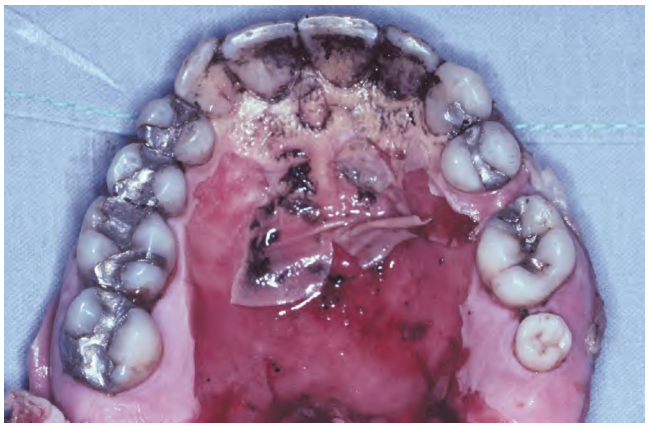
The US Department of Defense has initiated a policy of obtaining DNA samples on all military personnel. This DNA "fingerprint" has significantly reduced the possibility of another unknown soldier among future military casualties. Despite the positive effects of DNA evidence in resolving questions of identity, the technique is not without controversy. Challenges have been made by population geneticists, concerned about random matching and variations among racial subgroups.

Dental Evaluation

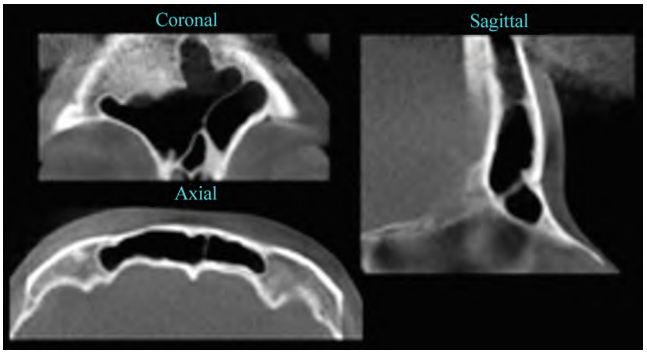
Basic Principles

In an identification case, the principal advantage of dental evidence is that, like other hard tissue, it is often preserved indefinitely after death. Although the status of a person's teeth changes throughout life, the combination of decayed, missing, and filled teeth is measurable, reproducible, and comparable at any fixed point in time. Therefore, like the comparison of unique patterns in a fingerprint, a scientific, objective analysis of antemortem and postmortem dental variables is achievable.

The presence and position of individual teeth and the respective anatomic, restorative, and pathologic components provide the database for the antemortem and postmortem comparison (Fig. 19-7). The pattern of the palatal rugae, ridges on the lip surface, and radiographic outline of the maxillary and frontal sinuses are also considered unique (Fig. 19-8). In addition, the legal community accepts the fact that dentists can recognize procedures that they have performed.



• **Fig. 19-7** The combination of decayed, missing, and filled teeth, along with unique anatomic and pathologic findings, provides the database for comparison in a dental identification. Note the microdont in the maxillary left quadrant.



• **Fig. 19-8** The outline shape of the frontal sinus is a unique morphometric factor that may be used in human identification when comparing cone-beam computed tomography (CBCT) and anterior-posterior radiographs of a known individual with those of an unknown person or decedent. (Courtesy of Dr. Robert Danforth.)

Problems associated with dental identification information are often related to acquiring and interpreting antemortem records. Most antemortem dental records are retrieved from private-sector dental providers. However, dental records may be recovered from insurance carriers, dental schools, hospitals, clinics, state and federal prisons, military files, and the FBI National Crime Information Center (NCIC) data bases.

To initiate a request for antemortem records, a putative (suspected) identification is required. Reports of missing and unidentified persons, obtained from law enforcement agencies, are the principal source for this material. Thousands of victims who cannot be identified by fingerprint methods remain unidentified because a putative identification has not been established.

The FBI-NCIC computer registry of missing and unidentified persons was established to help rectify this problem. This computer system maintains demographic, dental, and medical information on missing persons. It attempts to match these data with similar facts obtained from unidentified bodies. The latter information is submitted by various investigative and legal agencies. Potentially,

the otherwise unidentifiable victims of random violence, serial homicides, terrorist acts, and child abduction can now be identified without the need to determine a putative identification. A disadvantage of the NCIC computer identification system is that it does not have the capability to identify possible decedents based solely on dental information.

The National Dental Image Repository (NDIR) has been established to address this issue. Law enforcement agencies can voluntarily post supplemental dental images related to NCIC Missing, Unidentified, and Wanted Person records on the NDIR secure website. Thus access, retrieval, and review of dental information by qualified forensic odontologists who are members of the NDIR Review Panel can facilitate dental comparisons. The NDIR website is located at Law Enforcement Online (LEO) at http://cgate.leo.gov. This repository permits law enforcement, criminal justice, and public safety authorities to maintain a national and international method of electronic communication, education, and sharing of dental information.

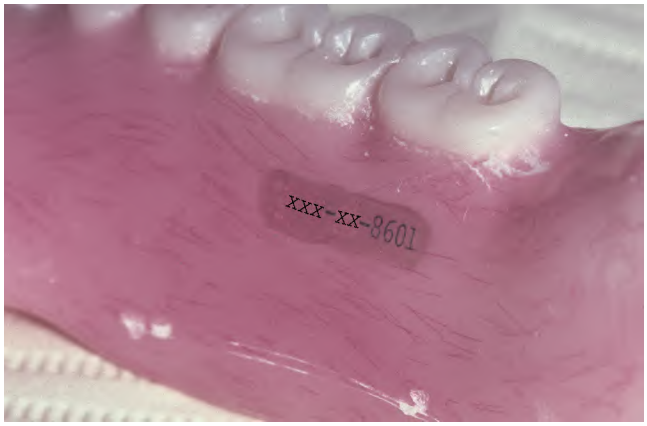
The Armed Forces, Department of Veterans Affairs, and many states require that identifying markings be placed on removable dental prostheses (Fig. 19-9). The American Dental Association also supports this policy. It is an attempt to provide a basis for identification among the substantial population of completely or partially edentulous individuals in the United States.

Identifying markings in dental prostheses are important because even if dental records of an edentulous person can be obtained, they may not reflect the current status of the ridges and alveolar bone. Commonly used information for identifying marking in removable dental prostheses includes the person's name, driver's license number, and/or other identification number.

Even when a suspected identification is achieved, it may still be difficult to secure antemortem dental records. The family or acquaintances of the victim may not know where dental treatment was sought. Reviewing the victim's canceled bank checks or medical deductions on tax records may be helpful in locating antemortem dental records in such cases.

Although records obtained from institutional or governmental dental facilities routinely indicate all restored teeth, this is not true of charts forwarded from private dentists. In these instances, previously restored teeth often are not charted unless the current dentist intends to re-treat them. Therefore, in these records, the antemortem radiographs and progress notes become the principal sources for dental information.

Unfortunately, the nomenclature associated with dental charting systems is not standardized (Table 19-2). In 1984,



• **Fig. 19-9** Denture identification is accomplished by inserting a typed name or code number (i.e., Social Security number or hospital patient number) in an area of the denture that will not interfere with the aesthetics of the prosthesis. This procedure is performed in the laboratory during the final acrylic pack. Information also can be engraved in the framework of an all-metal appliance.

TABLE 19-2 Dental Numbering Systems

Permanent Teeth

Maxillary Right	Maxillary Left
Mandibular Right	Mandibular Left

Universal Numbering System

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17

Zsigmondy/Palmer System

8	7	6	5	4	3	2	1 |	1	2	3	4	5	6	7	8
8	7	6	5	4	3	2	1 |	1	2	3	4	5	6	7	8

Federation Dentaire Internationale Two-Digit System

18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Deciduous Teeth

Universal Numbering System

A	B	C	D	E	F	G	H	I	J
T	S	R	Q	P	O	N	M	L	K

Alternate Universal Numbering System

4D	5D	6D	7D	8D	9D	10D	11D	12D	13D
29D	28D	27D	26D	25D	24D	23D	22D	21D	20D

Zsigmondy/Palmer System

E	D	C	B	A |	A	B	C	D	E
E	D	C	B	A |	A	B	C	D	E

Federation Dentaire Internationale Two-Digit System

55	54	53	52	51	61	62	63	64	65
85	84	83	82	81	71	72	73	74	75

the American Dental Association adopted the Universal Tooth Numbering System. All insurance companies, the Armed Forces, dental schools, and most dentists in the United States now use this system. It should be used in all forensic dental cases.

In the Universal Numbering System, a consecutive number from 1 to 32 is assigned to the adult dentition. It begins with the maxillary right third molar and ends with the mandibular right third molar. The deciduous dentition is identified by letters from A to T, beginning with the maxillary right deciduous second molar and ending with the mandibular right deciduous second molar. Thus the quadrants are identified in a clockwise direction, beginning with the maxillary right.

Other tooth numbering methods include the Zsigmondy/Palmer System and the Federation Dentaire Internationale (FDI) Two-Digit System. Each uses a different coding technique to identify dental quadrants and specific teeth.

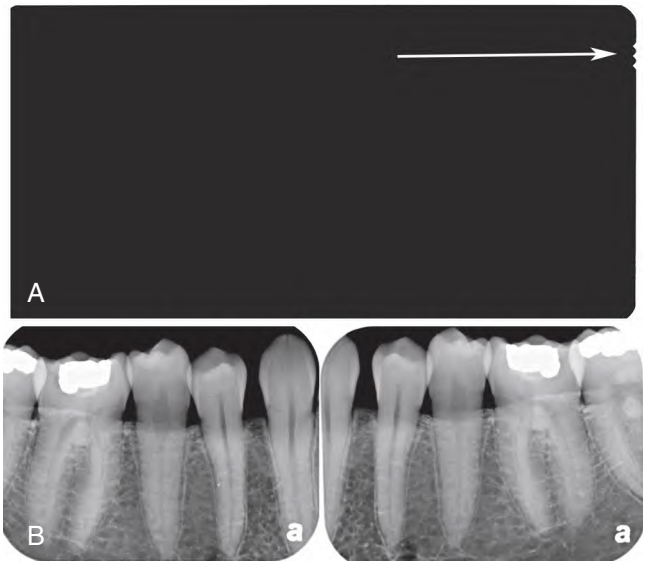
The Zsigmondy/Palmer System stresses the anatomic likeness of the eight tooth types in each symbolically identified dental quadrant. Homologous permanent teeth are assigned the same number from 1 to 8. Deciduous teeth are assigned letters *A* through *E*.

The FDI Two-Digit System is endorsed by the World Health Organization (WHO) and is used in most developed countries, except the United States. The first digit represents the quadrant. Quadrants 1 to 4 are assigned for permanent teeth; 5 to 8 represent quadrants for the primary dentition. As in the Universal Numbering System, the quadrants are identified in a clockwise direction, beginning with the maxillary right. The second digit designates the permanent tooth type from 1 to 8, or deciduous tooth type from 1 to 5.

Thus in the Universal Numbering System, tooth 12 is the maxillary left first bicuspid. In the FDI Two-Digit System, tooth 12 (one-two) is the maxillary right lateral incisor. In the Zsigmondy/Palmer System, all lateral incisors are designated with a No. 2 code. The position of a specific No. 2 tooth is diagrammatically indicated by a symbolic quadrant.

Unless the forensic dentist knows which system has been used to encode the teeth in the antemortem record, all teeth should be referred to by their actual names. This method will prevent errors because all dentists use the same anatomic nomenclature when referring to individual teeth.

Dental identification problems may be further compounded because dental radiographs can be mounted and viewed from right to left or vice versa. Intraoral radiographic duplicating film does not contain a raised dot to assist the dentist in orienting the film for mounting. The lack of this orienting device can lead to transposition of dental evidence and potential misidentification based on an incorrect comparison. Besides the lack of a raised dot, panoramic radiographic duplicating film can be detected because of its single-sided emulsion and series of notches on one edge to indicate that the image is not an original (Fig. 19-10, *A*).



• **Fig. 19-10** **A,** Panoramic duplicating film has a series of notches *(arrow)* on one edge to indicate that the image is not an original. **B,** When phosphor digital plates are inadvertently exposed from the wrong side, the error may not be detected because the **"a"** position marker always appears in the same location after processing regardless of which side of the sensor has been exposed. This problem can be prevented by placing a metal indicator on the side of the device that should not be exposed. (Courtesy of Dr. Richard A. Weems.)

Additionally, when using intraoral digital sensors the operator must be careful not to inadvertently expose the device from the wrong side. This orientation error can remain undetected because the "**a**" placed on the sensor (which serves the same function as the raised dot on radiographic film) always appears in the same position after processing regardless of which side of the sensor has been exposed (see Fig. 19-10, *B*).

With the advent of aesthetic materials for posterior restorations and the reduction in the prevalence of caries, it may be difficult for the forensic dentist to determine whether restorations are present by simple visual assessment of the teeth. In addition, the postmortem dental evaluation is often performed in an autopsy room, temporary morgue, or funeral home. In these locations, proper lighting and access to dental instruments, which can facilitate analysis of the oral structures, are not readily available for detailed examination.

Often, there are additional demands for immediacy in providing a coroner, ME, or other legal agent with the results of a dental identification. These demands further compound the forensic dentist's technical and stress-related problems while performing the tasks related to this discipline. Because of the previous caveats, the forensic dentist should prepare an equipment kit (Box 19-1). The kit should be portable, containing instruments and supplies specifically required for the performance of dental procedures in an autopsy room environment.

• BOX 19-1 Suggested Instrument Kit for Forensic Identification

Dental explorers
Dental mirrors
Periodontal probes
Bite blocks
Tissue scissors
Osteotome
Rubber air/water syringe
Cotton swabs
Gauze
Flashlight or headlamp
Specimen containers
Scalpels and blades
Cheek retractors
ABFO No. 2 ruler
Bone mallet
Photographic mirrors
SLR film-based camera
Digital camera
Photographic film, digital memory card
Radiographic film and digital sensors
Rubber, latex, and nitrile gloves
Tissue forceps
Tissue clamp
Tongue clamp
Disclosing solution
Stryker saw
Writing instruments
Case labels
Appropriate charts
Masks and HEPA filters

ABFO, American Board of Forensic Odontology; *HEPA,* high-efficiency particulate air; *SLR,* single-lens reflex.

Guidelines for Dental Identification

Although dental information can support the identification of a visually recognizable body, identification of dental remains is especially helpful when a decedent is skeletonized, decomposed, burned, or dismembered. Because each of these forensic situations presents different technical problems to the dentist, Body Identification Guidelines have been established by the American Board of Forensic Odontology (ABFO). The purpose of delineating these criteria is to assist dentists in comparing antemortem and postmortem dental information. Furthermore, the possibility of misidentification is reduced in both routine and mass-disaster cases.

Under the Body Identification Guidelines, provisions are made for the following:

- Examination of the postmortem dental remains in compliance with infection control and Occupational Safety and Health Administration (OSHA) requirements
- Examination of antemortem dental records
- Comparison of all dental and paradental information from the two databases
- Development of a written report listing conclusions and an opinion regarding the strength of the identification, for example positive, presumptive, insufficient, or exculpatory (Exculpatory evidence is favorable to the defendant in a criminal trial, clearing the defendant of guilt.)

Postmortem Examination

The postmortem dental evidence is gathered by photographic, radiographic, and charting techniques. All records should include the case number, date, demographic and anthropologic information, the name of the authority that is requesting the dental examination, the location of the examination, and the name of the examining dentist.

Photographs should be taken of full head and face views. Images of the occlusal planes of both dental arches and individual views of unusual pathologic or restorative findings are also obtained. A digital 35-mm single-lens reflex (DSLR) camera and appropriate electronic flash and lens systems for close-up photography should be used. Basic digital images should include color exposures which can also be converted to black and white images for analysis.

Jaw resection is no longer a commonly accepted method employed to facilitate access to the postmortem dentition. This change in practice has resulted from ethical and medico-legal challenges and concerns regarding its use. However, postmortem examination, dental impressions, and radiographs can be obtained by relieving the mandibular muscle attachments and those of the temporomandibular joint (TMJ). This procedure permits access to the oral structures by 180 degree reflection of the lower jaw. If requested by the coroner or ME, then the dental specimens from the autopsy may have to be retained and preserved in a 10% formalin solution.

The guidelines for body identification recognize that the dentist and dental auxiliary personnel involved in performing forensic dental procedures do so at the request and direction of a legal authority, such as a coroner or ME. Therefore, it is only with the permission of these individuals that techniques involving postmortem facial dissection or jaw resection are performed by the forensic dentist to achieve complete access to dental tissues.

These measures are used most often in decomposed, dismembered, or incinerated bodies to make postmortem dental charting and radiographic examination easier. Mandibular reflection or soft tissue dissection may be necessary in visually recognizable (viewable) bodies when the oral cavity is inaccessible because of rigor mortis. In this situation the procedure is performed from an inframandibular approach.

In those rare instances when the forensic dentist is authorized to remove the jaws this task is accomplished with a reciprocating (Stryker) saw or osteotome and mallet, causing a Le Fort I fracture of the maxilla. The dissection instruments are placed above the inferior nasal spine and malar processes to ensure that the apices of the maxillary teeth are not transected. Similarly, if the mandible is not removed by disarticulation, then cuts into the mandibular rami should be high enough to prevent damage to impacted third molars.

While obtaining postmortem radiographic evidence, the forensic dentist may encounter technical obstacles that need to be addressed. It often is difficult to place intraoral radiographic film or digital radiographic sensors securely against the mandible or maxilla of a deceased individual. A modified Rinn XCP self-supporting film holder, which does not require active participation from the examinee, has been developed for postmortem identification. Because all dental evidence may eventually be required to be relinquished in court, the use of double-pack intraoral radiographs permits the forensic dentist to retain a set of films. Digital radiographic exposure and storage of images precludes this problem.

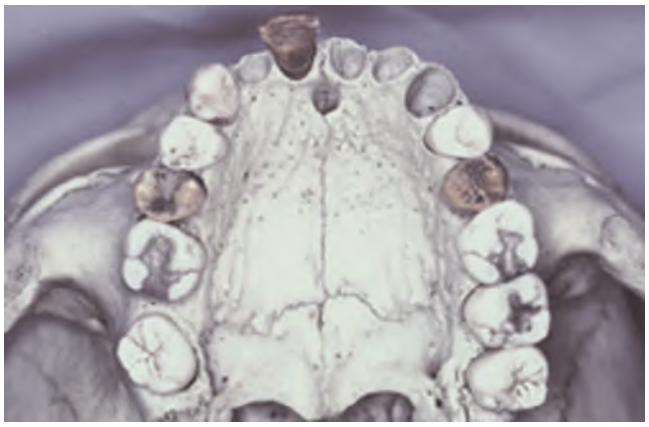
When the jaws cannot be resected postmortem changes in rigor mortis cases and in bodies that are partially decomposed may prevent the positioning of intraoral periapical radiographic films or digital sensors. Occlusal films, 5X7 lateral plates, and panoramic radiographs are often used in these situations. Additionally, charting of dental evidence in fourth-degree burn cases, in which charring of soft tissues results in contraction of the muscles of mastication, may preclude the placement of these devices. With the coroner or ME's permission, the entire skull can be removed from the rest of the remains and placed in a panoramic radiographic machine.

Fifth-degree burn cases result in cremation (sometimes referred to as **cremains**). Dental evidence may be lost or compromised in these cases as temperatures range between 870° C and 980° C (1600° F and 1800° F). Most cremated skeletal and dental remains are structurally recognizable, and it is only the processing of these structures in commercial crematoria that creates the ash most associated with this process. Cremated bones and teeth are fragile, crumble easily, and require extreme care when handled.

Fragmentation of dental structures in dismemberment cases and total loss of soft tissues in skeletonized remains necessitate alterations in routine radiation exposure settings. Generally, when radiographs of this type of material are taken, 10-mA and 65-kVp exposure settings are used. Because there is little or no soft tissue, standard exposure times or impulse settings are halved to prevent overexposure of the radiograph.

The maxilla can be split along the midsagittal suture, and each half can be placed horizontally on an occlusal film. This projection can be used to simulate antemortem panoramic radiographs or bite-wing views. Similar exposures can be obtained from the mandible by mounting the jaw on the edge of a table or bracket tray and placing an occlusal film under the supporting half. Exposures of the opposite side of the arch are made by simply flipping the mandible and repeating the procedure.

Databases have been created from elemental analysis or chemical characterization of various dental restorative and endodontic materials using scanning electron microscopic/energy-dispersive X-ray spectroscopy (SEM/EDS) and X-ray fluorescence (XRF) techniques. Referral to these resources may assist the forensic odontologist in the postmortem analysis of dental restorations when severe destruction of the dentition or cremation precludes the efficacy of using more traditional analytical methods.



• **Fig. 19-11** Postmortem tooth loss results in an alveolar socket with unfractured margins and no reossification. In this example, teeth Nos. 7, 9, 10, and 11 represent postmortem tooth loss. Tooth No. 2 is a result of antemortem loss. Teeth Nos. 4, 8, and 13 were found near the body and reinserted into their respective sockets.

The charting (odontogram) of the postmortem dentition should provide for situations in which teeth are missing after death. If such a discrepancy remains unexplained, then it may preclude the positive identification of the body. Scavenging animals or poor investigation of a crime or disaster scene can cause postmortem loss of teeth. Environmental conditions at or around the time of death, such as tidal action in a saltwater drowning, can also contribute to perimortem loss of teeth. When teeth are lost in this manner, the crest of the alveolar bone remains intact. In addition, there is no reossification of the socket (Fig. 19-11). This pattern is inconsistent with what is observed after extraction of a tooth.

Postmortem tooth loss is associated with decomposition of the periodontal ligament. Thus the tooth simply falls out when the body is moved by animals or during crime scene recovery efforts.

Antemortem Record Examination

Antemortem records are usually obtained directly from the police, coroner, or ME. Before accepting this evidence, the forensic dentist should determine that the records indicate the name of the person to be identified and the name and address of the submitting dentist. In addition, most jurisdictions require an evidence transfer document to be signed. This form indicates that the continuity of evidence has been maintained and specifies who is currently in possession of the material.

Several antemortem records of the same person may be submitted from different dental practices for comparison with postmortem dental evidence. It is not uncommon for the general dental records of a decedent and those obtained from the oral and maxillofacial surgeon, endodontist, orthodontist, and other dental specialty practices to be

forwarded for forensic analysis. Even if only one antemortem record is sent, the forensic dentist should re-chart all information obtained from the radiographs, progress notes, and odontograms on a standardized form or computer generated dental chart. This record should be identical to the one on which the postmortem information was documented. All of this material should be appropriately labeled as the antemortem record.

The use of computer software, such as the WinID3 program, in MFI situations accomplishes this same principle by entering all antemortem and postmortem dental information into the respective identification program. Besides making the comparison of records easier to manage, the creation of similar antemortem and postmortem analytic material is easier to present in court.

Comparison of Antemortem and Postmortem Records and Written Conclusions

After all dental information has been collected from the antemortem and postmortem data bases it is compared for similarities and discrepancies. Comparison of dental evidence is unique among the techniques used to identify a decedent. A positive identification may still be established, even when some reconcilable discrepancies are observed.

Various codes and symbols have been used to chart the antemortem and postmortem status of the jaws. Currently in the United States, the WinID3 and Unified Victim Identification System/UVIS Dental Identification Module (UVIS/UDIM) dental identification software programs are most commonly used to compare dental records of missing individuals to those of unknown human remains and have been used similarly in MFI situations. The odontogram charting codes employed in WinID3 are presented in Table 19-3.

TABLE 19-3 WinID3 Charting Codes

Primary Codes	Secondary Codes
M—Mesial	A—Annotation
O—Occlusal	B—Deciduous
D—Distal	C—Crown
F—Facial	E—Resin
L—Lingual	G—Gold
I—Incisal	H—Porcelain
U—Unerupted	N—Non-precious
V—Virgin	P—Pontic
X—Missing	R—Root canal
J—Missing crown	S—Silver amalgam
I—No data	T—Denture tooth
	Z—Temporary

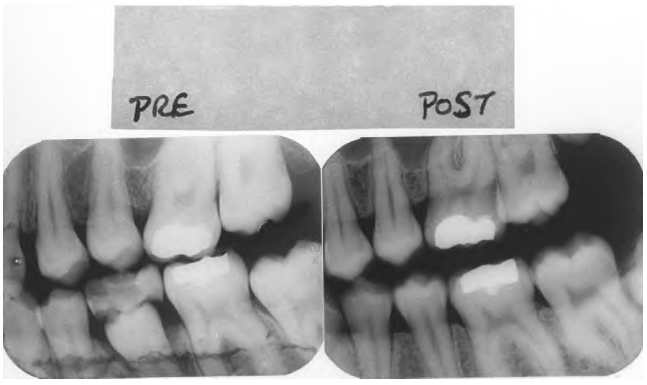
The UVIS/UDIM software and Plass Data DVI System International software have been employed by forensic odontologists in the office of the New York medical examiner and the International Organization (INTERPOL) National Central Bureau respectively. Although these computer programs can facilitate the process of comparison among the numerous antemortem and postmortem dental records presented in MFI or individual unknown/missing identification cases, the ultimate decision regarding the concordance of information between the antemortem and postmortem records rests with the forensic odontologist not the computer program.

Furthermore, the forensic dentist must routinely rely on the belief that antemortem records are truly those of the person they are purported to represent. The latter problem is best exemplified by the controversy associated with the antemortem dental records used to identify the bodies of Adolph Hitler and Eva Braun. Until recently, there was uncertainty concerning the reliability of those records. This uncertainty was based on the possibility that the records had been falsified to encourage the misidentification of Hitler and his wife.

The case demonstrated in Fig. 19-12 shows that all teeth, restorations, and anatomic structures are identical, except that deciduous tooth K is still present in the antemortem radiograph. Tooth No. 20 is erupted in the postmortem film. This difference could not support a positive identification if it were a component of fingerprint or DNA evidence. The facts that the deciduous tooth has exfoliated and the permanent tooth erupted before death are acceptable discrepancies in comparable dental evidence.

Comparison of dental evidence is often complicated by the quality of the evidence submitted. The physical status of the postmortem dental material can be compromised when teeth have fractured or are avulsed secondary to trauma. Often, only fragments of the jaws may be presented for comparison, and there may have been postmortem loss of teeth.

Dental restorations can be separated from the teeth or melted in a fire. Acrylic restorative material melts in



• **Fig. 19-12** Antemortem and postmortem radiographs demonstrating the fluid, changing nature of dental information.

temperatures less than 540° C (1000° F), gold and amalgam melt at 870° C (1600° F), and porcelain can withstand temperatures greater than 1100° C (2010° F). In addition, extreme temperature in a fire can cause the teeth to explode or appear shrunken. Although the principal role of the dentition of a fire victim is to provide data for identification, studies indicate that morphologic and microscopic tissue alterations of the teeth may assist forensic scientists, such as arson investigators, in determining temperature and duration of exposure to fire.

The problems associated with incomplete antemortem records are compounded when radiographs are of poor quality as a result of exposure and developing errors. Mischarted information in the antemortem record can also be considered a reconcilable discrepancy. This error often occurs when teeth have been extracted and adjoining teeth have moved into the position of the extraction site. Restorations may be inadvertently indicated on the wrong tooth when the clinician is charting or entering information into the progress record.

Regardless of the difficulties encountered when dental evidence is compared, the final conclusions must be based on an objective analysis of the data presented. The conclusions must be supportable and defensible when they are presented under oath in a court of law.

Dentistry's Role in Multiple (Mass) Fatality Incident Identification

The term *multiple (mass) fatality incident (MFI)* evokes images of a chaotic event, initiated by a destructive force, which results in numerous deaths necessitating identification. These mass disaster events resulting in MFIs can be classified in one of three ways:

1. Natural
2. Accidental
3. Criminal (e.g., serial homicide, mass suicide, and acts of terrorism)

Each type of MFI event results in the death of numerous victims. However, the problems faced by the forensic dental team responsible for identifying the decedents may vary, depending on the type of MFI encountered.

Natural Disasters

Natural MFIs include earthquakes, tornadoes, hurricanes, volcanic eruptions, fire storms, tsunamis, and floods. These may occur over relatively short periods or may be protracted over days or weeks. Victims may be scattered throughout broad areas, extending for miles. In addition, many victims in natural MFI situations may be unknowns who cannot be presumptively identified. Transients, homeless individuals, and tourists who are visiting an area involved in a natural MFI are often difficult to identify. Several countries or states can be affected, as in the 2004 Indian Ocean tsunami event.

In a natural disaster involving multiple fatalities, the principal problem for the dental identification team is that the environmental infrastructure is often compromised. For example, after Hurricane Katrina, medical and dental offices and hospital facilities containing antemortem records had been destroyed by tornadic activity and flooding. In addition, communication lines and roads were damaged, preventing the retrieval of most available antemortem records. All of these factors delayed or precluded the prompt identification of many victims.

Accidents

Accidental MFI events are most often associated with transportation accidents, fires, industrial and mining accidents, and military accidents. These situations usually occur over short time periods and are associated with defined populations (e.g., airplane, bus, or train passengers; mine or factory workers).

Airlines maintain passenger logs of individuals who are registered on specific flights. However, it has been estimated that at any given time as many as 10% of air travelers may purchase their tickets using an alias for identification. This occurred among the passengers of Malaysia Airlines Flight MH370 when it was determined that two of the victims of this accident were traveling with stolen passports.

The mining company, mill, or industrial plant can document those who have reported for work. In these examples, the victims of accidents should logically come from the defined population of employees on that shift. Therefore, antemortem records are first solicited from the families and health care providers of these individuals. Another source of medical and dental records in these cases is the occupational health files of workers, which are maintained by the employer.

Problems can be associated with the identification of victims of industrial and military accidents because these populations may be of similar age, sex, and ethnicity. Commonly, individuals working in industrial or military settings wear similar clothing. Thus military uniforms and protective industrial clothing decrease the potential use of personal recognition as an identification aid in these cases.

Criminal Disasters

Unlike natural and accidental MFIs, criminal situations resulting in multiple deaths may occur over extremely long time periods (years) and wide ranges of territory (e.g., different cities or states). This was the pattern of the rapes and murders committed by Ted Bundy, whose victims included young women residing in states from Washington to Florida from 1974 to 1978. The remains of the victims of serial killers can be hidden, as in the Green River homicides in the Pacific Northwest and the murders of young men committed by John Wayne Gacy in Chicago. Dismemberment and mutilation of victims is exemplified by the Jeffrey Dahmer case. Dental structures in these situations may not always be available for postmortem review.

Law enforcement agencies are often unaware of the victims of serial killers from other jurisdictions. Each agency may be investigating an individual homicide without recognizing a pattern of broader criminal involvement. Until

the development of the FBI-NCIC computer registry, coordinated efforts at identification were hampered.

The rise in national and international terrorism in the twenty-first century has changed the paradigm associated with the traditional participation of the dental profession in an MFI setting. Until recently, forensic odontologists and other dental professionals were simply tasked as experts in the identification of the decedents. Currently, there are ongoing efforts within organized dentistry to develop effective responses to acts of bioterrorism. These efforts are exemplified by the profession's encouragement of legislation authorizing dental professionals, in federally declared emergencies, to perform various procedures that are routinely not within the practice of the profession. Under these provisions, dentists registered and trained in emerging medical diseases, bioterrorism, and emergency medical care would be indemnified for actions taken in the performance of these services.

Acts of terrorism may include exposure to biologic agents, chemical toxins, and the discharge of nuclear devices. Thus the dentist involved in MFI recovery and identification after an act of terrorism may additionally be required to assist medical workers in providing care for the injured. In these scenarios, dentists must consider their personal safety and that of their families. Civil defense and emergency preparedness organizational plans are beginning to include dentists among those charged with triaging the injured. Additional roles for the dental professional in future acts of bioterrorism and nuclear or chemical attack include providing first aid care and immunizations to injured and exposed survivors.

Responsibilities

In the United States, the National Response Plan (NRP) provides a comprehensive, risk-based, emergency management plan to respond to any hazardous event. The NRP establishes guidelines to manage domestic response to radiological, technical, natural, or terrorist incidents by developing twelve emergency services functions and delineating the agencies charged with performing specific tasks in a response.

As part of the presidential directive that created the US Department of Homeland Security after the September 11, 2001, terrorist attacks, the National Incident Management System (NIMS) was also developed. The overall objective of this system is coordination of governmental agencies, nongovernmental organizations, and the private sector in the resolution of nationally significant incidents.

Regardless of the type of MFI, the local coroner or ME is ultimately responsible for performing the autopsies and identifying the victims. In accidents that involve modes of public transportation, the National Transportation Safety Board (NTSB) is empowered to investigate and determine the cause of the crash. Other agencies with jurisdiction at a disaster scene may represent local police, public safety, and funeral home personnel. In addition, there may be representatives of the Federal Emergency Management Agency (FEMA), members of the FBI fingerprint team, representatives of the United States Department of Health and Human Services (DHHS) National Disaster Medical System (NDMS) division personnel mobilized with a federal Disaster Mortuary Operational Response Team (DMORT) or Disaster Medical Assistance Team (DMAT), the clergy, and community volunteer organizations.

Although DMORT and DMAT units include dental personnel, these teams may not be mobilized in all MFIs. In these situations, forensic dentists and support staff responsible for identification or care of the injured should also be organized into teams. Several state dental associations (including California, Washington, Michigan, New York, South Carolina, Nevada, and Iowa) have developed, supplied, and trained such groups in preparation for emergencies requiring their expertise. Training sessions include mock MFI exercises. These drills can prepare the dental team members for dealing with the technical problems of cases involving multiple fatalities.

In addition, training sessions can be used to counsel the dental team and to inform members of the posttraumatic stress often associated with this type of forensic work. This delayed stress is a result of the sensory and psychological insults encountered by the dentist, hygienist, or dental assistant who is dealing with human death on a large scale.

During an MFI the NDMS, under its emergency support functions, is authorized and has responsibility to assist local authorities by establishing temporary morgue facilities; identifying victims using scientific techniques; and processing, preparing, and disposing of victims' remains to families, funeral homes, or proper legal representatives. This mission has been accomplished through the development of ten regional DMORTs administered by the DHHS. Each DMORT is composed of funeral directors, MEs, coroners, pathologists, forensic anthropologists, medical records technicians and transcribers, fingerprint specialists, forensic dentists, dental hygienists, dental assistants, radiology technicians, mental health specialists, computer professionals, administrative support staff, and security and investigative personnel.

These individuals are private citizens, each with a specific field of expertise, who are mobilized during a disaster. The licensure and certification of the DMORT members is recognized by all states because they are considered temporary federal employees during the emergency response.

Working with the authorization of the coroner or ME, a local dental disaster team or dental component of a DMORT is responsible for antemortem record assembly and interpretation, postmortem physical and dental radiographic examination, and final comparison of dental information. These are the same principles used to establish an individual identification. Yet, when numerous victims need to be identified in a short time, problems of identification are compounded exponentially.

No remains have been found for one-third of the 3000 victims who died in the World Trade Center terrorist attack in 2001. Less than 300 victims were found intact although

tens of thousands of fragmentary human remains and personal effects have been recovered and processed through the Staten Island landfill that has been used as a temporary sorting facility. Many of these remains have yet to be linked to a victim.

Dividing the team into subsections responsible for each of the three identification domains (antemortem, postmortem, and record comparison) permits a division of labor among the team members. This division reduces errors in identification, in that specific tasks in the identification process are assigned to separate subsections. A chain of command should be established, and the team leader of each shift should be directly responsible to the coroner or ME. This person is the only member of the team authorized to release the results of the dental identification process to appropriate investigative agencies.

Technologic Aids in Multiple Fatality Incident Analysis

Advances in photographic, radiographic, and computer technology have provided the forensic dental team with additional resources to enable recovery, documentation, storage, and comparison of forensic dental evidence in MFIs, as well as in other situations requiring forensic dental expertise (e.g., bite mark analysis and documentation of human abuse). Among these advances are developments in the following:

- **Digital photography.** The basic digital camera used for forensic evidence documentation should include a through-the-lens (TTL), light-metering, SLR, 35-mm digital camera body with interchangeable lenses or an adjustable lens capable of normal range (30 to 50 mm) to macro range (90 to 100 mm) focal length. A removable flash memory card with adequate storage capacity is also required. The Scientific Working Group on Imaging Technology (SWGIT) imaging guidelines provide the forensic odontologist with information regarding the limitations and parameters imposed by the judicial system regarding the manipulation and presentation of digital photographic evidence.
- **Digital radiography (DR) equipment.** Electronically generated and stored radiographic imaging can be accomplished by the following:
  - Scanning normally processed radiographic film into a computer
  - Using a phosphor substrate shaped and used like radiographic film to expose and scan radiographic information into the computer by a special proprietary device
  - Using a sensor sized and shaped like a radiographic film that is made of a scintillation screen and a charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS)
- **Direct digital radiography (DDR).** When energized by radiation, this device creates a direct image on the pixels of its CCD or CMOS. This radiographic image is then sent to a computer through wire or wireless technology. Thus because of its ability to save time, DDR technology is recommended for clinical and forensic casework. Additionally, DDR procedures reduce exposure times by requiring 90% less radiation than that required to expose a standard type D film radiograph and 50% less radiation than that required in exposure of type E film radiographs. The parameters by which the quality of a radiograph is evaluated include resolution and contrast sensitivity. Image resolution describes the detail an image holds. In film-based radiographs, this is expressed as a function of how close lines can be to each other and still be visibly distinguished. Digital imaging measures resolution as pixel counts. The contrast sensitivity is a measure of the smallest percentage change in an object's base thickness (density) that can be detected in a radiograph. The high resolution of the image produced by the DDR sensor is one of its most advantageous properties.
- **Cone-beam computed tomography (CBCT).** CBCT provides a 3D imaging modality to collect a complete maxillo-mandibular-facial anatomic volume of data. Computer software can be used to analyze the obtained image, and the diagnostic interpretation provided can be used for treatment planning, assessment of pathologic conditions, and evaluation of dental implants. Application of CBCT in forensic dental situations can overcome intraoral access problems with some specimens (e.g., fourth-degree burn cases).
- **Portable hand-held x-ray generation devices (e.g., Nomad manufactured by Aribex, and MinXray HF70DUL Type A).** The forensic dentist is able to expose film or digital radiographs quickly and effortlessly with a battery-powered unit that can be carried to the body on the gurney in the morgue. Additional applications for the use of these devices in the dental office include exposure of radiographs on pediatric or sedated patients or those having endodontic therapy.
- **X-ray fluorescence (XRF) methodology.** As discussed previously, analysis of dental materials in cremation and other difficult forensic identification cases may be facilitated by analysis of specimens with this technology.
- **Computer software technology.** The advent of computer software has assisted MFI dental identification teams in filing, storing, sorting, and matching bits of antemortem and postmortem information. Computer assistance has proved beneficial in disasters involving hundreds of victims. Commonly used programs include the following:
  - The FBI-NCIC program, based on the California Dental Identification System, developed by Dr. Norman Sperber and Dr. Robert Siegel (San Diego, CA)
  - CAPMI-4 (Computer-Assisted Postmortem identification—version 4.0), developed by Dr. Lewis Lorton of the US Army Institute of Dental Research (It was first used in 1985 in support of the Arrow Air-US military charter aviation runway accident in Gander, Newfoundland.)

- WinID3 dental comparison software, developed by Dr. James McGivney (St Louis, MO) (Bridged with the Dexis DR program, WinID3 facilitated comparison of antemortem and postmortem dental records in Hurricane Katrina recovery efforts and various transportation and industrial MFI events.)
- UDIM (UVIS Dental Identification Module), the dental recording/search component of the UVIS system, developed by Dr. Kenneth Aschheim (New York, NY)

Each of these computer software systems is user friendly, can be run on readily available and accessible hardware, is automated and capable of networking, and relies on objective data entry and storage of antemortem and postmortem dental records, digital radiographs, and digital images. The use of these computer software programs in MFI situations reduces the time and effort that had to be expended in past events. Before their use, an examiner in the dental identification team walked along tables with a postmortem record comparing the dental data and radiographs at each station containing an antemortem record.

Despite the fact that these technologic advances have facilitated forensic casework, the caveat for the forensic dentist remains that identification is the result of human thought processes and not the highly technical supportive procedures that provide the material being evaluated. To arrive at correct comparative conclusions based on the evidence, individual dental team members must evaluate the computer-generated matches for definitive identification.

◆ BITE PATTERN EVIDENCE

Basic Principles

A bite mark is a patterned injury or surface disturbance produced by teeth on the skin of an individual or inanimate object. Historically, analysis of this type of evidence presumes that the dentition of the biter (animal or human) is unique and can be compared scientifically and related to the resultant patterned mark on the surface of a victim or object. Although initial studies indicate the uniqueness of the human dentition, the debate among forensic odontologists and those in the legal profession relates to the ability of these "unique" features to be transferred into skin, which is acknowledged as a poor impression material.

Because it is reasonable to consider the teeth as cutting or mashing tools, the basis for accepting bite pattern evidence can be supported on the same scientific principles used to evaluate tool marks. However, it is now believed that although individual human dentitions may have distinctive features, the patterned marks left by the teeth may not be unique for each person as once thought. Variations in tooth size, wear, fractures, and position in the dental arch, diastemata, and restored surfaces contribute to the principle of distinctiveness within an individual dentition, but not uniqueness among human dentitions.

Thus, issues related to the validity, reliability, and admissibility of bite mark evidence continue to rest with the judicial system and its various rules pertaining to the introduction of scientific evidence in court. Significant legal appeals have resulted in bite mark evidence being overturned in several jurisdictions and because of this evidence those incarcerated have been released. Based on these legal decisions and a 2009 report from the National Academy of Sciences critical of this use of bite mark evidence, it has become the most controversial component of the forensic dental discipline. This has resulted in the current philosophy regarding the significance of bite mark evidence resting in its *exclusionary* rather than *inclusionary* power when comparing the dentition of a putative suspect to a bite mark on an inanimate object or bite mark patterned injury (BMPI) in most cases.

Victims of mammalian animal bites account for most bite injuries reported annually. Bite-related injuries represent approximately 1% of all hospital emergency visits that require medical attention. Of these, nearly 370,000 were associated with dog bites in 2001. The second and third most likely mammalian biters are cats and humans, respectively. Each represents from 5% to 20% of cases reporting to urban emergency rooms.

As the habitats of wild animals in North America continue to recede, humans are more likely to come in contact with these dangerous carnivores. This is reflected in the increase in attacks on humans by mountain lions and brown, black, and grizzly bears, resulting in biting injuries or death from biting and clawing.

Animal bites may be observed postmortem when a body has not been buried or discovered quickly. Commonly, insect bites are made by ants and roaches, which leave patterned injuries that can be mistakenly interpreted as antemortem human BMPIs or trauma (Fig. 19-13). Postmortem bites from rats and scavenging feral dogs and cats are often avulsive and of narrower or smaller diameter than human bites.

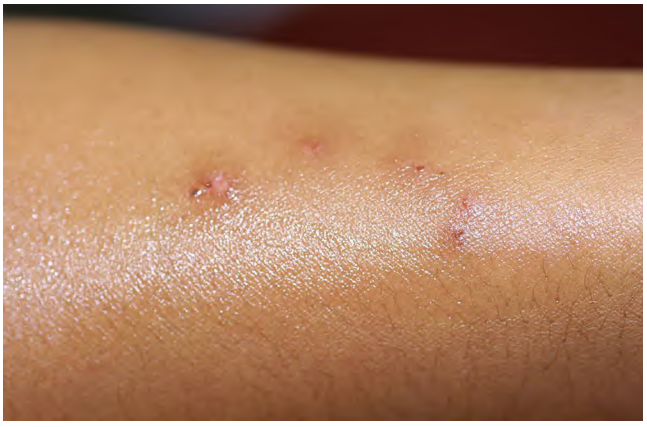


Fig. 19-13 Insect bites on the skin that mimic the pattern injury associated with bite mark trauma. In a decedent, this pattern may additionally be mistakenly interpreted as antemortem trauma. (Courtesy of Dr. David K. Ord.)

Injuries caused by human bites are routinely related to either aggressive or sexual behavior. Ironically, it is not uncommon for the perpetrator of an aggressive act to be bitten by the victim (as a means of self-defense). In children, biting is a form of expression that occurs when verbal communication fails. Biting injuries in children can result from playground altercations or sports competition. They are common among children who attend day care centers.

Self-inflicted bites are observed in **Lesch-Nyhan syndrome.** This syndrome is an X-linked, recessively transmitted disease manifesting insensitivity to pain and self-mutilation (among other signs) by chewing away the lips. This disease is rare, and self-inflicted bites are more commonly seen in adults and children who are victims of physical abuse or sexual assault. These individuals may bite their own forearms or hands in anguish or to prevent themselves from crying out while they are being traumatized.

Injuries resulting from animal or human bites may become septic or may progress to systemic infections. Secondary bacterial infections are more commonly associated with human bites than with animal bites, although 80% of domestic cat bites become infected because bacteria are injected into the deep puncture wounds inflicted by their needlelike, carnassial teeth. Infectious complications include tetanus, tuberculosis, syphilis, actinomycosis, cat-scratch disease (caused by *Bartonella henselae*), and those infectious complications related to streptococcal and staphylococcal organisms. Anaerobic organisms associated with bite injuries may eventually result in complications, such as osteomyelitis, septic arthritis, tenosynovitis, meningitis, and infections of the lymphatic system.

Viral complications, including hepatitis B virus, herpes simplex, and cytomegalovirus, have resulted from transmission through human bites. The human immunodeficiency virus (HIV) can also potentially be transmitted through the exchange of blood and saliva in a bite injury. The risk of seroconversion from this mode of HIV transmission, however, is believed to be extremely low. An immunocompromised individual who is already infected with the HIV virus is at increased risk of secondary infection when bitten by a cat.

Rabies is the most serious infectious complication that results from mammalian animal bites. It is often necessary to identify the specific offending animal for rabies control or potential litigation. This identification is not routinely done by matching the animal's teeth to the pattern injury. When humans bite, however, the marks left in injured tissue or inanimate objects are often analyzed and compared with the alleged perpetrator's dentition.

Historical and Legal Issues

References to biting during acts of passion or aggression can be found in the *Bible, Kama Sutra,* and Old English law. In colonial America, the Reverend George Burroughs was charged with the crime of biting one of the women accused of witchcraft during the Salem, Massachusetts, witch hunt incidents in 1692. He was hanged for this offense. Bite mark evidence was provided in expert dental testimony in the 1870 Ohio trial of Ansil L. Robinson, who was accused of murdering his mistress. Although the defendant was eventually acquitted, the expert dental presentation by Dr. Jonathan Taft became a benchmark for future experts in the discipline.

The concept of accepting evidence related to the analysis of patterns created by the dentition was first accepted by the appellate level courts of the United States justice system in 1954. At that time, *Doyle vs. State of Texas* became the first modern case in which a criminal conviction was based on evidence relating a suspect's dentition to pattern marks in an inanimate object (a piece of cheese). Because of the *Doyle* case, more than 260 decisions involving bite mark evidence have been entered into the case law records of the appellate courts of the United States.

The legal community has recognized tool mark and fingerprint pattern analysis as scientifically acceptable forensic disciplines for some time. The evidence presented by experts in these areas has been accepted in 20% of state courts under the *Frye* standard *(Frye vs. United States),* and the remaining 80% of state courts and all federal courts under the Federal Rules of Evidence 702-705. These are special rules dealing with the admissibility of scientific evidence in the American judicial system. Thus they are also applicable to bite mark information.

The *Frye* test had been the standard for scientific admissibility in most state and federal courts since 1923. The three components of scientific evidence admissibility that are considered under the *Frye* test include the following:

1. The scientific principle must be recognizable.
2. The scientific principle must be sufficiently established.
3. The scientific principle must have gained general acceptance within the scientific discipline to which it belongs.

Among the three requirements, only the concept of "general acceptance" must be met to satisfy the *Frye* test of admissibility.

In 1993, the US Supreme Court ruled on the admissibility of scientific evidence in *Daubert vs. Merrell Dow Pharmaceuticals.* It was the Court's decision in this case that the general acceptance aspect of the *Frye* test should no longer be the sole, determining factor used in considering admissibility of scientific evidence. Essentially, the Court replaced this principle with one that stresses scientific validity. This decision removes the responsibility of determining sound scientific evidence from the scientific community in which it has gained general acceptance.

Instead, the *Daubert* ruling gives great latitude to the trial judge in considering the admissibility of scientific evidence. Trial judges often have limited knowledge of scientific methodology; however, under *Daubert* they are required to determine if the weight and admissibility of expert testimony is not only scientifically valid but also relevant and germane to the issues in individual cases. Thus the results of the Supreme Court's decision in *Daubert* are to make the

judge a "gatekeeper" and the expert witness a provider of scientifically valid evidence.

The general acceptance concept is no longer the sole determinant of admissibility in *Daubert.* It becomes one of several factors that must be met for scientific evidence to be admissible. These factors include the following:

- Techniques used must be testable and tested.
- Peer review and publication of results are not required but may persuade the judge in admitting evidence.
- Standards should be established for evaluation of the scientific methods and error rates associated with the techniques used.
- Consideration is given to acceptance of scientific principles that have gained general acceptance within the scientific discipline to which they belong.

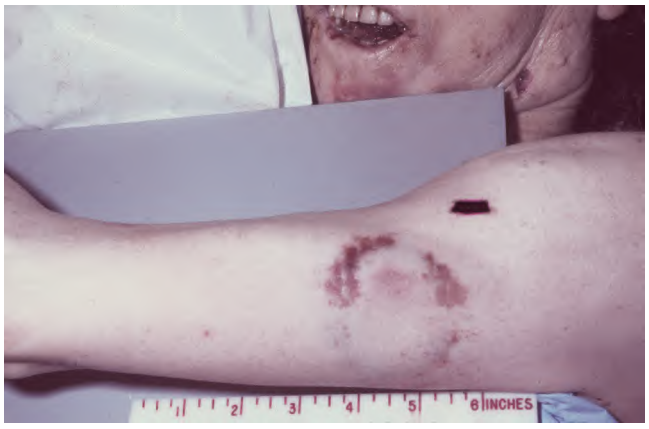
Bite mark evidence is currently admissible under the *Frye* standard and Federal Rules of Evidence as determined by the *Daubert* decision. Although some legal experts believe the Federal Rules of Evidence provide better guidelines for admissibility decisions, challenges to the scientific basis of bite mark evidence may be averted under either set of standards as this evidence is used more routinely to exclude rather than include a suspect.

Characteristics of Bite Marks

To evaluate a patterned mark, its characteristics must be recognizable and distinguishable. Reasonably, the mark should be consistent with the face of the instrument from which it was generated. Specific teeth can create representative patterns that are recognizable. These are described as individual characteristics of the entire bite mark. Human incisors make rectangular marks. Depending on the amount of attrition observed on the incisal edges of cuspids, these surfaces may be associated with point or triangular patterns. Unlike mandibular bicuspid teeth, which have a diminutive lingual cusp, maxillary bicuspids often mark in a pattern that resembles a "figure eight."

Class characteristics of a human bite mark are related to the shapes that are created when groups of teeth from both dental arches are impressed into a bitten surface. Semicircular, ovoid, or elliptical patterns are usually observed, but variations may be associated with tapered, square, and U-shaped arches. Typically, bite marks are composed of two arc-shaped areas corresponding to the maxillary and mandibular arches and their respective teeth. When only one arch contacts a surface, a crescent pattern may be formed. The greatest dimensions of an adult human bite mark do not usually exceed 4 cm (Fig. 19-14).

Individual and class characteristics of bite patterns are generated by groups of specific teeth. The dynamics of occlusion and muscle function must also be accounted for when variations in individual and class characteristics of a bite mark are considered. Such variations can be caused by malocclusion, individual tooth mobility associated with periodontal disease, and movement of facial muscles during biting. Class II malocclusion can cause the palatal surfaces of the maxillary anterior teeth, rather than their incisal edges, to contact the material being bitten. Shield-like imprints of the palatal surfaces are generated in the bite mark rather than the rectangular patterns routinely associated with these teeth.



• **Fig. 19-14** A bite mark pattern demonstrating the individual and class characteristics associated with impressions made by the human dentition. An ecchymotic area in the center of the ovoid pattern is observed, which is not always related to the sucking action of a sexual bite. Therefore, this finding should not be over-interpreted to imply sexual intent on the part of the biter. The impressions made by the teeth of the mandibular arch are more delicate.

Aberrant muscle forces associated with tongue thrusting can alter the way the teeth contact a bitten surface. Temporomandibular joint dysfunction can also contribute to variations in bite patterns. It can be associated with midline shifts or inability to achieve maximum opening while biting. Periodontal disease may result in individual tooth mobility, which could affect the bite mark pattern.

When bitten, many inanimate objects tend to act like dental-impression material, retaining the marks of the teeth. Such cases have involved bite marks in foods, chewing gum, paper toweling, and a roll of masking tape. Unlike inanimate material, the skin is a dynamic tissue that can change after it is injured. Swelling, caused by the acute inflammatory response of the tissue, can distort and affect the interpretation of the pattern. Bleeding into the area of a bite mark can mask the pattern.

The age of an injury is the time elapsed from its infliction to the analysis of the damaged tissue. Reliable determination of the age of antemortem skin injuries requires histopathologic and histochemical analysis to relate the injury to the time of the alleged incident (Table 19-4). Color changes in the bitten tissue, associated with the degradation of hemoglobin from lysed RBCs, can be used only to broadly estimate the time of occurrence and qualify the age of a bruise as recent or old. Environmental factors, including seasonal temperature, location of the body, and presence or absence of clothing, may additionally act as important variables requiring consideration when attempting to determine the age of injury patterns.

Contusions and areas of ecchymosis are not unusual in bite marks made in living tissue. The absence of bleeding

TABLE 19-4 Histopathologic and Clinical Changes Used to Monitor the Time Elapsed (Aging) in Skin Injuries Associated with Bite Marks

Time	Predominant Cellular Infiltrate and Deposits	Healing	Variable Clinical Color
Hours			
4-8	Polymorphonuclear leukocytes with a peripheral front		Red-blue-purple
12	Polymorphonuclear leukocytes		
16-24	Macrophages peak		Blue-black
24-36	Polymorphonuclear leukocytes peak	Peripheral fibroblasts	
Days			
1-3	Central necrosis		
3+	Hemosiderin		Green-blue
4		Collagen fibers	
4-5		Capillary growth	Brown-yellow-green
6		Lymphocytes peak at periphery	
10-14		Granulation tissue	Tan-yellow

into the injury may imply that it was inflicted after death. Additional postmortem soft tissue changes that can affect the quality of a bite pattern injury and its eventual weight as evidence include artifacts created by lividity (caused by the settling of blood pigments in dependent body areas), decomposition, and embalming.

Bite marks from sexual attacks are commonly found on the neck, breasts, arms, buttocks, genitalia, and thighs. Axillary bites and bite patterns on the back, shoulder, penis, and scrotum are often associated with homosexual activity. Abused children may be bitten in areas of the face, particularly the cheek, ear, and nose. Assailants also can be bitten. The analysis of these bite pattern injuries is just as incriminating as those found on the victim of a violent act.

A review of 778 bite mark injuries concerning the anatomic locations most often bitten, victim and biter demographics, the type of crimes in which biting occurred, and legal disposition of cases revealed the following information:

- Females were bitten more often than males.
- Perpetrators were male more often than female.
- The most common sites bitten were the arms. Bites in these locations occurred more commonly among males.
- Females were bitten on the breast more often than males. This location accounted for the second most commonly bitten area of the body.
- The type of crime and the age of the victim were related to patterns in location, distribution, and number of bites.

Guidelines for Bite Mark Analysis

In 1984, the American Board of Forensic Odontology (ABFO) established Guidelines for Bite Mark Analysis. Additional workshops of the Board have provided further insight into the techniques available to recover, store, analyze and evaluate bite mark evidence based on the Guidelines. The development of the Guidelines also created a scientific approach to the description of the bite mark, collection of evidence from suspect and victim, and subsequent analysis of the evidence.

The Guidelines do not mandate specific analytic methods for comparison. Through their careful use, however, the quality of the investigation and conclusions based on bite mark evidence follow customary procedures. Thus with these guidelines, it should be possible to determine the weight of bite mark evidence required to establish the validity of bite mark comparison. According to the current Guidelines, *bite mark, suggestive of a bite mark,* and *not a bite mark* are the terms used to indicate the confidence level of the odontologist that a patterned mark represents a bite mark.

Description of the Bite Mark

Demographic information (i.e., age, race, sex, and name of the victim; examination date; referring agency; case number) is obtained in cases involving both living and deceased victims. The names of the forensic dental examiner and referring agency contact person should also be included.

The location of the bite is then described. Attention is directed to the anatomic location, surface contour, and tissue characteristics of the bitten area. Underlying structures, such as bone or fat, may influence the analytic quality of the pattern injury. Relative skin mobility is also evaluated.

The shape, color, size, and type of injury are recorded. Metric measurements of the horizontal and vertical dimensions of the bite mark are determined. Irregularities and variations from the standard semicircular, ovoid, and crescent shapes associated with human bite marks are noted. Injury types include abrasion, laceration, ecchymotic and petechial hemorrhage, incision, and avulsion. Artifactual injuries, such as proximate stab and bullet wounds, should be recorded because these may distort the pattern by separating anatomic cleavage lines of the skin **(Langer lines)**.

Evidence Collection

Examination of the Victim and the Suspect

Both the victim and the suspect are examined, and evidence from each is gathered for comparative study and evaluation. Collection of evidence must be performed in a manner that protects the rights of the person who is providing the evidence and that permits the eventual acceptance of the evidence in court. Therefore, to ensure objective analysis, it is recommended that dental impressions, photographs, and demographic information obtained from the putative suspected biter be collected by a dentist other than the odontologist making the comparison.

A standard health history and informed consent are obtained before any evidence recovery procedure regarding the suspect is performed. An intraoral and extraoral examination of the suspect is completed, which includes dental charting, soft tissue and tongue evaluation, and probing of the periodontium. Therefore, knowledge of the medical history of the suspect relative to systemic problems associated with cardiovascular disease, allergy, seizure disorder, diabetes, and respiratory disease or requirements for antibiotic prophylaxis has medicolegal importance in forensic casework, as well as in traditional patient evaluation.

A search warrant, court order, or legal consent may be required before evidence is collected from a suspect. A specific list of the dental-related evidence desired should be recorded in the legal document. This list usually includes facial and oral photographs, impressions of the teeth, occlusal registrations and bite exemplars, and saliva samples. These documents protect the rights of the suspect against unreasonable search and seizure and provide for due process, as guaranteed by the Fourth and Fourteenth Amendments, respectively, to the US Constitution.

Bite marks are considered similar to such physical evidence as fingerprints, hair, blood, and semen samples, as well as to sobriety tests. Therefore, this material is not protected under provisions of the Fifth Amendment, which deals with self-incrimination.

Evidence collection from the victim entails non-invasive and invasive techniques. The former include photography, saliva trace evidence collection, fabrication of study casts of the bite mark, and stereolithography (SLA) to create 3D models of the BMPI. The latter may involve tissue incision, excision, and preservation of a BMPI in a decedent. Preservation of this tissue permits analysis of the injury by transillumination and observation of the area from the side opposite the light source.

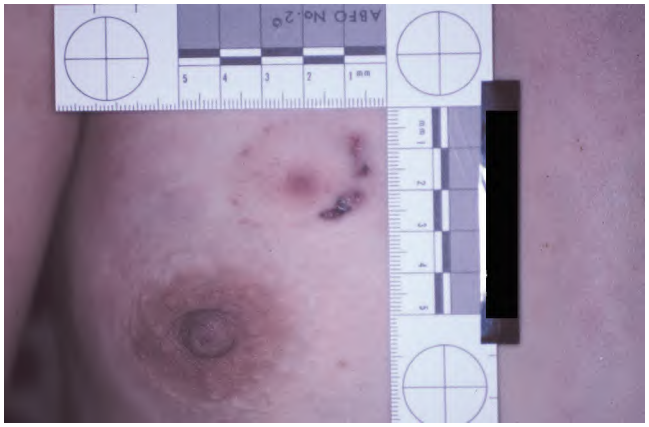
Photography

Because evidence associated with bite marks, human abuse, and sexual and physical assault is transitory, there is an immediacy associated with the collection of physical evidence in these cases. Initial photographs of the pattern mark should be taken before any investigative procedures that may alter the pristine bite mark evidence (e.g., touching, removing, impressing, swabbing, and cleansing).

Ideally, standard visible-light photographic techniques include the use of a 35-mm DSLR camera with a flat-field macro lens and dedicated electronic flash. Numerous images using different camera and lighting positions, exposure settings, and color and black-and-white exposures should be obtained. Additional legal considerations and protocols related to the documentation of image enhancement, restoration, compression, and analysis have been established for digital bite mark images.

Orientation positions and close-up views with a reference scale are required. A reference scale permits the bite mark images to be measured and prepared as life-size (i.e., 1:1) representations of the pattern injury. Ultimately, these images can then be compared with casts and other exemplars obtained from the suspect. The scale should be stabilized and positioned next to, and in the same plane as, the bite mark to eliminate potential distortion artifacts in the resultant images. It should never be hand-held. The scale should be omitted from at least one image to document that no marks or other injuries have been intentionally hidden by it.

The ABFO No. 2 photomacrographic reference scale (Lightning Powder Company, Inc.; Salem, OR) was developed by the ABFO for use in bite mark photography (Fig. 19-15). This standardized, L-shaped, accurate scale has



• **Fig. 19-15** The American Board of Forensic Odontology (ABFO) No. 2 Reference Scale.

become the gold standard in bite mark photographic analysis. Variations of it have eventually come to be used in all varieties of forensic casework requiring accurate measurement of evidence at crime scenes or in the laboratory.

This non-flexible instrument contains two metric scales, an 18% color gray scale, three circular symbols, and rectifying grids. Each of these components is used to account for photographic distortions, which can negate the value of the photographic evidence. Techniques using Adobe Photoshop and Mideo Systems CASEWORKSeis computer software have been used to rectify distortions observed in the ABFO No. 2 reference scale and ultimately to eliminate these from a bite mark image being analyzed.

With living victims, serial pictures of the BMPI are taken over several days. This series provides documentation of the color changes associated with healing of the wound. In addition, special advanced photographic techniques, using nonvisible energy sources at the extremes of the electromagnetic spectrum and fluorescent alternative light sources, can be used to identify latent images of the teeth that may remain after the bite mark has clinically disappeared. These techniques require special films and illumination sources, bracketing of aperture (f-stop) openings, variations in shutter speeds, and/or lens filters to work within the desired wavelengths and include the following (Table 19-5):

- **Reflective ultraviolet (UV) photography.** This technique enhances the bite mark image by selectively identifying photoactive **chromophores,** such as melanin and hemoglobin pigment in the superficial layers of the injured tissue. Variations in the amount of these natural light–absorbing organic pigments in the traumatized tissue are observable in images exposed with this energy source. This is based on the fluorescence created when the skin is exposed to UV light in the 200- to 400-nm wavelength range. Although there may be focusing problems associated with UV photography and exposures *must* be made with a tripod-mounted camera, the fact that this technique may permit recovery of latent evidence, even months after all clinical signs of a bite mark injury have disappeared, makes the effort worthwhile.
- **Infrared (IR) photography.** Tungsten lamps and quartz-halogen lamps are good sources of IR radiation when attempting to expose IR images from unfiltered light sources. To expose images specifically within the IR wavelengths of 750 to 1000 nm, a filter must be placed in front of the lens to absorb visible light. The Kodak 87 gel filter accomplishes this task by limiting all transmittance of light except at the designated wavelengths. Additionally, IR photography requires that the camera lens be refocused (focus shift) after initial focusing under visible light and before exposure of the image. Like alternate light source photography, the focal plane for IR photography lies below the skin surface. The deeper focal depth permits visualization of faded tattoos and wound damage within a blood stain. This technique is not the best for identifying individual characteristics in bite mark injuries.

TABLE 19-5 Comparison of Photographic Electromagnetic Energy Spectrum Sources and Their Forensic Imaging Capabilities

	Visible Light	Ultraviolet Light	Infrared Light	Alternate Light Imaging Fluorescence
Light wavelength	400-700 nm	200-400 nm	700-1000 nm	450 nm
Filter	None	Kodak Wratten Filter No. 18A gel (visibly opaque glass filter)	Kodak Gel 87	Kodak Gel 15
Target Pigment or Material				
Hemoglobin in pattern injuries and vessels	+	+	+	+
Melanin	+	+		+
Tattoos	+	+	+	+
Ink variations in document forgeries			+	+
Gunshot residues			+	+
Latent fingerprints				+
Serologic fluids (saliva, semen, and blood)				+
Residual fibers				+

- **Alternate light source (alternate light imaging [ALI]) photography.** This technique is also referred to as *fluorescent photography.* It is advantageous in assisting investigators to locate and document evidence involving the presence of ink residues, fingerprint patterns, and the chromophores previously indicated. ALI enhances visualization of pigments derived from chromophores that may be found within evidence involving latent serologic fluids and subdermal bruises or pattern injuries of victims of violent or sexual crimes. ALI techniques illuminate deeper tissue targets by using a predominantly monochromatic band of light between the wavelengths of 430 and 460 nm. To accomplish the visualization of the weak fluorescent glow from the desired pigments, ALI photography must be performed by eliminating all other sources of light from striking the imaging surface (film or digital sensor). This requires that ALI techniques be performed in total darkness with yellow filters, such as the Kodak gelatin No. 15. Because longer exposure times are also required, images exposed using ALI *must* be made with a tripod-mounted camera.

As previously stated, photographs of the suspect should involve the same attention to technical quality control. Extraoral, intraoral, and occlusal photographs are taken. Additional images of wax or acrylic test bites and measurements of maximum interincisal opening are also recorded.

Saliva Evidence

Although the forensic dentist is concerned principally with the analysis of the physical evidence associated with a bite mark, biologic evidence in the form of serologic and DNA material is also of probative importance. Collection of saliva trace evidence from the surface of the bite injury of the victim is performed before other evidence-gathering manipulation of the injury. There is an increase in the yield of recovered DNA for analysis when this procedure is carried out according to the two-swab protocol described previously.

Using this technique, a saliva sample is collected by first rubbing the bitten area with a cotton swab that has been moistened in sterile, distilled water. The swab should contain no preservatives. The bite mark is subsequently rolled with a second, dry, cotton swab. Both samples can be considered a single exhibit because they have been collected from the center of the pattern injury. They are placed in an evidence box and permitted to air-dry before submission to the laboratory. No control swabs are required from adjacent areas of the victim's skin.

DNA from the victim of a BMPI should be obtained from whole blood samples or buccal swabs. Additionally, autopsy tissue samples can be obtained from decedent victims. All samples can be used for DNA comparison with bodily fluid or tissue samples obtained from the suspect.

Because a victim may be bitten through the clothing, areas of garments that approximate a BMPI should also be retained and evaluated for saliva. Many victims of sexual abuse wash the area of a bite mark before reporting for treatment. This is unfortunate because biologic evidence associated with DNA recovery can be lost. In this regard, emergency room personnel should be trained to recognize potential BMPIs and be instructed not to wash or disinfect these areas until saliva evidence can be obtained.

Impressions and Study Casts

When a bite injury exhibits indentations that can be related to the dentition of an alleged biter, accurate, 3D, life-size exemplars (casts) can be obtained from molds of the area. Dental impression materials are used to create the molds that are then reinforced to prevent dimensional changes and distortions.

The Guidelines for Bite Mark Analysis deliberately do not dictate which impression materials should be used to create exemplars of a bite mark. Low- and medium-viscosity vinyl polysiloxane (VPS) impression materials are dimensionally stable, meet American Dental Association specifications, and are all acceptable. Hydrocolloid, polysulfide, polyether, and alginate materials are not recommended because of problems associated with long-term stability.

Orthopedic cast materials, heavy-body VPS materials, and non-exothermic resins have been used to create the rigid, stable trays for bite mark impressions. All impression trays and study casts should be appropriately labeled with demographic information for the specific case. Additionally, anatomic direction markers should be added to the impression tray before its removal from the skin surface. This will ensure that the impression is correctly oriented relative to the actual pattern injury.

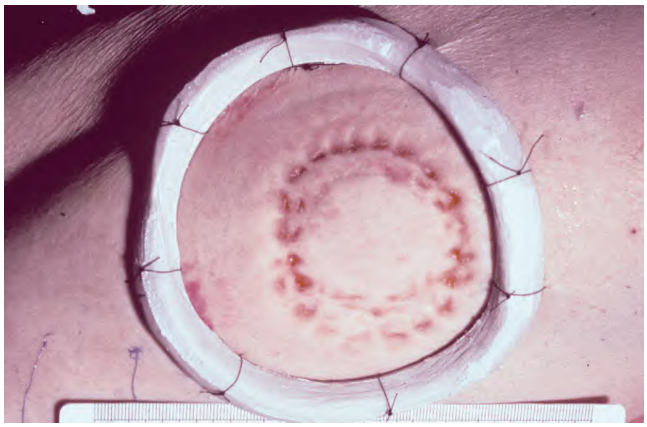
Original impression trays and study casts are retained for eventual presentation in court. Working casts and models should be duplicated from the original impression or master casts. It is recommended that master casts be poured in type IV stone, according to the manufacturer's specifications, and that these casts remain pristine.

Tissue Samples

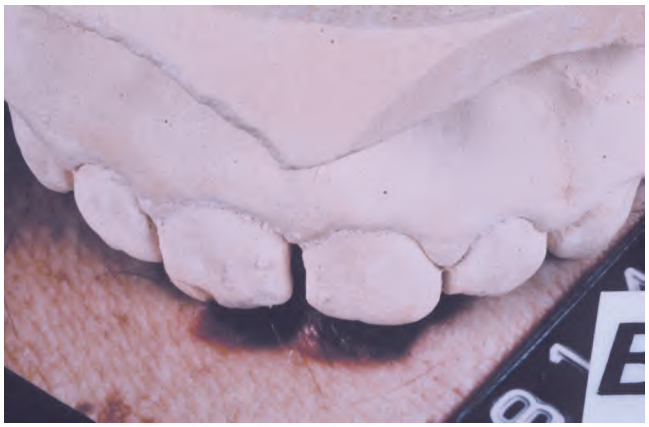
Tissue samples of a bite mark can be retained from decedents. With the permission of the ME or coroner, the epidermis, dermis, and underlying muscle and adipose tissue can be removed for transillumination analysis. Before excision, an acrylic ring or stent must be secured within 1 inch of the borders of the injured tissue sample. The ring or stent prevents shrinkage and distortion of the specimen when it is placed into a 4% formalin solution for fixation. The acrylic material is bound to the skin surface with cyanoacrylate and sutures (Fig. 19-16). These tissues samples can be transilluminated by backlighting. This process permits observation of the pattern injury in the bruised skin by a manner that is not possible when the tissue is *in situ.*

Evidence Analysis and Comparison

The responsibility of comparing the photographs of the bite pattern injury with the dentition of the suspect rests with the forensic dentist. As an expert in the analysis of these patterns, this person objectively evaluates the evidence. The



• **Fig. 19-16** An experimental bite pattern injury on a cadaver. This bite mark has had an acrylic stent glued and sutured around its circumference before dissection and fixation in 4% formalin. (Courtesy of Dr. E. Steven Smith.)



• **Fig. 19-17** An overlay of the maxillary cast of a suspect's dentition on a photograph of a bite pattern injury. Note the diastema between the central incisor teeth. The distal incisal surfaces of the lateral incisor teeth are not in the plane of occlusion.

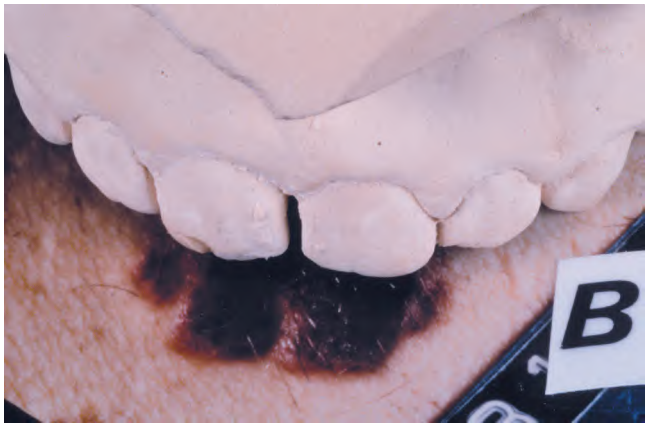
forensic dentist first determines whether the pattern is truly a result of biting or whether it is an artifact. Patterns of blood splatter around a wound, other tool marks, or insect artifacts unrelated to the teeth may be mistaken for bite marks in photographs provided for evaluation by crime scene investigators, police, and emergency room or autopsy personnel.

Once it is established that the pattern is related to the teeth, it can be compared to the dentition of the suspect for inclusionary or exclusionary purposes. An expert opinion is then made according to the results of the relationship of the bite pattern and suspect's teeth. According to the ABFO Guidelines for Investigative and Final Bite Mark Reports, *the biter, the probable biter, not excluded as the biter, excluded as the biter,* and *inconclusive* are the terms used to indicate the confidence level of the odontologist that the dentition of the putative suspect is concordant with a bite patterned mark observed on an inanimate object or victim.

To accomplish these goals, the dentist uses numerous methods that have been accepted in the courts. Images of the bite mark and the teeth can be digitized in a computer. This information can then be enhanced and subsequently overlaid for matching purposes.

Historically, a clear overlay of the chewing surfaces of the teeth was made by simply tracing these surfaces on a sheet of transparent acetate. Placing the incisal edges of the study casts on the glass of an office photocopier and duplicating on special paper achieved the same end. A similar effect was obtained by placing an opaque powder, such as barium sulfate, into wax or acrylic test bites and by obtaining radiographs of these exemplars. All of these overlays were then superimposed over the bite mark for comparison.

Studies indicate that there are limitations to the accuracy of these potentially subjective, biased overlay techniques and it has been suggested that hand-traced overlay methods be discontinued. Additionally, a stone cast exemplar of the dentition of a suspect has been placed over a 1:1 image of a BMPI for comparison (Figs. 19-17 and 19-18). This



• **Fig. 19-18** A repositioned overlay of the maxillary cast of a suspect's dentition on a photograph of a bite pattern injury (same case as depicted in Fig. 19-17). The drag marks, diastema space, and mesial contact points of the lateral incisor teeth become apparent in the pattern. (From Nuckles DB, Herschaft EE, Whatmough LN: Forensic odontology in solving crimes: dental techniques and bite-mark evidence, *Gen Dent* 42:210–214, 1994. Published with permission by the Academy of General Dentistry. © 1994 by the Academy of General Dentistry. All rights reserved.)

method of comparison may also have limitations considering that computer based technology that currently exists to more objectively assist the odontologist in bite mark casework.

Presently, images of the bite mark and the incisal edges of the teeth of the suspect are routinely digitized and computer-generated hollow volume overlays are fabricated, enhanced, and subsequently compared using Adobe Photoshop or other graphics editing programs (Fig. 19-19).

In court, bite mark evidence must be able to withstand legal challenges based on its scientific validity and the credibility of the expert witness who presents the evidence. This is true regardless of the techniques used to retrieve, compare, and determine a conclusion based on the evidence. When the Guidelines for Bite Mark Analysis are used, such challenges can be minimized.

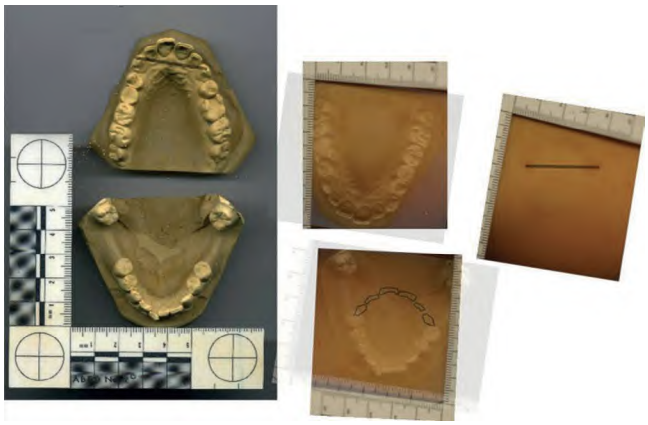


Fig. 19-19 On the left side, dental casts of an alleged suspect are being scanned and scaled to 1:1 before digitizing their image. The right half of the illustration shows three photographs of bite marks on the victim. Transparent overlays of the teeth of the alleged suspect have been digitally superimposed over 1:1 digital images of the victim's bite mark using a software program developed by Mideo Systems, Inc. (Huntington Beach, CA) (Courtesy of Dr. David K. Ord.)

BOX 19-2 Epidemiological, Statistical Overview of the United Nations Secretary-General's Study on Violence Against Children

- Almost 53,000 children died worldwide in 2002 as a result of homicide.
- Up to 80% to 98% of children suffer physical punishment in their homes, with one-third or more experiencing severe physical punishment resulting from the use of implements.
- 150 million girls and 73 million boys younger than 18 years experienced forced sexual intercourse or other forms of sexual violence during 2002.
- Between 100 and 140 million girls and women in the world have undergone some form of female genital mutilation/cutting. In sub-Saharan Africa, Egypt, and the Sudan, 3 million girls and women are subjected to genital mutilation/cutting every year.
- In 2004, 218 million children were involved in child labor. Among these, 126 million did hazardous work.
- Estimates from 2000 suggest that 1.8 million children were forced into prostitution and pornography, and 1.2 million were victims of trafficking.

HUMAN ABUSE

Epidemiology and Classification

Dental professionals are likely to encounter more victims of physical, neglective, sexual, and psychological abuse as the scope of the problems associated with violent human behavior become more recognized and openly discussed. Currently in the United States, statistics reveal more than 3 million cases of child abuse, 2 million cases of elder abuse, and 4 million victims of intimate partner violence (IPV) annually.

Child abuse is the non-accidental, physical, mental, emotional, or sexual trauma; exploitation; or neglect endured by a child younger than 18 years of age while under the care of a responsible person, such as a parent, sibling, babysitter, teacher, or other person acting *in loco parentis.* Elder abuse and abuse of the disabled are similar in all regards, except that they deal with geriatric victims or individuals who are physically and/or mentally impaired or disabled. These populations often require special care or have been institutionalized.

Victims of IPV are unique and differ from those of child, elder, or disabled abuse because they often have autonomy to choose their circumstances. Unlike the abused child, or geriatric or disabled resident in a nursing home, the abused intimate partner can make choices to leave the traumatic, violent environment.

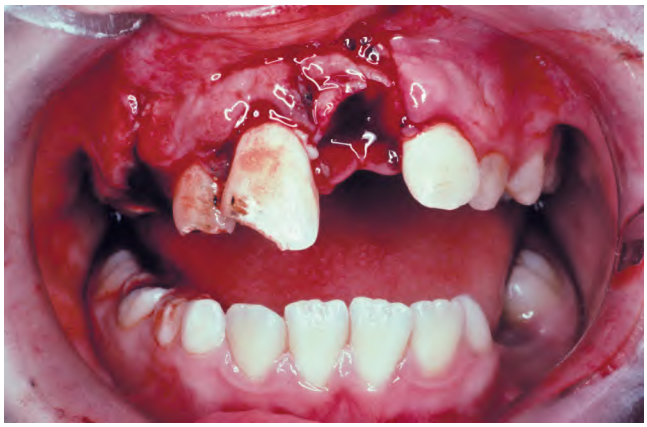
Of the 3 million cases of alleged child abuse or neglect investigated by state and local child protective services (CPS) in the United States in 2004, 872,000 children were determined to be victims of child maltreatment and 1490 cases resulted in death. The National Child Abuse and Neglect Data System (NCANDS) is a federally sponsored program directed by the Department of Health and Human Services to collect and analyze annual data on child abuse and neglect.

Recognizing the global problem, in 2006 the United Nations released the first *UN Secretary-General's Study on Violence against Children*. This document addresses violence against children in the home, school, workplace, community, and other settings. The project is the "first comprehensive, global study conducted by the United Nations on all forms of violence against children" (Box 19-2).

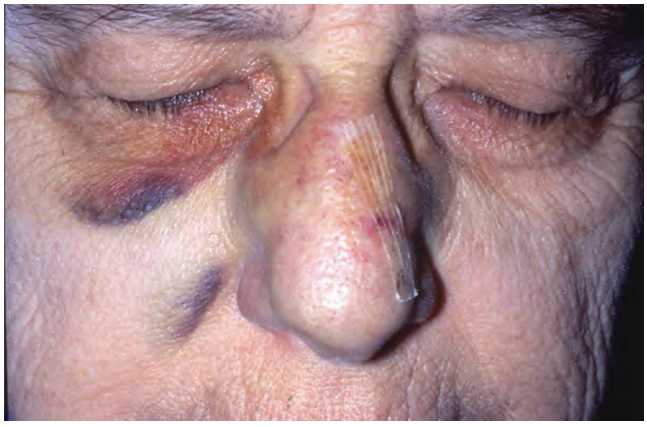
Victims and their abusers come from all racial, ethnic, religious, socioeconomic, and educational backgrounds. Reports concerning the distribution of cases among the different types of abuse vary widely. Up to 70% of child abuse cases may be the result of physical trauma. Some studies relate 15% to 25% of the cases to sexual abuse and 50% to neglect. Neglective abuse is subclassified by the caretaker's neglect of the child's medical, dental, and safety needs; physical well-being; or education.

Intentional drugging or poisoning and failure to thrive are additional types of maltreatment classified as abusive. Munchausen syndrome by proxy (MSBP) is a form of child abuse in which the caregiver intentionally overstates, contrives, and/or creates a physical, emotional, or behavioral problem in the child. The victim is made to appear sick or is harmed in some other way to deceive health care professionals and others in order to gain attention and sympathy for the caregiver.

Many abusive individuals were themselves abused as children. Criminal charges are often lodged against an abusing caretaker. It is recognized, however, that counseling and psychological and emotional support can also help to stabilize a violent, dysfunctional family unit.



• **Fig. 19-20** An avulsed tooth, a fractured tooth, and a torn labial frenum associated with oral facial injuries in physical child abuse.

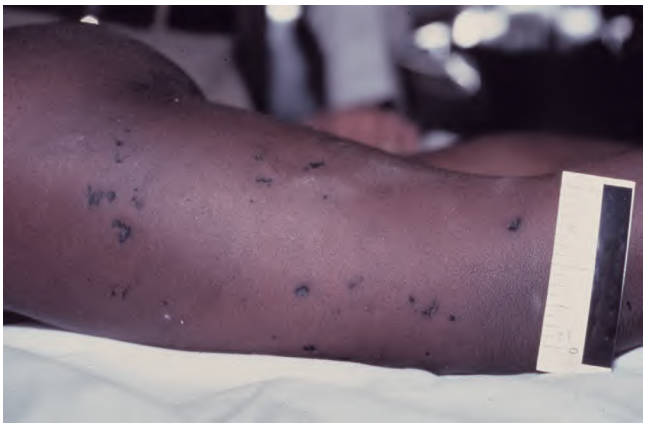


• **Fig. 19-21** Bilateral periorbital ecchymoses (raccoon mask) and fractured nasal bone in a 77-year-old white female victim of physical elder abuse. (Courtesy of Dr. John D. McDowell.)

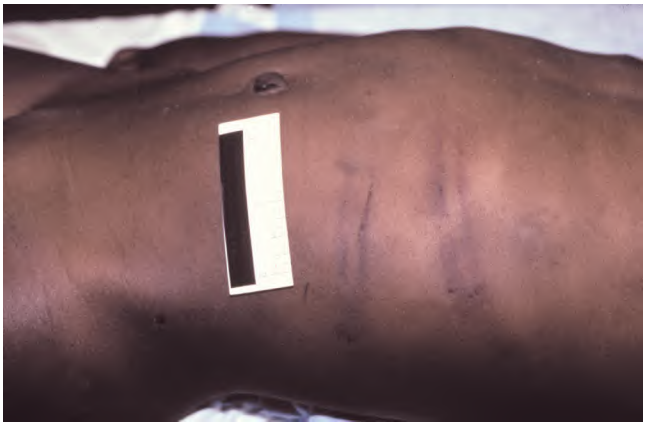
Signs and Symptoms

Regardless of the overall statistical variations in subclassification of the problem of abuse, the dentist is most likely to encounter physical and sexual abuse, as well as health care and safety neglect among pediatric, older adult, and disabled dental patients. Of the children and older adults who are physically abused, 50% manifest orofacial and scalp injuries (Figs. 19-20 and 19-21). These unexplained injuries are inappropriately reported by the caretaker or are inconsistent with the history provided. Abusive trauma to the face, mouth and skull includes the following:

- Laceration of the labial or lingual frenum, which results from a blow to the lip or forceful feeding
- Repeated fracture or the avulsion of teeth
- Zygomatic arch and nasal fractures
- Bilateral contusions of the lip commissures from the placement of a gag
- Bilateral periorbital ecchymoses (raccoon mask)
- Mastoid ecchymosis (Battle sign) indicating fracture of the middle cranial fossa and related traumatic brain injury
- Traumatic alopecia secondary to grabbing the head hair of the victim while throwing them



• **Fig. 19-22** Multiple circular ulcerated injuries are associated with intentional burns from a cigarette. When a child is accidentally burned by a cigarette, only one elliptic ulcer is observed.

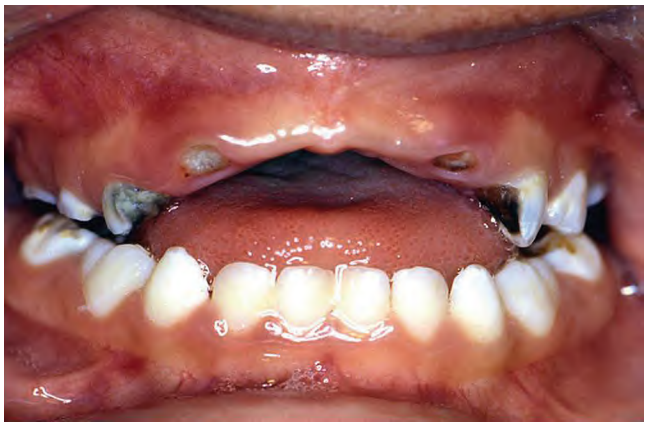


• **Fig. 19-23** Parallel linear ("railroad track") patterns are associated with blows to the skin with such straight-edged objects as a belt, a hanger, an electrical cord, and a ruler.

Pattern injuries can be associated with the semicircular or crescent shape of bite marks. Other instruments that contact the skin may leave parallel linear patterns; these include injuries made by a hanger, strap, belt, or ruler. Multiple parallel lines are associated with finger marks after an open-handed slap. Multiple circular, punched out, or ulcerated areas are caused by intentional burning with a cigarette or cigar. Loop patterns are created by electrical cord, rope, and wire (Figs. 19-22 and 19-23).

Other characteristics of child and elder abuse injuries are related to their multiplicity and repetitive nature. They often appear in various stages of resolution. Some injuries are acute; others are healing or even scarred. Therefore, the dentist should examine the skin of the pediatric, geriatric, or disabled dental patient. Suspicion of abuse is increased when the child or older patient appears overdressed for seasonal conditions; overdressing may be an attempt to mask or hide the physical signs of abuse.

By adulthood, 10% of men and 25% of women are the victims of sexual abuse. Oral infections associated with sexually transmitted diseases (STDs) are obviously signs of sexual abuse when they are observed in a minor.



• **Fig. 19-24** Pseudoprognathism or pseudo-Class III malocclusion observed in a neglected child with nursing bottle (baby bottle) decay. (Courtesy of Dr. Cynthia Hipp.)

Erythematous or petechial lesions of the palate or ulceration of the sublingual area should be noted because these findings can result from the physical trauma associated with performing fellatio or cunnilingus (see page 280).

Among siblings, nursing or "baby bottle caries" is a sign of neglective abuse and indicates the caretaker's inattention to the dental needs of the children. When infants and toddlers are placed to bed with a nursing bottle filled with cariogenic solutions (e.g., milk, soft drinks, and sweet juices), the maxillary incisors are bathed in the sugary solution and can manifest severe caries. The mandibular teeth, protected from the cariogenic material by the position of the tongue and nipple during sucking, are spared the destructive effects, and the child takes on the appearance of a pseudoprognathism or pseudo-Class III malocclusion (Fig. 19-24).

The dentist may become aware of other abusive behavior directed to a child or older patient by a responsible caretaker. Abusive behavior can involve refusal or delay in seeking treatment for serious medical or dental problems, abandonment, refusal to cooperate with planned treatment, and failure to return to the same physician or dentist for treatment.

Role of Dentistry in Recognizing and Reporting Human Abuse

Awareness of the signs and symptoms of abuse among individuals of all ages should be a goal for every dentist. As a component of the dental relicensure process, the state of New York requires documentation of continuing education credits in the area of child abuse recognition and the dental professional's responsibility to report such cases.

By statute, all states require that dental personnel, other health care professionals, teachers, and day care and nursing home employees report suspected cases of child and elder abuse. Unfortunately, the reporting of IPV is limited in most jurisdictions to cases involving the use of a weapon while committing a violent act. Although the dentist has no legal requirement to report IPV in these areas, the American Dental Association's Principles of Ethics and Code of Professional Conduct indicate a responsibility on behalf of dental professionals to intercede in cases involving family violence.

The agency to which the report is made varies among the different jurisdictions. Commonly, the police, social service, child welfare, senior services agencies, or family services departments are the governmental offices designated to accept reports. When a report is made in good faith, the dentist is immune from any counter prosecution or civil liability that might stem from a false report. Failure to report is considered a misdemeanor in most states. In addition, the dentist may be subject to license revocation or malpractice litigation by failing to make a report.

When a dentist determines that a report of child or elder abuse should be made, documentation of the physical evidence to support the charge is mandatory. All evidence is collected according to the principles described for identification and bite mark cases. Descriptions of the injuries and their locations, supporting photographs and radiographs, and information stating the basis for suspicion of abuse are included in the report. When abuse is considered, the dentist should examine the patient and assess the problem separately from the abusive caregiver. Parental consent is not required to obtain appropriate physical evidence from victims younger than the age of majority.

◆ DENTISTS AS EXPERT WITNESSES

Observational, or lay, witnesses testify only to the facts known to them. They are referred to as *witnesses of fact.* Such witnesses are permitted to make inferences about physical facts based on ordinary experience. The witness of fact is not entitled to present hearsay evidence related by another person.

The judicial system recognizes that people with a scientific background or specialized field of study that is admissible under the *Frye* rule or Federal Rules of Evidence can provide the courts with analyses or explanations relative to that discipline. The facts and opinions offered by such a witness are beyond the scope of information that could be expected to be provided by a lay person or witness of fact. A witness who is qualified to testify under this standard is acknowledged as an "expert."

Members of the dental profession are experts. They are qualified to testify by the judge, who bases his or her opinion on educational background, dental and forensic expertise, publications, and other professional qualifications. Dentists who have additional training in one of the dental specialties may be called on to present specific information from that discipline.

Dental experts assist attorneys and, ultimately, the triers of fact (judges and juries) in understanding the scope and complexities of dental science and practice in relation to questions of law. The dentist should not become an

advocate for either side in a case but should strive to be an educator and friend of the court.

As experts, dentists may be required to testify in civil litigation cases that involve the following situations:

- **Malpractice based on negligence.** This category includes battery (e.g., extraction of the wrong tooth); misdiagnosis; and failure to diagnose, refer, or inform. All of these actions fall outside the standard of care for the profession.
- **Personal injury.** TMJ damage or dental trauma suffered in vehicular, home, sports, recreational, and work-related accidents fall under this category.
- **Dental fraud.** Charging for materials or procedures that were not used or performed are examples of fraud.
- **Identification of multiple fatality incident victims.** In criminal court, dental expertise is requested in identification of homicide victims and in bite mark and human abuse cases.

Dentists are often unfamiliar with, and may be intimidated by, the adversarial nature of courtroom procedure and protocol. When presenting evidence, the dental expert should remember that his or her role in the legal process is to help the trier of fact understand the dental issues in the case. To this end, and as a scientist, the dental expert witness should present the evidence confidently, accurately, and objectively, relating information in nontechnical terms.

When cross-examined by the opposing attorney, the dental expert witness should remain composed and confident. As an expert, the dentist has the right to refer to records and exemplars prepared for the case. The dentist is entitled to read and review any books or articles proffered by the opposing attorney with the intent of discrediting the testimony.

Pretrial preparation is required if the dental expert and the attorney who has retained his or her services are to develop the evidence to be presented in court. Both must be aware of the strengths and weaknesses of the material and decide how best to provide the jury with this information. Adequate time must be allotted to prepare exhibits for court. It is also advantageous to attempt to determine the position that will be taken by dental experts called by the opposing side.

◆ SUMMARY

Each practitioner has a responsibility to understand the forensic implications associated with the practice of his or her profession. This understanding should include more than ethics and jurisprudence, which were traditionally the only aspects of knowledge of the law acquired by dental professionals. Appreciation of forensic dental problems involving body identification permits clinicians to maintain legally acceptable records and assist legal authorities in the identification of victims of multiple fatality incidents and crimes.

The pursuit of justice in cases of rape, homicide, and human abuse often relies on dental testimony to interpret bite marks or BMPIs. The development of UV and IR wavelength photographic techniques and equipment has given forensic dentists the opportunity to provide objective scientific evidence in these types of cases. Evidence gathered using these resources can be analyzed and assessed with computer software, laboratory, and clinical procedures that also enhance the ability of the forensic odontologist to interpret results.

The reliance of the legal community on the dental profession to continue to provide expertise in civil and criminal proceedings ensures that forensic dentistry will remain a viable component of the forensic sciences and the practice of dentistry.

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APPENDIX

Differential Diagnosis of Oral and Maxillofacial Diseases

The most important aspect of patient care is the accurate diagnosis of the patient's disease. Unfortunately, the clinical presentation of many disease processes can be strikingly similar, despite their vast differences in etiology and pathogenesis. Because treatment and, ultimately, prognosis are based on the diagnosis, the diagnostic process is critical in optimal patient management. This appendix provides some guidelines for expediting and facilitating the diagnostic process from a clinical perspective.

The first step in gathering information is the acquisition of a thorough history of the disease process. This step typically includes items such as the onset, severity, location, duration, character, and course of the signs and symptoms being experienced by the patient. Additional information regarding medical, social, and family history may be necessary. With this information, the clinician can often start the process of formulating a list of possible diagnoses, even before performing an examination.

The information obtained during the clinical examination is also important because many lesions have characteristic appearances. By evaluating these characteristics in conjunction with the patient's history, often the clinician can narrow the list of diagnostic possibilities. This list, known as a *differential diagnosis*, essentially includes possible pathologic entities, usually ranked in order from most likely to least likely.

DEFINITIONS

To better describe the appearances of lesions and communicate these features to colleagues, the clinician should be familiar with the following terms:

Macule. Focal area of color change that is not elevated or depressed in relation to its surroundings.

Papule. Solid, raised lesion that is less than 5 mm in diameter.

Nodule. Solid, raised lesion that is greater than 5 mm in diameter.

Sessile. Describing a tumor or growth whose base is the widest part of the lesion.

Pedunculated. Describing a tumor or growth whose base is narrower than the widest part of the lesion.

Papillary. Describing a tumor or growth exhibiting numerous surface projections.

Verrucous. Describing a tumor or growth exhibiting a rough, warty surface.

Vesicle. Superficial blister, 5 mm or less in diameter, usually filled with clear fluid.

Bulla. Large blister, greater than 5 mm in diameter.

Pustule. Blister filled with purulent exudate.

Ulcer. Lesion characterized by loss of the surface epithelium and frequently some of the underlying connective tissue. It often appears depressed or excavated.

Erosion. Superficial lesion, often arising secondary to rupture of a vesicle or bulla, that is characterized by partial or total loss of the surface epithelium.

Fissure. Narrow, slitlike ulceration or groove.

Plaque. Lesion that is slightly elevated and is flat on its surface.

Petechia. Round, pinpoint area of hemorrhage.

Ecchymosis. Nonelevated area of hemorrhage, larger than a petechia.

Telangiectasia. Vascular lesion caused by dilatation of a small, superficial blood vessel.

Cyst. Pathologic epithelium-lined cavity, often filled with liquid or semi-solid contents.

Unilocular. Describing a radiolucent lesion having a single compartment.

Multilocular. Describing a radiolucent lesion having several or many compartments.

By using these terms, the clinician can describe the characteristics of lesions efficiently and uniformly. Applying these clinical descriptors to the lesions also can help categorize them with respect to the differential diagnosis. By adding additional characteristics such as prevalence, patient race or nationality, patient age at diagnosis, patient sex, and sites of predilection, the clinician can hone the differential diagnosis list considerably.

HOW TO USE THIS APPENDIX

This appendix is designed to help the clinician formulate a differential diagnosis by organizing and categorizing disease entities according to their most prominent or identifiable

clinical features. Under each "clinical feature" heading is a list of lesions with that clinical feature as a prominent component. Diseases are listed according to estimated frequency relative to similar diseases or lesions.

The most common lesions are marked with triple asterisks (***), less common lesions are marked with double asterisks (**), and rare lesions are marked with a single asterisk (*). Such estimated frequency indicators should not be compared between lists; they are intended only for the single differential diagnosis list in which they occur.

Clinical features that most readily distinguish the lesions are listed with each disease process to help focus the clinician's search for the most accurate diagnosis. Finally, the corresponding page number in the book is provided for each disease entity so that the reader can refer to the text for a more detailed discussion.

INDEX TO THE APPENDIX: DIFFERENTIAL DIAGNOSIS LISTS

Part 1: Mucosal and Soft Tissue Pathology: Color Changes

Part 2: Mucosal and Soft Tissue Pathology: Surface Alterations

Part 3: Mucosal and Soft Tissue Pathology: Masses or Enlargements

Part 4: Radiographic Pathology

Part 5: Pathology of Teeth

PART 1: MUCOSAL AND SOFT TISSUE PATHOLOGY: COLOR CHANGES

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
A. White Lesions: Can Be Scraped Off			
***	White coated tongue	May be scraped off slightly, with difficulty	12
***	Pseudomembranous candidiasis	"Milk curd" or "cottage cheese" appearance; may leave red base when rubbed off	191
***	Morsicatio	Surface may appear to be peeling off	259
***	Toothpaste or mouthwash reaction	Filmy whiteness; leaves normal appearing mucosa when rubbed off	320
**	Thermal burn	Example: pizza burn	262
**	Sloughing traumatic lesion	Example: cotton roll "burn"	266
**	Chemical burn	Example: aspirin burn secondary to direct application for toothache	264
*	Secondary syphilis	Mucous patch; may be only partially scraped off	171
*	Diphtheria	Gray-white pseudomembrane of oropharynx	168
B. White Lesions: Cannot Be Scraped Off			
***	Linea alba	Buccal mucosa along occlusal plane	259
***	Leukoedema	Primarily in blacks; milky white alteration of buccal mucosa bilaterally; disappears when stretched	7
***	Leukoplakia	May show benign hyperkeratosis, epithelial dysplasia, or invasive carcinoma	355
***	Tobacco pouch keratosis	Usually in mandibular vestibule; associated with use of snuff or chewing tobacco	364
***	White coated tongue	Diffuse involvement of dorsal tongue	12
**	Lichen planus	Wickham's striae; typically bilateral on buccal mucosa	729
**	Morsicatio	Most common on anterior buccal mucosa, labial mucosa, and lateral border of tongue; exhibits ragged surface	259
**	Actinic cheilosis	Pale, gray-white, scaly alteration of lower lip; usually in older men with history of chronic sun exposure; precancerous	370
*	Nicotine stomatitis	Usually associated with pipe smoking; occurs on hard palate	368
*	Hairy leukoplakia	Usually lateral border of tongue; rough surface with vertical fissures; usually associated with HIV infection	242
*	Hyperplastic candidiasis	Most commonly affects anterior buccal mucosa	195
*	Lupus erythematosus	Most common on buccal mucosa; may mimic lichen planus or leukoplakia; associated skin lesions usually present	740
*	Skin graft	History of previous surgery	—
*	Submucous fibrosis	More common in South Asia; associated with betel quid chewing	366
*	White sponge nevus	Hereditary; onset in childhood; generalized lesions, especially buccal mucosa	691
*	Hereditary benign intraepithelial dyskeratosis	Hereditary; onset in childhood; generalized lesions, especially buccal mucosa; ocular involvement possible	692
*	Pachyonychia congenita	Hereditary; onset in childhood; most common on dorsal tongue and areas of trauma; nail, palmar, and plantar changes also present	693
*	Dyskeratosis congenita	Hereditary; onset in childhood; dystrophic nail changes	695
*	Uremic stomatitis	Renal failure	793

PART 1: MUCOSAL AND SOFT TISSUE PATHOLOGY: COLOR CHANGES—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
C. White and Red Lesions			
***	Erythema migrans	Geographic tongue; continually changing pattern; rarely involves other oral mucosal sites	726
***	Candidiasis	White component may be rubbed off	191
**	Lichen planus	Atrophic or erosive forms; Wickham's striae; typically bilateral on buccal mucosa	729
**	Burns	Examples: pizza burn, aspirin burn, other chemical burns; white component may be rubbed off	262
**	Actinic cheilosis	Pale, gray-white and red alteration to lower lip; usually in older men with history of chronic sun exposure	370
**	Erythroleukoplakia	Usually shows epithelial dysplasia or carcinoma	359
**	Cinnamon reaction	Related to cinnamon flavored gum; typically on buccal mucosa and lateral tongue	322
*	Nicotine stomatitis	Usually associated with pipe smoking; occurs on hard palate	368
*	Lupus erythematosus	Most common on buccal mucosa; may mimic lichen planus or leukoplakia; associated skin lesions usually present	740
*	Scarlet fever	Secondary to β-hemolytic streptococcal infection; strawberry/raspberry tongue	167
*	Verruciform xanthoma	Most common on gingiva and hard palate; surface may be papillary	341
D. Red Lesions			
***	Pharyngitis	Examples: strep throat, viral pharyngitis	166
***	Traumatic erythema	Caused by local irritation	—
***	Denture stomatitis	Denture-bearing palatal mucosa	194
***	Erythematous candidiasis	Example: central papillary atrophy (median rhomboid glossitis)	192
***	Erythema migrans	Geographic tongue (cases with absence of white borders); continually changing pattern; rarely involves other mucosal sites	726
***	Angular cheilitis	Erythema and cracking at labial commissures	194
**	Thermal burns	Example: caused by hot liquids	262
**	Erythroplakia	Usually shows epithelial dysplasia or carcinoma	363
*	Anemia	Atrophic, red tongue; can be due to pernicious anemia, iron-deficiency anemia, hypovitaminosis B	771
*	Hemangioma	Develops in younger patients; may blanch; may show bluish hue	504
*	Lupus erythematosus	Usually with associated skin lesions	740
*	Scarlet fever	Secondary to β-hemolytic streptococcal infection; strawberry/raspberry tongue	167
*	Plasma cell gingivitis	Allergic reaction usually related to flavoring agents	145
*	Radiation mucositis	Patient currently undergoing radiotherapy	266
E. Petechial, Ecchymotic, and Telangiectatic Lesions			
***	Nonspecific trauma	History of injury to lesional site	279
**	Upper respiratory infections	Soft palate petechiae	280

Continued

PART 1: MUCOSAL AND SOFT TISSUE PATHOLOGY: COLOR CHANGES—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
*	Infectious mononucleosis	Soft palate petechiae; tonsillitis and/or pharyngitis may be present	229
*	Idiopathic thrombocytopenic purpura	Areas of trauma; gingival bleeding possibly present	545
*	Trauma from fellatio	Posterior palatal petechiae or ecchymosis	280
*	Hemophilia	Hereditary; childhood onset; gingival bleeding may be present	534
*	Leukemia	Caused by secondary thrombocytopenia; gingival bleeding may be present	547
*	Hereditary hemorrhagic telangiectasia	Multiple, pinhead-sized telangiectasias; possible history of nosebleeds or gastrointestinal bleeding	702
*	CREST syndrome	Multiple, pinhead-sized telangiectasias; **C**alcinosis cutis, **R**aynaud's phenomenon, **E**sophageal motility defect, **S**clerodactyly, **T**elangiectasias	747
F. Blue and/or Purple Lesions			
***	Varicosities	Especially after 45 years of age; most common on ventral tongue and lips	13
***	Submucosal hemorrhage	Also see Appendix List, Part 1, E. (previous topic) Petechial, Ecchymotic, and Telangiectatic Lesions	279
***	Amalgam tattoo	Most common on gingiva; blue-gray; radiopaque amalgam particles sometimes discovered on radiographs	281
***	Mucocele	Especially on lower labial mucosa; typically pale blue; cyclic swelling and rupturing often exhibited	422
**	Eruption cyst	Overlying an erupting tooth	635
**	Salivary duct cyst	Usually pale blue	425
**	Hemangioma	Usually red-purple; may blanch under pressure; onset in younger patients	504
**	Ranula	Pale blue, fluctuant swelling of lateral floor of mouth	424
*	Kaposi sarcoma	Especially in AIDS patients; usually purple; most common on palate and maxillary gingiva	244
*	Nasopalatine duct cyst	Midline of anterior palate	26
*	Salivary gland tumors	Especially mucoepidermoid carcinoma and pleomorphic adenoma; usually pale blue; most common on posterior lateral palate	Chapter 11
*	Gingival cyst of the adult	Most common in mandibular bicuspid-cuspid region	644
*	Blue nevus	Most common on hard palate	354
*	Melanoma	Most common on hard palate and maxillary gingiva; may show mixture of deep blue, brown, black, and other colors	401
G. Brown, Gray, and/or Black Lesions			
***	Racial pigmentation	Most common on attached gingiva in darker complexioned patients	—
***	Amalgam tattoo	Most common on gingiva; usually slate-gray to black; opaque amalgam particles may be found on radiographs	281
***	Black/brown hairy tongue	Discoloration and elongation of filiform papillae	12
***	Melanotic macule	Brown; most common on lower lip	348
**	Smoker's melanosis	Most common on anterior facial gingiva	289

PART 1: MUCOSAL AND SOFT TISSUE PATHOLOGY: COLOR CHANGES—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Non-amalgam tattoos	Example: graphite from pencil	281
*	Melanocytic nevus	Most common on hard palate; can be flat or raised	350
*	Melanoma	Most common on hard palate and maxillary gingiva; may show mixture of deep blue, brown, black, and other colors	401
*	Oral melanoacanthoma	Rapidly enlarging pigmented lesion; usually occurs in blacks	349
*	Drug ingestion	Examples: chloroquine, chlorpromazine, minocycline; especially on hard palate	290
*	Peutz-Jeghers syndrome	Freckle-like lesions of vermilion and perioral skin; intestinal polyps; hereditary	701
*	Addison disease	Chronic adrenal insufficiency; associated with bronzing of skin	784
*	Neurofibromatosis type I	*Café au lait* pigmentation; cutaneous neurofibromas	495
*	McCune-Albright syndrome	*Café au lait* pigmentation; polyostotic fibrous dysplasia; endocrine disorders	593
*	Heavy metal poisoning	Typically along marginal gingiva (e.g., lead, bismuth, silver)	286
*	Melanotic neuroectodermal tumor of infancy	Anterior maxilla; destroys underlying bone	499
H. Yellow Lesions			
***	Fordyce granules	Sebaceous glands; usually multiple submucosal papules on buccal mucosa or upper lip vermilion	6
**	Superficial abscess	Example: parulis from nonvital tooth	123
**	Accessory lymphoid aggregate	Most common in oropharynx and floor of mouth; may exhibit orange hue	533
**	Lymphoepithelial cyst	Most common on lingual and palatine tonsils, and floor of mouth; may be yellow-white	34
**	Lipoma	Most common on buccal mucosa; soft to palpation	488
*	Jaundice	Generalized discoloration, especially involving soft palate and floor of mouth; sclera usually affected also	765
*	Verruciform xanthoma	Most common on gingiva and hard palate; surface may be rough or papillary	341
*	Pyostomatitis vegetans	"Snail-track" pustules; associated with inflammatory bowel disease	792

PART 2: MUCOSAL AND SOFT TISSUE PATHOLOGY: SURFACE ALTERATIONS

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
A. Vesiculoerosive and Ulcerative Lesions: Acute (Short Duration and Sudden Onset)			
***	Traumatic ulcer	Mild-to-moderate pain; history of local trauma	260
***	Aphthous stomatitis	Extremely painful; may be single or multiple; nonkeratinized movable mucosa; often recurs	303
***	Recurrent herpes labialis	Vermilion and labial skin; begins as multiple vesicles; often recurs	220
**	Primary herpetic gingivostomatitis	Fever and malaise; children and young adults; multiple vesicles; gingiva consistently affected	219
**	Necrotizing ulcerative gingivitis (NUG)	Painful destruction of gingival papillae; fetid odor; mostly in teenagers and young adults	143
**	Mucosal burns	Chemical or thermal	262
**	Recurrent intraoral herpes simplex	Gingiva or hard palate (except in immunocompromised); focal cluster of vesicles and shallow ulcers	220
**	Allergic reactions	Example: Caused by topical medications or dental materials; erythema and vesicles	320
**	Erythema multiforme / Stevens-Johnson syndrome	Predominantly in children and young adults; multiple blisters and ulcers; often crusting, hemorrhagic lip lesions; may have associated "target" skin lesions or involvement of ocular and genital mucosa	723
**	Herpangina	Especially in children; multiple small ulcers on soft palate and tonsillar pillars	233
*	Varicella (chickenpox)	Associated with skin eruption; few oral vesicles and ulcers; usually in children	224
*	Herpes zoster	Unilateral involvement along nerve distribution; usually middle-aged and older adults; painful vesicles and ulcers	227
*	Hand-foot-and-mouth disease	Especially in children; multiple vesicles and ulcers; associated vesicles on hands and feet	233
*	Necrotizing sialometaplasia	Usually posterior lateral hard palate; prior swelling may be present; deep crater-like ulcer; may be only minimal pain	439
*	Anesthetic necrosis	Usually at site of palatal injection	277
*	Primary syphilis	Chancre at site of inoculation; usually painless with clean ulcer bed	170
*	Behçet syndrome	Aphthous-like ulcers; genital ulcers and ocular inflammation	308
B. Vesiculoerosive and Ulcerative Lesions: Chronic (Long Duration)			
***	Erosive lichen planus	Associated with white striae; usually in middle-aged and older adults; most common on buccal mucosa and gingiva ("desquamative gingivitis")	729
**	Traumatic granuloma	Solitary, non-healing ulcer	260
**	Squamous cell carcinoma	Usually in middle-aged and older adults; usually indurated and may have rolled border; may be painless	374
**	Mucous membrane pemphigoid	Most common in middle-aged and older women; most commonly presents as a "desquamative gingivitis"; may involve ocular and genital mucosa	718
*	Lupus erythematosus	May have associated red and white change; usually with skin involvement	740
*	Pemphigus vulgaris	Usually in middle-aged and older patients; multiple oral blisters and ulcers usually precede skin lesions	712
*	Deep fungal infections	Examples: histoplasmosis, blastomycosis; may be painless	Chapter 6
*	Tuberculosis	Associated mass may be present; may be painless	176

PART 2: MUCOSAL AND SOFT TISSUE PATHOLOGY: SURFACE ALTERATIONS—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
*	Sarcoidosis	May be associated with erythematous macules or plaques; may be painless	310
*	Epidermolysis bullosa	Hereditary (except epidermolysis bullosa acquisita); onset in infancy and childhood; multiple skin and oral blisters or ulcers in areas of trauma; may result in extensive scarring	708
*	Pyostomatitis vegetans	Yellowish "snail-track" pustules; associated with inflammatory bowel disease	792
*	Wegener granulomatosis	Usually palatal ulceration and destruction; associated lung and kidney involvement may be present; may show "strawberry gingivitis"	315
*	Extranodal NK/T-cell lymphoma, nasal-type (midline lethal granuloma)	Palatal lymphoma with ulceration and destruction of underlying bone; may be painless	562
*	Noma	Gangrenous necrosis secondary to necrotizing ulcerative gingivitis; usually in malnourished children or immunocompromised individuals	181
*	Tertiary syphilis	Gumma; associated mass may be present; may be painless; may perforate palate	172
C. Papillary Growths: Focal or Diffuse			
***	Hairy tongue	Usually brown or black discoloration; hyperkeratotic elongation of filiform papillae on posterior dorsal tongue	12
***	Papilloma	Can be white or pink; most common on soft palate and tongue; usually pedunculated	332
***	Inflammatory papillary hyperplasia	Usually involves midportion of hard palate beneath denture	478
**	Leukoplakia (some variants)	Examples: proliferative verrucous leukoplakia, granular or nodular leukoplakia	355
**	Squamous cell carcinoma	Examples with papillary surface changes	374
**	Giant cell fibroma	Usually in children and young adults; most common on gingiva	473
*	Verruca vulgaris	Common wart; especially in younger patients; most common on labial mucosa	334
*	Hairy leukoplakia	Usually lateral border of tongue; rough surface with vertical fissures; usually associated with HIV infection	242
*	Verruciform xanthoma	Most common on gingiva and hard palate	341
*	Verrucous carcinoma	Especially in older patients with long history of snuff or chewing tobacco use; especially in mandibular vestibule and buccal mucosa; may be white or red	389
*	Condyloma acuminatum	Venereal wart; broad-based lesions with blunted projections; frequently multiple	335
*	Multifocal epithelial hyperplasia	Usually multiple, flat-topped papular lesions; usually in children; most common in Native Americans and Inuit; color may vary from normal to white	336
*	Darier's disease	Most commonly appears as pebbly appearance of hard palate; associated crusty, greasy skin lesions; hereditary	699
*	Acanthosis nigricans (malignant type)	Most commonly appears as generalized pebbly alteration of upper lip; pigmented, pebbly skin changes in flexural areas; associated gastrointestinal malignancy	748

PART 3: MUCOSAL AND SOFT TISSUE PATHOLOGY: MASSES OR ENLARGEMENTS

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
A. Soft Tissue Masses (Lumps and Bumps): Lower Lip			
***	Mucocele	Typically pale blue; often exhibits cyclic swelling and rupturing; labial mucosa only	422
***	Fibroma	Usually normal in color	473
**	Pyogenic granuloma	Red, ulcerated, bleeds easily; usually on vermilion border	483
**	Squamous cell carcinoma	Tumor with rough, granular, irregular surface; usually on vermilion border	374
*	Other mesenchymal tumors	Examples: hemangioma, neurofibroma, lipoma	Chapter 12
*	Salivary duct cyst	May be bluish; labial mucosa only	425
*	Salivary gland tumor	Usually mucoepidermoid carcinoma	Chapter 11
*	Keratoacanthoma	Volcano-shaped mass with central keratin plug; rapid development; vermilion border only	372
B. Soft Tissue Masses (Lumps and Bumps): Upper Lip			
**	Fibroma	Usually normal in color	473
**	Minor gland sialolith	Small, hard submucosal mass: may be tender	427
**	Salivary gland tumor	Usually canalicular adenoma (older than age 40) or pleomorphic adenoma (younger than age 40)	Chapter 11
*	Salivary duct cyst	May be bluish	425
*	Other mesenchymal tumors	Examples: hemangioma, neurofibroma, schwannoma	Chapter 12
*	Nasolabial cyst	Fluctuant swelling of lateral labial vestibule	24
C. Soft Tissue Masses (Lumps and Bumps): Buccal Mucosa			
***	Fibroma	Usually normal in color; along occlusal plane	473
**	Lipoma	May be yellow; soft to palpation	488
**	Mucocele	Typically pale blue; often exhibits cyclic swelling and rupturing	422
*	Hyperplastic lymph node	Usually buccinator node; movable submucosal mass	533
*	Other mesenchymal tumors	Examples: hemangioma, neurofibroma	Chapter 12
*	Squamous cell carcinoma	Tumor with rough, granular, irregular surface	374
*	Salivary gland tumor	Pleomorphic adenoma and mucoepidermoid carcinoma most common	Chapter 11
D. Soft Tissue Masses (Lumps and Bumps): Gingiva/Alveolar Mucosa			
***	Parulis	Fistula from nonvital tooth	124
***	Epulis fissuratum	Ill-fitting denture	475
***	Pyogenic granuloma	Usually red, ulcerated, easily bleeding; increased frequency in pregnant women	483
***	Peripheral ossifying fibroma	May be red or normal in color; may be ulcerated	487
***	Fibroma	Usually normal in color	473
**	Peripheral giant cell granuloma	Reddish purple; frequently ulcerated	485

PART 3: MUCOSAL AND SOFT TISSUE PATHOLOGY: MASSES OR ENLARGEMENTS—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
*	Squamous cell carcinoma	Tumor with rough, granular, irregular surface	374
*	Metastatic tumors	May be painful and destroy bone	525
*	Gingival cyst of the adult	Most common in mandibular bicuspid-cuspid region; may be blue	644
*	Traumatic neuroma	Edentulous mandible in mental foramen area; often painful to palpation	489
*	Kaposi sarcoma	Especially in AIDS patients; usually purple	244
*	Peripheral odontogenic tumors	Example: peripheral ameloblastoma	660
*	Congenital epulis	Usually in females; especially anterior maxilla	503
*	Melanotic neuroectodermal tumor of infancy	Anterior maxilla; destroys underlying bone; may be pigmented	499
*	Other mesenchymal tumors	Examples: hemangioma, neurofibroma	Chapter 12
E. Soft Tissue Masses (Lumps and Bumps): Floor of Mouth			
***	Ranula/mucocele	Typically a pale blue, fluctuant swelling	424
**	Sialolith	Usually hard mass in submandibular duct; may be associated with tender swelling of affected gland; radiopaque mass	427
**	Lymphoepithelial cyst	Small, yellow-white submucosal lesion	34
**	Squamous cell carcinoma	Tumor with rough, granular, irregular surface	374
*	Epidermoid or dermoid cyst	Midline yellow-white submucosal lesion	30
*	Salivary gland tumors	Especially mucoepidermoid carcinoma	Chapter 11
*	Mesenchymal tumors	Examples: lipoma, neurofibroma, hemangioma	Chapter 12
F. Soft Tissue Masses (Lumps and Bumps): Tongue			
***	Fibroma	Usually normal in color; most common on margins of tongue	473
**	Squamous cell carcinoma	Tumor with rough, granular, irregular surface; usually lateral or ventral border	374
**	Mucocele	Usually anterior ventral surface; usually bluish or clear color	422
**	Pyogenic granuloma	Usually red, ulcerated, easily bleeding	483
*	Granular cell tumor	Dome-shaped; usually on dorsum of tongue	502
*	Other mesenchymal tumors	Examples: lymphangioma, hemangioma, neurofibroma, osseous choristoma	Chapter 12
*	Salivary gland tumors	Especially mucoepidermoid carcinoma and adenoid cystic carcinoma	Chapter 11
*	Lingual thyroid	Usually posterior midline of dorsal surface; usually in women	10
G. Soft Tissue Masses (Lumps and Bumps): Hard or Soft Palate			
***	Palatal abscess	Associated with nonvital tooth	123
***	Leaf-like denture fibroma	Pedunculated hyperplastic growth beneath ill-fitting denture	477
**	Salivary gland tumors	Especially pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma; may have bluish hue	Chapter 11

Continued

PART 3: MUCOSAL AND SOFT TISSUE PATHOLOGY: MASSES OR ENLARGEMENTS—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Nasopalatine duct cyst	Fluctuant swelling of anterior midline palate	26
*	Lymphoma	Often boggy and edematous; may have bluish hue; may be bilateral	555
*	Kaposi sarcoma	Usually purple; may be multiple; usually associated with AIDS	244
*	Other mesenchymal tumors	Examples: fibroma, hemangioma, neurofibroma	Chapter 12
*	Squamous cell carcinoma	Tumor with rough, granular, irregular surface; occasionally arises from maxillary sinus	374
*	Mucocele/salivary duct cyst	Usually has bluish hue	422
*	Melanocytic nevus/ melanoma	Usually pigmented	350, 401
*	Necrotizing sialometaplasia	Early stage lesion; often associated with pain or paresthesia	439
*	Adenomatoid hyperplasia of minor salivary glands	Asymptomatic, painless mass	438
H. Soft Tissue Masses (Lumps and Bumps): Multiple Lesions			
**	Multiple fibromas	Some patients may develop more than one fibroma on the oral mucosa	473
*	Kaposi sarcoma	Usually purple lesions of palate and maxillary gingiva; usually associated with AIDS	244
*	Neurofibromatosis type I	Oral and skin neurofibromas; *café au lait* skin pigmentation	495
*	Multifocal epithelial hyperplasia	Usually flat-topped papular lesions; usually in children; most common in Native Americans and Inuit; color may vary from normal to white	336
*	Amyloidosis	Pale, firm deposits, especially in tongue; periocular cutaneous lesions frequently present; most often associated with multiple myeloma	766
*	Granulomatous diseases	Examples: sarcoidosis, Crohn disease, leprosy	310
*	Multiple endocrine neoplasia type 2B	Mucosal neuromas of lips and tongue; adrenal pheochromocytomas; medullary thyroid carcinoma; marfanoid body build	497
*	Tuberous sclerosis	Small fibroma-like growths on gingiva; angiofibromas of face; epilepsy; intellectual disability	705
*	Multiple hamartoma syndrome	Cowden syndrome; small fibroma-like growths on gingiva; multiple hamartomas of various tissues; breast cancer in affected women	707
I. Soft Tissue Masses (Lumps and Bumps): Midline Neck Lesions			
**	Thyroid gland enlargement	Examples: goiter, thyroid tumor	—
*	Thyroglossal duct cyst	May move up and down with tongue motion	32
*	Dermoid cyst	Soft and fluctuant	30
*	Plunging ranula	Soft and compressible	424
J. Soft Tissue Masses (Lumps and Bumps): Lateral Neck Lesions			
***	Reactive lymphadenopathy	Secondary to oral and maxillofacial infection; often tender to palpation	533
**	Epidermoid cyst	Soft and movable	29

PART 3: MUCOSAL AND SOFT TISSUE PATHOLOGY: MASSES OR ENLARGEMENTS—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Lipoma	Soft mass	488
**	Metastatic carcinoma	Deposits from oral and pharyngeal carcinomas; usually indurated and painless; may be fixed	383
**	Lymphoma	May be unilateral or bilateral; usually painless; Hodgkin and non-Hodgkin types	553
*	Infectious mononucleosis	Fatigue; sore throat; tender lymph nodes	229
*	Salivary gland tumors	Arising from submandibular gland or tail of parotid gland	Chapter 11
*	Submandibular sialadenitis	Example: secondary to sialolithiasis	429
*	Branchial cleft cyst	Soft and fluctuant; most common in young adults	33
*	Granulomatous diseases	Examples: tuberculosis, sarcoidosis	176, 310
*	Cat-scratch disease	History of exposure to cat	184
*	Cystic hygroma	Infants; soft and fluctuant	510
*	Plunging ranula	Soft and compressible	424
*	Other mesenchymal tumors	Examples: neurofibroma, carotid body tumor	Chapter 12
K. Generalized Gingival Enlargement			
***	Hyperplastic gingivitis	Examples: associated with puberty, pregnancy, diabetes	140
**	Drug-related gingival hyperplasia	Examples: phenytoin, calcium-channel blockers, cyclosporine; may be fibrotic	148
*	Gingival fibromatosis	May be hereditary; onset in childhood	151
*	Leukemic infiltrate	Usually boggy and hemorrhagic	547
*	Wegener granulomatosis	"Strawberry" gingivitis; may have palatal ulceration and destruction; lung and kidney involvement	315
*	Scurvy	Vitamin C deficiency	770

PART 4: RADIOGRAPHIC PATHOLOGY

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
A. Unilocular Radiolucencies: Pericoronal Location			
***	Hyperplastic dental follicle	<5 mm in thickness	633
***	Dentigerous cyst	>5 mm in thickness	632
**	Eruption cyst	Bluish swelling overlying erupting tooth	635
**	Odontogenic keratocyst	—	636
*	Orthokeratinized odontogenic cyst	—	639
*	Ameloblastoma	Especially unicystic type	653
*	Ameloblastic fibroma	Usually in younger patients	669
*	Adenomatoid odontogenic tumor	Usually in anterior region of jaws; most often with maxillary canine; usually in teenagers	664
*	Calcifying odontogenic cyst	Gorlin cyst	647
*	Carcinoma arising in dentigerous cyst	Mostly in older adults	651
*	Intraosseous muco-epidermoid carcinoma	Mostly in posterior mandible	457
*	Other odontogenic lesions	Examples: calcifying epithelial odontogenic tumor, odontogenic myxoma, central odontogenic fibroma	Chapter 15
B. Unilocular Radiolucencies: Periapical Location			
***	Periapical granuloma	Nonvital tooth	117
***	Periapical cyst	Nonvital tooth	119
**	Periapical cemento-osseous dysplasia (early)	Especially in black females; usually apical to mandibular anteriors; teeth are vital	597
*	Periapical scar	Usually endodontically treated tooth with destruction of cortical plate	119
*	Dentin dysplasia type I	Multiple periapical granulomas or cysts; shortened, malformed roots	102
C. Unilocular Radiolucencies: Other Locations			
***	Developing tooth bud	Within alveolar bone	—
**	Lateral radicular cyst	Nonvital tooth; lateral canal	120
**	Nasopalatine duct cyst	Between and apical to maxillary central incisors; palatal swelling may occur	26
**	Lateral periodontal cyst	Especially in mandibular bicuspid-cuspid region	645
**	Residual (periapical) cyst	Edentulous area	121
**	Odontogenic keratocyst	—	636
**	Central giant cell granuloma	Especially in anterior mandible	584
**	Stafne bone defect	Angle of mandible below mandibular canal	22
*	Cemento-osseous dysplasia	Early stage; usually in young adult and middle-aged black women; usually in mandible	596
*	Central ossifying fibroma	Early-stage lesion	602

PART 4: RADIOGRAPHIC PATHOLOGY—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
*	Ameloblastoma	Especially unicystic type	653
*	Buccal bifurcation cyst	Buccal aspect of erupting mandibular first or second molar	650
*	Other odontogenic cysts and tumors	Examples: ameloblastic fibroma, central odontogenic fibroma, calcifying odontogenic cyst	Chapter 15
*	Langerhans cell histiocytosis	"Histiocytosis X"; usually in children or young adults	550
*	Melanotic neuroectodermal tumor of infancy	Anterior maxilla; may be pigmented	499
*	Median palatal cyst	Clinical midline swelling of hard palate	28
*	Schwannoma/ neurofibroma	Usually associated with mandibular nerve	494
D. Multilocular Radiolucencies			
***	Odontogenic keratocyst	—	636
***	Ameloblastoma	Especially in posterior mandible; often associated with impacted tooth	653
**	Central giant cell granuloma	Especially in anterior mandible	584
*	Ameloblastic fibroma	Especially in young patients	669
*	Odontogenic myxoma	"Cobweb" trabeculation	679
*	Central odontogenic fibroma	—	676
*	Calcifying epithelial odontogenic tumor	Often associated with impacted tooth	666
*	Orthokeratinized odontogenic cyst	Often associated with impacted tooth	639
*	Lateral periodontal cyst (botryoid type)	Especially in mandibular bicuspid-cuspid region	645
*	Calcifying odontogenic cyst	Especially in cases with minimal or no calcifications; often associated with impacted tooth	647
*	Central hemangioma/ arteriovenous malformation	Especially in younger patients; may have honeycombed radiographic appearance; may pulsate	506
*	Aneurysmal bone cyst	Especially in younger patients	591
*	Cherubism	Hereditary; onset in childhood; multiple quadrants involved	587
*	Hyperparathyroidism (brown tumor)	Usually elevated serum calcium levels	781
*	Intraosseous muco-epidermoid carcinoma	Usually in posterior mandible	457
*	Fibrous dysplasia	Very rarely on panoramic films of mandibular lesions	592
E. Radiolucencies: Poorly Defined or Ragged Borders			
***	Periapical granuloma or cyst	Nonvital tooth	117
***	Focal osteoporotic marrow defect	Especially edentulous areas in posterior mandible; more common in females	579

Continued

PART 4: RADIOGRAPHIC PATHOLOGY—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Osteomyelitis	Usually painful or tender	128
**	Medication-related osteonecrosis of the jaw	Exposed necrotic bone; most often associated with bisphosphonate drugs	271
*	Simple bone cyst	Mandibular lesion that scallops up between roots of teeth; usually in younger patients	589
*	Metastatic tumors	Painful; paresthesia; usually in older adults	622
*	Osteoradionecrosis	History of radiation therapy; painful	269
*	Multiple myeloma	May be painful; in older adults	563
*	Primary intraosseous carcinomas	Odontogenic or salivary origin	661
*	Osteosarcoma	Often painful; usually in young adults	614
*	Chondrosarcoma	—	618
*	Ewing sarcoma	Usually in children	621
*	Other primary bone malignancies	Examples: fibrosarcoma, lymphoma	—
*	Desmoplastic fibroma of bone	Especially in younger patients	613
*	Massive osteolysis	Phantom (vanishing) bone disease	581
F. Radiolucencies: Multifocal or Generalized			
***	Cemento-osseous dysplasia	Early stage lesions; usually in black females; usually in mandible	596
**	Nevoid basal cell carcinoma syndrome	Odontogenic keratocysts	640
**	Multiple myeloma	Painful; in older adults; "punched-out" lesions	563
*	Cherubism	Usually multilocular; onset in childhood; hereditary	587
*	Hyperparathyroidism	Multiple brown tumors	781
*	Langerhans cell histiocytosis	"Histiocytosis X"; in children and young adults; teeth "floating in air"	550
G. Radiopacities: Well-Demarcated Borders			
***	Torus or exostosis	Associated with bony surface mass	18
***	Retained root tip	Remnants of periodontal ligament usually seen	—
***	Idiopathic osteosclerosis	Most commonly associated with roots of posterior teeth; no apparent inflammatory etiology	579
***	Pseudocyst of the maxillary sinus	Homogeneous, dome-shaped relative opacity rising above bony floor of maxillary sinus	293
**	Condensing osteitis	Usually at apex of nonvital tooth	134
**	Odontoma, compound	Toothlike structures with thin, radiolucent rim at junction with surrounding bone; may prevent eruption of teeth; more common in anterior segments of jaws	674
**	Odontoma, complex	Amorphous mass with thin, radiolucent rim at junction with surrounding bone; may prevent eruption of teeth; more common in posterior segments of jaws	674
**	Cemento-osseous dysplasia	Late-stage lesions; especially in middle-aged and older black women; usually in mandible	596

PART 4: RADIOGRAPHIC PATHOLOGY—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Soft tissue radiopacity superimposed on bone	Examples: sialoliths, calcified nodes, phleboliths, bullet fragments, shotgun pellets, amalgam tattoos (See also Appendix List, Part 4, Q, page 867)	—
*	Intraosseous foreign body	—	—
*	Osteoma	Associated with bony surface mass	605
*	Enamel pearl	Furcation area of molar tooth	85
*	Osteoblastoma/osteoid osteoma/ cementoblastoma	Late-stage lesions	608
H. Radiopacities: Poorly Demarcated Borders			
**	Cemento-osseous dysplasia	Late stage lesions; especially in middle-aged and older black women; usually in mandible	596
**	Medication-related osteonecrosis of the jaw	Sclerosis of alveolar crestal bone; exposed necrotic bone; most often associated with bisphosphonate drugs	271
**	Condensing osteitis	Usually at apex of nonvital tooth	134
**	Sclerosing osteomyelitis	May be painful	131
*	Fibrous dysplasia	"Ground glass" appearance; onset usually in younger patients	592
*	Paget disease of bone	"Cotton wool" appearance; late-stage lesions; in older patients	582
*	Proliferative periostitis	"Onion-skin" cortical change; in younger patients; often associated with nonvital tooth	134
*	Osteosarcoma	May have "sunburst" cortical change; frequently painful; usually in young adults	614
*	Chondrosarcoma	—	618
I. Radiopacities: Multifocal or Generalized			
**	Florid cemento-osseous dysplasia	Late-stage lesions; especially in middle-aged and older black women; usually in mandible	598
**	Medication-related osteonecrosis of the jaw	Multifocal sites of involvement; sclerosis of alveolar crestal bone; exposed necrotic bone; most often associated with bisphosphonate drugs	271
*	Idiopathic osteosclerosis	Occasionally may be multifocal	579
*	Paget disease of bone	"Cotton wool" appearance; late-stage lesions; in older patients; more common in maxilla	582
*	Gardner syndrome	Multiple osteomas; epidermoid cysts; gastrointestinal polyps with high tendency toward malignant transformation; hereditary	606
*	Polyostotic fibrous dysplasia	"Ground glass" appearance; onset usually in younger patients; may be associated with *café au lait* skin pigmentation and endocrine abnormalities (McCune-Albright syndrome)	593
*	Osteopetrosis	Hereditary; recessive form may be associated with secondary osteomyelitis, visual and hearing impairment	574
J. Mixed Radiolucent/Radiopaque Lesions: Well-Demarcated Borders			
***	Developing tooth	—	—
***	Cemento-osseous dysplasia	Intermediate-stage lesions; especially in middle-aged black women; usually in mandible	596

Continued

PART 4: RADIOGRAPHIC PATHOLOGY—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Odontoma	Compound or complex type; in younger patients; may prevent eruption of teeth	674
*	Central ossifying fibroma	—	602
*	Ameloblastic fibro-odontoma	Usually in children	671
*	Adenomatoid odontogenic tumor	Usually in anterior region of jaws; most often with maxillary canine; usually in teenagers	664
*	Calcifying epithelial odontogenic tumor	Pindborg tumor; often associated with impacted tooth; may show "driven snow" opacities	666
*	Calcifying odontogenic cyst	Gorlin cyst; may be associated with odontoma	647
*	Osteoblastoma/osteoid osteoma	Intermediate-stage lesion; usually in younger patients; often painful	608
*	Cementoblastoma	Intermediate-stage lesion; attached to tooth root	610
K. Mixed Radiolucent/Radiopaque Lesions: Poorly Demarcated borders			
**	Medication-related osteonecrosis of the jaw	Exposed necrotic bone; most often associated with bisphosphonate drugs	271
**	Osteomyelitis	With sequestrum formation or with sclerosing type; often painful	128
*	Metastatic carcinoma	Especially prostate and breast carcinomas; may be painful	622
*	Osteosarcoma/ chondrosarcoma	May be painful	614
L. Mixed Radiolucent/Radiopaque Lesions: Multifocal or Generalized			
**	Florid cemento-osseous dysplasia	Intermediate-stage lesions; especially in middle-aged black women; usually in mandible	598
**	Medication-related osteonecrosis of the jaw	Exposed necrotic bone; most often associated with bisphosphonate drugs	271
*	Paget disease of bone	In older patients; more common in maxilla	582
M. Unique Radiographic Appearances: "Ground Glass" (Frosted Glass) Radiopacities			
*	Fibrous dysplasia	Onset usually in younger patients	592
*	Hyperparathyroidism	May cause loss of lamina dura	781
N. Unique Radiographic Appearances: "Cotton Wool" Radiopacities			
**	Cemento-osseous dysplasia	Especially in middle-aged black women; usually in mandible	596
*	Paget disease of bone	In older patients; more common in maxilla	582
*	Gardner syndrome	Multiple osteomas; epidermoid cysts; gastrointestinal polyps with high tendency toward malignant transformation; hereditary	606
*	Gigantiform cementoma	Hereditary; facial enlargement may be present	601
O. Unique Radiographic Appearances: "Sunburst" Radiopacities			
*	Osteosarcoma	Often painful; usually in young adults	614
*	Intraosseous hemangioma	Especially in younger patients	506

PART 4: RADIOGRAPHIC PATHOLOGY—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
P. Unique Radiographic Appearances: "Onion-Skin" Radiopacities			
*	Proliferative periostitis	In younger patients; often associated with nonvital tooth; best seen with occlusal radiograph	134
*	Ewing sarcoma	In young children	621
*	Langerhans cell histiocytosis	"Histiocytosis X"; usually in children or young adults	550
Q. Soft Tissue Radiopacities			
***	Amalgam tattoo	Markedly radiopaque; associated with surface discoloration	281
**	Other foreign bodies	Examples: bullet fragments, shotgun pellets	—
**	Sialolith	Glandular pain may be present while patient is eating	427
**	Tonsilloliths	Superimposed on mandibular ramus	168
*	Phlebolith	May occur in varicosities or hemangiomas	14
*	Calcified lymph nodes	Example: tuberculosis	178
*	Osseous and cartilaginous choristomas	Most common on tongue	515
*	Calcinosis cutis	May be seen with systemic sclerosis (especially CREST syndrome)	747
*	Myositis ossificans	Reactive calcification in muscle	—

PART 5: PATHOLOGY OF TEETH

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
A. Hyperdontia (Extra Teeth)			
***	Idiopathic supernumerary teeth	Mesiodens, paramolar, distomolar	70
**	Cleft lip and palate	Extra lateral incisor or canine	1
*	Gardner syndrome	Osteomas and gastrointestinal polyps	606
*	Cleidocranial dysplasia	Hypoplastic or missing clavicles; failure of tooth eruption	576
B. Hypodontia (Missing Teeth)			
***	Idiopathic hypodontia	Missing third molars, lateral incisors	70
**	Cleft lip and palate	Missing lateral incisor or canine	1
*	Hereditary hypohidrotic ectodermal dysplasia	Cone-shaped teeth	690
*	Incontinentia pigmenti	Cone-shaped teeth	698
*	Radiotherapy during childhood	Stunted tooth development	52
C. Macrodontia (Larger Than Normal Teeth)			
**	Fusion	Joining of two tooth germs	77
**	Gemination	Incomplete splitting of a tooth germ	77
*	Idiopathic macrodontia	—	76
*	Facial hemihyperplasia	Affected side only; nondental tissues also enlarged	35
*	Gigantism	Abnormally tall stature	775
D. Microdontia (Smaller Than Normal Teeth)			
***	Supernumerary teeth	Mesiodens; fourth molars	70
***	Peg-shaped lateral incisors	Cone-shaped teeth	76
**	Dens invaginatus	Cone-shaped teeth; tendency for pulpal death and periapical pathosis	82
*	Idiopathic microdontia	Usually generalized	76
*	Hereditary hypohidrotic ectodermal dysplasia	Cone-shaped teeth; sparse, blond hair; diminished sweating	690
*	Radiotherapy during childhood	Stunted tooth development	52
*	Congenital syphilis	Hutchinson's incisors	172
*	Hypopituitarism	Associated dwarfism	774
E. Malformed Crown			
***	Mesiodens and other supernumeraries	Cone-shaped teeth or microdont	70
**	Environmental enamel hypoplasia	Example: high fever during tooth development	49
**	Peg-shaped lateral incisors	Cone-shaped teeth	76
**	Dens invaginatus	Cone-shaped teeth; tendency toward pulpal death and periapical pathosis	82
**	Turner tooth	Infection or trauma to associated primary tooth	50

PART 5: PATHOLOGY OF TEETH—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
**	Fusion or gemination	"Double" tooth	77
*	Talon cusp	Extra cusp on lingual of anterior tooth	80
*	Dens evaginatus	Extra cusp on occlusal of premolar tooth	81
*	Amelogenesis imperfecta	Hereditary defect in enamel formation	92
*	Dentinogenesis imperfecta	Fracturing away of enamel due to hereditary defect in dentin formation; gray-yellow opalescent teeth; calcified pulp chambers	98
*	Regional odontodysplasia	Poor tooth formation in a focal area; "ghost teeth"	104
*	Congenital syphilis	Hutchinson's incisors; mulberry molars	172
*	Vitamin D–resistant rickets	Hereditary condition; high pulp horns	789
*	Renal osteodystrophy	Abnormal calcium and phosphate metabolism	782
*	Hypoparathyroidism	Possible associated endocrine-candidiasis syndrome	780
*	Pseudohypoparathyroidism	—	781
*	Epidermolysis bullosa	Hereditary blistering skin disease	708
*	Radiotherapy during childhood	Stunted tooth development	52
*	Globodontia	Associated with otodental syndrome	91
*	Lobodontia	Cusp anatomy resembles teeth of carnivores	91
F. Enamel Loss After Tooth Formation			
***	Caries	—	—
***	Trauma	Fractured tooth	—
***	Attrition	Physiologic loss of tooth structure	55
***	Abrasion	Pathologic loss of tooth structure	56
**	Erosion	Chemical loss of tooth structure	56
*	Dentinogenesis imperfecta	Hereditary defect in dentin formation; poor junction between enamel and dentin	98
*	Amelogenesis imperfecta	Hereditary defect in enamel formation; especially hypocalcified types	92
G. Extrinsic Staining of Teeth			
***	Tobacco	Black or brown	63
***	Coffee, tea, and cola drinks	Brown or black	63
**	Chromogenic bacteria	Brown, black, green, or orange	63
**	Chlorhexidine	Yellow-brown	63
H. Intrinsic Discoloration ("Staining") of Teeth			
***	Aging	Yellow-brown; less translucency	—
***	Death of pulp	Gray-black; less translucency	64
**	Fluorosis	White; yellow-brown; brown; mottled	52
**	Tetracycline	Yellow-brown; yellow fluorescence	65
**	Internal resorption	"Pink tooth of Mummery"	58

Continued

PART 5: PATHOLOGY OF TEETH—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
*	Calcific metamorphosis	Yellow	114
*	Dentinogenesis imperfecta	Blue-gray; translucent	98
*	Amelogenesis imperfecta	Yellow-brown	92
*	Congenital erythropoietic porphyria	Yellow; brown-red; red fluorescence	64
*	Erythroblastosis fetalis	Yellow; green	64
I. Abnormally Shaped Roots			
***	External root resorption	Secondary to infection, cyst, tumor	58
***	Dilaceration	Abnormal curvature	89
**	Hypercementosis	Excessive cementum production	88
**	Supernumerary roots	—	90
**	Concrescence	Joining of teeth by cementum	77
**	Taurodontism	Enlarged pulp chambers; shortened roots	86
**	Enamel pearl	Ectopic enamel in furcation	85
*	Benign cementoblastoma	Tumor attached to root	610
*	Radiotherapy during childhood	Stunted root development	52
*	Dentinogenesis imperfecta	Shortened roots; obliterated pulps	98
*	Dentin dysplasia type I	Shortened, pointed roots ("rootless teeth"); obliterated pulps; periapical pathosis	102
J. Enlarged Pulp Chamber or Canal			
**	Internal resorption	Secondary to caries or trauma	58
**	Taurodontism	Enlarged pulp chambers; shortened roots	86
*	Dentinogenesis imperfecta	"Shell teeth"	98
*	Regional odontodysplasia	"Ghost teeth"	104
*	Vitamin D–resistant rickets	High pulp horns	789
*	Hypophosphatasia	—	788
*	Dentin dysplasia type II	"Thistle-tube" pulps; pulp stone formation	101
K. Pulpal Calcification			
***	Pulp stones	Asymptomatic radiographic finding	115
***	Secondary dentin	Response to caries	113
**	Calcific metamorphosis	Pulpal obliteration secondary to aging or trauma	114
*	Dentinogenesis imperfecta	Pulpal obliteration by excess dentin	98
*	Dentin dysplasia type I	Pulpal obliteration by excess dentin; "chevron"-shaped pulp chambers	102
*	Dentin dysplasia type II	Pulpal obliteration of primary teeth; pulp stones in permanent teeth	101

PART 5: PATHOLOGY OF TEETH—cont'd

Frequency of Occurrence	Lesion or Condition	Comments or Special Characteristics	Page
L. Thickened Periodontal Ligament			
***	Periapical abscess	Focal thickening at apex of nonvital tooth; painful, especially on percussion of involved tooth	123
***	Current orthodontic therapy	—	—
**	Increased occlusal function	—	—
*	Systemic sclerosis (scleroderma)	Generalized widening	744
*	Sarcoma or carcinoma infiltration	Especially osteosarcoma; localized to teeth in area of tumor	616, 623
M. Generalized Loss of Lamina Dura			
*	Hyperparathyroidism	Calcium removed from bones; bone may have "ground glass" appearance	781
*	Osteomalacia	Vitamin D deficiency in adults	771
*	Paget disease of bone	"Cotton wool" change hides lamina dura	582
*	Fibrous dysplasia	"Ground glass" change hides lamina dura	592
N. Premature Exfoliation of Teeth			
***	Trauma	Avulsed tooth	—
**	Aggressive periodontitis	Premature alveolar bone loss	157
**	Immunocompromised states	AIDS, leukemia, chemotherapy	246
**	Diabetes mellitus	Increased susceptibility to infection and severity of periodontitis	785
*	Osteomyelitis	Bone destruction loosening teeth	128
*	Cyclic or chronic neutropenia	Increased susceptibility to infection; premature alveolar bone loss	544
*	Langerhans cell histiocytosis	"Histiocytosis X"; eosinophilic granuloma; premature alveolar bone loss	550
*	Dentin dysplasia type I	"Rootless teeth"	102